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Chemistry of Heterocyclic Compounds **2020**, *56*(2), 145–160

The versatility of DABCO: synthetic applications of its basic, nucleophilic, and catalytic properties

Part 2*. Catalysis of Michael and Biginelli reactions and nucleophilic addition at C=X and C≡X bonds

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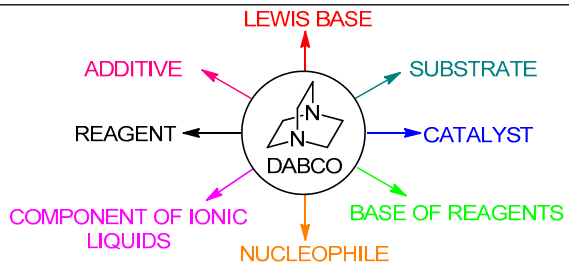


The second part of review is devoted to the catalytic role of DABCO in Michael and Biginelli reactions, as well as nucleophilic addition at C=X and C≡X bonds.

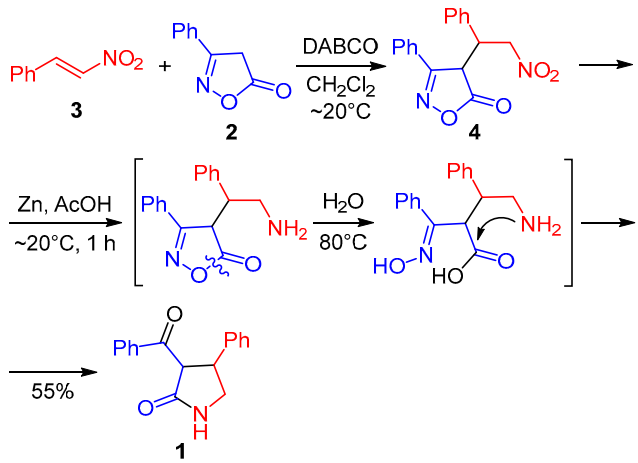
Keywords: 1,4-diazabicyclo[2.2.2]octane, Brønsted base, Lewis base, nucleophile, Biginelli reaction, Michael reaction.

The catalytic role of DABCO in Michael reaction and nucleophilic addition at C=X and C≡X bonds

The first part of this review article[1a] demonstrated the important and versatile applications of DABCO as a reagent for organic synthesis,[1b–f] in particular, in the role of a catalyst for the commonly used classic Morita–Baylis–Hillman and Knoevenagel reactions. In the second part, we will describe the use of DABCO as a catalyst for nucleophilic addition reactions at activated C=C bonds (Michael reaction), as well as at C=X and C≡X bonds. The primary attention will be focused on the Michael reaction, which is of particular importance in the synthesis of heterocyclic compounds. DABCO is most often employed in this reaction as a basic organic catalyst, which deprotonates the reactants, producing reactive anionic nucleophiles of various nature, which are readily added to unsaturated substrates.

For example, the key step during the synthesis of pyrrolidin-2-one **1** from oxazole **2** and nitroalkene **3** was the initial Michael addition of C(4)-anion derived from isoxazol-5(4*H*)-one **2** to the activated alkene **3** in the presence of DABCO as a catalyst (Scheme 1).[2] The intermediate Michael adduct **4** then underwent a series of one-pot transformations – nitro group reduction, ring cleavage, and recyclization – with the formation of pyrrolidin-2-one derivative **1**. The reaction was characterized by high diastereoselectivity, with the predominant formation of *trans*-isomer.

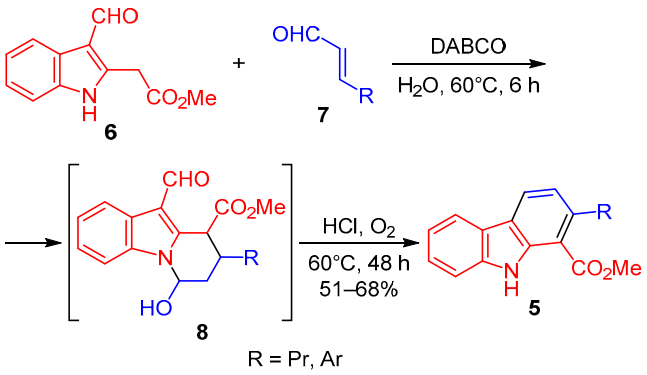
Scheme 1



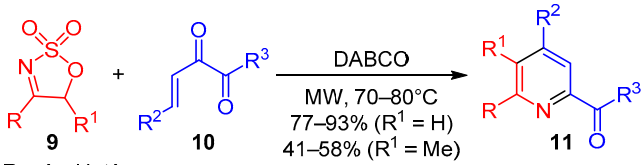
* For Communication 1, see [1a].

A new type of one-pot synthesis in aqueous media in the absence of transition metal catalysts was achieved using methyl (3-formyl-1*H*-indol-2-yl)acetic acid ester (**6**) and alkyl/aryl-substituted β-acroleins **7** in the presence of 20 mol % DABCO, followed by treatment with HCl at elevated temperature, providing moderate yields (51–68%) of functionalized 2-alkyl(aryl)-1-methoxycarbonyl-9*H*-carbazole derivatives **5** (Scheme 2).[3] The initial step involved the addition of C-nucleophile to the unsaturated carbonyl compound according to Michael reaction mechanism. The Michael adduct further underwent a series of transformations, including intramolecular cyclization to tricyclic hemiaminal **8**, followed by ring cleavage and Friedel–Crafts recyclization and concluding with decarbonylation and oxidation.

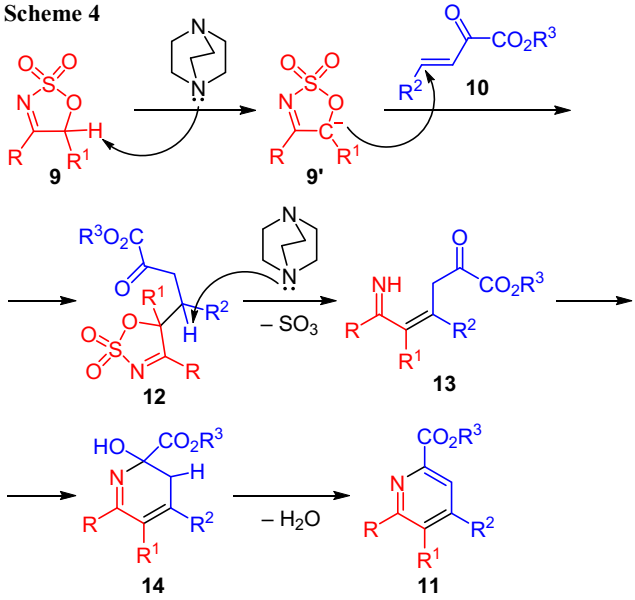
Scheme 2



Scheme 3



Scheme 4



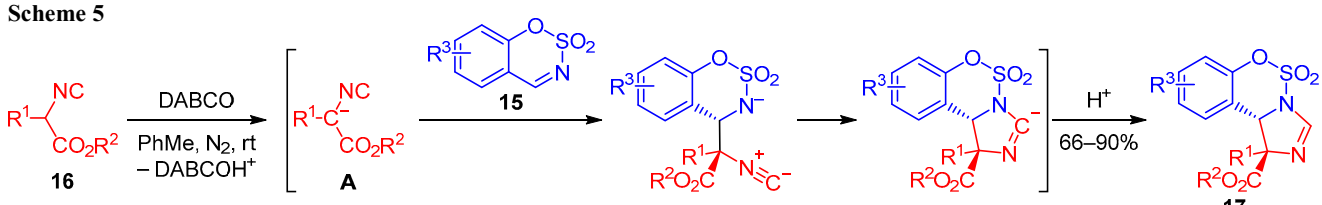
The efficient, solvent-free domino reactions of 5-membered cyclic sulfamidate imines **9** with various β,γ-unsaturated α-ketocarbonyl compounds **10** proceeded under mild conditions in the presence of DABCO as catalyst upon microwave irradiation and were employed for the assembly of new types of polyfunctionalized picolinates **11**[4] (Scheme 3). The mechanism of these reactions also started by a Michael addition step. Analogous reactions were performed with the participation of 6-membered cyclic sulfamidate imines.[4] 2,4-Disubstituted pyridines were obtained from sulfamidate imines **9** and α,β-unsaturated aldehydes in the presence of proline and DABCO.[5]

As the first step, DABCO deprotonated the methylene group of cyclic sulfamidate imine, resulting in carbanionic intermediate **9'** (Scheme 4). This intermediate subsequently underwent a Michael addition to β,γ-unsaturated α-keto ester **10** with the formation of adduct **12**, which immediately underwent the elimination of SO_3 by the action of a base, leading to the reactive intermediate **13**. The latter was converted into intermediate **14** *via* an iminocyclization step, followed by dehydration that gave the final product of this reaction.

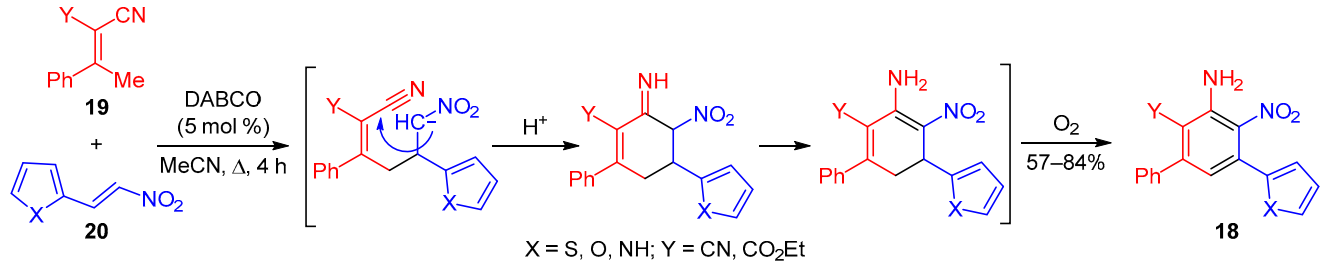
The [3+2] annulation of cyclic imine sulfamates **15** with isocyanoacetates **16** in the presence of DABCO as catalyst occurred under mild conditions and led to 2-imidazolines **17** that were condensed with cyclic sulfamates. This reaction was diastereoselective and gave moderate to excellent yields (Scheme 5).[6] In the presence of DABCO in the role of a Lewis base, isocyanoacetate **16** was deprotonated, generating the nucleophilic anion **A**. This intermediate attacked the sulfamate moiety of cyclic imine **15**, leading to the formation of intermediate **B**. The subsequent nucleophilic addition at the activated C≡N bond and protonation led to the target compound **17**, while regenerating DABCO.

A simple and efficient one-pot synthesis of hetaryl-substituted benzene derivatives **18** proceeded *via* the

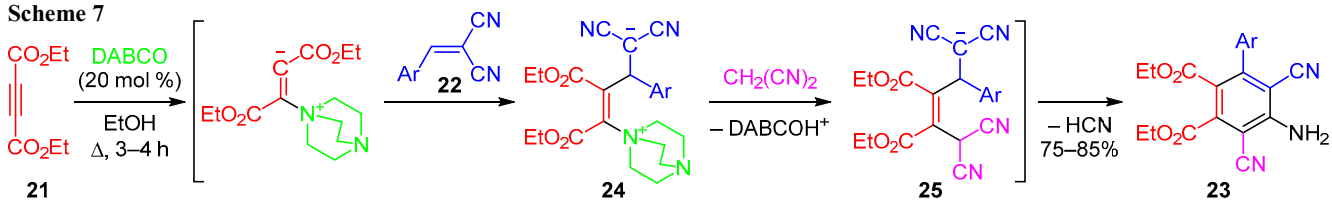
Scheme 5



Scheme 6



Scheme 7

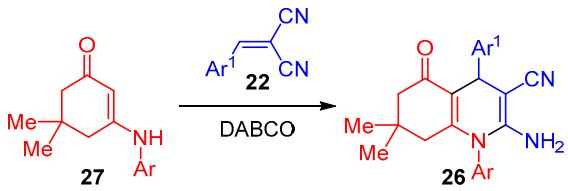


cyclocondensation of vinylmalononitriles **19** with hetaryl-nitroalkenes **20** in the presence of DABCO (Scheme 6).[7] The reaction included a Michael addition of C-anion, generated in the presence of DABCO, to the hetaryl-nitroalkene. Aromatization of the formed dihydro species occurred in the presence of air oxygen. The obtained compounds exhibited tuberculostatic, antibacterial, and antifungal activity at various concentrations.

A three-component reaction of acetylenedicarboxylic ester **21**, arylidenemalononitriles **22**, and malononitrile in the presence of DABCO as catalyst led to 4-amino-3,5-dicyanophthalate esters **23** (Scheme 7).[8] DABCO in this case played the role of N-nucleophile, which reacted with acetylenedicarboxylic ester **21**, resulting in the formation of reactive zwitterionic intermediate **24**, which then underwent a Michael addition to arylidenemalononitrile **22** (Scheme 7). The obtained zwitterion **24** reacted with malononitrile anion, resulting in nucleophilic substitution of DABCO, followed by the cyclization of adduct **25**, accompanied by elimination of an HCN molecule.

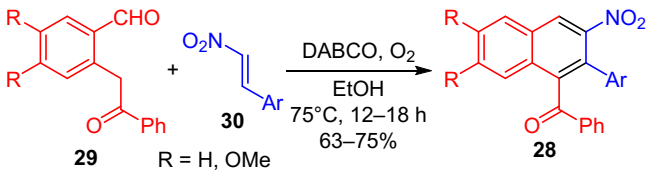
Hexahydroquinolines **26** were obtained in good to excellent yields according to a simple and effective procedure, including the reaction of enamines **27** with substituted arylidenemalononitriles **22** while employing DABCO as a basic catalyst (Scheme 8).[9] The regio-chemical outcome of the Michael addition was confirmed by 2D NMR spectroscopy (^{1}H–^{13}C HMBC experiment).

Scheme 8



A series of naphthalene derivatives **28** bearing carbonyl and nitro groups at positions 1 and 3, respectively, were synthesized in good yields by a one-pot domino reaction of some 2-(2-formylaryl)acetophenone derivatives **29** with various 1-aryl/hetaryl-2-nitroalkenes **30** in alcohol medium in the presence of DABCO as a catalyst (30 mol %)

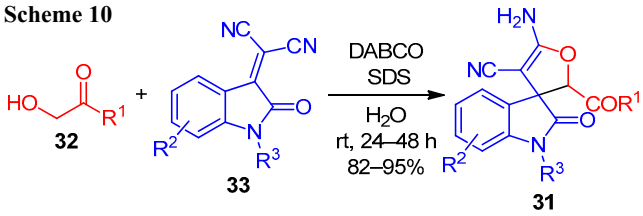
Scheme 9



(Scheme 9).[10] The reaction mechanism involved an interaction with basic catalyst *via* the formation of a stable benzyl carbanion, its Michael addition to nitroalkene, closure of a 6-membered ring through an intramolecular Henry reaction and, finally, aromatization by elimination of a water molecule.[10]

Isatindihydrofuran spiro compounds **31** were synthesized in good yields (up to 95%) and excellent diastereoselectivity (*de* 99%) by a simple tandem Michael addition of α-anions derived from α-hydroxycarbonyl compounds **32** to the exocyclic double bond of isatinylidenemalononitrile **33**, followed by a cyclization in aqueous medium at room temperature in the presence of DABCO as catalyst and sodium dodecyl sulfate (SDS) as promoter (Scheme 10).[11] Some of the synthesized compounds showed antibacterial properties that were superior to those of the antibiotic ampicillin.

Scheme 10

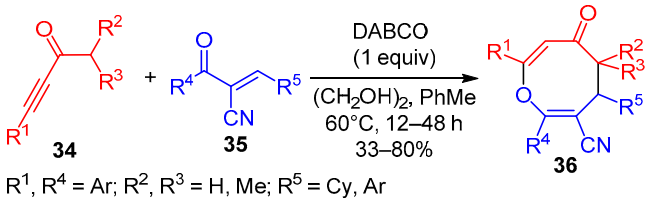


R^1 = Ph, *p*-Tol, 1-Nphth; R^2 = H, Hal, Me, MeO, CF_3O; R^3 = Me, Bn

The generation of C-nucleophiles for the addition to Michael acceptors can be also associated with the enolization of carbonyl compounds by the action of DABCO. This process, for example, occurs during the domino [4+4] annulation reactions of ynones **34** and α-cyano-α,β-unsaturated ketones **35** that are promoted by DABCO

(Scheme 11).[12] This method provides an alternative route to eight-membered cyclic ketones **36** in good yields under mild conditions.

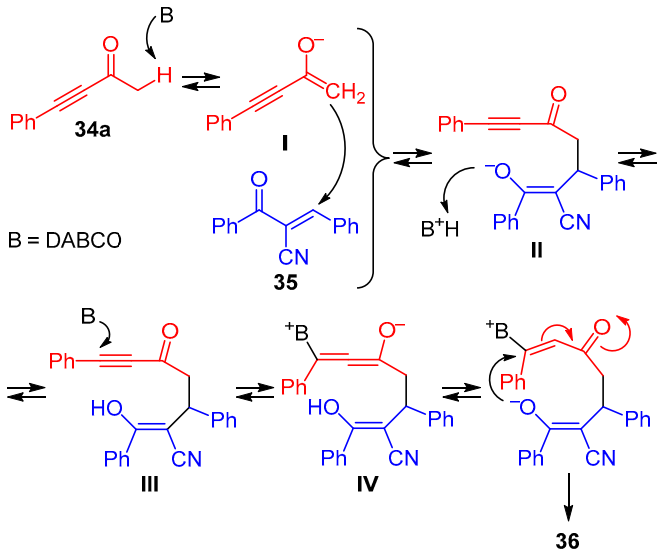
Scheme 11



R^1, R^4 = Ar; R^2, R^3 = H, Me; R^5 = Cy, Ar

The mechanism of this process can be illustrated by using the example of reaction with 4-phenylbut-3-yn-2-one (**34a**). As the first step, compound **34a** was enolized by the action of DABCO (intermediate **I**), then enolate **I** underwent a conjugated nucleophilic addition to the α,β-unsaturated ketone **35**, with the formation of intermediate **II**, where DABCO served as a base in this process (Scheme 12). The subsequent protonation of enol **II** led to vinyl alcohol **III**, which after another Michael addition step generated zwitterion **IV**. The further steps of 1,7-hydride shift, intramolecular nucleophilic addition, and, finally, the elimination of DABCO led to the reaction product **36**.

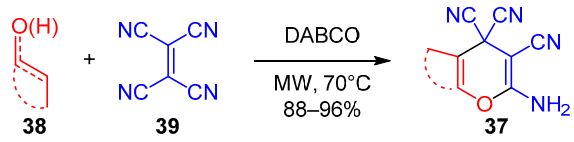
Scheme 12



DABCO has been used as an efficiently regenerated basic catalyst for rapid "green" synthesis of fused pyran systems **37** *via* the reactions of various cyclic enols or 1,3-diketones **38** with tetracyanoethylene (**39**) under the conditions of microwave irradiation (Scheme 13).[13] These conditions allowed to obtain excellent yields while using a short reaction duration (5–7 min). The CH-acidic compound **38** in the presence of DABCO was converted to enolate, which underwent a Michael addition to tetracyanoethylene, followed by an intramolecular cyclization.

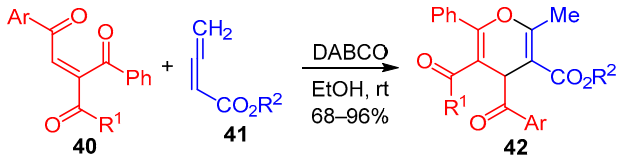
A convenient and effective formal [4+2] cycloaddition of 3-acyl- or 3-(alkoxycarbonyl)-1,4-enediones **40** to 2,3-butadienes (allenes) **41** in the presence of DABCO as

Scheme 13



catalyst proceeded under mild conditions and also led to polysubstituted pyrans **42** in moderate to good yields (Scheme 14).[14]

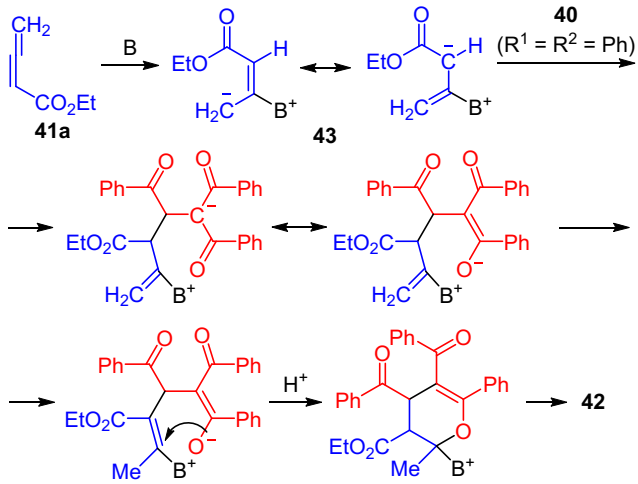
Scheme 14



R^1 = Ph, OEt; R^2 = Me, Et, Bn

The mechanism of this process can be illustrated in the following way (Scheme 15): DABCO added to allene **41a**, leading to the active zwitterionic intermediate **43**, which underwent a Michael addition to 3-acyl-1,4-enedione **40**. After a series of proton shifts, the O-anion site in the enol form of the adduct attacked the electrophilic carbon atom of the quaternized enamine fragment, leading to intramolecular cyclization into dihydropyran, which was converted to the respective pyran by eliminating a molecule of DABCO.

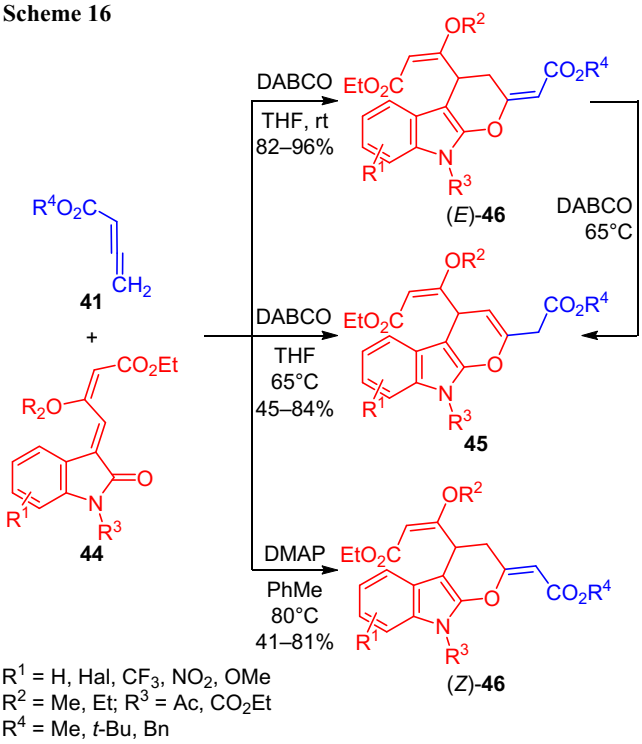
Scheme 15



An example of separated synthesis of pyrano[2,3-*b*]-indole and dihydropyrano[2,3-*b*]indole from the same starting materials has been described. During these domino reactions of oxindoles **44** and allenoates **41**, by controlling the reaction conditions it is possible to obtain three types of products – pyrano[2,3-*b*]indole **45** or dihydropyrano[2,3-*b*]-indoles **46** with *E*- or *Z*-exocyclic double bond (Scheme 16).[15] By using DABCO as catalyst in THF medium, dihydropyrano[2,3-*b*]indole (*E*)-**46** was obtained at room temperature, while pyrano[2,3-*b*]indole **45** formed at 65°C.

In contrast to that, dihydropyrano[2,3-*b*]indole (*Z*)-**46** was obtained by using DMAP as catalyst in PhMe medium at 80°C. Under these conditions, oxindole derivatives played the role of Michael acceptors. The reaction mechanism of this formal [2+4] cycloaddition of methyl allenoate to 3-methylideneoxindole in the presence of DABCO as catalyst was studied by density functional theory calculations (M06-2X method).[16] The reaction included nucleophilic addition of catalyst to methyl allenoate, the addition of a second reactant, and intramolecular cycloaddition followed by the elimination of catalyst.

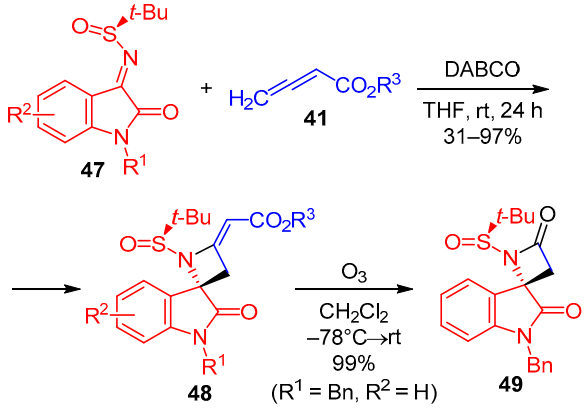
Scheme 16



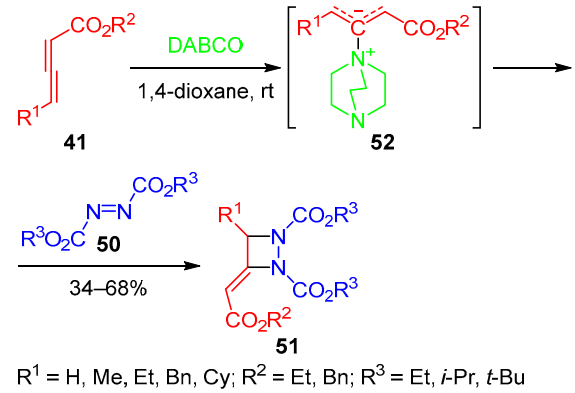
The diastereoselective reaction of isatin ketimines **47** with allenoates **41** was also based on the activation of allenoates with DABCO. The generated zwitterionic allyl carbanion added at the imine C=N bond, followed by intramolecular nucleophilic attack that led to azetidine **48** while regenerating a molecule of DABCO (Scheme 17).[17] By using the stereodirecting effect of the bulky *tert*-butylsulfinyl auxiliary group, it was possible to achieve the formation of spiroisatins in the form of single diastereomer with 4-methylideneazetidine moiety at the spiro atom. The advantages of this method were demonstrated by the possibilities for further transformations of azetidines **48** into spiro-β-lactams **49**.

The [2+2] annulation reaction of allenoates **41** with azodicarboxylate esters **50** in the presence of Lewis base catalyst (DABCO) led to 3-alkylidene-1,2-diazetidines **51** in moderate yields, with excellent regio- and stereoselectivity (Scheme 18).[18,19] Allenoate in the presence of DABCO as catalyst generated the reactive unsaturated zwitterion **52**, which was added to azodicarboxylate **50**, after which a second Michael addition occurred at the C=C double bond.

Scheme 17



Scheme 18

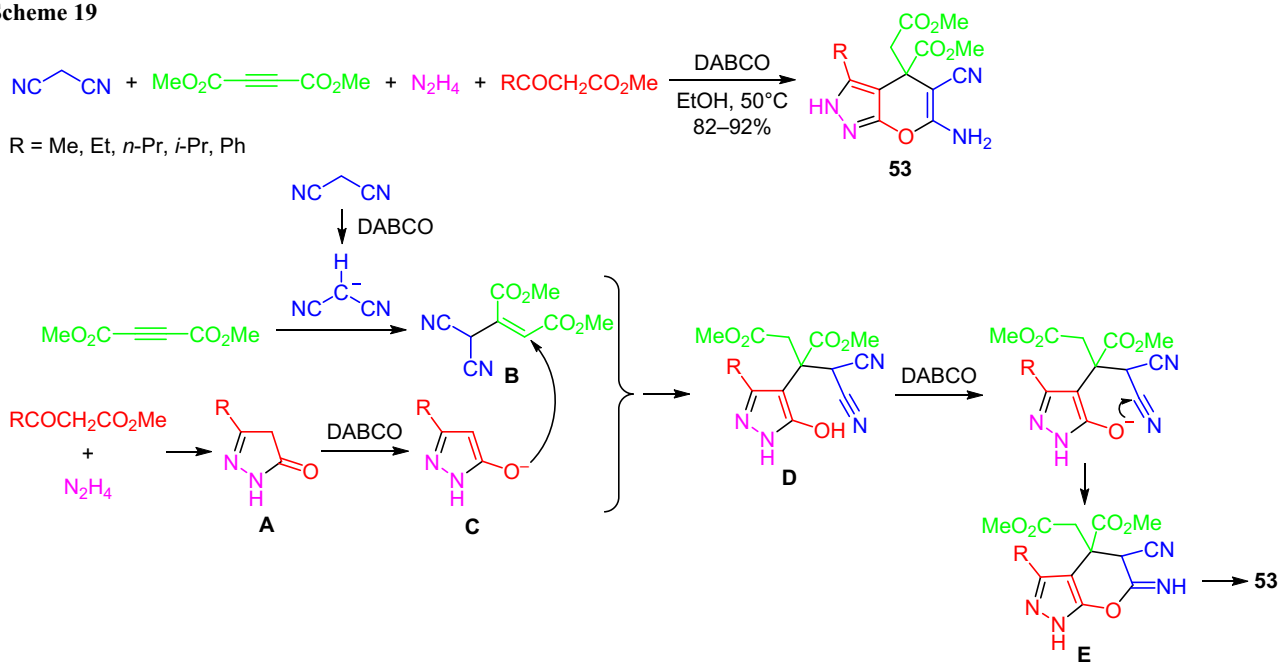


DABCO was employed as an effective general base in a simple one-pot synthesis of polysubstituted 2,4-dihydropyrano[2,3-*c*]pyrazoledicarboxylates **53** from β-keto esters, hydrazine, acetylenedicarboxylate ester, and malononitrile in alcohol medium[20] (Scheme 19). The spontaneous condensation of β-keto ester with hydrazine led to pyrazol-5-one **A**, while the Michael addition of malononitrile to acetylenedicarboxylate ester gave intermediate **B**. Subsequently, the addition of intermediate **C** to intermediate **B** in the presence of DABCO resulted in the formation of intermediate **D**, which underwent nucleophilic attack of oxygen atom at the nitrile group, leading to the formation of intermediate **E**. In the final step, intermediate **E** was isomerized to the bicyclic target molecule **53**.

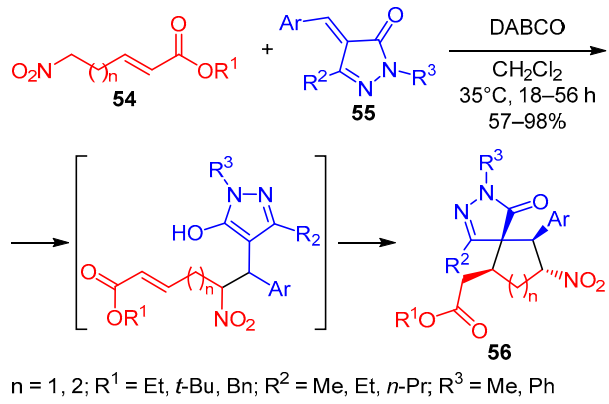
An effective domino process involving a tandem Michael reaction of ω-nitro-α,β-unsaturated esters **54** with 3-alkylidenepyrazolones **55** was accomplished by using DABCO as organocatalyst (Scheme 20).[21] The process led to carbocyclic spiropyrazolones **56** containing tertiary and quaternary stereogenic centers with excellent diastereoselectivity (*dr* > 30:1).

A convenient, environmentally benign method for obtaining new derivatives of 3-oxo-3*H*-benzo[*a*]pyrano[2,3-*c*]-phenazines **57** and 3-(5-hydroxybenzo[*a*]phenazin-6-yl)-acrylates **58** comprised a three-component domino condensation of 2-hydroxynaphthalene-1,4-dione **59**, 1,2-di-

Scheme 19

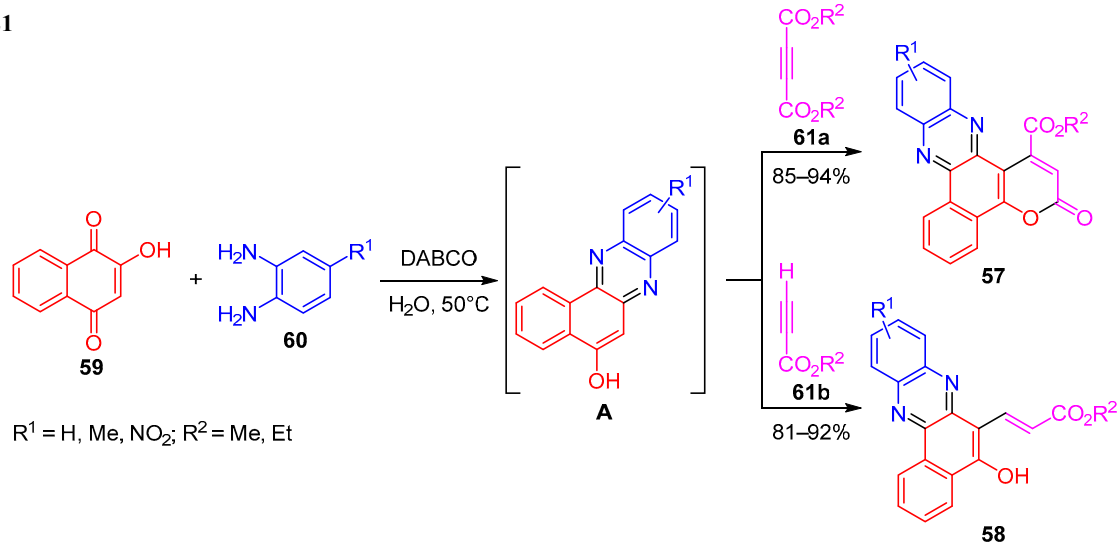


Scheme 20



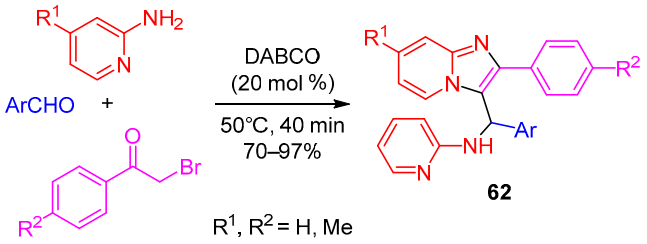
aminobenzenes **60**, and acetylenedicarboxylate esters **61a**,**b** in H_2O and in the presence of DABCO as a basic catalyst (Scheme 21).[22] This "green" process led to the biologically and pharmacologically relevant heterocycles **57** and **58** *via* a simple one-pot procedure characterized by several substantial advantages: the simplicity of experimental procedure, short reaction duration, high yields, multiple cycles of catalyst reuse, lack of laborious workup and purification steps, avoidance of hazardous reagents and solvents. The nucleophilic addition of DABCO to acetylenedicarboxylate ester formed a zwitterion, which was protonated by phenolic intermediate adduct **A**. As a result of this, the two components were activated, an enolate anion and activated double bond were formed, creating favorable conditions for a carbo-Michael reaction. The subsequent lactonization step provided the target compounds **57** and **58**. It should be noted that the regioselectivity issues and the formation of quinoxaline derivative **A** have not been studied in detail and, in our opinion, remain unresolved.

Scheme 21



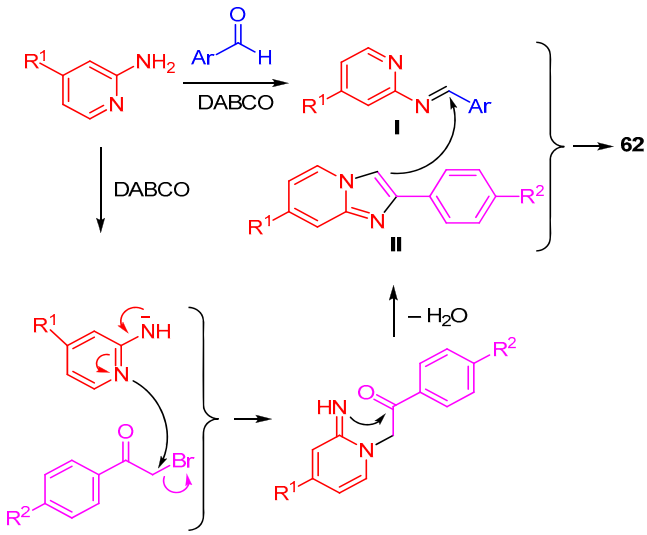
The one-pot synthesis of imidazo[1,2-*a*]pyridines **62** relied on the interaction of various 2-aminopyridines, benzaldehydes, and phenacyl bromides in the presence of DABCO, with the introduction of an alkylamino functionality at position 3 of the formed bicyclic molecule (Scheme 22).[23]

Scheme 22



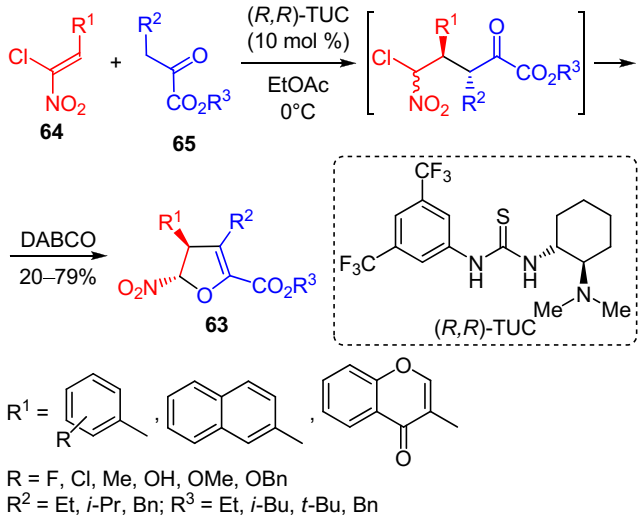
As the initial step, the reaction of 2-aminopyridine and aldehyde in the presence of DABCO (which catalyzed the formation of imine) gave imine intermediate (**I**) (Scheme 23). After the addition of phenacyl bromide to the aminopyridine and the formation of 2-arylimidazo-[1,2-*a*]pyridine (**II**) (with DABCO playing a role during the deprotonation of amidine system), the latter immediately added to imine, with the formation of the target compound **62**.[23] The use of 2-aminothiazoles according to an analogous methodology led to the formation of imidazo-[2,1-*b*]thiazoles.[24]

Scheme 23



A variant of enantioselective Michael reaction assisted by a chiral catalyst is also known. Thus, 4,5-dihydrofuran-2-carboxylate esters **63** were efficiently formed in the presence of organic catalysts by an enantioselective sequence of reactions between (*Z*)-(2-chloro-2-nitroethenyl)benzenes **64** and α-keto esters **65** (Scheme 24).[25] This sequence consisted of a Michael addition promoted by (*R*,*R*)-TUC as catalyst and an intramolecular *O*-alkylation in the presence of DABCO, leading to a single diastereomer with the enantiomeric excess ranging from 86 to 97%.

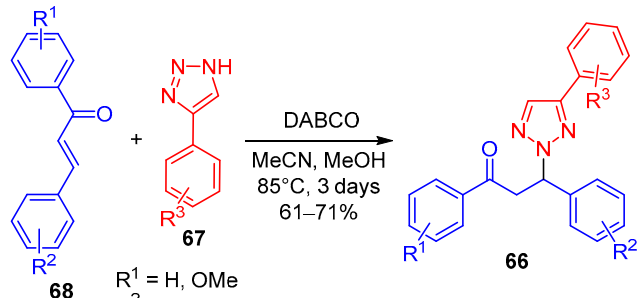
Scheme 24



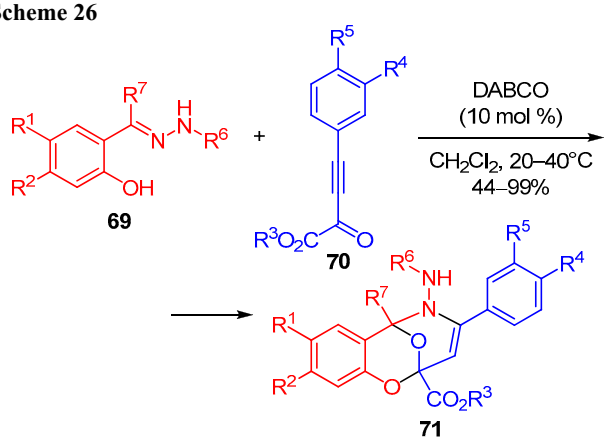
Aza-Michael reactions involve the addition of N-nucleophiles to activated multiple bonds. The role of DABCO in these processes consists, as a rule, of generating reactive N-anions by the deprotonation of NH-acidic compounds.

Thus, a method for the synthesis of 2,4-disubstituted 1,2,3-triazoles was based on the alkylation of triazoles in basic medium (Scheme 25).[26] This synthesis can be performed as a Michael addition of 4-aryl-1*H*-1,2,3-triazoles **67** to α,β-unsaturated ketones **68** in the presence of DABCO

Scheme 25



Scheme 26

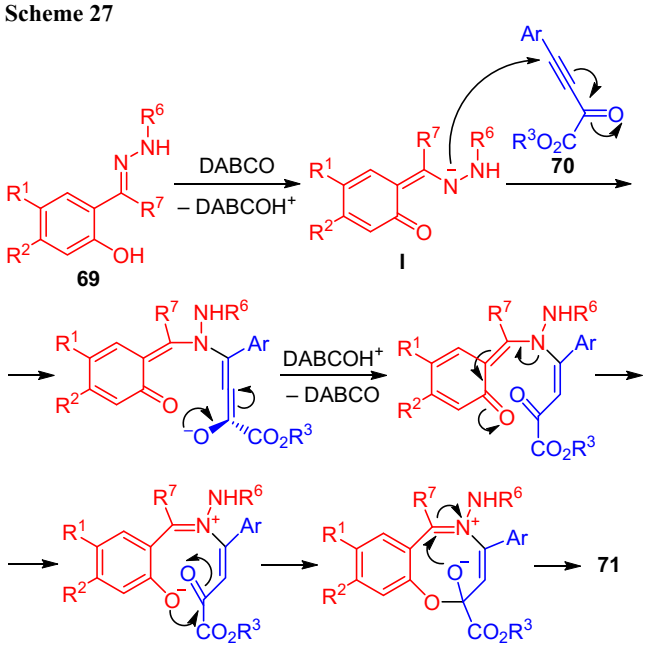


as a catalyst. The reaction proceeded regioselectively and the Michael adducts – 1,3-diaryl-3-(4-aryl-2*H*-1,2,3-triazol-2-yl)propan-1-ones **66** – were obtained in high yields.

The complex cascade reaction of salicylhydrazones **69** with electron-deficient internal alkynes **70** was achieved in the absence of metal catalysts by using only DABCO and led to the formation of oxygen-bridged heterocyclic products – 2,6-epoxy-1,5-benzoxazocines **71** (Scheme 26).[27]

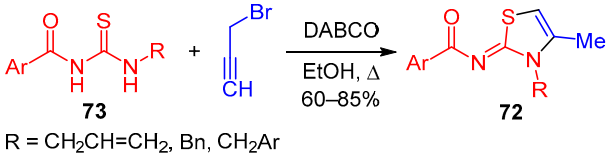
The developed method includes the generation of *o*-quinoidal intermediate **I**, an aza-Michael addition, stereoselective protonation, aromatization with the participation of enamine moiety, the formation of acetal and cyclic hemiaminal **71** (Scheme 27).

Scheme 27



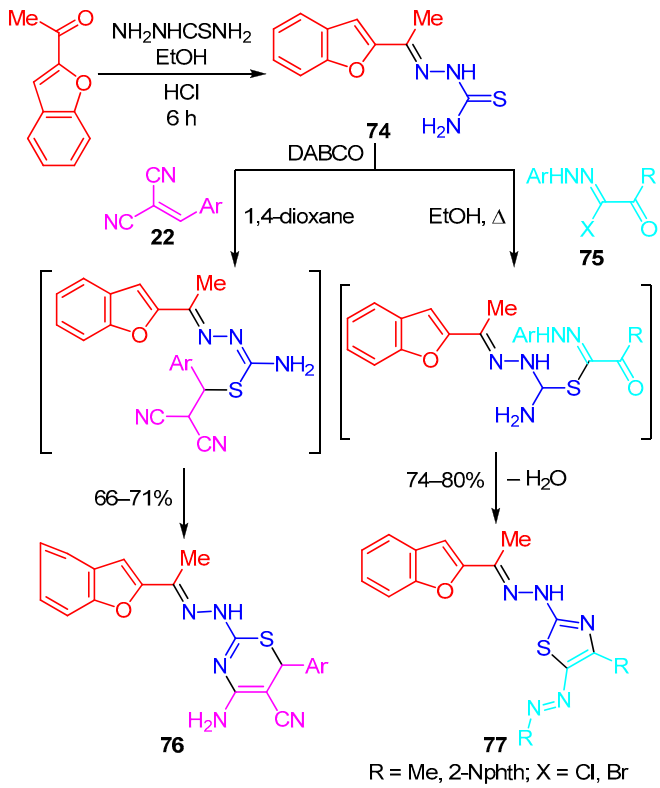
An effective, universal method for the synthesis of 4-methylthiazol-2(3*H*)-ylideneamides **72** in good yields from various acylated thiourea derivatives **73** and propargyl bromide also includes a sequence of alkylation and cyclization according to the aza-Michael reaction mechanism in the presence of DABCO in refluxing EtOH (Scheme 28).[28]

Scheme 28



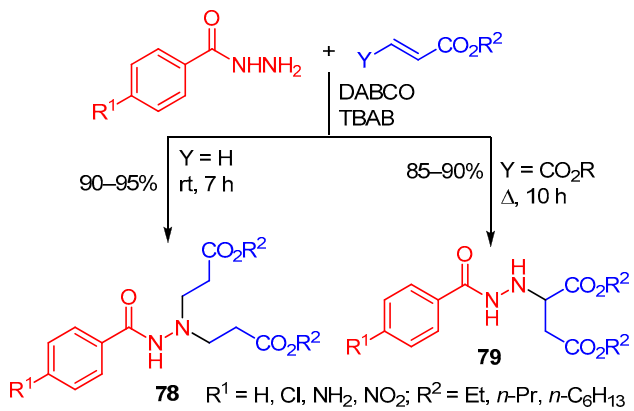
The interaction of 2-[(1-(benzofuran-2-yl)ethylidene]-hydrazinecarbothioamide (**74**) with arylidenemalononitriles **22** and hydrazonoyl halides **75** in the presence of DABCO led to the formation of 1,3-thiazines **76** and thiazoles **77** containing benzofuran ring systems in their molecules (Scheme 29). The reaction between thioamide **74** and malononitrile derivative **22** proceeded as a conjugated Michael addition, while the reaction of thioamide **74** with hydrazonoyl halide **75** followed an addition–elimination mechanism.[29]

Scheme 29



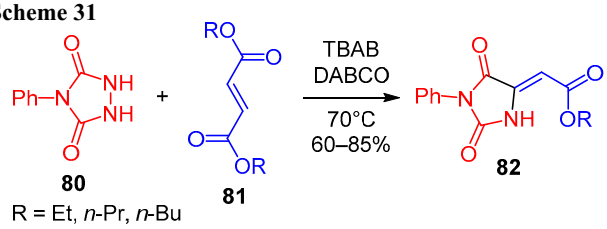
An effective strategy has been described for the preparation of substituted acyl hydrazides through the reactions of various hydrazides with α,β-unsaturated esters in the presence of DABCO as an affordable base for deprotonating the hydrazide and tetrabutylammonium bromide (TBAB) as organic salt under solvent-free conditions. When acrylates were used as Michael acceptors, double addition products **78** were formed in good yields (Scheme 30), while fumarate esters unexpectedly gave only monoadducts **79**.[30]

Scheme 30



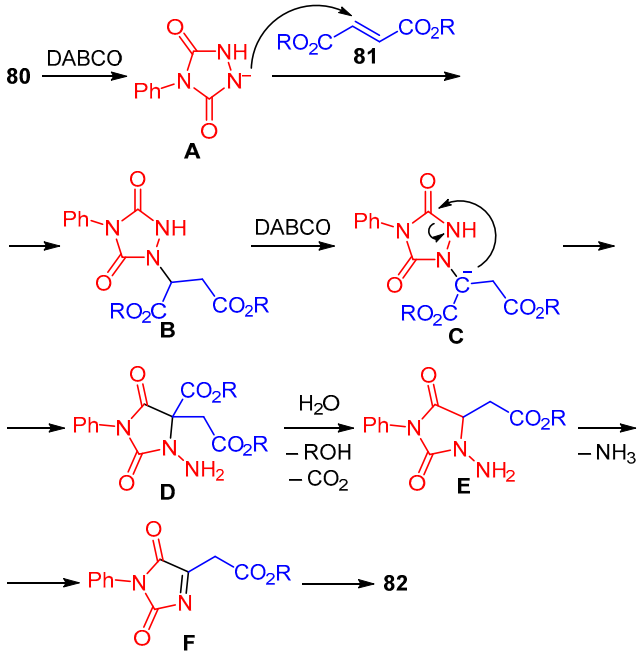
The interaction of 4-phenylurazole (**80**) with fumarate ester **81** led to the substituted hydantoin alkylidene derivatives **82** (Scheme 31).[31] The reaction proceeded in the presence of TBAB and DABCO without solvents at 70°C. The first step of this cascade process was an aza-Michael reaction, which was catalyzed by DABCO.

Scheme 31



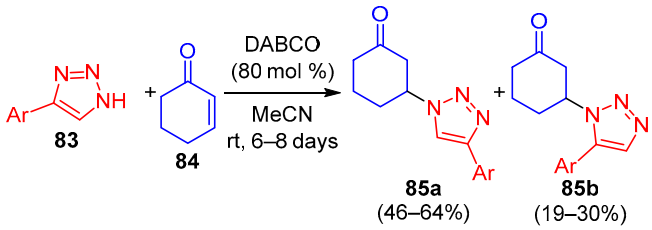
The reaction was initiated by deprotonation of urazole **80** in the presence of DABCO, leading to the formation of anionic intermediate **A**, which underwent a Michael addition to fumarate ester **81** with the formation of adduct **B** (Scheme 32). This adduct in the presence of DABCO was capable of transformation into anionic intermediate **C**. The urazole ring opening in this intermediate led to compound **D**, which was hydrolyzed by the liberated water and then decarboxylated with the formation of compound **E**. The elimination of an ammonia molecule led to compound **F**, which was converted to alkyl (*Z*)-(2,5-dioxo-1-phenylimidazolidin-4-ylidene)acetate **82**.

Scheme 32



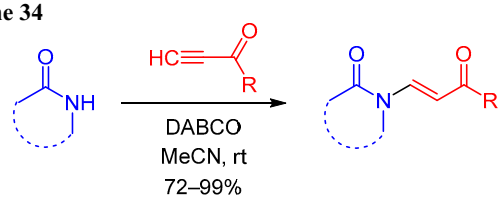
The aza-Michael reaction of 4-aryl-1*H*-1,2,3-triazoles **83** and 2-cyclohex-2-en-1-ones (**84**) in MeCN at room temperature in the presence of DABCO as organic base led to a mixture of 1,4- and 1,5-disubstituted triazoles **85a**,**b**, with the former identified as the major component (Scheme 33).[32] The isomers could be separated chromatographically. Substituents of any electronic nature were found to be compatible with the reaction conditions.

Scheme 33



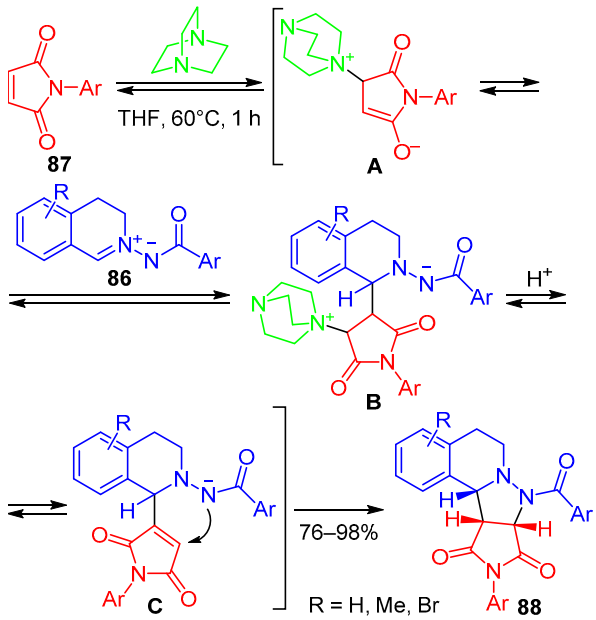
The Michael addition of lactams, imides, (*S*)-4-benzyl-1,3-oxazolidin-2-one, 2-pyridone, pyrimidine-2,4-dione, or inosines at the electron-deficient triple bond of methyl propionate, *tert*-butyl propionate, 3-butyn-2-one, *N*-methoxy-*N*-methylpropynamide in the presence of DABCO gave a superior outcome (faster reaction rate, higher *E*/*Z* ratio) compared to the other catalysts, for example, DMAP, while $RuCl_3$, $RuClCp^*(PPh_3)_2$, AuCl, $AuCl(PPh_3)$, CuI, and $Cu_2(OTf)$ failed to catalyze this process (Scheme 34).[33] DABCO was capable of nucleophilic addition to the triple bond, forming an activated allene system, as well as generating N-anions from the starting materials.

Scheme 34



A [3+2] cycloaddition reaction of azomethine imines **86** to maleimide **87** was achieved in the presence of DABCO as catalyst, providing access to fused heterocyclic compounds **88** containing two nitrogen atoms, while providing a high degree of diastereoselectivity (*dr* up to 25:1) and good yields (76–98%) (Scheme 35).[34] The

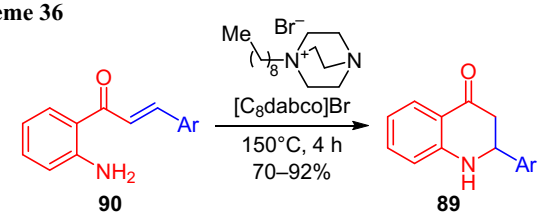
Scheme 35



process was initiated by a reaction of the catalyst with *N*-arylmaleimide **87** with the formation of zwitterionic intermediate **A**, which then added to the azomethine imine (giving intermediate **B**). The elimination of a catalyst molecule provided intermediate **C**, which was converted to the target compound by an intramolecular aza-Michael reaction.

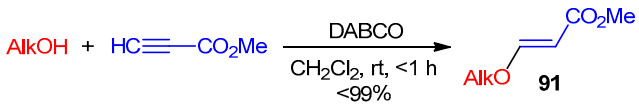
A new, convenient synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **89** was based on the intramolecular cyclization of 2-aminochalcones **90** (aza-Michael reaction), catalyzed by a novel catalyst on the basis of DABCO – [C_8dabco]Br.[35] The remarkable advantages of this procedure included the potential for catalyst recovery, high yields, straightforward workup of the reaction mixture, and good atom economy.

Scheme 36



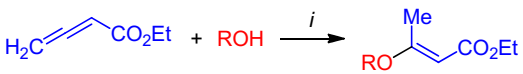
At least equally promising was the addition of O-nucleophiles to Michael acceptors in the presence of DABCO as catalyst, including applications for the synthesis of oxygen-containing heterocycles. For example, a convenient general procedure is known for the synthesis of β-alkoxyacrylates **91** from primary, secondary, and tertiary alcohols by using an oxa-Michael reaction in the presence of tertiary amines as catalysts (Scheme 37).[36] Among the examined basic catalysts, DABCO showed the best results. Correct selection of the reaction conditions enabled the conversion of primary and secondary alcohols, as well as a large set of tertiary alcohols into the respective β-alkoxyacrylate derivatives. The different reactivity of alcohols provided an opportunity for selective transformations of diols containing two different hydroxy groups.

Scheme 37



The Michael addition of phenols and alcohols to ethyl 2,3-butadienecarboxylate (allenoate) in the presence of DABCO as catalyst also provided synthetic access to (*E*)-β-aryloxy- and (*E*)-β-alkoxyacrylates (Scheme 38).[37] The notable advantages of this method included the great molecular diversity of substrates, mild reaction conditions, high *E*-selectivity (>99:1), and good yields.

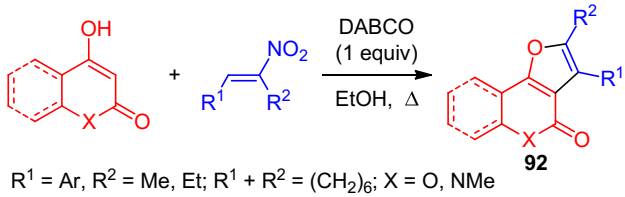
Scheme 38



R = Ar (79–99%; *i*: DABCO (5 mol %), *i*-PrOH, rt)
R = Alk (40–69%; *i*: DABCO (5 mol %), neat, 80°C)

The intramolecular cyclization of enols and nitrostyrenes in the presence of DABCO as catalyst proceeded regioselectively, giving high yields of the fused coumarin derivatives **92** after the elimination of nitro group (Scheme 39).[38a] The method was applicable to various enol derivatives, including 4-hydroxyquinolinones, 4-hydroxycoumarins, and 4-hydroxypyranones. Coumarins, which are analogs of compounds **92**, are of interest for potential applications in fluorescent probes.[38b]

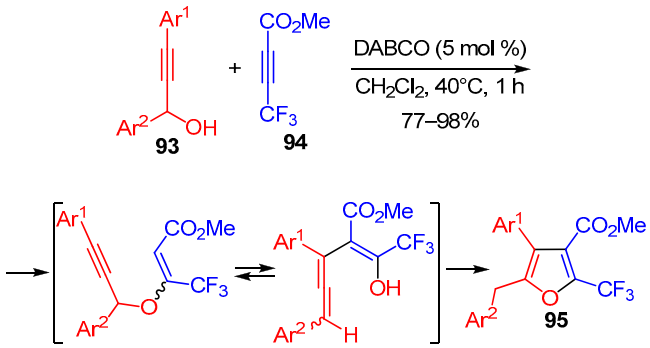
Scheme 39



R^1 = Ar, R^2 = Me, Et; $R^1 + R^2 = (CH_2)_6$; X = O, NMe

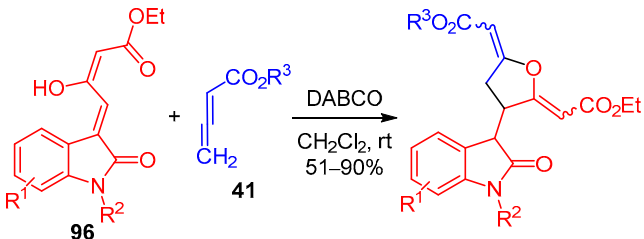
DABCO as catalyst also promoted the reaction of propargylic alcohols **93** with methyl 2-trifluoroalkynylcarboxylate (**94**), leading to the formation of trifluoromethylated furans **95** under mild conditions in up to 98% yields (Scheme 40).[39] Control experiments showed that the reaction proceeded *via* Michael addition with the formation of the respective vinyl esters, a Claisen rearrangement, and cyclization.

Scheme 40



A domino reaction of 3-oxo-4-(2-oxindolyl-3-ylidene)-butanoates **96** and allenoates **41** occurred in the presence of DABCO as catalyst and gave good yields of 2,3,5-substituted tetrahydrofuran derivatives **97** containing an oxindole substituent and two exocyclic double bonds (Scheme 41).[40] One of the steps in this complex process was an oxo-Michael reaction.

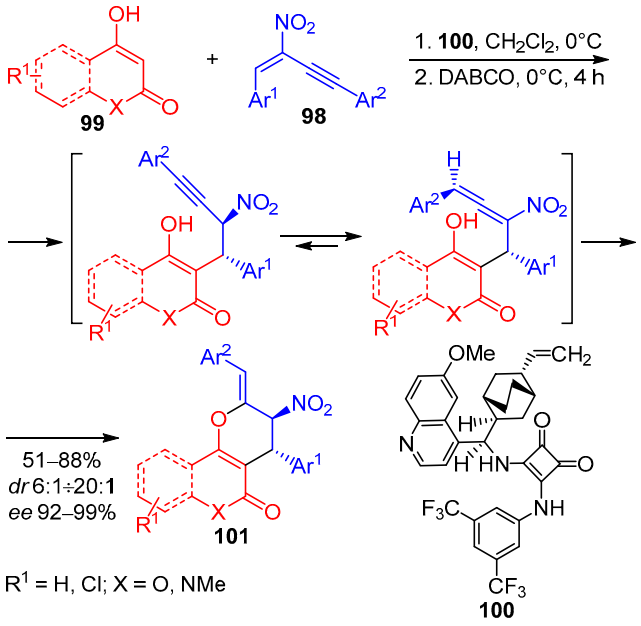
Scheme 41



R^1 = H, Alk, OMe; R^2 = H, Me; R^3 = Me, Et, Bn

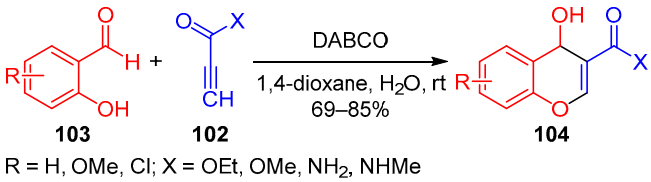
The reaction of 1,3-nitroenynes **98** with 4-hydroxy-6-methyl-2-pyrones **99** in the presence of the chiral catalyst **100** led to the formation of annulated pyrans **101** in high yields (up to 88%) and excellent stereoselectivity (*dr* >20:1 and *ee* >99%) (Scheme 42).[41] The reaction proceeded through a sequence of conjugated addition, allene formation, stereoselective intramolecular oxo-Michael reaction (6-*endo-dig* cyclization), and alkene isomerization in the presence of DABCO as catalyst. The analogous transformation in the presence of DABCO instead of specialized organocatalyst also allowed to obtain pyrano-[3,2-*c*]chromenes with excellent stereoselectivity (*Z*- and *E*-isomer ratio up to >96:4) and good yields (72–89%).[42]

Scheme 42



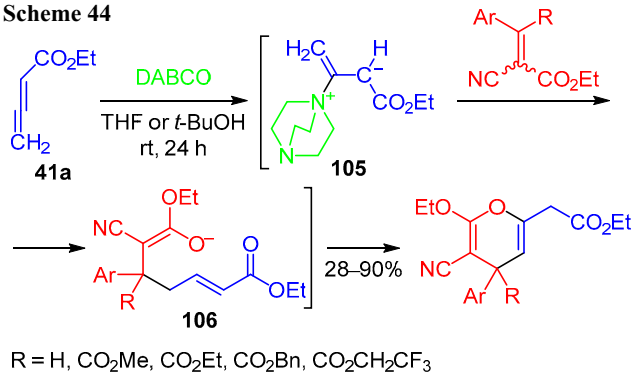
Terminal alkynes containing an ester or amide group (Michael acceptors **102**) reacted regioselectively with salicylic aldehyde **103** in the presence of DABCO in aqueous dioxane medium, forming 3-substituted 4-hydroxy-4*H*-chromenes **104** (Scheme 43).[43] The reaction comprised deprotonation of salicylic aldehyde in the presence of DABCO, a Michael addition of phenolate anion to the triple bond, an intramolecular aldol condensation, and deprotonation.

Scheme 43



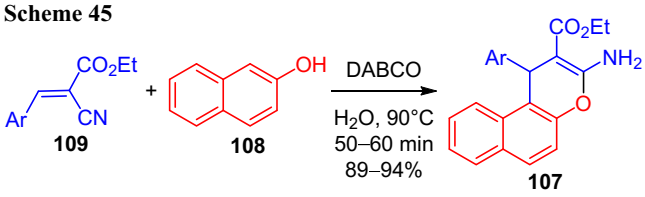
The stereoselective formal [4+2] annulation of fully substituted alkenes with allenoates in the presence of DABCO, which led to smooth formation of functionalized 4*H*-pyran derivatives, represented a cascade of carbo- and oxo-Michael reactions.[44,45] The addition of DABCO to allenoate **41a** at the β-position generated the active stabilized zwitterion **105**, which added to alkene molecule according to the carbo-Michael mechanism, leading to the formation of intermediate **106**, which underwent further intramolecular cyclization *via* the addition of enolate anion at the double bond (Scheme 44).[44]

Scheme 44



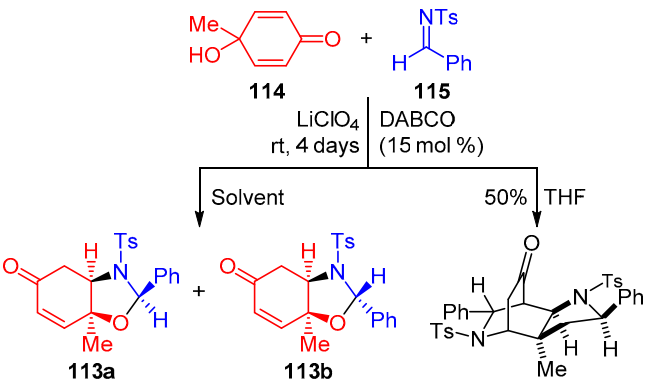
An environmentally benign, simple, and effective method for the synthesis of ethyl 3-amino-1-aryl-1*H*-benzo-[*f*]chromene-2-carboxylates **107** consists of a reaction between β-naphthol (**108**) and 3-arylcyanoacrylates **109** in aqueous medium in the presence of DABCO as catalyst (Scheme 45).[46] All of the reaction products precipitated from the reaction mixture and were isolated by simple filtration, without need for further purification.

Scheme 45



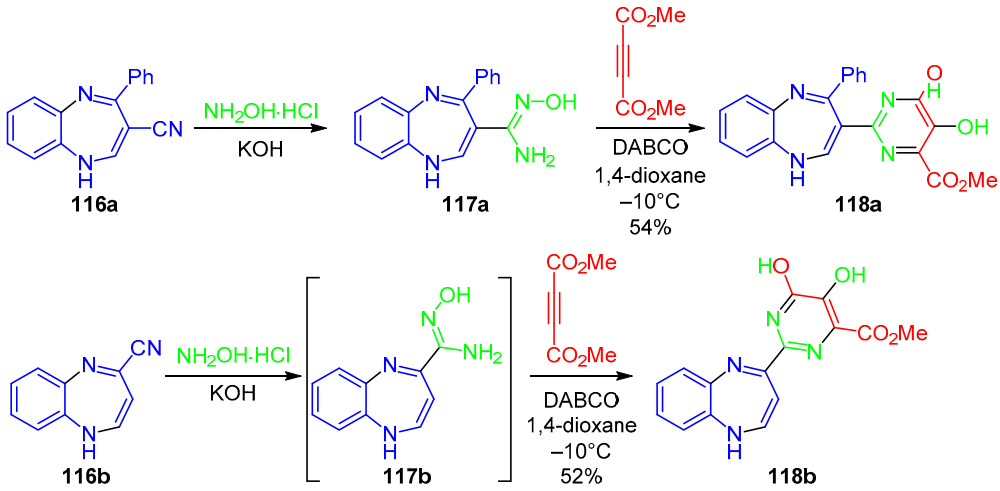
Tetrahydro-1,3-benzoxazolones **113a**,**b** were synthesized stereoselectively from *p*-quinol **114** *via* a reaction with tosylaldimine **115** under the conditions of basic catalysis (Scheme 46).[47] It is important to note that after

Scheme 46

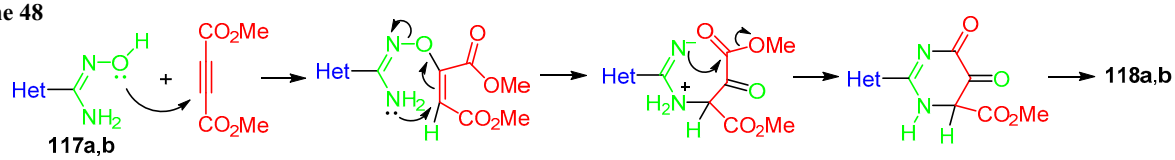


Solvent	113a/113b	Conversion, %
CH_2Cl_2	90:10	44
MeOH	70:30	42

Scheme 47



Scheme 48



changing the solvent to THF the reaction proceeded toward the formation of tricyclic product through the addition of another molecule of tosylaldimine **115** to tetrahydro-1,3-benzoxazolone **113**. The process consisted of an experimentally straightforward domino sequence of oxa- and aza-Michael reactions.

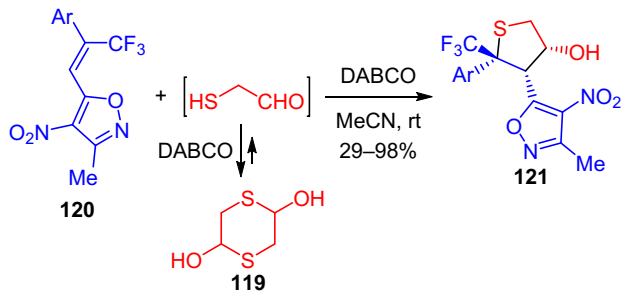
A one-pot methodology has been described, starting from 1,5-benzodiazepine amidoximes **117a**,**b** that were obtained from nitrile derivatives **116a**,**b**, enabling the synthesis of new pyrimidine derivatives **118a**,**b** in the presence of DABCO as catalyst under the conditions of microwave irradiation, which were then characterized with respect to their antimicrobial properties (Scheme 47).[48]

The mechanism for the formation of pyrimidine ring can be interpreted according to this route: an oxa-Michael reaction is followed by a rearrangement of the N-adduct and then a cyclization step (Scheme 48).

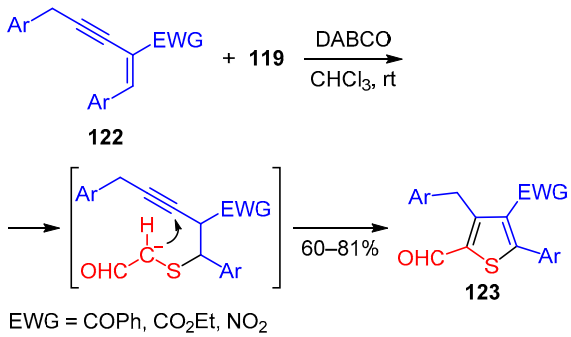
S-Nucleophiles also actively participated in the addition to activated multiple bonds. Thus, an effective diastereoselective [3+2] annulation of mercaptoacetaldehyde, obtained from 1,4-dithiane-2,5-diol (**119**) by the action of DABCO, with the trifluoromethyl-substituted styrylisoxazoles **120**, also catalyzed by DABCO, led to the formation of functionalized tetrahydrothiophenes **121** containing a quaternary atom decorated with a trifluoromethyl group, resulting in excellent yields and diastereoselectivity (Scheme 49).[49] The process consisted of a cascade of sulfo-Michael reaction and a Henry reaction.

The selection of 1,3-enynes **122** as Michael acceptors for the reactions with mercaptoacetaldehyde, which was generated *in situ* from 1,4-dithiane-2,5-diol (**119**) in the presence of DABCO at room temperature, enabled the preparation of tetrasubstituted thiophenes **123** (Scheme 50).[50] The domino process consisted of a Michael reaction, 5-*exo*-*dig* cyclization, and an oxidation step.

Scheme 49



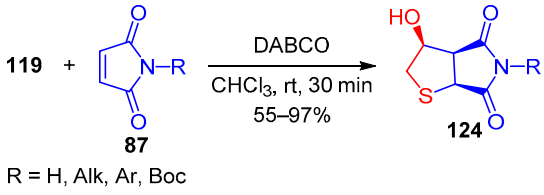
Scheme 50



The highly diastereoselective (*dr* >20:1) intermolecular [3+2] annulation reaction of 1,4-dithiane-2,5-diol (**119**) to maleimide **87** in the presence of DABCO as catalyst led to the formation of a series of polyfunctionalized bisheterocyclic tetrahydrothiophene and pyrrolidine derivatives **124** in up to 97% yields (Scheme 51).[51] The sequence consisting of a Michael reaction and enol reaction can be performed in organic solvents, as well as in water.

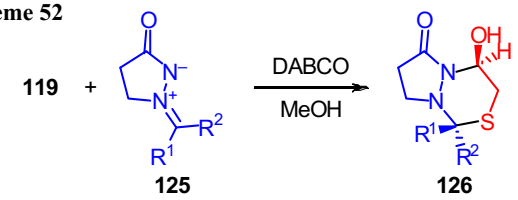
The mechanism of the domino reaction between 1,4-dithiane-2,5-diol (**119**) and azomethine imines **125**, leading to the formation of 4-hydroxytetrahydropyrazolo[1,2-*c*]-

Scheme 51



[1,3,4]thiadiazin-6-ones **126** (Scheme 52), was studied by a computational approach using the B3LYP and MO6-2X functionals (for the case of R^1 = H, R^2 = Ph).[52] The most energetically favorable reaction pathway consisted of three steps: the deprotonation of mercaptoacetaldehyde by the action of DABCO, accompanied by the formation of thiolate anion, which then acted as a nucleophile by attacking azomethine imine **125**, leading to intramolecular cyclization. It was noted that the reaction proceeded most effectively in the presence of DABCO and MeOH, while hydrogen bonds played a key role in the diastereoselectivity of this process.

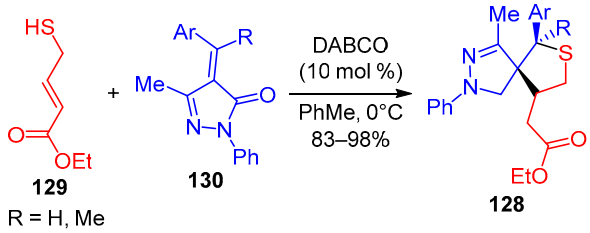
Scheme 52



The products from the Michael addition of 2-mercaptobenzyl alcohol to nitroalkenes containing a carbohydrate moiety were used as starting materials for the synthesis of chiral 3-nitro-2*H*-thiochromenes **127a**,**b** (Scheme 53), which exhibited antioxidative and antiproliferative properties against human tumor cells.[53]

The diastereoselective formation of spiro[pyrazole-3,3'-tetrahydrothiophene] **128** was achieved by a tandem Michael cyclization (Scheme 54).[54] DABCO deprotonated

Scheme 54

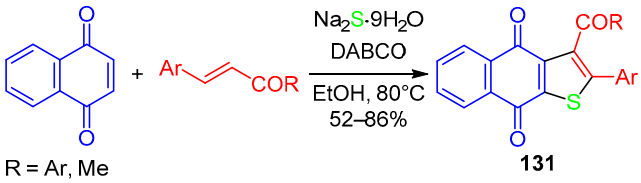


mercaptoester **129**, the obtained intermediate participated in intermolecular addition to the exocyclic double bond of pyrazolone **130**, followed by the second, intramolecular Michael addition. The reaction was demonstrated using the example of ethyl *trans*-4-mercaptobutenoate (**129**) with various 4-benzylidene-5-methyl-2-phenylpyrazolones **130** in the presence of DABCO as catalyst in PhMe medium at 0°C. The process proceeded rapidly and led to the respective spiro derivatives **128** with excellent yields and diastereoselectivity (*dr* >20:1).

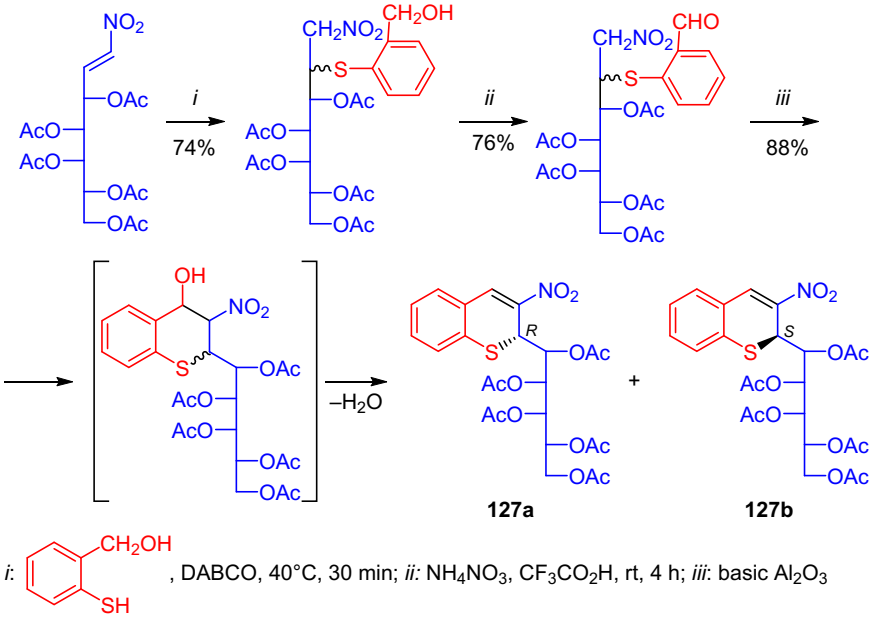
An effective method was also developed for the synthesis of naphtho[2,3-*b*]thiophene-4,9-diones **131** by a three-component reaction of 1,4-naphthoquinone, various α,β-unsaturated ketones, and aqueous Na_2S in the presence of DABCO as catalyst (Scheme 55).[55] The process included a sequential Michael addition of Na_2S to α,β-unsaturated ketones, the obtained sulfide adduct – to naphthoquinone, followed by intramolecular oxidative cyclization and aromatization.

A simple and effective one-pot procedure for the synthesis of 2-aryl-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]-indole derivatives **132**, which are of interest to researchers

Scheme 55

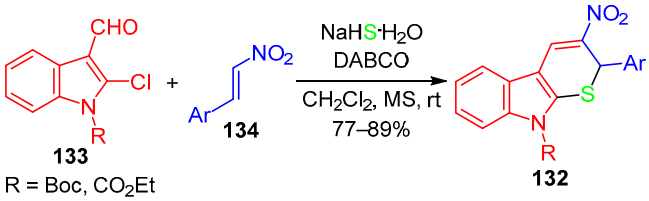


Scheme 53



in the field of medicinal chemistry,[56a] was performed in CH_2Cl_2 at room temparature by a sequence of three-component reactions between *N*-protected 2-chloro-3-formyl-indole **133**, NaHS, and β-substituted nitroalkenes **134** or β-substituted nitrodienes, while using DABCO in the role of organocatalyst and performing dehydration in the presence of activated 4Å molecular sieves (Scheme 56).[56b]

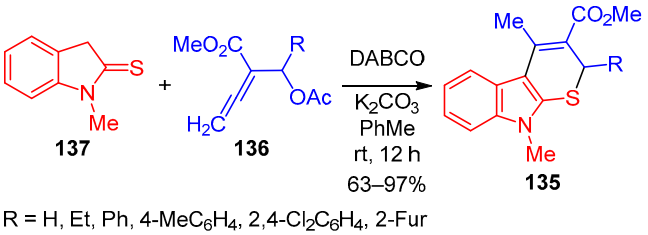
Scheme 56



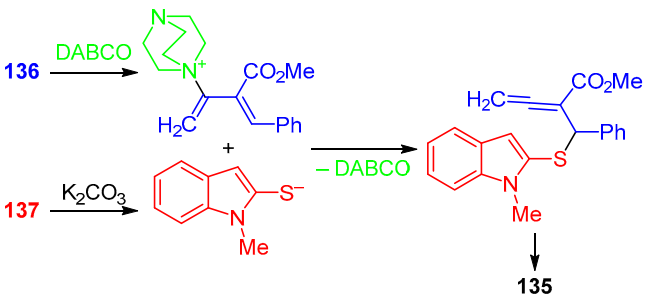
One of the key steps in this process was apparently a thio-Michael reaction, followed by a cyclization according to the Henry reaction. The synthesized compounds were fluorescent and showed a large positive Stokes shift (5632–6081 cm^{-1}).

Analogous thiopyrano[2,3-*b*]indoles **135** were obtained in the reactions of β-acetoxyallenoates **136** with indoline-2-thione (**137**) by addition of DABCO and K_2CO_3, followed by intramolecular Friedel–Crafts reaction at position 3 of indole ring and the central atom of allene (Scheme 57).[57] The proposed reaction mechanism is shown in Scheme 58.

Scheme 57

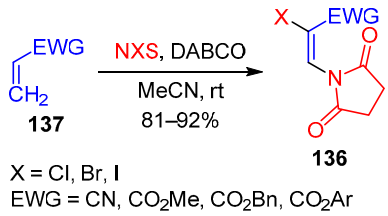


Scheme 58



In some cases, the Michael addition served as the initial step in very complex cascade transformations. For example, an effective and rapid synthesis of enamides **136** from alkenes **137**, promoted by DABCO, proceeded through an unusual cascade of transformations, including an aza-Michael reaction, bromination, elimination, and a Morita–Baylis–Hillman-type reaction that concluded by the elimination of DABCO, resulting in regio- and stereoselective synthesis of enamides **136** (Scheme 59).[58]

Scheme 59

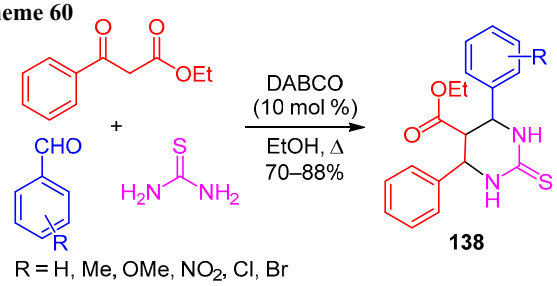


Biginelli reaction catalyzed by DABCO

While it appears quite logical that DABCO can serve as a good catalyst in traditionally base-catalyzed reactions, we consider it rather unexpected that DABCO has been employed also in well-known acid-catalyzed processes. Thus, for example, the classic variant of the Biginelli reaction represents a synthesis of tetrahydropyrimidines by an acid-catalyzed condensation of ureas, β-keto esters, and aldehydes.[59] However, studies published in recent years have shown that this process can be successfully performed in the presence of Lewis base catalysts, such as DABCO.

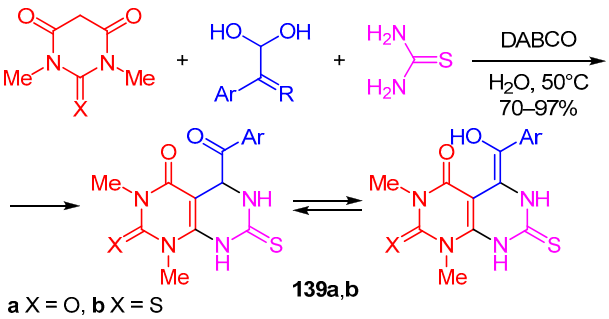
Heterocyclic compounds containing a pyrimidine ring are of particular interest to researchers in the field of medicinal chemistry. Some of these compounds have been characterized with respect to antifungal, antibacterial, anticancer, and tuberculostatic activity. Due to these reasons, the Biginelli reaction has a great practical value. For example, a series of tetrahydropyrimidine derivatives **138** were synthesized on the basis of Biginelli reaction by using DABCO as a catalyst. Some of these products exhibited pronounced antibacterial activity (Scheme 60).[60]

Scheme 60



An effective, environmentally benign regio- and stereoselective method was also developed for the synthesis of 5-aroyl-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydro[4,5-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione derivatives **139a** and 5-aroyl-1,3-dimethyl-2,7-dithioxo-2,3,5,6,7,8-hexahydro[4,5-*d*]pyrimidin-4(1*H*)-one derivatives **139b** in good to excellent yields by a one-pot three-component Biginelli-type condensation between arylglyoxal monohydrates, *N*,*N*-di-

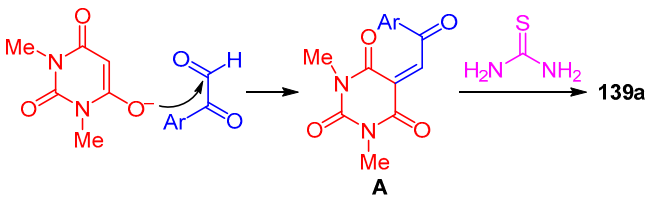
Scheme 61



methylbarbituric acid or *N*,*N*-dimethyl-2-thiobarbituric acid, and thiourea in H_2O at 50°C in the presence of DABCO as a "green" catalyst (Scheme 61).[61]

The reaction mechanism has been described in the literature:[62] the anion of barbituric acid enol form, created by the action of DABCO, underwent a condensation step with glyoxal, leading to the formation of biselectrophilic intermediate **A**, which was cyclized by a reaction with the bisnucleophilic thiourea (Scheme 62).

Scheme 62



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