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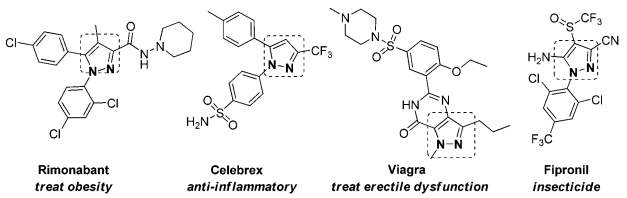
Copper-mediated pyrazole synthesis from 2,3-allenoates or 2-alkynoates, amines and nitriles†

Bo Chen,‡[a] Can Zhu,‡[a] Yang Tang[a] and Shengming Ma*[ab]

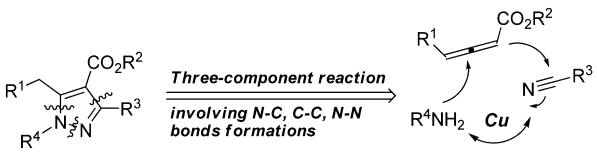
An efficient copper-mediated three-component reaction of 2,3-allenoates or 2-alkynoates, amines, and nitriles affording fully substituted pyrazoles with a very nice diversity has been developed. A tandem conjugate addition, 1,2-addition, and N–N bond formation mechanism has been proposed for this diverse synthesis of pyrazoles based on mechanistic studies.

Pyrazoles are some of the most important heteroaromatic compounds considering their wide existence in natural products as well as in pharmacologically active substances.[1] Many pyrazole-containing compounds such as rimonabant, celebrex, viagra, and fipronil have been successfully commercialized as medicines or pesticides (Scheme 1).[2] Additionally, pyrazoles are used in polymer and supramolecular chemistry, and as cosmetic colorings and UV stabilizers.[3] Poly-substituted pyrazoles have also been utilized as ligands for some transition metal-catalyzed reactions.[4]



Scheme 1 Some commercialized bioactive pyrazole compounds.

Typical approaches towards the synthesis of poly-substituted pyrazoles[1] are based on the reaction of hydrazines with 1,3-dicarbonyl compounds or unsaturated hydrocarbons,[5] the reaction of diazo compounds with unsaturated compounds,[6] the reaction of aryl amines with 1,3-dicarbonyl compounds forming β-amino-α,β-enoates or enones, which would react further with nitriles,[7] and catalyzed azacyclization of propargylic hydrazines or *N*-propargylic sulfonylhydrazones.[8] Most of these reported approaches are based on starting materials, which are either with a limited scope or not readily available and should be obtained *via* multi-step synthesis or even with danger. On the other hand, functionalized allenes, especially 2,3-allenoates, have been proven to be useful building blocks due to the reactivity and substituent-loading capability of the allene unit. Based on our studies on the reactivities of 2,3-allenoates, we envisioned that the reaction of 2,3-allenoates, amines, and nitriles may offer an efficient and convenient three-component approach to pyrazole skeletons *via* a conjugated addition of amines to 2,3-allenoates,[9] subsequent 1,2-addition to nitriles, and copper-involved N–N bond formation process (Scheme 2). We wish to disclose the realization of such a three-component reaction with diversity due to the substituent loading ability of the three readily available starting materials.



Scheme 2 Concept of the diverse synthesis of pyrazoles *via* 2,3-allenaotes.

At first, we treated the parent 2,3-allenoate **1a** with $BnNH_2$ (1.1 equiv) in PhCN using $Cu(OAc)_2$ as the oxidant at 120 °C for 12 h (Table 1, entry 1). The desired product **3a** was formed in 56% yield based on NMR analysis. The yield was improved to 85% by increasing the loading of $BnNH_2$ from 1.1 to 1.5 equiv. (entries 1–3). Further study on the effect of temperature led to the observation that the reaction at 120 °C afforded the best result (entries 5 and 6). Reducing the amount of $Cu(OAc)_2$ or switch to other oxidants such as dioxygen or $PhI(OAc)_2$ did not afford better results (entries 8–10). Thus, we defined the reaction of 2,3-allenoate **1a** with 1.5 equiv. $BnNH_2$ and 2 equiv. $Cu(OAc)_2$ in PhCN at 120 °C for 6 h as the standard conditions (entry 4, Table 1).

[a] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, P. R. China*

[b] *Shanghai Key Laboratory of Green Chemistry and Chemical Process, Department of Chemistry, East China Normal University, 3663 North Zhongshan Road, Shanghai 200062, P. R. China. E-mail: masm@sioc.ac.cn; Fax: +86-21-6260-9305*

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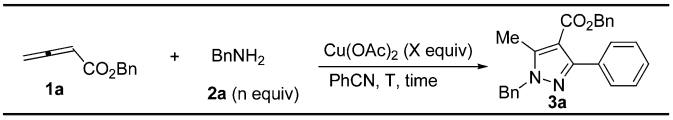
‡ These two authors contributed equally to this work.

Table 1 Optimization of reaction conditions: reaction of 2,3-allenoate **1a** with $BnNH_2$ in PhCN[a]

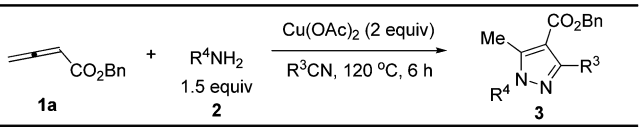


Entry	*n*	*X*	*T* (°C)	Time (h)	Yield of **3a**[b] (%)
1	1.1	2	120	12	56
2	1.3	2	120	12	81
3	1.5	2	120	12	85
4	1.5	2	120	6	85
5	1.5	2	100	6	43
6	1.5	2	130	6	77
7	1.5	2	120	3	68
8	1.5	0.1	120	12	10[c]
9	1.5	0.1	120	12	Trace[d]
10	1.5	1.5	120	12	71

[a] The reaction was conducted with 0.2 mmol of 2,3-allentoate and 0.3 mmol of $BnNH_2$ which were pre-stirred for 0.5 h. [b] Determined by NMR using mesitylene as the internal standard. [c] Dioxygen balloon was used as the oxidant. [d] 2 equiv. of $PhI(OAc)_2$ were used as the oxidant.

The scope of this transformation was then investigated under the standard conditions (Table 2). The reaction of 2,3-allenoate **1a** with different alkylic and benzylic amines in PhCN afforded the corresponding pyrazoles in moderate to good yields: substituents on the aromatic ring of benzylic amine may be halide, methyl and methoxy groups (entries 2–9, Table 2); either *n*-alkyl or cyclohexyl amines may react with 2,3-allenoate **1a** affording the corresponding pyrazoles in moderate yields (entries 6–9, Table 2). It is worth noting that alkyl nitriles may also be applied, although a longer reaction time is required (entries 10 and 11, Table 2).

Table 2 Substrate scope: reaction of allenoate **1a** with amines in different nitriles[a]

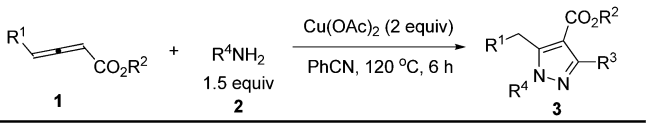


Entry	R^3	R^4	Isolated yields of **3** (%)
1	Ph	Bn	75 (**3a**)
2	Ph	*p*-FBn	80 (**3b**)
3	Ph	*p*-ClBn	65 (**3c**)
4	Ph	*p*-MeOBn	61 (**3d**)
5	Ph	*p*-MeBn	71 (**3e**)
6	Ph	*n*-Bu	67 (**3f**)
7	Ph	n-C_6H_{13}	56 (**3g**)
8	Ph	n-C_8H_{17}	60 (**3h**)
9	Ph	Cy	52 (**3i**)
10	*n*-Bu	Bn	49 (**3j**)[b,c]
11	Me	Bn	60 (**3k**)[d]

[a] The reaction was conducted with 0.2 mmol of **1a**, 0.3 mmol of amines, 0.4 mmol of $Cu(OAc)_2$ in 2 mL of nitrile at 120 °C. [b] The reaction was conducted for 48 h. [c] 4 Å MS was used. [d] The reaction was conducted in a sealed tube for 24 h.

Further studies on the substrate scope were carried out using 1,3-disubstitued allenoates: allenoates with a normal linear substituent such as n-C_9H_{19}, n-C_4H_9, or Me and a secondary alkyl group, such as cyclohexyl, could also react with benzylic amine and PhCN, producing the pyrazoles **3l–3o** in decent yields, showing the diversity (Table 3).[10]

Table 3 Substrate scope: reaction of allenoates with amines in PhCN[a]

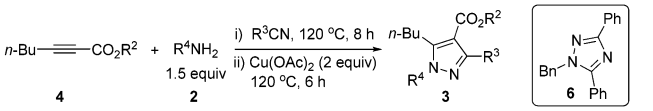


Entry	R^1	R^2	R^4	Isolated yields of **3** (%)
1	n-C_9H_{19}	Et	Bn	51 (**3l**)
2	*n*-Bu	Et	*p*-FBn	51 (**3m**)
3	Me	Bn	*p*-FBn	59 (**3n**)
4	Cy	Me	*p*-FBn	61 (**3o**)

[a] The reaction was conducted with 0.2 mmol of 2,3-allentoates, 0.3 mmol of amines, 0.4 mmol of $Cu(OAc)_2$ in 2 mL of PhCN at 120 °C.

The reaction may also be extended to 2-alkynoates and amines in different nitriles (Table 4).[10]

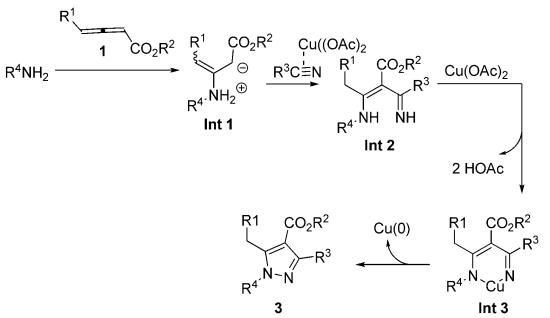
Table 4 Synthesis of pyrazoles from 2-alkynoates[a]



Entry	R^2	R^3	R^4	Isolated yields of **3** (%)
1	Me	Ph	Bn	50[b] (**3p**) + 14 (**6**)[10]
2	*p*-O_2NBn	Ph	Bn	44 (**3q**)[c]
3	*p*-O_2NBn	Ph	*p*-FBn	44 (**3r**)[d]
4	*p*-O_2NBn	Ph	n-C_8H_{17}	52 (**3s**)
5	*p*-O_2NBn	*m*-MeC_6H_4	n-C_8H_{17}	33 (**3t**)

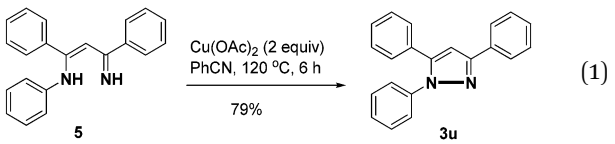
[a] The reaction was conducted with 0.2 mmol of **4**, 0.3 mmol of amines, 0.4 mmol of $Cu(OAc)_2$ in 0.5 mL of nitrile at 120 °C. [b] For details see the ESI. [c] Purity = 97% based on the ^1H NMR analysis with CH_3NO_2 as the internal standard. [d] Purity = 93% based on the ^1H NMR analysis with CH_3NO_2 as the internal standard.

A possible mechanism has been proposed (Scheme 3). In terms of pyrazole formations, the Michael addition of 2,3-allenoate with amine may give the intermediate **Int 1**, which would react with the Cu(II)-activated nitrile followed by C=C bond migration allowing the formation of bisimine **Int 2**. This intermediate would react with $Cu(OAc)_2$ to produce metallacyclic intermediate **Int 3** by releasing two molecules of HOAc. Subsequent reductive elimination furnishes the pyrazole products **3**.



Scheme 3 Possible mechanism for the diverse synthesis of pyrazoles.

In order to confirm this mechanism, especially the possibility of forming the N–N bond under the current reaction conditions, the **Int 2**-type of compound **5** was prepared.[11] It indeed underwent the $Cu(OAc)_2$-mediated N–N formation reaction to afford pyrazole **3u** in 79% isolated yield (eqn (1)). This evidence supports the mechanism presented in Scheme 3.



5 3u (1)

In conclusion, we have developed three-component reactions affording fully substituted pyrazoles from 2,3-allenoates or 2-alkynoates, alkyl amines, and nitriles with diversity. Because of the easy availability of starting materials,[12] the easy transformation nature of the carboxylic acid ester functionality and potential of the products,[1] this chemistry will be of high interest of organic and medicinal chemists. Further studies involving pyrazole chemistry are currently underway in our laboratory.

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