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Copper/Diethyl Azodicarboxylate Mediated Regioselective Alkynylation of Unactivated Aliphatic Tertiary Methylamine with Terminal Alkyne

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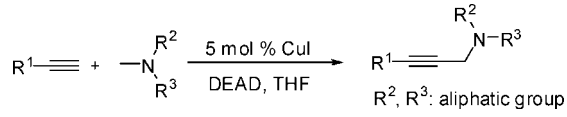
ABSTRACT



Mediated by copper/diethyl azodicarboxylate, regioselective alkynylation of unactivated aliphatic tertiary methylamine with terminal alkyne was successfully established. It is not necessary for the tertiary methylamines to be aryl substituted to modulate the properties of amines. The alkynylation reaction described here has the advantage of simple operation, mild reaction conditions, good to excellent yields, and no need to exclude air and moisture.

Carbon−carbon bond formation reactions are the most important processes in organic synthesis. Traditional methods usually employ prefunctionalized substrates. However, due to the requirement of environmental concerns, the carbon−carbon bond formation via cross oxidative coupling of two C−H bonds has attracted great interest in recent years.[1] The starting materials could be used directly in such transformations without prefunctionalization, and the synthetic procedure could be shorter, simpler, and atom economical. A number of excellent achievements have been made, and a variety of substrates with different types of hybridized carbons could be coupled.[1,2]

Propargylic amine derivatives have received much attention over the past decades and found wide application in medicinal chemistry and synthetic chemistry.[3] Traditional synthetic methods included nucleophilic alkynyl of functionalized amines and transition-metal-catalyzed addition of alkynes to imines.[4] Although these are effective methods, they require the presence of a leaving group or the use of imines prepared from the prefunctionalized aldehydes and

(1) For examples: (a) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (b) Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7075. (c) Deng, G.; Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278. (d) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (e) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (f) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449. (g) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137. (h) Rech, J. C.; Yato, M.; Duckett, D.; Ember, B.; LoGrasso, P. V.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 490. (i) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666. (j) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528. (k) Takahashi, M.; Masui, K.; Sekiguchi, H.; Kobayashi, N.; Mori, A.; Funahashi, M.; Tamaoki, N. *J. Am. Chem. Soc.* **2006**, *128*, 10930. (l) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476. (m) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097. (n) Brown, S. H.; Crabtree, R. H. *J. Am. Chem. Soc.* **1989**, *111*, 2935.

(2) (a) Li, Z.; Yu, R.; Li, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7497. (b) Cheng, D.; Bao, W. *J. Org. Chem.* **2008**, *73*, 6881. (c) Cheng, D.; Bao, W. *Adv. Synth. Catal.* **2008**, *350*, 1263. (d) Zhang, Y.; Li, C.-J. *Eur. J. Org. Chem.* **2007**, 4654. (e) Li, Z.; Cao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6505. (f) Li, Q.; Wei, Y.; Hao, J.; Zhu, Y.; Wang, L. *J. Am. Chem. Soc.* **2007**, *129*, 5810. (g) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069. (h) Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 4242. (i) Zhang, Y.; Li, C.-J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1949. (j) DeBoef, B.; Pastine, S. J.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 6556.

(3) (a) Sienkiewich, P.; Bielawski, K.; Bielawska, A.; Palka, J. *Environ. Toxicol. Pharmacol.* **2005**, *20*, 118. (b) Greenhill, J. V.; Lue, P. *Prog. Med. Chem.* **1993**, *30*, 203.

(4) Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263. and references therein.

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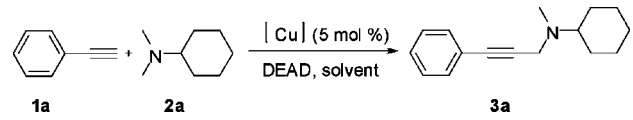
amines. Direct oxidative functionalization of tertiary amines represents an alternative method for the synthesis of propargylic amine derivatives[5] and other nitrogen-containing compounds.[6] Recently, Li reported an efficient method for the direct synthesis of propargylic amines by copper-catalyzed coupling of sp^3 C−H adjacent to nitrogen with a terminal alkyne.[5b,c] However, the reaction required an aryl or benzyl substituted on the tertiary methylamine nitrogen so as to induce the coupling. Fu reported a new method for the cross coupling of aliphatic tertiary amines with terminal alkynes promoted by copper/NBS; however, the yields were very low in most cases.[5a] Herein, we report a novel oxidative coupling of terminal alkynes with tertiary methylamines where the nitrogen is substituted only by alkyls. This reaction is mediated by copper and diethyl azodicarboxylate (DEAD) and has the advantage of simple operation, mild conditions, good to excellent yields, and no need to exclude air and moisture.

DEAD, as a versatile reagent, has been widely used in organic synthesis.[7] Recently, we reported DEAD promoted dehydrogenation of tertiary amine and tandem reaction with sulfonyl azide.[8] As far as the mechanism was concerned, it revealed that a zwitterionic intermediate may be formed in the reaction.[8,9] Accordingly, we envisioned that it is probable for this intermediate to subsequently react with terminal alkyne and thus form the alkynylation product. In the mechanism, when an ethyl is present, the elimination of both α- and *β*-hydrogens of nitrogen was inevitable.[8] However, with a methyl group, the elimination could not happen due to the absence of a *β*-hydrogen. Then, what will happen with the coexistence of isopropyl and methyl?

Our study initiated with *N*,*N*-dimethylcyclohexylamine and phenylacetylene as the substrates. In the presence of DEAD and with copper as a catalyst, it was found that the reaction between this pair of substrates afforded **3a** as a product. This result indicated that the dehydrogenation under this reaction system occurred regioselectively at the methyl group, whereas the α-hydrogen located at the cyclohexyl remained intact although *N*,*N*-dimethylcyclohexylamine has two types of α-hydrogens adjacent to the nitrogen atom.

The optimization of the reaction conditions for the formation of **3a** was done by screening several solvents and copper catalysts. No reaction occurred in the absence of copper catalyst (Table 1, entry 1). CuI proved to be the best

Table 1. Synthesis of **3a** Under Various Conditions[a]



1a 2a 3a

entry	catalyst	solvent	time (h)	yield (%)[b]
1	–	THF	6	0
2	CuI	THF	6	87[c]
3	CuBr	THF	12	83
4	CuCl	THF	16	85
5	CuI	toluene	7	81
6	CuI	CH_3CN	8	78
7	CuI	1,4-dioxane	7	86
8	CuI	CH_2Cl_2	7	77
9	CuI	$ClCH_2CH_2Cl$	7	79
10	CuI	DMF	10	57

[a] DEAD (1.1 mmol), *N*,*N*-dimethylcyclohexylamine (1 mmol), phenylacetylene (1.5 mmol), copper catalyst (0.05 mmol) in solvent (2 mL). [b] Isolated yields. [c] 2H-DEAD was isolated in 85% yield.

catalyst compared with CuBr and CuCl (Table 1, entries 2−4). After prolonging the reaction for several hours, CuBr and CuCl can also give excellent results. Using CuI as a catalyst under room temperature, satisfactory yields could be obtained using several solvents, such as CH_3CN, CH_2Cl_2, DCE, toluene, and 1,4-dioxane (Table 1, entries 5−9). DMF gave the desired product in only 57% yield (Table 1, entry 10). The reaction rate varied with different solvents. The reaction proceeded most rapidly in THF while most sluggishly in DMF.

With the optimized conditions (Table 1, entry 2), a variety of terminal alkynes and aliphatic tertiary methylamines were examined, and the corresponding alkynylation products were obtained in good to excellent yields (Table 2). Aromatic alkynes substituted at the phenyl ring with MeO, Me, CF_3, F, Cl, and *n*-pentyl were all converted into the corresponding products efficiently, indicating no remarkable electronic and position effects of the substituents on the reaction (Table 2, entries 2−6 and 16). 3-Ethynylpyridine and 3-ethynylthiophene were successfully coupled with *N*,*N*-dimethylcyclohexylamine and afforded the corresponding propargylic amines smoothly (Table 2, entries 9 and 10). Benzyl acetylene also served as a good partner (Table 2, entry 7). It is noteworthy that 1-hexyne and phenethylacetylene, two aliphatic alkynes, afforded the desired products in good yields as well (Table 2, entries 8 and 11). Trimethylsilyl could be tolerated under the conditions (Table 2, entry 12). Several types of aliphatic tertiary methylamines can be used in this study. The dehydrogenation of an α-hydrogen at the isopropyl and analogous group was not observed. Bulky groups, such as *iso*-propyl and *tert*-butyl, have exerted no appreciable influence on the reaction efficiency. In the case of *N*,*N*-dimethylbenzylamine, the ratio for the alkynylation of methyl and methylene is ∼63:37 in 82% overall yield (Table 2, entry 19). However, when *N*,*N*-dimethylaniline was used as the substrate, the desired propargylic amine could not be obtained in spite of the attempts with more reaction conditions, and

(5) (a) Niu, M.; Yin, Z.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2008**, *73*, 3961. (b) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (c) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997.

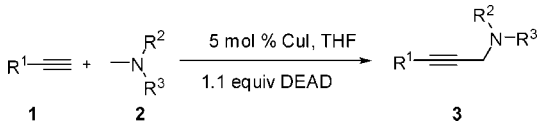
(6) (a) Murahashi, S.-I.; Nakae, T.; Terai, H.; Komiya, N. *J. Am. Chem. Soc.* **2008**, *130*, 11005. (b) Li, Z.; Bohle, S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928. (c) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935. (d) Doye, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3351. (e) Murahashi, S.-I. *Pure Appl. Chem.* **1992**, *64*, 403.

(7) (a) Nair, V.; Biju, A. T.; Mathew, S. C.; Babu, B. P. *Chem. Asian J.* **2008**, *3*, 810. (b) Berlin, J. M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 7048. (c) Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427.

(8) Xu, X.; Li, X.; Ma, L.; Ye, N.; Weng, B. *J. Am. Chem. Soc.* **2008**, *130*, 14048.

(9) Huisgen R. In *The Adventure Playground of Mechanisms and Novel Reaction: Profiles, Pathwanys and Dreams*; Seeman, J. I., Eds.; ACS: Washington DC, 1994; p 62.

Table 2. Synthesis of **3**[a] Promoted by CuI/DEAD



1 **2** **3**

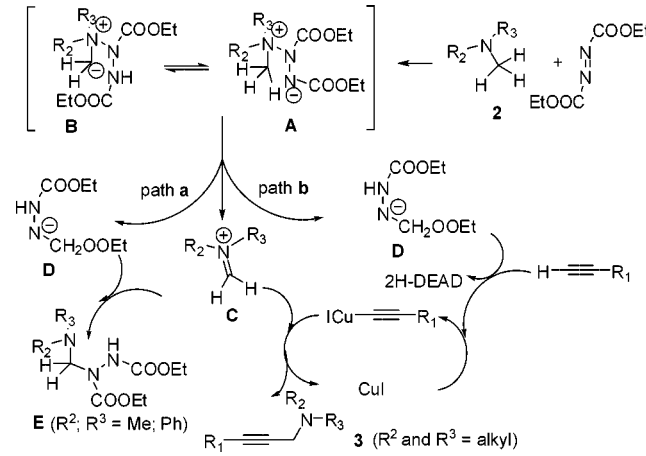
entry	R^1	R^2; R^3	yield (%)[b]
1	Ph (**1a**)	Me; *c*-hexyl (**2a**)	**3a**; 87
2	4-$MeOC_6H_4$ (**1b**)	**2a**	**3b**; 90
3	4-MeC_6H_4 (**1c**)	**2a**	**3c**; 83
4	2-$CF_3C_6H_4$ (**1d**)	**2a**	**3d**; 72
5	3-FC_6H_4 (**1e**)	**2a**	**3e**; 74
6	3-ClC_6H_4 (**1f**)	**2a**	**3f**; 69
7	$PhCH_2$ (**1g**)	**2a**	**3g**; 71
8	$PhCH_2CH_2$ (**1h**)	**2a**	**3h**; 73
9	3-pyridyl (**1i**)	**2a**	**3i**; 66
10	3-thienyl (**1j**)	**2a**	**3j**; 64
11	*n*-butyl (**1k**)	**2a**	**3k**; 82
12	Me_3Si (**1l**)	**2a**	**3l**; 81
13	**1a**	Me; *c*-pentyl (**2b**)	**3m**; 83
14	**1a**	Me; *c*-heptyl (**2c**)	**3n**; 90
15	**1a**	*c*-hexyl; *c*-hexyl (**2d**)	**3o**; 94
16	4-$CH_3(CH_2)_4C_6H_4$ (**1m**)	Me; Pr^i (**2f**)	**3p**; 75
17	**1a**	Pr^i; Bu^t (**2g**)	**3q**; 82
18	**1a**	Me; 3′-Me-2-pentyl (**2f**)	**3r**; 77
19	**1a**	Me; $PhCH_2$ (**2e**)	**3s**+**3t**; 82[c]

[a] DEAD (1.1 mmol), aliphatic tertiary methylamine (1 mmol), alkyne (1.5 mmol), CuI (0.05 mmol), THF (2 mL), 6−12 h (see Supporting Information). [b] Isolated yields. [c] Mixture of isomers.

only the adduct of DEAD with *N*,*N*-dimethylaniline was isolated in excellent yield.

According to the literature,[8,9] a tentative mechanism was proposed in Scheme 1. First, DEAD and aliphatic tertiary methylamine **2** undergoes a nucleophilic addition reaction and forms a 1:1 adduct **A**, which could be in equilibrium with **B** by an intramolecular hydrogen transfer. Then adduct **A** cleaves to form an ion pair consisting of imine cation **C** and 1H-DEAD **D**. The nitrogen anion of **D** further abstracts a hydrogen from the terminal alkyne with itself being transformed into 2H-DEAD in the presence of the copper catalyst, and the terminal alkyne is transformed into copper alkynylide (path **b**). A further addition of the in situ generated

Scheme 1. Proposed Mechanism



copper alkynylide on **C** gives the desired product **3** and liberates the copper catalyst to complete the catalytic cycle. When the R^2 or R^3 is a phenyl group, the reaction route follows path **a** to form the adduct product **E** preferably.

In conclusion, an efficient CuI/DEAD mediated alkynylation of aliphatic tertiary methylamines with alkynes is successfully established. The reaction described here is mild, general, and efficient, thus providing an extremely preferable way for the alkynylation of aliphatic tertiary methylamine.

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Supporting Information Available: Experimental details and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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