Tetrahedron Letters 49 (2008) 7230–7233

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of allenes via CuBr-catalyzed homologation of alk-1-ynes accelerated by microwave

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ARTICLE INFO

Article history:
Received 18 September 2008
Accepted 6 October 2008
Available online 8 October 2008

Keywords:
Allenes
Homologation
Alk-1-ynes
Microwave

ABSTRACT

CuBr-catalyzed homologation of alk-1-ynes **1** with paraformaldehyde and *N,N*-diisopropylamine (or *N,N*-dicyclohexylamine) was accelerated by microwave irradiation at 150 °C to afford the corresponding allenes **2** in good to high yields in 1–10 min. Bisalkynes **5** and **7** were also converted to the corresponding bisallenes **6** and **8** in 63% and 61% yields, respectively, under the current condition.

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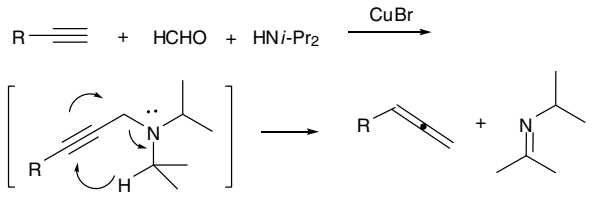
Microwaves have been recognized as an efficient heating source for organic synthesis.[1,2] Microwave-accelerated transformations are considered as an environmentally friendly alternative to standard heating methodologies in view of use of less volume of solvents, milder reagents, and reduced energy consumption.[3] Numerous protocols have been developed due to the advantages of the convenience and special characteristics of microwave chemistry. In many cases, the surpassing heating performance by microwave has affected in improvement of reaction rates and yields with minimizing side reactions in the shorter intervals of reaction time.[4]

In this Letter, we developed the microwave-assisted CuBr-catalyzed homologation of alk-1-ynes to allenes. Allenes have extraordinary properties such as an axial chirality of the elongated tetrahedron and a higher reactivity than alkenes, hence, these have been paid attention not only as an attractive building block for organic synthesis but also as a potent functional group for improvement of the biological and pharmacological active compounds.[5–7] Therefore, development of simple protocols for the introduction of an allenic moiety into the existing backbone of the molecules is still an important requirement.[8] Allenes can be generally prepared from propargylic alcohol derivatives by S_N2'-type displacement with organocopper species named Crabbé reaction.[9] Crabbé and co-workers also developed a simple method for CuBr-catalyzed homologation of alk-1-ynes to terminal allenes with peraformaldehyde and *N,N*-diisopropylamine in refluxing dioxane.[10] They proposed a two-step mechanism in this transformation; the first step being a CuBr-catalyzed Mannich-type reaction and the second, a 1,5-sigmatropic rearrangement of hydrogen (Scheme 1). We found that this Crabbé-type allene formation was dramatically accelerated by microwave irradiation[11] and various allenes were able to be synthesized from the corresponding terminal alkynes.[12]



Scheme 1.

The reaction of propargyl benzyl ether **1a** with formaldehyde and various amines was examined in the presence of copper and palladium catalysts under microwave conditions. The results are summarized in Table 1. The reaction of **1a** with paraformaldehyde and *N,N*-diisopropylamine proceeded in the presence of CuBr (50 mol %) at 110 °C under microwave irradiation condition to give the corresponding allene **2a** in 24% yield (entry 1). The reaction was complete within 10 min at 150 °C and **2a** was obtained quantitatively (entry 2). When the reaction was carried out without microwave irradiation, it took 3 h to obtain **2a** in 78% yield at 110 °C (entry 3), and the lower yield was observed at 150 °C (entry 4). Although the reaction was complete within 5 min using a 30 mol % of CuBr, **2a** was generated only in 45% for 1 min (entries 5–7). *N,N*-Dicyclohexylamine was more effective for this transformation[13] and **2a** was obtained in 76% yield even for 1 min at

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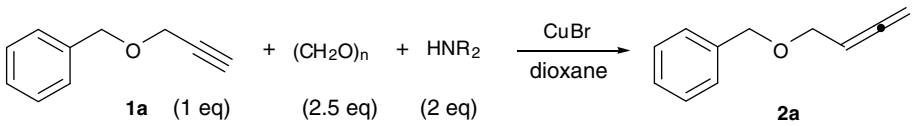
doi:10.1016/j.tetlet.2008.10.019

Table 1
CuBr-mediated homologation of propargyl benzyl ether **1a** to allene **2a**[a]

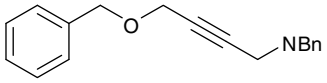


1a (1 eq) (2.5 eq) (2 eq) **2a**

Entry	R_2NH	Catalyst (mol %)	Condition	Time (min)	Yield[b] (%)
1	*i*-Pr_2NH	CuBr (50)	110 °C/MW	10	24
2	*i*-Pr_2NH	CuBr (50)	150 °C/MW	10	>99
3	*i*-Pr_2NH	CuBr (50)	110 °C	180	78
4	*i*-Pr_2NH	CuBr (50)	150 °C	30	49[c]
5	*i*-Pr_2NH	CuBr (30)	150 °C/MW	10	>99
6	*i*-Pr_2NH	CuBr (30)	150 °C/MW	5	>99
7	*i*-Pr_2NH	CuBr (30)	150 °C/MW	1	45
8	Cy_2NH	CuBr (30)	150 °C/MW	10	>99 (86)[d]
9	Cy_2NH	CuBr (30)	150 °C/MW	5	>99
10	Cy_2NH	CuBr (30)	150 °C/MW	1	76
11	Cy_2NH	CuBr (20)	150 °C/MW	5	54
12	Cy_2NH	CuBr (10)	150 °C/MW	5	49
13	Cy_2NH	CuBr (5)	150 °C/MW	5	29
14	Cy_2NH	CuCl (30)	150 °C/MW	5	47
15	Cy_2NH	CuI (30)	150 °C/MW	5	48
16	Cy_2NH	CuOAc (30)	150 °C/MW	5	7
17	Cy_2NH	$CuCl_2$ (30)	150 °C/MW	5	47
18	Cy_2NH	$PdCl_2$ (30)	150 °C/MW	5	NR
19	Cy_2NH	$PdCl_2(PPh_3)_2$ (30)	150 °C/MW	5	NR
20	Et_2NH	CuBr (30)	150 °C/MW	5	70
21	*i*-Bu_2NH	CuBr (30)	150 °C/MW	5	89
22	Bn_2NH	CuBr (30)	150 °C/MW	5	—[e]

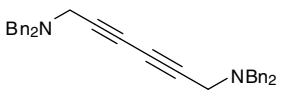
[a] All reactions were carried out in a sealed vial tube. The mixture was heated with stir using the microwave apparatus (Initiator™, Biotage, Co. Ltd). The initial heating was carried out with 380 W of microwave power, and then the reaction was irradiated with 75 W of microwave to maintain the reaction temperature at 110 or 150 °C for an appropriate period.
[b] GC yields based on **1a** using hexadecane as an internal standard.
[c] Longer reaction time resulted in decomposition of the products.
[d] Isolated yield based on **1a** was indicated in the parentheses.
[e] Mannich-type three-component coupling product was observed instead of **2a**.

150 °C (entries 8–10). The amounts of catalyst also affected the reaction and use of less amounts of CuBr resulted in lower yields of **2a** (entries 11–13). Other cupper catalysts, such as CuCl, CuI, CuOAc, and $CuCl_2$ were not effective for this transformation (entries 14–17) and the reaction did not proceed under palladium-catalyzed conditions (entries 18 and 19). Effect of amines was also examined. Although *N,N*-diethylamine and *N,N*-diisobutylamine were effective (entries 20 and 21), the use of *N,N*-dibenzylamine did not afford the corresponding allene **2a** but afforded the Mannich-type three-component coupling product **3** (entry 22).[14]



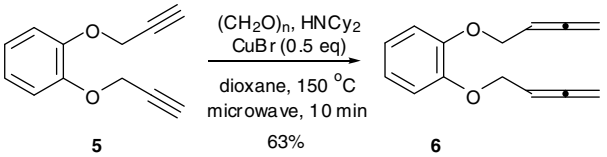
3 (Mannich-type product)

We next examined synthesis of various allenes from the corresponding terminal alkynes under the microwave condition. The results are shown in Table 2. Propargylic ethers **1a** and **1b** underwent the allene formation with paraformaldehyde and *N,N*-dicyclohexylamine to give the corresponding allenes **2a** and **2b** in 86% and 77% isolated yields, respectively (entries 1 and 2). The phenoxy ether **1c** also gave **2c** in 62% yield (entry 3). In this case, **2c** was obtained in 44% yield without microwave irradiation at 110 °C for 4 h. Although the reaction of *N*-propargylphthalimide **1d** gave **2d** in 61% yield, *N*-propargyldibenzylamine **1e** gave the corresponding allene **2e** in 37% yield along with the dimer product **4** (entries 4 and 5).[15] Reaction of the propargylic alcohols **1f–i** and the acetate **1j** also proceeded without affecting OH and OAc groups[8] to afford the corresponding allenyl carbinols **2f-i** and allenyl acetate **2j** in good to high yields (entries 6–10). The current transformation was able to be applied for aliphatic alkyne **1k**, aromatic alkyne **1l**, and biologically active alkynes **1m–n** (entries 11–14).[16,17]

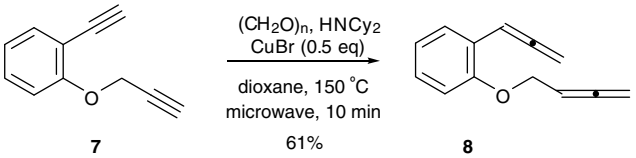


4 (dimer product)

Recently, bisallenes have been paid attention as important building blocks in transition-metal catalyzed cyclization reactions.[19] We applied the current microwave-accelerated homologation reaction for bisallene synthesis. The symmetric bisalkyne **5**, which was prepared from catechol and propargylbromide, underwent the homologation reaction with paraformaldehyde (5 equiv) and *N,N*-dicyclohexylamine (4 equiv) in the presence of CuBr (0.5 equiv) to give the corresponding bisallene **6** in 63% yield. In a similar manner, the unsymmetric bisalkyne **7** was also converted to the corresponding bisallene **8** in 61% yield.[20]

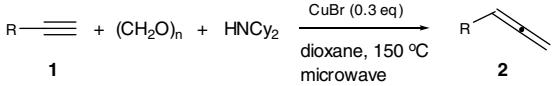


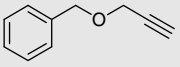
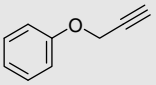
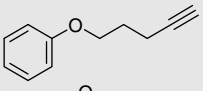
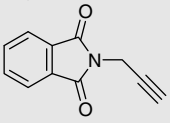
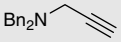
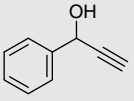
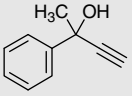
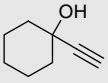
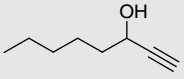
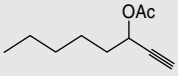
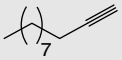
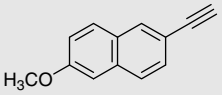
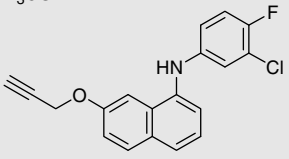
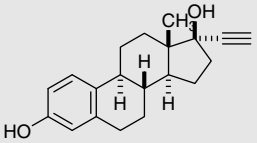
5 **6** (1)



7 **8** (2)

Table 2
Synthesis of allenes **2** from various terminal alkynes **1** under the microwave condition[18]



Entry	1		Time (min)	Yield[a] (%)
1		**1a**	5	86
2		**1b**	5	77
3		**1c**	5	62
4		**1d**	5	61
5		**1e**	10	37
6		**1f**	10	74
7		**1g**	10	91
8		**1h**	10	95
9[b]		**1i**	20	76
10		**1j**	10	65
11		**1k**	10	62
12		**1l**	10	60
13		**1m**	5	63
14		**1n**	10	52

[a] Isolated yield based on **1a**.
[b] The reaction was carried out using 0.5 equiv of CuBr.

In conclusion, we found that CuBr-catalyzed homologation of alk-1-ynes to terminal allenes was dramatically accelerated by microwave irradiation. We believe that the current finding is significantly important in aspects of widely applicable methodology and reduction of energy consumption for organic synthesis.

Acknowledgment

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas 'Advanced Molecular Transformations of Carbon Resources' from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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17. Nakamura, H.; Onagi, S. *Tetrahedron Lett.* **2006**, *47*, 2539.
18. A representative procedure for the microwave-assisted allene formation from terminal alkynes is as follows: To a mixture of alkyne **1a** (73.3 mg, 0.50 mmol) and CuBr (22 mg, 30 mol %) in dioxane (2.0 mL) were added paraformaldehyde (37.5 mg, 1.25 mmol) and *N*,*N*-dicyclohexylamine (0.20 mL, 1.0 mmol) in a sealed vial tube. The mixture was heated to 150 °C with stir using the microwave apparatus (Initiator™, Biotage, Co. Ltd). When the reaction temperature was set at 150 °C on the apparatus, it took 3 min to reach this temperature with 380 W of microwave power, and then reaction temperature was maintained at 150 °C for 10 min with 75 W of microwave irradiation. During the reaction course, the pressure in the sealed vial was less than 2 bar. The mixture was filtered with a short column chromatography on silica gel eluted with ether and concentrated. The residue was purified by column chromatography on silica gel to give **2a** in 86% yield (69.0 mg, 0.43 mmol) as a

colorless liquid: IR (neat) 3030, 2858, 1956, 1722, 1497, 1454, 1360, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.28 (q, J = 6.8 Hz, 1H), 4.80 (dt, J = 6.8, 2.4 Hz, 2H), 4.54 (s, 1H), 4.07 (dt, J = 6.8, 2.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.3, 138.1, 128.4, 127.8, 127.6, 87.7, 75.7, 71.8, 67.8; Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.49; H, 7.70.

19. (a) Jiang, X.; Cheng, X.; Ma, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 8009; (b) Kang, S.-K.; Ha, Y.-H.; Kim, D.-H.; Lim, Y.; Jung, J. *Chem. Commun.* **2001**, 1306; (c) Pasto, D. J.; Yang, S-H.; Muellerleile, J. A. *J. Org. Chem.* **1992**, *57*, 2976.
20. *Spectral data for 1,2-Bis(buta-2,3-dienyloxy)benzene* **6**: Colorless liquid: IR (neat) 3065, 2928, 2868, 2359, 1956, 1717, 1506, 1456, 1375, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (m, 4H), 5.39 (q, J = 6.8 Hz, 2H), 4.80 (dt, J = 6.8, 2.4 Hz, 4H), 4.61 (dt, J = 6.8, 2.4 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.5, 148.3, 121.4, 114.6, 87.3, 66.9; MS(EI) m/z 214 (M^+); Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.46; H, 6.64.
1-(Buta-2,3-dienyloxy)-2-(propa-1,2-dienyl)benzene **8**: Colorless liquid: IR (neat) 3398, 2926, 2854, 2332, 1956, 1596, 1456, 1242, 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 7.6, 1.6 Hz, 1H), 7.15 (dt, J = 8.4, 2.0 Hz, 1H), 6.93 (dt, J = 7.6, 1.2 Hz, 1H), 6.87 (dd, J = 9.2, 1.2 Hz, 1H), 6.60 (t, J = 6.8 Hz, 1H), 5.41 (q, J = 6.8 Hz, 1H), 5.11 (d, J = 6.8 Hz, 1H), 4.86 (dt, J = 6.8, 2.8 Hz, 2H), 4.58 (dt, J = 6.8, 2.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2, 209.3, 154..7, 127.8 (d), 122.9, 121.1, 112.7, 87.9, 87.2, 78.0, 76.6, 66.4; MS(EI) m/z 184 (M^+); Anal. Calcd for $C_{13}H_{13}O$: C, 84.75; H, 6.57. Found: C, 84.55; H, 6.78.