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COMMUNICATION

Synthesis of diversely 1,3,5-trisubstituted pyrazoles *via* 5-*exo-dig* cyclization†

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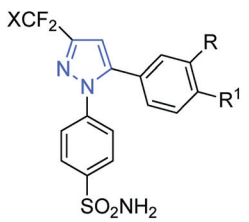
5-*Exo-dig* cyclocondensation of alk-3-yn-1-ones with hydrazines, in the presence of montmorillonite K-10, provides an effective method with a high atom economy for the synthesis of diversely 1,3,5-trisubstituted pyrazoles. The microwave-accelerated reaction proceeds in the absence of solvent and leads to 5-benzyl substituted pyrazoles with good yields (72–91%). The regiochemistry of the process was confirmed by the X-ray crystallographic structure determination of 1-(2-fluorophenyl)-5-(4-methylbenzyl)-3-phenyl-1*H*-pyrazole.

The pyrazole moiety is present in many important agrochemical and pharmaceutical products, such as the pesticides Cyenopyrafen, Tebufenpyrad, Tolfenpyrad, Fenpyroximate, and non-steroidal anti-inflammatory drug Celecoxib (Celebrex, **1a**, Fig. 1). Deracoxib (Deramaxx, **1b**) is a marketed agent for the treatment of inflammation and pain for dogs. In addition, pyrazoles are used as anticancer agents,[1] show anti-inflammatory and molluscicidal activity,[2] are cannabinoid-1 receptor (CB1R) inverse agonists for the treatment of obesity,[3] cyclooxygenase-2,[4] *N*-myristoyltransferase,[5] cancer kinases,[6] and one of the most active histone deacetylase (HDAC8) inhibitors.[7]



1a R = H, R^1 = CH_3, X = F
Celecoxib (Celebrex)
1b R = F, R^1 = OCH_3, X = H
Deracoxib (Deramaxx)

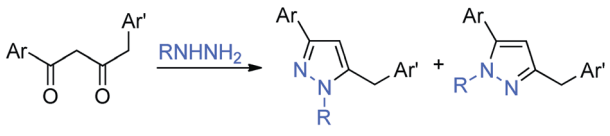
Fig. 1 Examples of biologically active pyrazoles.

Although a variety of methodologies and protocols have been reported, the development of contemporary synthetic routes that allow the regionselective assembly of substituted pyrazoles from simple, readily available starting materials, still remains an important objective.

Substituted pyrazoles are commonly accessed *via* ring derivatization, addition or cyclization of acyclic precursors.[8] The latter one includes the variety of oxygen-containing substrates. In a classical reaction, hydrazine, and alkyl- or arylhydrazines undergo cyclocondensation with 1,3-dicarbonyl compounds to give pyrazoles. However, the use of unsymmetrical 1,3-diketones gives a mixture of regioisomers. In addition, most traditional methods require two steps; a cyclization and a subsequent aromatization (oxidation). Several advances have recently been reported including a synthesis starting from alk-2-yn-1-ones[9] or a continuous flow protocol.[10,11]

Pyrazoles containing benzyl groups were recently investigated and proved to be potent, selective, and orally active human glucagon receptor antagonists.[12] The synthesis of 5-benzyl substituted compounds has been achieved through a cyclization reaction of a diketone **2** with a hydrazine. Not surprisingly two regioisomers **3** and **4** were formed with 45% and 36% yield, respectively (Scheme 1) and had to be separated. Similarly, in a reaction of 1,3-diynes with phenylhydrazine, the two regioisomers were obtained in 20% and 28% yield.[13]

Alk-3-yn-1-ones (propargyl ketones, **5**)[14] are proven versatile bifunctional materials for the synthesis of five-membered heterocycles. Their cycloisomerization and related electrophilic cyclization reactions lead to substituted furans.[15,16] Continuing our efforts on the development of synthetic methods,[17] herein regioselective synthesis of trisubstituted pyrazoles is described.



2 **3**, 45% **4**, 36%

Ar = *p*-$CF_3OC_6H_4$, Ar' = *p*-BrC_6H_4, R = *c*-C_6H_{11}

Scheme 1 Synthesis of pyrazoles **3** and **4** *via* cyclocondensation of diketone **2** and hydrazine.

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†Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra for pyrazoles **3a–j**. CCDC 866543. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25580d

Table 1 Catalyst optimization for cyclization reaction of butynone **5** with phenyl hydrazine

5 **3d**

p-Tol = C_6H_4-*p*-Me

Entry	Catalyst/load	Temperature[a] [°C]	Yield[b] [%]
1	—	80	60
2	—	100	57
3	$H_4SiW_{12}O_{40}$/10 mol%	100	63
4	Amberlyst-15/50 mg	100	66
5	Nafion-H/50 mg	100	79
6	CF_3COOH/10 mol%	100	96
7	CF_3SO_3H/10 mol%	100	98
8	K-10/50 mg	80	92[c]
9	K-10/50 mg	100	99

[a] Discover Benchmate microwave reactor, 10 min; reaction in 0.050 mmol scale for **5** and 0.075 mmol (1.5 equiv) of phenyl hydrazine in the absence of solvent. [b] As determined by GC/MS. [c] Comparable result was obtained using conventional heating at 100 °C for 10 min.

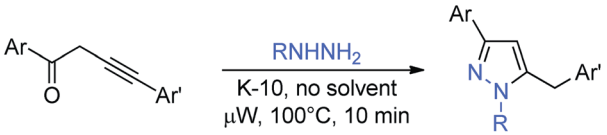
Preliminary optimization experiments were carried out for the cyclization reaction of phenyl/*p*-tolyl substituted butynone **5** (1 equiv, 0.05 mmol) and phenyl hydrazine (1.5 equiv, Table 1). Since an elevated temperature is required, microwave heating was applied to accelerate the reaction rate, moreover, the reaction was carried out solvent-free. Even without a catalyst the reaction proceeded, albeit with moderate yields and with formation of other products (entries 1–2). Subsequently acidic catalysts were screened, mostly heterogeneous, due to our interest in sustainable methods. The use of Keggin-type tungsten-based heteropolyacid catalyst or Amberlyst-15 acidic ion-exchange resin did not procure improvements (entries 3–4) as compared to the non-catalyzed reaction. More promising results were observed with the use of Nafion-H, a fluoropolymer sulfonic acid (entry 5).[18] The use of homogeneous catalysts, such as trifluoroacetic and triflic acid, facilitated very good progress (entries 6–7); however, the separation and recycling of the catalyst hampered the practicality of this system.

Among the viable alternatives available for green synthetic methods, clay-based catalysts have attracted attention due to their versatile properties.[19] These materials provide broad possibilities for synthetic applications,[20] particularly in the synthesis of heterocycles.[21] The layered structure of these aluminosilicates allows for the intercalation of different organic molecules, and the ion-exchange capabilities procures the commutation of specific metal ions. We turned our attention to montmorillonite K-10, which has already been employed as a catalyst in the synthesis of pyrazoles.[22]

The application of montmorillonite K-10 (entries 8–9) led to the formation of the pyrazole **3a** at 100 °C, with 99% yield, after 10 min, in the absence of solvent.

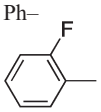
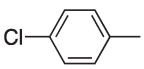
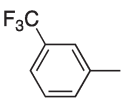
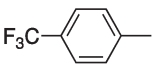
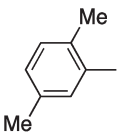
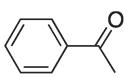
Since montmorillonite K-10 was found to be an effective catalyst (Table 1), a preparative synthesis for a series of pyrazoles was developed, as illustrated in Table 2. The reactions were carried out solvent-free using microwave heating. The products were isolated using preparative TLC. Although we focused on fluoroaryl-substituted pyrazoles due to potential biological activity, hydrazines with alkyl (methyl and *tert*-butyl) as well as benzoyl groups were also examined. The results of the reactions of ketone **5** with various substituted hydrazines are provided in Table 2. Although diminished nucleophilicity could be expected for the benzoyl hydrazine, no detrimental effect on reactivity was observed.

Table 2 Synthesis of pyrazoles **3a–j** *via* cyclocondensation of **5** and hydrazines



5 **3a-j**

Ar = Ph, Ar' = *p*-MeC_6H_4

Entry	Hydrazine R–	Pyrazole	Yield[a]
1	H–	**3a**	91
2	Me–	**3b**	85
3	*t*-Bu–	**3c**	76
4	Ph–	**3d**	85
5		**3e**	82
6		**3f**	86
7		**3g**	74
8		**3h**	73
9		**3i**	75
10		**3j**	83

[a] [%], isolated yield; reactions were carried out in a microwave vial on a 0.250 mmol scale with 0.375 mmol of hydrazine and 250 mg of K-10 catalyst, at 100 °C in the absence of solvent; reaction time 10 min.

The structure of the new pyrazoles was confirmed by NMR and MS. The characteristic NMR features for **3a–j** include the ^{1}H H-4 signals (6.14–6.51 ppm) and ^{13}C C-4 and CH_2 (benzyl) signals (102.3–108.5/31.8–34.3 ppm). Mass spectra for **3** exhibited intense molecular ions.

The molecular structure of a representative 1,3,5-trisubstituted pyrazole and the regiochemistry of the method was confirmed by X-ray crystallography.[23] The molecule of expected 5-(4-methylbenzyl)-1*H*-pyrazole **3e** is shown in Fig. 2.

We confirmed that the reaction is also applicable to 1-ethyl as well as 4-cyclopropyl-substituted butynones, leading to 3-ethyl

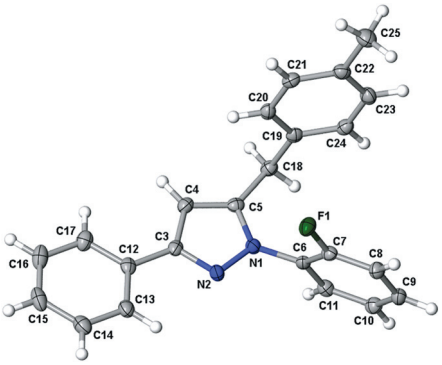
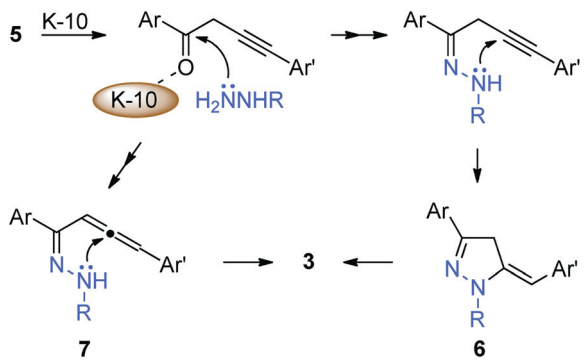


Fig. 2 An ORTEP view of the **3e** illustrating atom labeling scheme and thermal ellipsoids (50% probability level). Selected interatomic distances (Å): N1–N2 1.364(2), N2–C3 1.335(2), C3–C4 1.411(2), C4–C5 1.374(3), C5–N1 1.362(2). Key angles (°): N1–N2–C3 104.64(13), N2–C3–C4 110.77(15), C3–C4–C5 106.22(15), C4–C5–N1 105.64(15), C5–N1–N2 112.73(14).

and 5-cyclopropylmethylene-substituted pyrazoles. ^{1}H and ^{13}C NMR spectra are provided in the electronic ESI.†

Presumably the reaction mechanism includes a sequence of consecutive formation of a hydrazone and intramolecular 5-*exo-dig* cyclization reaction that constitute a formal hydrohydrazidation of an alkyne (Scheme 2). Isomerization of benzylidene derivative **6**, driven by aromatization, leads to the final product **3**. Required hydrogen migration may contribute to a necessity of elevated temperature for this reaction to proceed. However, initial formation of an allene, such as **7**, that would subsequently cycloisomerize cannot be excluded.[24]



Scheme 2 Mechanistic outline for the synthesis of pyrazoles **3** *via* cyclocondensation of **5** and hydrazines.

In summary, we have demonstrated that the combination of a condensation reaction with subsequent 5-*exo-dig* cyclization provides an efficient system for the synthesis of pyrazoles. The method provides effective access to diversely substituted 1,3,5-trisubstituted pyrazoles. The solvent-free conditions provide an appealing protocol that includes formation of two C–N bonds and does not even require isolation of hydrazone. This method facilitates the regioselective positioning of hydrazine within two available locations. Moreover, it also allows for the introduction of benzyl type substituents (such as *p*-methylbenzyl) at the C-5 of pyrazole that is not easily carried out by currently available methods.[25]

Acknowledgements

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