ANGEWANDTE CHEMIE
International Edition in English
Volume 19 · Number 3
March 1980
Pages 151–230

Electrophilic Reagents—Recent Developments and Their Preparative Application

By Franz Effenberger[*]

Dedicated to Professor Matthias Seefelder on the occasion of his 60th birthday

The most widely known electrophilic agents are protic acids and compounds with an electron-sextet partial structure. Recent research has aimed at the development of new electrophilic reagents, with greater reactivity on the one hand and higher selectivity on the other, which would largely obviate the addition of Lewis acids (Friedel-Crafts catalysts), and also allow control of the isomer ratio in reactions with ambivalent substrates. Compounds with "super-leaving groups", such as trifluoromethanesulfonate and fluorosulfate, have been demonstrated as most advantageous in this respect since they are sufficiently polarized or dissociated for reactions to take place even in the absence of Friedel-Crafts catalysts. Heterocycles such as pyridones or imidazole are likewise suitable leaving groups; they are employed for their high selectivity, and also because they allow working under non-aqueous conditions.

1. Introduction

The terms "electrophile" and "electrophilic reagent" were introduced into organic chemistry by *C. K. Ingold*[1a]; his definitions, given in a comprehensive review[1b] and in his standard work "Structure and Mechanism in Organic Chemistry"[1c], are still valid today:

> "Reagents which act by acquiring electrons, or share in electrons which previously belonged to a foreign molecule will be called electrophilic reagents, or sometimes electrophiles."

Ingold distinguishes here between electrophiles which actually take over the electrons from another molecule (oxidants in the true sense), and those which form covalent bonds and thence place only a partial demand on the substrate electrons. This definition smoothly accommodates both protic acids and compounds with an electron-sextet structure which coordinate with lone electron pairs of other molecules in an electrophilic manner.

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The basic principle underlying the interaction between acid/base, acceptor/donor, and electrophile/nucleophile has been a controversial issue for a long time, and has led to frequent attempts at an optimum systematization or classification[2]. *Ingold* had already recognized clearly, though, that a formal (electric) charge is not prerequisite for the electrophilicity of a certain species; rather, the actual electrophilic moiety may be formed *in situ* in the reactant mixture.

In electrophilic bond formation, the bonding electrons must by definition stem from the substrate. Thus only compounds with lone pairs or π-electrons are as a rule susceptible to electrophilic attack; electrophilic reactions of σ bonds remain exceptional for energetic reasons[3]. Alcohols and amines, as compounds with lone electron pairs, consequently number among the most important substrates for electrophiles, *e.g.* in alkylation or acylation. Usually, these reactions are considered under the aspect of the nucleophile; because of the considerable influence of the electrophilic partner, however, recent developments in this field will be discussed here too.

The most frequently employed reactions of unsaturated compounds are the electrophilic substitution of arenes and hetarenes, the electrophilic addition to alkenes and alkynes, respectively, and their substitution; in this context, enols and

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enol derivatives (enol ethers, acylates, and silyl enol ethers) as well as enamines must be considered as specially substituted olefins.

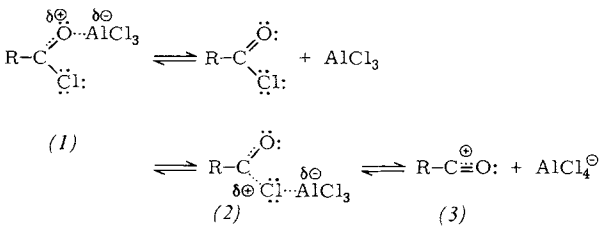
The quest for new electrophiles has been directed primarily towards greater reactivity and higher selectivity; such reagents should render the addition of equimolar amounts of Friedel-Crafts catalysts superfluous, and allow at least some control of the isomer distribution in reactions with ambivalent substrates (*e.g.* substituted aromatics or enols).

A decisive factor for both the generation and the reaction potential of an electrophile is whether the reagent is dissociated into anion and cation (as the actual electrophilic species), or whether a more or less polarized bond is cleaved in the desired direction only under the influence of the co-reactant:

$$E-A \leftrightarrow E^{\delta\oplus} \blacktriangleleft A^{\delta\ominus} \rightleftharpoons E^{\oplus}\,A^{\ominus} \rightleftharpoons E^{\oplus} + A^{\ominus}$$

In the absence of a suitable substrate, bond polarization is determined primarily by the electronegativity difference between E and A; the extent of bond cleavage mainly depends on the stability of the ions $E^{\oplus}$ and $A^{\ominus}$ in a given solvent, as long as the system provides the necessary energy for dissociation.

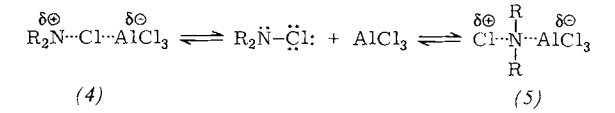
The described bond polarization or cleavage of a reagent E–A is frequently catalyzed by electron acceptors (Brønsted or Lewis acids) which in this context are generally designated summarily as Friedel-Crafts catalysts. The mode of interaction of these electron acceptors is not the same, though, for the various potential electrophiles—as, for example, in Friedel-Crafts alkylation and acylation; a general classification with respect to their catalytic effectiveness is therefore not feasible. A compound with lone pairs at different atoms, for example, can be attacked by the catalyst at each of the nucleophilic sites; this in turn may lead to the formation of different electrophiles, rendering predictions as to the actual reagent rather difficult. The presence of both oxonium complexes *(1)* and acylium ions *(3)*, for instance, has been established for Friedel-Crafts acylation with acyl chlorides and $AlCl_3$[4a,b]. Additionally, the acyl halide suffers halogen exchange—proven by isotopic labeling—which also can be rationalized only *via* the intermediate *(2)* and an equilibrium with the acylium ion *(3)*[4c].



(1) *(2)* *(3)*

From kinetic experiments, it has been deduced that a further intermediate is involved in the formation of *(3)* in which the carbonyl oxygen is likewise complexed by $AlCl_3$[4d]. All three potential electrophiles [*(1), (2), (3)*] now can act as the effective acylating agent in Friedel-Crafts acylation.

Another striking example is the amination with chloroamines in the presence of Friedel-Crafts catalysts. Attack of the Lewis acid at a lone pair of the chlorine atom produces an aminating agent *(4)*, whereas attack at the nitrogen lone pair results in the formation of a chlorinating agent *(5)*[5].



(4) *(5)*

This problematical situation in electrophilic reactions with Friedel-Crafts catalysts has been dealt with comprehensively in several reviews[6]. In the development of new, both more reactive and selective electrophiles, attempts have been made to eliminate the difficulties inherent in the application of Lewis acids, and, by introducing better leaving groups, to achieve sufficient polarization or dissociation of the reagents E—A *per se*. The present review will focus attention primarily on these aspects.

2. Importance of the Leaving Group for Electrophile Formation

A decisive factor for the reactivity of an electrophile is the degree of its polarization or dissociation. Numerical values for the leaving tendency of different groups have been derived mainly from the kinetics of nucleophilic substitution at a saturated carbon atom. For estimating relative reactivities of electrophiles with different leaving groups, solvolysis probably represents the best model; here, the dissociation step is rate-determining and, consequently, the influence of the leaving group on the reaction rate far greater than in S_N2 substitution[7]. For some of the more common leaving groups, relative rates in S_N1 reactions are given below (relative to bromide):

Leaving group $Z^{\ominus}$:	$CF_3SO_3^{\ominus}$	p-CH_3—C_6H_4—$SO_3^{\ominus}$	$Br^{\ominus}$
k_Z/k_{Br}:	5×10^8	5×10^3	1
Leaving group $Z^{\ominus}$:	$Cl^{\ominus}$	p-O_2N—C_6H_4—$COO^{\ominus}$	
k_Z/k_{Br}:	2.5×10^{-2}	2×10^{-6}	

Yet even in S_N1 reactions, the influence of the leaving group on the reaction rate depends to some extent on the stability of the carbenium ion formed upon dissociation, diminishing with increasing cation stability[7]. If dissociation of E–A, as stated above, is in fact determined principally by the stability of the ions $E^{\oplus}$ and $A^{\ominus}$, then, for any given electrophile $E^{\oplus}$, the stability of $A^{\ominus}$ alone should determine its leaving tendency; in this case, the pK_a of the conjugate acid could provide a quantitative measure. Good correlation indeed exists between leaving tendency and conjugate acid strength in many cases, even though pK_a values are defined for H–A bond dissociation while in S_N1-type solvolyses >C–A bonds are cleaved heterolytically. Within the halide series, for instance, the leaving tendencies parallel the pK_a values of the hydrohalic acids (I > Br > Cl > F).

For the solvolysis of sulfonates, with C–O bond cleavage, a good correlation has been established between the leaving tendency of the sulfonate anion, $XSO_3^{\ominus}$, and the acid strength of XSO_3H (X = CF_3, F, C_6F_5, p-CH_3—C_6H_4)[8].

According to a recent investigation, acid strength and leaving tendency are loosely correlated even for very strong acids[9]. The rates of solvolysis of methyl trifluoromethanesulfonate (= methyl triflate), fluorosulfate, and perchlorate, for instance, are graduated comparably in the three solvent media water, methanol, and acetonitrile ($CF_3SO_3CH_3$ >

$FSO_3CH_3 > ClO_4CH_3$); the differences, though, are fairly small. Conductometric determinations in aprotic media and in CH_3COOH, on the other hand, give similar acidities for perchloric and trifluoromethanesulfonic acid, and a somewhat lower value for fluorosulfuric acid[10].

The exceptionally high leaving tendency of the trifluoromethanesulfonate ("triflate") ion has been attributed to specific electronic interaction of the CF_3 group in the dissociation step[11]. However, the paramount importance of triflate as leaving group is due to the extraordinary thermal stability and resistance towards oxidative and reductive degradation of both triflate ion and the free acid. In a recent summary of preparative applications of trifluoromethanesulfonic acid and its derivatives, *Howells* and *McCown* have particularly stressed this point[12].

Since the quantitative data on the leaving tendency of various moieties Z have all been derived from the solvolysis of C—Z bonds, they are not directly applicable to "hetero-electrophiles" (O, N, halogen electrophiles). For this, the other types of bonds involved in heterolysis, the changed bond polarization due to the altered electronegativity differences, and the disparate cation stabilization must all be taken into account. Nevertheless, the correlations between reactivity and stability of the leaving group, established for carbon electrophiles, have been applied successfully also in the development of new hetero-electrophiles.

A fundamental problem which so far has thwarted satisfactory quantification is the solvent effect in reactions with electrophiles. In the case of nucleophiles, reactivity is affected by solvent and gegenion in a well defined manner[13]. In contrast to these generally stable particles, most cationic electrophiles are stable and detectable only in superacid systems[13,14]; their high reactivity additionally limits the choice of organic reaction media to haloalkanes, nitriles, sulfones, and the like. Even so, most electrophiles do not undergo regular solvation; rather, they form definite 1:1 adducts with the solvent which constitute the actual electrophilic species. Thus, upon reaction in acetonitrile, nitrilium salts are produced[9,15], and in haloalkanes halonium derivatives[16]; even in SO_2, addition compounds of the following type are observed[14a,16].

This, of course, severely affects the reactivity of the electrophiles. Nitronium salts, for instance, in inert solvents such as dichloroethane or sulfolane are weaker nitrating agents—despite their established ionic structure $[NO_2^{\oplus}]Z^{\ominus}$—than the normal mixtures of HNO_3 and H_2SO_4[17] since in the less nucleophilic acid mixture electrophile/solvent interaction is much less pronounced. Some information about the influence of solvation on carbenium ions has been obtained from a comparison of the relative stabilities of cations in the gas phase and in solution[18].

3. Halogen Electrophiles[19]

Apart from perchloryl fluoride, which is utilized for introducing the ClO_3 group into aromatics[20], the only halogen electrophiles of practical interest are the monovalent cations $I^{\oplus}$, $Br^{\oplus}$, $Cl^{\oplus}$, and $F^{\oplus}$. So far, however, they have not been observed directly either in solution or in the solid state[21a]; attempts at their generation, usually in superacid systems, always afforded only $X_2^{\oplus}$ and $X_3^{\oplus}$ species[21b]. The stability of these poly-ions increases, as expected, in the order $F < Cl < Br < I$, and with the number of halogen atoms incorporated, *i.e.* from $X_2^{\oplus}$ to $X_3^{\oplus}$[22]. Several of these polyhalo cations have been isolated in the solid state[23], yet nothing has been reported about their use as electrophilic halogenating agents.

Preferentially, therefore, reagents of the type $Z^{\delta\ominus} \blacktriangleright X^{\delta\oplus}$ are employed in electrophilic halogenation where the crucial bond is polarized in the requisite direction by linking the halogen to a more electronegative element (O, N, or another halogen), and Z at the same time is a good leaving group. These conditions are met, *inter alia*, by interhalogen compounds, halogen nitrates, fluorosulfates, and trifluoromethanesulfonates, by the hypohalites and some organic *N*-halo derivatives, as well as by carbon-halogen compounds with a $C \blacktriangleright X$ bond polarized sufficiently by electron withdrawing substituents.

With interhalogen compounds themselves only iodination and bromination of activated arenes such as phenols and aromatic amines is possible[24]. Mixtures of $SbCl_5$ and Br_2 or I_2 in which interhalogens are also assumed to be present as reactive species allow the substitution of less reactive aromatics too, for instance *meta*-bromination of nitrobenzene in 65% yield[25].

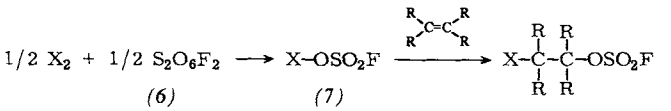
Halogen nitrates are prepared either from the anhydrides of the constituent acids[26] or, as pyridine complexes, with silver nitrate in pyridine directly from the halogens[27a]. The positivation of the halogen atoms in these reagents has been ascertained from spectroscopic results[28] as well as from their reaction behavior[26]: for example, their addition to double bonds proceeds both regioselectively and—*via* halonium intermediates—stereospecifically to give the *trans* adduct[27b].

$$Cl_2O + N_2O_5 \xrightarrow{0\,^{\circ}C} 2\,Cl{-}ONO_2$$

$$X_2 + AgNO_3 \xrightarrow[\text{Pyridine}]{CHCl_3} [X \cdot 2\,\text{Pyridine}]^{\oplus}NO_3^{\ominus} + AgX$$

$X = Br, I$

Halogen fluorosulfates *(7)* are usually prepared from the halogens with peroxodisulfonyl difluoride *(6)*[29,30]; their facile addition to olefins has been investigated extensively and is supposed to proceed *via* an electrophilic mechanism.



(6) *(7)*

X = F, Cl, Br; R = H, F, Cl

Recent investigations have confirmed the exceptional halogenating potential of halogen triflates *(8)*. Iodine triflate *(8a)*, for instance, though known for some time[31], has only recently been employed in iodination reactions.

$$6\,CF_3SO_3H + I_2 + 3\,S_2O_6F_2 \xrightarrow[-6\,HSO_3F]{} 2\,I(OSO_2CF_3)_3$$

(6)

$$\xrightarrow[140\,^\circ C]{+2\,I_2} 6\,I{-}OSO_2CF_3$$

(8a)

Chlorine triflate *(8b)* was synthesized almost simultaneously by two independent pathways[32, 33].

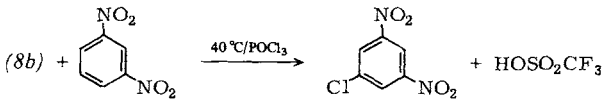
$$CF_3SO_3H + ClF \xrightarrow[-HF]{-111\text{ to }-78\,^\circ C} Cl{-}OSO_2CF_3$$

(8b)

$$\xrightleftharpoons{-80\text{ to }-40\,^\circ C} 1/2\,Cl_2O + 1/2\,(CF_3SO_2)_2O$$

Not unexpectedly, *(8b)* is an extremely powerful electrophile and chlorinates even *m*-dinitrobenzene in good yield[33]. Since the trifluoromethanesulfonic acid liberated in the course of the reaction is converted back into trifluoromethanesulfonic anhydride by the solvent $POCl_3$, only 20 mol-% need be employed[33].

$$Cl_2O + (CF_3SO_2)_2O \rightleftharpoons 2\ (8b)$$

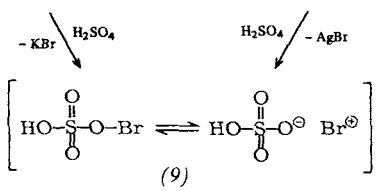


62%

$$2\,CF_3SO_2OH + POCl_3 \longrightarrow (CF_3SO_2)_2O + Cl_2P(O)OH + HCl$$

Bromine[34] and iodine triflate *(8a)*[35], prepared *in situ* from silver triflate and bromine or iodine, respectively, have also been successfully employed for the halogenation of deactivated arenes[34]. The findings with other halogen sulfonates[34] have led to the conclusion that for brominations in sulfuric acid, bromine hydrogen sulfate *(9)* is the reactive species, both in the presence of silver sulfate[36a] and with potassium peroxodisulfate[34].

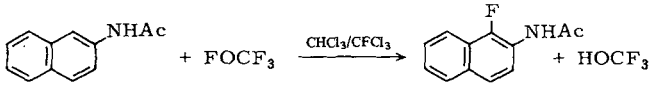
$$1/2\,K_2S_2O_8 + Br_2 \qquad 1/2\,Ag_2SO_4 + Br_2$$



(9)

Cesium fluoroxysulfate, obtained from cesium sulfate and fluorine, is both a powerful oxidant and fluorinating agent[36b].

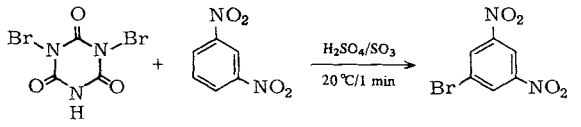
Among the hypohalites, which have long been used as main source of electrophilic halogen, fluoroxytrifluoromethane *(10)* has gained increasing importance[37a], particularly for the introduction of fluorine into the steroid skeleton. Reaction with both π- and σ-bonds[37b] most probably proceeds *via* an electrophilic mechanism.



(10) > 50%

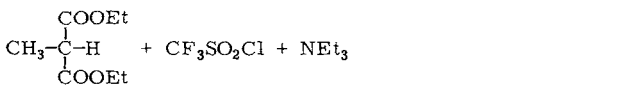
The XeF_6-graphite occlusion compound $C_{19}\cdot XeF_6$ which is more stable and thence easier to handle than the usually employed XeF_2[19b], has been applied specially for the fluorination of polycyclic arenes[38].

The halogen in the widely used *N*-halo derivatives can react either as radical or as electrophile[19b], depending on the further substituents at the nitrogen. With the extremely reactive *N,N*-dibromocyanuric acid *(11)*, for example, even strongly deactivated arenes are brominated in 15% oleum in good yield[39a], protonated *(11)* most likely being the reactive species[39b].



(11) 86%

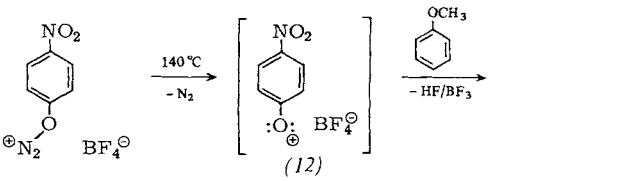
A very mild reagent for the chlorination of CH-acidic substrates is trifluoromethanesulfonyl chloride; it gives much better yields than *N*-chlorosuccinimide[40].



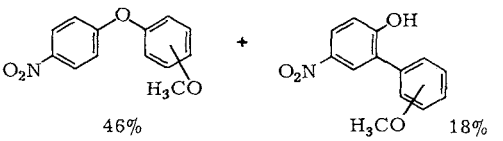
100%

4. Oxygen Electrophiles

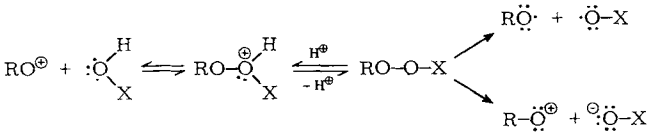
The oxygen electrophiles mainly used are compounds $RO^{\delta\oplus}{-}Z^{\delta\ominus}$ (R = H, organic group), with a sufficiently polarized O—Z bond and a good leaving group; because of the high electronegativity of oxygen itself, this must be either fluorine, another oxygen moiety, or a positively charged function ($-N_2^{\oplus}$, $-S^{\oplus}R_2$). The aryloxylium ion *(12)* so far is the only cationic oxygen electrophile $R{-}\ddot{O}^{\oplus}$ for which there is definite proof[41].



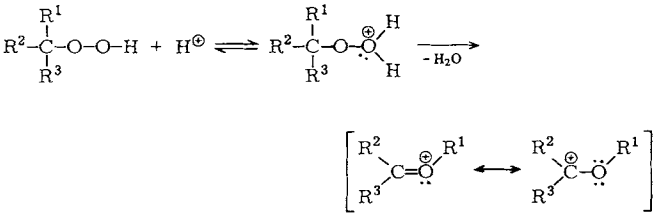
(12)



In practice, oxygen electrophiles are obtained mainly from hydrogen peroxide and its derivatives (peroxides, hydroperoxides, peroxo acids, peroxycarboxylic acids)[42]. Preferentially, peroxy functions are cleaved homolytically; a polar cleavage of the fairly weak O—O bond can be achieved, though, in polar solvents, also by substituents which are able to stabilize charges, and under the influence of proton or Lewis acids which polarize the O—O bond and, at the same time, generate better leaving groups[43].

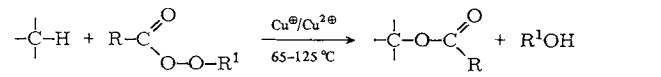


In generating oxygen electrophiles from peroxy precursors, heterolysis of the O–R bond may occur besides O–O bond cleavage[44]. Much more frequent and detrimental, however, is the rearrangement of the primarily formed cations into the well-stabilized carbenium ions[44].



Since in aryloxylium ions, *e.g. (12)*, analogous rearrangements are not possible, their existence could be demonstrated unequivocally by follow-up reactions[41].

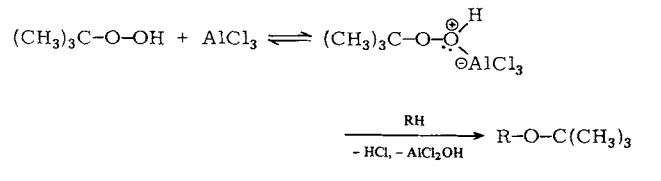
Acoxylation with peroxides is carried out with addition of transition metal ions; the reaction is employed regularly, and proceeds *via* radical intermediates[45].



R^1 = *t*Bu, ArylCO,...

An electrophilic mechanism, on the other hand, is assumed—on the basis of reactivity gradation and isomer distribution—for the reactions of the more electrophilic diaryl- and bis(arylsulfonyl) peroxides with nucleophilic arenes[46].

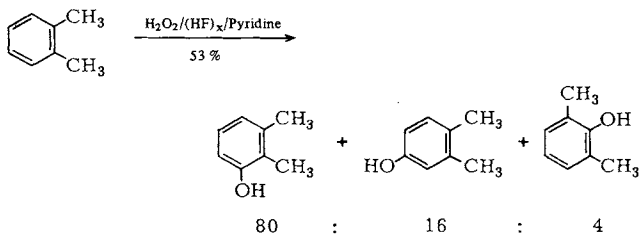
In the electrophilic hydroxylation of aromatics, the main problems are secondary (poly)hydroxylation—due to the enhanced reactivity of the hydroxyarenes formed—and oxidative processes which lead to a wide spectrum of products[47]. Polyhydroxylation can be avoided by using *tert*-butylperoxy isopropyl carbonate[48] or *tert*-butyl hydroperoxide[49] in the presence of Friedel-Crafts catalysts; in this case, the primary product, aryl *tert*-butyl ether, is transformed into the aryloxyaluminum dichloride *(13)* and thus deactivated.



R = Aryl *(13)*

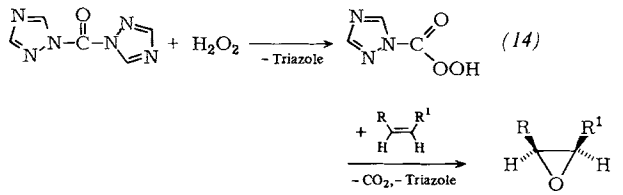
Electrophilic hydroxylation with peroxycarboxylic acids has gained increasing importance[42], especially since the ready accessibility of various peracids allows variation of the electrophilic potential within wide limits[50]. The yields in arene hydroxylation can be improved by addition of BF_3[51]; addition of $AlCl_3$ or $SbCl_5$, on the other hand, only favors the formation of oxidation products[47]. So far, inorganic peracids have found little use for arene hydroxylation—probably because of their instability in non-aqueous media. One example is the hydroxylation of alkyl- and hydroxybenzenes with peroxomonophosphoric acid; the high percentage of *ortho*-substitution products has led to the assumption of a cyclic transition state for this reaction[52].

Attempts within the past few years to utilize hydrogen peroxide itself as source of electrophilic oxygen were highly successful, and have made arene hydroxylation now possible on an industrial scale. Good yields of mono-hydroxylation products are thus obtained with highly concentrated hydrogen peroxide in the presence of $AlCl_3$[53] or strong acids[54] since in this case secondary reactions of the newly formed phenols are largely suppressed by protonation or complexation. The mixtures H_2O_2/HF[55a,b] and $H_2O_2/(HF)_x$/pyridine[55c] have proven exceptionally advantageous in this respect.

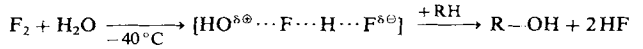


Surprisingly, poly-hydroxylation is also largely suppressed by the addition of CO_2[55a]. With H_2O_2/urea adducts and $AlCl_3$, arenes can likewise be hydroxylated in good yields[56].

Reaction of concentrated hydrogen peroxide with isocyanates[57a] or carbonyldiazolides[57b] affords peroxycarbamidic acids *(14)* which can serve as source of electrophilic oxygen in absolutely neutral medium, *e.g.* for the epoxidation of acid-labile olefins.



Hypofluoric acid HOF is one of the few oxygen electrophiles not derived from hydrogen peroxide. Other than HOCl, it yields only phenols in the reaction with arenes and no halogen derivatives. It has been supposed[58] that the electrophilicity of HOF is significantly enhanced by formation of the adduct *(15)* since with H_2O_2/HF no hydroxylation occurs under these conditions.



(15)

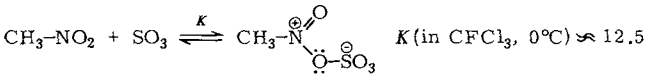
R = aryl

5. Sulfur Electrophiles

Among the reactions with electrophilic sulfur derivatives, sulfonation, sulfonylation, and likewise sulfenylation are of great importance; reactions with sulfurous acid derived electrophiles, on the other hand, have attracted much less attention[59].

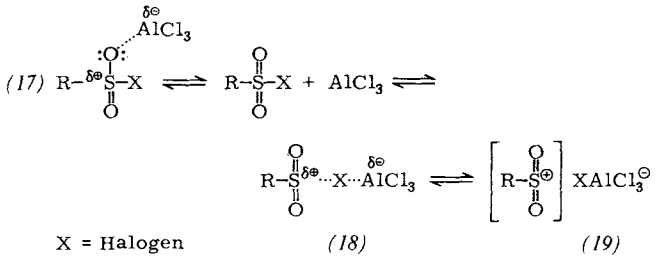
5.1. Sulfonation and Sulfonylation

Sulfonation is carried out prevalently with sulfuric acid of varying concentration—aqueous, concentrated, or SO_3-containing; SO_3-content and acid strength strongly affect both the formation of the electrophile and its reaction behavior[60]. With higher SO_3 concentration, for instance, more pyrosulfuric acids are formed ($H_2S_2O_7$, $H_2S_4O_{13}$) whose enhanced sulfonating potential is rationalized in terms of the higher leaving tendency of the respective larger anions[60b]. Adducts of SO_3 and cyclic ethers, pyridine, or tertiary amines are employed as selective sulfonating agents[61]. An addition complex *(16)* is present, too, in equilibrium in the sulfonation with SO_3 in nitromethane or nitrobenzene; though less reactive, *(16)* is significantly more selective than free SO_3 in haloalkane media[62].



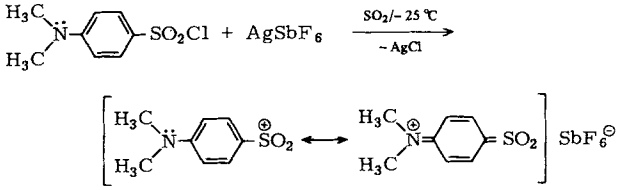
(16)

Sulfonylations are usually carried out with sulfonyl halides in the presence of Friedel-Crafts catalysts; as active electrophile in this case, either the oxygen- or the halogen-complexed intermediates, *(17)* or *(18)*, respectively, or the sulfonylium salts *(19)* are to be considered.

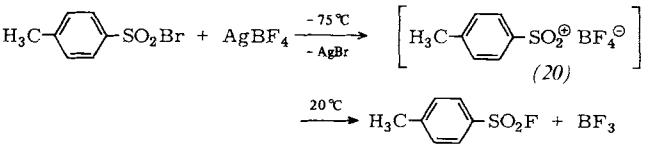


X = Halogen *(18)* *(19)*

Oxygen-addition products *(17)* result from the action of antimony pentahalides upon alkyl- and arylsulfonyl halides which bear no strong donor substituents[63a,b]; if the positive charge is sufficiently stabilized, *e.g.* by dialkylamino or alkoxy groups, sulfonylium salts *(19)* are formed[63b,c].



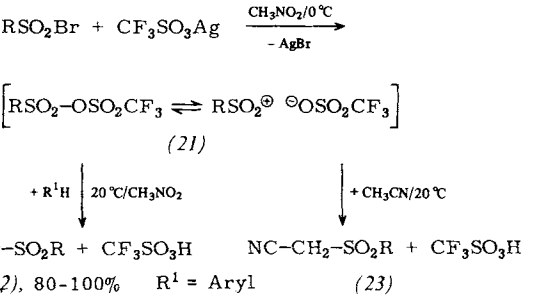
Klages et al.[64] who first investigated the reaction of toluenesulfonyl halides with silver perchlorate and tetrafluoroborate had already recognized the ionic nature of the powerful sulfonylating agents formed at low temperature with silver halide precipitation. Isolation of these sulfonylium salts



(20)

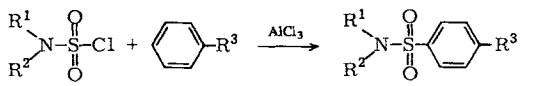
is not possible, though, since they decompose at slightly higher temperatures. The electrophilic potential of the *p*-toluenesulfonylium ion in *(20)*, for instance, is sufficient to strip off one fluoride from the gegenion $BF_4^{\ominus}$[64b].

In preparing new sulfonylating agents from aliphatic and aromatic sulfonyl bromides and silver triflate, the considerable stability of the triflate ion could be utilized to great advantage: The mixed anhydrides *(21)* can thus be obtained in neat form; their exceptional electrophilic potential allows, for instance, arylsulfone *(22)* formation in very good yields already at room temperature without addition of any Friedel-Crafts catalyst[65]. If preparation of the anhydrides *(21)* is attempted in acetonitrile as solvent, the cyanomethyl sulfones *(23)* are formed.



(22), 80-100% R^1 = Aryl *(23)*

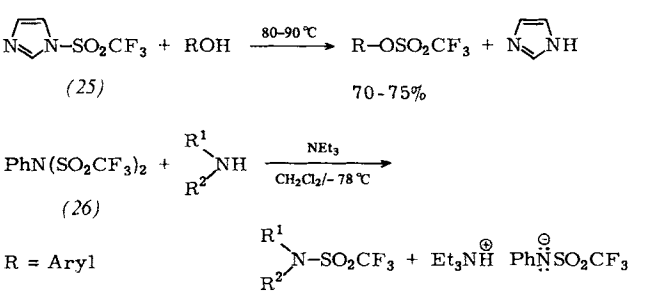
The way in which the relative reactivities in aryl sulfonylation depend on the rest R in the sulfonyl moiety indicate the dissociated form of *(21)* as the reactive species. The aliphatic anhydrides *(21)*, R = alkyl, are thermally labile; their rate of decomposition increases with increasing stability of the alkyl cations generated upon SO_2 expulsion ($CH_3^{\oplus} < C_2H_5^{\oplus} < (CH_3)_2CH^{\oplus}$)[65a].



(24) 50-100%

R^1, R^2 = C_2H_5, $-(CH_2)_5-$; R^3 = H, CH_3, Cl

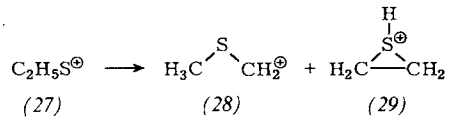
With the dialkylsulfamoyl chlorides *(24)*, *N,N*-dialkylsulfamoyl groups may be introduced into the *p*-position of mono-substituted arenes[66]. For the sulfonylation of OH- and NH-functions, both *N*-trifluoromethylsulfonylimidazolide *(25)*[67] and phenyl-*N,N*-bis(trifluoromethylsulfonyl)amide *(26)*[68] are very mild and highly selective reagents.



R = Aryl

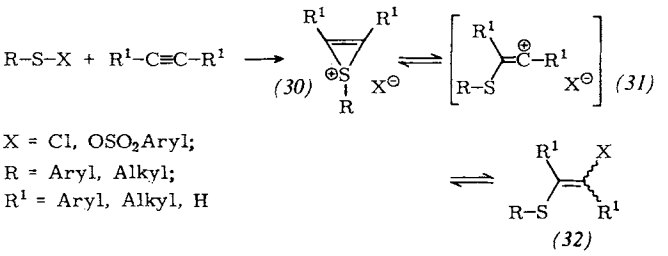
5.2. Sulfenylation

A comprehensive review of sulfenylium ions and other sulfenylating agents has appeared in 1976[69]; therefore, only work of the last few years will be commented upon here. Despite many efforts, free sulfenylium ions could so far not be detected in solution; once formed, they immediately stabilize by interaction or co-ordination with the solvent. In the gas phase, sulfenylium ions very rapidly rearrange into more stable species (*e.g.* the ethanesulfenylium ion *(27)* into *(28)* and *(29)*[70]). In general, electrophilic sulfenylating agents are generated from sulfenyl halides with Friedel-Crafts catalysts or *via* substitution of the halogen by a better leaving group[69].



(27) *(28)* *(29)*

The electrophilic addition of sulfenic acid derivatives to olefins[71] and acetylenes[72] has been investigated most extensively. Thiirenium salts *(30)* could be isolated from the reactions with acetylenes, partly in crystalline form. In solution, an equilibrium exists between these salts and the vinyl cations *(31)* and vinyl sulfides *(32)*; this equilibrium is the more shifted towards the side of the vinyl sulfides *(32)* the more nucleophilic the anion $X^{\ominus}$[72].

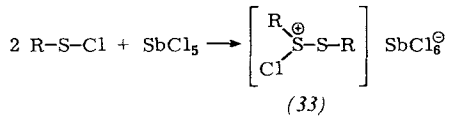


(30) *(31)*

X = Cl, OSO_2Aryl;
R = Aryl, Alkyl;
R^1 = Aryl, Alkyl, H

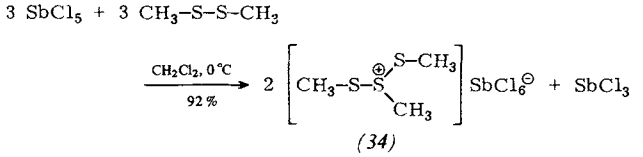
(32)

No free sulfenylium ions could be detected either in these reactions; rather, the attack of Lewis acids upon sulfenyl chlorides leads to the addition compounds *(33)* which then react as actual electrophilic species with the alkyne[72].



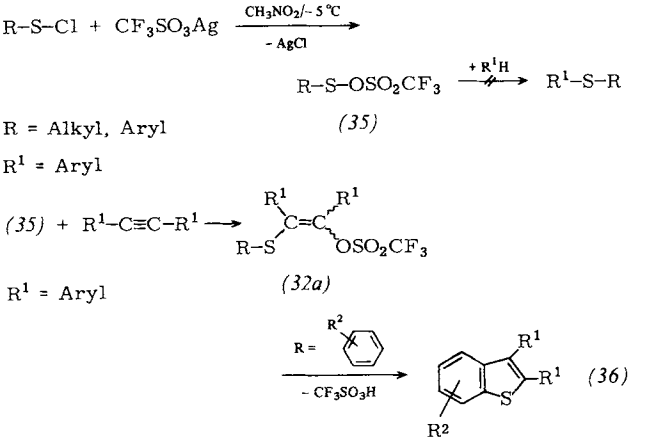
(33)

The sulfonium salts *(34)*, easily accessible from disulfides and antimony pentachloride, are excellent sulfenylating reagents[73].



(34)

The electrophilicity of the sulfenylating agents *(35)*, obtained from sulfenyl chlorides and silver triflate[74], does not suffice for arene sulfenylation; they add smoothly, though, to acetylenes. Due to the presence of the good triflate leaving group, the vinyl sulfides *(32a)* thus formed are subject to facile dissociation into vinyl cations; in the case of R = aryl, benzothiophenes *(36)* are formed in good yield by rearrangement of these vinyl cations[74].



(35)

R = Alkyl, Aryl
R^1 = Aryl

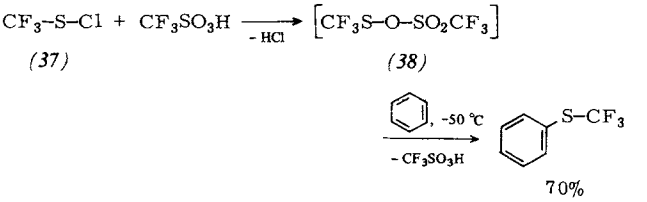
(32a)

R^1 = Aryl

(36)

An analogous benzothiophene formation upon heating arylsulfenic trinitrobenzenesulfonic anhydride with acetylenes had already been observed in earlier work[75].

The CF_3S function can be introduced directly into arenes and hetarenes with trifluoromethanesulfenyl chloride *(37)* in the presence of trifluoromethanesulfonic acid, for which the sulfenic sulfonic anhydride *(38)* formed intermediately is assumed as effective electrophile[76].

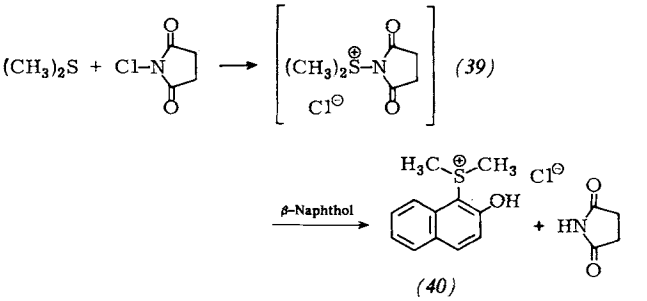


(37) *(38)*

70%

Iron[77] and silica gel[78] have proven exceptionally good catalysts for electrophilic aromatic substitution with sulfenyl halides.

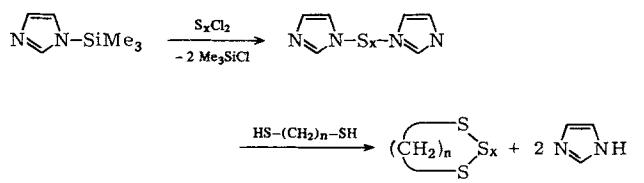
Salts of the type *(39)*[79], prepared from sulfides with chlorine[80] or from sulfoxides with mineral acids, allow electrophilic introduction of the R_2S moiety into arenes with formation of sulfonium salts such as *(40)*[69,81].



(39)

(40)

Electrophilic sulfurization has recently been carried out by utilizing the imidazolide procedure[82].



A mixture of $Pb(SCN)_2$ and $SbCl_5$ in CCl_4 permits introduction of the thiocyanato function into alkyl- and halobenzenes, probably *via* ($SCN^{\oplus}SbCl_6^{\ominus}$) as reactive species[83].

6. Nitrogen Electrophiles

Organic derivatives are known of practically all oxidation states of the N atom. Among the reactions with nitrogen electrophiles, though, only nitration, amination, nitrosation, and diazonium coupling reactions are of practical significance. Our discussion will be focused primarily on nitration and amination since, as far as diazonium salts as electrophiles are concerned, no fundamentally new aspects have appeared in recent years, and since, on the other hand, conditions for nitrosation are fairly similar to those for nitration.

6.1. Nitration and Nitrosation

Aromatic nitration is of great technical and scientific consequence and has therefore been investigated very thoroughly; the relevant earlier literature is adequately covered in some recent summaries[84–87].

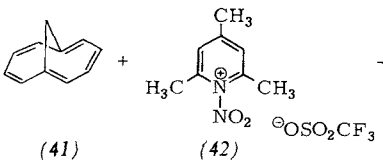
Replacement of the sulfuric acid in the usual nitration mixtures, made up of nitric acid and sulfuric acid of varying concentration, has a marked effect on the product spectrum in aromatic nitration. Thus trifluoromethanesulfonic acid[88a] and HF[88b] have both proven most advantageous for directing anthraquinone nitration into the 1-position. With combinations of nitric acid and either an arylsulfonic or phosphoric acid[89], a significantly higher *o/p*-ratio results on toluene nitration.

Since the use of HNO_3/H_2SO_4 mixtures is ecologically rather problematical, considerable efforts are being made to either curtail their use or, better, to completely replace them by other nitrating agents. Use of dichloromethane as solvent for nitrations with HNO_3/H_2SO_4 mixtures not only gives higher yields, *e.g.* in the reaction with equimolar amounts of nitric acid, since much less oxidation and sulfonation products are formed, but also permits recovery of sulfuric acid from the reaction mixture[90].

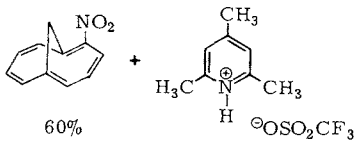
Nitryl salts were introduced by *Olah* and *Kuhn*[87,91] into preparative organic chemistry as effective nitrating reagents; they also allow nitration under non-aqueous conditions which is especially advantageous in the case of solvolysis- or oxidation-prone substrates.

Salts of the nitryl ion $NO_2^{\oplus}$ with complex perfluoro anions (*e.g.* $BF_4^{\ominus}$, $PF_6^{\ominus}$, $SbF_6^{\ominus}$, $SeF_5^{\ominus}$, $IF_6^{\ominus}$) have been known for some time; their spectral properties have recently been critically evaluated[92]. In addition, nitryl triflate[17,93] as well as the respective hydrate[94] and also nitryl hydrogen sulfate[90] have been synthesized in recent years. The reactivity of these various nitryl salts in organic solvents critically depends on both solubility and the extent of ion/solvent interaction[17].

Just as in the case of the well-known reactions with *N*-nitropyridinium salts[95,96], highly interesting results may still be expected[87] from the adducts of nitryl salts with donor molecules (alcohols, ethers, sulfides), namely with respect to special selectivity in nitration. With the 1:1-addition compound *(42)* of nitryl triflate and collidine[97], which is readily soluble in dichloromethane, acid-labile substrates such as 1,6-methano[10]annulene *(41)* can be selectively nitrated in good yield[98].

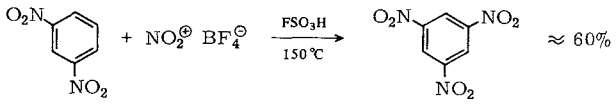


(41) *(42)*



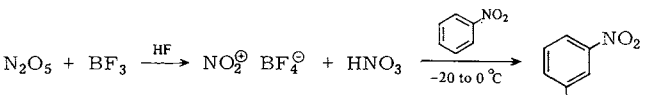
60%

Nitryl tetrafluoroborate in fluorosulfuric acid represents an exceptionally reactive nitrating species which converts *m*-dinitrobenzene into trinitrobenzene in relatively high yield[99].



Nitration with nitryl halides in the presence of Friedel-Crafts catalysts[87], though possible in principle, so far has gained no practical significance. On the one hand, the nitrogen-halogen bond is not polarized unequivocally because of the comparable electronegativities of N and the halogens, and on the other, attack of the catalyst at an oxygen atom of the nitro group can render the nitryl halide a potential halogenating species.

Among the oxides of nitrogen, both dinitrogen tetroxide and dinitrogen pentoxide can be employed for nitration reactions; nitrations with N_2O_5 are well known and have been investigated extensively[87]. Nitryl salts are generated from N_2O_5 by the action of protic or Lewis acids, which then react as described above; if HF is used as solvent, or the pyridinium/polyhydrogen fluoride mixture[4] which is experimentally easier to handle, an effective electrophile of especially high nitrating potential is obtained.



> 90%

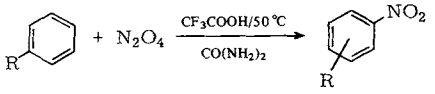
Sensitive substrates are nitrated preferentially in organic solvents[100], *e.g.* CCl_4, where N_2O_5 apparently reacts in the undissociated form.

Dinitrogen tetroxide, which as a rule dissociates into two NO_2 radicals, can also be cleaved heterolytically under the influence of Lewis acids. Since a potential nitrating and nitrosating agent are generated simultaneously, this has no great practical importance[87,101].

$$N_2O_4 + 3\,H_2SO_4 \rightleftharpoons NO_2^{\oplus} + NO^{\oplus} + H_3O^{\oplus} + 3\,HSO_4^{\ominus}$$
$$3\,N_2O_4 + 8\,BF_3 \rightarrow 3\,NO_2^{\oplus}BF_4^{\ominus} + 3\,NO^{\oplus}BF_4^{\ominus} + B_2O_3$$

Use of N_2O_4 as nitrating species is limited to some special cases, for instance the nitration of arylthallium compounds; toluene thus can be nitrated prevalently in *para*-position in

an overall yield of 98% (*o/m/p*-ratio 11:2:87)[102]. High yields are likewise achieved for N_2O_4 nitration in the presence of palladium salt catalysts[103], in trifluoroacetic acid with addition of at least a molar amount of urea—in this case without any Pd salts—[103], and in the case of reactive arenes even without added urea[104]. In all these N_2O_4 reactions, effective trapping of the nitrous acid seems to be the decisive factor.



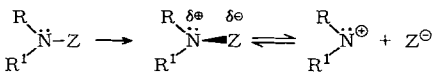
R	Yield [%]	Ratio of isomers *o* : *m* : *p*
H	99	
CH_3	76	55 : 2 : 43
Cl	100	36 : — : 64

In the presence of Lewis acids, *e.g.* Nafion-H (a perfluorosulfonic resin) or BF_3, alkyl nitrates and 1-cyano-1-methylethyl nitrate ("acetone cyanohydrin nitrate") are mild, non-oxidating nitrating reagents[105]. Titanium(IV) nitrate, employed for arene nitration in CCl_4, might, because of its low substrate selectivity, gain some preparative interest for the nitration of deactivated arenes and hetarenes[106].

The practical importance of nitrosation is much less than that of nitration. Since the weak electrophilicity of the nitrosating reagents is coupled with a relatively high oxidation potential, only strongly activated arenes such as phenols or aminobenzenes can be nitrosated successfully. The preparative aspects of nitrosation with the more common reagents have been summarized recently[84]. Nitrosyl salts[91b]—readily prepared and easy to handle—likewise are only weakly electrophilic, yet strongly oxidizing[107]; they are widely employed for the nitrosation of amines, alcohols, and anionic species[91b, 107]. However, their electrophilic potential is not sufficient for rection with scarcely activated aromatic substrates.

6.2. Amination[108]

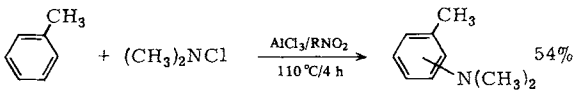
By introducing a good leaving group Z, ammonia and amines can be converted into electrophilic aminating agents. For all H_2N–Z derivatives reported so far, only N–Z bond polarization may be assumed; there are no indications for the existence of free $NH_2^{\oplus}$[109]. Investigations by *Gassman et al.* on the occurrence and chemical behavior of nitrenium ions $RR^1N^{\oplus}$ (R, R^1 = alkyl, aryl) have shown that these ions are much less stable than the structurally analogous carbenium ions[109]. The effect of the leaving group on heterolysis of the N–Z bond displays the same graduation as in carbenium ion formation[110]. Because of their high electronegativity, halogen and oxygen functions are mainly incorporated as leaving groups Z.



R, R^1 = H, Alkyl, Aryl

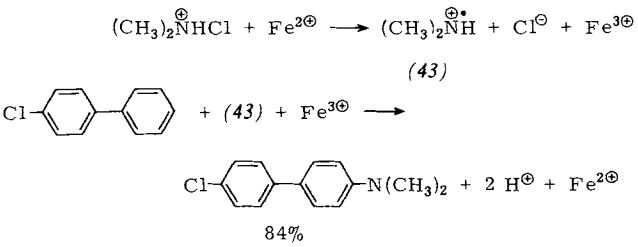
The long-known electrophilic introduction of amino groups with haloamines has been reviewed in considerable detail[108, 111]. Satisfactory yields of amination products are generally obtained only with relatively strong nucleophiles (*e.g.* amines, alcohols), indicating a S_N2 character of these reactions[112]. With weakly nucleophilic substrates such as arenes, one observes competing electrophilic amination, amination *via* radical intermediates, and halogenation[111]. The isomer distribution for the amination of toluene with chlorodimethylamine, under the conditions given in the scheme below, points towards an electrophilic mechanism (R = CH_3, *n*-C_3H_7, $C(CH_3)_3$, C_6H_5).

Reaction of anisole with chlorodimethylamine under comparable conditions, on the other hand, exclusively affords chlorinated products (67% yield)[113].

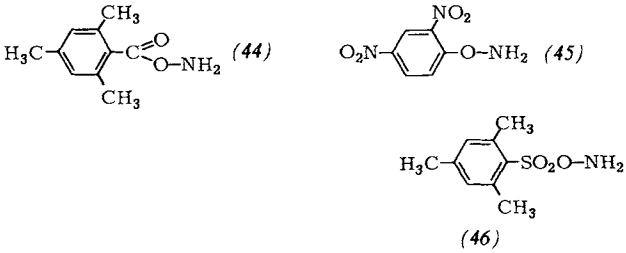


o:*m*:*p* = 7:15:32

The amination of arenes with chloroamines in highly acidic medium and in the presence of redox catalysts ($Fe^{2\oplus}$, $Ti^{3\oplus}$) is of great preparative value because of the good yields and high selectivities obtained[114]. Amino radical cations *(43)*, which have some electrophilic character, are the reactive species in this case[114]; the only isomers formed are the 4,4′-disubstituted biphenyls.



Far more important for electrophilic aminations than the haloamines are hydroxylamine derivatives. For this, however, the hydroxylamine OH function must first be converted into a good leaving group (as in the case of the alcohols in the carbon compound domain). Hydroxylamine-*O*-sulfonic acid[115] was the first and, for quite some time, the only such derivative whose manifold reactions with nucleophiles were investigated extensively[108]. Because of their higher reactivity, due to the presence of a better leaving group, the reagents *(44)*, *(45)*, and *(46)*[116, 117] are now mainly used in practice.



The instability of some of these aminating agents is a great drawback. For instance, *(46)* is highly explosive[118]; all attempts to prepare the triflate derivative *(47) via* the hydroxyl-

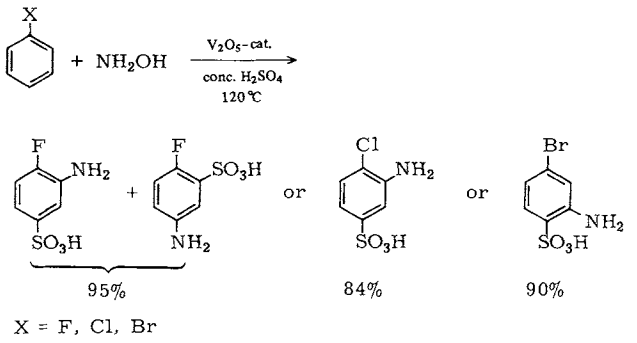
amine thallium salt have likewise failed[119]. This instability of the hydroxylamine derivatives could be due to an α-elimination to give nitrene and follow-up reactions.

$$H_2N{-}O{-}Tl + Cl{-}SO_2CF_3 \xrightarrow[-TlCl]{-40\,^\circ C} [H_2N{-}OSO_2CF_3] \xrightarrow{?} [\ddot{N}H] \rightarrow \cdots$$

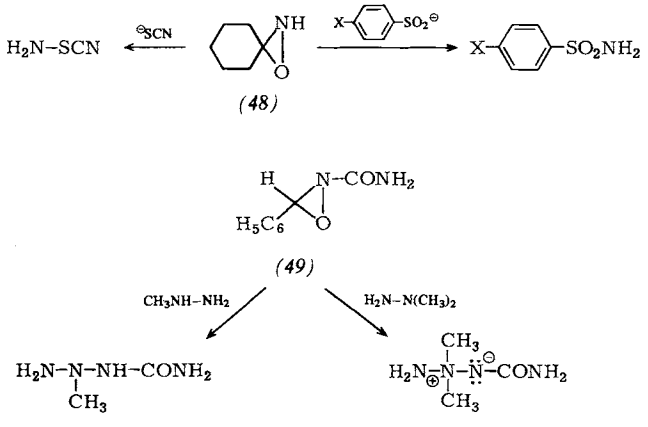
(47)

If α-elimination is prevented by suitable *N*-substituents, stable compounds result, *e.g.* the bis(trimethylsilyl) derivatives[120] of *(44)* and *(46)* and a *N,N*-diacyl derivative of *(47)*[121]. Nothing is known, though, about the usefulness of these compounds as aminating agents[121]. Besides nitrogen- and sulfur-containing substrates, carbanions have also been aminated with *N,N*-dialkyl derivatives of *(46)*[117].

Amination of haloarenes with acidic solutions of hydroxylamine according to the Turski method gives good yields[123]; however, the product distribution is strongly dependent on the halogen substituent. No radical intermediates could be detected in this process[122].



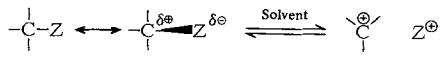
The oxaziridines *(48)* and *N*-carbamoyloxaziridines *(49)*, prepared *via* electrophilic amination processes, are themselves aminating agents which can be used for transferring amino or ureido functions respectively[108].



7. Alkylating Agents[6b, 124]

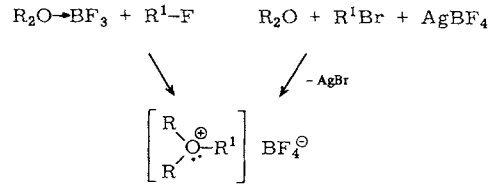
The electrophilic introduction of alkyl groups into organic compounds, under formation of a new C–C, C–O, C–N, or C–S bond, is preparatively of the utmost importance, but has also played a decisive role in the development of mechanistic concepts: carbocations were first postulated as intermediates in organic reactions for this type of reactions—with all the ensuing consequences.

The various alkylating reagents differ primarily in the degree of positivation of the reactive carbon center. In principle, this covers the whole range from mere bond polarization to the formation of free carbenium ions, influenced, as many investigations have shown, by the stability of the cation formed, by the leaving tendency of Z, and by the solvent medium[125].

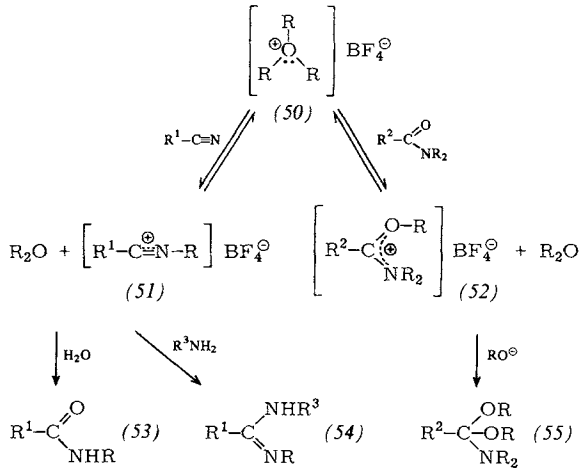


The electrophilicity of a given alkylating agent goes up, of course, with increasing positivation of the carbon center. Thus, alkyl halides react with strong nucleophiles—such as anions, amines, and alcohols—even in non-dissociated form; the reaction with weakly nucleophilic substrates (arenes, olefins, σ-bonds), on the other hand, requires the addition of Friedel-Crafts catalysts. In the following, our attention will be directed primarily to those alkylating reagents with good leaving groups which were developed within the last few years in the course of the investigation of onium structures[91b] and have found a broad preparative application.

Among the onium compounds, the trialkyloxonium salts discovered by *Meerwein et al.*[126] have long been known as excellent alkylating agents. They are prepared from alkyl halides with BF_3, SbF_5, or $SbCl_5$ in ethereal solution[127].

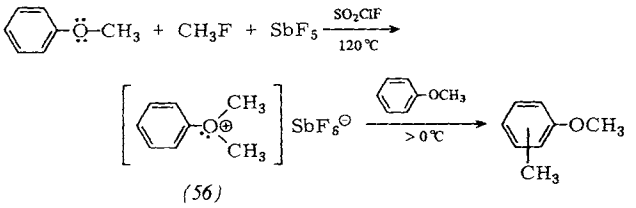


Although their electrophilic potential is not sufficient for alkylation of normal arenes, reactions are possible already with substrates which have such slight nucleophilic character as azulenes, nitriles, and carboxamides[126a].



The salts *(51)* and *(52)*, formed from nitriles and amides, respectively, and in equilibrium with the oxonium precursors *(50)*, are themselves alkylating agents. However, their addition to nucleophiles (water, amines, alcohols) affords *N*-alkyl amides *(53)*, amidines *(54)* and amide acetals *(55)*.

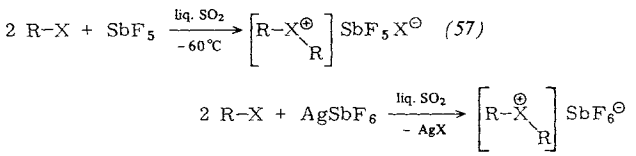
Dialkylaryloxonium salts *(56)*, accessible by alkylation of aryl alkyl ethers, have a higher alkylating potential than the trialkyl analogues and can be employed for arene alkylation[128].



(56)

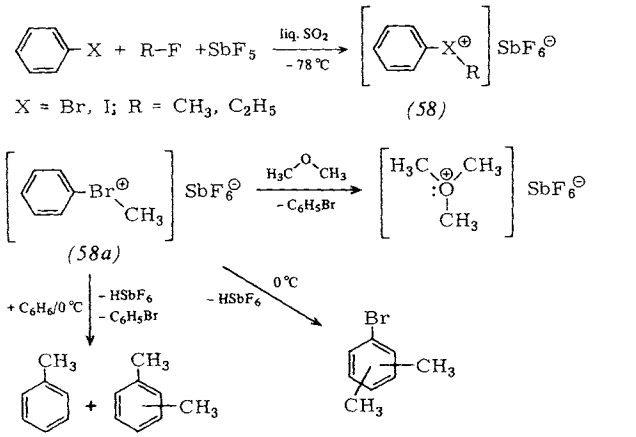
Triaryloxonium salts may be obtained in <2% yield from diaryl ethers and benzenediazonium salts; since they are practically inert towards nucleophiles, they are of no consequence as arylating agents[129].

The alkylhalonium compounds *(57)*, recently prepared by *Olah* and *DeMember*, can be used as highly reactive alkylating agents in the same manner as the oxonium salts[130, 131].



X = Cl, Br, I; R = CH_3, C_2H_5, $(CH_3)_2CH$

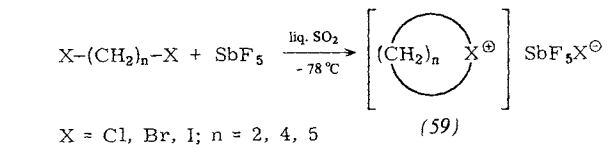
Alkylarylhalonium salts *(58)* are accessible analogously from halobenzenes[132] and are likewise used as powerful alkylating agents[130, 132].



X = Br, I; R = CH_3, C_2H_5 *(58)*

(58a)

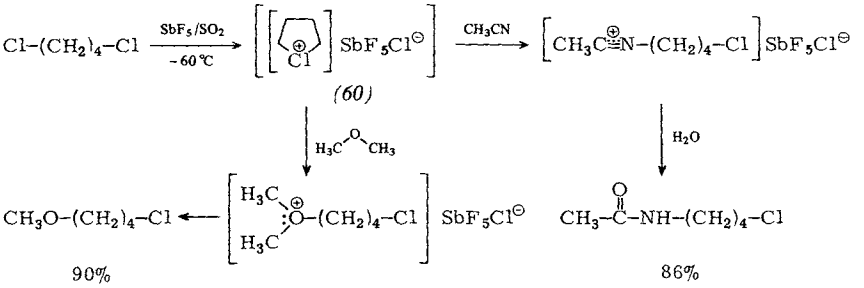
The cyclic halonium ions *(59)*, postulated as intermediates in the electrophilic addition of halogens to olefins for a long time, could now be isolated under like conditions as the open-chain analogues as well as directly from the halogenation of olefins[130, 133].



X = Cl, Br, I; n = 2, 4, 5 *(59)*

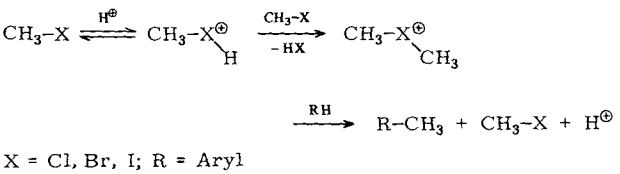
These cyclic halonium derivatives, *e.g. (60)*, have also proven to be effective alkylating agents[133].

From our present knowledge about halonium salts, many Friedel-Crafts alkylations with primary and partly also with secondary alkyl halides now are assumed to proceed *via* dialkylhalonium ions; they have definitely been established as intermediates in proton-catalyzed alkylations[134].



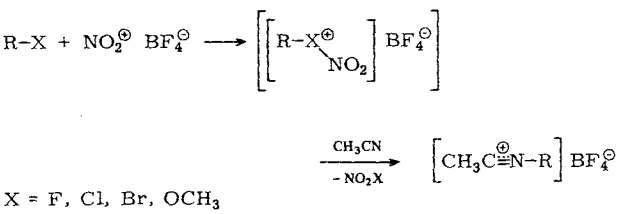
(60)

90% 86%



X = Cl, Br, I; R = Aryl

Onium complexes are formed from alkyl halides and ethers also with other strong electrophiles, such as nitryl[135a] or nitrosyl[135b] salts; they react as powerful alkylating agents.



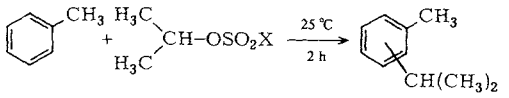
X = F, Cl, Br, OCH_3

Apart from these efforts to improve the reactivity, chemists have also endeavored to suppress secondary alkylation and isomerization in the Friedel-Crafts alkylation of arenes as far as possible; attempts with heterogeneous catalysts ($AlCl_3$ on graphite[136] or Nafion-H[137]) have met with at least partial success. Solvents such as nitroalkanes where the effectiveness of the catalyst is attenuated by complexation likewise improve the selectivity and curb isomerization[138].

Arene alkylation with secondary or tertiary carbenium ions in the gas phase gives a product spectrum comparable with that obtained for reactions of strong alkylating agents in a weakly solvating medium[139].

Among the new alkylating reagents, alkyl triflates[12] command special interest, due not only to the good leaving properties of the triflate ion but, as outlined above, also because of the high stability of both the trifluoromethanesulfonic acid and its alkyl esters. The instability of alkyl perchlorates[141], in contrast, renders them unsuitable as practical alkylating agents even though most can be prepared in high yield[140], and in spite of the good leaving group $ClO_4^{\ominus}$.

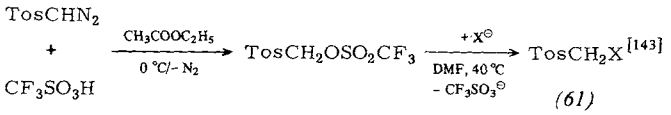
Isopropyl triflates and fluorosulfates allow the non-catalyzed alkylation of arenes such as benzene and toluene in good yield; the esters of primary alcohols, on the other hand, still require Friedel-Crafts catalysts[142].



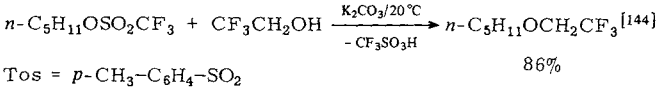
≈ 50%

X	*o*	: *m*	: *p*
F	44.3	17.7	38.0
CF_3	46.5	19.1	34.4

In the alkylation of anions[143] and of highly acidic alcohols[144], good yields could likewise be obtained only with alkyl triflates; for example, 96, 82, 79, and 76% of *(61)* were obtained with X = Cl, I, N_3, and SCN, respectively. In contrast, elimination and rearrangements are observed to a large extent under the rather more severe reaction conditions required for the usual alkylating agents such as tosylates.



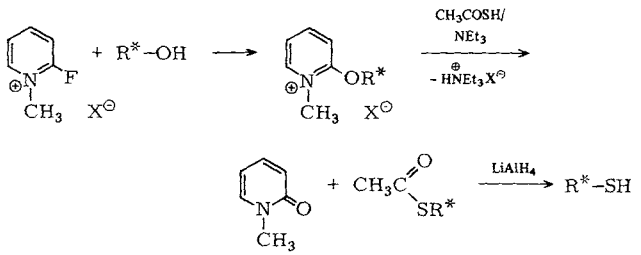
(61)



Tos = *p*-CH_3–C_6H_4–SO_2

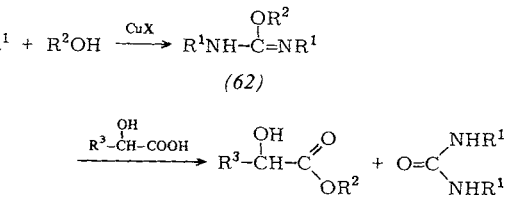
Generation and unequivocal proof of the existence of the extremely unstable vinyl cations was also achieved only by solvolysis of the respective triflates[145]. Deactivated arenes (*e.g.* halobenzenes) have already been alkenylated with vinyl cations without added Friedel-Crafts catalyst although their preparative application is still in its preliminary stages[146].

Heterocyclic moieties sometimes have proven to be advantageous leaving groups in alkylation processes. Thiols, for instance, can be prepared smoothly by reaction of thiolacetic acid with 2-alkoxy-*N*-methylpyridinium salts *(61)* and subsequent hydrogenolysis; optically active alcohols show Walden inversion in this reaction[147].



Pyridine itself has also been employed as leaving group in alkylation reactions[148], as have ureas. With *O*-alkylisoureas *(62)*, for instance, obtained by addition of alcohols R^2OH to carbodiimides, the alkylation of carboxylic and phosphoric acids, of thiols, amines and alcohols can be carried out under very mild conditions[149]. These reactions proceed with good yields and high selectivity, and thence are especially applicable in natural product synthesis.

The term hydroxyalkylation denotes reactions of aldehydes and ketones with nucleophilic arenes[124]. These reactions frequently are complicated by secondary processes since, under the conditions employed, the hydroxyalkyl products *(63)* are readily converted into the carbocations *(64)*; once formed, these immediately react either with the nucleophilic substrate still present to give *(65)*, or with the primary products *(63)* to give *(66)*. Both of these secondary products for their part can again be alkylated by unreacted carbonyl compound.



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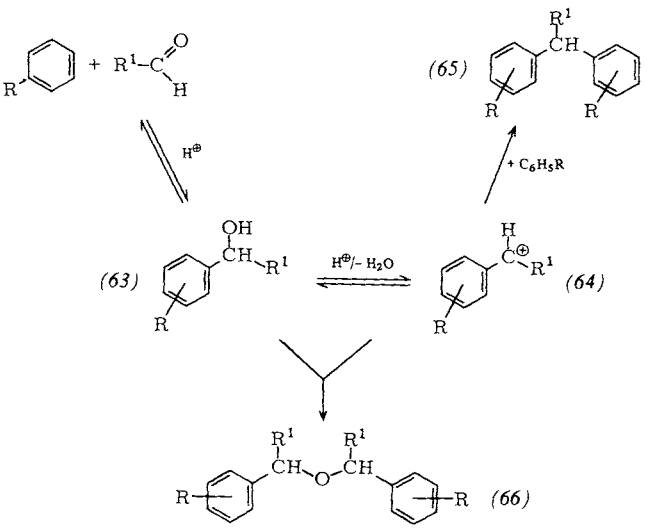
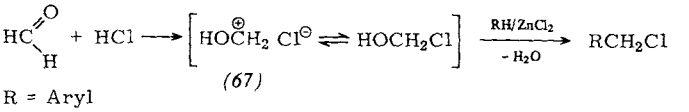
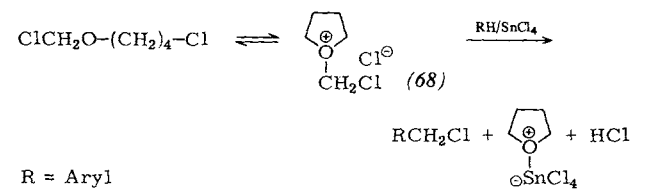


These reactions are of great technical significance in the synthesis of resins (*e.g.* phenol/formaldehyde, urea/formaldehyde). Undesirable secondary reactions can be circumvented by the use of hydrohalic acids which trap the carbenium ions, as soon as they are set free, in the form of haloalkyl derivatives (haloalkylation)[24]. Direct chloromethylation with formaldehyde/HCl[150], in which the carcinogenic hydroxymethyl cation *(67)* is considered as the attacking species, is preparatively very important.



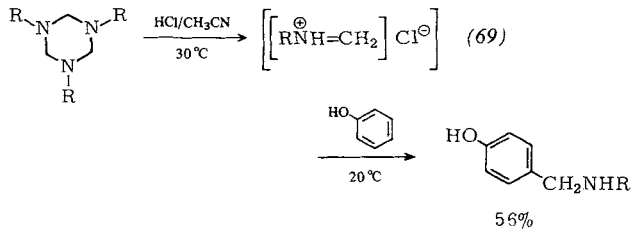
R = Aryl

Instead of formaldehyde/HCl, α-halo ethers may be applied; they likewise have been shown to be carcinogenic. Efforts to replace chloromethylation, especially in technical processes, by less precarious procedures so far have met only with limited success. In one variant, less volatile reagents such as *(68)* are employed[151]; in another, the iminium deri-



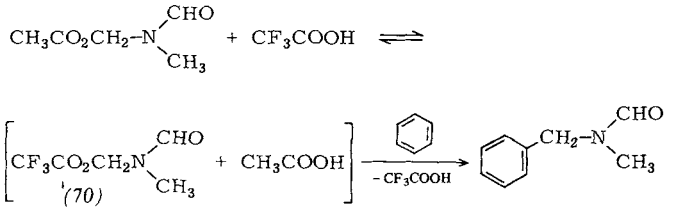
R = Aryl

vatives *(69)* of the parent carbonyl compounds are utilized as electrophiles[152]. This reaction results in aminoalkylation, and has successfully been applied to carbanions (Mannich reaction), heteroatom-H bonds, electron-rich π-systems (enol ethers, enamines, ynamines), and reactive arenes and hetarenes (*e. g.* phenols or furans[153]).



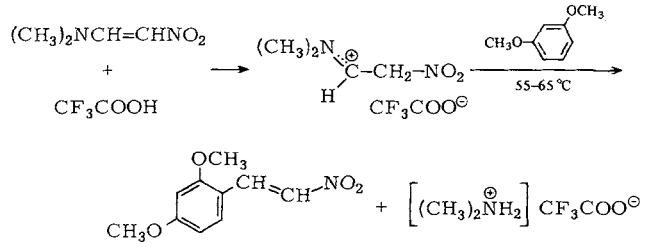
(69)

Aminoalkylation of less reactive arenes requires amino reagents such as *(70)* where the electrophilic potential is enhanced by both electron-withdrawing N-substituents and by a good leaving group as gegenion ($ClO_4^\ominus$, $BF_4^\ominus$, $CF_3COO^\ominus$)[154,155].

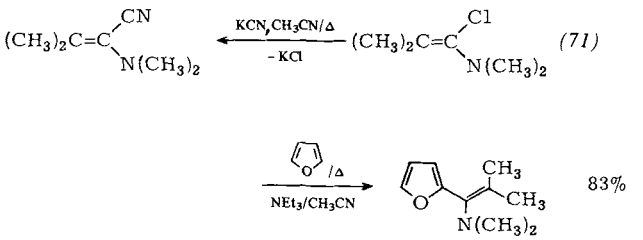


(70)

The nitro-olefination of indenes and electron-rich arenes such as resorcinol dimethyl ether actually is an aminoalkylation too; dimethylamine is immediately eliminated in the process, though, and the more favorable conjugated system developed[156].

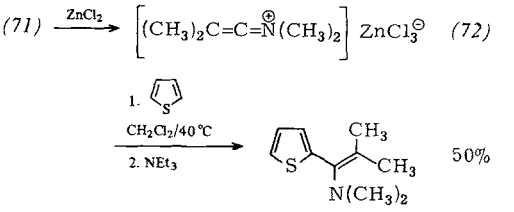


Reaction of nucleophiles with α-halo enamines *(71)* likewise represents a variant of aminoalkylation[157].



(71)

With less nucleophilic aromatic substrates, ketene-iminium chlorides, formed in a predissociation step, are assumed as reactive species. The primary formation of such a salt *(72)* has been established for the reactions with thiophene and anisole whose lower reactivity requires addition of a Lewis acid[157].



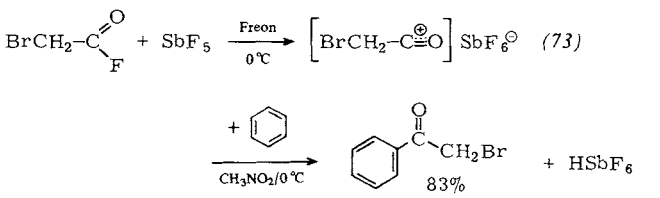
(72)

8. Acylating Agents

In electrophilic acylation, carboxylic acid derivatives are made to react with hetero- or carbon-nucleophiles, usually with substitution of a hydrogen atom[158]; in this review, the accent is placed on new, highly reactive acylating reagents for aromatic substrates.

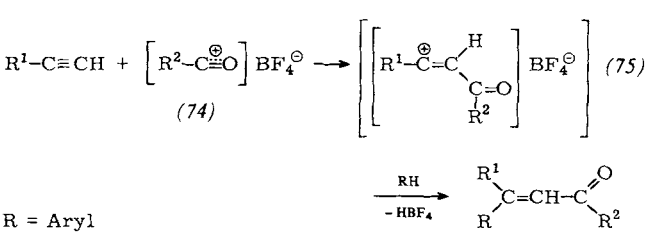
For arene acylation, the electrophilicity of regular acyl derivatives—esters, halides, anhydrides—has to be enhanced, as a rule by addition of a Friedel-Crafts catalyst (proton or Lewis acid)[6a,159]. The actual attacking electrophile in these catalyzed processes is not known with certainty; as outlined in the introduction, equilibria have been established for these systems in which both oxonium species *(1)* and acylium ions *(3)* are present[4b,160].

Since Friedel-Crafts acylation normally requires at least equimolar amounts of Lewis acid for acceptable yields, interest has recently been concentrated on truly catalytic processes. Thus, several groups almost simultaneously reported the catalytic effectiveness of traces of Fe salts (≤1 mol-%)[161]. On the basis of our present knowledge of the structure of acylating reagents, it was an obvious step to also try isolated salts of acylium ions *(3)*. An acylium salt was characterized for the first time by *Seel*[162]; the general modes of preparation and especially the preparative applicability of acylium salts have been investigated extensively by *Olah et al.*[159,160,163]. As a rule, these hygroscopic salts, *e.g. (73)*, are treated with a large excess of aromatic substrate in nitromethane solution.



(73)

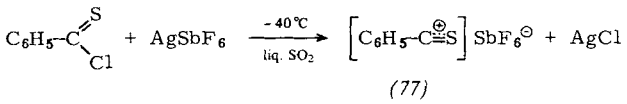
So far, this method of arene acylation has been utilized only sparingly—despite the very good yields of phenone products obtained in most cases. With olefinic[164] and acetylenic substrates[165], however, acylium salts undoubtedly have their advantages compared with the usual acylation reagents. Acylation at low temperature of alkynes with acylium tetrafluoroborates *(74)*, for instance, in the presence of arenes yields the α,β-unsaturated ketones *(76)*[165], *via* reaction of



(74) *(75)* *(76)*

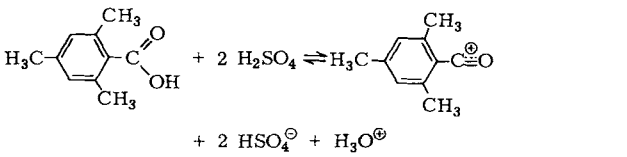
the primarily formed vinyl cations *(75)* with the aromatic substrate.

Thioacylium salts *(77)* are easily prepared[166a]; apparently, they are more stable than the O-analogues[166b].

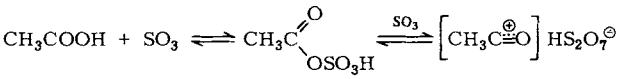


(77)

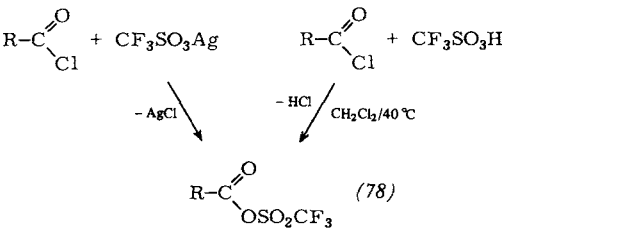
From the observed freezing point depression, it was deduced fairly early that acylium ions are generated by the action of strong mineral acids on carboxylic acids, esters, or anhydrides[167]. This acylium ion formation is particularly pronounced with 2,6-disubstituted benzoic acids.



If carboxylic anhydrides or SO_3-containing sulfuric acid are employed, primary formation of mixed anhydrides is assumed which then dissociate into acylium ions under the influence of a second molecule of SO_3[160,168].

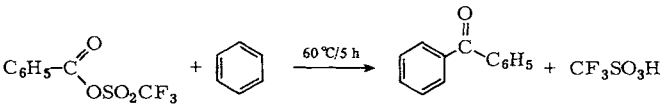


Even diacylium salts of substituted terephthalic acids could thus be obtained and made to react with several nucleophiles[169]. Spectroscopic investigations have shown the presence of mixed anhydrides between carboxylic and very strong inorganic acids in equilibrium with acylium ions and protonated species[160,170]. The reaction of acyl chlorides with silver triflate, and also that of acyl chlorides with trifluoromethanesulfonic acid in inert solvents, gives good yields of carboxylic trifluoromethanesulfonic anhydrides *(78)* in pure form[171].



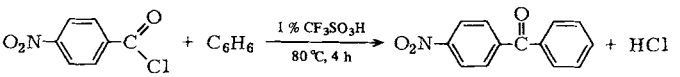
The anhydrides *(78)* can likewise be prepared by reaction of *S*-methyl thiolcarboxylic esters with methyl triflate (with dimethyl sulfide elimination)[172a] or by dehydration of a 1:1-mixture of trifluoroacetic and trifluoromethanesulfonic acid with P_2O_5[172b].

From the high leaving tendency of the triflate ion, the anhydrides *(78)* could be expected to be good acylating agents. This was fully confirmed: their acylation potential is greater than that of all known reagents. With other carboxylic sulfonic anhydrides, for instance, xylenes show no reaction after 24 h at 100 °C[173]; in contrast, the even less reactive benzene is smoothly acylated upon warming with *(78a)* without addition of any Friedel-Crafts catalyst[171]. The trifluoromethanesulfonic acid liberated in the course of the reaction can be recovered quantitatively as barium salt.



(78a) 90%

Since the anhydrides *(78)*, on the other hand, are accessible also directly from the acyl chlorides and trifluoromethanesulfonic acid, a way was open for the development of a catalytic arene acylation. The general procedure, worked out along these lines, is specially suited for substrates that otherwise give undesirable side-reactions with the usual Friedel-Crafts catalysts (*e.g.* nitro compounds)[174].

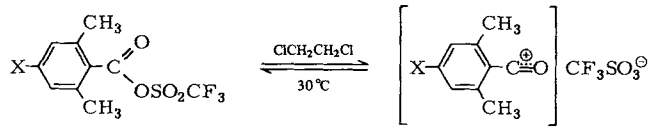


82%

The exceptional position of trifluoromethanesulfonic acid in this respect is exemplified strikingly if one compares the yields for the acylation of *p*-xylene with benzoyl chloride under addition of one 1% each of various strong acids[174]. Heterogeneous acid catalysis for Friedel-Crafts acylation with Nafion-H has recently also been reported[175].

Acid:	CF_3SO_3H	FSO_3H	*p*-H_3C C_6H_4	SO_3H
Ketone yield [%]:	82	20	31	
Acid:	conc. H_2SO_4	$HClO_4$	CF_3COOH	$HPOF_2$
Ketone yield [%]:	28	14	21	4

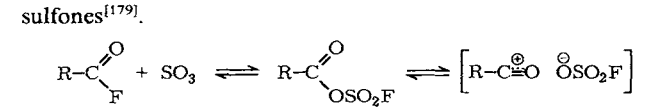
The extent to which the anhydrides *(78)* are dissociated in inert solvents, *e.g.* dichloroethane, depends in the expected manner on steric and electronic factors in the acyl moiety; the equilibrium concentration of the acylium ions *(79)* correlates fairly well with *Brown*'s σ^+-constants for the substituents X[176], and thus with former results on the relative stability of benzoyl cations[177].



(78) *(79)*

X	X= OCH_3	CH_3	H	Cl	NO_2
Eq. conc. of *(79)* [%]	= 87	66	45	33	10

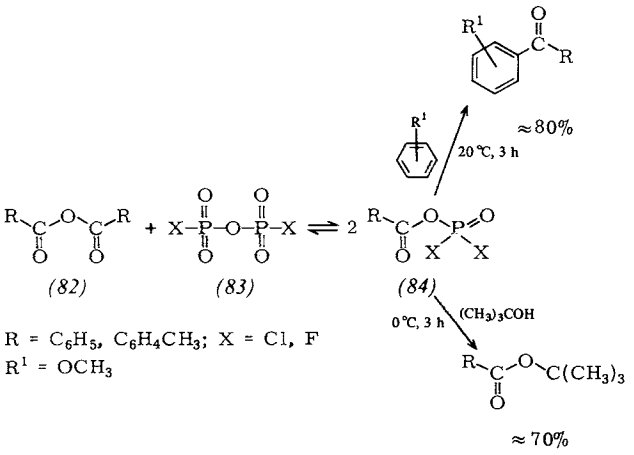
Mixed anhydrides could also be prepared from carboxylic acids and other strong inorganic acids; however, they exhibited no special potential for the acylation of arenes. The carboxylic fluorosulfuric anhydrides *(80)*, for instance, were synthesized by insertion of SO_3 into the C–F bond of acyl fluorides[178,179]. In solution, the anhydrides *(80)* are dissociated into acylium ions *(81)* and fluorosulfate anions[179]; upon reaction with arenes, though, only moderate yields of ketones are obtained, the main side-products being diaryl sulfones[179].



(80) *(81)*

R	= C_6H_5	*p*-CH_3 C_6H_4	*p*-Cl C_6H_4
Yield of *(80)* [%]	= 70	50	50

The anions of dihalophosphoric acids are likewise good leaving groups[180] but, with few exceptions[181], have not yet been applied in organic preparative practice. Recently, carboxylic dihalophosphoric anhydrides *(84)* were prepared in good yield from the anhydrides of the constituent acids, *(82)* and *(83)*. Upon investigation of their reaction behavior[182], they were found to display an exceptional acylation potential which, for example, allows arene acylation under mild conditions without addition of Friedel-Crafts catalysts, and also the esterification of tertiary alcohols in good yield.



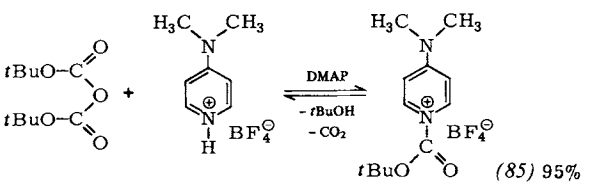
(82) *(83)* *(84)*

R = C_6H_5, $C_6H_4CH_3$; X = Cl, F
R^1 = OCH_3

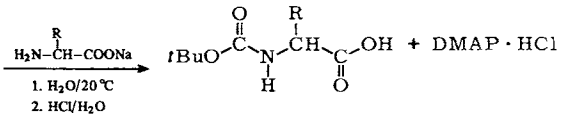
The anhydrides *(84a)*, X = Cl, are also formed as intermediates in the reaction of carboxylic acids with $POCl_3$[182], as already postulated by *Th. Wieland*[183]. Carboxylic perchloric anhydrides, which can be prepared in good yield from acyl chlorides and silver perchlorate, are explosive and therefore unsuitable as practical acylating reagents[184].

Acylium ions are certainly the reactive species in many normal Friedel-Crafts acylations and also frequently in reactions of the mixed anhydrides of carboxylic and strong inorganic acids described above; it has been doubted[160], though, whether they are sufficiently electrophilic to react with σ-bonds. Protonated acylium ions have therefore been postulated as the effective electrophile in superacid systems[160]; recent calculations have provided additional strong evidence for their existence[185].

The interest of preparative chemists is naturally focused on acylating agents which react both very selectively *and* under mild conditions. Out of the multitude of investigations on reagents for the acylation of OH, NH, and SH functions, we shall discuss primarily those in which heterocyclic moieties are employed as leaving groups. The acylazolides developed by *Staab*'s group[186] are among the most versatile reagents of this type.

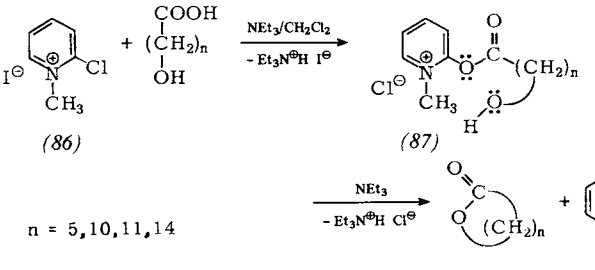


(85) 95%



In recent years, the importance also of pyridines and pyridones as leaving groups has grown steadily. Acylation with anhydrides or acyl chlorides in the presence of pyridine has been known for a long time; however, the acceleration of acylation on use of 4-dimethylaminopyridine (DMAP) instead of pyridine was not recognized until comparatively late[187]. The best yields in this procedure are obtained with carboxylic anhydrides and catalytic amounts of DMAP in aprotic and slightly polar solvents; thus, a 96% yield of *N-tert*-butoxycarbonyl amino acid is obtained in the reaction shown below. Pyridinium salts *(85)*, in equilibrium with the reactants, are considered as the reactive electrophiles. Sometimes it is better to employ isolated pyridinium salts, preferentially with anions of low nucleophilicity, in aqueous medium as acylating agents[188]. L-Proline, for instance, can thus be transformed into *N*-butoxycarbonyl L-proline in 96% yield.

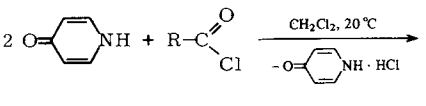
The reagents, prepared by *Mukaiyama et al.* from the *N*-alkyl-2-halopyridinium salts *(86)* and carboxylic acids, *e.g. (87)*, allow reaction under very mild conditions[189]; apart from acylated alcohols, thiols, and amines, difficultly accessible lactones could likewise be obtained in good yield by this method[189].



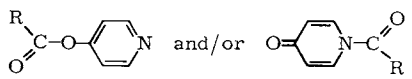
(86) *(87)*

n = 5,10,11,14

Upon acylation of 4-pyridones, acyloxypyridines *(88)* and/or *N*-acylpyridones *(89)* are formed in good yields, respectively, *via N*- or *O*-reaction[190].



R = Aryl, Alkyl



(88) *(89)*

Acylation with these nonionic acylpyridones, *(88)* and *(89)*[190], as well as with the 2-acyloxypyridines[191], can be carried out in inert solvents under neutral or weakly acidic conditions. In solution, *(88)* and *(89)* are in equilibrium at room temperature; its position strongly depends on the nature of the acyl moiety[190, 192], and in the case of the 2-pyridone is shifted more to the *O*-acyl side[191, 193].

Pentafluorophenyl acetate has recently been reported as a highly selective agent for the acetylation of amino alcohols[194].

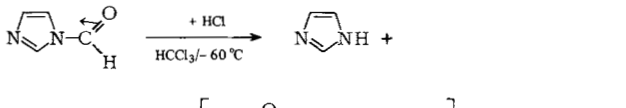
9. Formylating and Carboxylating Reagents

Formylation and carboxylation differ from the principally comparable acylation reactions mainly in generation, stability, and reactivity of the requisite electrophiles. For instance, the formyl derivatives required for a Friedel-Crafts formylation are unstable even at room temperature. Interaction be-

tween Friedel-Crafts catalysts and carbonic acid derivatives, the appropriate electrophiles for carboxylation, appears even more complex than for the carboxylic acid derivatives. Furthermore, the electrophilic potential of carboxylating agents is lowered substantially, relative to that of acylating reagents, by the mesomeric influence of yet another heteroatom (O, N).

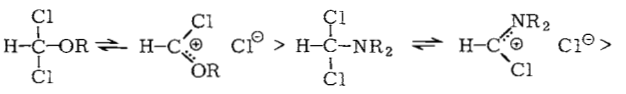
9.1. Formylation[195]

The facile decarbonylation of an intermediate formyl cation *(90)* makes formylations with formyl derivatives problematical; this decomposition reaction is probably also responsible for the instability of formyl chloride and formic anhydride[196].

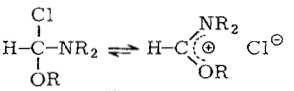


(90)

With formyl reagents where the oxygen atom is suitably substituted or replaced by a nitrogen function, CO elimination can be avoided[197,198]. *(91)*, *(92)*, and *(93)*, for instance, meet these requirements; their definite graduation of reactivity can be derived straightforwardly from the general substituent effects.

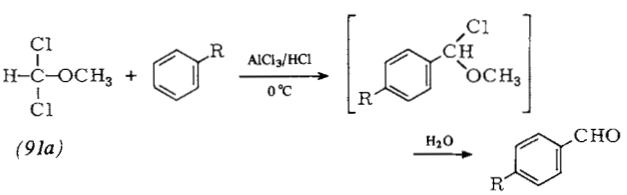


(91) *(92)*



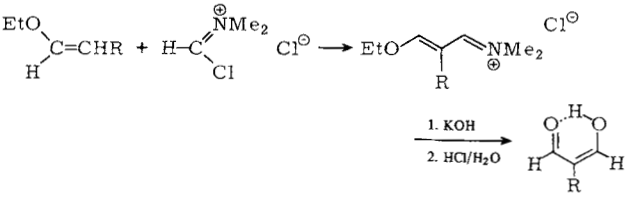
(93)

The stability of the cations generated upon dissociation increases markedly from *(91)* to *(93)*; of course their formylation potential declines concomitantly[197,199]. The non-dissociated α,α-dichlorodimethyl ether *(91a)*, for example, allows formylation even of non- or slightly-activated arenes in the presence of a Friedel-Crafts catalyst; thus, benzene is formylated in 37% yield, and toluene even in 80% yield[200].



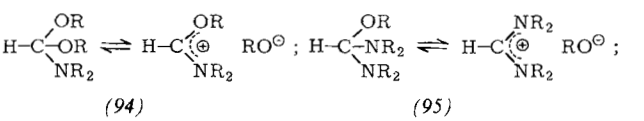
(91a)

The α,α-dichlorotrialkylamines *(92)* (chloromethyliminium chlorides), which are fully dissociated, can be used as formylating agents without Friedel-Crafts catalysis, though only for the more reactive arenes[195,201]. They are also employed in the Vilsmeyer-Haack-Arnold formylation of activated olefins (enol ethers and acetates, enamines); this reaction is of great consequence since it makes polycarboxy compounds accessible, *e.g.* malondialdehyde[202], which constitute important synthetic building blocks.

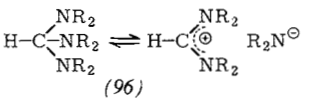


The graduated reactivity of the various formylating agents, accessible from dimethylformamide and, *inter alia,* phosgene, phosphorus oxide chloride, dimethyl sulfate, and mineral acids, has been the subject of a comprehensive investigation[203]. The (expected) reactivity difference between compounds of type *(92)* and *(93)* was shown to depend not only on the stability of the carbenium ion, but also on the nature of the anion[203]. In the formylation of *N,N*-dimethylaniline, the unequal reactivity of some carboxamide complexes of type *(92)* had already been recognized before[204].

Orthoformic acid derivatives have found general interest as formylating agents only since the monoamide diesters *(94)*, diamide esters *(95)*, and triamides *(96)* have become available[205]; their autodissociation (as indicated above) could be demonstrated by conductivity measurements[206].



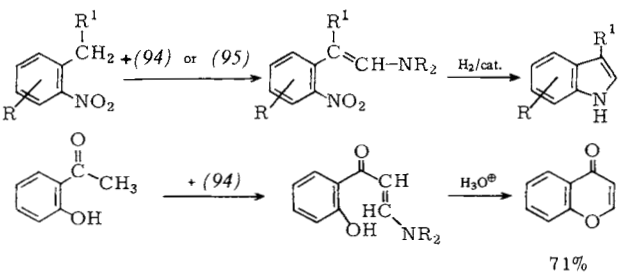
(94) *(95)*



(96)

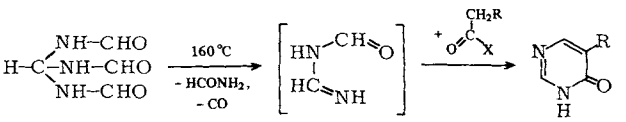
Reactivity decreases markedly in the order *(96)* > *(95)* > *(94)*. This can be rationalized (i) in terms of the degree of dissociation (which in turn is determined by the stability of the ions generated) and (ii) in terms of the different base strength of compounds *(94)*—*(96)*. Higher base strength of the orthoamide derivatives or of the anions $RO^{\ominus}$ and $R_2N^{\ominus}$, respectively, promotes the formation of anions from the CH-acidic substrate which is to be formylated, and hence favors electrophilic attack.

Owing to their low electrophilicity, the orthoamide derivatives listed above are generally unsuitable for the formylation of arenes; they are especially effective formylating agents, though, for CH-acidic substrates[205,207]. Of the respective manifold applications, only a general indene synthesis[208] and a simple preparation of chromone[209] need be mentioned specifically. Sensitive substrates may be formylated in a straightforward manner with *tert*-butoxy-bis(dimethylamino)methane [*"Bredereck's* reagent", see *(95)*][210].



71%

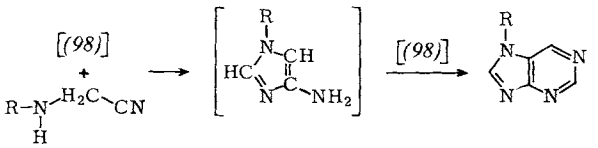
N,N',N''-Methylidinetriformamide *(97)*[211], *s*-triazine, and formamidine acetals [see *(95)*] all represent important formylating agents in the field of heterocyclic synthesis since they at the same time incorporate the amidine component for a subsequent ring closure. For instance, *N*-formyl formamidine *(98)*[212] which is liberated from *(97)* upon heating reacts with carbonyl substrates[213a] or nitriles[213b] smoothly and in good yields to give 5-substituted pyrimidines *(99)*.



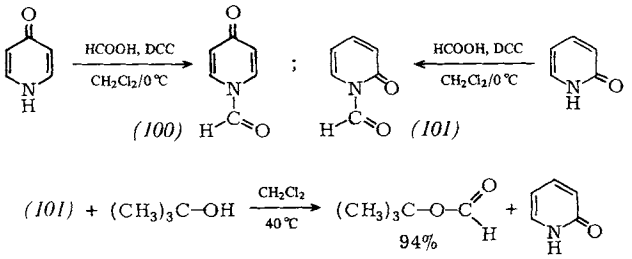
(97) *(98)* *(99)*

R = $COOR^1$, CN, $CONH_2$; X = OR^1, NH_2

This synthetic principle permits facile and efficient purine syntheses[214a], starting from aminoacetonitrile and proceeding *via* a 4-aminoimidazole with subsequent annelation of the pyrimidine ring[214b] (R = CH_3, C_2H_5, C_6H_5; yield 43, 46, 70%, respectively).



The *N*-formyl pyridones *(100)* and *(101)*, easily accessible from formic acid and dicyclohexylcarbodiimide (DCC), are excellent formylating agents for amines, alcohols, and thiols[215].

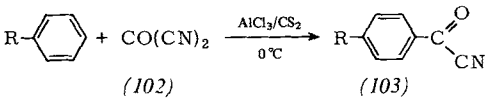


(100) *(101)*

(101) also allows a highly selective formylation of a mixture of primary, secondary, and tertiary alcohols, the tertiary substrates reacting least well, the primary ones best[215]. Even tertiary alcohols which are sterically severely hindered, such as 17α-hydroxyprogesterone, can be transformed into formates with *(101)* in dichloromethane at 40 °C[215]. Above 40 °C, *(101)* also shows a considerable extent of decarbonylation.

9.2. Carboxylation[6b, 159]

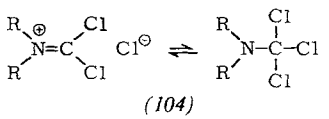
The general aspects of Friedel-Crafts acylation of course apply also to carboxylation; as in the case of the formylation reaction, though, there are no carbonic acid derivatives which might be used as generally applicable reagents[216]. For acylations, halides are nearly always employed in practice; the corresponding haloformates, however, decarboxylate under the action of Friedel-Crafts catalysts[217], and then act as alkylating agents. With the dihalide phosgene, aroyl chlorides are formed from arenes in the presence of Friedel-Crafts catalysts; as a rule, though, these are further converted into aromatic ketones under the reaction conditions. With carbonyl dicyanide *(102)* in place of phosgene, this secondary reaction is avoided[218], and aroyl cyanides *(103)* are obtained in good yield; the drawback of the procedure is that *(102)* is not as easily accessible as $COCl_2$[218].



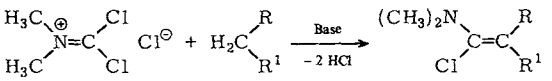
(102) *(103)*

R	= H	CH_3	Cl
Yield [%]	= 71	79	16

The more reactive dichloromethyleneiminium chlorides *(104)* (phosgeneiminium salts) constitute far better carboxylating agents[219]; they are specially suited for the carboxylation of CH-acidic substrates which are thus converted into α-chloroenamines *(105)*[219, 220].



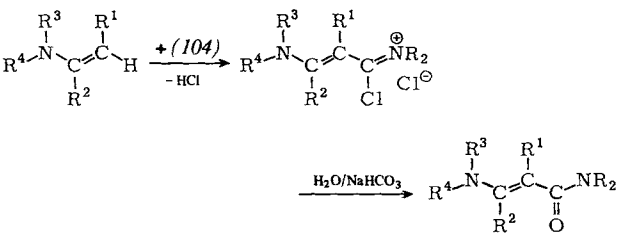
(104)



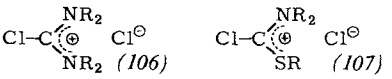
(104a) *(105)*

R	= CN	CN	COOEt
R^1	= CN	COOEt	$Ph_3P^{\oplus}$
Yield [%]	= 77	85	62

Enamines[221] and enol ethers[219] can likewise be carboxylated in good yield with these phosgeneiminium salts. However, their electrophilic potential in general is not sufficient for carboxamidation of arenes, except in the case of highly activated substrates such as *N,N*-dimethylaniline or resorcinol dimethyl ether[219].

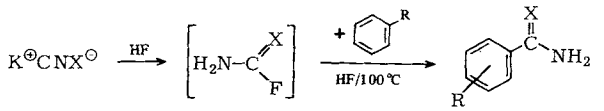


On replacement of one Cl atom in the phosgeneiminium salts *(104)* by another hetero substituent, they still remain potential carboxylating agents; since the higher +*M* effect of these substituents diminishes their reactivity, however, chloro formamidinium salts *(106)*[222a] and also the sulfur compounds *(107)*[222b] are of little significance as carboxylating agents.



(106) *(107)*

The carboxamidation of arenes (Gattermann amide synthesis) presents some preparative problems since the unstable carbamidic chloride is difficult to handle. This disadvantage can be avoided by using KOCN in HF[223]; under these conditions, the carbamoyl fluoride formed *in situ* immediately reacts with the aromatic substrate to give the benzamides *(108)*. Potassium rhodanide may analogously be employed for the synthesis of *thio*amides *(109)*[223].

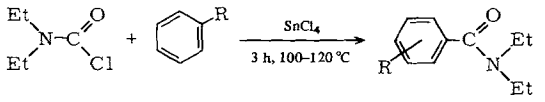


X = O, S

(108), X = O
(109), X = S

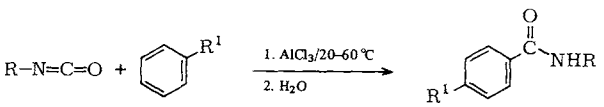
R	= H	CH_3	Cl
Yield of *(108)* [%]	= 63	70	9

Carboxamidation of alkyl arenes with *N,N*-diethylcarbamoyl chloride is less complicated and gives better yields[224].



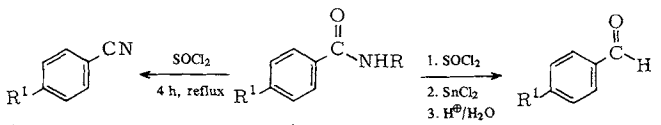
R = Alkyl 69-93% (≥80% *p*-Isomer)

Arene carboxylation with isocyanates and isothiocyanates has proven exceptionally advantageous. *Leuckart* had already obtained *N*-substituted amides *(110)* from the reaction of aromatic isocyanates with activated arenes in the presence of $AlCl_3$[225]. This facile synthesis for aromatic carboxamides was later extended also to less activated aromatic substrates and aliphatic isocyanates[226a].



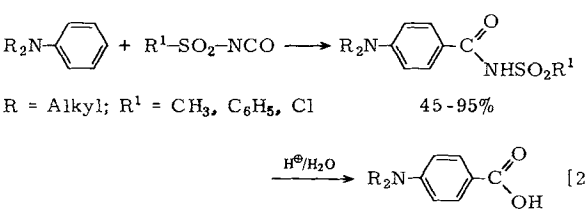
R^1 = Alkyl, Halogen, Alkoxy *(110)* 65-100%

Use of aliphatic isocyanates is preparatively advantageous since the *N*-alkyl amides *(110a)*, R = alkyl, offer the possibility of further chemical conversion; upon warming with thionyl chloride, for instance, they are transformed into the nitriles *(111)*, and, *via* the imidoyl chlorides, with Sn(II) chloride into the aldehydes *(112)*[226b].



(111), 90-100% *(110a)* *(112)*
R^1 = F, 83%

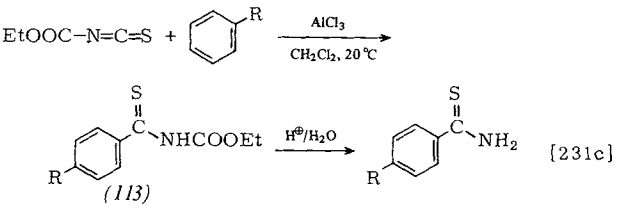
With the more reactive sulfonyl isocyanates, *Seefelder*[227] and *Graf*[228] succeeded in carboxamidating electron-rich arenes (dialkylanilines, resorcinol dimethyl ether) and hetarenes (pyrrole, thiophene, indene, carbazole) in good yields even without addition of Friedel-Crafts catalysts[229,230].



R = Alkyl; R^1 = CH_3, C_6H_5, Cl 45-95%

[227]

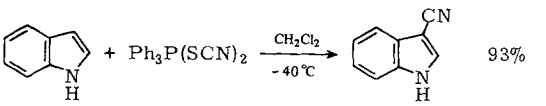
Isothiocyanates can similarly be reacted with arenes, though in the presence of $AlCl_3$, to *N*-substituted thioamides *(113)*[231].



R	= H	CH_3	*t*-Bu	CH_3O	Cl
Yield of *(113)* [%]	= 52	63	41	90	29

[231c]

By the use of cyanogen halides or alkyl cyanates, a direct electrophilic introduction of the CN function is possible with highly nucleophilic groups (OH, SH, NH); only poor yields are obtained with aromatic substrates[232]. Good yields of cyanation products are achieved with triphenylphosphane/dirhodane in the case of reactive hetarenes (indene, pyrrole)[233].



10. Concluding Remarks

I have tried in this contribution to delineate the general trends in the development of new electrophilic species and, at the same time, to show up the preparative advantages and the applicability of these novel reagents.

The "super-leaving groups", known from carbenium ion chemistry (*e.g.* triflate and fluorosulfate), are doubtless of crucial importance in this context. Since their paramount importance in solvolysis reactions had already been recognized in the sixties, it is indeed surprising that their specific properties were not utilized until so much later for the development of new, highly effective electrophiles.

A second trend noted in recent years is towards more and more selective electrophiles. To this end, heterocyclic moieties in particular have been employed as leaving groups; in many instances, this also allows working under neutral and/or aprotic conditions. At the same time, it has been recognized more and more clearly that the interaction of charged electrophiles with solvents containing lone pairs (*e.g.* nitriles, tertiary amines, ethers, thioethers, nitro and halo compounds) constitutes a decisive factor; reactivity and selectivity of the electrophile can thus be varied in a controlled fashion.

Electrophilic metalation, phosphorylation, and silylation have deliberately been excluded from this account, since the alternative mechanistic routes which would have to be discussed for these reactions lie outside the scope of this review.

My sincere thanks go to my dedicated co-workers, both former and present, who have collaborated in the work cited here. Generous support of our investigations by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

Received: December 3, 1979 [A 305 IE]
German version: Angew. Chem. *92*, 147 (1980)
Translated by Priv.-Doz. Dr. *Peter Fischer*, Stuttgart

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Coupling of Solvolysis and C—C Linkage: A Promising Synthetic Route to Functionalized Carboxylic Acids, Aldehydes, and Ketones

By Kaspar Bott[*]

Dedicated to Professor Matthias Seefelder on the occasion of his 60th birthday

Numerous additions of carbocations to chloroolefins or acetylenes can be coupled with a solvolysis step when performed in a suitable acid; the products are variously substituted carboxylic acids, aldehydes, and ketones. Factors determining the success of these syntheses are the stability of the intermediate carbocations and suppression of the competing addition of protons to the unsaturated reaction component. Under the conditions of the Tscherniac-Einhorn reaction, amidomethylation of chloroolefins and acetylenes, *i.e.* the introduction of acylaminomethyl groups, is shown not to involve a trigonal α-chloro carbocation or a linear vinyl cation, but instead to proceed *via* a cyclic oxazinium ion intermediate.

1. Introduction

Many syntheses in organic chemistry are possible only if C—C linkage is followed by an energetically favored step, such as salt formation. Typical examples of this strategy are the carbonylation of aromatic hydrocarbons according to *Gattermann-Koch*[1] and ester condensation according to *Claisen*[2].

In the following we shall survey those reactions in which the formation of an intermediate *(3a–c)* from the carbocation *(1)* and the unsaturated component *(2a–c)* is forcibly coupled with the energetically particularly favorable hydrolysis to

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