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Chalcones as Versatile Synthons for the Synthesis of 5- and 6-membered Nitrogen Heterocycles

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Abstract: Chalcones belong to the flavonoid family which constitutes one of the major classes of naturally occurring oxygen heterocyclic compounds. The α,β-unsaturated carbonyl system of chalcones possesses two electrophilic reactive centers allowing them to participate in addition reactions *via* attack to the carbonyl group (1,2-addition) or involving the β-carbon (1,4-conjugate addition), leading to the synthesis of promising bioactive heterocyclic compounds. The purpose of this review is to present a systematic survey of the most recent literature that uses chalcones in the synthesis of biologically active 5- and 6-membered nitrogen heterocycles such as pyrroles, indoles, isoxazoles, imidazoles, pyrazoles, indazoles, triazoles, tetrazoles, pyridines and pyrimidines. Efficiency, easy-to-handle and cheap reagents, alternative heating conditions and greener protocols will be highlighted. In this review we will cover the literature since the beginning of the 21st century in more than 400 publications.

Keywords: Chalcones, cycloaddition reactions, Michael addition, nitrogen heterocyclic compounds, reactivity, synthetic methods.

#Author's Biography: Artur M. S. Silva studied chemistry at the University of Aveiro (Portugal) where he graduated in chemistry physics in 1987. In 1993 he received his PhD in chemistry at Aveiro University. He began his independent career at Aveiro University as an Assistant Professor in 1994. He was appointed to Associate Professor with tenure in 1998 and Full Professor in 2001. Professor Artur Silva has published over 430 papers 17 book chapters. He supervised more than 15 PhD and 25 MSc students and several post-doctoral fellows. His research interests range over the chemistry of polyphenolic and nitrogen heterocyclic compounds, with special emphasis on the development of new synthetic routes, and also on the organocatalytic transformations. However, the second passion of his research is centred in the isolation and structural characterization of natural products from diverse terrestrial and marine sources.

1. INTRODUCTION

1,3-Diaryl-2-propen-1-ones commonly named as chalcones are naturally occurring α,β-unsaturated ketones with two aromatic rings (A and B) belonging to the flavonoid family [1]. The numbering system is different from that presented by other flavonoids, being the A-ring numbered from 1' to 6' and the B-ring from 1 to 6 (Fig. **1**). Chalcones are widely spread in nature (fruits, vegetables, spices, tea and soy based foodstuff) and their 2'-hydroxy derivatives play an important role in the flavonoid synthesis and biosynthesis as both precursors and products [1].

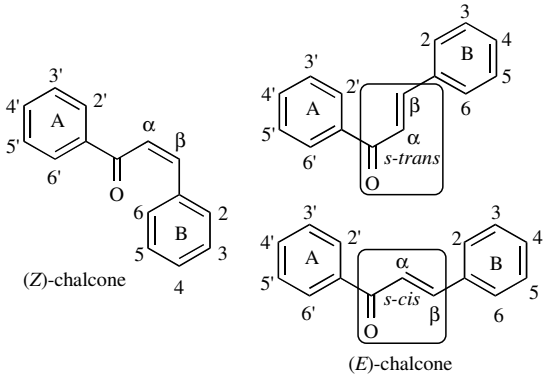

Fig. (1). General structure of chalcones **1**.

Chalcones are the subject of continuous experimental and theoretical investigations. These flexible molecules appear in various conformations, and their properties depend on a suitable ring substitution as well as on the presence of the α,β-unsaturated ketone moiety. The Cα=Cβ double bond can exist either in the (*E*)- or (*Z*)-configuration (Fig. **1**), being the (*E*)-form the thermodynamically most stable and consequently, the majority of the chalcones isisolated as the (*E*)-isomer [2]. The *s-cis* conformation for the O=C-Cα=Cβ system is adopted by the most stable conformer [3] (Fig. **1**). In addition, planar [3] and non-planar [4] structures have been reported for the most stable conformers using different computational levels.

The parent (*E*)-chalcone was not found as a natural product but some simple derivatives such as 4'-hydroxy- and 4'-methoxy-chalcones have been found in plants of the genus *Citrus* and *Flemingia*, respectively. Natural derivatives can present substituents in both aromatic rings being the hydroxyl, methoxyl, methyl and isopentenyl the most frequent ones. These compounds can also be isolated in the free form or as *O*- or *C*-glycosides, with glucose and rhamnose as the predominant sugar residues [5].

In nature, (*E*)-chalcones have shown to display an important role in pigmentation of flowers and can act as protecting agents against microorganisms, insects and ultraviolet radiation. They can also present other biological, pharmacological and biocidal properties, such as antibacterial [6], anti-inflammatory [7-9], antifungal [6], antimalarial [10-12], antitumor [13], antimicrobial [14, 15], antiviral [16], antitubercular [17], antioxidant [18], antimitotic [19], antileishmanial [20], antiplatelet [21], anticancer [22] activities, among others [23, 24].

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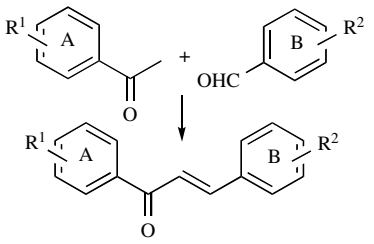
The referred biological properties are closely related to important structural features of chalcones, however there is only a small number of studies on the structure-activity relationship. For instance, it has been shown that a Cα=Cβ double bond is essential for a high antimalarial activity, while substitution in this double bond causes a significant decrease in the inhibitory activity. The presence of chloro, fluoro or small, lipophilic nitrogen heterocycles as substituents on the A ring and electron-donating substitution or small hydrophobic functionality on the B ring increases the antimalarial activity [25, 26]. A QSAR study has shown that hydrophobic and steric properties seem to play an important role in the explanation of the antimalarial activity (inhibitory activity of *P. falciparum* cysteine protease) of chalcones [27], although other authors recommended simultaneous substitutions in both A and B rings which weaken specific bonds of the chalcone structure [28]. There are other few studies on the structure-biological activity of chalcones, namely on antibacterial [29] and antitumor [30, 31] activities.

The simple skeleton of chalcones, its diversified biological activities, and also the small amounts obtained by isolation from natural sources, still prepare the synthesis of chalcones and chalcone-type functionalized derivatives an important and challenging topic. In fact, several academic and industrial chemists dedicate their efforts to the search of alternative and more efficient routes for the synthesis of this type of compounds and even novel derivatives with improved biological applications. Recent literature provides a series of procedures for the synthesis of chalcones; among them Aldol condensation and cross-Aldol condensation known as Claisen–Schmidt condensation are the most often used. The Claisen–Schmidt condensation involves the reaction of acetophenones with benzaldehydes and the resulting chalcones include A-ring substituents supplied by the acetophenone (R^1) and B-ring substituents given by the benzaldehyde (R^2) (Scheme **1**) [32].



Scheme 1. Synthesis of chalcones by a Claisen–Schmidt condensation.

The traditional Claisen–Schmidt reaction is usually carried out in aqueous NaOH or KOH or in ethanolic sodium ethoxide at room temperature for several hours. The Claisen–Schmidt condensation can also be performed in the presence of other bases [*e.g.* $Ba(OH)_2$, LiOH, anhydrous K_2CO_3] and even in acidic conditions (HCl, BF_3•OEt_2, B_2O_3, *p*-toluenesulfonic acid). This reaction can also be performed by using solid-phase catalysts, heterogeneous catalysis, acidic ionic liquids, zeolites, iodine, among other catalysts. Some improved strategies include solvent-free conditions, microwave and ultrasound irradiation and the grinding technique [33].

Chalcones can also be synthesized by palladium-catalyzed cross-coupling reactions. Under microwave heating, direct cross-coupling reaction of benzoyl chlorides and potassium styryltrifluoroborates using $PdCl_2(d^tbpf)$ as catalyst provides a series of chalcones [34]. Other derivatives are obtained by a Suzuki cross-coupling reaction of benzoyl chlorides with arylvinylboronic acids mediated by $Pd(PPh_3)_4$ and using cesium carbonate as base [35]. Other approaches for the synthesis of chalcones include the Friedel–Crafts reaction of phenols with cinammoyl chloride [5] and the use of heteroarylsulfonylarylethanones as coupling reagents in the Julia–Kocienski olefination of benzaldehydes in the presence of DBU in THF [36].

Among all the described synthetic routes the base-catalyzed Claisen-Schmidt reaction is the method of primary choice for the synthesis of chalcones, because of the accessibility of the preliminary materials such as acetophenones and benzaldehydes. In the acidic conditions, the method using BF_3•OEt_2 has particular relevance due to high yields, simple work-up, short reaction times and no side reactions. This method is used in solvent free reactions and is appropriate for reactions concerning liquid reactants possessing base sensitive functional groups *e.g.* esters and amides.

Compounds with an α,β-unsaturated carbonyl system (as chalcones) possess two electrophilic reactive centers, due to delocalization of electron density in the C=C-C=O system, allowing them to participate in addition reactions *via* attack to the carbonyl group (1,2-addition) or involving the β-carbon (1,4-conjugate addition), leading to the synthesis of promising bioactive heterocyclic compounds. The purpose of this review is to present a systematic survey of the most recent literature that uses chalcones in the synthesis of biologically active 5- and 6-membered nitrogen heterocycles such as pyrroles, indoles, isoxazoles, imidazoles, pyrazoles, indazoles, triazoles, tetrazoles, pyridines and pyrimidines.

The reactivity of α,β-unsaturated carbonyl compounds devoted to the synthesis of 5- and 6-membered azaheterocycles was the subject of a book published in 1998 [37] and another in 2008 [38]. Although the most recent chapter describes the most important aspects of pyrazoles, isoxazoles, pyridines and pyrimidines up to 2007, we will cover the literature from the 21st century trying to have a coherent and complete review in the transformation of chalcones to 5- and 6-membered heterocyclic compounds, in more than 400 publications. Efficiency, easy-to-handle and economic reagents, alternative heating conditions and greener protocols will be highlighted.

2. TRANSFORMARTION OF CHALCONES

2.1. 5-Membered Nitrogen Heterocycles

2.1.1. Transformation of Chalcones to Pyrroles

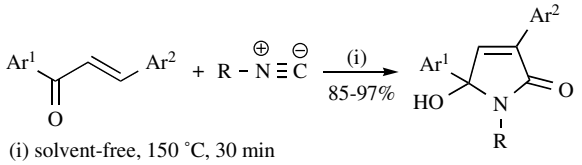
The pyrrole moiety is an important part of many natural products [39]. Highly substituted pyrrole derivatives have been extremely attended, because they are the structural units in many pharmacologically active compounds, such as porphyrins (*e.g.* heme and chlorophylls) [40], and some pyrrole-based alkaloids (*e.g.* hygrine, nicotine, tropine, and cocaine) [41].

Several synthetic pyrrole derivatives have shown to possess interesting biological and/or biomedical properties. For example, the 3-(4-pyridyl)-2-(4-fluorophenyl)-5-(4-methylsulfinylphenyl)-1*H*-pyrrole was reported to be a potent, orally bioactive inhibitor of p38 mitogen-activated protein (MAP) kinase [42], which was found to be implicated in Alzheimer's disease [43, 44], cancer [45, 46], asthma [47] and cardiovascular diseases [48]. Also, other pyrrole derivatives such as 1,2-diaryl-1*H*-pyrroles [49, 50] and 2,3-diaryl-1*H*-pyrroles [51, 52] were identified as cyclooxygenase-2 (COX-2)-selective inhibitors [53, 54]. Some 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones have been shown to be useful in the treatment of patients suffering from intellectual or nervous asthenias, memory failures, senescence or mental strain [55].

The cycloaddition reaction of chalcones with isocyanides seems to be a straightforward route towards the synthesis of pyrroles or pyrrolones. It appears that the reaction of isocyanides with 3-

benzylidenepenta-2,4-dione was a convenient route for the preparation of substituted 2-aminofurans [56]. However, it was later proved that 2-aminofurans were only the intermediates of this reaction and 5-hydroxy-2*H*-pyrrol-2-ones were the products of the [1+4] cycloaddition reaction of alkyl isocyanides with highly electron-deficient benzylidene-1,3-diketones [57]. Thus, Adib *et al.* reported in 2007 the reaction of isocyanides with less-electrophilic chalcones under solvent-free conditions for the formation of substituted 5-hydroxy-2*H*-pyrrol-2-ones, in excellent yields (Scheme **2**) [58].

2-Isocyanoacetates can also be used in the DBU-promoted cascade reaction with (*E*)-2-alkynylchalcones to afford tetrahydroindeno[2,1-*b*]pyrroles. The reaction occurs in an air atmosphere, under mild conditions and without loss of efficiency for a wide range of substituents (Scheme **3**) [59].



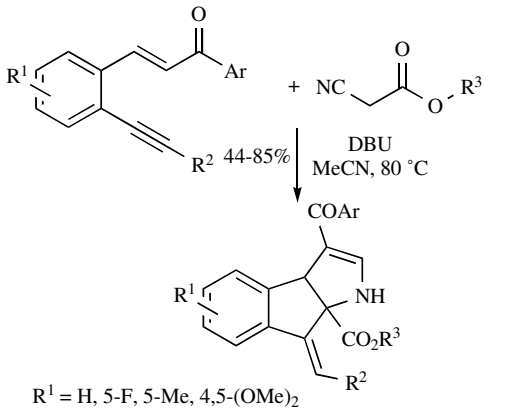
(i) solvent-free, 150 ˚C, 30 min

R = alkyl

Ar^1 = Ph, 4-$MeOC_6H_4$

Ar^2 = Ph, ClC_6H_4, FC_6H_4, MeC_6H_4, $MeOC_6H_4$

Scheme 2. Solvent-free synthesis of 5-hydroxy-2*H*-pyrrol-2-ones.



R^1 = H, 5-F, 5-Me, 4,5-$(OMe)_2$

R^2 = ^{n}Bu, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$

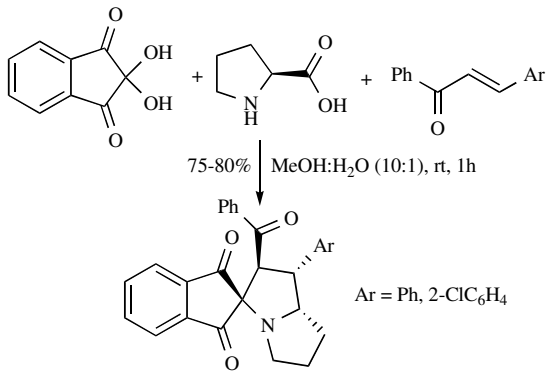
R^3 = ^{t}Bu, Me

Ar = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$

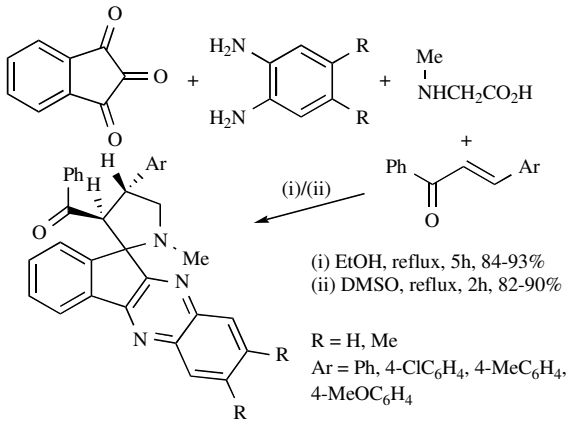
Scheme 3. DBU-mediated cascade reaction of (*E*)-2-alkynylchalcones with 2-isocyanoacetates.

Regioselective synthesis of polysubstituted pyrroles occurred through the reaction of α-azidochalcones with 1,3-dicarbonyl compounds. This microwave assisted reaction is promoted by indium trichloride in water and provides substituted pyrroles in 71-94% yield [60].

In the past few years, multicomponent intermolecular 1,3-dipolar cycloaddition reactions have earned a great interest due to their synthetic efficiency, intrinsic atom economy and simple experimental procedures [61-63]. Therefore, the 1,3-dipolar cycloaddition reaction of ninhydrin, L-proline and chalcones provided spiroindane-1,3-dione pyrrolizidines in good yields and with high regio- and stereoselectivity (Scheme **4**) [64]. Chalcone dendrimers undergo 1,3-dipolar cycloaddition reaction with sarcosine and an excess of paraformaldehyde in refluxing toluene to prepare *N*-methylpyrrolidine dendrimers [65].



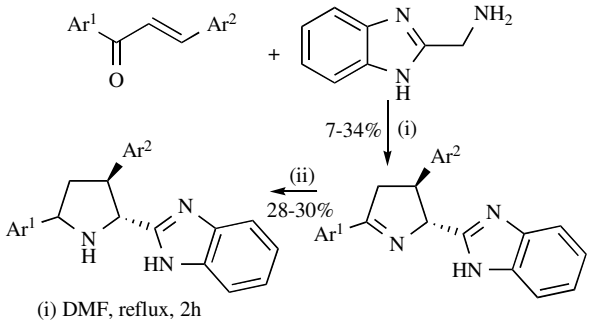
Scheme 4. 1,3-Dipolar cycloaddition reaction of ninhydrin, L-proline and chalcones.



Scheme 5. Four-component 1,3-dipolar cycloaddition reaction of ninhydrin, arylenediamines, sarcosine and chalcones.

Moemeni *et al.* used a one-pot four-component 1,3-dipolar cycloaddition reaction of ninhydrin, arylenediamines, sarcosine and chalcones to prepare highly substituted pyrrolidines in good yields and stereoselectivity (Scheme **5**) [66].

A range of polysubstituted 3,5-diaryl-4,5-dihydropyrroles can be achieved in a one-pot protocol through a Michael addition of nitroalkanes to chalcones and subsequent reductive cyclization in aqueous media [67]. The reaction of chalcones with 2-(aminomethyl)benzimidazole gave access to *trans*-3,5-diaryl-2-benzimidazol-2-yl-4,5-dihydropyrroles in moderate to good yields (Scheme **6**) [68]. Reduction of some derivatives with sodium borohydride in methanol led to the corresponding pyrrolidines.



(i) DMF, reflux, 2h

(ii) $NaBH_4$, MeOH, rt, 1.5 h

Ar^1 = Ph, 4-ClC_6H_4, 4-IC_6H_4, 4-MeC_6H_4

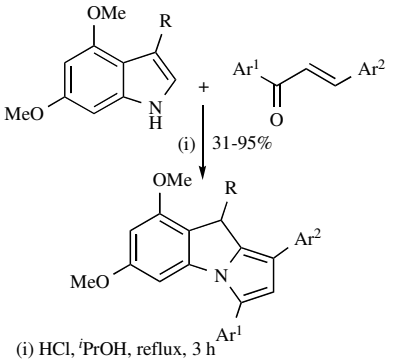
Ar^2 = Ph, 2-ClC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4

Scheme 6. Reaction of 2-(aminomethyl)benzimidazol with chalcones.

9*H*-Pyrrolo[1,2-*a*]indoles was achieved through the one-pot reaction of 3-substituted-4,6-dimethoxyindoles with chalcones in the presence of hydrochloric acid (Scheme **7**) [69].

2.1.2. Transformation of Chalcones to Indoles

The indole heterocyclic system is an important scaffold in medicinal chemistry since it is incorporated into proteins in the tryptophan residue, is the basis of drugs like indomethacin and also because it provides the skeleton of indole alkaloids. The indole nucleus possesses a wide range of biological activities being a biologically accepted pharmacophore in medicinal compounds. Anti-inflammatory [70], antifungal [71], antimicrobial [72], anticancer [73, 74], anti-HIV [75], antioxidant [76], and antiviral [77] activities, among many others, are some examples of the biological potential of indole derivatives.



(i) HCl, ^{i}PrOH, reflux, 3 h

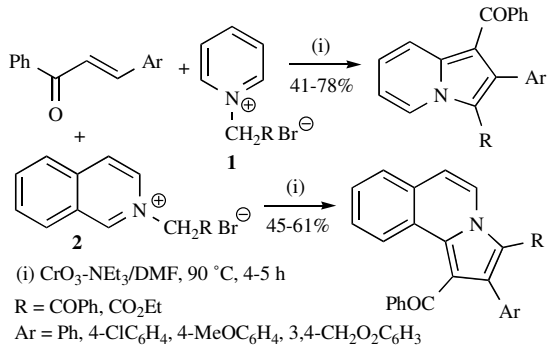
R = Me, Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$

Ar^1 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$

Ar^2 = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$

Scheme 7. Synthesis of 9*H*-pyrrolo[1,2-*a*]indoles.

There was only one report concerning the synthesis of indole-type compounds using chalcones as starting materials. In this report, 2-aryl-1-benzoylindolizine derivatives were prepared in moderate yields through CrO_3/Et_3N-promoted 1,3-dipolar cycloaddition reaction of *N*-pyridinium bromides **1** with chalcones (Scheme **8**) [78]. The use of *N*-isoquinolinium bromides **2** instead of *N*-pyridinium derivatives **1** afforded the corresponding 2-aryl-1-benzoylpyrrolo[2,1-*a*]isoquinolines (Scheme **8**) [78].



(i) CrO_3-NEt_3/DMF, 90 °C, 4-5 h

R = COPh, CO_2Et

Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 3,4-$CH_2O_2C_6H_3$

Scheme 8. CrO_3/NEt_3-promoted 1,3-dipolar cycloaddition of pyridinium *N*-ylides **1** and isoquinolinium *N*-ylides **2** with chalcones.

2.1.3. Transformation of Chalcones to Isoxazoles

As the majority of azaheterocycles, isoxazoles are associated to an extensive range of biological activities. Amongst them we can find antiviral [79], antihelmintic [80], anti-inflammatory [81], anti-convulsant [82], and anticancer activities [83]. Several reports also showed that substituted isoxazoles, *e.g.* isouron, isoxaben and isoxathion are effective and degradable pesticides [84].

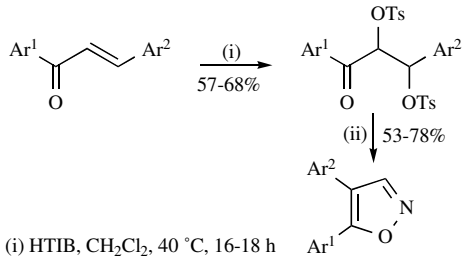
3,5-Diarylisoxazoles can be prepared through the reaction of chalcones with hydroxylamines. The formation mechanism of the isoxazole moiety involves the formation of oxime intermediates while hydrazones are formed in the case of pyrazoles. Several authors used this reaction successfully in refluxing ethanol and using NaOH [85] or KOH [86-91] as base. The reaction of chalcones with hydroxylamine hydrochloride can also be performed in the presence of NaOAc and glacial acetic acid to give 3,5-diarylisoxazoles [92, 93]. Using the same conditions, the condensation of benzimidazolyl-, benzofuranyl-, indolyl- and quinoxalinyl-type chalcones with hydroxylamine hydrochloride provided, respectively, benzimidazolyl- [94], benzofuranyl- [95], indolyl- [96] and quinoxalinyl-isoxazoles [97].

3,5-Diarylisoxazoles were also obtained in excellent yields from chalcone oximes under solvent-free conditions [98].

A few 3,4,5-trisubstituted isoxazoles were accomplished when α,β-disubstituted chalcones reacted with hydroxylamine hydrochloride in ethanol at 65-80 °C [99].

High yields of methylenebis-isoxazoles arise from the condensation of methylenebischalcones with hydroxylamine hydrochloride and NaOAc in refluxing ethanol [100].

4,5-Disubstituted isoxazoles can also be obtained in a two-step synthesis starting from the tosylation of chalcones to give the corresponding α,β-ditosylate derivatives and subsequent reaction with hydroxylamine to afford the desired isoxazoles (Scheme **9**) [101]. A similar approach involves the reaction of α,β-dibromo-chalcones with hydroxylamine hydrochloride in ethanol and using KOH as base [102-104].



(i) HTIB, CH_2Cl_2, 40 °C, 16-18 h

(ii) NH_2OH HCl, NaOAc, EtOH, reflux, 3 h

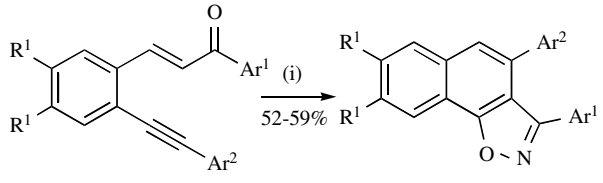
HTIB = hydroxy(tosyloxy)iodobenzene

Ar^1 = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$

Ar^2 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-thienyl, 5-methyl-2-thienyl

Scheme 9. Synthesis of 4,5-disubstituted isoxazoles from α,β-ditosylate chalcones.

An iodine-mediated tandem reaction of 2-alkynylchalcones with hydroxylamine hydrochoride gave naphtho[2,1-*d*]isoxazoles (Scheme **10**). This one-pot reaction involves an oxidative cyclocondensation followed by an electrophilic hydroarylation [105].



(i) NH_2OH·HCl, I_2, AcOH, reflux, 8 h

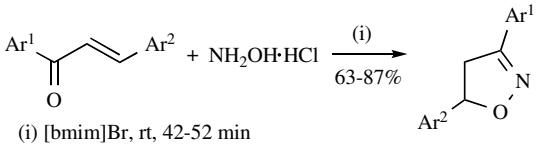
R^1 = H, MeO

Ar^1 = Ph, 4-BrC_6H_4, 4-$MeOC_6H_4$

Ar^2 = Ph, 4-$MeOC_6H_4$

Scheme 10. Iodine-promoted tandem oxidative cyclocondensation of 2-alkynylchalcones with hydroxylamine hydrochloride.

Instead of 3,5-diarylisoxazoles, a series of 3,5-diaryl-2-isoxazoline derivatives is attained from the reaction of chalcones with hydroxylamine hydrochloride with minor modifications in an appropriate solvent (usually a protic solvent such as ethanol and methanol) and using a catalytic amount of a base such as KOH [102, 106-109], NaOH [102-115] and NaOAc [116-119]. Replacing the solvent by acetic acid, a series of 2-isoxazolines arises from the reaction of hydroxylamine hydrochloride in the presence of NaOAc with chalcone-based compounds bearing pyrrole [120], methylenebisthiazolidinone [121] and benzimidazole [122] moieties. Other modifications involve the use of pyridine [123-125] or triethanolamine [126] that act as both solvent and base. Refluxing bischalcones with hydroxylamine hydrochloride in pyridine afforded bis-isoxazolines in high yields [127]. Few examples of 3,5-diaryl-2-isoxazolines were obtained when chloro-substituted chalcones reacts with hydroxylamine hydrochloride in refluxing DMF containing piperidine [128]. An ecofriendly reaction occurs efficiently in the presence of the ionic liquid butylmethylimidazolium bromide {[bmim]Br}, acting as solvent and catalyst (Scheme **11**) [123].



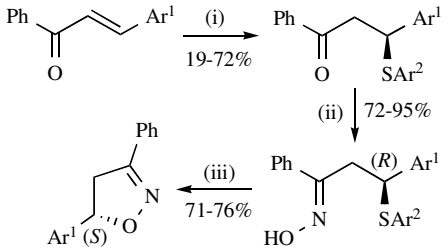
(i) [bmim]Br, rt, 42-52 min

Ar^1 = Ph, 4-BrC_6H_4, 4-MeC_6H_4

Ar^2 = Ph, 4-BrC_6H_4, 4-Cl_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-OHC_6H_4

Scheme 11. Synthesis of 3,5-diaryl-2-isoxazolines mediated by the ionic liquid [bmim]Br.

Varying the conditions, cyclocondensation of hydroxylamine hydrochloride with other chalcone-type compounds with different scaffolds such as benzo[*b*][1,4]diazepine [129], naphtho[2,1-*b*]furan [130], pyrazole [131], pyrazoline [132], indole [133-135], quinazoline [82, 136], triazinylaminophenyl [137] and benzimidazole under microwave irradiation [138] give access to several functionalized 2-isoxazolines.



(i) Ar^2SH, cinchonine Ar^1 = Ph, 4-$MeOC_6H_4$

(ii) NH_2OH, EtOH Ar^2 = Ph, 4-$MeOC_6H_4$

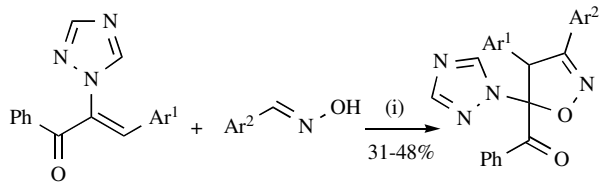
(iii) NaH, dry DMF, 70 °C, 1-1.5 h

Scheme 12. Stereospecific synthesis of chiral isoxazolines from oximes of chiral Michael adducts of thiophenols to chalcones.

Several antimicrobial nitrogen heterocycles bearing an isoxazole moiety or substituted isoxazole derivatives were also obtained from the condensation of the appropriate chalcones with hydroxylamine hydrochloride [139-143].

The stereospecific synthesis of chiral isoxazolines from oximes of chiral Michael adducts of thiophenols to chalcones was reported in 2005 by Zielinska-Błajet *et al.* [144]. The key step of this synthesis is the ring-closure reaction, which occurs by a stereospecific intramolecular S_N2-type reaction with thiophenoxide as a leaving group. The desired isoxazolines were obtained in good yields and dextrorotatory level (57-86% *ee*) which after recrystallization achieved a high enantiomeric excess (> 98% *ee*) (Scheme **12**).

1,3-Dipolar cycloaddition reaction of 1,2,4-triazol-substituted chalcones with a variety of benzaldoximes in the presence of chloramine-T gave access to the corresponding isoxazolines in moderate yields (Scheme **13**) [145].



(i) chloramine-T, MeOH, reflux, 7 h

Ar^1 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$

Ar^2 = Ph, 4-ClC_6H_4, 4-MeC_6H_4

Scheme 13. Synthesis of 1,2,4-triazole-substituted 2-isoxazolines.

A liquid-phase synthesis of 3,4,5-trisubstituted isoxazolines using poly(ethyleneglycol) (PEG) as support was reported in 2008 [146]. This methodology involves the 1,3-dipolar cycloaddition reaction of the *in situ* generated soluble-polymer-supported nitrile oxide with chalcones to afford the polymer-supported isoxazolines, which after cleavage with sodium methoxide provided the substituted isoxazoles (Scheme **14**).

Some improvements in yields and reaction time were achieved through microwave assisted synthesis. 2-Isoxazolines were obtained with only a few minutes of irradiation in the reaction of chalcones with hydroxylamine hydrochloride [147-152]. Kidwai *et al.* used K_2CO_3 as solid support in the cyclization of the Michael adducts from the reaction of hydroxylamine with chalcones [153]. Similar reactions are carried out in the presence of basic alumina as solid support and under microwave irradiation [124, 154].

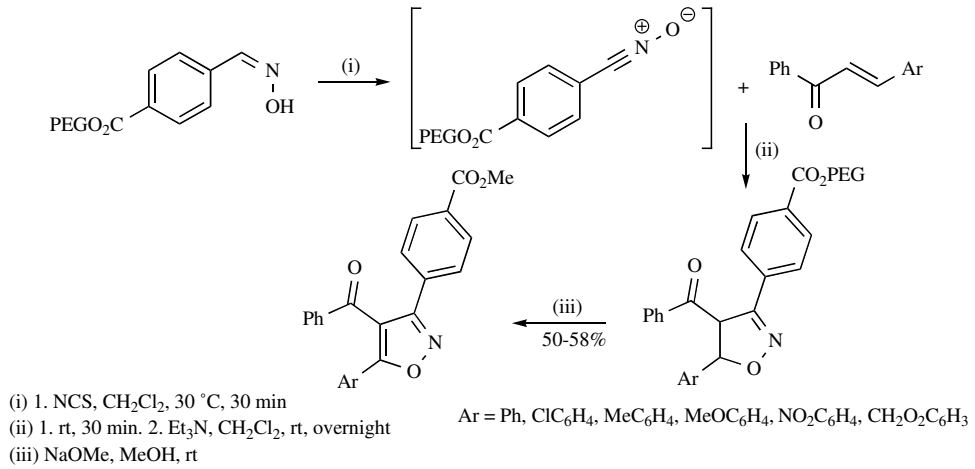
Not only hydroxylamines are used to synthesize isoxazoles. An unusual nitrone (*N*-hydroxy-2-pyridone **3**) underwent a [3+2] cycloaddition reaction with the parent chalcone in the presence of iodobenzene diacetate to provide two 2,3,4,5-tetrasubstituted isoxazolidine isomers (Scheme **15**). The regiochemical control of the reaction is consistent with the addition of the nitrone oxygen to the β-carbon of the chalcone [155].

1,3-Dipolar cycloaddition reaction of chalcones with *N*-arylaldonitrones afforded two diastereomeric isoxazolidine cycloadducts **4a,b**. Replacing the *N*-aryl group to an *N*-methyl group, three isoxazolidine isomers **4a-c** were isolated (Scheme **16**) [156].

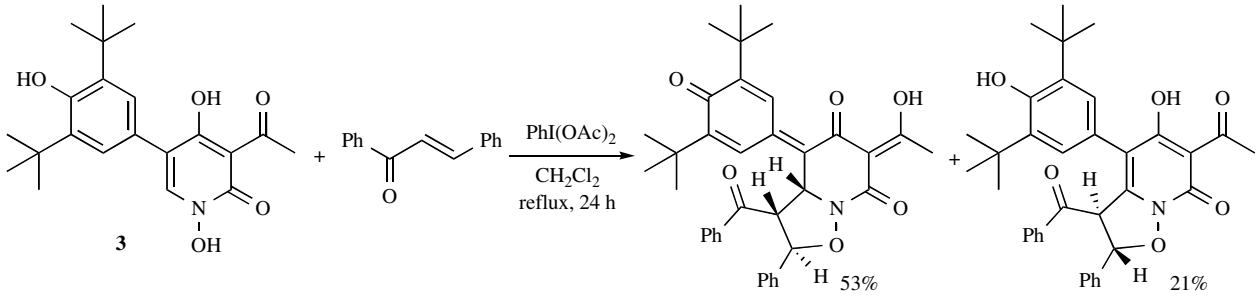
Four isomers were generated in the reaction of chalcone with *C*-ethoxycarbonyl-*N*-methylnitrone. Using aluminum tris(2,6-diphenylphenoxide) (ATPH) as catalyst increased the yields obtained but the low regio- and stereoselectivities remains [157]. The *C*-diethoxyphosphoryl-*N*-methylnitrone **5** was used by Piotrowska *et al.* in the 1,3-dipolar cycloaddition reaction with chalcones to obtain a new series of four isomeric isoxazolidin-3-yl-3-phosphonates (Scheme **17**). Treating these cycloadducts with trimethylsilyl bromide provided the corresponding phosphonic acids in good to excellent yields [158].

2.1.4. Transformation of Chalcones to Imidazoles

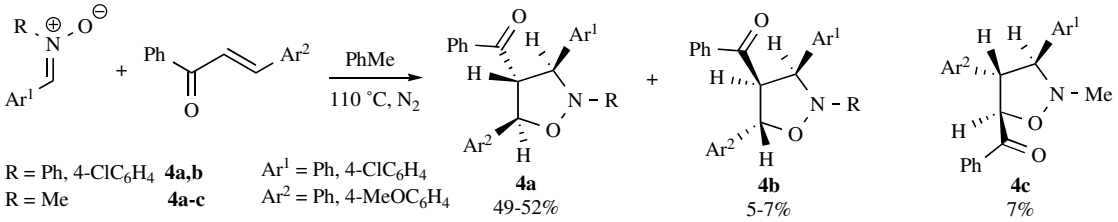
Imidazole and its derivatives play an important role in biological systems, particularly in enzymes, acting as both proton donors and/or acceptors, as coordination ligands, and as the base of charge-



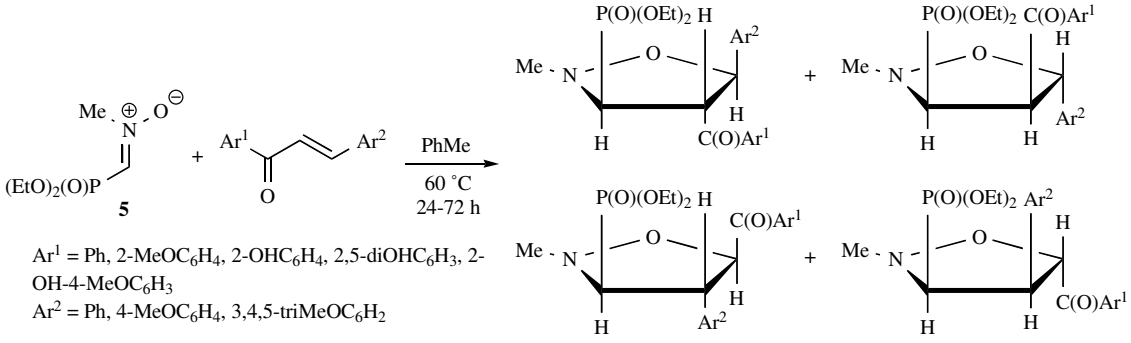
Scheme 14. PEG-supported synthesis of 3,4,5-trisubstituted isoxazolines.



Scheme 15. 1,3-Dipolar cycloaddition reaction of chalcones with nitrone **3**.



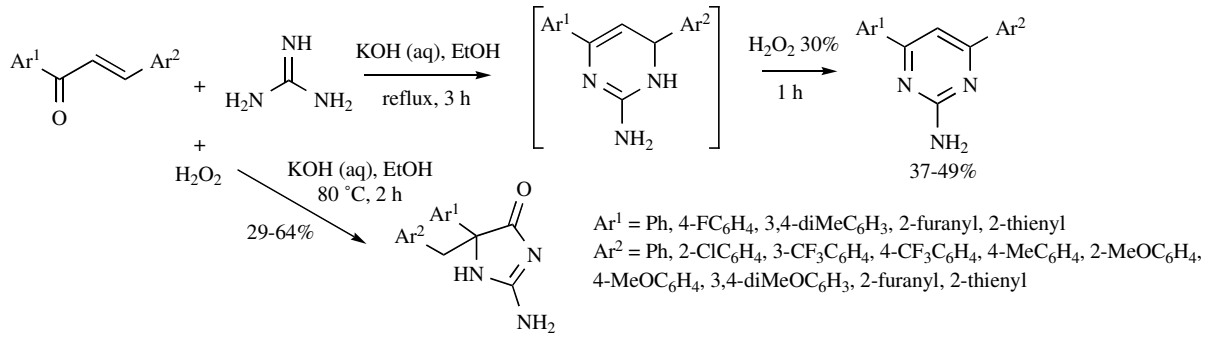
Scheme 16. 1,3-Dipolar cycloaddition reaction of chalcones with *C*,*N*-disubstituted aldonitrones.



Scheme 17. 1,3-Dipolar cycloaddition reaction of chalcones with *C*-diethoxyphosphoryl-*N*-methyl nitrone **5**.

transfer processes [159]. It was also reported other biological effects such as antitumor [160-162], antimalarial [163], and antifungal activities [164], and tubulin polymerization inhibitors [165, 166] of certain of these derivatives.

There are only a couple of references involving the synthesis of imidazoles from chalcones. In 2003 Varga *et al.* studied the reaction of chalcones with guanidine in the presence of an oxidizing agent in order to establish a new route towards the synthesis of 4,6-diaryl-2-aminopyrimidine derivatives [167]. The authors concluded that depending in the order of reagents addition could obtained either 4,6-diarylpyrimidin-2-ylamine or 2-amino-5,5-disubstituted-3,5-dihydroimidazol-4-ones. When the addition of reagents and the oxidizing agent was made at the same time, 2-amino-5,5-disubstituted-3,5-dihydroimidazol-4-ones were obtained in moderate yields and their structures confirmed by several NMR techniques and X-ray analysis (Scheme **18**) [167].

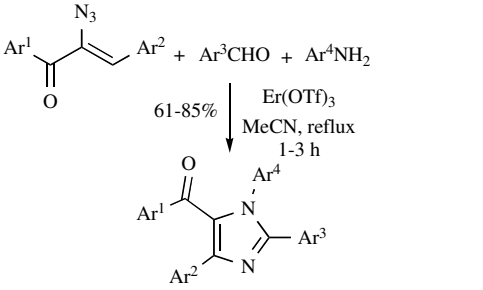


Scheme 18. Reaction of chalcones with guanidine in the presence of an oxidizing agent.

Recently, excellent yields of highly substituted imidazoles were achieved from the multicomponent reaction of α-azidochalcones, aryl-aldehydes and anilines mediated by erbium triflate (Scheme **19**) [168].

2.1.5. Transformation of Chalcones to Pyrazoles

The pyrazole nucleus is present in many bioactive compounds exhibiting a wide range of chemotherapeutic potential. It has been well-documented that some pyrazoles possess antileukemic [169, 170], antitumor [171], and antiproliferative [172, 173] properties, many of them associated to the inhibition of enzymes involved in cell division [174, 175]. Moreover, the introduction of a pyrazole ring between the two aryl rings of chalcones played a remarkable increase in the cytotoxic activity against a series of human cancer cell lines [176].

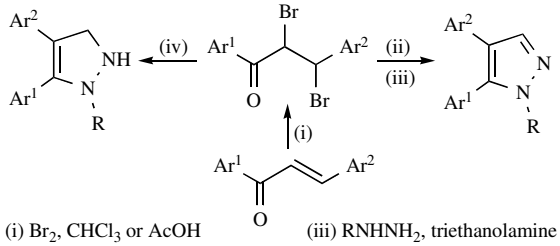


Scheme 19. Synthesis of highly substituted imidazoles from the multicomponent reaction of α-azidochalcones, aryl-aldehydes and anilines mediated by erbium triflate.

The reaction of chalcones with dipolar molecules or 1,2-binucleophiles is one of the most important practical pathways towards the synthesis of pyrazole derivatives. Chalcones usually have a high polar double bond which gives them the ability to react with dipolar molecules (reaction with diazoalkanes). On the other hand, reaction of chalcones with 1,2-binucleophilic compounds, *e.g.* hydrazine derivatives, is the most used and well-known approach for the synthesis of pyrazoles. These one-step or two-steps transformations are usually carried under acidic conditions, being ethanol or acetic acid the most common solvents [177-179]. Few derivatives were prepared through the one-pot reactions of chalcones with phenylhydrazine in the presence of iodine [180] or tetrakispyridinecobalt(I) dichromate (TPCD) [181] in acetic acid and with hydrazine hydrate in the presence of iodine in DMSO [182]. Other examples for the one-pot synthesis of pyrazoles under neutral conditions were the condensation of hydrazine hydrate with sugar-chalcones [183] or hydrazine hydrate / phenylhydrazine with α,β-disubstituted chalcones [99], in refluxing ethanol. Faidallah *et al.* reported the synthesis of 3,5-disubstituted pyrazoles in a three-step sequence: condensation of chalcones with *p*-sulfamylphenylhydrazine hydrochloride in the presence of NaOAc gave the corresponding hydrazones, subsequent addition of a few drops of hydrochloric acid in ethanol at reflux provided pyrazolines which after oxidation with aqueous bromine afforded the target pyrazoles [184]. Although these methods were reviewed by Chebanov in a book published in 2008, we also have considered here the references that appear since the beginning of the 21st century to be coherent with all the others families of heterocyclic compounds.

A highly efficient and environmentally friendly one-pot method was recently developed for the synthesis of 3,5-diphenyl-1*H*-pyrazoles under mechanochemical ball-milling conditions. The advantages of this reaction of chalcones with hydrazine hydrate are the short reaction time, high efficiency, no separation of the *in situ* generated 2-pyrazoline intermediates, and the use of cheap sodium persulfate as the oxidant, together with a very simple work-up procedure [185].

Chalcones dibromides, obtained from the treatment of chalcones with bromine, afforded pyrazoles by the reaction with benzoylhydrazines [186] and phenylhydrazines [115] in dry pyridine or hydrazines in triethanolamine [187], and 2-pyrazolines by the reaction with phenylhydrazine or isonicotinic acid hydrazide in DMF (Scheme **20**) [188]. A series of bispyrazoles can be accomplished through the reaction of bischalcones tetrabromo derivatives with hydrazine hydrate in refluxing methanol [189].

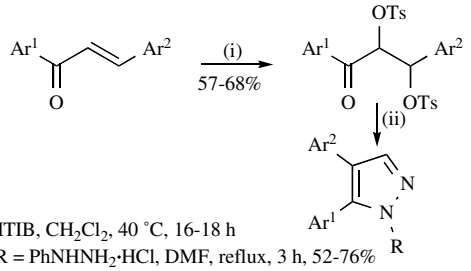


Scheme 20. Chalcone dibromides as precursors of pyrazoles and 2-pyrazolines.

Following the previous reports concerning the reaction of dibromochalcones towards the synthesis of pyrazoles, Prakash *et al.* reported a new synthetic route starting from α,β-ditosylate chalcones. The reaction with phenylhydrazine hydrochloride, semicarbazide hydrochloride and thiosemicarbazide afforded the corre-

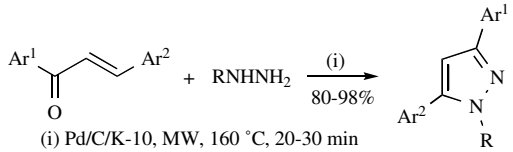
sponding 1,4,5-trisubstituted pyrazoles in moderate to good yields (Scheme **21**) [190]. At the same time Aggarwal and co-workers used iodobenzene diacetate for the oxidation of the intermediates *N*-substituted hydrazones from chalcones to afford 1,3,5-trisubstituted pyrazoles under mild conditions in high yields [191].

The one-pot cycloaddition reaction of hydrazine hydrate with chalcone-epoxides followed by dehydration is an efficient and convenient procedure for the preparation of 3,5-diaryl-1*H*-pyrazoles [192, 193]. A similar two-steps approach involved the isolation of 4-hydroxypyrazolines [85, 176]. An ecofriendly synthesis of 1,3,5-triarylpyrazoles occurs through the one-pot addition-cyclocondensation reaction of chalcones with arylhydrazines in the ionic liquid ([bmim][PF_6]) promoted by Cu(OTf)$_2$ in good to high yields (71-84%) [194].



(i) HTIB, CH_2Cl_2, 40 °C, 16-18 h
(ii) R = $PhNHNH_2$·HCl, DMF, reflux, 3 h, 52-76%
R = $NH_2CONHNH_2$·HCl, NaOAc, EtOH, reflux, 2-3 h, 53-65%
R = $NH_2CSNHNH_2$, EtOH, reflux, 2-3 h, 59-65%
Ar^1 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$
Ar^2 = Ph, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-thienyl, 3-methyl-2-thienyl, 5-methyl-2-thienyl

Scheme 21. Chalcone ditosylates as precursors of pyrazoles.



(i) Pd/C/K-10, MW, 160 °C, 20-30 min
R = Me, Ph, 3-$CF_3C_6H_4$, 4-$NO_2C_6H_4$
Ar^1 = Ph, 4-FC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$
Ar^2 = Ph, 4-FC_6H_4

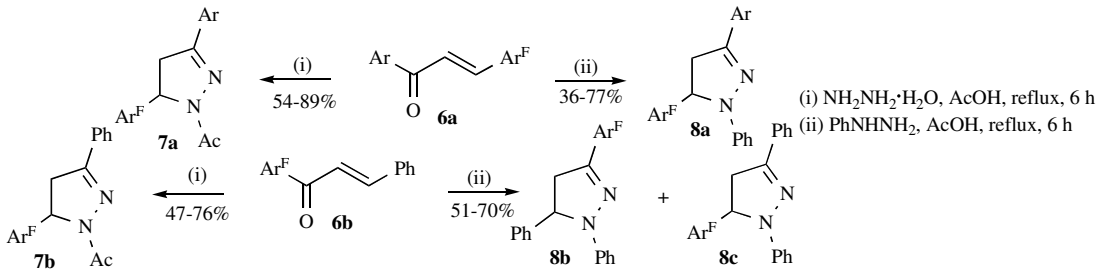
Scheme 22. Microwave-assisted one-pot synthesis of pyrazoles catalyzed by Pd/C/K-10 montmorillonite.

Under microwave irradiation, a range of 3,5-disubstitued pyrazoles was prepared when chalcones react with hydrazine hydrate [151, 195]. Better yields and shorter reaction times were observed when compared with classic heating methods. A similar approach was developed for the reaction with p-toluenesulfonylhydrazide in DMF [196]. Landge *et al.* reported a good example of a one-pot solvent-free microwave assisted synthesis of pyrazoles using a bifunctional noble-metal/solid-acid catalyst, Pd/C/K-10 montmorillonite (Scheme **22**). The reaction of chalcones with substituted hydrazines provided 1,3,5-trisubstituted pyrazoles in good to excellent yields with high selectivity (85-100%). In some cases, small amounts of 2-pyrazolines were also isolated [197].

The most common approach for the synthesis of 2-pyrazolines starting from chalcones involves the reaction with hydrazines in refluxing ethanol [93, 113, 198-209] or methanol [113, 125, 133, 210]. Under these conditions, a large variety of substituents can be found in the synthesis of functionalized 2-pyrazolines such as benzodioxane [211], benzofuran [118, 212, 213], coumarin [214], indenoquinoxaline [215], naphthalene [125], quinoline [216, 217], 1,3-thiazole [218] and thiophene [219-221]. The introduction of bases such as pyridine [122, 222-224], piperidine [129, 225, 226], triethylamine [227, 228], KOH [107], NaOH [229-241] and NaOAc [242] or acids as formic [243, 244], acetic [82, 108, 116, 131, 208, 243, 245-248], hydrochloric [249, 250] and sulfuric [130] led to other functionalized derivatives. Alternative solvents for this type of reaction are acetic acid [106, 251-272], formic acid [251, 252, 273], pyridine [274, 275], acetic acid/pyridine [276], THF [22], triethanolamine [126], dioxane [137, 277, 278] and propan-1-ol [279].

Smuilovich *et al.* studied the reaction of polyfluorinated chalcones with hydrazines in boiling acetic acid. Cycloaddition of hydrazine hydrate to chalcones 6a and 6b provided polyfluorinated 1-acetyl-3,5-diarylpyrazolines **7a** and **7b**. Different results were obtained from the reaction with phenylhydrazine: chalcones **6a** gave the expected triarylpyrazolines **8a**, while chalcones **6b** led to an equimolar amount of two regioisomeric pyrazolines at the positions C-3 and C-5 **8b** and **8c** (Scheme **23**) [280]. Using the same conditions, a series of pyrazolyl-2-pyrazolines arise from the reaction of chromone-derived chalcones with an excess of phenylhydrazine. Here, both the chromone and the α,β-unsaturated ketone moieties are implicated in the attack of phenylhydrazine to afford respectively, the pyrazole and pyrazoline units [281]. A wide variety of chalcones afforded 1-acetyl- or 1-phenyl-3,5-diaryl-2-pyrazolines from the reaction with hydrazine hydrate or phenylhydrazine in refluxing acetic acid, respectively [274, 282-285]. 1-Chloroacetyl- and 1-propionyl-3,5-diaryl-2-pyrazolines arise from the reaction of chalcones with hydrazine hydrate in chloroacetic acid [286] and propionic acid [274, 285], respectively. The condensation of a range of chalcones with several acid hydrazides provided 1-acyl-3,5-diaryl-2-pyrazolines, using acetic acid as solvent [287, 288]. The synthesis of 3,5-diaryl-1-(5-tetrazolyl)-2-pyrazolines can be achieved through two general routes: reaction of chalcones with 1,5-diaminotetrazole in DMF at 150 °C or with 5-tetrazolohydrazine in refluxing ethanol [289].

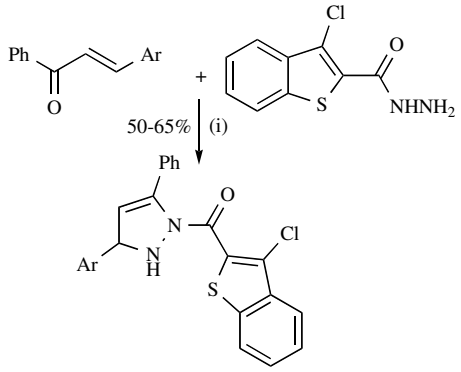
The introduction of substituents in the hydrazine molecule can change the most reactive nitrogen atom, and thus give a different



6a, 7**a**, **8a**, **8b**: Ar = Ph, Ar^F = C_6F_5, C_6F_4OPh, $C_6H_4N(CH_2)_5$; Ar = Ar^F = C_6F_5, C_6F_4OPh, $C_6F_4N(CH_2)_5$
6b, **7b**, **8c**: Ar^F = C_6F_5, C_6F_4OPh, $C_6F_4N(CH_2)_5$

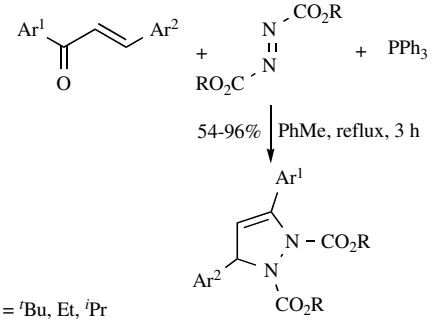
Scheme 23. Synthesis of polyfluorinated 3,5-diarylpyrazolines.

pyrazole isomer as reported by Kumara *et al.* [290]. The reaction of 3-chlorobenzo[*b*]thiophene-2-carboxyhydrazide with chalcones using a catalytic amount of acetic acid in 1,4-dioxane afforded a less common pyrazoline isomer (Scheme **24**). A similar approach uses naphtha[2,1-*b*]furan-2-carboxyhydrazide [291].



(i) AcOH, 1,4-dioxane, reflux, 26 h
Ar = Ph, 4-ClC_6H_4, 4-$NO_2C_6H_4$

Scheme 24. Reaction of chalcones with 3-chloro-benzo[*b*]thiophene-2-carboxyhydrazide.



R = ^{t}Bu, Et, ^{i}Pr
Ar^1 = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$
Ar^2 = Ph, 4-$CF_3C_6H_4$, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$, 9-antryl, 2-furyl, naphthyl

Scheme 25. Reaction of chalcones with "Huisgen zwitterions".

The reaction of chalcones with "Huisgen zwitterions", derived from dialkyl azodicarboxylates and triphenylphosphane, provided a series of highly functionalized 2-pyrazolines (Scheme **25**) [292].

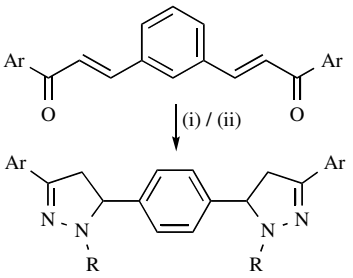
Bispyrazolines have been achieved through the cycloaddition of bischalcones with hydrazine hydrate in acetic/formic acids [293, 294], methanol [189] or DMF at reflux [295] or with thiosemicarbazides under basic conditions [296] (Scheme **26**).

Numerous biologically active *N*-unsubstituted or *N*-substituted 2-pyrazolines have been prepared from the reaction of chalcones with hydrazine hydrate or hydrazine derivatives, respectively [136, 143, 297-306].

Similar to the stereospecific synthesis of chiral isoxazolines from oximes of chiral Michael adducts of thiophenols to chalcones, Zielinska-Błajet *et al.* extended their study to the reaction with the *N*-arylhydrazones of the Michael adduct to afford chiral 2-pyrazolines [144].

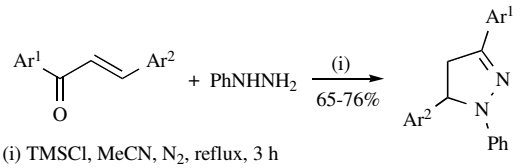
In 2008 Xie *et al.* reported a novel synthesis of substituted 2-pyrazolines using chlorotrimethylsilane (TMSCl) as a Lewis acid to promote the cyclization reaction of chalcones with phenylhydrazine in good yields (Scheme **27**) [307].

1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) catalyzed the reaction of chalcones with a range of acylhydrazines giving access to 3,5-diaryl-2-pyrazolines in good yields. The reaction proceeds through a regioselective alkylation of the secondary amine moiety of hydrazines and the products possess an electron-withdrawing group at N-1 (Scheme **28**) [308].



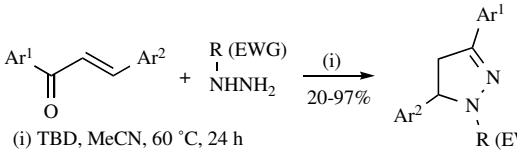
(i) Ar = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 2,4-ClC_6H_3, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$; R = NH_2NH_2, DMF, reflux, 5 h
(ii) Ar = Ph; R = NH_2NHCSN-substituted, NaOH, EtOH, reflux, 72 h

Scheme 26. Synthesis of bispyrazolines from bischalcones.



(i) TMSCl, MeCN, N_2, reflux, 3 h
Ar^1 = Ph, 4-$MeOC_6H_4$, 2-naphthyl
Ar^2 = Ph, 4-BrC_6H_4, 2-ClC_6H_4, 2-MeC_6H_4, 3-MeC_6H_4, 4-$MeOC_6H_4$, 2,3-di$MeOC_6H_3$, 4-^{i}PrOC_6H_4

Scheme 27. Synthesis of 1,3,5-trisubstituted 2-pyrazolines mediated by chlorotrimethylsilane.



(i) TBD, MeCN, 60 °C, 24 h
R (EWG) = COMe, COPh, $CO_2{}^t$Bu, CO-2-furyl, CO-4-Pyr, CONHPh, $CSNH_2$, Ts
Ar^1 = Ph, 4-FC_6H_4, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-thienyl
Ar^2 = Ph, 4-ClC_6H_4, 2-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2OC_6H_4$, 2-thienyl

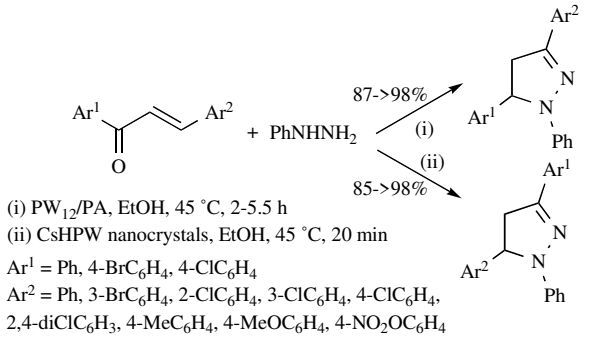
Scheme 28. Regioselective addition of acylhydrazines to chalcones promoted by TBD.

1,3,5-Triaryl-2-pyrazolines were synthesized in high yields from chalcones and phenylhydrazine, using an heterogeneous catalyst constructed from polyoxometalate ($H_3PW_{12}O_{40}$) and poly(amidoamine) (PW_{12}/PA) [309]. One year later, the same author reported this reaction using another heterogeneous catalyst based on CsHPW ($Cs_{2.5}H_{0.5}PW_{12}O_{40}$) nanocrystals [310]. The reaction afforded two different isomers, depending on the catalyst used (Scheme **29**).

The enantioselective synthesis of 3,5-diaryl-2-substituted-2-pyrazolines was achieved through an aza-Michael-cyclocondensation cascade addition of *N*-Boc hydrazine or (thio)semicarbazides to chalcones, under phase transfer organocatalytic conditions (Scheme **30**) [311].

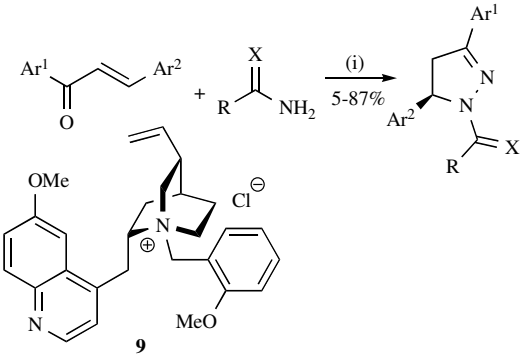
Substituted 2-pyrazolines were achieved when chalcones react with phenylhydrazine using an imidazolium-based ionic liquid {1,2[bis-(3'-methyl-imidazolium hydrogen sulfate)]ethane} that acts as both solvent and catalyst [312]. A novel one-pot synthesis of pyrazoles and pyrazolines was reported in 2012, starting from aryl halides, styrenes, carbon monoxide and hydrazines. The reaction

involves the palladium-catalysed carbonylative vinylation of aryl halides to give the corresponding chalcones (Scheme **31a**) [313], which undergo *in situ* cyclocondensation with hydrazines to afford 2-pyrazolines (Scheme **31b**). Further oxidation with DDQ at room temperature for 2 hours provided pyrazoles in moderate overall yields for the three-step sequence [314].



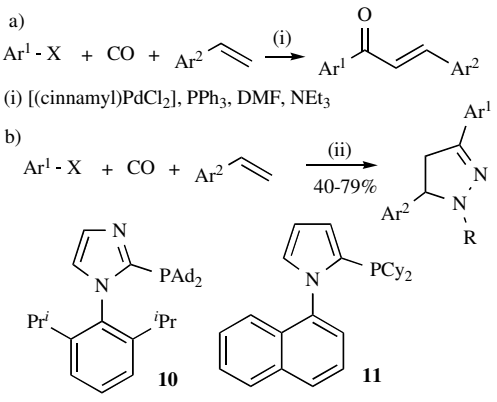
(i) PW_{12}/PA, EtOH, 45 ˚C, 2-5.5 h
(ii) CsHPW nanocrystals, EtOH, 45 ˚C, 20 min
Ar^1 = Ph, 4-BrC_6H_4, 4-ClC_6H_4
Ar^2 = Ph, 3-BrC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2,4-diClC_6H_3, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2OC_6H_4$

Scheme 29. Synthesis of 1,3,5-triaryl-2-pyrazolines using heterogeneous catalysts.



(i) **9**, Cs_2CO_3, THF, 0 ˚C, 24 h
Ar^1 = Ar^2 = Ph, R/X = PhNH/O, NH_2/S, O^{t}Bu/O
Ar^1 = 4-$OTHPC_6H_4$, Ar^2 = 2-ClC_6H_4, R/X = O^{t}Bu/O

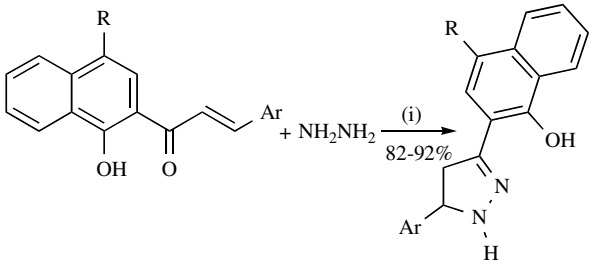
Scheme 30. Enantioselective synthesis of 3,5-diaryl-2-pyrazolines under phase transfer organocatalytic conditions.



(ii) 1. [(cinnamyl)$PdCl_2$], **10** or **11**, Et_3N, 100-120 ˚C, 20 h.
2. $RNHNH_2$, rt, 1 h
X = Br, I
R = Me, Bn, CH_2CF_3
Ar^1 = Ph, 4-BrC_6H_4, 4-^{t}BuC_6H_4, 4-ClC_6H_4, 4-EtC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 3,5-diMeC_6H_3, 4-$MeOC_6H_4$, 3-thienyl
Ar^2 = Ph, 4-^{t}BuC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$

Scheme 31. One-pot synthesis of 3,5-diaryl-2-pyrazolines starting from aryl halides, styrenes, carbon monoxide and hydrazines.

The synthesis of 2-pyrazolines by the reaction of chalcones with hydrazines generally occurs in good yields. However, the constant seek for new mild and ecofriendly processes are still on. Thus, a green and efficient protocol for the synthesis of 3,5-disubstituted 2-pyrazolines was achieved by the reaction of chalcones with hydrazine hydrate under irradiation with tungsten light. The reaction occurs with no need of catalyst and in a short reaction time giving quantitative yields of the 2-pyrazolines (Scheme **32**) [315].

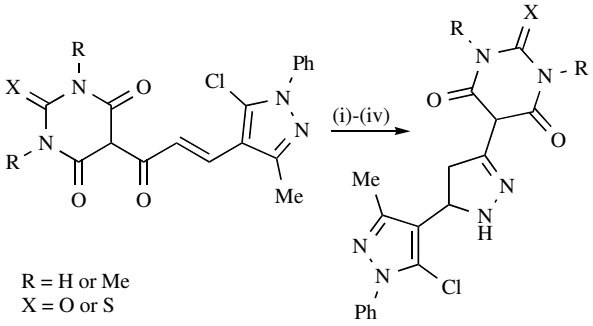


(i) AcOH, 2-methoxyethanol, tungsten light (100 W), 25-32 min
R = H, Br, I
Ar = 3-Br-4,5-di$MeOC_6H_2$, 4-ClC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$

Scheme 32. Synthesis of 3,5-disubstituted 2-pyrazolines using irradiation of a tungsten light.

Poly(ethyleneglycol) (PEG)-400 was used as an alternative solvent in the synthesis of 1-thiazolyl-2-pyrazoline derivatives starting from 4-(4'-chlorophenyl)-2-hydrazinothiazole and chalcone-type compounds. The reaction occurred in the presence of NaOH at 80 °C, in excellent yields [316]. Using the same solvent, a series of 2-pyrazoline derivatives containing an imidazole moiety was synthetized by the treatment of chalcones with hydrazine hydrate and phenylhydrazine [317].

Some authors reported the synthesis of 2-pyrazolines starting from chalcones and hydrazines using microwave assisted reactions [318-325] and in some cases, even in solvent-free conditions [326, 327]. Several improvements were also achieved under microwave irradiation in the reaction of hydrazines with chalcones containing indole [328, 329], pyrazole [330], quinolone [331] and benzimidazole [332] moieties. The synthesis of pyrazolyl-2-pyrazolines occurred under solvent-free conditions in the absence of any acidic or basic catalyst [333]. Comparative studies indicate that a reduction in the time of reaction and better yields were accomplished (Scheme **33**).

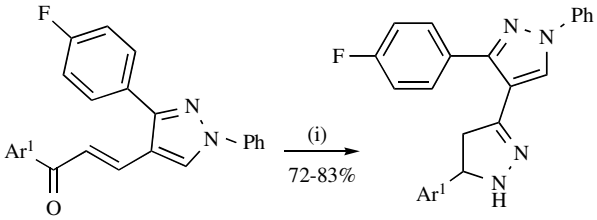


R = H or Me
X = O or S
(i) NH_2NH_2, EtOH, pyridine, reflux, 35 min-14 h, 66-78%
(ii) NH_2NH_2, MeOH, piperidine, reflux, 25 min-142h, 64-73%
(iii) NH_2NH_2, AcOH, NaOAc, reflux, 45 min-20 h, 62-76%
(iv) NH_2NH_2, 80 ˚C, 5-20 min, 82-91%

Scheme 33. Synthesis of pyrazolyl-2-pyrazolines using conventional heating or thermal solvent-free heating.

Sharma *et al*. synthetized substituted 2-pyrazolines from the reaction of chalcones with hydrazine hydrate or phenylhydrazine using green techniques: solvent-free conditions, grindstone method and microwave irradiation [334]. Other grindstone approach [335] and the use of solid supports such as basic alumina under microwave irradiation [154, 336] and K_2CO_3 [153] provided the target 2-pyrazolines in high yields in a few minutes instead of few hours regarding the case of thermal activation.

Ultrasound irradiation can also be used and presents similar advantages to microwave irradiation. Good yields, shorter reaction times and mild conditions were generally obtained when compared with conventional methods [337]. Good yields were achieved in the reaction of chalcones with hydrazines using this green technique [338-340]. A different isomer was obtained when pyrazole-derived chalcones react with hydrazine hydrate in the presence of acetic acid in ethanol, under ultrasonic irradiation (Scheme **34**) [341].



(i) $NH_2NH_2{\cdot}H_2O$, ultrasound, AcOH, EtOH, rt, 10-15 min
Ar^1 = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4

Scheme 34. Synthesis of 3,5-disubstituted 2-pyrazolines under ultrasound irradiation.

A totally different approach for the synthesis of 3,4-disubstituted 2-pyrazolines consisted in the reaction of chromone-derived chalcones with diazomethane. This 1,3-dipolar cycloaddition reaction is carried out in an equimolar mixture of chloromethane and diethyl ether at 0 °C to provide 3-aroyl-4-(3-chromonyl)-2-pyrazolines in good yields (Scheme **35**) [342].

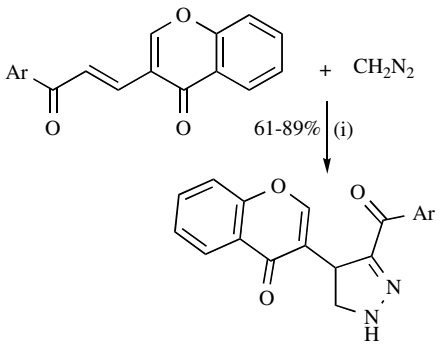
The diastereoselective 1,3-dipolar cycloaddition reaction of trifluoromethylated *N*-monosubstituted phenylhydrazone with chalcones were conditions-controlled: using triflic acid as catalyst at room temperature afforded pyrazolidines while in the presence of the catalytic system copper(II) triflate in trifilic acid, a range of 2-pyrazolines were obtained (Scheme **36**) [343].

2.1.6. Transformation of Chalcones to Indazoles

Indazole moiety is rather scarce in natural products, and maybe for this reason there are limited number of publications on indazole chemistry [344]. However, indazole derivatives were extensively studied as bioactive compounds, such as anti-aggregator and vasorelaxant activity by NO release, increase of cGMP levels and anticancer effects, antimicrobial and antiparasitic properties, among others. Recently, the research and development in the medicinal chemistry of these systems have produced compounds with contraceptive activities for men, for the treatment of osteoporosis, inflammatory disorders and neurodegenerative diseases [345].

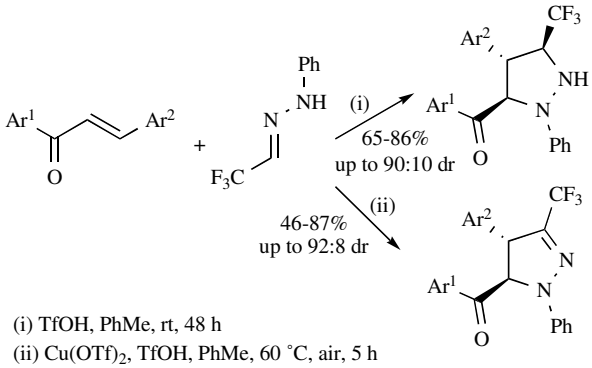
Michael addition of ethyl acetoacetate to chalcones in the presence of base gave the corresponding cyclohexenone derivatives, after internal Claisen condensation. Further treatment with hydrazine hydrate can convert these intermediates into the corresponding 2,3,4,5-tetrahydro-1*H*-indazol-3-ones (Scheme **37**) [346-350].

Under the same conditions, microwave irradiation was used to synthesize indazole derivatives. A wide range of 2,3,4,5-tetrahydro-1*H*-indazol-3-ones were prepared when 2'-hydroxychalcones reacted with ethyl acetoacetate in the presence of either K_2CO_3 in acetone or under solvent-free conditions using basic alumina and subsequent condensation with hydrazine hydrate [351]. Starting from benzimidazolylchalcones a series of 2,3,4,5-tetrahydro-1*H*-indazol-3-ones were obtained [352] while with typical chalcones it were isolated 4,5-dihydro-2*H*-indazol-3-ols [353] (Scheme **38**). The same good yields that the conventional heating methods or even better were accomplished in a shorter reaction time.



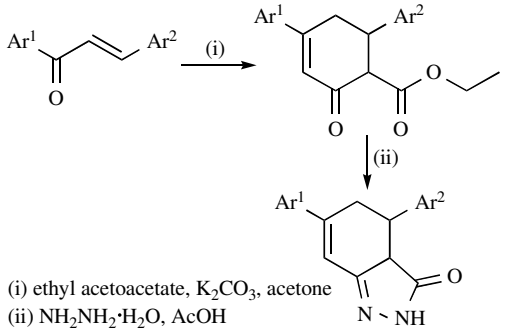
(i) CH_3Cl/diethyl ether (1:1), 0 °C, 48 h
Ar = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$

Scheme 35. Synthesis of 3,4-disubstituted 2-pyrazolines starting from chromone-derived chalcones and diazomethane.



(i) TfOH, PhMe, rt, 48 h
(ii) $Cu(OTf)_2$, TfOH, PhMe, 60 °C, air, 5 h
Ar^1 = Ph, 4-BrC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-furyl, 2-thienyl
Ar^2 = Ph, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 4-ClC_6H_4, 2-FC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-furyl, 2-thienyl

Scheme 36. Diastereoselective synthesis of pyrazolidines and 2-pyrazolines from the reaction of trifluoromethylated *N*-monosubstituted phenylhydrazone with chalcones.

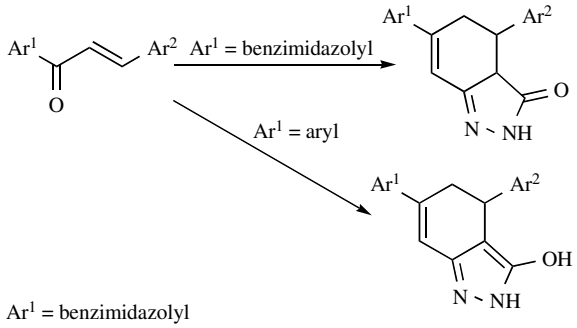


(i) ethyl acetoacetate, K_2CO_3, acetone
(ii) $NH_2NH_2{\cdot}H_2O$, AcOH

Scheme 37. Synthesis of 2,3,4,5-tetrahydro-1*H*-indazol-3-ones from chalcones.

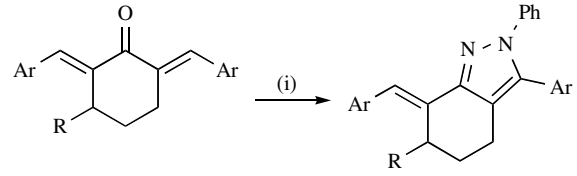
Bischalcones, obtained from the reaction of benzaldehydes with cyclohexanones, can react directly with phenylhydrazine in the presence of pyridine to yield 2,3-diaryl-7-benzylidene-4,5,6,7-tetrahydro-2*H*-indazoles (Scheme **39**) [354].

A new tandem approach for the synthesis of benzindazoles from *o*-alkynylarene chalcones and hydrazines has appeared. This method involves an iodine-promoted tandem oxidative cyclocondensation to provide *o*-alkynylarylpyrazoles which after electrophilic hydroarylation yielded benzo[*g*]indazoles (Scheme **40**) [105].



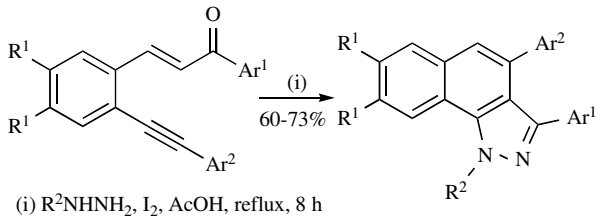
Ar^1 = benzimidazolyl
Classical conditions: 1. ethyl acetoacetate, piperidine, basic Al_2O_3, EtOH, reflux, 5-7 h; 2. $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 5-7 h.
MW: 1. ethyl acetoacetate, piperidine, basic Al_2O_3, MW, 3-5 min; 2. $NH_2NH_2{\cdot}H_2O$, MW, 4-6 min.
Ar^1 = aryl
Classical conditions: 1. ethyl acetoacetate, K_2CO_3, acetone, rt, 5 h; 2. $NH_2NH_2{\cdot}H_2O$, AcOH, EtOH, reflux, 6 h.
MW: 1. ethyl acetoacetate, K_2CO_3, silica, MW, 6-8 mim; 2. $NH_2NH_2{\cdot}H_2O$, AcOH, EtOH, MW, 3 min.

Scheme 38. Synthesis of 2,3,4,5-tetrahydro-1*H*-indazol-3-ones or 4,5-dihydro-2*H*-indazol-3-ols starting from chalcone derivatives.



(i) $PhNHNH_2$, EtOH, pyridine, reflux, 3 h
R = H, Me
Ar = Ph, $CF_3C_6H_4$, ClC_6H_4, FC_6H_4, MeC_6H_4, $MeOC_6H_4$

Scheme 39. Synthesis of 2,3-diaryl-7-benzylidene-4,5,6,7-tetrahydro-2*H*-indazoles from bischalcones.

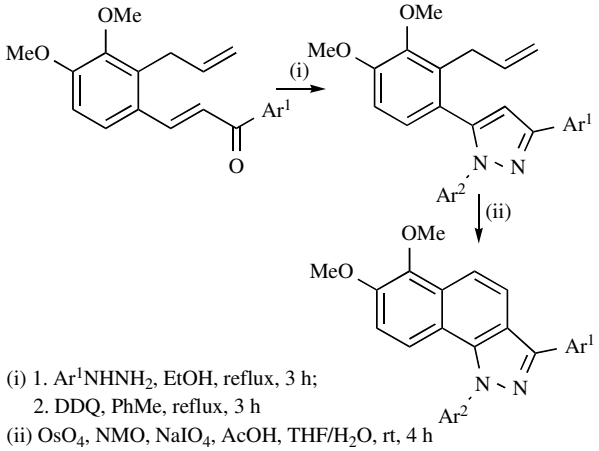


(i) R^2NHNH_2, I_2, AcOH, reflux, 8 h

R^1 = H, MeO	Ar^1 = Ph, 4-BrC_6H_4, 4-$MeOC_6H_4$
R^2 = H, Ph, 4-BrC_6H_4	Ar^2 = Ph, 4-$MeOC_6H_4$

Scheme 40. Iodine-mediated tandem oxidative cyclocondensation of *o*-alkynylarene chalcones with hydrazines.

A three-step sequence was developed to prepare 1,3-diaryl-6,7-dimethoxy-1*H*-benzo[*g*]indazoles from chalcones. The reaction with arylhydrazines followed by DDQ-mediated aromatization afforded pyrazole intermediates, which underwent oxidative cleavage annulation in the presence of OsO_4/$NaIO_4$/AcOH (Scheme **41**) [355].



(i) 1. Ar^1NHNH_2, EtOH, reflux, 3 h; 2. DDQ, PhMe, reflux, 3 h
(ii) OsO_4, NMO, $NaIO_4$, AcOH, THF/H_2O, rt, 4 h
Ar^1 = Ph, 2-FC_6H_4, 2-$MeOC_6H_4$, 3,4,5-tri$MeOC_6H_2$
Ar^2 = Ph, 4-$CHOC_6H_4$, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-tosyl

Scheme 41. Synthesis of 1,3-diaryl-6,7-dimethoxy-1*H*-benzo[*g*]indazoles.

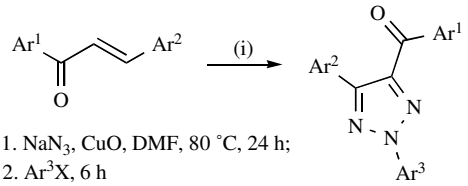
2.1.7. Transformation of Chalcones to Triazoles and Tetrazoles

Triazoles have been applied in various research fields such as biochemistry, pharmaceutical, and material science. Thus, triazoles are used as drugs [356-358] and present a range of biological properties, such as anti-HIV-type I protease [359], antihyperglycemic [360], and antimicrobial [361] activities. In addition, they are commercially used as anticorrosive agents [362], agrochemicals [363], photostabilizers and dyes [364].

1,3-Dipolar cycloaddition of azides to electron poor alkenes and alkynes (dipolarophiles) leads to 1,2,3-triazoles. This approach is the most common method for the synthesis of 1,2,3-triazoles from chalcones.

In 2012, Zhang *et al.* exploited a one-pot three-component oxidative cycloaddition reaction of chalcones with sodium azide catalyzed by CuO, followed by post-triazole arylation in order to prepare *N*-2-aryl-substituted 1,2,3-triazoles in high yields and with high regioselectivity (Scheme **42**) [365]. Chalcones with electron-withdrawing substituents exhibit higher yields while electron-donating groups led to lower yields. A similar strategy uses a catalytic amount of commercially available iron oxide nanoparticles to promote the 1,3-dipolar cycloaddition reaction [366].

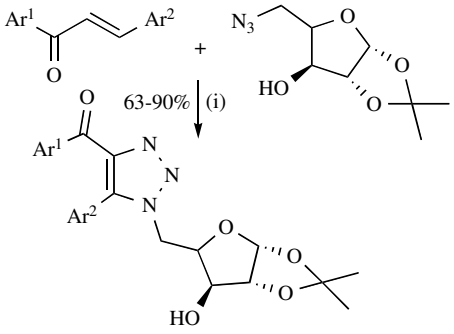
Regioselective [3+2] cycloaddition reaction of chalcones with a sugar azide followed by the *in situ* oxidation catalyzed by tetrabutylammonium hydrogen sulfate (TBAHS) gave 1,4,5-trisubstituted 1*H*-1,2,3-triazoles in good yields (Scheme **43**) [367].



(i) 1. NaN_3, CuO, DMF, 80 °C, 24 h; 2. Ar^3X, 6 h
Ar^1 = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$
Ar^2 = Ph, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 3,4-diMeC_6H_3, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$
Ar^3X = 2-$NO_2C_6H_4F$, 2,4-di$NO_2C_6H_3Cl$, 2,5-di$FC_6H_3NO_2$, 3,4-di$FC_6H_3NO_2$

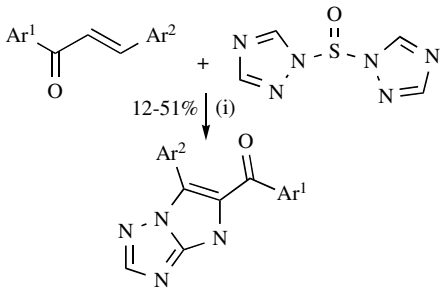
Scheme 42. CuO-promoted one-pot three-component oxidative cycloaddition reaction of chalcones with sodium azide.

Katritzky *et al.* reported a novel approach for the synthesis of substituted 1,2,4-triazoles involving the reaction of chalcones with bis(1*H*-1,2,4-triazolyl) sulfoxide to give thiazolo[3,2-*b*]1,2,4-triazoles in moderate yields (Scheme **44**) [368].



(i) TBAHS, DMF, 100 ˚C, 24 h
Ar^1 = Ph, 4-ClC_6H_4, 4-FC_6H_4
Ar^2 = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 2-naphthyl

Scheme 43. Regioselective synthesis of 1,4,5-trisubstituted 1*H*-1,2,3-triazoles by the reaction of chalcones with a sugar azide.



(i) PhMe, 90 ˚C, overnight
Ar^1 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$NO_2C_6H_4$
Ar^2 = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$

Scheme 44. Synthesis of thiazolo[3,2-*b*]1,2,4-triazoles.

Tetrazoles are known to possess hypotensive, antifungal, antimicrobial, antiviral, cytostatic and other biological activities [369]. They are also successfully used as components of materials for medical purposes, including components of filter materials for dialysis and ultrafiltration, disease diagnosis and cosmetics [369].

There is no methodology reported for the direct transformation of chalcones to tetrazoles. However, tetrazoles can be synthesized from chalcone-type compounds *via* pyrazole intermediates, through the reaction with hydrazines [273]. The reaction of chalcones with hydrazine hydrate in acetic acid afforded the intermediate 4,5-dihydropyrazolylethanones. These intermediates react with arylhydrazines in ethanol to give the corresponding Schiff bases which heated with acetic anhydride afforded the target tetrazole derivative (Scheme **45**).

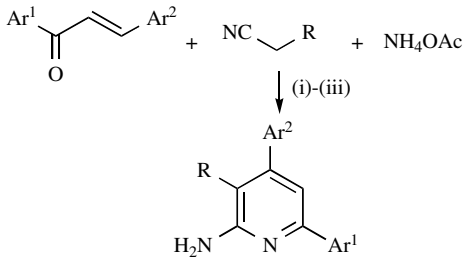
2.2. 6-Membered Nitrogen Heterocycles

2.2.1. Transformation of Chalcones to Pyridines

In the last recent years, several substituted pyridines claimed attention due to their numerous biological and pharmacological potentials [370]. They can exhibit antibacterial [371-373], antimicrobial [374], antitumor [375, 376] and antiviral [377-379] activities, among others.

The pyridine heterocycles can easily be obtained by condensation of chalcones with 1,3-binucleophiles containing a CH-acidic nucleophilic center, but in the last years there are examples with only malononitrile [85, 86, 93, 97, 118, 370, 380-382]. The reaction is usually carried out in ethanol in the presence of ammonium acetate. This approach has been extensively used for the preparation of a wide range of pyridines and was improved through a solvent-free reaction under microwave irradiation [383, 384] and even in a solid supported synthesis (Scheme **46**) [384, 385]. Some bispyridines have also been prepared using ammonium acetate in ethanol starting from bischalcones and malononitrile [294].

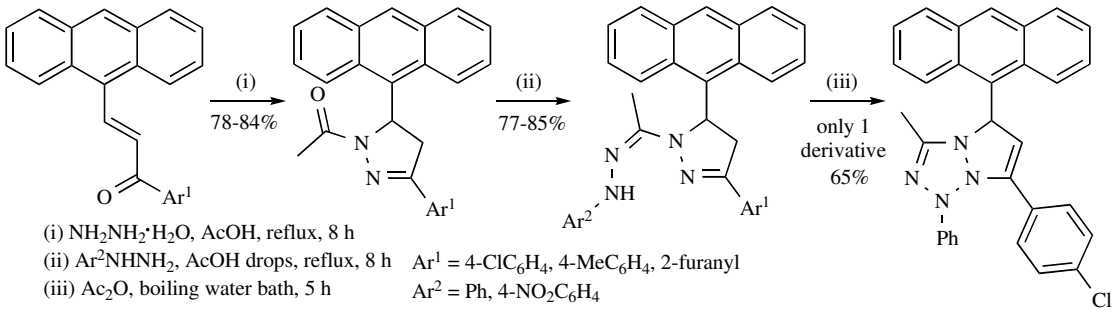
Annelated (dihydropyridines, tetrahydroquinolines, naphthyridines) and substituted pyridines can be synthesized in moderate to good yields (31-70%) in a consecutive one-pot, four-component process by a coupling-isomerization-enamine addition-cyclocondensation sequence of an electron-poor (hetero)aryl halide, a terminal propargyl alcohol, an enamine, and ammonium chloride or benzylamine (Scheme **47**) [386].



(i) R = CN, MW, 3.1-4.2 min, montmorillonite clay K-10, 76-84%
(ii) R = CN, MW, 4.2-5.1 min, neutral Al_2O_3, 74-83%
(iii) R = CO_2Et, MW, 7-9 min, neutral Al_2O_3, 80-88%

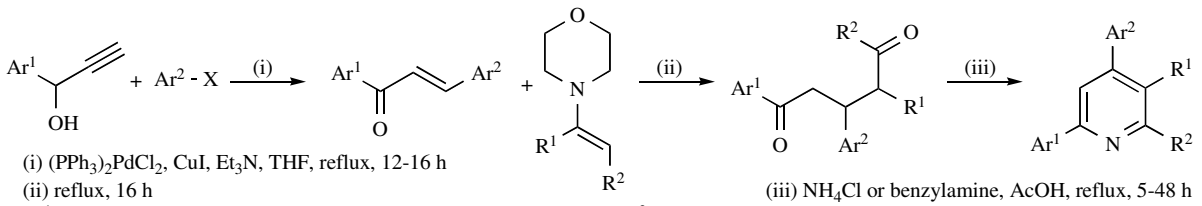
Ar^1 = Ph, 4-BrC_6H_4, 3,4-diMeC_6H_3, 4-$MeOC_6H_4$
Ar^2 = Ph, 4-$MeOC_6H_4$, 3,4-diMeC_6H_3, 2-furyl, 3-indolyl, benzo[1,3]dioxol-5-yl

Scheme 46. Solvent-free, solid supported synthesis of 4,6-disubstituted 2-aminopyridines, under microwave irradiation.



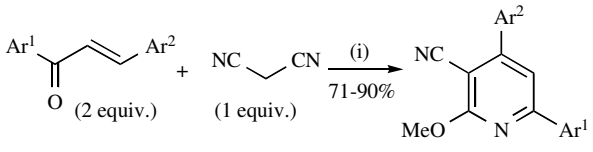
(i) $NH_2NH_2{\cdot}H_2O$, AcOH, reflux, 8 h
(ii) Ar^2NHNH_2, AcOH drops, reflux, 8 h
(iii) Ac_2O, boiling water bath, 5 h
Ar^1 = 4-ClC_6H_4, 4-MeC_6H_4, 2-furanyl
Ar^2 = Ph, 4-$NO_2C_6H_4$

Scheme 45. Multi-step synthesis of 5-(anthracen-9-yl)-7-(4-chlorophenyl)-3-methyl-1-phenyl-1,5-dihydropyrazolo[1,2-*a*]tetrazole.



(i) $(PPh_3)_2PdCl_2$, CuI, Et_3N, THF, reflux, 12-16 h
(ii) reflux, 16 h
(iii) NH_4Cl or benzylamine, AcOH, reflux, 5-48 h
Ar^1 = 4-$CF_3C_6H_4$, 4-CNC_6H_4, 4-$CO_2EtC_6H_4$, 2-pyridyl, 2 pyrimidyl; Ar^2 = Ph, 4-$MeOC_6H_4$
R^1,R^2 = -$(CH_2)_3$-; -$(CH_2)_4$-; -$(CH_2)_2$-N(CO_2Et)-CH_2-; R^1 = Ph, R^2 = H; R^1 = 4-$MeOC_6H_4$, R^2 = H; R^1 = 2-thienyl, R^2 = H

Scheme 47. One-pot synthesis of annelated and substituted pyridines.



(i) K_2CO_3, MeOH, MW + ultrasound, 2-6 min
Ar^1 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$
Ar^2 = Ph, 3-BrC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$CHMe_2C_6H_4$, 3,4-(O-CH_2-O)C_6H_3, 3,4,5-tri$MeOC_6H_2$

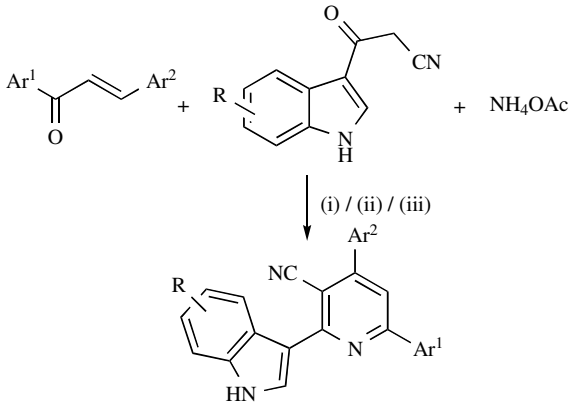
Scheme 48. K_2CO_3-mediated multi-component tandem reaction of chalcone, malononitrile and methanol under combined microwave and ultrasound irradiation.

Feng and co-workers reported the K_2CO_3-promoted tandem reaction of malononitrile with chalcones using methanol as nucleophilic agent under combined microwave and ultrasound irradiation to obtain polysubstituted pyridines in good yields (Scheme **48**) [387].

One-pot multicomponent reactions of chalcones, 3-cyanoacetylindoles and ammonium acetate provided 2-(indol-3-yl)pyridine derivatives in good yields, under classical heating conditions [388] and microwave irradiation (Scheme **49**) [388-390], while 4,6-diaryl-3-aminoisoxazolo[3,4-*b*]pyridines resulted from the one-pot reaction of chalcones, malononitrile, and hydroxylamine [391].

The multicomponent reaction of chalcones with pyridinium salts and ammonium acetate was explored to synthesize dihydroxylated 2,4,6-triphenylpyridines as anticancer agents (Scheme **50**) [392]. Other pyridine derivatives arise from the reaction of 4-hydroxycoumarin-derived chalcones with phenacyl pyridinium bromide and ammonium acetate [393] or by the reaction of thienyl/furyl-based chalcones with 1-(2-oxo-2-thienyethyl)pyridinium iodides in the presence of ammonium acetate in methanol [375].

Katritzky *et al.* studied the synthesis of 2-alkylamino-4,6-diarylpyridines using solid-phase-bound chalcones [394]. Thus, secondary amines were treated with a solution of α-(benzotriazol-1-yl)acetonitrile in 2-methoxyethanol and the intermediate formed reacted with the resin-bound chalcones to afford the target 2-alkylaminopyridines (Scheme **51**).

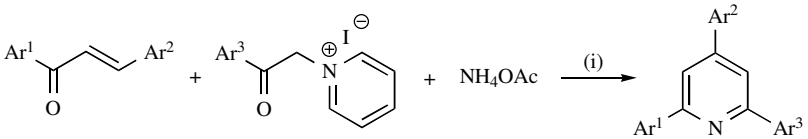


(i) Classical conditions: AcOH:glycol (1:2), reflux, 5 h, 69-76%
MW: AcOH:glycol (1:2), MW, 12-15 min, 75-85%
(ii) AcOH:glycol (1:2), MW, 10-12 min, 70-87%
(iii) AcOH:glycol (1:2), MW, 8-12 min, 74-86%

Scheme 49. Synthesis of 2-(indol-3-yl)pyridines *via* a one-pot three-component reaction of chalcones, 3-cyanoacetylindoles and ammonium acetate.

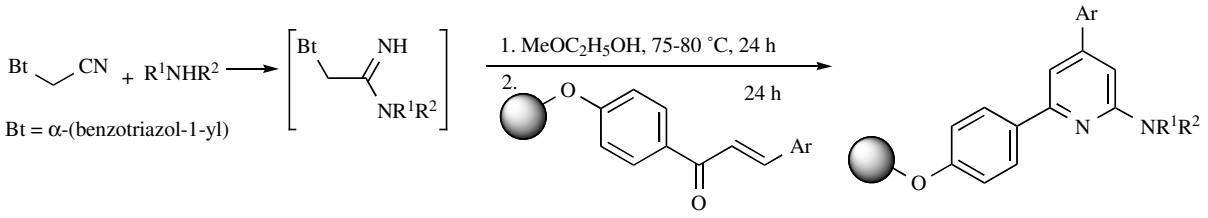
The reaction of chalcones with aminoazoles is a useful and straightforward method to synthesize fused pyridines. Some reports exploited the reaction of chalcones with 5-amino-1-phenylpyrazoles to synthesize 1*H*-pyrazolo[3,4-*b*]pyridines in good yields. The reactions were carried out in refluxing DMF [395] or under microwave assisted conditions (Scheme **52**) [396]. Other diversely fused pyridines are attained from the reaction of chalcones with several heterocyclic amines [397]. KF/alumina-catalyzed reaction of chalcones with 2,6-diamino-4-hydroxylpyrimidine is conditions-controlled: in an air atmosphere 5,7-diarylpyrido[2,3-*d*]pyrimidines are isolated, while under dry nitrogen, the unaromatized intermediates dihydropyrido[2,3-*d*]pyrimidines are obtained (Scheme **53**) [398].

Chalcone-type compounds with different moieties represent a useful starting material for the synthesis of functionalized pyridines. This feature of chalcone-type compounds was explored by Radwan and co-workers in the reaction of 2-chalconylpyrroles with malononitrile either in sodium ethoxide/ethanol or sodium methoxide/methanol to obtain the corresponding 2-alkoxycyanopyridines bearing a pyrrole moiety at C-6 (Scheme **54**) [120].



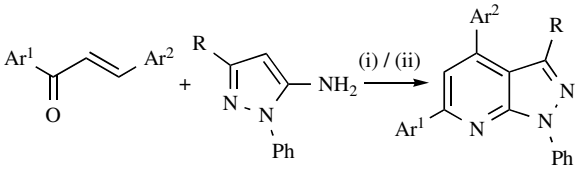
(i) AcOH, 90-100 °C 12-24 h, 20-97%
Ar^1, Ar^2, Ar^3 = Ph, OHC_6H_4

Scheme 50. Synthesis of dihydroxylated 2,4,6-triphenylpyridines through a one-pot three-component reaction of chalcones, pyridinium salts and ammonium acetate.



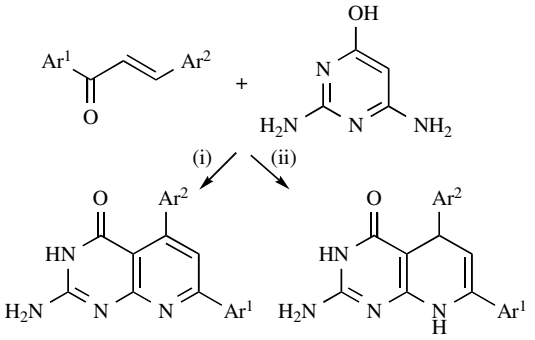
R^1, R^2 = -$(CH_2)_4$-; -$(CH_2)_2$-O-$(CH_2)_2$-; -CH_2(*o*-C_6H_4)CH_2CH_2-; -$(CH_2)_3CH(CO_2H)$-; $CH_2CH{=}CH_2$, H; $CH_2CH(CH_3)_2$, H; *cyclo*-C_5H_9, H; $CH(CH_3)C_2H_5$, H; $CH_2C_6H_5$, H; $CH_2CH_2CO_2H$, H
Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_5$

Scheme 51. One-pot synthesis of 2-alkylamino-4,6-diarylpyridines using solid-phase-bound chalcones.



(i) R = H, DMF, reflux, 10 h, 52-68%
(ii) R = Me, $ZnCl_2$, glycol, MW, 8-12 min, 85-92%
Ar^1 = 2-ClC_6H_4, 2,4-diClC_6H_3, 4-FC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$
Ar^2 = 4-BrC_6H_4, 4-ClC_6H_4, 3,4-diClC_6H_3, 4-FC_6H_4, 4-$MeOC_6H_4$, 3-$NO_2C_6H_4$

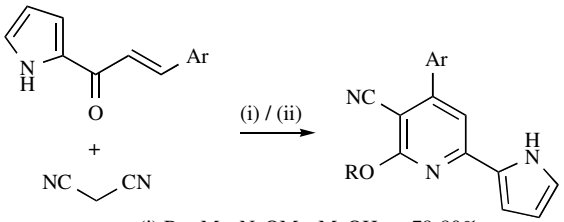
Scheme 52. Synthesis of 1*H*-pyrazolo[3,4-*b*]pyridines through the reaction of chalcones with 5-amino-1-phenylpyrazoles.



(i) KF/Al_2O_3, EtOH, 80 ˚C, 8-12 h
(ii) KF/Al_2O_3, EtOH, N_2, 80 ˚C, 40-60 min
Ar^1 = Ph, 4-BrC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$
Ar^2 = Ph, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 3-MeC_6H_4, 4-$MeOC_6H_4$, 3-$NO_2C_6H_4$, 2-thiophenyl

Scheme 53. Synthesis of pyrido[2,3-*d*]pyrimidine derivatives *via* reaction of chalcones with 2,6-diamino-4-hydroxylpyrimidine.

Trilleras *et al.* reported a tandem Claisen–Schmidt condensation–Michael addition reaction of 4-chalconylpyrazoles with acetophenones, followed by the reaction of the formed adducts with NH_4OAc, under solvent-free conditions and microwave irradiation, to obtain 2,6-diaryl-4-pyrazolylpyridines (Scheme **55**) [399].



(i) R = Me, NaOMe, MeOH, rt, 78-80%
(ii) R = Et, NaOEt, EtOH, rt, 81-83%
Ar = 5-Me-2-furanyl, 4-ClC_6H_4

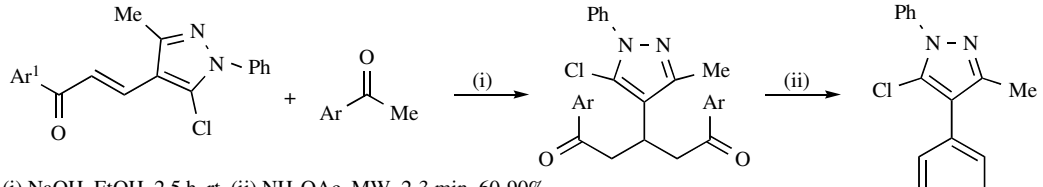
Scheme 54. Synthesis of 2-alkoxycyanopyridines.

The reaction of benzodiazepine-based chalcones with several cyanoacetamide derivatives carried out in ethanol with a catalytic amount of piperidine afforded a wide range of 1,2,5,6-tetrahydro-2-oxopyridine-3-carbonitriles [129].

2.2.2. Transformation of Chalcones to Pyrimidines

Pyrimidines are widely spread in a large variety of natural compounds as well as in several interesting nucleoside and non-nucleoside compounds. Being a building block of DNA and RNA, pyrimidines have been shown many interesting biological effects namely, antimicrobial [85, 400, 401], antitubercular [402], antitumor [403, 404] activities and as selective A_3 adenosine receptor antagonists [405].

The most common method towards the synthesis of 2,6-disubstituted pyrimidines is the treatment of chalcones with urea and its analogues - thiourea, guanidine and amidines. The most common catalysts for this kind of heterocyclizations are NaOH [122, 227, 273, 406-413] or KOH [86, 89, 106, 137, 277, 278], sodium ethoxide [414, 415], NaH [416] and the gentler NaOAc [116]. This reaction can also be done in the absence of catalyst [130] or solid supports [394] with good results. Using concentrated hydrochloric acid as cyclizing agent, the condensation of chalcones with urea, thiourea and guanidine provided also 2-hydroxy-, 2-thio- and 2-aminopyrimidines, respectively [417, 418]. Other examples of 2-aminopyrimidines can be achieved through the condensation of chalcones with guanidine hydrochloride in the presence of NaH in

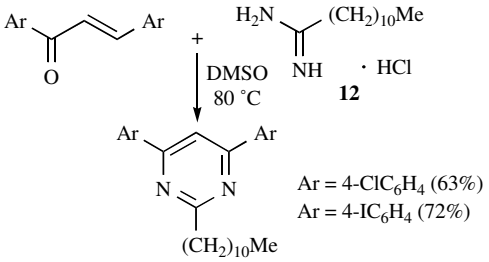


(i) NaOH, EtOH, 2.5 h, rt. (ii) NH_4OAc, MW, 2-3 min, 60-90%
Ar = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3,4,5-tri$MeOC_6H_2$, 2-thiophenyl

Scheme 55. Multi-step synthesis of 2,6-diaryl-4-pyrazolylpyridines.

DMF [419]. Katritzky *et al.* reported the synthesis of substituted pyrimidines from the reaction of chalcones with amidine hydrochloride **12** in DMSO at 80 °C (Scheme **56**) [420].

A few substituted chalcones reacted with urea and thiourea to afford pyrimidin-2(1*H*)-ones and pyrimidin-2(1*H*)-thiones, respectively [85, 116]. Functionalized pyrimidines were synthetized through the condensation of coumarin-chalcones with an unusual hydrazine 13 (resulted from the treatment of nalidixic acid ester with guanidine carbonate in DMF) (Scheme **57**) [421].



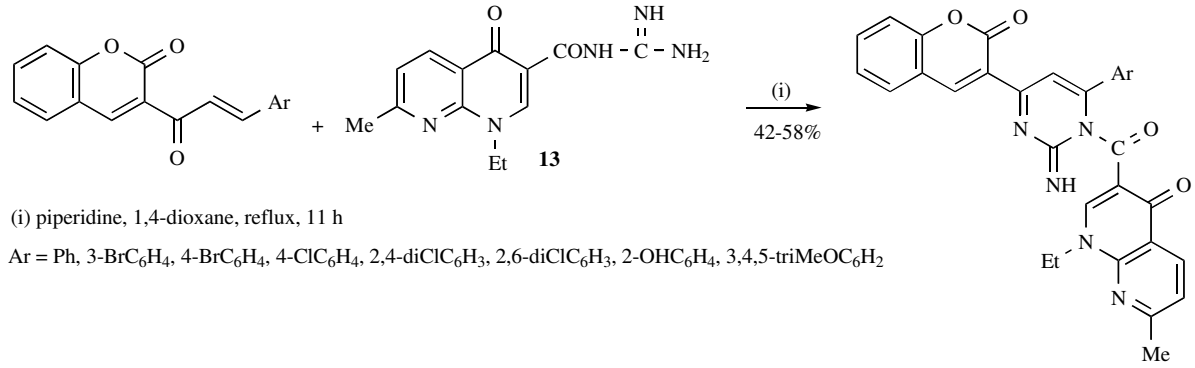
Scheme 56. Condensation of chalcones with amidine hydrochloride **12** for the synthesis of pyrimidines.

Nagaraj *et al.* reported the synthesis of a series of bispyrimidines from the reaction of bischalcones with guanidine hydrochloride in aqueous NaOH in ethanol [422]. More examples arise from the reaction of bischalcones with guanidine hydrochloride in 1,4-dioxane [423] and with pyrrolidine-1-carboxamidine hydrochloride or piperidine-1-carboxamidine hydrochloride in sodium isopropoxide / isopropanol (Scheme **58**) [424].

The reaction of two equiv of chalcones with a bis-2-aminothiazole in refluxing 1,4-dioxane led to the synthesis of bisthiazolo[3,2-*a*]pyrimidines in 79-85% yield (Scheme **59**) [425].

High yields of 1,6-dihydropyrimidines result from the reaction of chalcone-type compounds with urea [426], thiourea and guanidine hydrochloride [427], under basic conditions (Scheme **60**). A facile microwave assisted synthesis of 4,5-dihydropyrimidin-2-amines occurs through the reaction of benzofuran-chalcones and guanidine hydrochloride in the presence of NaOH [428].

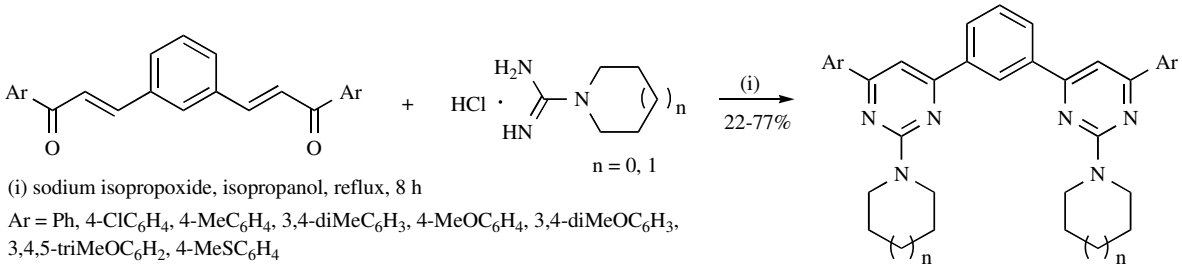
The reaction of 3,4,5,3',4'-pentamethoxychalcone with urea in the presence of concentrated hydrochloric acid in refluxing ethanol provided the corresponding 3,4-dihydropyrimidin-2(1*H*)-one in 42% yield. The reaction with substituted thioureas using basic cata-



(i) piperidine, 1,4-dioxane, reflux, 11 h

Ar = Ph, 3-BrC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 2,4-diClC_6H_3, 2,6-diClC_6H_3, 2-OHC_6H_4, 3,4,5-tri$MeOC_6H_2$

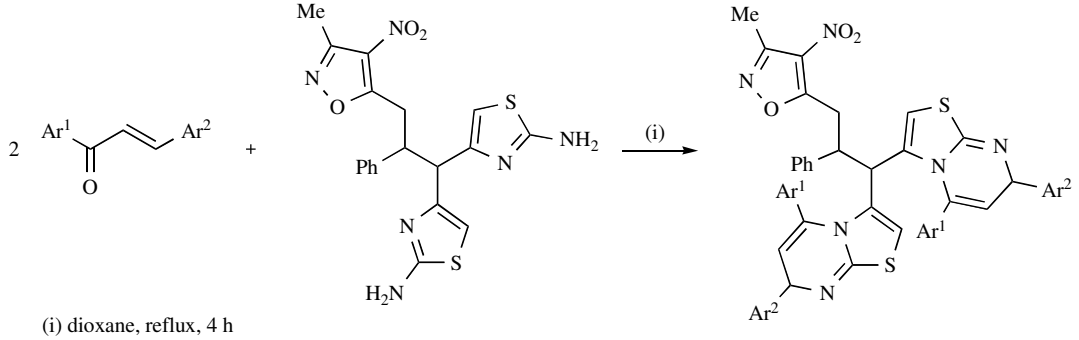
Scheme 57. Synthesis of functionalized pyrimidines from the reaction of coumarin-chalcones with hydrazine **13**.



(i) sodium isopropoxide, isopropanol, reflux, 8 h

Ar = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 3,4-diMeC_6H_3, 4-$MeOC_6H_4$, 3,4-di$MeOC_6H_3$, 3,4,5-tri$MeOC_6H_2$, 4-$MeSC_6H_4$

Scheme 58. Synthesis of bispyrimidines by condensation of chalcones with aminoazoles.



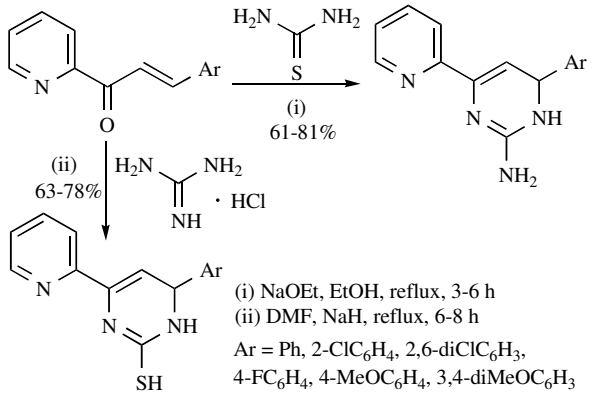
(i) dioxane, reflux, 4 h

Ar^1 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-OHC_6H_4

Ar^2 = Ph, 2-ClC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$

Scheme 59. Synthesis of bisthiazolo[3,2-*a*]pyrimidines from the reaction of chalcones with bis-2-aminothiazoles.

lysts afforded 3,4-dihydropyrimidin-2(1*H*)-thiones, in moderate yields [429]. Other 3,4-dihydropyrimidin-2(1*H*)-(thi)ones can be synthetized through the condensation of chalcone-type compounds with (thio)urea under the effect of KOH in refluxing ethanol (Scheme **61**) [120, 430]. Using the same conditions, functionalized 5,6-dihydropyrimidin-2(1*H*)-(thi)ones bearing thiophene [220] and benzofuran [118] moieties were prepared. An ecofriendly approach for the synthesis of 1,2,3-triazolyldihydropyrimidine-2(1*H*)-thiones involves the reaction of 1,2,3-triazolylchalcones with thiourea in the presence of aqueous KOH (40 min of reaction with 79-95% yield). Similar results were obtained using ethanol as solvent (30 min of reaction with 74-95% yield) [431].

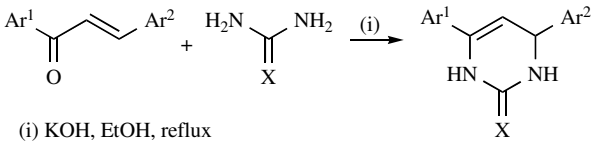


Scheme 60. Synthesis of 1,6-dihydropyrimidines through the reaction of chalcone derivatives with thiourea and guanidine hydrochloride.

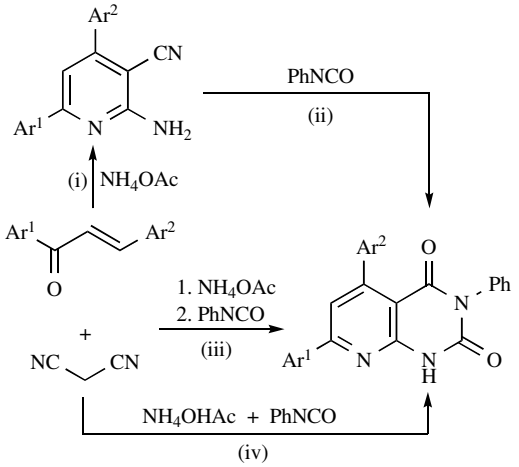
A couple of 5,6-dihydropyrimidin-2(1*H*)-(thi)one arise from the reaction of a chalcone bearing a sulfonamide moiety with (thio)urea [93]. Other examples of 5,6-dihydropyrimidin-2(1*H*)-(thi)ones were obtained from the reaction of chalcones with (thio)urea in ethanol using NaOH [115] or piperidine [129] as base.

Cyclocondensation of aminoazoles with chalcones is also a very commonly used approach for the synthesis of pyrimidine derivatives such as dihydro[1,2,3]-triazolo[1,5-*a*]pyrimidines **14** [432], pyrazolo[1,5-*a*]pyrimidines **15** [433, 434], pyridopyrazolopyrimidines **16** [395], isoxazolo[2,3-*a*]pyrimidines **17** [435] (Scheme **62**).

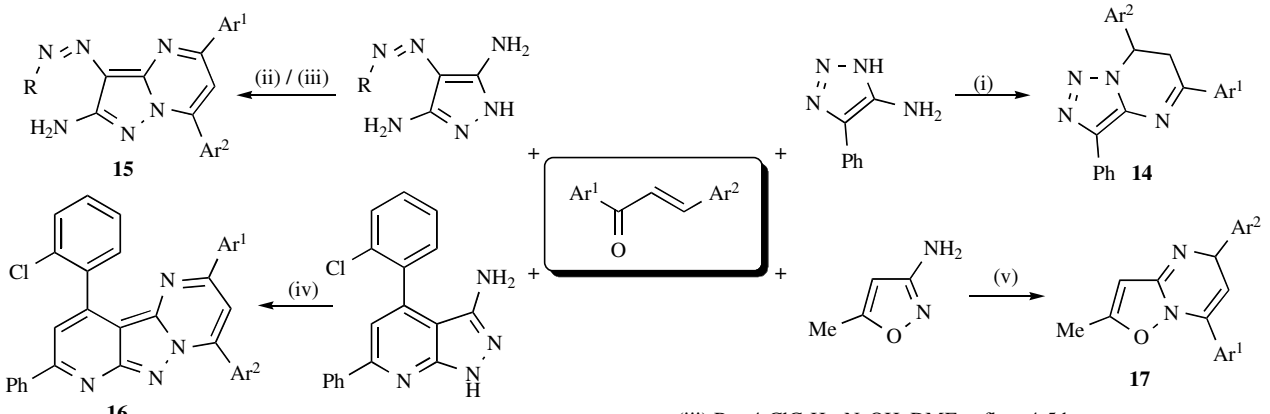
The synthesis of pyrido[2,3-*d*]pyrimidine derivatives occurred in a two-step or in a one-pot procedure involving the reaction of chalcones, malononitrile, ammonium acetate and phenyl isocyanate, under microwave irradiation on a solid support (montmorillonite clay K-10 or alumina). The one-pot protocol without the solid support and in solvent-free conditions also afforded pyridopyrimidines in excellent yields (Scheme **63**) [385].



Scheme 61. Synthesis of 3,4-dihydropyrimidin-2(1*H*)-(thi)ones through the reaction of chalcone-type compounds with urea analogs.



Scheme 63. Ecofriendly synthesis of substituted pyrido[2,3-*d*]pyrimidine derivatives.



Scheme 62. Synthesis of pyrimidine derivatives by condensation of chalcones with aminoazoles.

4. CLOSING REMARKS

In summary, the chemistry of chalcones has attracted the attention of scientists not only for their synthesis but also by their transformations to other biologically important compounds, namely 5- and 6-membered nitrogen heterocyclic compounds. The most recent advances in the synthesis of pyrroles, indoles, isoxazoles, imidazoles, pyrazoles, indazoles, triazoles, tetrazoles, pyridines and pyrimidines from chalcone-type compounds are reviewed. The efforts made to improve the synthetic efficiency rely on the application of easy-to-handle and cheap reagents, alternative heating conditions and greener protocols. Furthermore, the huge library of novel compounds reported since the beginning of the 21st century highlights the importance of this heterocyclic chemistry.

Undoubtedly, chalcones and their analogues continue to be a privileged building block in the synthetic and biological domain being expected further progresses in these fields.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

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ABBREVIATIONS

Ac	=	Acetyl
DBU	=	1,8-diazabicycloundec-7-ene
DDQ	=	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	=	*N*,*N*-dimethylformamide
DMSO	=	Dimethylsulfoxide
Et	=	Ethyl
HTIB	=	Hydroxy(tosyloxy)iodobenzene
Me	=	Methyl
MW	=	Microwave
NCS	=	*N*-chlorosuccinimide
NMO	=	*N*-methylmorpholine-*N*-oxide
OTf	=	Trifluoromethanesulfonate
rt	=	Room temperature
TBAHS	=	Tetrabutylammonium hydrogen sulfate
TBD	=	1,5,7-triazabicyclo[4.4.0]dec-5-ene
THF	=	Tetrahydrofuran
TMS	=	Trimethylsilyl

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