JOC*Note*

An Efficient Synthesis of Terminal Allenes from Terminal 1-Alkynes

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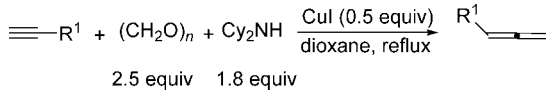
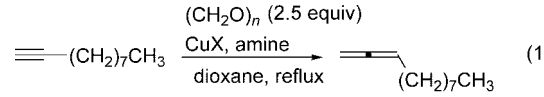


We have developed a modified method for the synthesis of terminal allenes from terminal 1-alkyne: The reaction of 1-alkynes with 1.8 equiv of Cy_2NH and 2.5 equiv of paraformaldehyde mediated by CuI (0.5 equiv) in refluxing dioxane may produce terminal allenes in much higher yields than the previously reported protocol and many functional groups such as mesylate, hydroxyl group, ether, amide, etc. may be tolerated.

Allenes have become more and more important in organic synthesis,[1,2] thus, efficient new methods for the synthesis of allenes from the commonly used starting materials are highly desirable.[3] Terminal alkynes are readily available organic compounds and may be efficiently converted to terminal allenes by reaction with paraformaldehyde in the presence of *i*-Pr_2NH and CuBr in dioxane.[4] However, in many cases the reaction provides the products in relatively low yields. To further improve this one-step procedure, we reasoned that the amine may be crucial for this transformation since the *i*-Pr_2NH used also provides the "H" for the reduction of the in situ formed propargylic amine from the Mannich-type reaction of terminal 1-alkyne, paraformaldehyde, and *i*-Pr_2NH.[4e] In addition, recently, Nakamura et al. reported the Pd-catalyzed hydride-transfer reactions of propargylic diisopropyl or dicyclohexyl amines for the formation of allenes.[5] In this Note, we wish to report our recent observation that the commercially available dicyclohexylamine is a superior amine and CuI is a better mediator for this transformation leading to much higher yields for the formation of terminal allenes in the presence of different functional groups, such as mesylate, hydroxyl group, ether, amide, etc.

TABLE 1. Optimization of Conditions for the Reaction of 1a with $(CH_2O)_n$, Amine, and CuX



1a **2a**

entry	amine (equiv)	catalyst (equiv)	yield of **2a** (%)
1	*i*-Pr_2NH (1.8)	CuBr (0.5)	33
2	Cy_2NH (1.8)	CuBr (0.5)	43
3	Cy_2NH (1.8)	CuCl (0.5)	26
4	Cy_2NH (1.8)	CuI (0.5)	59
5	Cy_2NH (1.8)	CuI (0.2)	36
6	Cy_2NH (1.8)	CuI (0.8)	54
7	Cy_2NH (1.5)	CuI (0.5)	21
8	Cy_2NH (2.0)	CuI (0.5)	45

1-Decyne was chosen as the model substrate in search of a better protocol (eq 2). Under the reported conditions,[4] the reaction of 1-decyne with *i*-Pr_2NH and CuBr in dioxane afforded terminal allene **2a** in only 33% yield (entry 1, Table 1). As expected no reaction was observed with 2-imidazolidone and 2-imidazolidinethione; 1-phenylpiperazine did not work either; diallyl or dibenzyl amine also failed to promote this reaction. Amines with one secondary alkyl group such as (1*R*,2*R*)-1,2-diaminocyclohexane, (*R*)-phenylalanine, benzyl α-naphthylethyl amine, benzyl isopropyl amine, ethyl isopropyl amine, 2-methyl-1,4-diazacyclohexane, and *N*,*N*-diisopropyl ethylenediamine also failed or afforded a trace amount of the product.

Fortunately, when dicyclohexylamine was used, the yield was improved to 43% (entry 2, Table 1). Further study led to the observation that CuI is better than CuBr or CuCl (entries 2 and 3, Table 1) affording **2a** in 59% yield. Screening on the amounts of dicyclohexylamine and CuI indicated that 1.8 equiv of this amine and 0.5 equiv of CuI are the best (compare entries 4−8,

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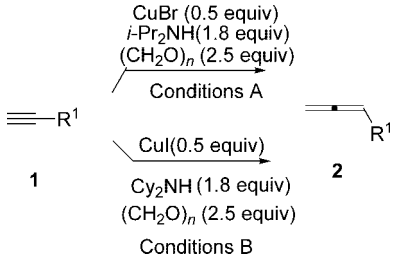
TABLE 2. The Cu(I)-Mediated Reaction of 1-Alkyne, Paraformaldehyde, and *i*-Pr_2NH or Dicyclohexyl Amine in Dioxane



		conditions A		conditions B	
entry	**1**: R^1	time (h)	yield of **2**[a] (%)	time (h)	yield of **2**[a] (%)
1	$CH_3(CH_2)_7$ (**1a**)	2.7	42	2.7	66 (**2a**)
2	$CH_3(CH_2)_9$ (**1b**)	2.5	36	2.5	60 (**2b**)
3	*p*-$C_6H_4C_6H_4$ (**1c**)	1.9	59	2.2	70 (**2c**)
4	$MsO(CH_2)_7$ (**1d**)	2.3	30	2.3	53 (**2d**)
5	$PhCH_2OCH_2$ (**1e**)	1.5	53	1.5	81 (**2e**)
6	*p*-$O_2NC_6H_4CH_2OCH_2$ (**1f**)	2.9	59	2.9	98 (**2f**)
7	*p*-$EtC_6H_4CH(OH)CH_2$ (**1g**)	2.0	40	3.0	74 (**2g**)
8	*p*-$ClC_6H_4CH(OH)CH_2$ (**1h**)	3.0	32	3.0	72 (**2h**)
9	*o*-$ClC_6H_4CH(OH)CH_2$ (**1i**)	1.9	33	1.9	52 (**2i**)
10	*p*-$BrC_6H_4CH(OH)CH_2$ (**1j**)	2.3	35	2.3	65 (**2j**)
11	$HOCH_2C(Me)_2NTsCH_2$ (**1k**)	2.2	27	2.2	42 (**2k**)

[a] Isolated yield.

Table 1). Thus, we defined the reaction of 1-alkyne with 2.5 equiv of paraformaldehyde, 1.8 equiv of dicyclohexylamine, and CuI (0.5 equiv) in dioxane as the standard (conditions B).

With the standard conditions B, the scope and generality of this new procedure were studied and the results are summarized in Table 2. For alkyl or *p*-phenylphenyl-substituted terminal alkynes, the reaction afforded the corresponding allenes **2a**−**c** in 60−70% isolated yields (entries 1−3, Table 2). The reaction of the terminal alkyne with a methanesulfonate functionality **1d** afforded allene **2d** in 53% isolated yield (entry 4, Table 2). Terminal alkynes with a benzyl ether functionality are high yielding (entry 5 and 6, Table 2). The reaction of homopropargylic alcohols yielded β-allenols[6] **2g**−**j** in 52−74% isolated yields (entry 7−10, Table 2). Finally the terminal homopropargylic tosylamide with a free hydroxyl group was converted to the corresponding allene **2k** in 42% yield (entry 11, Table 2). In all cases the modified protocol afforded the allenes in higher yields (compare conditions A with B in Table 2).

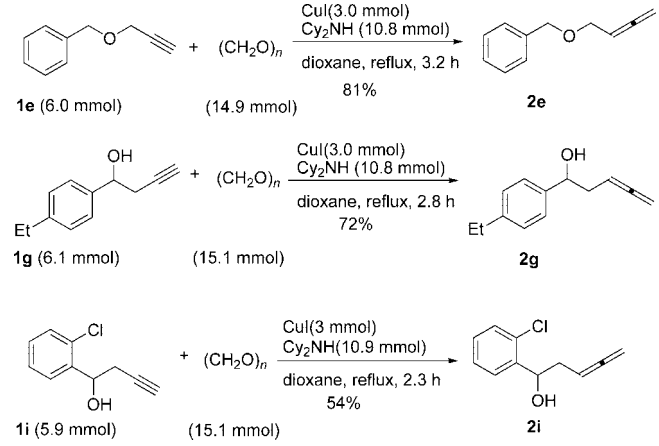
Three examples of large-scale reactions also have been demonstrated (Scheme 1).

In conclusion, we have developed a modified one-step procedure for converting terminal alkynes to terminal allenes by applying 0.5 equiv of CuI, 1.8 equiv of dicyclohexylamine, and 2.5 equiv of paraformaldehyde. Due to the increasing importance of allenes in organic chemistry and the commercial availability of all the reagents, this method will be of interest for organic chemists since many functional groups such as mesylate, hydroxyl group, ether, amide, etc. may be tolerated. Further studies in this area are being actively pursued in this laboratory.

Experimental Section

Starting alkynes **1a** and **1b** are commercial available from Sigma-Aldrich; Compound **1c** was prepared by the coupling of acetylenyl magnesium bromide with *p*-phenylphenyl iodide with $Pd(PPh_3)_4$ as the catalyst.[7] Alkyne **1d** was prepared by the tosylation of 8-nonyn-1-ol.[8] Alkynes **1e** and **1f** were prepared by the reaction of the corresponding benzyl alcohols with propargyl bromide in DMSO at room temperature with KOH as the base and in THF at 50 °C with NaOH as the base, respectively.[9] Homopropargyl alcohols **1g**, **1h**, and **1j** were prepared by the Zn-promoted Barbier-type reaction of the related aldehydes with propargyl bromide under solvent-free conditions at room temperature.[10] Homopropargyl alcohol **1i** was obtained by the reaction of 2-chlorobenzaldehyde with the Grignard reagent of propargyl bromide in Et_2O.[11] Terminal alkyne **1k** was prepared by the reaction of 2-hydroxytosylamide with propargyl bromide, using K_2CO_3 (2 equiv)−TBAB (0.5 equiv) as the base in THF at room temperature.[12] The ^{13}CNMR data are H-decoupled.

SCHEME 1



General Procedure for the Synthesis of Allenes (2a−k). $(CH_2O)_n$ (0.5 mmol), CuI (0.1 mmol), dioxane (1 mL), alkyne (0.2 mmol), and amine (0.36 mmol) were added sequentially into an oven-dried reaction tube equipped with a reflux condenser under an argon atmosphere. The resulting mixture was stirred under reflux. When the reaction was complete as monitored by TLC, it was cooled to rt. Water (5 mL) and ether (10 mL) were added and then the aqueous solution was separated and extracted with ether (3 × 5 mL). The organic layer was then washed with brine and dried over anhydrous Na_2SO_4. Evaporation and column chromatography on silica gel (eluent: petroleum ether or petroleum ether/Et_2O) afforded the terminal allene.

(1) Synthesis of undeca-1,2-diene (2a). Conditions A: The reaction of dec-1-yne (27.9 mg, 0.20 mmol), paraformaldehyde (15.3 mg, 0.51 mmol), diisopropylamine (37.0 mg, 0.37 mmol), and CuBr (14.4 mg, 0.10 mmol) in dioxane (1 mL) afforded **2a**[4e] (12.9 mg, 42%) as a liquid (eluent: petroleum ether): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.15−5.04 (m, 1 H), 4.70−4.60 (m, 2 H), 2.05−1.93 (m, 2 H), 1.47−1.18 (m, 12 H), 0.88 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5, 90.1, 74.5, 31.9, 29.5, 29.3, 29.2, 29.1, 28.3, 22.7, 14.1; MS (EI) *m*/*z* 152 (M^+, 0.04), 137 ($M^+ - CH_3$, 1.87), 54 (100); IR (neat) 1957, 1466, 1378, 841 cm^{-1}.

Conditions B: The reaction of dec-1-yne (27.8 mg, 0.20 mmol), paraformaldehyde (15.0 mg, 0.50 mmol), dicyclohexylamine (65.5

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mg, 0.36 mmol), and CuI (19.1 mg, 0.10 mmol) in dioxane (1 mL) afforded **2a** (20.2 mg, 66%).

(2) Synthesis of 1-(4-Ethylphenyl)penta-3,4-dien-1-ol (2g). Into a 50-mL three-necked flask equipped with a reflux condenser were added 0.453 g (15.1 mmol) of paraformaldehyde, 0.571 g (3.0 mmol) of CuI, 9 mL of dioxane, 1.062 g (6.1 mmol) of **1g**, and 1.955 g (10.8 mmol) of dicyclohexylamine sequentially. The resulting mixture was gently refluxed with stirring. After 2.5 h as monitored by TLC, the resulting mixture was then cooled to room temperature and filtered. The filtrate was concentrated under vacuum to a gummy residue and then diluted with 5 mL of water followed by the addition of 10 mL of ether. The resulting mixture was then acidified with 1 N hydrochloric acid to pH 1−2. The organic layer was separated and the aqueous solution was extracted with ether (3 × 10 mL). The combined organic layer was washed with small portions of water until pH 6−7. The organic layer was then washed with brine and dried over anhydrous Na_2SO_4. Evaporation and column chromatography on silica gel (eluent: petroleum ether/Et_2O) afforded the terminal allene **2g**[6c] (0.824 g, 72%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 8.1 Hz, 2 H), 7.19 (d, J = 8.1 Hz, 2 H), 5.18−5.06 (m, 1 H), 4.78−4.68 (m, 3 H), 2.65 (q, J = 7.5 Hz, 2 H), 2.50−2.41 (m, 2 H), 2.12 (s, 1 H), 1.24 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.4, 143.6, 140.9, 127.9, 125.8, 86.2, 74.9, 73.5, 38.3, 28.5, 15.6.

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Note Added after ASAP Publication. There were errors in the Supporting Information file published ASAP January 5, 2009; the corrected version was published January 22, 2009.

Supporting Information Available: Typical experimental procedure and analytical data for all new products not listed in the text and ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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