Copper(I)-Catalyzed Synthesis of Pyrazoles from Phenylhydrazones and Dialkyl Ethylenedicarboxylates in the Presence of Bases

Chaowei Ma, Yanmei Li, Ping Wen, Rulong Yan, Zhiyong Ren, Guosheng Huang*

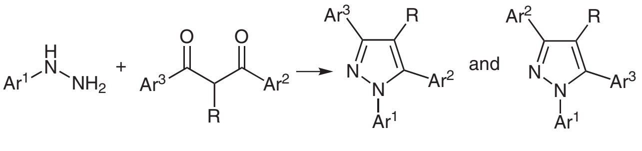
State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. of China
Fax +86(931)8912582; E-mail: hgs@lzu.edu.cn

Received 5 March 2011

Abstract: An easy and efficient copper-catalyzed reaction for the synthesis of polysubstituted pyrazoles from phenylhydrazones and dialkyl ethylenedicarboxylates is described. This reaction can tolerate a range of functionalities, and the corresponding adducts can be obtained in moderate to good yields.

Key words: heterocycles, copper catalysis, hydrazones, dialkyl ethylenedicarboxylates, pyrazoles

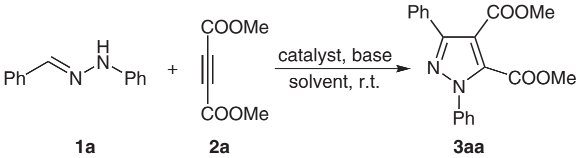
Pyrazoles are a well-known class of nitrogen containing heterocycles that find extensive use in the pharmaceutical and agrochemical substances.[1] For instance, pyrazoles constitute the core structures of some well-known drugs such as Celebrex, Viagra, and Acomplia,[2] as well as in therapeutic areas such as anti-inflammatory,[3] analgesic,[4] and anticancer.[5] Due to the attractive medicinal properties of the pyrazole skeleton, easy and efficient methods for the preparation of such compounds are of considerable interest in synthetic organic chemistry. By far the classical methods for synthesis of these heterocycles are reactions between 1,3-diketones with hydrazines.[6] However, such procedures suffer a major drawback in that there is a lack of regioselectivity with unsymmetrically substituted 1,3-diketones (Scheme 1).[7] Other methods of obtaining pyrazoles that do not require 1,3-diketones have been reported,[8] but often have serious drawbacks such as being step intensive. Recently, several new approaches to access pyrazoles have been reported.[9–11] Hence, the development of new and more efficient procedures is a subject of great importance.



Scheme 1 Pyrazoles synthesis from 1,3-diketones and hydrazines

With the emergence of the concepts of atom economy[12] and green chemistry,[13] new methods to construct heterocycles with simple and readily accessible substances are both important and highly desirable. Although there were a lot of excellent results about C–N bond formation through C–H activation,[14] examples of the reactions under copper-catalyzed conditions are rare.[15] In addition, because of the economic attractiveness and potential large-scale application of copper catalysts, during the past few years there have been remarkable advances in the use of copper catalysis in organic chemistry.[16] As a part of our continuing study on the utilization of copper catalysis in organic synthesis,[17] herein we wish to report an easy and efficient one-pot synthesis of pyrazoles from phenylhydrazones and dialkyl ethylenedicarboxylates. The reac-

Table 1 Survey of Catalysts, Bases, and Solvent Effects of the Reaction[a]



Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	CuI	NaOAc	DME	73
2[c]	CuI	NaOAc	DME	44
3	CuI	–	DME	trace
4[d]	CuI	NaOAc	DME	75
5[e]	CuI	NaOAc	DME	75
6	–	NaOAc	DME	0
7	CuCl	NaOAc	DME	27
8	CuBr	NaOAc	DME	trace
9	$CuBr_2$	NaOAc	DME	0
10	CuI	NaOAc	THF	0
11	CuI	NaOAc	MeCN	66
12	CuI	NaOAc	DCE	0
13	CuI	Na_2CO_3	DME	53
14	CuI	K_2CO_3	DME	57
15	CuI	KOH	DME	54

[a] Reaction conditions: **1a** (0.24 mmol), **2a** (0.2 mmol), base (0.2 mmol), catalysts (0.02 mmol) in 2 mL of solvent for 2 h under air.
[b] Isolated yield.
[c] Reaction was carried out with 0.2 equiv of base.
[d] Reaction was carried out with 2 equiv of base.
[e] Reaction was carried out with 1.0 equiv of base under nitrogen.

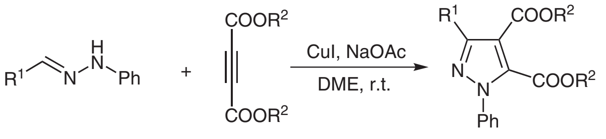
SYNLETT 2011, No. 9, pp 1321–1323
Advanced online publication: 05.05.2011
DOI: 10.1055/s-0030-1260552; Art ID: W06311ST

tions proceeded smoothly, and the corresponding adducts were achieved in moderate to good yields.

We initiated our study by examining the reaction of benzaldehyde phenylhydrazone (**1a**) and dimethyl acetylenedicarboxylate (**2a**) in the presence of 1.0 equivalent of NaOAc in dimethyl ether (DME) at room temperature under air. To our delight, the desired dimethyl 1,3-diphenylpyrazole-4,5-dicarboxylate (**3aa**) was obtained in 73% yield in the reaction catalyzed by CuI after two hours (Table 1, entry 1). When the base loading was reduced, a lower yield of **3aa** was obtained (Table 1, entries 2 and 3). By increasing the base loading to 2 equivalents, the yield of **3aa** only had a slight change (Table 1, entry 4). Furthermore, different copper salts such as CuCl, CuBr, and $CuBr_2$ were examined (Table 1, entries 7–9), but no better results were obtained. In addition, in the absence of metal salts, no desired product was found (Table 1, entry 6). Among the solvent systems examined, changing the solvent to THF, MeCN, and 1,2-dichloroethane (DCE) did not improve the yields (Table 1, entries 10–12). The results indicated that the choice of DME as a solvent was crucial for the reaction. Other bases such as Na_2CO_3, K_2CO_3, and KOH were also evaluated (Table 1, entries 13–15), NaOAc was found to provide the product in the highest yield. It is worth mentioning that when the reaction was carried out under nitrogen, product **3aa** was isolated in good yield too (Table 1, entry 5). Thus, the most suitable reaction conditions for the formation of **3aa** were established, and optional conditions featured 10 mol% CuI, DME, room temperature, and 1.0 equivalent of NaOAc (Table 1, entry 1), which provide product **3aa** in good yield.

With these optimized conditions in hand, we then attempted to extend the scope of this reaction to test the generality of this method, and the results are illustrated in Table 2. Generally, reaction of phenylhydrazones with dialkyl ethylenedicarboxylates proceeded smoothly and led to the desired polysubstituted pyrazoles in moderate to good yields. Gratifyingly, the reaction was found to tolerate a range of functionalities, including aryl- and heterocyclic-substituted phenylhydrazones. Good yields of pyrazole products **3** were usually obtained with electron-withdrawing-group-substituted phenylhydraz-ones (Table 2, entries 3–12). However, even at reflux temperature and a longer reaction time, electron-donating-group-substituted phenylhydrazones gave lower yields of pyrazole products (Table 2, entries 13–15). Phenylhydrazones bearing heterocycles, such as 2-furan-carboxaldehyde phenylhydrazone (**1j**) could also react to give **3ja** in 57% yield (Table 2, entry 16). Further investigations demonstrated that the reaction of phenylhydrazone and diethyl acetylenedicarboxylate (**2b**) gave higher yields than the dimethyl acetylenedicarboxylate (**2a**). The substrates **1e** and **1k** reacted with **2a** to form the corresponding products **3ea** and **3ka** in 68% and 61% yields, respectively (Table 2, entries 9 and 17).

Table 2 Synthesis of Pyrazoles from Phenylhydrazones and Dialkyl Ethylenedicarboxylates[18]



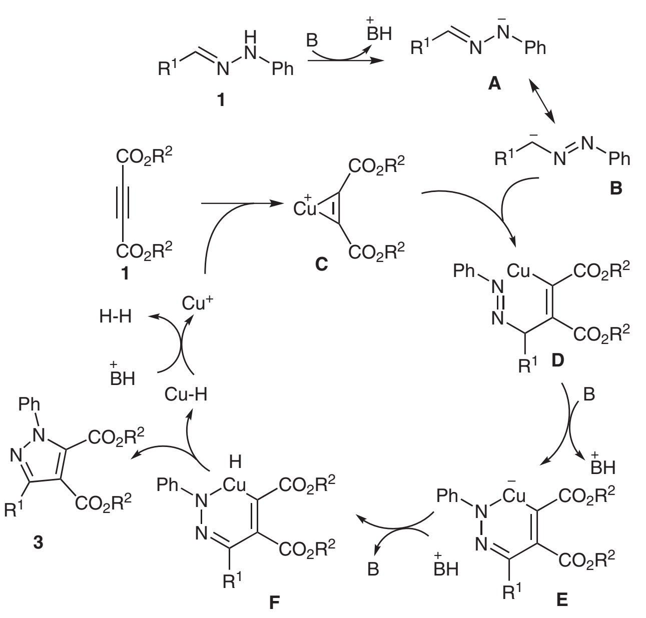
1 **2** **3**

Entry	R^1	R^2	Product	Yield (%)[a]
1	**1a** Ph	**2a** Me	**3aa**	73
2	**1a** Ph	**2b** Et	**3ab**	78
3	**1b** 4-ClC_6H_4	**2a** Me	**3ba**	85
4	**1b** 4-ClC_6H_4	**2b** Et	**3bb**	88
5	**1c** 4-BrC_6H_4	**2a** Me	**3ca**	76
6	**1c** 4-BrC_6H_4	**2b** Et	**3cb**	78
7	**1d** 4-NCC_6H_4	**2a** Me	**3da**	81
8	**1d** 4-NCC_6H_4	**2b** Et	**3db**	86
9	**1e** 4-$O_2NC_6H_4$	**2a** Me	**3ea**	68
10	**1e** 4-$O_2NC_6H_4$	**2b** Et	**3eb**	87
11	**1f** 2-ClC_6H_4	**2a** Me	**3fa**	72
12	**1g** 2,4-$Cl_2C_6H_3$	**2a** Me	**3ga**	75
13	**1h** 4-MeC_6H_4	**2a** Me	**3ha**	53
14[b]	**1h** 4-MeC_6H_4	**2a** Me	**3ha**	52
15	**1i** 3,4-$Me_2C_6H_3$	**2a** Me	**3ia**	58
16	**1j** 2-furan	**2a** Me	**3ja**	57
17	**1k** 4-$CHOC_6H_4$	**2a** Me	**3ka**	61

[a] Isolated yield.
[b] The reaction was carried out at reflux temperature for 10 h.

On the basis of the results obtained above, a plausible pathway for this reaction is illustrated in Scheme 2. The reaction of **1** and **2** under reaction conditions presumably led to the formation of intermediates **A** and **C**. The next step involved the coupling of **B**, another resonance form of **A**, and **C** to produce intermediate **D**. Then, the intermediate **E** was formed via tautomerization in the presence of bases. Subsequently, protonation of **E** led to the formation of intermediate **F** which then underwent reductive elimination of CuH, which further reacted with the conjugate acid of the base to afford hydrogen and regenerated the catalyst.[19]

In conclusion, an efficient copper-catalyzed approach to the construction of a polysubstituted pyrazole skeleton in the presence of base from phenylhydrazones and dialkyl ethylenedicarboxylates has been developed. A range of functionalities including aryl- and heterocyclic-substituted phenylhydrazones were proven possible. This reaction



Scheme 2 Possible reaction pathway

could proceed smoothly, and the corresponding products were achieved in moderate to good yields.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We thank the State Key Laboratory of Applied Organic Chemistry for financial support. We also thank our reviewers' suggestion.

References and Notes

(1) (a) Lamberth, C. *Heterocycles* **2007**, *71*, 1467. (b) Elguero, J. In *Comprehensive Heterocyclic Chemistry*, Vol. 5; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, **1966**. (c) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*, 2nd ed.; J. Wiley and Sons: New York, **2003**, 179.

(2) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. *Pyrazoles as Drugs: Facts and Fantasies,* In *Targets in Heterocyclic Systems Chemistry and Properties*, Vol. 6; Attanasi, O. A.; Spinelli, D., Eds.; Italian Society of Chemistry: Rome, **2002**, 52.

(3) (a) Sui, Z.; Guan, J.; Ferro, M. P.; Mccoy, K.; Wachter, M. P.; Murray, W. V.; Singer, M.; Steber, M.; Ritchie, D. M.; Argentieri, D. C. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 601. (b) Bekhit, A. A.; Abdelaziem, T. *Bioorg. Med. Chem.* **2004**, *12*, 1935. (c) Selvam, C.; Jachak, S. M.; Thilagavathi, R.; Chakraborti, A. K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1793.

(4) Katoch-Rouse, R.; Pavlova, L. A.; Caulder, T.; Hoffman, A. F.; Mukhin, A. G.; Horti, A. G. *J. Med. Chem.* **2003**, *46*, 642.

(5) (a) Stauffer, S. R.; Coletta, C. J.; Tedesco, R.; Nishiguchi, G.; Carlson, K.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2000**, *43*, 4934. (b) Stauffer, S. R.; Huang, Y.; Coletta, C. J.; Tedesco, R.; Katzenellenbogen, J. A. *Bioorg. Med. Chem.* **2001**, *9*, 141.

(6) (a) Knorr, L. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2587. (b) Kost, A. N.; Grandberg, I. I. *Adv. Heterocycl. Chem.* **1966**, *6*, 347.

(7) (a) Silva, V. L. M.; Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S.; Elguero, J. *Eur. J. Org. Chem.* **2004**, 4348. (b) Heller, S. T.; Natarajan, S. R. *Org. Lett.* **2006**, *8*, 2675.

(8) (a) Huang, Y. R.; Katzenellenbogen, J. A. *Org. Lett.* **2000**, *2*, 2833. (b) Katritzky, A. R.; Wang, M.; Zhang, S.; Voronkov, M. V.; Steel, P. J. *J. Org. Chem.* **2001**, *66*, 6787. (c) Singer, R. A.; Caron, S.; McDermott, R. E.; Arpin, P.; Do, N. M. *Synthesis* **2003**, 1727. (d) Aggarwal, V. K.; De Vicente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381. (e) Ahmed, M. S. M.; Kobayashi, K.; Mori, A. *Org. Lett.* **2005**, *7*, 4487.

(9) Monteiro, N.; Balme, G.; Delaunay, T. *Org. Lett.* **2010**, *12*, 3328.

(10) Moses, J.; Spiteri, C.; Keeling, S. *Org. Lett.* **2010**, *12*, 3368.

(11) Wada, A.; Okitsu, T.; Sato, K. *Org. Lett.* **2010**, *12*, 3506.

(12) (a) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

(13) Winterton, N. *Green Chem.* **2001**, *3*, G73.

(14) (a) Davies, H. M. L.; Long, M. S. *Angew. Chem. Int. Ed.* **2005**, *44*, 3518. (b) Wasa, M.; Yu, J. Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (c) Brasche, G.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1932. (d) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833. (e) Inamoto, K.; Hasegawa, C.; Hiroya, K.; Doi, T. *Org. Lett.* **2008**, *10*, 5147. (f) Reed, S.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 3316.

(15) (a) Stahl, S. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 3400. (b) Tsang, W. C. P.; Munday, R.; Brasche, G.; Zheng, N.; Buchwald, L. L. *J. Org. Chem.* **2008**, *73*, 7603. (c) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607.

(16) (a) Brasche, G.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1932. (b) Ueda, S.; Nagasawa, H. *Angew. Chem. Int. Ed.* **2008**, *120*, 6511.

(17) (a) Yan, R.; Huang, J.; Luo, J.; Wen, P.; Huang, G.; Liang, Y. *Synlett* **2010**, 1071. (b) Yan, R.; Luo, J.; Wang, C. X.; Ma, C. W.; Huang, G.; Liang, Y. *J. Org. Chem.* **2010**, *75*, 5395.

(18) **Typical Procedure for the Synthesis of Pyrazoles**
An oven-dried reaction tube was charged with CuI (3.8 mg, 0.02 mmol), NaOAc (16.4 mg, 0.20 mmol), benzaldehyde phenylhydrazone (**1a**, 47.0mg, 0.24 mmol), and dimethyl acetylenedicarboxylate (**2a**, 28.4mg, 0.20 mmol). Then DME (2 mL) was added to the reaction system. The mixture was stirred at r.t. for 2 h. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (EtOAc–PE, 1:8) to give **3aa** (49.0 mg, 73%) as white solid (Table 2, entry 1); mp 152–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.75$ (dd, $J = 7.4$, 1.8 Hz, 2 H), 7.54 (dd, $J = 8.2$, 1.4 Hz, 2 H), 7.50–7.40 (m, 6 H), 3.85 (s, 3 H), 3.82 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 163.37$, 160.64, 151.98, 139.03, 136.82, 131.33, 129.16, 129.06, 128.87, 128.77, 128.16, 124.53, 114.13, 53.11, 52.12. IR (neat): 2952, 1733, 1499, 1447, 1266, 911, 732 cm^{-1}. HRMS: *m/z* calcd for $C_{19}H_{16}N_2O_4$ $[M + H]^+$: 337.1183; found: 337.1175.

(19) Cacchi, S.; Bernini, R.; Fabrizi, G.; Sferrazza, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 8078.