Alkylation, Acylation and Silylation of Azoles

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Begtrup, M. and Larsen, P., 1990. Alkylation, Acylation and Silylation of Azoles. – Acta Chem. Scand. 44: 1050–1057.

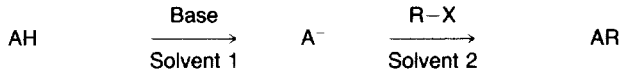
Performing alkylation, acylation and silylation reactions in separate deprotonation and nucleophilic displacement steps allows for better control of reaction conditions and facilitates problem handling in these processes. In the alkylation of azoles the alkylating agents and solvents possess individual reaction capabilities which seem to be approximately additive. Monoalkylation occurs if the sum of the normalized reaction potentials is equal or larger than the pK_a value of the azole. Dialkylation is avoided by keeping the sum of the normalized reaction potentials below the pK_a value of the alkylazole. The applicability of these principles is demonstrated by the development of effective procedures for the methylation, benzylation, acetylation, methoxycarbonylation and trimethylsilylation of azoles.

Alkylation, acylation and silylation are important and frequently used reactions in organic chemistry. Reported procedures are not always effective and sometimes produce unsatisfactory yields. this also pertains to *N*-alkylation, -acylation, or -silylation of 5-membered nitrogen-containing heteroaromatics (azoles). Using azoles as models in these reactions, some general aspects and guidelines for optimization have been revealed. Azole sodium salts were chosen for the alkylation study since their pK_a values are distributed over a broad range (4.9–14.4)[1] (Table 1) and since high selectivity is required in order to avoid further alkylation of the basic products with production of quaternary salts. Most alkylations, acylations and silylations invovle two steps: deprotonation and nucleophilic displacement (Scheme 1). The reactions are usually run in one pot, that is, the same solvent is used in both steps. The process is then optimized by selection of base, solvent and electrophile. If however, the two steps are considered separately the following requirements must be specified. 1. The base should deprotonate the substrate. 2. The base and/or the substrate should be sufficiently soluble in solvent 1 to secure deprotonation. 3. The substrate anion and/or the electrophile should be sufficiently soluble in solvent 2 to ensure their reaction. 4. The base should not destroy substrate or solvent 1. 5. The electrophile should attack neither the product nor solvent 2. Finally, a smooth reaction is more likely if 6, solvent 2 enhances the nucleophilicity of the substrate anion.

Table 1. pK_a Values of azoles and *N*-methylazoles.[1]

Azole	pK_a[a]
Imidazole	14.4
Pyrazole	14.2
4-Bromopyrazole	12.7
4-Bromoimidazole	12.2
1,2,4-Triazole	10.0
4-Nitropyrazole	9.6
1,2,3-Triazole	9.3
Tetrazole	4.9
1-Methylimidazole	7.1
1-Methyl-1,2,4-triazole	3.2
4-Methyl-1,2,4-triazole	3.4
1-Methylpyrazole	2.1
1-Methyl-1,2,3-triazole	1.2
4-Bromo-1-methylpyrazole	0.2
1-Methyl-4-nitropyrazole	−2.2
1-Methyltetrazole	−3.0
2-Methyltetrazole	−3.3
2-Methyl-1,2,3-triazole	−3.5

[a]For *N*-unsubstituted azoles the pK_a value for the proton loss is given.



Scheme 1.

Results

Deprotonation. Sodium and potassium hydroxide are both good reagents for the abstraction of the proton at the nitrogen atom of azoles. The hydroxides can be used with or without a solvent. In the absence of solvents, a 1:1 mixture of the hydroxides is preferable since it has the lowest melting point. As solvents, water and methanol are

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suitable. After deprotonation, the azole salts were obtained dry on being heated to 200 °C at 0.4 mmHg for ca. 0.5 h. Of the compounds studied, only 4-nitropyrazole sodium salt did not tolerate these conditions. Alkali-metal hydroxides cannot be used in the deprotonation if (i) they are not basic enough to abstract the proton, (ii) the substrate is insoluble in water or methanol, (iii) the substrate is hydrolyzed, or (iv) high drying temperatures cannot be tolerated. In such cases sodium hydride may be an alternative. It may be used in solvents such as *N,N*-dimethylformamide (DMF), pyridine or acetonitrile. Acetonitrile is the first choice, being stable to sodium hydride and easy to remove with production of the dry azole sodium salts. All of the compounds studied could conveniently be deprotonated with sodium hydride in acetonitrile.

Nucelophilic displacement. (a) Alkylation. The dissolved or suspended dry sodium salts were methylated with methyl iodide or dimethyl sulfate. Benzylation was performed using benzyl chloride, bromide or iodide. Different combinations of alkylation agents, solvents, reaction temperatures, and reaction times were attempted on the individual azole sodium salts. Results of preparative interest are shown in Tables 2 and 3. Products were usually isolated by removal of the solvent followed by distillation. In many cases, the yields are the best reported for methylation and benzylation of these azoles. In cases where two isomeric alkylazoles arise, their ratio was found to depend upon the conditions used. Effective, preparative scale methods for the separation of the isomers have been designed in all cases except for the bromo(methyl)imidazoles.

In the course of this systematic study it became apparent that alkylation was only successful if the combination of alkylation agent and the solvent (as well as temperature and time) matched the pK_a value of the azole anion. The alkylation capability of different combinations of alkylation agents and solvents was tested at fixed reaction temperature and time against azole anions of decreasing pK_a in order to establish the maximum alkylation potential of the individual alkylation agents and solvents. Since the reaction mixtures were frequently heterogeneous, kinetic measurements were not feasible and an empirical approach was used: the alkylation capability was considered satisfactory if the yield of alkylazole under standard conditions was 75 % or more. The reasoning behind this arbitrary choice is that 75 % can be qualified as a good practical yield which allows for losses during work-up. This choice also gave rise to few borderline cases with yields slightly below the 75 % limit (see Table 4). Each entry in Table 4 can be expressed as an equation. In order to match the alkylation capability with the pK_a value of the substrate, the alkylation capabilities must be normalized to pK_a units and an arbitrary reference point on the pK_a scale chosen. A value of 20 was chosen for practical reasons since this gives rise to positive values for all alkylation potentials P_a. The number of equations is too low to allow a solution using analysis of variance. Instead step-by-step reasoning was applied as follows. The first entry in Table 4 indicates that methyl iodide in dichloromethane is capable of methylating 4-bromoimidazole but not 1,2,4-triazole. This can now be expressed as:

Table 2. Methylation of azoles[a] – preparative experiments.

Product(s)	Yield[b](%)	Product ratio[c]	Solvent	Conditions[d]
1-Methylimidazole[e]	98		MeCN	C
	86		MeOH	C
4- and 5-bromo-1-methylimidazole	96	2.9:1	CH_2Cl_2	C
	94	1.2:1	MeOH	C
1-Methylpyrazole[f]	67		MeOH	C
1-Methyl-4-nitropyrazole[g]	91		MeCN	B
1- and 4-methyl-1,2,4-triazole	90	4.5:1[h]	CH_2Cl_2	C
	100	8.8:1	MeCN	E
	92	11.3:1	MeOH	D
1- and 2-methyl-1,2,3-triazole	88	1.9:1[h]	CH_2Cl_2	C
	87	1.4:1	MeCN	E
			MeOH	D
1- and 2-methyl-tetrazole	77	1.5:1[h]	CH_2Cl_2	C
	78	2.8:1	MeCN	F
	85	1.9:1	MeOH	F

[a]With methyl iodide, unless otherwise stated. [b]When a single product is formed the yield of balltube-distilled or recrystallized product is given. When two isomers are formed the yield of the mixture is given. Mixtures were separated as described in the Experimental section. [c]Product compositions were determined by ^1H NMR spectroscopy. [d]A: 20 °C for 1 h; B: 20 °C for 24 h; C: 20 °C for 72 h; D: 20 °C for 120 h; E: 80 °C for 3 h; F: 100 °C for 1 h; G: 100 °C for 3 h; H: 100 °C for 24 h. [e]Balltube distilled at 200 °C/10 mmHg. [f]Distilled using a Podbielniak column.[11] B.p. 125–128 °C (Reported 126–128 °C). [g]M.p. 92 °C (ethyl acetate) (Reported[12] 91–92 °C). [h]Dimethyl sulfate was used as the alkylating agent.

$$20 - pK_a(1,2,4\text{-triazole}) > P_a(MeI) + P_a(CH_2Cl_2) \geq 20 - pK_a(4\text{-bromoimidazole}).$$

In order to relate the alkylation potentials to the pK_a scale, one of the potentials must be fixed. So, P_a(MeI) was arbitrarily set to 7.0 pK_a units. Again, this choice is entirely practical in leading to positive values for all alkylation potentials. Insertion into the above relation gives:

$$3.0 > P_a(CH_2Cl_2) \geq 0.8.$$

Since the 1,2,4-triazole anion is not methylated at all $P_a(CH_2Cl_2)$ must be close to the lower limit, that is $P_a(CH_2Cl_2)$ is ca. 1. Analogously, entry 6 in Table 4 leads to:

$$P_a(Me_2SO_4) + P_a(CH_2Cl_2) \geq 20 - pK_a \text{ (tetrazole)}$$

that is, $P_a(Me_2SO_4) \geq 14.3$. Similarly, entry 7 leads to:

$$20 - pK_a(4\text{-bromoimidazole}) > P_a(BnCl) + P_a(CH_2Cl_2) \geq 20 - pK_a(\text{imidazole}).$$

Table 3. Benzylation of azoles[a] – preparative experiments.

Product(s)	Yield[b](%)	Product ratio[c]	Solvent	Conditions[d]
1-Benzylimidazole[e]	94		CH_2Cl_2	B
	97		MeCN	C
	100		DMF	C
1-Benzyl-4- and 5-bromoimidazole	100	4.9:1	MeCN	C
	91	1.8:1	MeOH	C
1-Benzylpyrazole[f]	99		DMF	C
1- and 4-benzyl-1,2,4-triazole	99	3.3:1[g]	CH_2Cl_2	C
	100	5.5:1	MeCN	G
	100	4.1:1	MeOH	D
	95	7.3:1	DMF	C
1- and 2-benzyl-1,2,3-triazole	100	4.8:1	MeOH	C
1- and 2-benzyltetrazole	100	1.3:1	MeCN	H
	96	2.1:1	MeOH	F
	92	1.9:1	DMF	C

[a]With benzyl chloride, unless otherwise stated. [b]When a single product is formed the yield of recrystallized product is given. When two isomers are formed the yield of the mixture is given. Mixtures were separated as described in the Experimental section. [c]Product compositions were determined by ^{1}H NMR spectroscopy. [d]See Table 2, footnote *d*. [e]M.p. 71–72 °C (ethyl acetate–hexane) (reported[13] 76–79 °C). [f]Balltube distilled at 130 °C/0.6 mmHg. [g]Benzyl bromide was used as alkylating agent.

Table 4. Maximum alkylation capability of combinations of alkylation agents and solvents by alkylation of azole anions under standard conditions.

Alkylation agent	Solvent	Conditions[a]	Least basic azole anion to be alkylated	Yield (%)	Most Basic azole anion not to be significantly alkylated	Yield (%)
MeI	CH_2Cl_2	C	4-Bromoimidazole	96	1,2,4-Triazole	0
	MeCN	C	1,2,3-Triazole	87	Tetrazole	8
		G	Tetrazole	78	–	
	MeOH	C	1,2,3-Triazole	100	Tetrazole	0
		G	Tetrazole	85	–	
Me_2SO_4	CH_2Cl_2	C	Tetrazole	77		
$PhCH_2Cl$	CH_2Cl_2	C	Imidazole	94	4-Bromoimidazole	0
	MeCN	C	4-Bromoimidazole	100	1,2,4-Triazole	0
		G	1,2,3-Triazole		Tetrazole	70
	MeOH	C	1,2,3-Triazole	100	Tetrazole	22
		G	Tetrazole	100	–	
	DMF	C	Tetrazole	92	–	
$PhCH_2Br$	CH_2Cl_2	C	1,2,3-Triazole	100	Tetrazole	0
$PhCH_2I$	CH_2Cl_2	C	–		Tetrazole	0

[a]See Table 2, footnote *d*.

Insertion gives $6.3 > P_a(\text{BnCl}) \geq 4.8$. Since the 4-bromoimidazole anion is not benzylated at all $P_a(\text{BnCl})$ must be close to the lower limit, that is $P_a(\text{BnCl})$ is ca. 5. Entry 13 leads to:

$$20 - \text{p}K_a(\text{tetrazole}) > P_a(\text{BnBr}) + P_a(\text{CH}_2\text{Cl}_2) \geq 20 - \text{p}K_a(1,2,3\text{-triazole})$$

which leads to $14.3 > P_a(\text{BnBr}) \geq 9.9$. Since alkylation of tetrazole completely fails under these conditions, the potential must be at the lower part of this interval, that is $P_a(\text{BnBr}) = 10$–12. Benzyl iodide possesses similar alkylating power. Entry 8 leads to:

$$20 - \text{p}K_a(1,2,4\text{-triazole}) > P_a(\text{BnCl}) + P_a(\text{MeCN}) \geq 20 - \text{p}K_a(4\text{-bromoimidazole})$$

which leads to $5.2 > P_a(\text{MeCN}) \geq 3.0$. Since 1,2,4-triazole does not react at all, $P_a(\text{MeCN})$ must be ca. 3. A refined estimate can be elucidated from entry 2 which leads to:

$$8.1 > P_a(\text{MeCN}) \geq 3.7.$$

Therefore, $P_a(\text{MeCN})$ must be close to 3.7. Entries 10 and 12, which express the benzylation capability of benzyl chloride in DMF and in methanol, similarly give:

$$P_a(\text{DMF}) \geq 10.3 \text{ and } 7.4 > P_a(\text{MeOH}) \geq 5.9.$$

In methanol tetrazole is benzylated to an extent of 22 %, so $P_a(\text{MeOH}) = 6.5$ seems a good estimate.

Some alkylations are not feasible at 20 °C in 72 h but can be effected by heating. Such alkylation experiments can be used to estimate the potential of heating normalized in the same way as the kind of alkylation agent and solvent. The alkylation potential of heating to 100 °C for 3 h was studied as an example since such conditions are realistic in practical alkylation procedures. The effect of such heating appears from entry 9 which can be expressed as:

$$20 - \text{p}K_a(\text{tetrazole}) > P_a(\text{BnCl}) + P_a(\text{MeCN}) + P_a(100\,^\circ\text{C}, 3\,\text{h}) \geq 20 - \text{p}K_a(1,2,3\text{-triazole})$$

From this it follows that $6.6 > P_a(100\,^\circ\text{C}, 3\text{ h}) \geq 2.2$. Tetrazole is benzylated to an extent of 70 %. Hence, $P_a(100\,^\circ\text{C}, 3\text{ h}) = 6$ is a reasonable estimate. A survey of the alkylation potential values found is given in Table 6. Allthough the reaction potentials have been estimated on an empirical basis the *result* seems consistent, and it is very useful in planning. Using the values in Table 6, conditions for alkylation of any azole anion can be predicted: alkylation occurs if the reference point value 20 minus the sum of the reaction potentials is equal to or less than the $\text{p}K_a$ value of the azole anion in concern.

The alkylated azoles are also basic and may undergo further alkylation with production of quaternary azolium salts. It has been reported that the rates of alkylation of 1-methylimidazole and 1-methylpyrazole with methyl iodide or dimethyl sulfate in dimethyl sulfoxide is correlated with the basicity of the azoles.[2] Our systematic study revealed that quaternization only was successful if the combination of alkylation agent and the solvent matched the $\text{p}K_a$ value of the alkylazole. The quaternization capability of different combinations of alkylation agents and solvents

Table 5. Maximum alkylation capability of combinations of alkylation agents and solvents by quaternization of methylazoles under standard conditions.

Alkylation agent	Solvent	Conditions[a]	Least basic azole to be alkylated	Yield (%)	Most Basic azole not to be significantly alkylated	Yield (%)
MeI	CH_2Cl_2	C	1-Methyl-1,2,3-triazole	76	4-Bromo-1-methylpyrazole	0
	MeCN	C	1-Methyl-1,2,3-triazole	67[b]	4-Bromo-1-methylpyrazole	0
		G	–		4-Bromo-1-methylpyrazole	44
	MeOH	C	1-Methylimidazole	30	1-Methyl-1,2,4-triazole	11
		G	1-Methyl-1,2,3-triazole	76	4-Bromo-1-methylpyrazole	61
	DMF	C	1-Methyl-1,2,3-triazole	83	4-Bromo-1-methylpyrazole	15
		G	–		4-Bromo-1-methylpyrazole	68
Me_2SO_4	CH_2Cl_2	C	1-Methyl-4-nitropyrazole		2-Methyltetrazole	53
$PhCH_2Cl$	CH_2Cl_2	C	1-Methylimidazole	100	1-Methyl-1,2,4-triazole	2
	MeCN	C	1-Methylimidazole	100	1-Methyl-1,2,4-triazole	11
		G	–		1-Methyl-1,2,4-triazole	47
	MeOH	C	1-Methylimidazole	63[b]	1-Methyl-1,2,4-triazole	5
		G	–		1-Methyl-1,2,4-triazole	49
	DMF	C	1-Methylimidazole	99	1-Methyl-1,2,4-triazole	29
		G	–		1-Methyl-1,2,4-triazole	48
$PhCH_2Br$	CH_2Cl_2	C	1-Methyl-1,2,3-triazole	92	4-Bromo-1-methylpyrazole	1
$PhCH_2I$	CH_2Cl_2	C	1-Methyl-1,2,3-triazole	88	4-Bromo-1-methylpyrazole	6

[a]See Table 2, footnote *d*. [b]The yield is below 75 %, but is shown for reasons of comparison.

Table 6. Estimated reaction potentials of alkylating agents and solvents by alkylation and quaternization of azoles.

	Reaction potential P_a by alkylation of azole anions / pK_a units[a]	Reaction potential P_q by quaternization of methylazoles/pK_a units[a]
MeI	7.0	7.0
Me_2SO_4	≥14.3	10.5
BnCl	5	1
BnBr	10–12	7
BnI	10–12	7
CH_2Cl_2	1	12
MeCN	3.7	11.5–12
MeOH	6.5	10–12
DMF	≥10.3	12
100 °C 3 h	6	0.5

[a] By reaction at 20 °C for 72 h, unless otherwise stated.

was tested at fixed reaction temperature and time against alkylazoles of decreasing pK_a in order to establish the maximum quaternization potential of the individual alkylation agents and solvents. The result is shown in Table 5. Each entry can be expressed in equations which can be solved as above – again arbitrarily setting the reference point at pK_a = 20 and the methyl iodide alkylation potential to 7.0 pK_a units. The resulting estimates of the magnitude of the individual quaternization potentials are presented in Table 6. It is noticeable, that a given alkylation agent or solvent exhibits alkylation and quaternization potentials of different magnitude.* In the quaternization reactions the solvent potentials are all similar, except that of methanol which is reduced by ca. 2 when using methyl iodide. This is the only observed exception from simple additivity of reaction potentials.

Another remarkable and useful feature is that heating promotes alkylation but has only a limited effect on quaternization. Even though heating to 100 °C for 3 h leads to increased quaternization yields,† it does not lead to extension of the quaternization potential to effect quaternization of an alkylazole with higher pK_a. Hence P_a(100 °C, 3 h) is estimated to be ca. 0.5.

Quaternization of any alkylazole can now be predicted. It takes place if 20 minus the sum of the quaternization potentials is equal to or less than the pK_a value of the alkylazole. In many reported procedures for synthesis of alkylazoles, unintentional quaternization occurs and reduces the yield of alkylazole.[3] That is, condition 5 (see above) is not fulfilled. Selective monoalkylation of azole anions requires that the sum of the potentials be sufficient to allow alkylation of the azole anion but not quaternization of the alkylazole. Thus, the tetrazole anion is not benzylated by benzyl chloride in acetonitrile at 20 °C since 20 − 5 [= P_a(BnCl)] − 3.7 [= P_a(MeCN)] = 11.3 which is far above the pK_a of tetrazole. Benzylation requires heating to 100 °C for at least 3 h, or change to DMF, or change to benzyl bromide. There is no risk of quaternization under these conditions since e.g. 20 − 7.0 [= P_q(BnCl)] − 12 [= P_q(DMF)] = 1.2 which is above the pK_a value of the benzyltetrazoles (ca. −3). Another example is the benzylation of the pyrazole anion in dichloromethane (see Table 6). Both benzyl chloride and benzyl bromide serve well in the benzylation. However, only benzyl chloride is incapable of alkylating the benzylpyrazole in dichloromethane and is therefore the safest choice.

In general, the sum of reaction potentials is smaller in quaternization than in alkylation reactions when DMF is the solvent or when the reaction is performed at elevated temperatures. This should be taken into account and put to use in selective monoalkylations of azole anions. Another possibility exists in methylation reactions with methyl iodide in which methanol offers a lower quaternization potential than other solvents.

If it cannot be avoided that the sum of the reaction potentials is so as to allow quaternization of the alkylazole, the risk that quaternization actually occurs is high when (i) an excess of alkylation agent is used; (ii) the azole anion is less soluble than the alkylazole; or (iii) the pK_a difference between azole anion and alkylazole is small. Small pK_a differences of 7–8 exist when 1,3 dialkylation is possible. This situation occurs for 1-alkylimidazole, 1- and 4-alkyl-1,2,4-triazole, 1-alkyl-1,2,3-triazole, as well as for 1- and 2-alkyltetrazole. In contrast, large pK_a differences of 12–13 exist when only 1,2-dialkylation is possible as in 1-alkylpyrazole and 2-alkyl-1,2,3-triazole. Therefore, if the sum of the reaction potentials unavoidably extends to the alkylazole, quaternization is minimized by using only equimolar amounts of the alkylating agent,‡ a solvent which dissolves the azole anion, and the smallest possible sum of reaction potentials.§ These points are illustrated by the methylation of the imidazole anion. The smallest sum of reaction potentials results when using methyl iodide in dichloromethane. With one equivalent of methyl iodide, these conditions give rise to 19 % of 1-methylimidazole since it is alkylated further to afford 1,3-dimethylimidazolium iodide. If methyl iodide is replaced with dimethyl sulfate the sum of reaction potentials increases and the yield of methylimidazole drops to 14 %. If dichloromethane in the first experiment is replaced with the more polar acetonitrile or methanol, the

* Methyl iodide is an exception since its alkylation potential was set to 7.0 both in alkylation and quaternization.

† Compare the yields of entries 6 and 7 in the second column of Table 5. Similarly the yields of entries 10, 11, 12 and 13, or 14 and 15 reflect this fact.

‡ Unintentional loss of methyl iodide is avoided by performing the reaction in a closed vessel.

§ Finally, an alkylation filter may be added. It consists of a base with a pK_a value between those of the azole anion and the alkylazole. The alkylation filter protects the alkylazole towards quaternization and allows the use of an excess of the alkylating agent.

Table 7. Methoxycarbonylation and trimethylsilylation of azoles.

Starting material	1-Methoxycarbonyl derivative				1-Trimethylsilyl derivative		
	Yield (%)	M.p./°C	Recryst. solv.	Reported m.p./°C	Yield (%)	B.p./°C/mmHg	Reported b.p./°C/mmHg
Imidazole	81	40–42	Hexane	35–39[23]	95	60–65/0.5	97/12[4]
Pyrazole	94	36–37	Hexane	35[24]	100	40/0.5	153/760[4]
1,2,4-Triazole	94	68–70	Hexane	68–70[25]	56 11[b]	20–70/1.5[a] 70–200/1.5[a]	74/12[4]
Tetrazole	68	41–42	Hexane		85	110/0.5[a]	66/0.1[26]

[a]Balltube distillation. [b]4-Trimethylsilyl-1,2,4-triazole.

latter even dissolving the imidazole anion, the yield increases to 98 and 86 %, respectively, but the yield drops if methyl iodide is used in excess.

Alkylation of azoles exhibiting tautomerism may give rise to more than one alkylazole. The ratio between the alkylazoles depends on the reaction conditions used. This also influences the choice of alkylation agent and solvent. Effective methods for the separation of the isomers have been designed in all cases except the bromo(methyl)imidazoles. The separation procedures are usually based on different boiling points (methylazoles) or different pK_a values (benzylazoles) (see the Experimental).

As a result of these studies the following general strategy is recommended in planning the alkylation of an anion. First, it should be considered whether dichloromethane may be used as the solvent since it is inert and low-boiling, thus facilitating isolation of volatile products. Next, the alkylation agent is selected. It should be capable of alkylating, in dichloromethane, the anion but not the product. If no alkylation agent fulfils the latter condition, the risk of dialkylation of readily soluble products is high when the anions are only sparingly soluble. Therefore, a change of solvent to one which better dissolves the anion may be advantageous. Methanol is usually the best in this respect. However, strong basic anions deprotonate methanol whereupon the methoxide ion may be alkylated. When no alkylation agent is capable of alkylating the anion in dichloromethane, acetonitrile or methanol – with the reservations mentioned above – is the next choice. If the reactivity in these solvents is also insufficient or if high temperatures are not tolerated DMF may be employed.

Nucleophilic displacement. (b) Acylation and sulfonylation. Reaction of the imidazole anion with acetyl, benzoyl, methoxycarbonyl, or methanesulfonyl chloride failed when acetonitrile or DMF were used as the solvent since these solvents are attacked by the chlorides. If, however, dichloromethane is employed as the solvent, a smooth reaction takes place with production of 1-acetyl-, 1-benzoyl-, 1-methoxycarbonyl-, or 1-methanesulfonyl-imidazole, respectively. This provides an effective and general method for the synthesis of *N*-acyl- and *N*-sulfonyl-azoles.

Nucleophilic displacement. (c) Silylation. Acetonitrile or DMF could not be used for trimethylsilylation of azole sodium salts due to reaction between solvent and silylation agent. However, a smooth reaction takes place in dichloromethane suspension to afford *N*-trimethylsilylazoles in excellent yields (Table 7). This procedure seems to be superior to those previously reported.[4] Its advantages are use of inexpensive starting materials, mild reaction conditions, a simple work-up procedure, and high yields.

Conclusions

The results of the present model study can be expressed in general terms. If problems in alkylation, acylation or silylation reactions are encountered the two-step nature of the processes should be considered. The individual steps should be analyzed in order to confirm that all conditions 1–6 (see above) are met. Next, the deprotonation step should be analyzed in detail along the lines given in the section above about deprotonation. Finally, the nucleophilic displacement step should be planned using the strategy recommended in the section on alkylation or the results in the sections dealing with acylation and silylation.

Experimental

Dichloromethane was dried over sodium hydride. Acetonitrile,[5] methanol[6] and DMF[7] were dried as described in the references. All alkylation and acylation reagents were distilled before use. Flash chromatography was performed as described in Ref. 8. All new compounds were colorless. The purity and identity of all compounds were confirmed using melting or boiling points and ^{1}H and ^{13}C NMR spectra,[9] recorded at 250 and 62.90 MHz, respectively, on a Bruker AC-250 instrument.

Deprotonation. (a) Aqueous sodium hydroxide (33 %, 10 mmol as determined by titration) and the azole (10 mmol) were heated to 100 °C for 10 min. The solution was cooled to 20 °C. Evaporation at 0.5 mmHg until a solid remained and final drying at 200 °C and 0.5 mmHg for 0.5 h gave the hygroscopic azole sodium salt as a crystalline powder in

97–98 % yield, except the pyrazole sodium salt which was obtained in 92 % yield.

(b) Solid potassium hydroxide (10 mmol as determined by titration) and the azole (10 mmol) were heated to 200 °C at 0.5 mmHg for 0.5 h to produce the hygroscopic azole potassium salt as crystalline lumps in 97–98 % yield.

(c) Dry acetonitrile (20 ml) was added with stirring and cooling in an ice bath to a mixture of a 55 % suspension of sodium hydride in mineral oil (1.57 g) and the azole* (30.0 mmol) under a nitrogen atmosphere. After 24 h of stirring, the acetonitrile was removed at 20 °C and 1 mmHg and the residue washed with hexane (3×4 ml) to give the azole sodium salt in quantitative yield.

Methylation. The azole sodium salt (10 mmol), the solvent specified in Table 2 (4.3 ml) and dimethyl sulfate (0.95 ml) or methyl iodide (0.62 ml) were mixed with stirring at −25 °C in a closed reaction vessel.[10] The vessel was kept in the bath while its temperature was raised to 20 °C in ca. 1 h. Stirring was continued under the conditions specified in Table 2. When dichloromethane was used as the solvent, dichloromethane (40 ml) was then added. Filtration and removal of the dichloromethane by distillation gave the crude product which was purified as described below. When acetonitrile or methanol was used as the solvent it was removed *in vacuo* at 20 °C. The residue was extracted with dichloromethane (3×8 ml). The dichloromethane was removed and the residue purified as described below. By the methylation of pyrazole and 1,2,3-triazole the solvent was removed and the product distilled using a Podbielniak column.[11] The following crude methylazoles were purified by balltube distillation for 0.5 h. Distillation data are given in brackets. The 4.5:1 mixture of methyl-1,2,4-triazoles (Table 2) gave 74 % of 1-methyl-1,2,4-triazole (150 °C/ 10 mmHg) and 11 % of 4-methyl-1,2,4-triazole (200 °C/ 0.4 mmHg). The 8.8:1 mixture similarly gave 93 % of 1-methyl-1,2,4-triazole. The 1.5:1 mixture of methyltetrazoles gave 30 % of 2-methyltetrazole (150 °C). The 2.8:1 mixture similarly gave 58 % of 1-methyltetrazole (200 °C/ 0.4 mmHg.

Benzylation. The azole sodium salt (10 mmol), the solvent specified in Table 3 (4.3 ml), and benzyl chloride (1.15 ml) or benzyl bromide (1.19 ml) were mixed as in the methylation and the reaction performed as specified in Table 3. When dichloromethane was used as the solvent the mixture was then filtered and the dichloromethane removed. The residue was extracted with boiling ethyl acetate (18 + 3×5 ml). Removal of the ethyl acetate gave the crude product. When acetonitrile or methanol was used, the solvent was removed, the residue extracted with ethyl acetate as above, and the ethyl acetate removed. When DMF was used, it was removed *in vacuo* at 40 °C. The residue was extracted with boiling ethyl acetate (3×8 ml), and the ethyl acetate removed. The 4.9:1 mixture of 1-benzyl-4- and 1-benzyl-5-bromoimidazole (1.00 g) was separated by addition of 1 M sulfuric acid (7.6 ml). Extraction with chloroform (8×7.6 ml) and removal of the chloroform gave 0.66 g (66 %) of 1-benzyl-4-bromoimidazole m.p. 91–93 °C (diethyl ether). Anal. $C_{10}H_9BrN_2$: C, H, N. $\delta_H(CDCl_3)$ 7.41–7.35 and 7.19–7.15 (3 H + 2 H, m, C_6H_5), 7.35 (1 H, d, J = 1.29 Hz, H-2), 6.66 (1 H, d, J = 1.29 Hz, H-5), 5.06 (2 H, s, CH_2). 1.29 Hz is a typical H-2, H-5 coupling.[14] To the aqueous solution was added potassium carbonate until pH = 8 was attained. Extraction with dichloromethane (3×10 ml) and removal of the dichloromethane gave 0.33 g (33 %) of 1-benzyl-5-bromoimidazole, m.p. 76–78 °C (ethyl acetate). Anal. $C_{10}H_9BrN_2$: C, H, N. $\delta_H(CDCl_3)$ 7.57 (1 H, d, J = 0.88 Hz, H-2), 7.37–7.33 and 7.18–7.12 (3 H + 2 H, m, C_6H_5), 7.06 (1 H, d, J = 0.88 Hz, H-4), 5.13 (2 H, s, CH_2). 0.88 Hz is a typical H-2, H-4 coupling.[14] The 5.5:1 mixture of benzyl-1,2,4-triazoles (1.00 g) was separated by addition of 1 M hydrochloric acid (6.2 ml). Extraction with dichloromethane (3×29 ml) and removal of the dichloromethane gave 0.89 g (89 %) of 1-benzyl-1,2,4-triazole, m.p. 54–55 °C (ethyl acetate) (reported[15] m.p. 54–55 °C). To the aqueous solution was added potassium carbonate until pH = 8 was attained. Extraction with dichloromethane (2×6 ml) and removal of the dichloromethane gave 0.10 g (10 %) of 4-benzyl-1,2,4-triazole, m.p. 110–111 °C (toluene). (Reported[16] m.p. 114–115 °C). The benzyl-1,2,3-triazoles (1.0 g) were separated by extraction with boiling ether (3×8 ml) and cooling to −25 °C before decantation. This left 1-benzyl-1,2,3-triazole, m.p. 59–61 °C (diethyl ether) (reported[17] m.p. 61 °C). The combined extracts were evaporated to dryness. Addition of an excess of ether saturated with hydrogen chloride, filtration, and removal of the ether gave 0.22 g (22 %) of 2-benzyl-1,2,3-triazole, identical with an authentic specimen.[18] The separated hydrochloride was neutralized with aqueous sodium hydroxide. Extraction with dichloromethane, drying ($MgSO_4$), and removal of the dichloromethane gave another crop of 1-benzyl-1,2,3-triazole. The total yield of this compound was 0.78 g (78 %). The 2.1:1 mixture of benzyltetrazoles (1.00 g) was separated by addition of 50 % sulfuric acid (2.8 ml). Extraction with chloroform (6.5 + 2.8 ml), drying (magnesium sulfate), removal of the chloroform, and balltube distillation at 150 °C/0.3 mmHg gave 0.45 g (43 % overall yield) of 2-benzyltetrazole, m.p. ca. 18 °C. Anal. $C_8H_8N_4$: C, H, N. $\delta_H(CDCl_3)$ 8.51 (1 H, s, H-5), 7.43–7.38 and 7.32–7.27 (3 H + 2 H, m, C_6H_5), 5.80 (2 H, s, CH_2). The aqueous solution was diluted with water (7.0 ml) and extracted with dichloromethane (3×5.6 ml). Removal of the dichloromethane gave 0.50 g (48 % overall yield) of 1-benzyltetrazole, m.p. 56–58 °C (ethyl acetate). (Reported[19] m.p. 59–60 °C).

Quaternization. The alkylazole (10 mmol), the solvent (4.0 ml), and the alkylating agent (10 mmol) in a screw-cap

* Due to the violent reaction of tetrazole, sodium hydride was added to the suspension of tetrazole and acetonitrile.

sealed reaction vessel were either kept for 3 days or heated to 100 °C for 3 h. Removal of the solvent and washing with dry ether (3×5 ml) gave the azolium salt. Yields exceeding 75 % were used as a criterion for the alkylation potential under these specific conditions. Results are given in Table 5.

Acetylation, benzoylation and methylsulfonylation. The imidazole sodium salt (10 mmol), dichloromethane (20 ml), and acetyl, benzoyl, or methanesulfonyl chloride (10 mmol) were mixed with stirring and cooling in an ice bath under a nitrogen atmosphere. After being stirred at 35 °C (screw-cap sealed reaction vessel) for 24 h the mixture was pressure filtered and extracted with dichloromethane (3×5 ml) under nitrogen. The dichloromethane was removed and the crude product recrystallized with cooling to −25 °C. In this way was obtained 76 % of 1-acetylimidazole, m.p. 99–101 °C (toluene). (Reported[20] m.p. 104 °C), 90 % of 1-benzoylimidazole as an oil. (Reported[21] m.p. 19–20 °C). 82 % of 1-methylsulfonylimidazole, m.p. 85–87 °C (toluene). (Reported[22] m.p. 92–94 °C).

Methoxycarbonylation. Similarly the azole sodium salt (10 mmol), dichloromethane (20 ml), and methyl chloroformate (10 mmol), after being stirred at 20 °C for 24 h, worked up as above, and recrystallized at low temperature from hexane, afforded the 1-methoxycarbonylazoles. Details in Table 7.

Trimethylsilylation. Similarly, the azole sodium salt (10 mmol), dichloromethane (20 ml) and trimethylchlorosilane (10 mmol), after 24 h of stirring at 20 °C, removal of the dichloromethane at 50 °C and 100 mmHg, and distillation of the residue, gave the 1-trimethylsilylazoles. Details in Table 7.

Acknowledgements. The project was supported by the Danish Council for Technical and Scientific Research. The 250 MHz NMR instrument was provided by the Danish National Agency of Industry and Trade. Microanalyses were performed by Leo Pharmaceutical Products.

References

1. Catalan, J., Abboud, J. L. M. and Elguero, J. *Adv. Heterocycl. Chem. 41* (1987) 187.
2. Deady, L. W. *Aust. J. Chem. 26* (1973) 1949.
3. Quast, H. and Schmitt, E. *Chem. Ber. 101* (1968) 4012.
4. Birkofer, L. and Ritter, A. *Angew. Chem. 77* (1965) 414.
5. Burfield, D. R., Lee, K.-H. and Smithers, R. H. *J. Org. Chem. 42* (1977) 3060.
6. Lund, H. and Bjerrum, J. *Ber. Dtsch. Chem. Ges. 64* (1931) 210.
7. Burfield, D. R. and Smithers, R. H. *J. Org. Chem. 43* (1978) 3966.
8. Still, W. C., Cahn, M. and Mitra, A. *J. Org. Chem. 43* (1978) 2923.
9. Begtrup, M., Elguero, J., Faure, R., Camps, P., Estopa, C., Ilavsky, D., Fruchier, A., Marzin, C. and de Mendoza, J. *Magn. Reson. Chem. 26* (1988) 134.
10. Begtrup, M. *J. Chem. Educ. 64* (1987) 974.
11. Cason, J. and Rapoport, H. *Laboratory Texts in Organic Chemistry,* Prentice-Hall, New York 1962, p.237.
12. Grimmett, M. R. and Lim, K. H. *Aust. J. Chem. 31* (1978) 689.
13. Iversen, P. E. and Lund, H. *Acta Chem. Scand. 10* (1966) 2647.
14. Matthews, H. R. and Rapoport, H. *J. Am. Chem. Soc. 95* (1973) 2297.
15. Jones, R. G. and Ainsworth, C. *J. Am. Chem. Soc. 77* (1955) 1538.
16. Bartlett, R. K. and Humphrey, I. R. *J. Chem. Soc. C* (1967) 1664.
17. Wiley, R. H., Hussung, K. F. and Moffat, J. *J. Org. Chem. 21* (1956) 190.
18. Begtrup, M. and Nytoft, H. P. *Acta Chem. Scand., Ser. B 40* (1986) 262.
19. Zimmerman, D. M. and Olofson, R. A. *Tetrahedron Lett.* (1969) 5081.
20. Staab, H. A. *Chem. Ber. 89* (1956) 1927.
21. Gerngross, O. *Ber. Dtsch. Chem. Ges. 46* (1913) 1908.
22. Dabkowski, W., Michalski, J., Radzijewski, C. and Skrzypczynski, Z. *Chem. Ber. 115* (1982) 1636.
23. Iwasaki, S. *Helv. Chim. Acta 59* (1976) 2738.
24. Hückel, W. and Breitschneider, H. *Ber. Dtsch. Chem. Ges. 70* (1937) 2024.
25. Klemm, K., Prüsse, W., Baron, L. and Daltrozzo, E. *Chem. Ber. 114* (1981) 2001.
26. Birkofer, L., Ritter, A. and Richter, P. *Chem. Ber. 96* (1963) 2750.

Received April 12, 1990.