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Copper-Catalyzed Coupling of Tertiary Aliphatic Amines with Terminal Alkynes to Propargylamines via C−H Activation

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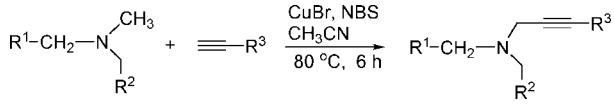

We have developed a convenient and efficient method for coupling of tertiary aliphatic amines with terminal alkynes to propargylamines via C−H activation. The protocol uses CuBr as the catalyst, NBS as the free radical initiator, CH_3CN as the solvent, and the alkynylation was selectively performed on the methyl of tertiary aliphatic amines at 80 °C. This is an economical and practical method for the synthesis of propargylamines.

Direct and selective conversion of carbon−hydrogen bonds to new bonds (such as C−C, C−O, and C−N) is an important and long-standing goal in chemistry, and this process has great potential in synthesis because it avoids the preparation of functional groups and makes synthetic schemes shorter and more efficient.[1] Recently, great progress has been achieved on the direct transformation of C−H bonds into C−C bonds without prefunctionalizations.[2,3] The synthesis of these nitrogen-containing compounds widely present in nature has attracted much attention in industrial and academic research because of their biological and pharmaceutical properties. Recently, some excellent examples based on the direct sp^3 C−H bond activation adjacent to a nitrogen atom for the C−C bond formations were reported.[4,5] Very recently, we have also developed an inexpensive and effective CuBr/tBuOOH system for the amidation of unactivated sp^3 C−H bonds adjacent to a nitrogen atom.[6] Propargylamines are major skeletons[7] or versatile and key intermediates[8] for the synthesis of many biologically active compounds, such as β-lactams, oxotremorine analogues, confirmationally restricted peptides, isosteres, and natural products

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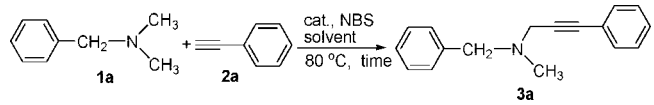
TABLE 1. Reactions of Phenylacetylene with *N*,*N*-Dimethylbenzylamine: Optimization of Conditions[a]



entry	cat. (equiv)	NBS (equiv)	solvent	time	yield (%)[b]
1	CuBr (0.1)	2	DMSO	10	13
2	CuBr (0.1)	2	EtOAc	10	10
3	CuBr (0.1)	2	CH_3CN	10	15
4	CuBr (0.1)	0.1	CH_3CN	10	trace
5	CuBr (0.1)	4	CH_3CN	6	20
6	CuBr (0.4)	2	CH_3CN	6	52
7	CuCl (0.4)	2	CH_3CN	6	50
8	CuI (0.4)	2	CH_3CN	6	45
9	$CuCl_2$ (0.4)	2	CH_3CN	6	28
10	$Cu(O_2CCF_3)_2$ (0.4)	2	CH_3CN	6	35

[a] Reaction condition: under nitrogen atmosphere, *N*,*N*-dimethylbenzylamine (1 mmol), phenylacetylene (0.5 mmol), solvent (1 mL), catalyst (0.2 mmol), NBS (1 mmol). [b] Isolated yield.

and therapeutics drug molecules,[9] so their preparation has attracted great interest. Three-component one-pot coupling reactions of aldehydes, alkynes, and amines are prevalent in the previous methods, and their reaction mechanism is by the addition of alkynes to in situ generated iminium ions from aldehydes and secondary amines.[10] Although these methods are effective, they need imines formed by the prefunctionalized aldehydes and amines. Obviously, the direct C−C bond formation of terminal alkynes with tertiary amines via C−H activation is an economical and practical approach. Recently, Li and workers have developed copper-catalyzed alkynylations of the tertiary aryl amines in the presence of oxidant *t*BuOOH.[11] As a complement of the previous methods, we have developed an inexpensive and practical catalyst/free radical initiator system to efficiently reach alkynylations of tertiary aliphatic amines under mild conditions.

Since direct introduction of a substituent at the α-position of tertiary amines is performed in two steps—α-C−H activation to produce iminium ion intermediates and subsequent reaction with nucleophiles[12−14]we chose *N*-bromosuccinimide (NBS) as the oxidant[15] or free radical initiator[16] to promote iminium formation of tertiary aliphatic amines. *N*,*N*-Dimethylbenzylamine and phenylacetylene were used as the model substrates to optimize reaction conditions including optimization of the copper catalysts and solvents at 80 °C under nitrogen atmosphere as shown in Table 1, and the alkynylation was performed on one methyl of *N*,*N*-dimethylbenzylamine. The effect of solvents (DMSO, ethyl acetate, CH_3CN) was first investigated (entries 1−3) by using 10 mol % CuBr (relative to phenylacetylene) as the catalyst and 2 equiv of NBS as the free radical initiator, and CH_3CN proved to be the best solvent (entry 3). We attempted to change the amount of CuBr and NBS (entries 3−6), and the results showed that use of 40 mol % CuBr and 2 equiv of NBS relative to phenylacetylene was the best choice (entry 6). Several copper salts, CuBr, CuCl, CuI, $CuCl_2$ and $Cu(O_2CCF_3)_2$, were tested in CH_3CN (entries 6−10), Cu(I) salts showed higher catalytic activity than Cu(II) ones, and CuBr was the most effective catalyst. No alkynylation product was observed in the absence of copper catalyst or NBS. After the optimization process for catalysts, solvents, and amount of catalyst and NBS, the following alkynylation reactions were performed under our standard conditions: 40 mol % CuBr as the catalyst, 2 equiv of NBS as the free radical initiator (relative to alkynes), and CH_3CN as the solvent at 80 °C under nitrogen atmosphere.

As shown in Table 2, various substrates were examined, and they provided the corresponding propargylamines in different yields. For the tertiary aliphatic amines, *N*,*N*-dimethylbenzylamine, *N*,*N*-dimethyldodecylamine, *N*,*N*-dimethylcyclohexylamine, and *N*-benzyl-*N*-ethylmethylamine, the stereo effect is a key factor. For example, *N*,*N*-dimethylbenzylamine with less hindrance gave higher yields, while *N*,*N*-dimethylcyclohexylamine with a bulky group (cyclohexyl) provided a lower yield (entry 11). Several terminal alkynes, phenylacetylene, 4-ethynyltoluene, 4-ethynylanisole, 1-ethynyl-4-nitrobenzene, 1-bromo-2-ethynylbenzene, 1-ethynylnaphthalene, cyclopropylacetylene, and 1-octyne, were examined, and aryl alkynes showed higher reactivity than aliphatic ones. For aryl alkynes, the substrates containing electron-donating groups gave higher yields. The alkynylation selectively occurred on the methyl group because of the stereo effect for tertiary aliphatic amines containing different alkyl groups, such as compound **1d** with one methyl, one ethyl, and one benzyl. In fact, the palladium-catalyzed selective C−H activation to C−O bond formation on methyl of Boc-protected *N*-methylamines was found by Yu and coworkers before.[17] In addition, the electronic effect of tertiary amines also affects the activity of alkynylation, and tertiary aryl

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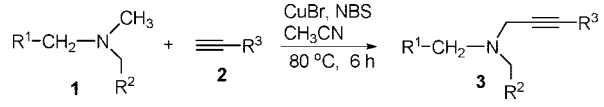
TABLE 2. Couplings of Tertiary Aliphatic Amines with Terminal Alkynes to Propargylamines via C−H Activation[a]



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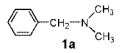
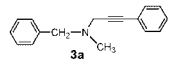
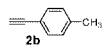
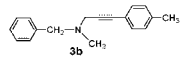
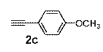
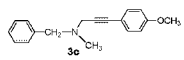
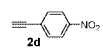
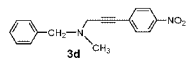
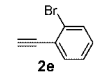
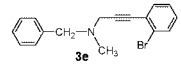
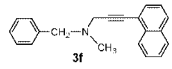
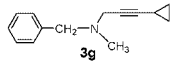
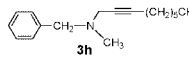
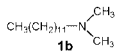
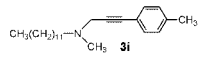
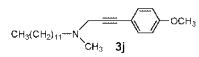
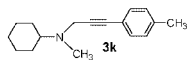
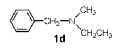
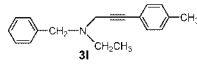
1				52
2	**1a**			61
3	**1a**			65
4	**1a**			40
5	**1a**			60
6	**1a**			53
7	**1a**			35
8	**1a**			31
9		**2b**		44
10	**1b**	**2c**		41
11		**2b**		29
12		**2b**		43

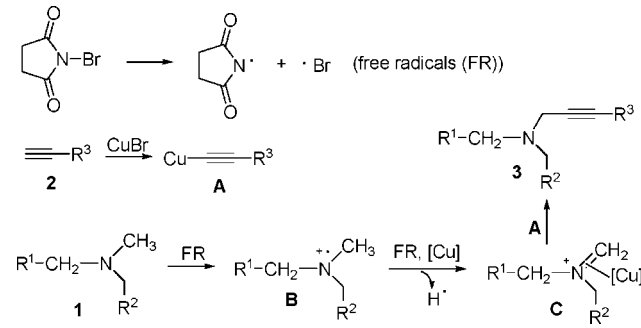
[a] Reaction condition: under nitrogen atmosphere, amine (1 mmol), alkyne (0.5 mmol), CuBr (0.2 mmol), NBS (1 mmol), CH_3CN (1 mL). [b] Isolated yield.

amines are weak substrates. For example, reaction of *N*,*N*-dimethyl-*p*-toluidine with phenylacetylene only gave a trace amount of alkynylation product. Although the present method is only suitable to alkynylation of tertiary aliphatic amines, it is a valuable complement for the previous methods.[11]

According to our results and the related literature,[11–14] a possible mechanism for alkynylation of tertiary aliphatic amines is proposed in Scheme 1. NBS first yields succinimide and chlorine free radicals (**FR**), and reaction of alkyne with CuI unexceptionally formed copper(I) acetylide (**A**).[18] Reaction of the tertiary aliphatic amine with free radicals **FR** produces new free radical **B**, removal of hydrogen free radical at the α-position of **B** gives the iminium ion intermediate whose combination with copper ion forms **C**, and nucleophilic attack of **A** to **C** leads to the target product **3**.

(18) Ito, H.; Arimoto, K.; Sensui, H.; Hosomi, A. *Tetrahedron Lett.* **1997**, *38*, 3977.

SCHEME 1. Possible Mechanism for Coupling of Tertiary Aliphatic Amines with Terminal Alkynes to Propargylamines via C−H Activation



In summary, we have developed a simple and effective catalyst/free radical initiator system (CuBr/NBS) to promote alkynylations of tertiary aliphatic amines to propargylamines via C−H activation at 80 °C, and the alkynylation was selectively performed on the methyl of tertiary amines. The method is economical and practical for the synthesis of propargylamines and a valuable complement to the previous methods.

Experimental Section

General Experimental Procedure for the Synthesis of Propargylamines. NBS (1.0 mmol) was added to a mixture of CuBr (0.2 mmol), tertiary aliphatic amine (1.0 mmol), and terminal alkyne (0.5 mmol) in CH_3CN (1.0 mL) under nitrogen atmosphere at room temperature, and the solution was stirred at 80 °C for 6 h. The reaction mixture was cooled to room temperature, and 10 mL of chloroform and 10 mL of Na_2CO_3 saturated solution were added to the flask. The separated organic phase was dried over anhydrous Na_2SO_4 and concentrated under rotary evaporation, and the residue was purified by column chromatography on silica gel (eluting with petroleum ether/ethyl acetate = 10:1) to provide the target compound. Two selected examples are shown as follows.

***N*-Benzyl-*N*-methyl-[3-(2-bromophenyl)-2-propynyl]amine (3e).** Colorless oil, 95 mg, yield 60%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14−7.59 (m, 9H), 3.70 (s, 2H), 3.57 (s, 2H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 133.5, 132.3, 129.2, 129.1, 128.3, 127.2, 126.9, 125.4, 89.4, 84.2, 59.9, 45.6, 42.0. HRMS *m*/*z* calcd for $C_{17}H_{17}NBr$ $[M + H]^+$ 314.0544, found 314.0549.

***N*-Dodecyl-*N*-methyl-[3-(4-methylphenyl)-2-propynyl]amine (3i).** Colorless oil, 71 mg, yield 44%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.2 Hz, 2H), 3.53 (s, 2H), 2.46 (t, J = 7.6 Hz, 2H), 2.36 (s, 3H), 2.34 (s, 3H), 1.47−1.52 (m, 2H), 1.25−1.29 (m, 18H), 0.88 (t, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 131.6, 128.9, 120.2, 85.3, 83.7, 56.1, 46.4, 41.9, 31.9, 29.6, 29.3, 27.6, 27.5, 22.7, 21.4, 14.1. HRMS *m*/*z* calcd for $C_{23}H_{38}N$ $[M + H]^+$ 328.3004, found 328.3001.

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Supporting Information Available: Synthetic procedures, characterization data and ^{1}H, ^{13}C NMR spectra of these synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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