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An Efficient Copper-Catalyzed Formation of Highly Substituted Pyrazoles Using Molecular Oxygen as the Oxidant

Mamta Suri, Thierry Jousseaume, Julia J. Neumann and Frank Glorius*

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An efficient Cu-catalyzed formation of tetra-substituted pyrazoles is reported. In this atom economic process, readily available enamines and nitriles are reacted by C-C and N-N bond formation. Oxygen has been successfully used as the 10 oxidant, which has important economic and environmental advantages. A broad scope of enamines and nitriles can be utilized in this process.

Pyrazoles are an intriguing class of important heterocycles: although rarely found in nature, many man-made biologically ¹⁵ active compounds possessing agricultural¹ and pharmaceutical activities² contain pyrazole moieties. Surprisingly, the efficient and selective synthesis of highly substituted pyrazoles still represents a major challenge. The most commonly used approaches to the synthesis of tetrasubstituted pyrazoles involve ²⁰ either the classical condensation of hydrazines with 1,3dicarbonyl compounds (or their equivalents), the 1,3-dipolar [3+2] cycloadditions or the transition metal catalyzed C-N and/or C-C cross coupling on the preformed pyrazoles.^{3,4}

- Recently, we have published a novel method for the synthesis ²⁵ of tetrasubstituted pyrazoles involving the coupling of enamines⁵ with nitriles by oxidative C-C/N-N bond formation.^{6,7} This approach leads to a highly efficient regioselective synthesis of a variety of tetrasubstituted 1*H*-pyrazoles. It provides an alternative to the use of carcinogenic hydrazines, with a broad substrate ³⁰ scope and a convenient practical synthesis. However, it required the use of a stoichiometric amount of Cu(OAc)₂ as Lewis acid and oxidant. In addition, an excess amount of nitrile without any additional solvent was employed which lower the atom-economy and also it limited the use of a wide range of nitriles.
- With the growing concern over the production of environmentally hazardous chemical wastes, the development of more efficient, catalytic oxidative processes would be highly desirable. The use of molecular oxygen as the terminal oxidant coupled with the catalytic metal system provides a challenging 40 but attractive greener approach to it owing to its high abundance,
- low cost and reduction of toxic by-product formation.⁸

Herein, we report a novel synthetic approach to tetrasubstituted pyrazoles using equivalent amounts of nitriles with an efficient metal catalyst system employing molecular oxygen as the sole 45 stoichiometric oxidant.



 Table 1 Optimization of the amount of the nitrile with other reaction

 parameters^a

Entry	Eq. PhCN	Solvent	Yield% ^b
1°	10	2,4-DCT	74
2	10	2,4-DCT	82
3	10	1,2-DCB	78
4	10	DCE	80
5	10	DMF	97 (90)
6	10	1,4-Dioxane	88
7	10	DMSO	95
8	1.5	DMF	64 (61)
9^{d}	1.5	DMF	54
10 ^e	1.5	DMF	53
11^{f}	1.5	DMF	46
12	3.0	DMF	(72)
13	5.0	DMF	(79)

^aReaction conditions: 1a (0.25 mmol), Cu(OAc)₂ (1.5 eq.), PhCN, solvent ⁵⁰ (0.26 mL), air (closed tube), 110 °C, 24 h; ^b determined by GC analysis with mesitylene as an internal standard; isolated yield of 3aa (1 mmol scale reaction) is given in parentheses; ^c with Cu(OAc)₂ (1.0 eq.); ^d time 48h; ^eat 140 °C. ^f DMF (0.13 mL); 2,4-DCT = 2,4-dichlorotoluene, 1,2-DCB = 1,2-dichlorobenzene, DCE = 1,2-dichloroethane, DMF = *N*,*N*-⁵⁵ dimethylformamide, DMSO = dimethyl sulfoxide.

We commenced our study by first optimizing the amount of nitrile while keeping the stoichiometric amount of Cu(OAc)₂. Choosing (Z)-methyl 3-(phenylamino)but-2-enoate (1a) and 60 benzonitrile as the standard substrates, we started screening different solvents (Table 1). It can be seen that both the polar solvents as well as the non-polar solvents furnish the product (3aa) in good yields. Lewis acids were also tested as additives for the activation of the nitrile.⁹ However, they do not provide any 65 promising results.¹⁰ Among the different solvents screened, DMF was found to be the best solvent. Interestingly, either increasing the time or the temperature of the reaction, the yield of the product (3aa) did not improve (Table 1, entries 9 and 10). However, it has been observed that the yield of the product (3aa) 70 could be improved by increasing the equivalents of benzonitrile with respect to the enamine (1a), (Table 1, entries 8, 12, 13 and 5).

With the first goal - optimizing the amount of the nitrile with

respect to the enamine achieved, the second goal to develop the reaction catalytic with molecular oxygen as the stoichiometric oxidant was set up. Under the atmosphere of molecular oxygen (1 bar), choosing again (*Z*)-methyl 3-(phenylamino)but-2-enoate 5 (1a) and benzonitrile as the standard substrates, different solvents were screened. Among them DCE was found to be the best solvent (Table 2, entries 1-8). Combining different terminal metal oxidants as well as benzoquinone (Table 2, entries 9-15), the yield of the product was found deteriorated. Also, using Cu(I) ¹⁰ sources instead of Cu(OAc)₂ yielded no product.¹⁰ Carrying out the reaction at higher pressure of molecular oxygen, the yield

dropped drastically (Table 2, entry 16). Among the different additives screened¹⁰ it was found that 2-picolinic acid (5 mol%) not only improved the yield but also allowed lowering of the ¹⁵ catalyst loading (Table 2, entry 19).



 Table 2 Screening the catalytic conditions with different reaction

 parameters^a

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Entry	Additive (eq.)	Solvent	Yield% ^b
1		Toluene (1 M)	7
2		DMF (1 M)	< 5
3		Dioxane (1 M)	31
4		DMSO (1 M)	14
5		t-amyl alcohol	21
		(1 M)	
6		DCE (1 M)	39
7		DCE (0.5 M)	58
8		DCE (0.25 M)	50
9	FeCl ₃ (0.25)	DCE (0.5 M)	0
10	$Fe(acac)_3 (0.25)$	DCE (0.5 M)	19
11	Fe(NO ₃) ₃ .H ₂ O (0.25)	DCE (0.5 M)	0
12	$FeF_3(0.25)$	DCE (0.5 M)	39
13	CuBr (0.25)	DCE (0.5 M)	59
14	FeBr ₂ (0.25)	DCE (0.5 M)	0
15	Benzoquinone (0.25)	DCE (0.5 M)	26
16 ^c		DCE (0.5 M)	8
17 ^d	N-methoxy pivalamide	DCE (0.5 M)	69 (65)
	(0.05)		
18^{a}	<i>N</i> -acetamido benzoic acid	DCE (0.5 M)	69 (64)
1 od	(0.05)	DCE (A 7 M)	04 (60)
19"	2-picolinic acid (0.05)	DCE (0.5 M)	84 (68)

^a Reaction conditions: 1a (0.25 mmol), Cu(OAc)₂ (25 mol%), PhCN (3.0 20 eq.), additive, solvent, 110 °C, 24 h, under an atmosphere of O₂ (1 bar, closed tube); ^b determined by GC analysis with mesitylene as an internal standard; isolated yield of analytically pure product is given in parentheses; ^c under O₂ (2 bar), closed tube; ^d Cu(OAc)₂ (10 mol%).

²⁵ The exact role of 2-picolinic acid as an additive in the catalytic reaction condition is not clearly understood. However, it has been found that the rate of the reaction is higher than the reaction without the additive (Figure 1).¹⁰ It can be assumed that it acts as a catalytic H⁺ source and helps in the redox cycle in regenerating ³⁰ Cu(II) from Cu(I); it may also act as a better coordinating anion

than acetate and helps in stabilizing various intermediates.

Interestingly, it was observed that addition of an equivalent amount of the pyrazole (**3aa**) to the reaction of (*Z*)-methyl 3-(p-



Fig. 1 Kinetic study of the effect of 2-picolinic acid on the the formation of 3aa; data points with (●) and without (▲) the additive; (R = Standard deviation).

tolylamino)but-2-enoate (**1d**) and 4-fluorobenzonitrile as the coupling partners, inhibited the formation of desired product (**3db**).¹¹ It seems that under the reaction condition the nitrile and ⁴⁰ the pyrazole compete with each other to chelate with copper hence, the pyrazole in higher amount slows down/quenches/poisons the reaction.

With the optimized conditions in hand (Table 1, entry 12 and Table 2, entry 19), we explored the substrate scope of this 45 reaction (Table 3). Using (Z)-methyl 3-(phenylamino)but-2enoate (1a) as the coupling partner, different nitriles were successfully coupled to give the respective products in good vields (Table 3, entries 3aa-3an). Both aromatic and heteroaromatic (Table 3, entries 3aa-3aj) as well as aliphatic 50 (Table 3, entries 3ak-3am) nitriles furnished good results. Among the aromatic nitriles, different ortho-, meta- and parasubstituted groups, both electron-withdrawing and electrondonating were well tolerated. Also, the styryl group at 3-position can be introduced into the pyrazole which can be further modified 55 by a plenty of known coupling reactions (Table 3, entry 3an). In addition to different nitriles - solid and liquid, the gaseous nitrile trifluoroacetonitrile has been coupled for the first time with the enamine (1a) in good yield (Table 3, 3am).

To investigate the scope of R^1 , R^4 and R^5 groups, differently 60 substituted enamines were reacted with 4-fluorobenzonitrile as the coupling partner (Table 3, entries 3bb-3rb). Both electrondonating (Table 3, entries 3bb-3db) and electron-withdrawing groups (Table 3, entries 3ib-3kb) at o-, m- and p-positions on the aryl group at R¹ gave good yields. Also, different functional 65 groups were well tolerated (Table 3, entries 3eb-3hb). Sterically demanding groups at R^1 position (Table 3, entries **3lb-3mb**) do not affect the reactivity of the enamines with the nitrile and gives the products in good to moderate yields, which were difficult to obtain by the classical methods of pyrazole formation owing to 70 the expensive and difficult formation of their respective hydrazines. In addition, N-alkyl pyrazoles have also been obtained in good yields (Table 3, entries 3nb-3pb), which were also difficult to obtain by classical methods due to the limited availability of their respective hydrazines.12 R4 can also be varied 75 from OMe, OEt to Ph, giving pyrazole ester to pyrazole ketone (Table 3, entry **3rb**). Hence, the scope of the reaction yielding differently substituted products was found to be quite broad.

The following mechanism can be proposed for the catalytic

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 Table 3 Substrate scope under the optimized reaction conditions.



Isolated yield of analytically pure product is given. Reaction conditions ^a A: 1 (1.0 mmol), 2 (3.0 eq.), Cu(OAc)₂ (1.5 eq.), DMF (1 M), 110 °C, 24 h, air (closed tube); ^bB: 1 (0.25 mmol), 2 (3.0 eq.), Cu(OAc)₂ (10 mol%), 2-picolinic acid (5 mol%), DCE (0.5 M), 110 °C, 24 h, under an atmosphere of O₂ (1 5 bar, closed tube). ^c Reaction condition A, after adding the substrate **1a**, the reagents and the solvent to a Schlenk tube (10 mL, 0.5 mmol scale), the tube was evacuated (in an ice bath) and filled with trifluoroacetonitrile gas. ^dReaction condition A, nitrile (7.0 eq.), *N*,*N*-dimethylacetamide (1 M).



Fig. 2 Proposed mechanism of the catalytic reaction (X = OAc or OPic, where HOPic = 2-picolinic acid)

¹⁰ reaction (Figure 2). CuX_2 coordinates with the (Z)-enamine via removal of HX to give Cu^{II} -chelate I, which undergoes anion exchange with HOPic (if X = OAc) to generate Cu^{II} -chelate II. The nitrile coordinates with the Cu-complexes present in the reaction mixture. The coordinated enamine attacks the activated ¹⁵ nitrile in either intramolecular or intermolecular fashion to give

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complex IV. Complex IV undergoes a σ -bond rotation followed by the loss of one equivalent HOPic to generate Cu^{II}-(1,3-imineenamine) chelate V. With reductive elimination, complex V gives the desired product and Cu⁰ or two equivalents of Cu^I, which are s oxidized by HX and molecular oxygen to CuX₂ that enters again into the catalytic cycle.

Conclusions

In conclusion, we have reported an efficient, atom economic and greener method for the regioselective synthesis of tetrasubstituted ¹⁰ pyrazoles as opposed to our previously reported method. This represents the first preparation of tetrasubstituted pyrazoles catalytic in copper and with molecular oxygen as the sole oxidant. This provides a new set of products, which could not be synthesized by the earlier methods. This highly practical and ¹⁵ modular synthesis represents an alternative to the known methods of pyrazole synthesis with a broad substrate scope, high atom efficiency, without the need of carcinogenic hydrazines and less formation of toxic by-products.

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This Cu-catalyzed C-C/C-N-bond formation cascade allows the efficient synthesis of pyrazoles from solid, liquid or gaseous nitriles and enamines.