Heterocycles

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Efficient Synthesis of Pyrazoles: Oxidative C–C/N–N Bond-Formation Cascade**

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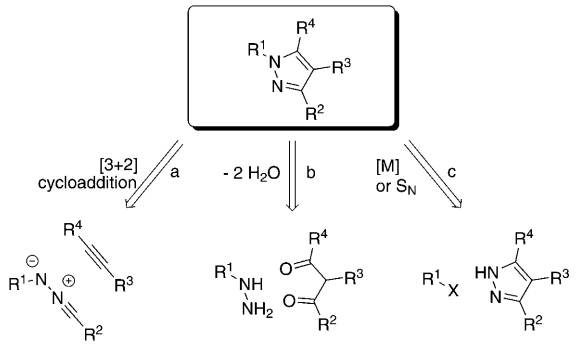
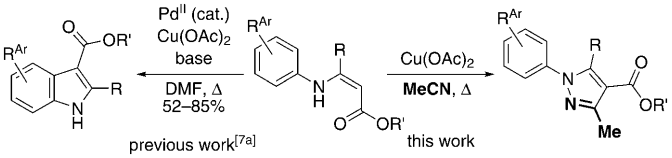
Dedicated to Professor Lutz F. Tietze

Although pyrazoles are rarely found in natural products, they represent an important motif of manmade biologically active compounds like the anti-inflammatory drug Celecoxib and the insecticide Fipronil.[1] Arguably, the most popular methods for the preparation of 1,3,4,5-tetrasubstituted pyrazoles are the dipolar [3+2] cycloaddition between a CN_2 and a C_2 moiety or the classical cyclocondensation of a monosubstituted hydrazine with a 1,3-dicarbonyl compound or surrogates thereof (Schemes 1a and b).[2] Another increasingly used approach is the functionalization of preformed trisubstituted pyrazoles by either nucleophilic substitution or transition metal catalyzed C–N bond formation (Scheme 1c).[3] However, the use of carcinogenic hydrazines,[4,5] regioselectivity issues (arising for pyrazoles with $R^3 \neq R^5$),[6] and somewhat limited substrate scope greatly reduce the attractiveness of these methods.



Scheme 1. Most popular approaches to tetrasubstituted pyrazoles.

In the course of our study on the intramolecular oxidative cyclization of enaminones to indoles,[7] we made an interesting finding (Scheme 2): the use of acetonitrile as solvent instead of the previously employed DMF resulted in an intermolecular oxidative formation of a pyrazole. Furthermore, experiments showed that neither palladium nor a base are required for this C–C/N–N bond-formation cascade. Herein we disclose our preliminary results of this efficient formation of pyrazoles from readily available and simple starting materials, namely amines, ketones, and nitriles.



Scheme 2. *N*-Aryl-enaminones as versatile synthetic intermediates, allowing the oxidative cyclization to indoles or, alternatively, the intermolecular reaction with nitriles to pyrazoles.

Enaminoesters are versatile synthetic intermediates that combine the nucleophilicity of an enamine with the electrophilicity of an enone. Their synthesis and their structural and pharmacological properties have been extensively investigated.[8] Several studies have shown that enamines bearing a secondary nitrogen atom react with electrophiles preferably at the nucleophilic enamine carbon atom, and that strong electrophiles such as acid chlorides or iso(thio)cyanates are required.[9] Therefore, the reaction with acetonitrile as a rather weak electrophile was unexpected and worth exploration. Moreover, the oxidative formation of N–N bonds is rare in organic synthesis, often being limited to intramolecular reactions and mostly promoted by strong oxidants like hypervalent iodine(III) reagents.[10,11]

Optimization of the reaction conditions[12] showed that

- acid or base additives deteriorate the yield,
- the reaction is sensitive to moisture and pure oxygen, however, can be run conveniently with good results under an atmosphere of air (or argon),
- an excess of the nitrile is required.

In addition, employing catalytic amounts of Cu^{II} salts in combination with other stoichiometric oxidants like air has not yet furnished satisfactory results. Under the optimized reaction conditions (Table 1), the reactions were run in an excess of nitrile without an additional solvent (enaminone

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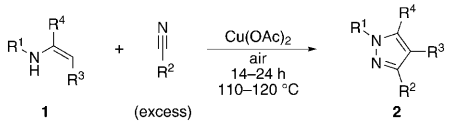
Table 1: Substrate scope.



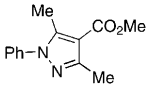
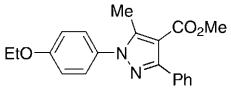
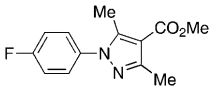
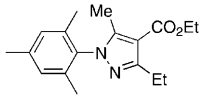
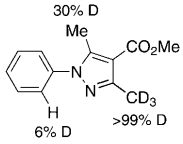
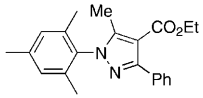
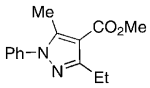
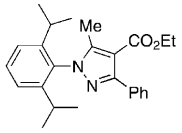
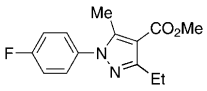
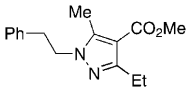
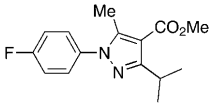
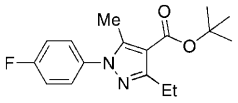
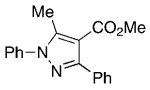
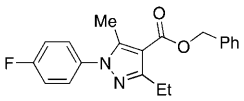
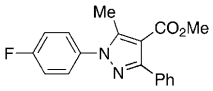
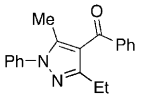
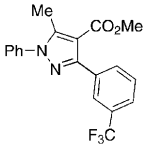
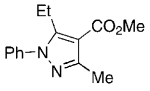
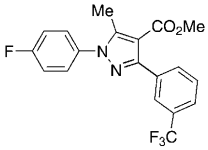
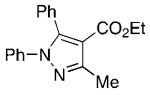
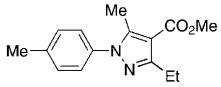
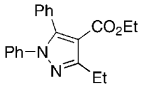
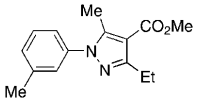
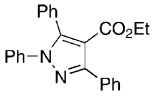
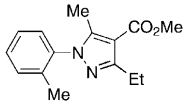
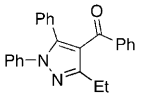
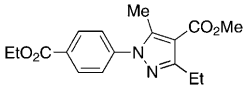
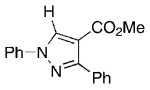
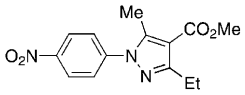
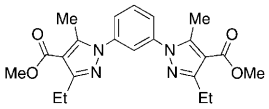
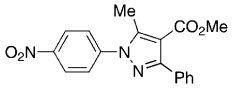
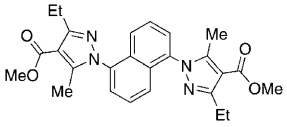
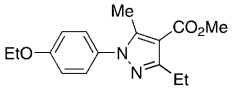
Entry	Pyrazole		Yield [%][a]	Entry	Pyrazole		Yield [%][a]
1		**2a**	80[b] 81[c]	18		**2r**	87[c]
2		**2b**	87[c]	19		**2s**	92[c]
3		**2c**	82[b]	20		**2t**	83[c]
4		**2d**	77[b]	21		**2u**	35[c]
5		**2e**	83[c]	22		**2v**	58[c]
6		**2f**	71[c]	23		**2w**	73[c]
7		**2g**	76[b]	24		**2x**	84[c]
8		**2h**	90[c]	25		**2y**	43[c]
9		**2i**	72[b]	26		**2z**	77[b]
10		**2j**	81[b]	27		**2aa**	88[c]
11		**2k**	77[b]	28		**2ab**	87[c]
12		**2l**	72[b]	29		**2ac**	82[c]
13		**2m**	75[b]	30		**2ad**	53[b]
14		**2n**	73[b]	31		**2ae**	39[c]

Table 1: (Continued)

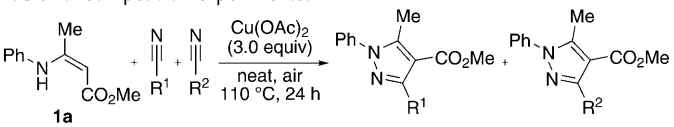
Entry	Pyrazole		Yield [%][a]	Entry	Pyrazole		Yield [%][a]
15		**2o**	65[c]	32		**2af**	70[d]
16		**2p**	75[c]	33		**2ag**	73[d]
17		**2q**	88[c]				

[a] Yield of analytically pure, isolated pyrazole product **2**. [b] Reaction conditions A: enamine **1** (1.0 mmol), $Cu(OAc)_2$ (1.5 equiv), RCN (1.5 mL), 110 °C, 24 h. [c] Reaction conditions B: enamine **1** (1.0 mmol), $Cu(OAc)_2$ (3.0 equiv), RCN (3.0 mL), 120 °C, 14–24 h. [d] Reaction conditions C: enamine **1** (1.0 mmol), $Cu(OAc)_2$ (6.0 equiv), R^2CN (6.0 mL), 110–120 °C, 16–24 h.

concentration 0.33 M), in the presence of 3.0 equivalents of $Cu(OAc)_2$ under an atmosphere of air at 120 °C. Alternatively, using half the amount of $Cu(OAc)_2$ (1.5 equiv) and nitrile (0.66 M) generally provided the desired products in only slightly reduced yields.

With the optimized reaction conditions in hand, we explored the substrate scope of this reaction (Table 1). Using (*Z*)-methyl-3-(phenylamino)but-2-enoate (**1a**) and its *para*-fluoro derivative, several different nitriles were successfully coupled in good yields (Table 1, entries 1–10). Aliphatic (Table 1, entries 1–6) as well as aromatic nitriles worked well (Table 1, entries 7–10). Competition experiments clearly show that the aromatic benzonitrile reacts faster than aliphatic propionitrile and that electron-withdrawing groups on the aromatic nitrile render the substrate even more reactive (Table 2). For example, employing equimolar

Table 2: Competition experiments.[a]



Entry	R^1	R^2	Ratio of pyrazole products[b]
1[c]	Et	Me	**2d**/**2a** = 63:37
2[d]	Et	Ph	**2d**/**2g** = 22:78
3[e]	Ph	*m*-$CF_3C_6H_4$	**2g**/**2i** = 9:91

[a] Reaction conditions: Enamine **1a** (1.0 mmol), $Cu(OAc)_2$ (3.0 equiv), R^1CN, R^2CN, 110 °C, 24 h. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] R^1CN (28.5 equiv), R^2CN (28.5 equiv); [d] R^1CN (21.0 equiv), R^2CN (21.0 equiv); [e] R^1CN (14.7 equiv), R^2CN (14.7 equiv).

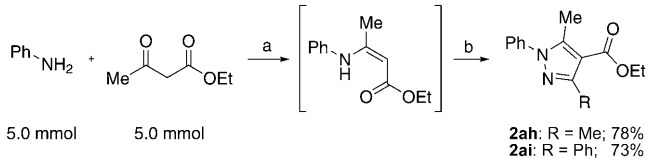
amounts of benzonitrile and *meta*-trifluoromethylbenzonitrile, and using the enaminone substrate **1a** as the limiting component resulted in a 9:91 ratio of the corresponding products (Table 2, entry 3). Interestingly, the more electron-rich propionitrile proved to be more reactive than acetonitrile (Table 2, entry 1).[13]

Moreover, it is important to note that unsymmetrical pyrazoles ($R^2 \neq R^4$) were formed with complete regioselectivity (Table 1, entries 4–33), for example providing 3-ethyl-5-methyl-pyrazoles (Table 1, entries 4, 5, 11—15, 17, 19, 22–25, 32, 33). By using deuterated acetonitrile the origin of the 3-methyl group could be clearly proven and the advantage of regiospecificity emphasized (Table 1, entry 3).

To investigate the substrate scope regarding the substituents R^1, R^3, and R^4, several differently substituted enamines were reacted with representative nitrile reaction partners: First of all, the scope of the N substituents was found to be impressively broad. The *ortho*-, *meta*- and *para*-substituted aryl groups, as well as the electron-rich and electron-poor aryl groups were well tolerated, including functional groups such as nitro or ester moieties (Table 1, entries 11–21). Especially noteworthy is the synthesis of *N*-mesityl pyrazoles (Table 1, entries 19 and 20), since their construction by classical methods involves the expensive and rather sensitive mesityl hydrazine. The possibility of employing exceedingly sterically demanding aromatic systems as nitrogen substituents of the pyrazole, represents a special feature of this C–C/N–N bond-forming cascade. This culminates in the creation of the first 2,6-diisopropylphenyl-substituted pyrazole **2u** (Table 1, entry 21). In addition, since alkylhydrazines are generally not readily available, the use of non-aromatic substituents on the nitrogen is especially valuable (Table 1, entry 22).[14]

A certain level of variation is possible at the 4-position of the pyrazole ring. For example, the ester group can be changed from methyl to *tert*-butyl or benzyl esters (73 % and 84 % respectively; Table 1, entries 23 and 24), allowing the mild ester cleavage and decarboxylation of the pyrazole products. Interestingly, enaminoketones also provide the corresponding pyrazoles, albeit **2y** is formed in lower yield (Table 1, entry 25). Concerning the 5-position of the pyrazoles, aliphatic (Table 1, entries 1–26) and aromatic (Table 1, entries 27–30) substituents can be placed equally successfully. Furthermore, the 5-unsubstituted system can be formed, although only in lower yield (Table 1, entry 31). Finally, two bispyrazoles, which might represent a new class of easily obtainable, highly modular ligands, were efficiently prepared in good yields (Table 1, entries 32 and 33).

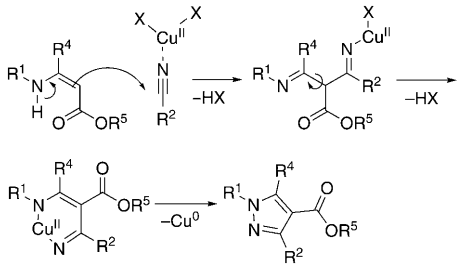
Finally, we succeeded in performing the reaction in a one-pot fashion using a mild and efficient Lewis acid ($InBr_3$) for the fast initial formation of the enamine (Scheme 3).[15] Key to



Scheme 3. One-pot pyrazole synthesis. Reaction conditions: a) 1. $InBr_3$ (1.0 mol%), closed vessel, argon, RT, 1 h; 2. water resulting from the condensation was removed by freeze/pump/thaw cycles; b) $Cu(OAc)_2$ (1.5 equiv), RCN (7.5 mL, 14–29 equiv), air, closed vessel, 110 °C, 24 h; reported yields are of isolated products.

the high yield of the overall transformation is the removal of water formed in the initial condensation step by freeze/pump/thaw cycles. By using this procedure, some pyrazole products could be conveniently obtained on a 5 mmol scale in yields similar to the ones for the pyrazole formation step only (e.g., **2ah**: 78% versus 77%, respectively). Thus, the pyrazoles **2ah** and **2ai** were accessible from three very simple and commercially available starting materials—amines, ketones, and nitriles. This efficient and highly modular one-pot procedure significantly increases the practicality and usefulness of this new method.

The following mechanism can be proposed, utilizing copper as a Lewis acid activator and as an oxidizing agent (Scheme 4). First, the nitrile is activated by the copper(II) Lewis acid allowing the addition of the nucleophilic enamine. Loss of one molecule of HOAc (X = OAc) leads to a 1,3-bisimine. After rotation around the former *Z* double bond and elimination of another HX molecule, a Cu^{II}-chelate complex forms. Reductive elimination furnishes the pyrazole product as well as copper(0).



Scheme 4. Proposed reaction mechanism (X = OAc).

In conclusion, we have reported a new method for the preparation of tetrasubstituted pyrazoles from enamines and nitriles involving an oxidative N–N bond formation. It obviates the need for hydrazine substrates, has a broad substrate scope, and provides the products regiospecifically. Considering the large variety and ready availability of the starting materials and the operational simplicity (reaction, work-up, and purification), a convenient, practical and highly modular pyrazole synthesis has been developed.

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