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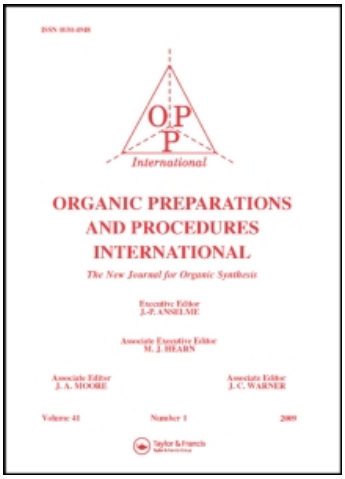

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Recent Advances in the Synthesis of Pyrazoles. A Review

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Introduction

Pyrazole (*Figure 1*), a five-membered, two-nitrogen-containing heterocycle ring, is widely found as the core structure in a large variety of compounds that possess important agrochemical and pharmaceutical activities.[1,2] Classical methods for the synthesis of substituted pyrazoles involve approaches based either on the condensations of hydrazines with 1,3-dicarbonyl compounds and their 1,3-dielectrophile equivalents, or on intermolecular [3+2] cycloadditions of 1,3-dipoles to alkynes.[3,4] Over the past few years, however, more and efficient and broadly applicable methodologies have been developed with the aim of increasing the regioselectivity in the preparation of 1,3,5-tri- and 1,3,4,5-tetrasubstituted pyrazoles.

Figure 1

The chemistry of pyrazole has been reviewed extensively for the period up until the middle of the last decade.[3,4] In the present review, we have thus chosen to summarize the most relevant advances in the construction of the pyrazole ring reported in the literature from 1995 until mid-2008. The various methods reviewed include reactions in solution only. Some of these approaches have been successfully applied to the synthesis of substituted pyrazoles with important biological properties such as alkoxycarbonyl and fluorinated derivatives.

In general, all the products mentioned in this review have been unequivocally identified through NMR studies and, in some cases, their structures have been confirmed by means of X-ray diffraction of appropriate single crystals, as indicated in the respective papers. We will not describe the characterization techniques used.

The methodologies summarized focus mainly on procedures for the generation of the pyrazole ring and, in some cases, for the preparation of various building blocks. Subsequent

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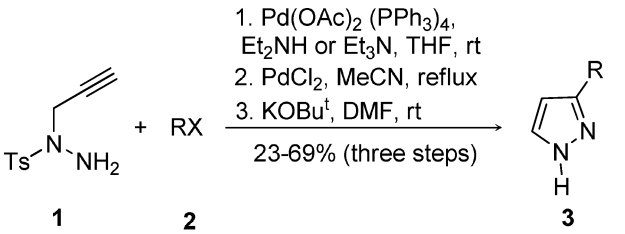
substitution reactions either at the carbon or nitrogen atoms of the nucleus of the newly formed pyrazole are, in general, beyond the scope of this review.

I. 1*H*-Pyrazoles

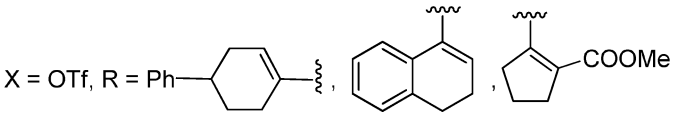
1. 3(5)-Substituted-1H-pyrazoles

A strategy based on the concept of palladium-catalyzed coupling/annulation was applied to the one-pot synthesis of a large number of 3-(5)aryl/vinyl-1*H*-pyrazole derivatives **3** from the readily available *N*-tosyl-*N*-propargylhydrazine **1** and aryl iodides or vinyl triflates **2**.[5] This process allows the introduction of a variety of aryl groups bearing electron-donating and electron-withdrawing substituents (*Scheme 1*).



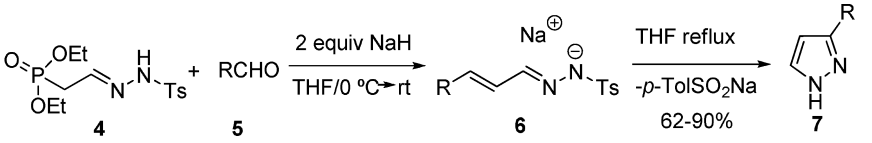
1 **2** **3**

X = I; R = Ph,2/4-$O_2NC_6H_4$, 4-$MeCOC_6H_4$, 3-$CF_3C_6H_4$, 3/4-$EtOOCC_6H_4$, 2/3-FC_6H_4, 4-MeC_6H_4, 3-$HOCH_2C_6H_4$, 4-$MeOC_6H_4$, 3/4-$MeCONHC_6H_4$



Scheme 1

A [1+4] approach was developed by Santagostino *et al.* to prepare 3-(5)-substituted pyrazoles **7** from diethoxyphosphorylacetaldehyde tosylhydrazone **4** and aldehydes **5** *via* α,β-unsaturated tosylhydrazones **6** (*Scheme 2*).[6] This method is quite general in that the reaction conditions leave a number of functional groups unscathed; in addition, it can be applied to enolizable as well as unsaturated or aromatic aldehydes.



4 **5** **6** **7**

R = 2-propenyl, styryl, ferrocenyl, 2-thienyl, 2-(5-hydroxymethyl)furyl, 2-(5-tributylsilyloxymethyl)furyl, 2-(5-acetyloxymethyl)furyl, 4-BrC_6H_4, 4-$(EtO)_2CHC_6H_4$, 4-$Me_2NC_6H_4$, $HOOCC_6H_4$, Bn, cyclohexyl

Scheme 2

The 1,3-dipolar cycloaddition of diazo compounds to triple bonds is an important [3+2] method for the preparation of pyrazoles. Thus, diazo compounds **9** generated *in situ*

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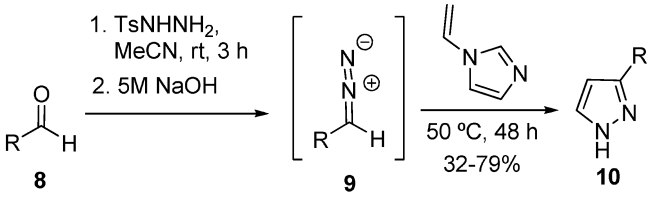
from tosylhydrazones of aldehydes **8** react with *N*-vinylimidazole–an acetylene equivalent bearing a leaving group–to afford pyrazoles **10** in moderate yields (*Scheme 3*).[7]



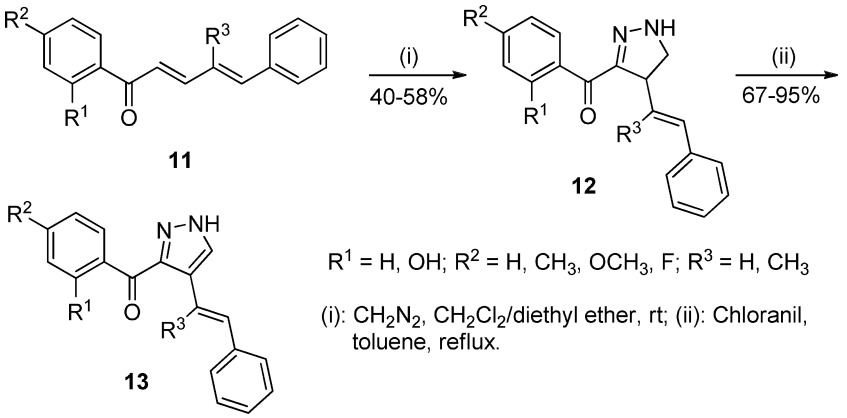
R = Ph, 2-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-CNC$_6$H$_4$, 4-ClC$_6$H$_4$, 2-furyl, 2-thienyl, 3-pyridyl

Scheme 3

2. 3,4- and 3,5-Disubstituted-1H-pyrazoles

a. 3,4-Disubstituted-1H-pyrazoles

The oxidation of pyrazolines is a suitable method for obtaining pyrazoles. One of the most common synthetic procedures for the preparation of pyrazolines is based on the cycloaddition of diazoalkanes to α,β-unsaturated ketones. Silva *et al.*[8] applied this approach to the synthesis of 3-benzoyl-4-styryl-2-pyrazolines **12** by treatment of (*E,E*)-cinnamylideneacetophenones **11** with diazomethane. Subsequent oxidation with chloranil afforded 3-(5)benzoyl-4-styrylpyrazoles **13** in good yields (*Scheme 4*).



R^1 = H, OH; R^2 = H, CH$_3$, OCH$_3$, F; R^3 = H, CH$_3$

(i): CH_2N_2, CH_2Cl_2/diethyl ether, rt; (ii): Chloranil, toluene, reflux.

Scheme 4

The same authors also prepared *bis*(pyrazoles) through 2,3-dichloro-5,6-dicyanoquinone (DDQ) oxidation of pyrazolyl-2-pyrazolines previously obtained from substituted chromen-4-ones.[9]

Recently, an efficient three-component, one-pot reaction for the preparation of 3,4-diarylpyrazoles **16** has been reported. The strategy involves sequential Suzuki coupling

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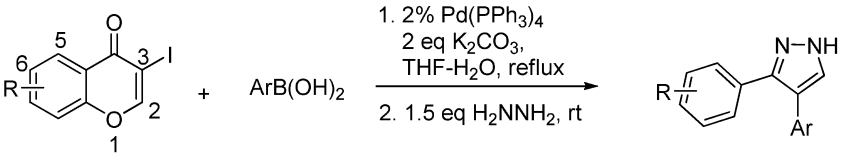
between iodochromones **14** and phenylboronic acids **15** in the presence of $Pd(PPh_3)_4$ and K_2CO_3, followed by condensation with hydrazine hydrate (*Scheme 5*).[10] This process tolerates a broad range of functional groups.



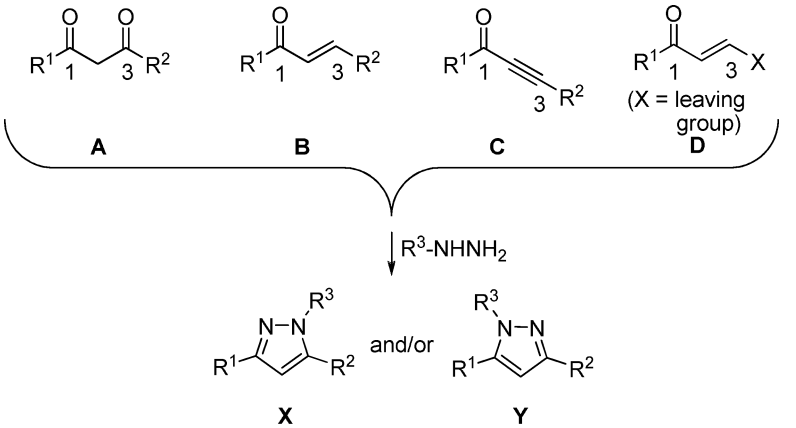
14 **15** **16**

R = H: Ar = 4-$MeOC_6H_4$, 82%; 4-$CF_3C_6H_4$, 73%; 3-$MeOC_6H_4$, 84%; 3-$CF_3C_6H_4$, 80%; 3-HOC_6H_4, 88%; 2-FC_6H_4, 95%; 3-thienyl, 90%
Ar = Ph: R = 6-Me, 92%; 6-MeO, 95%; 6-Cl, 90%; 6-NO_2, 48%

Scheme 5

b. 3,5-Disubstituted-1H-pyrazoles

The most common synthetic method for the preparation of 3,5-disubstituted pyrazoles involves cyclocondensation of an appropriate hydrazine, which acts as a bidentate nucleophile, with other three-carbon units featuring two electrophilic carbons in a 1,3-relationship, such as either 1,3-dicarbonyl (**A**; *Scheme 6*) or α,β-unsaturated carbonyl compounds (**B**, **C** and **D**; *Scheme 6*).



Scheme 6

With unsymmetrical substrates having two electrophilic centers such as **A, B, C, D** in *Scheme 6* ($R^1 \neq R^2$), mixtures of regioisomers **X** and **Y** are often obtained in reactions with substituted hydrazines ($R^3 \neq H$). However, when $R^3 = H$, the prototropic tautomerism of pyrazoles renders **X** equivalent to **Y**.

i. From 1,3-Diketones

Most of the 1,3-diketones used in the synthesis of pyrazoles must be previously prepared and purified, often being obtained as mixtures of condensation products. Recently, an efficient, rapid, and general one-pot synthesis of 3,5-disubstituted pyrazoles

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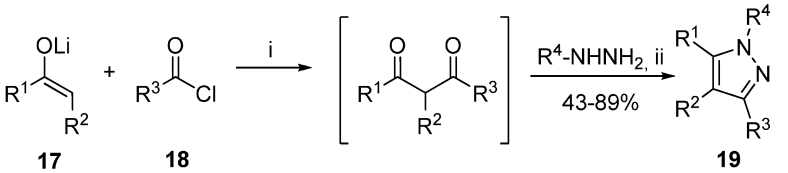
19 starting with enolates **17** and acid chlorides **18** has been reported (*Scheme 7*). The 1,3-diketones thus formed were not isolated, but rather converted *in situ* into pyrazoles through the addition of hydrazines.[11] The process seems to tolerate a wide range of functional groups.

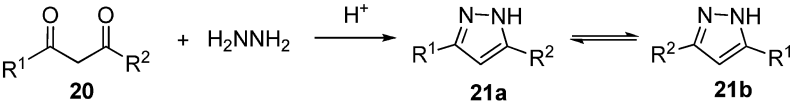


(i): LiHMDS, toluene, 0 ºC, 2 min. (ii): AcOH, EtOH, THF, auto-reflux, 5 min.

R^1 = Aryl, heteroaryl; R^2 = H, *n*-propyl, Ph; R^1/R^2 = $CH_2CH_2OCH_2$, $CH_2CH_2N(Boc)CH_2$, $(CH_2)_4$; R^3 = Aryl, *n*-C_5H_{11}; R^4 = H, Me, Ph

Scheme 7

Compared to reactions in organic solvents, solventless reactions are often faster, occur in higher yields, and have both environmental and economic advantages. Thus, a solventless condensation of 1,3-diketones **20** with hydrazine in the presence of a catalytic amount of sulfuric acid at room temperature afforded 3,5-disubstituted pyrazoles **21** in high yields (*Scheme 8*).[12] The reactions were carried out in a mortar, in which the diketone and hydrazine hydrate were mixed with a drop of concentrated sulfuric acid.



R^1 = R^2 = Me, 96%; R^1 = R^2 = Bu^t, 92%; R^1 = CO_2Et, R^2 = Me, 90%; R^1 = Me, R^2 = Ph, 96%

Scheme 8

ii. From α,β-Unsaturated Carbonyl Compounds

Bhat *et al.* reported an effective procedure for the preparation of 3,5-diphenyl-1*H*-pyrazoles **24** from chalcones **22** through the action of hydrazine hydrate on chalcone-epoxide **23**, followed by dehydration (*Scheme 9*). The epoxidation reactions took place in high yields (85–94%), with the two latter steps being carried out as a one-pot reaction.[13]

α-Acetylenic ketones are also suitable 1,3-dielectrophilic templates for the preparation of 3,5-disubstituted pyrazoles. *N*-Alkyl (Me, Et, *i*-Pr, *t*-Bu)-substituted phthalimides **25** were thus transformed into 3,5-diarylpyrazoles **28** through a one-pot addition-decyclization-cyclocondensation process (*Scheme 10*).[14] The requisite substrates were easily obtained from commercially available phthalic anhydride and phthalimide. The best results were achieved when an *N-tert*-butyl phthalimide (R^1 = *t*-Bu) was used as starting material, probably because the steric effect between the *N-tert*-butyl group and the 3-alkynyl groups of the *N*-alkylated 3-alkynyl-3-hydroxyisoindoline intermediates **26** facilitates the formation of the α-acetylenic ketone **27** through ring cleavage at the C-N bond of the 3-hydroxyisoindoline.

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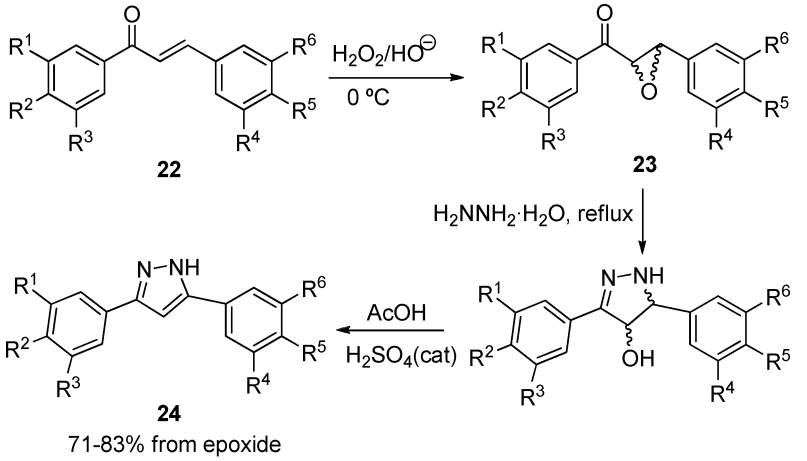
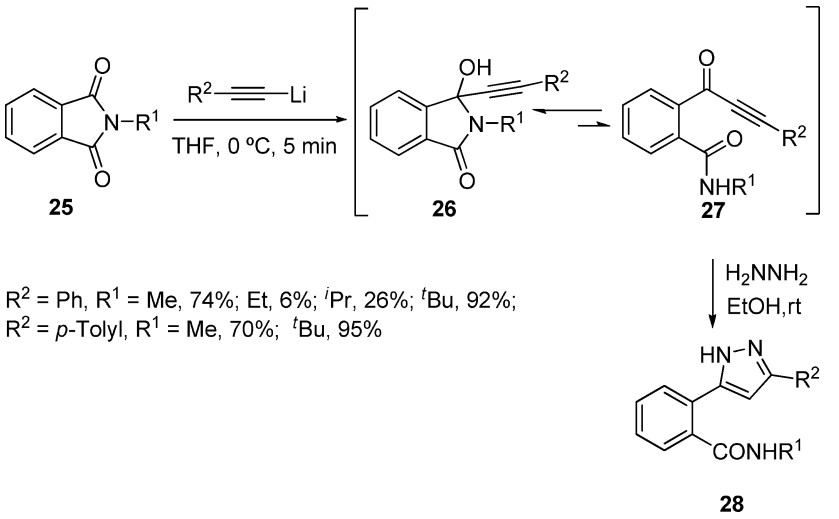


Scheme 9



Scheme 10

With lithium (trimethylsilyl)acetylide (R^2 = TMS), the corresponding 3-(5)aryl-substituted pyrazole **28** (R^1 = ^{t}Bu, R^2 = H) was obtained in 96% yield (*Scheme 10*). Methyl, phenyl, and *p*-nitrophenylhydrazines also reacted regioselectively through a conjugate addition of the NH_2 of the hydrazine with the ynone **27** to afford the corresponding 1,3,5-trisubstituted pyrazoles (R^1 = ^{t}Bu) in high yields (71–95%).

Grotjahn *et al.* synthesized 1*H*-pyrazoles **31** containing a functionalized side-chain at C-3(5) from readily available tetrahydropyranyl (THP) acetylenic ethers **29**, which were coupled with acid chlorides to yield conjugated acetylenic ketones **30**. Subsequent condensation with hydrazine hydrate afforded, after alcohol deprotection and conversion to a chloride, 5-substituted 3(5)-(chloromethyl)- or 3(5)-(2-chloroethyl)pyrazoles **32**.[15]

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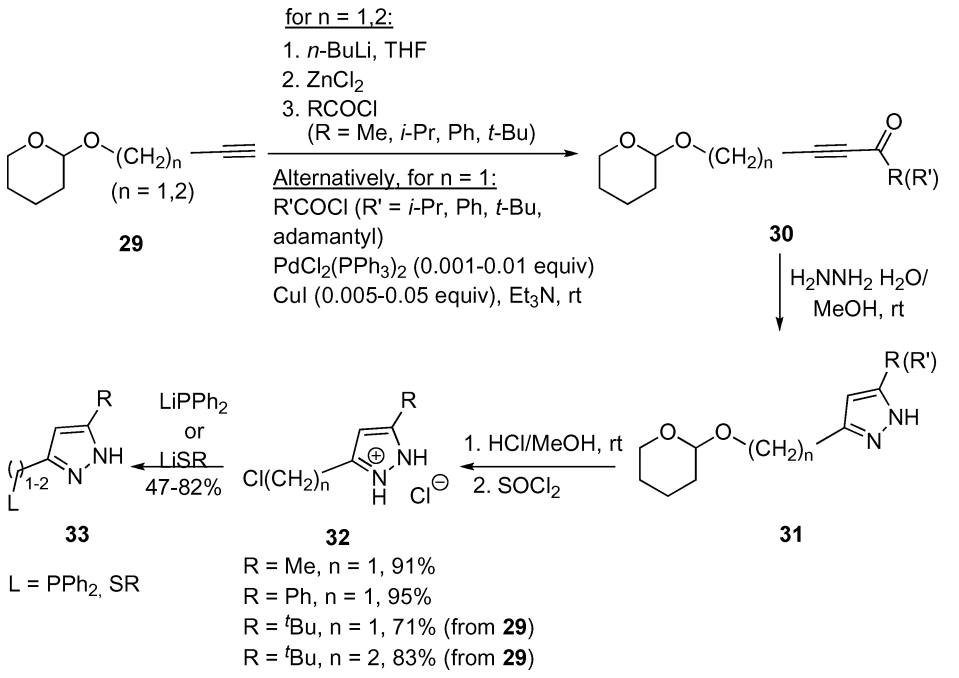
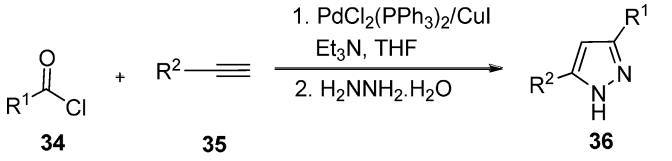


Scheme 11

Finally, pyrazole hydrochloride salts **32** were converted to sulfur- and phosphorus-based ligands **33** through nucleophilic substitution (*Scheme 11*).

Jiang *et al.* carried out a coupling-cyclocondensation sequence in a one-pot, three-component (acid chlorides, terminal alkynes, and hydrazine) procedure catalyzed by $Pd(PPh_3)_2Cl_2$/CuI (*Scheme 12*).[16] 3,5-Diaryl-1*H*-pyrazoles **36** were obtained in moderate to good yields from aroyl chlorides **34** and aryl terminal alkynes **35**; however, the aliphatic alkyne 1-octyne led to its corresponding pyrazole derivative in only 15% yield.



R^1 = Ph, R^2 = Ph, 76%; 4-Me-C_6H_4, 63%; 2-naphthyl, 41%; *n*-hexyl, 15%;
R^2 = Ph, R^1 = 2-furyl, 73%; 4-Me-C_6H_4, 68%; 4-O_2N-C_6H_4, 52%;
2-thienyl, 85%; cyclohexyl, 51%

Scheme 12

iii. Through 1,3-Dipolar Cycloaddition

The one-pot 1,3-dipolar cycloadditon of diazo compounds developed by Aggarwal *et al.*[7] was applied to phenyl- and 3-pyridylacetylenes to afford the 3,5-disubstituted pyrazoles **37** with excellent 3,5/3,4 regioselectivity (95:5 to 99.8:0.2) (*Scheme 13*).

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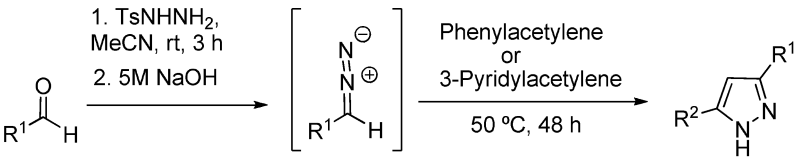
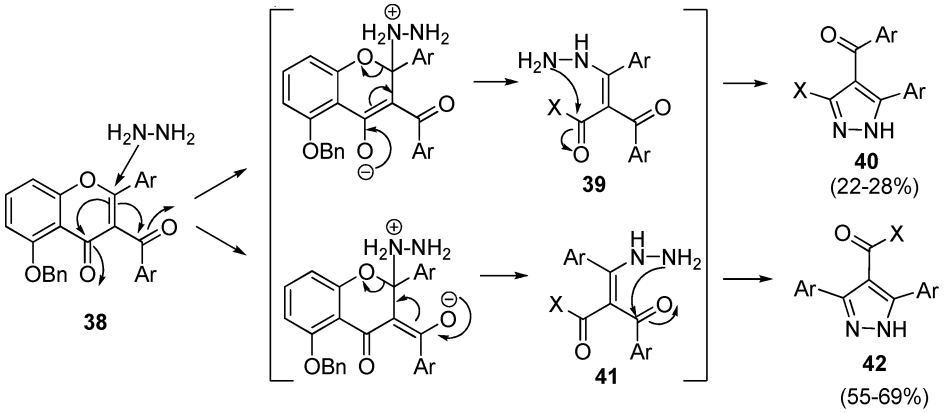


R^2 = Ph, R^1 = Ph, 61%; 4-NCC_6H_4, 67%; 4-$MeOC_6H_4$, 51%; 3-pyridyl, 33%
R^2 = 3-pyridyl, R^1 = Ph, 36%; 4-NCC_6H_4, 19%; 4-$MeOC_6H_4$, 54%; 3-pyridyl, 24%

Scheme 13

3. 3,4,5-Trisubstituted-1H-pyrazoles

In their work, Pinto *et al.* showed that 3-aroyl-5-benzyloxyflavones **38**, after undergoing nucleophilic attack by hydrazine at C-2 of the chromone nucleus followed by subsequent ring-opening process, provide intermediates **39** and **41**, which can then cyclize into pyrazoles **40** and **42** through two possible pathways. The more reactive carbonyl of the 3-aroyl group leads to the major product **42** (*Scheme 14*).[17]



Ar = Ph, 4-$O_2NC_6H_4$, 4-ClC_6H_4, 4-$CH_3OC_6H_4$, 4-$CH_3C_6H_4$
X = 2-HO-6-$BnOC_6H_3$

Scheme 14

Similarly, pyrazoles were obtained through treatment of 3-benzylchromones, 3-benzylflavones, and their 4-thio analogues with hydrazine hydrate.[18]

Recently, a general and efficient method for the preparation of 3(5)-mono-, 3,5-di-, and 3,4,5-trisubstituted pyrazoles was reported. The target compounds **45** were obtained in good to excellent overall yields through a Cu-catalyzed domino amidation of a haloenyne **43** followed by an *in situ* intramolecular hydroamination of the latent alkyne **44**. *bis*(Boc)hydrazine was used as the nucleophile and the protecting group was subsequently removed with trifluoroacetic acid (*Scheme 15*). The method is highly flexible and, despite the acidic treatment, many functional groups, such as alkyl halides, esters, benzyl ethers, and even silyl ethers, are tolerated.[19]

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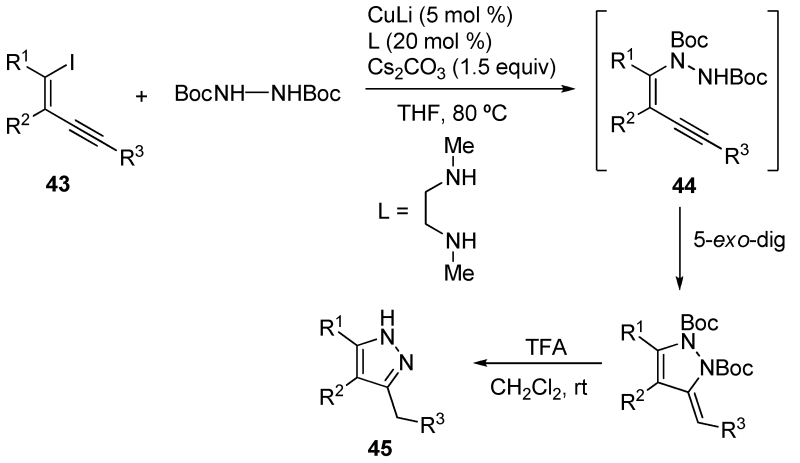

$R^1 = R^2 = H$, R^3 = *n*-Pentyl, 92%; Ph, 93%
$R^2 = H$, R^1 = *n*-Pr, R^3 = *n*-Pr, 83%
R^1 = *n*-Bu, $R^3 = CO_2Et$, 81%
R^1 = Bn, $R^3 = CH_2CH_2OBn$, 72%
$R^1 = TIPSOCH_2$, R^3 = *n*-Pentyl, 78%

$R^1/R^2 = -(CH_2)_3$, $R^3 = (CH_2)_3$-Cl, 89%; Ph, 86%
R^1 = *n*-Bu, R^2 = Et, R^3 = *n*-Octyl, 66%
R^1 = Ph, R^2 = Et, R^3 = *n*-Pentyl, 72%

Scheme 15

II. *N*-Substituted Pyrazoles

1. 1,3,5-Trisubstituted Pyrazoles

1,3,5-Trisubstituted pyrazoles are a particularly interesting class of compounds for medicinal chemists. All the methods for the preparation of 3,5-disubstituted-1*H*-pyrazoles described above have also been applied to the synthesis of their *N*-substituted counterparts.

a. From 1,3-Dicarbonyl Compounds

Wang *et al.* regioselectively prepared 1-aryl-3-alkyl(aryl)-5-substituted pyrazoles **49** through $Pd(PPh_3)_4$-promoted cross-coupling of 1-aryl-3-alkyl(aryl)-5-bromopyrazoles **48** with alkynes, vinyltins, and arylboronic acids.[20] Bromopyrazoles **48** were obtained in good yields from β-ketoesters **46** *via* the formation of 1-arylpyrazolones **47** and subsequent treatment with PBr_3 (*Scheme 16*).

A systematic study correlating regiochemistry with the specific reaction conditions and the electronic/steric characteristics of 1,3-diketones and aromatic hydrazines in the synthesis of 1,5-diaryl-3-substituted pyrazoles was carried out by Singh *et al.*[21]

Usually, cyclocondensations between arylhydrazines and 1,3-diketones are carried out in polar, protic solvents such as alcohols or acetic acid. However, excellent yields and regioselectivities were obtained in reactions of 1-arylbutane-1,3-diones **50** with arylhydrazine hydrochlorides in *N*,*N*-dimethylacetamide (DMAc) in the presence of 0.5 equiv. of 10 N aqueous hydrochloric acid (*Scheme 17*).[22] Nevertheless, when similar reactions were performed in ethanol under reflux, the regioselectivities were lower (80:20–86:14).

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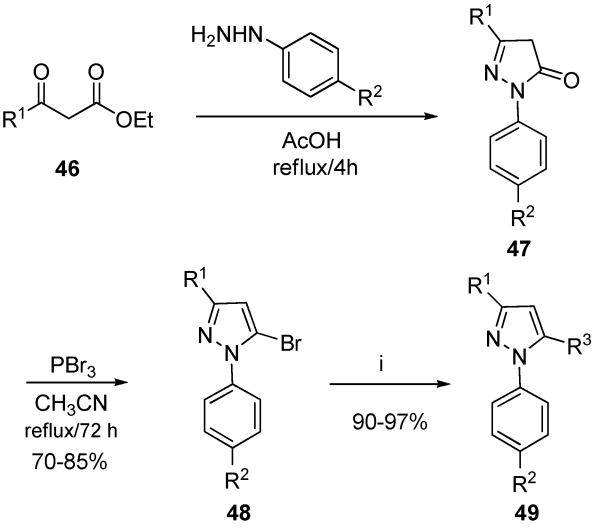
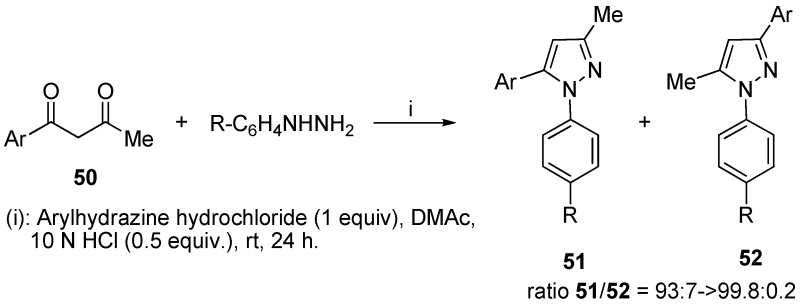


R^1 = Me, Pr^i, Ph, 4-$O_2NC_6H_4$
R^2 = NO_2, Cl, H
R^3 = —≡—TMS, —≡—CH_2OH, —≡—$C(CH_3)OH$, —≡—C_7H_{15}, , Ph, 4-$MeOC_6H_4$
(i): Reaction conditions: with alkynes (2% $Pd(PPh_3)_4$, 4% CuBr·SMe_2, Et_3N/70 ºC/1 h)
with vinyltins (2% $Pd(PPh_3)_4$, THF/reflux/4-6 h)
with boronic acids (2% $Pd(PPh_3)_4$, 2M Na_2CO_3/THF/reflux/4 h)

Scheme 16



(i): Arylhydrazine hydrochloride (1 equiv), DMAc, 10 N HCl (0.5 equiv.), rt, 24 h.

ratio **51**/**52** = 93:7->99.8:0.2

Ar = Ph, R = SO_2NH_2, 77%; Br, 98%; H, 83%
Ar = 4-$MeOC_6H_4$, R = SO_2NH_2, 91%; Br, 91%; H, 87%

Scheme 17

The condensation of unsymmetrical 1,3-diketones **53** (R^1 = Me, R^2 = COOEt, Ph) with phenyl- and *p*-tolylhydrazines in a solventless reaction catalyzed by sulfuric acid afforded mixtures of the two regioisomers **54** and **55**, generally in good to excellent yields.[12] However, reactions of 1-phenylbutane-1,3-dione with acylhydrazines led to 4,5-dihydro-5-hydroxypyrazole derivatives **56** with complete regioselectivity. These compounds were then thermally dehydrated and deacylated (R = Ph) in the presence of a catalytic amount of sulfuric acid (*Scheme 18*).

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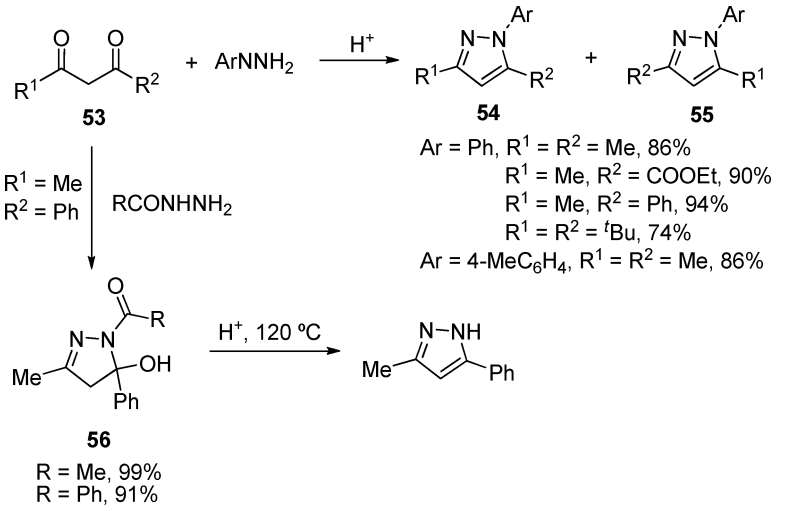
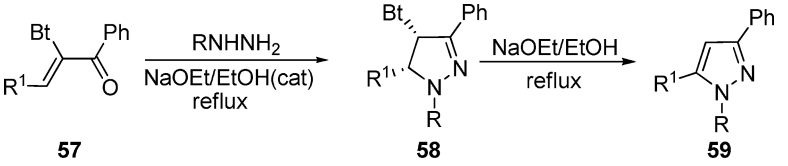


Scheme 18

b. From α,β-Unsaturated Ketones

Examples of regioselective syntheses of substituted *N*-methylpyrazoles with methylhydrazine as the reagent are scarce in the literature. Katritzky *et al.* described the synthesis of 1-methyl(aryl)-3-phenyl-5-alkyl(aryl)pyrazoles **59** by means of regioselective condensation of α-benzotriazolyl-α,β-unsaturated ketones **57** with methyl- and phenylhydrazines *via* intermediate pyrazolines **58** (*Scheme 19*).[23] Upon treatment with a mild base, these intermediates were converted into the desired pyrazoles in high yields.



Scheme 19

An interesting and versatile approach for the regioselective preparation of 1-methyl- and 1-aryl-3,5-diarylpyrazoles **61** and **62**, respectively, from β-arylacetylenic arylketones **60** and methyl- and arylhydrazines was reported by Bishop *et al.*[24] The reactions were carried out in ethanol (*Scheme 20*).

c. From β-Aminoenones and Related Compounds

Alberola *et al.*[25, 26] published a study on the effect of the substitution type at both the carbonyl group and the β-carbon of β-aminoenones on the regioselective synthesis of 1,3,5-trisubstituted pyrazoles **64** and **65**. Reaction of a series of pairs of regioisomeric

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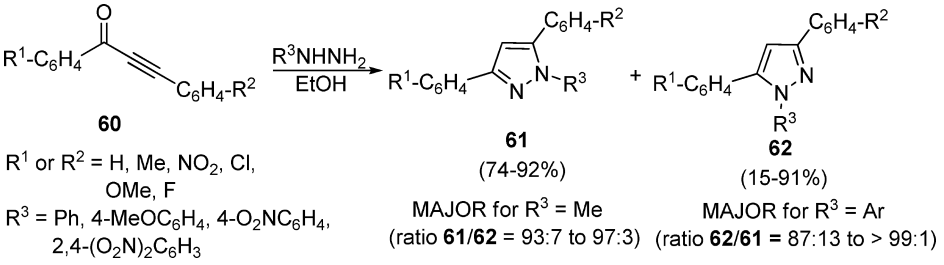
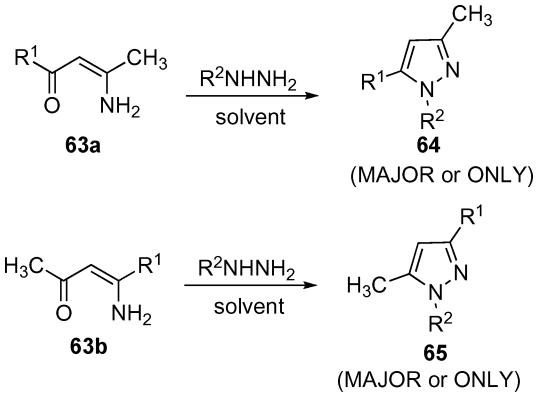


Scheme 20

β-aminoenones **63a**,**b** with monoalkyl-, acetyl- and methoxy-carbonylhydrazine and semicarbazide (*Scheme 21*) and concluded that both the mechanism and the ratio of the two regioisomer pyrazoles depended on the substitution pattern of the substrates and the reaction conditions. Interestingly, this method allows for the preparation of 1,3,5-trialkylpyrazoles that are not accessible from 1,3-diketones.



R^1 = Me, $Ph(CH_2)_2$, *i*-Pr, *t*-Bu
R^2 = Me, Bn, *t*-Bu
Reaction conditions: DMSO, 20-80°C
Yield: 49-86%

R^1 = Me, $Ph(CH_2)_2$, *t*-Bu, Ph, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$
R^2 = CO_2Me, COMe, $CONH_2$
Reaction conditions: EtOH or H_2O/ rt or reflux/H^+ cat.
Yield: 80-98%

Scheme 21

d. By 1,3-Dipolar Cycloadditions

Deng and Mani[27] used readily available *N*-monosubstituted hydrazones **66** and nitroolefins **67** to develop a simple and highly regioselective one-pot method for the synthesis of 1,3,5-trisubstituted pyrazoles **68** in moderate to excellent yields (*Scheme 22*). The process is quite broad in scope; either aryl or alkyl groups at the R^3 position of the nitroolefins afforded the

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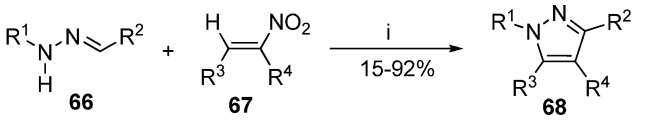


66 67 68

(i): MeOH/H_2O, air, rt, **or** CF_3CH_2OH, 10 equiv TFA, rt→ 75 ºC, air,
or ethylene glycol, 120-150 ºC, air

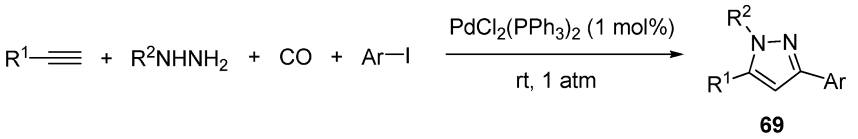
R^1 = Alkyl, aryl; R^2 = Bn, ^{t}Bu, aryl; R^3 = Aryl, 3,4-methylenedioxyphenyl;
R^4 = H, Me; R^3/R^4 = -$(CH_2)_4$

Scheme 22

corresponding pyrazoles in excellent yields. The substitution at the R^4 position to afford 1,3,4,5-trisubstituted pyrazoles (2 examples) was also tolerated.

e. Other Methods

Recently, Mori *et al.* have described an elegant one-pot, four-component coupling of a terminal alkyne, methylhydrazine, carbon monoxide, and an aryl iodide to prepare 1-methyl-3,5-diarylpyrazoles **69** in the presence of a palladium catalyst.[28] The reaction proceeds at room temperature and at 1 atm of carbon monoxide in THF-H_2O (*Scheme 23*). With aqueous hydrazine, the corresponding 3,5-diarylpyrazoles were also obtained (2 examples). However, no reaction was observed with phenylhydrazine. The reaction is highly regioselective, with the substituent at the 5-position being derived from the terminal alkyne.



69

R^1 = Ph, R^2 = H, Ar = Ph, 59%; 4-$MeOC_6H_4$, 80%
R^2 = Me, Ar = Ph, 91%; 4-$MeOC_6H_4$, 83%; 4-MeC_6H_4, 88%; 2-thienyl, 85%
R^1 = 4-MeC_6H_4, R^2 = Me, Ar = Ph, 65%
R^1 = *n*-C_6H_{13}, R^2 = Me, Ar = 4-$MeOC_6H_4$, 93%; 4-MeC_6H_4, 93%

Scheme 23

2. 1,3,4,5-Tetrasubstituted Pyrazoles

Strategies involving syntheses both in solution and in the solid phase have been developed to prepare libraries of 4-alkyl-1,3,5-triaryl and 5-alkyl-1,3,4-triarylpyrazoles, which have been widely investigated as ligands for the estrogen receptor (ER).[29–35] Initially, tetrasubstituted pyrazoles **72** were synthesized through the classic 1,3-diketone-hydrazine condensation route. To this end, two strategies were developed to introduce the C-4 alkyl group into the pyrazole derivatives: either through alkylation at C-2 of the 1,3-diketone precursor or through the use of an appropriate alkylphenone as a building block. The former method was described by Marzinzik and Felder[34] in the solid phase, but is not general. In contrast, the latter method developed by Katzenellenbogen and co-workers,[30,31] allows the introduction of a variety of alkyl groups in both solution and solid phase. In solution,[30]

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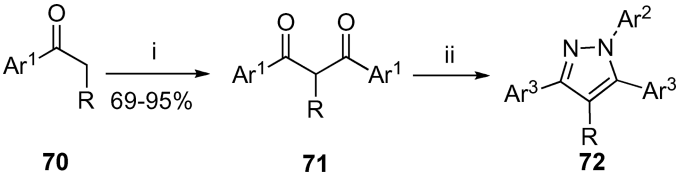
the synthetic sequence involves a crossed-Claisen condensation between an appropriate 4-methoxy alkylphenone **70** and methyl 4-nitrophenyl 4-methoxybenzoate, followed by reaction of the C2-alkylated 1,3-diketone **71** with an arylhydrazine (*Scheme 24*). When this methodology was applied to unsymmetrical 1,3-diketones, a lack of regioselectivity was observed.



70 **71** **72**

i) Methyl 4-nitrophenyl 4-methoxybenzoate, LHMDS/THF
ii) 1. Ar^2NHNH_2.HCl, THF/DMF (1:3), 110-120 C, 53-87%
2. BBr_3/CH_2Cl_2, 30-98%
Ar^1 = 4-$MeOC_6H_4$; R = Me, Et, *n*-Pr, *i*-Bu, *n*-Bu;
Ar^2 = Ph, 4-HOC_6H_4; Ar^3 = 4-HOC_6H_4

Scheme 24

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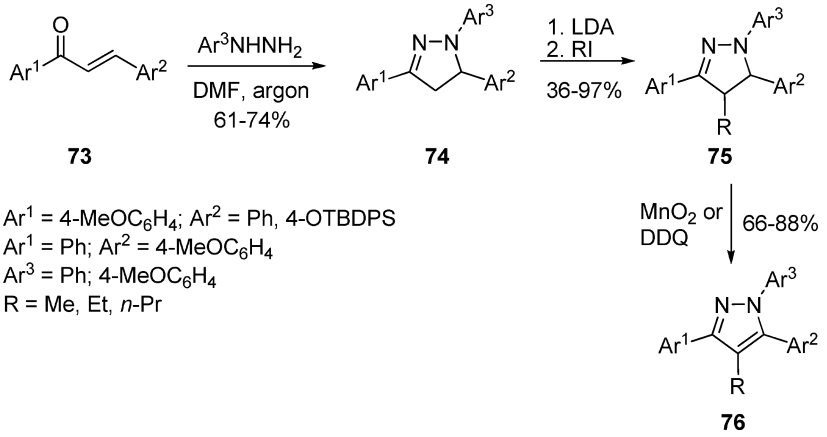
Subsequently, a series of 4-alkyl-1,3,5-diarylpyrazoles **76** were obtained regioselectively through oxidation of pyrazolines **75**, which had previously been prepared by means of a regioselective cyclocondensation between arylhydrazines and diarylenones **73** in DMF under inert atmosphere followed by alkylation of the C-4 of the pyrazoline ring of **74** (*Scheme 25*).[35]

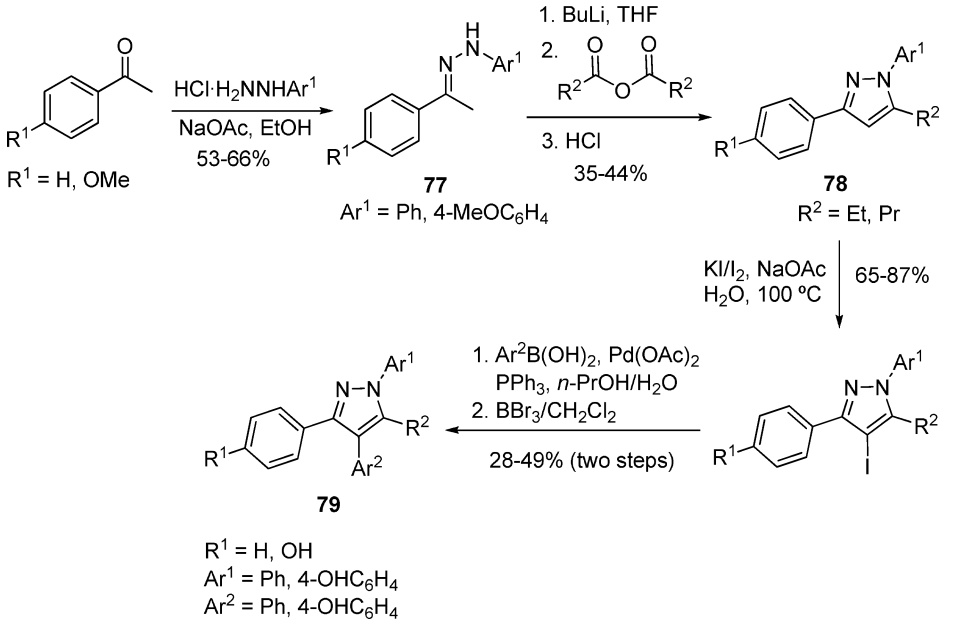


73 **74** **75** **76**

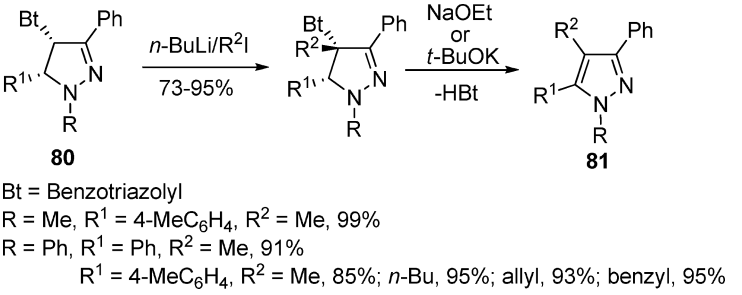
Ar^1 = 4-$MeOC_6H_4$; Ar^2 = Ph, 4-OTBDPS
Ar^1 = Ph; Ar^2 = 4-$MeOC_6H_4$
Ar^3 = Ph; 4-$MeOC_6H_4$
R = Me, Et, *n*-Pr

Scheme 25

A series of 1,3,4-triaryl-5-alkylpyrazoles **79** was also prepared regioselectively from acetophenone derivatives through a five-step sequence involving an acylation of the dianion of the hydrazone **77** with an alkyl anhydride and subsequent cyclization to the trisubstituted pyrazoles **78**. These were then iodinated at the C-4 of the pyrazole ring and subjected to Suzuki coupling conditions to introduce the aryl substituent (Ar^2) (*Scheme 26*).[32]



Scheme 26



Scheme 27

Katritzky *et al.*[23] synthesized 1,3,4,5-tetrasubstituted pyrazoles **81** in excellent yields and with complete regioselectivity *via* alkylation of 4-benzotriazolylpyrazolines **80** and a subsequent elimination reaction (*Scheme 27*).

Only the 1,3-regioisomers **84** were formed through a sequence of reactions involving a 1,3-dipolar cycloaddition of the nitrilimines generated from the α-chlorohydrazines **82** to cycloalkenes **83** and subsequent oxidation of the pyrazoline intermediates (*Scheme 28*).[36]

3,4-Dialkyl tetrasubstituted pyrazoles **86** were regioselectively synthesized in good yields by treatment of Baylis-Hillman adducts **85** with monosubstituted hydrazine hydrochlorides in 1,2-dichloroethane.[37] The formation of pyrazoles most likely occurred through the formation of the hydrazone derivative (**I**), acid-catalyzed cyclization to (**II**), and subsequent 1,3-hydrogen transfer (*Scheme 29*).

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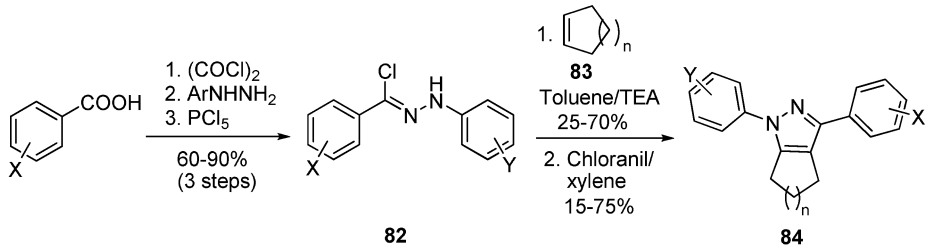
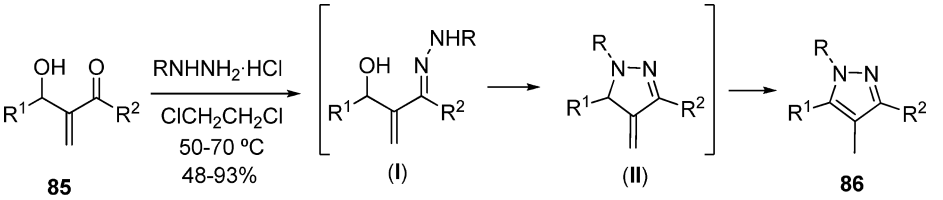


X = H, Cl, F, OMe; Y = H, Cl, SO_2Me, OMe.
n = 1,2,3.

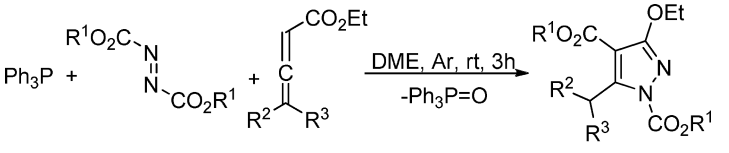
Scheme 28



R^1 = Aryl, *n*-C_5H_{11}; R^2 = Alkyl; R = Aryl, ^{t}Bu

Scheme 29

Highly functionalized 1,3,4,5-tetrasubstituted pyrazoles **89** (*Scheme 30*) were obtained in moderate to good yields through reaction of the Huisgen zwitterion from triphenylphosphine and dialkyl azodicarboxylates **87** with 3-substituted allenoates **88**.[38] Pyrazole formation proceeded *via* a nitrogen to carbon migration of the carboalkoxy group.



R^1 = *i*-Pr, R^2 = Ph, R^3 = H, 56%; Ph, 41%
R^2 = Me, R^3 = H, 62%
R^2 = 4-ClC_6H_4, R^3 = H, 44%
R^1 = Et, R^2 = Ph, R^3 = H, 54%
R^2 = Me, R^3 = H, 72%
R^2 = 4-$MeOC_6H_4$, R^3 = H, 35%

Scheme 30

3. Miscellaneous Pyrazoles

Phenanthro[9,10-*d*]pyrazoles **92** were conveniently prepared through a sequence of reactions involving synthesis of *o*,*o*′-dihalogenated diarylenaminones, tandem amine-exchange/heterocyclization, and biaryl coupling.[39] Enaminones **90** reacted with phenylhydrazine chlorhydrate to yield 4,5-diaryl-1-phenylpyrazoles **91** as the only isomers in

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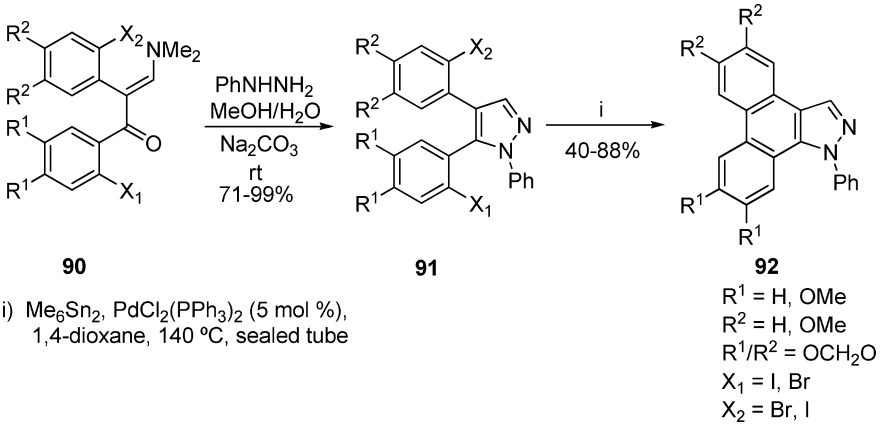
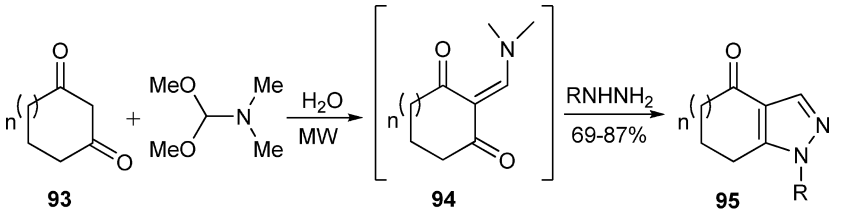


Scheme 31

high to excellent yields. A subsequent Stille-Kelly reaction based on a tandem stannylation/biaryl coupling afforded the target compounds **92** in 44–88% yield (*Scheme 31*).

Similar 1,4,5-triarylpyrazoles **91** ($X_1 = OH$, $X_2 = I$; $X_1 = I$, $X_2 = OH$) were converted into dibenzoxepino[4,5-*d*]pyrazoles (57–88%) through treatment with the complex $CuBr{\cdot}SMe_2$ in pyridine.[40]

Organic reactions in aqueous media have numerous environmental and economic advantages. Molteni *et al.*[41] described an aqueous one-pot synthesis of 4,5-fused-1-substituted pyrazoles **95** from 1,3-cycloalkanediones **93** through enaminoketones **94** in which microwave irradiation is used (*Scheme 32*). The short reaction times (120 seconds at 200° C) and the simple purification through precipitation of the products in aqueous media make this a remarkably elegant procedure.



Scheme 32

Mukaiyama-Michael-type addition/heterocyclization of Danishefsky's diene **97** with 1,2-diaza-1,3-butadienes **96** was used to synthesize functionalized 1,3-disubstituted pyrazoles **99** through the 1,4-adducts **98**, which contain an amide group.[42] The reaction was carried out in THF in the presence of wet Amberlyst 15(H) (*Scheme 33*).

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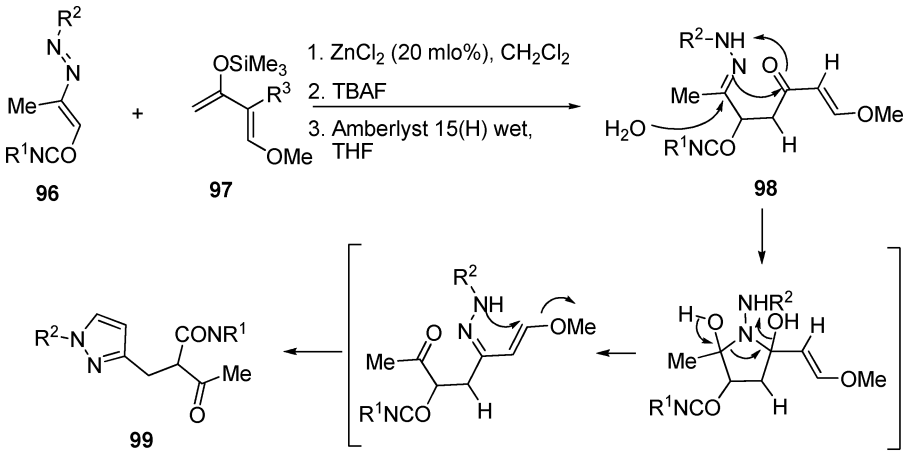

$R^1 = NMe_2$, $R^2 = CONH_2$, 66%; CONHPh, 65%
$R^1 = NEt_2$, $R^2 = CONH_2$, 82%
R^1 = Morpholin-4yl; R^2 = CONHPh, 83%

Scheme 33

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III. Substituted Pyrazole-3(5)-carboxylic Acid Derivatives

Pyrazolecarboxylic acid derivatives are of considerable pharmacological relevance and also represent useful synthetic building blocks in both organic and medicinal chemistry. Moreover, they are important intermediates in the preparation of agrochemicals, microbicides, herbicides, plant growth regulators, and crop protectants.

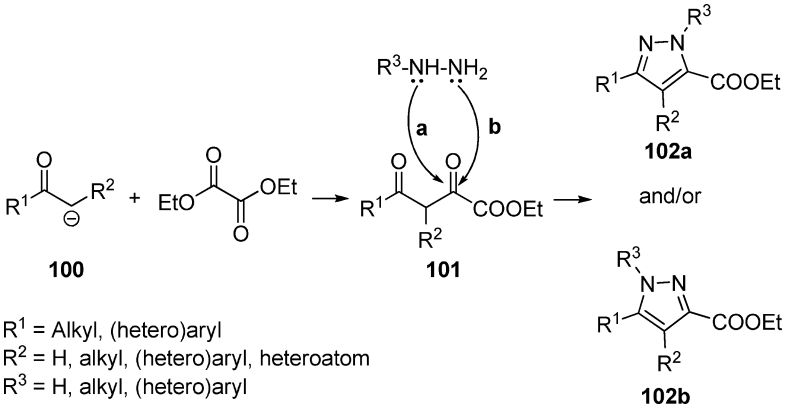
1. From 1,3-Diketoesters

The approach most often used to prepare pyrazole-3(5)-carboxylic acid esters involves [3+2] cycloadditions between hydrazines and 1,3-diketoesters. In general, Claisen condensation of the enolate of a ketone **100** with diethyl oxalate is the method most commonly employed in the preparation of the 1,3-diketoesters **101** (*Scheme 34*). These, in turn, constitute important building blocks for most of the pyrazole-3(5)-carboxylic acid derivatives **102** reported in the literature, some which have been found to display important pharmaceutical activities.[43–49]

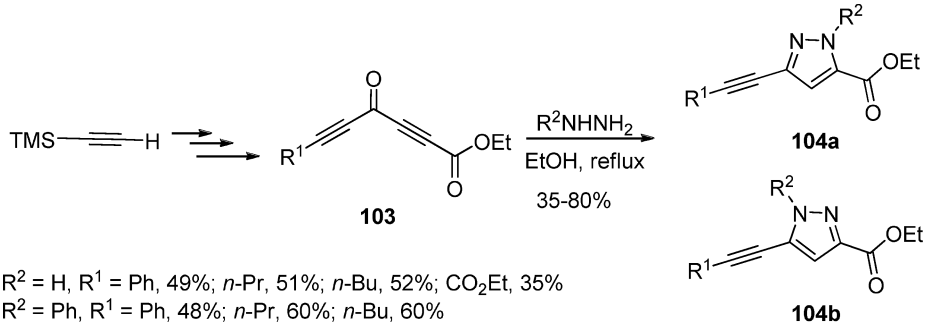
2. From α,β-Unsaturated β-Ketoesters

Baldwin *et al.*[50, 51] obtained 3(5)-alkynyl-5(3)-ethoxycarbonylpyrazoles **104** (R^2 = H) in acceptable yields from the diacetylenic ketoesters **103** (*Scheme 35*). When phenylhydrazine was used, a mixture of regioisomers **104a** and **104b** was formed in ratios ranging from 2:1 to 3:2.

However, acetylenic ketoesters are rare synthetic intermediates. More recently, Persson and Nielsen[52] developed an efficient approach to pyrazole carboxylates from Weinreb amides, hydrazines, and ethyl propynoate. Weinreb amides **105** reacted with the



Scheme 34



Scheme 35

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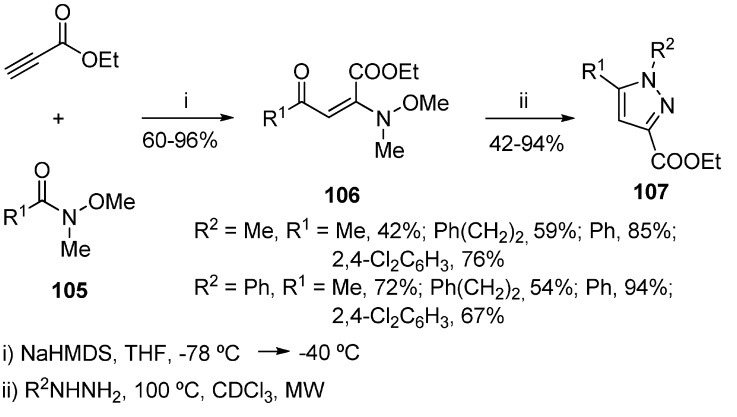
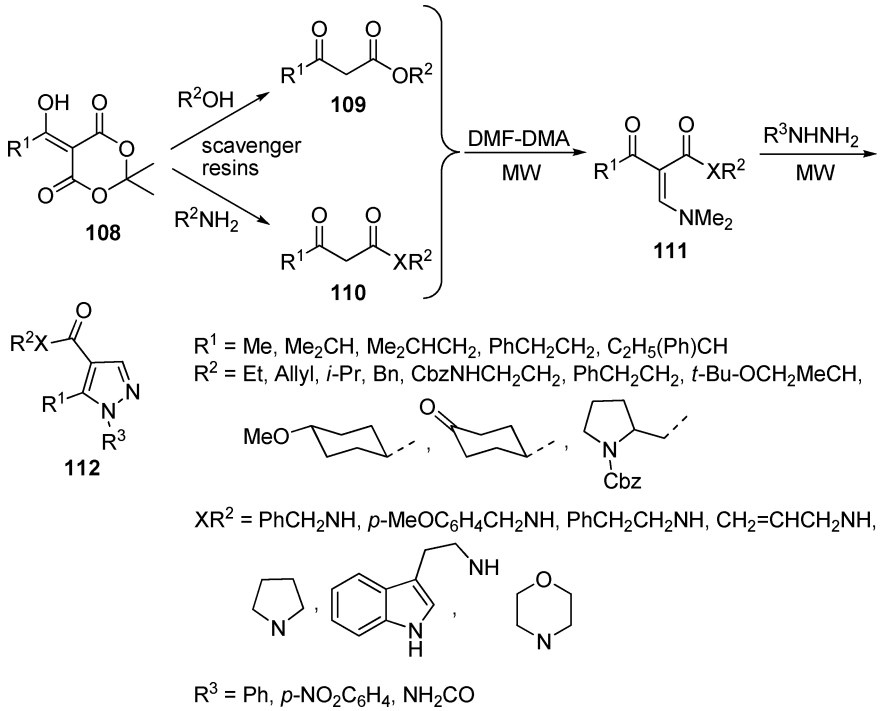
sodium acetylide of ethyl propynoate in an acyl substitution-conjugate addition sequence to furnish (*E*)-*N*-methoxy-*N*-methyl-β-enaminoketoesters **106**, which condensed regioselectively with methyl- and phenylhydrazines in a microwave-assisted reaction to afford the target pyrazoles **107** (*Scheme 36*).



Scheme 36

3. From α-Enamino-β-ketoesters(amides) and Related Compounds

A small but versatile parallel library of 1,5-disubstituted-4-pyrazolecarboxylic acid derivatives **112** (*Scheme 37*) was prepared in solution by means of a three-step procedure starting from Meldrum's acid, which was acylated with acyl chlorides to Meldrum's acid derivatives **108**. The resulting products then underwent ring-opening with a variety of aliphatic, aromatic, and heterocyclic alcohols and amines to afford substituted β-keto esters **109** and β-keto amides **110**. Further reaction with *N,N*-dimethylformamide dimethylacetal yielded the α-enamino-β-keto esters and amides **111**. Subsequent condensation with monosubstituted hydrazines regioselectively afforded pyrazoles **112** of high purities and in high yields.[53]



Scheme 37

The trichloromethyl group can be converted to an alkoxycarbonyl group under mild conditions through alcoholysis. Condensation of β-alkoxyvinyl trichloromethyl ketones **113** with hydrazine hydrochloride in EtOH or with phenylhydrazine in MeOH or EtOH afforded 5(3)-alkoxycarbonylpyrazole derivatives **114** in good yields (*Scheme 38*).[54,55]

More recently, an interesting, straightforward, and regiospecific synthesis of 4-acylpyrazole-5-carboxylates **116** from unsymmetrical enaminodiketone ethyl esters **115** has been reported.[56] The regioselectivities observed were independent of the structure of the R substituent present in the enaminodiketone (*Scheme 39*). When enaminodiketones **115** were reacted at room temperature with carboxymethylhydrazine, 1*H*-pyrazoles **117** were obtained regioselectively.

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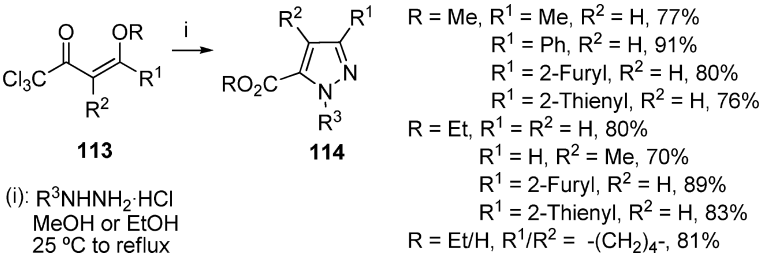
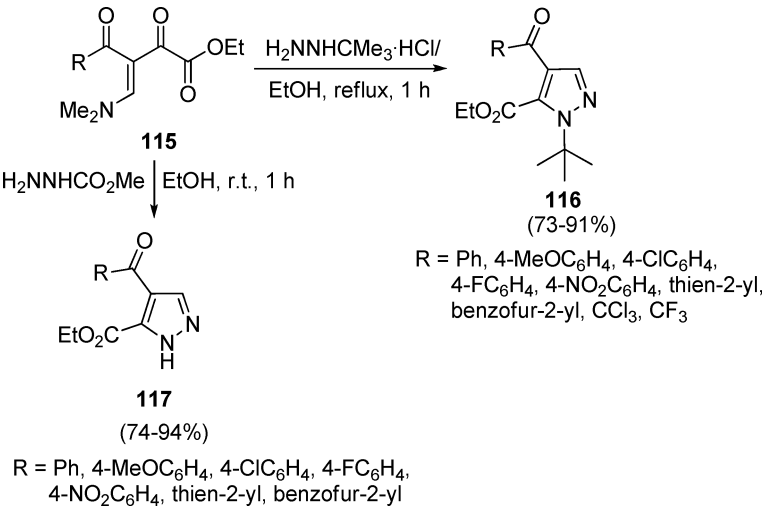


Scheme 38



Scheme 39

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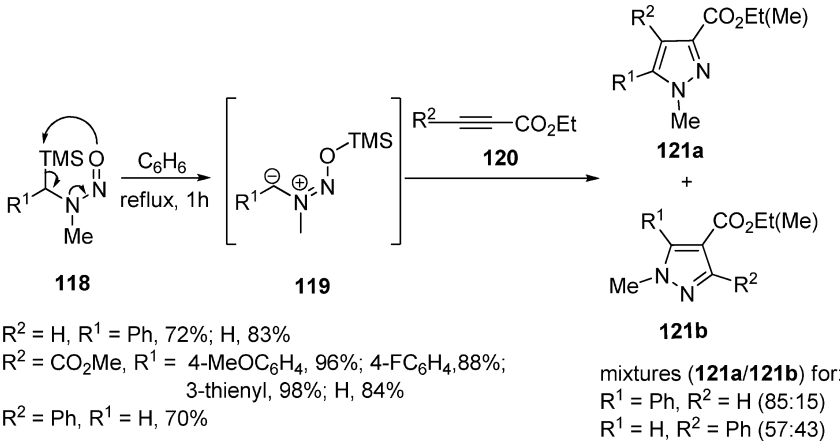
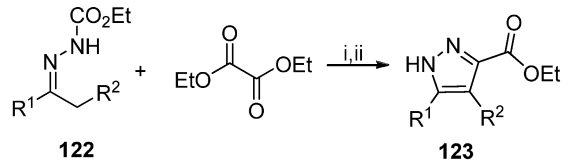
4. Other Methods

The 1,3-dipolar cycloaddition approach has also been applied to the synthesis of pyrazolecarboxylic acid derivatives. Azomethine imines **119**, easily generated from α-silylnitrosamines **118**, were used as 1,3-dipole intermediates in reactions with ethyl propiolates **120** and dimethyl acetylenedicarboxylate (DMAD) as dipolarophiles to furnish a variety of mono- and dialkyloxycarbonyl substituted 1-methylpyrazoles **121** in high to excellent yields (*Scheme 40*).[57,58]

Cyclizations of hydrazone dianions with esters, acid chlorides, and nitriles had previously been described as convenient procedures for the preparation of pyrazolecarboxylic acid derivatives.[59–61] However, the first one-pot approach to ethyl pyrazole-3-(5)carboxylates **123** through cyclization of hydrazone 1,4-dianion of **122** with diethyl oxalate has only recently been reported.[62] (*Scheme 41*). This methodology is quite general and has already been applied to acyclic aryl and alkyl ketones.



Scheme 40



Scheme 41

IV. Fluorinated Pyrazole Derivatives

Many pyrazoles containing fluorine or fluorocarbon groups are either already in use or under active investigation in the fields of agrochemistry and pharmacology.[1,63–67] The methods for synthesizing these compounds include the direct introduction of fluorine into the preformed heterocycles[68] as well as the formation of heterocyclic systems through the use of fluorinated precursors.[3,4] The latter is usually achieved by starting with hydrazine derivatives and 1,3-bifunctional fluoro-building blocks such as fluoro-1,3-diketones, fluorinated acetylacetylenes, and β-trifluoroacetyllactams. Among fluorinated pyrazoles, the trifluoromethyl derivatives are the most common in the literature due to their important biological properties.[69–73] The main methods for the preparation of these compounds entail [3+2] heterocyclization of trifluoromethyl building blocks derived from 1,3-dicarbonyl, enaminones, and β-alkoxyketones with hydrazine derivatives. Interesting studies concerning the influence of the reagents' structure (1,3-dielectrophile and hydrazine) and the reaction conditions on both the regioselectivity and the mechanism of the cyclization have also appeared in the literature.

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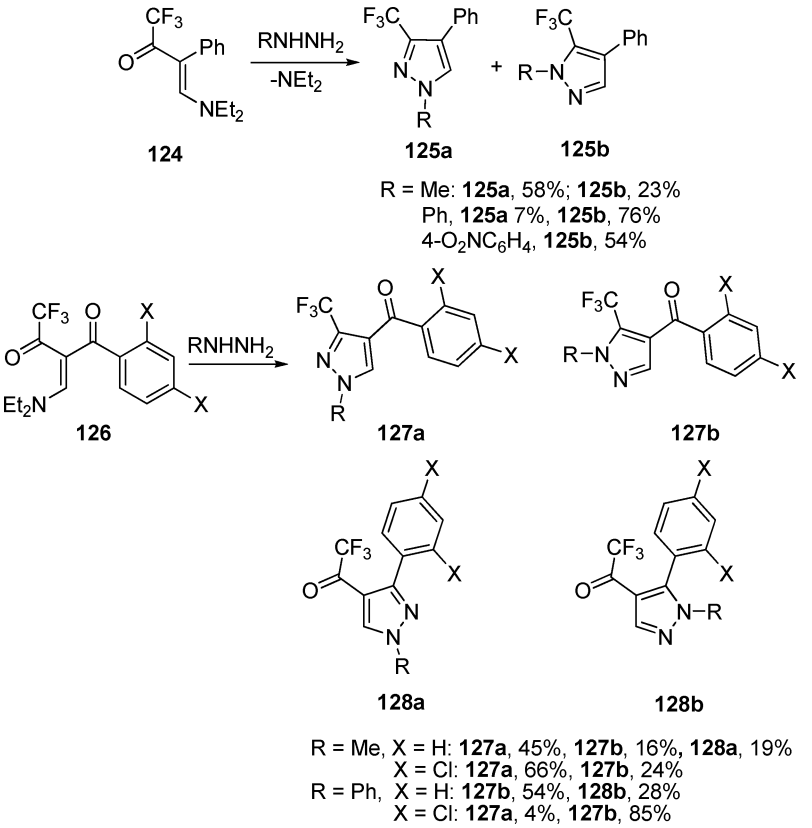
1. From β-Aminoenones

Enaminone **124** reacts with methylhydrazine in CH_3CN to afford a 2.5:1 mixture of regioisomeric pyrazoles **125a** and **125b** (*Scheme 42*). The regioselectivity was improved in similar reactions with phenylhydrazine (ratio **125a**:**125b** = 1:10) and 4-nitrophenylhydrazine (only **125b** was isolated). When enaminodiketones **126** were used as starting materials, mixtures of the trifluoromethylpyrazoles **127a**, **127b**, and **128a** (X = H) or **127a** and **127b** (X = Cl) were formed in reactions with methylhydrazine; the same reactions with phenylhydrazine led to mixtures of **127b** and **128b** (2:1; X = H) or **127a** and **127b** (1:20; X = Cl).[74]



Scheme 42

2. From β-Alkoxyvinylketones

Bonacorso *et al.*[75] obtained a series of 3-aryl(alkyl)-5-trifluoromethyl-1*H*-pyrazoles **131** by reaction of 4-alkoxy-4-aryl(alkyl)-1,1,1-trifluoro-3-buten-2-ones **129** with thiosemicarbazide in methanol. The reaction occurred through the formation of the 5-hydroxy-5-trifluoromethyl-1-pyrazole thiocarboxamides **130**, followed by dehydration and the simultaneous removal of the thiocarboxyamide group with sulfuric acid (*Scheme 43*).

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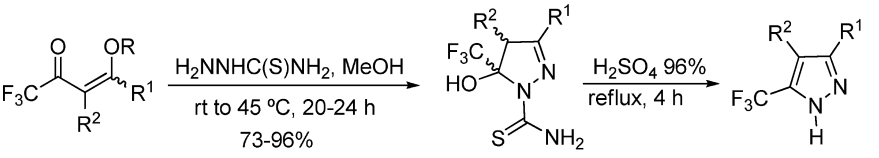
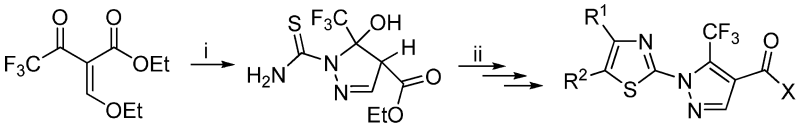


129 **130** **131**

R = Me, R^2 = H, R^1 = Me, 67%; Ph, 72%; 4-MeC_6H_4, 75%; 4-BrC_6H_4, 75%; 4-$O_2NC_6H_4$, 75%
R^2 = Me, R^1 = H, 72%
R = Et, R^1 = R^2 = H, 57%

Scheme 43



132 **133**

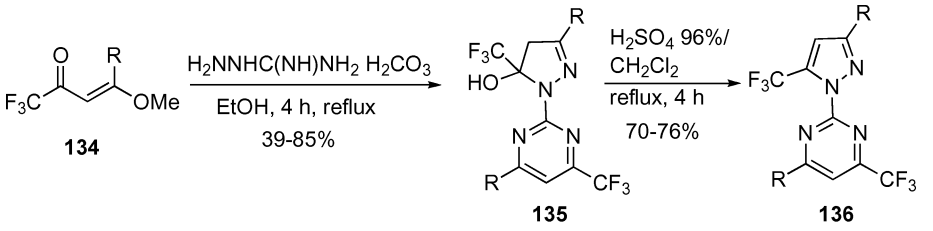
X = OH, OEt, NR^3R^4

(i): $H_2NC(S)NHNH_2$, EtOH, -15 ºC to rt
(ii): a) $R^1C(O)CHR^2Br$, EtOH, reflux, b) KOH, EtOH, reflux, c) $(COCl)_2$, DMF, CH_2Cl_2, d) R^3R^4NH, PS-morpholine, CH_2Cl_2, e) PS-isocyanate

Scheme 44

Tice *et al.*[76] used this procedure to prepare a library of 1-(2-thiazolyl)-5-trifluoromethylpyrazole-4-carboxylic acid derivatives **133** in solution, starting from ethyl 2-ethoxymethylene-3-oxo-4,4,4-trifluorobutanoate **132** (*Scheme 44*).

An elegant, efficient one-pot synthesis of a series of trifluoromethylated 2-[1*H*-pyrazol-1-yl]pyrimides **136** was carried out by means of regioselective condensation of **134** with aminoguanidine bicarbonate in refluxing ethanol.[77] The 5-trifluoromethyl-5-hydroxypyrazoline intermediates **135** were dehydrated upon treatment with a mixture of sulfuric acid and dichloromethane under reflux (*Scheme 45*).



134 **135** **136**

R = Me, *n*-Pr, *t*-Bu, Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$

Scheme 45

Zhu *et al.* studied the reactivity of the β-alkoxyvinyltrifluoromethyl ketones **137** and **138** with a variety of monosubstituted hydrazines in ethanol under reflux.[78] In all cases, the 5-trifluoromethylpyrazoles (**139** and **142**) or the 5-trifluoromethyl-5-hydroxypyrazolines

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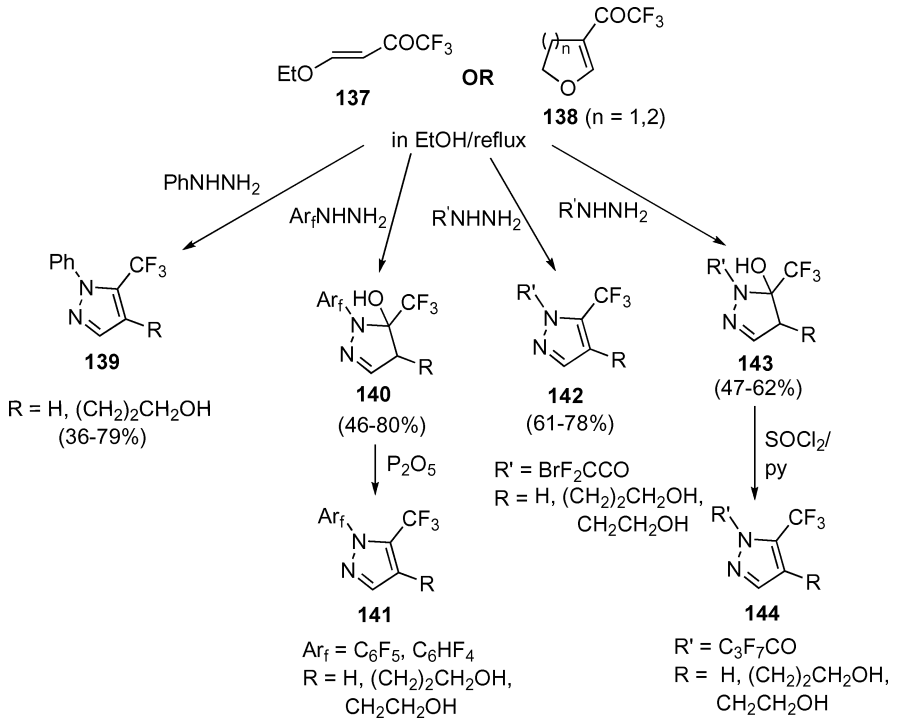

Scheme 46

(**140** and **143**) were the major regioisomers obtained; the latter were subsequently dehydrated to the corresponding pyrazoles **141** and **144**, respectively (*Scheme 46*).

Similar regioselectivities were observed in reactions of 1,1,1-trifluoro-4-(2-furyl/thienyl)-4-methoxybut-3-en-2-ones with hydrazine hydrochloride in MeOH or EtOH. However, cyclocondensations with phenylhydrazine were dependent on both the heteroaryl group and the reaction conditions.[55]

3. From 1,3-Dicarbonyl Compounds

The condensation of a fluorinated 1,3-dicarbonyl compound with an aryl(heteroaryl) hydrazine constitutes the main approach for the synthesis of fluorinated 1,3,5-trisubstituted pyrazoles, some of which have been found to have significant biological activities.[79–90]

Several research groups have studied the mechanism or mechanisms of this apparently simple reaction. Elguero *et al.*[91, 92] proposed a general mechanism for the reaction of 1,3-diketone **145** with a hydrazine involving the initial formation of 3,5-dihydroxypyrazolidine **146a** as the key intermediate, followed by the sequential loss of two molecules of water. The formation of the two N-C bonds of the carbinolamine **146** is considered reversible whereas the dehydration steps (**146** → **147** and **147** → **148** → **150a**) are irreversible; the first dehydration is actually the kinetically controlling step. The dehydration **147** → **150a** involves intermediate **149**, the formation of which may explain why when R is an electron-withdrawing group, the dehydration either does not occur or occurs with difficulty. When

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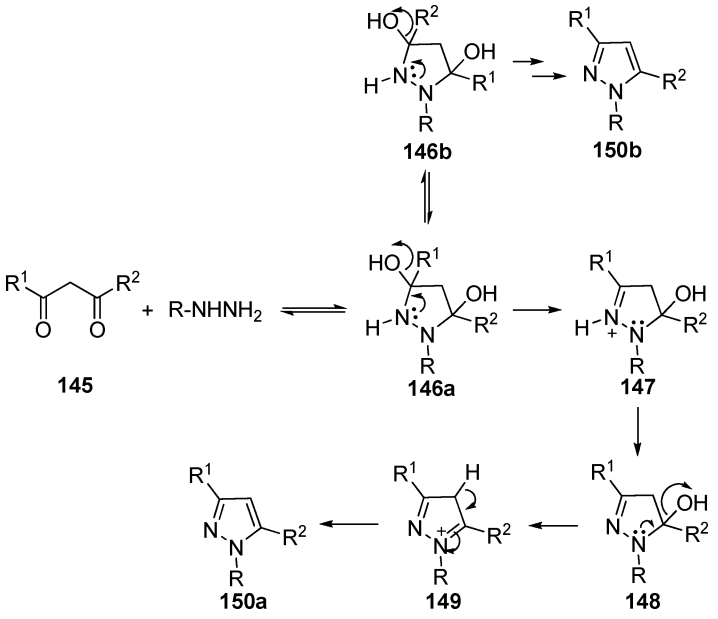

Scheme 47

$R^1 \neq R^2$, the dihydroxypyrazolidines **146a** and **146b** are in equilibrium. The regioisomer pyrazole **150b** is formed from the latter (*Scheme 47*).

After an exhaustive study concerning the influence of substituents R^1 and R^2 on the regioselectivity of the cyclization of trifluoromethyl-1,3-diketones with a variety of hydrazines, these authors[92] concluded that the orientation was the result of the difference in the dehydration rates of the two 3,5-dihydroxypyrazolidines **146a** and **146b** in equilibrium.

The condensation of 2-hydrazino-4-methylquinoline with aliphatic trifluoromethyl-1,3-diketones **151** (R^1 = Me, CF_3; *Scheme 48*) in boiling ethanol regioselectively afforded 5-hydroxy-5-trifluoromethylpyrazolines **153b** as the only products. In contrast, the aryl analogues of these compounds (R^1 = Ph, 2-thienyl) gave mixtures of **153b** (61–62%) and 3-trifluoromethylpyrazoles **154a** (8–10%).[93] The proposed mechanism involves an initial conjugate addition of the terminal nitrogen of the hydrazinoquinoline to the two enols of the substrate, followed by cyclization to the isomeric but not observed, dihydroxytetrahydropyrazoles **152a** and **152b**. Subsequent elimination of one molecule of water leads to the hydroxydihydropyrazoles **153a** and **153b**, respectively, and further elimination of water affords the pyrazoles **154a** and **154b**. The regioisomeric ratio depends on the proportion of the two enols at equilibrium.

In a subsequent work, the same authors studied the effect of various substituents of both hydrazine and 1,3-diketone on the ease of elimination of water during the condensation reactions.[94] They concluded that the presence of electron-withdrawing groups at the C-3, C-5, and N-1 of the dihydropyrazole **153** (*Scheme 48*) inhibited the second dehydration process. The CF_3 group at C-5 destabilizes any carbocationic character in an *E*1-like mechanism for the dehydration.

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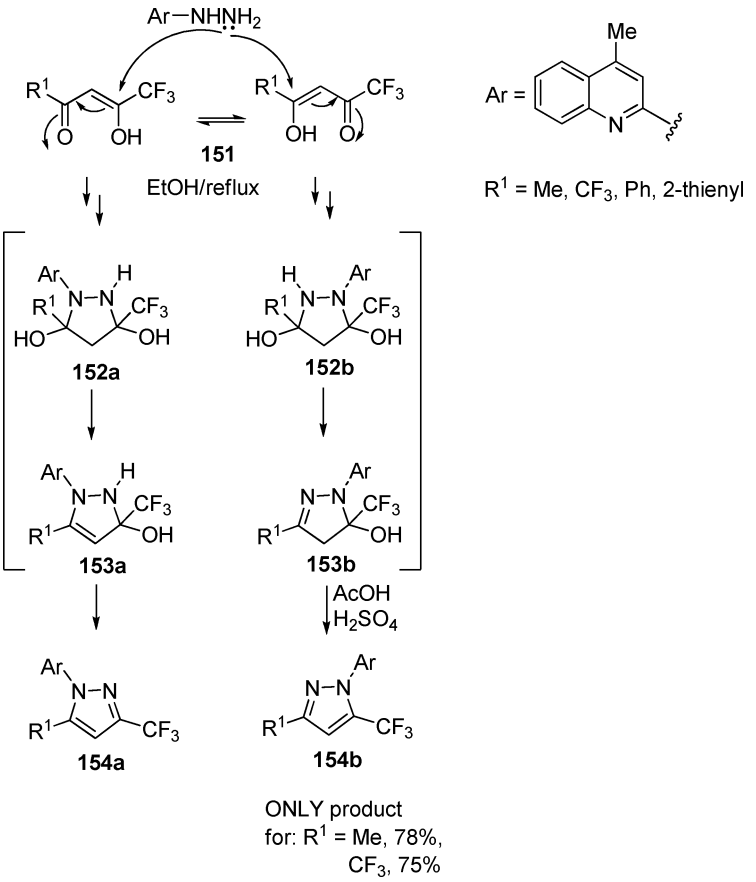

Scheme 48

5-Trifluoromethyl-5-hydroxypyrazolines **154b** were also the major or only observed regioisomers in reactions of aliphatic (R^1 = Me) and aromatic (R^1 = 2-thienyl) trifluoromethyl-1,3-diketones with per(poly)fluorophenylhydrazines in ethanol.[95] Like Singh *et al.*[92] these authors explained the results on the basis of the proportion of the two enols at equilibrium.

Under acidic conditions, trifluoromethyl hydroxypyrazolines such as **153** were not observed in reactions between arylhydrazines and trifluoromethyl-1,3-diketones **155** or 2-fluoro-1,3-diketones **157a**,**b**.[96] Interestingly, the major (**156a**) or the only (**158**) regioisomer afforded was the 3-trifluoromethylpyrazole derivative, except in the case of **155** (R = Me) (*Scheme 49*). The formation of **158** as the sole regioisomer was explained by the fact that the substrates were present in the diketo form exclusively. Thus, the NH_2 of the phenylhydrazine attacks the more electrophilic carbonyl group ($COCF_3$ in **157a** and $COCH_3$ in **157b**).

Similar results were obtained by Norris *et al.*[97] in the heterocyclization of 1-phenylbutane-1,3-dione **159c** and its 4,4,4-trifluoro and 4,4-difluoro derivatives **159a**,**b**, respectively, with phenyl- and 5-methanosulfonylpyridin-2-ylhydrazines **160a**,**b**, respectively, in refluxing 2-propanol under neutral and acidic conditions (*Scheme 50*). Interestingly, the observed regioselectivity in the reaction of **159a** with 5-methanosulfonylpyridin-2-ylhydrazine (**160b**) under neutral conditions is completely the opposite of that observed

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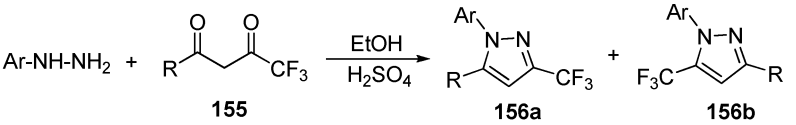


ONLY regioisomer **156a**:

Ar = Ph, R = *t*-Bu, 75%; 2-FC_6H_4, 100%; 2-MeC_6H_4, 73%; 2-$MeOC_6H_4$, 83%; 4-FC_6H_4, 67%; 4-MeC_6H_4, 85%; 4-$MeOC_6H_4$, 85%; 4-NCC_6H_4, 70%; 4-$O_2NC_6H_4$, 60%; 2-pyrrolyl, 78%; 2-furyl, 75%; 2-thienyl, 78%

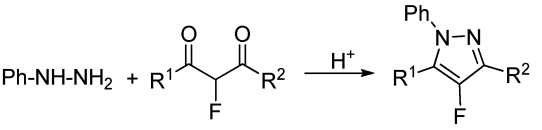
MIXTURES of regioisomers (**156a**/**156b** (in parentheses, % of **156a**):

Ar = Ph, R = Me (50), 70%; Et (62), 65%; *i*-Pr (88), 73%; *i*-Bu (70), 74%; *n*-hexyl (73), 67%; Ph (82), 79%; 2-naphthyl (93), 74%; 2-pyridyl (90), 74%

Ar = 4-$O_2NC_6H_4$, R = Me (50), 70%

Ar = 4-$MeOC_6H_4$, R = Me (50), 40%

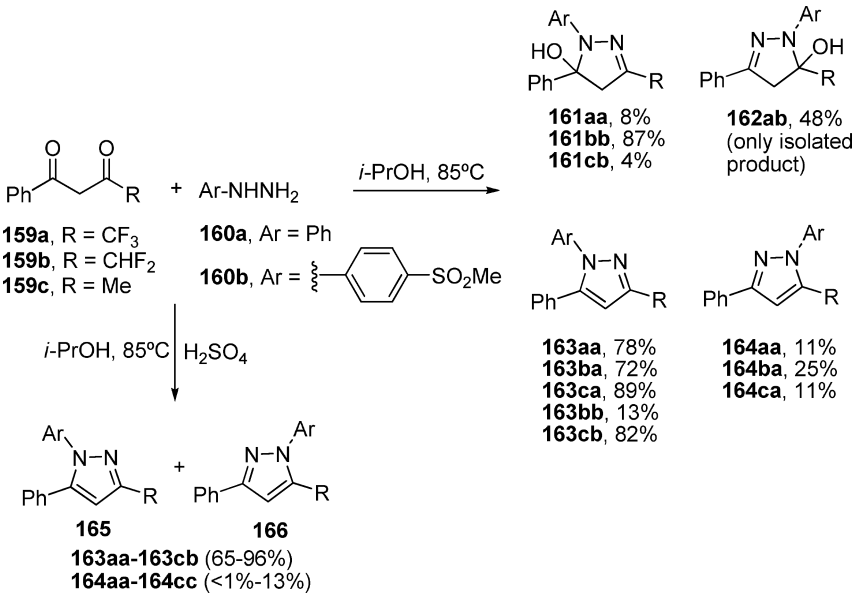
Ar = 2,4-$(O_2N)_2C_6H_3$, R = Me (20), 35%



158a: R^1 = Me, 86%; Et, 70%; *i*-Pr, 71%; *t*-Bu, 68%; CF_3, 69%; Ph, 70%

158b: R^1 = Ph, 70%

Scheme 49



Scheme 50

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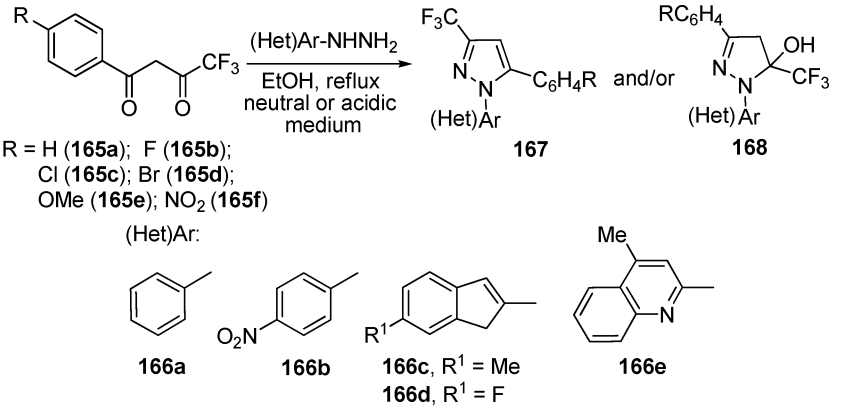
in acidic medium. To explain the formation of the hydroxypyrazoline **162ab**, the authors proposed the presence of a significant concentration of the enol form of **159a**, which results in initial hydrazone formation at the phenyl-bearing carbonyl group and subsequent dehydration.

A systematic study on the regioselectivity of the reaction of aryl trifluoromethyl 1,3-diketones **165** with aryl and heteroarylhydrazines **166** in refluxing ethanol under neutral and acidic conditions was carried out by Elguero *et al.* (*Scheme 51*).[98] From the results, the authors concluded that: i) in going from neutral to acidic conditions, the proportion of 3-trifluoromethylpyrazoles **167** always increases; ii) when the electron-withdrawing effect of the substituent on the hydrazine increases, so does the percentage of 5-hydroxypyrazoline **168**, and iii) when the substituent on the phenyl ring of the 1,3-diketone has a greater electron-withdrawing character, the proportion of 5-hydroxypyrazoline is higher.



NEUTRAL MEDIUM — ACIDIC MEDIUM

With hydrazine **166a**

165a-e ⟶ **165a-e** — **165a-f** ⟶ **167a-f**

165f ⟶ 70% **167f**/30% **168f**

With hydrazine **166b**

165a-f ⟶ 19-38% **167a-f**/ 62-81% **168a-f** — **165a-f** ⟶ **167a-f**

With hydrazine **166c**

165c,f ⟶ **168c,f** — **165c,f** ⟶ **167c,f**

With hydrazine **166d**

165c,d ⟶ **168c,d** — **165c,d** ⟶ **167c,d**

With hydrazine **166e**

165c,d ⟶ **168c,d** — **167c** ⟶ 54% **167c**/ 38% **168c**

Scheme 51

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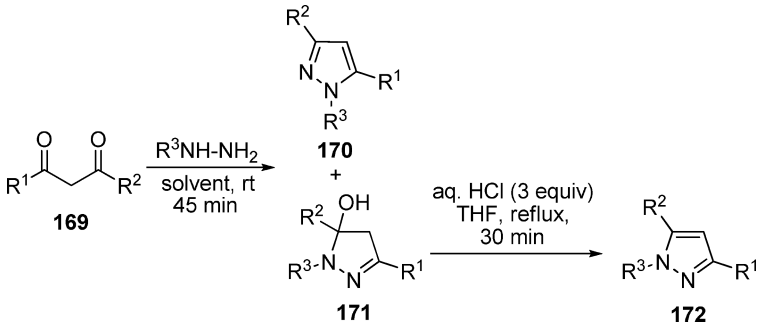
Condensation reactions of fluorinated 1,3-diketones with methylhydrazine are scarce in the literature. Yonetoku *et al.*[99] reported that the reaction of 4,4,4-trifluoro-1-(2-thienyl)butane-1,3-dione with methylhydrazine in a boiling mixture of AcOH-EtOH regioselectively led to 3-trifluoromethyl-1-methyl-5-(2-thienyl)pyrazole in 60% yield.

More recently, Fustero *et al.*[100] published a study concerning the regioselectivity in the preparation of fluorinated 1-methyl- and 1-phenylpyrazoles. In this synthesis, fluoroalkyl 1,3-diketones and methyl- and phenylhydrazine are used as starting materials, while either ethanol or fluorinated alcohols serve as solvents (*Scheme 52* and *Table 1*).



Scheme 52

In ethanol at room temperature, the condensation reactions between the fluoroalkyl 1-aryl-1,3-diketones **169** and the hydrazines were complete in less than one hour to afford mixtures of 3-fluoroalkylpyrazoles **170** and 5-fluoroalkyl-5-hydroxypyrazolines **171** in good to excellent yields but, in general, with very low regioselectivities. Pyrazolines **171** were then converted into their respective 5-fluoroalkylpyrazoles **172** in nearly quantitative yields through treatment with 3 M HCl in THF solution under reflux (*Scheme 42*). In sharp contrast, the regioselectivity for this reaction improved to 99:1 in favor of **170** when the reactions were carried out at room temperature in more acidic alcohols trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP). An NMR experiment involving the addition of an excess of CD_3OH to an NMR sample tube containing **169** (R^1 = 2-furyl; $R^2 = CF_3$) revealed the formation of a mixture of the adduct at the $COCF_3$ carbonyl (hemiketal) and the diketone starting material in a ratio of 8:1 in favor of the former. In contrast, when TFE-d_3 or HFIP-d_2 were added to the same 1,3-diketone, the corresponding adduct was not detected. From these results, the authors concluded that the low regioselectivities observed in EtOH were caused by the competition between the two nucleophiles, hydrazine and alcohol, towards the more reactive fluorinated carbonyl group. As TFE and HFIP are non-nucleophilic, they do not compete with hydrazine in the attack on the fluorinated carbonyl group; the regioselectivity thus increases. A stepwise pathway has been proposed for this process.

Interestingly, analogous 3-fluoroalkylpyrazoles **170** were obtained as major regioisomeric products with either methyl- or phenylhydrazine, in spite of the fact that the primary amino group is more nucleophilic in phenylhydrazine, and less so in methylhydrazine. To explain the apparent anomaly observed in the case of methylhydrazine, the authors proposed that the attack of the more nucleophilic NH group on the more reactive carbonyl group leads to a hemiaminal (*Scheme 53*) which does not easily undergo dehydration to

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Table 1
Results of the Cyclocondensation of Fluoroalkyl-1,3-diketones **171** with Methyl- and Phenylhydrazine

			EtOH	TFE	HFIP
R^1	R^2	R^3	**172** : **173** (%)[a]		
2-Furyl	CF_3	CH_3	36:64 (99)	85:15 (99)	97:3 (98)
2-Furyl	CF_2CF_3	CH_3	64:36 (93)	98:2 (99)	> 99:< 1 (99)
2-Furyl	CF_2CH_3	CH_3	45:55 (99)	98:2 (99)	98:2 (98)
2-Furyl	CO_2Et	CH_3	44:56 (86)	89:11 (99)	93:7 (98)
Ph	CF_3	CH_3	36:64 (99)	79:21 (98)	92:8 (98)
PMP	CF_3	CH_3	30:70 (99)	80:20 (99)	88:12 (99)
2-Furyl	CF_3	Ph	48:52 (75)	87:13 (93)	97:3 (92)
Ph	CF_3	Ph	24:76 (60)	81:19 (98)	99:1 (96)
PMP	CF_3	Ph	55:45 (60)	90:10 (80)	99:1 (85)
2-Furyl	CF_2CF_3	Ph	18:72 (52)	91:9 (92)	99:1 (93)
2-Furyl	CF_2CH_3	Ph	33:67 (62)	99:1 (65)	99:1 (65)
2-Furyl	CO_2Et	Ph	49:51 (69)	89:11 (65)	94:4 (67)
CH_3	CF_3	CH_3	65:35 (98)	88:12 (99)	96:4 (98)
CH_3	CF_3	Ph	5:95 (60)	30:70 (50)	99:1 (73)
p-ClC_6H_4	CF_3	CH_3	12:88 (90)	80:20 (85)	88:12 (94)
p-ClC_6H_4	CF_3	Ph	33:67 (90)	86:14 (89)	99:1 (94)
2,4-$Cl_2C_6H_3$	CF_3	CH_3	70:30 (93)	75:25 (97)	80:20 (90)
2,4-$Cl_2C_6H_3$	CF_3	Ph	87:13 (63)	99:1 (40)	99:1 (61)

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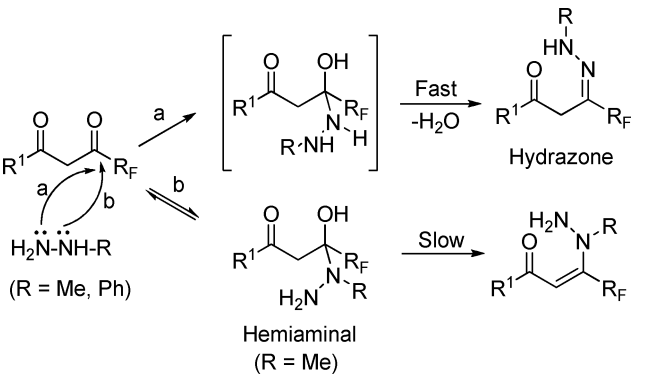
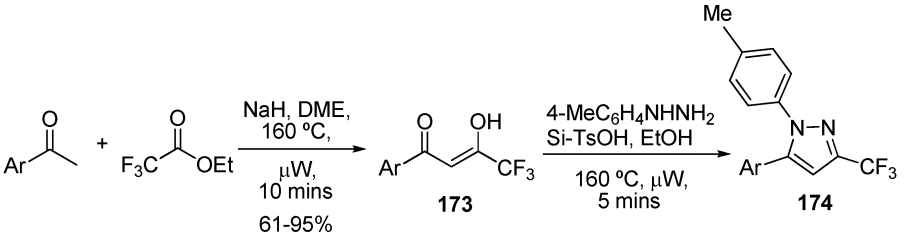
yield a hydrazone and can thus revert back to the starting materials. Indeed, the dehydration is disfavored because of the presence of the fluoroalkyl group. In contrast, the NH_2 group of methylhydrazine attacks the fluoroalkylated carbonyl, thus leading to irreversible hydrazone formation. This is in agreement with Elguero's claim that the kinetically controlling step is the first dehydration.



Scheme 53

Finally, a combination of supported reagents for solution-phase synthesis and ultrasound irradiation was used to prepare a series of 1,5-diaryl-3-trifluoromethylpyrazoles **174** by means of microwave-assisted 4-methylphenylhydrazine addition to silica-supported aryltrifluoromethyl-1,3-diketones **173**.[101] Interestingly, the reactions were complete within 5 minutes and no work-up was necessary to isolate the target pyrazoles. The starting materials **173** were obtained in 10 minutes through microwave-assisted condensation of commercially available arylmethylketones and ethyl trifluoroacetate (*Scheme 54*).



Ar = 4-EtC$_6$H$_4$, 71%; 3,4-(Me)$_2$C$_6$H$_3$, 48%; 4-FC$_6$H$_4$, 66%; 3-MeOC$_6$H$_4$, 50%; 2-MeOC$_6$H$_4$, 42%; 3-MeC$_6$H$_4$, 74%; 3-CNC$_6$H$_4$, 71%; 4-CyclohexylC$_6$H$_4$, 73%; 4-MeC$_6$H$_4$, 95%; 2-pyridyl, 75%; 3-pyridyl, 67%; 4-pyridyl, 64%

Scheme 54

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Conclusions

The last few years have seen a considerable expansion in research on the chemistry of pyrazoles due to the numerous applications of these heterocyclic compounds in various fields such as medicine, agrochemistry, organic synthesis, and catalysis. Although the classical methods involving either cyclocondensations of hydrazines with 1,3-dicarbonyl compounds and their 1,3-dielectrophile equivalents or intermolecular [3+2] cycloadditions of 1,3-dipoles to alkynes are still the most commonly used procedures, new approaches have been developed with the aim of increasing both yields and regioselectivities in the preparation of substituted pyrazoles. These new methods include metal-catalyzed coupling reactions or Mukaiyama-Michael-type additions/heterocyclizations. In addition, new substrates such as Baylis-Hillman adducts, Weinreb amides, and Meldrum acid derivatives have been successfully employed as building blocks. Furthermore, both polar aprotic and fluorinated solvents have proven to be excellent reaction media for increasing the regioselectivity in the synthesis of 1,3,5-trisubstituted pyrazoles. Finally, interesting studies on the cyclocondensation mechanism of fluoroalkyl 1,3-diketones and hydrazines have also been published.

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