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Atom-Economical Chemoselective Synthesis of 1,4-Diynes and Polysubstituted Furans/Pyrroles from Propargyl Alcohols and Terminal Alkynes

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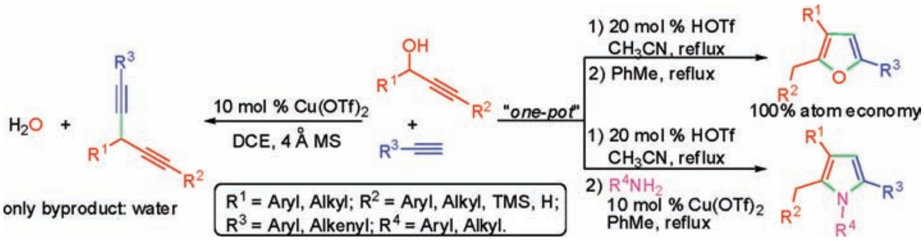
ABSTRACT



Under different conditions, the reaction of propargyl alcohols and terminal alkynes leads to the selective formation of 1,4-diynes and polysubstituted furans/pyrroles. Water is the only byproduct in the selective synthesis of 1,4-diynes and pyrroles, and the strategy for the furan synthesis is of 100% atom economy.

In modern organic chemistry, a key but challenging goal must be maximizing synthetic efficiency in the transformation of starting materials to the target molecules. Readily available starting materials, high selectivity, and atom economy are three attractive features of efficient synthetic methods.[1]

Although considerable progress has been made, many reactions still suffer from low efficiency. For instance, 1,4-diynes are traditionally accessed by the nucleophilic substitution of propargyl halides or sulfonates with metal acetylides. Thus, large amounts of salt waste are generated simultaneously.[2] Recently, the coupling of propargyl alcohols and alkynylsilanes has emerged as an attractive alternative.[3] However, in this protocol, a stoichiometric amount of trimethylsilanol is formed as a byproduct.

Among the numerous approaches to polysubstituted furans and pyrroles, cycloisomerizations of alkynyl- and allenyl-functionalized compounds are particularly attractive.[4]

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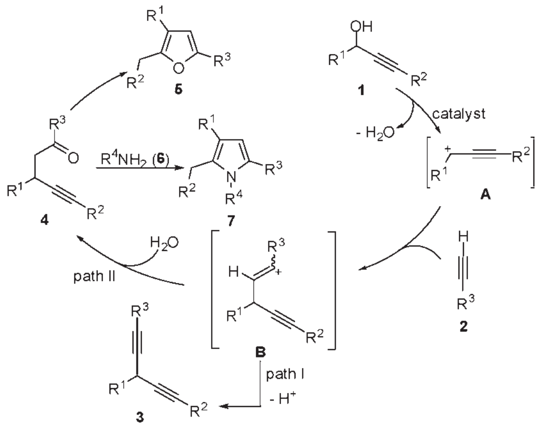
(4) For representative examples on furan syntheses, see: (a) Kang, J. Y.; Connell, B. T. *J. Org. Chem.* **2011**, *76*, 2379. (b) Chen, Z; Huang, G.; Jiang, H.; Huang, H.; Pan, X. *J. Org. Chem.* **2011**, *76*, 1134. (c) Albrecht, L.; Ransborg, L. K.; Gschwend, B.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 17886. (d) Zhang, X.; Lu, Z.; Fu, C.; Ma, S. *J. Org. Chem.* **2010**, *75*, 2589. (e) Kao, T.-T.; Syu, S.-e.; Jhang, Y.-W.; Lin, W. *Org. Lett.* **2010**, *12*, 3066. (f) Li, W.; Zhang, J. *Chem. Commun.* **2011**, *47*, 809. For representative examples on pyrrole syntheses, see: (g) Trost, B. M.; Lumb, J.-P.; Azzarelli, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 740. (h) Wang, Y.; Bi, X.; Li, D.; Liao, P.; Wang, Y.; Yang, J.; Zhang, Q.; Liu, Q. *Chem. Commun.* **2011**, *47*, 809. (i) Ngwerume, S.; Camp, J. E. *Chem. Commun.* **2011**, *47*, 1857. (j) Kramer, S.; Madsen, J. L. H.; Rottlander, M.; Skrydstrup, T. *Org. Lett.* **2010**, *12*, 2758. (k) Donohoe, T. J.; Race, N. J.; Bower, J. F.; Callens, C. K. A. *Org. Lett.* **2010**, *12*, 4094. (l) Saito, A.; Konishi, T.; Hanzawa, Y. *Org. Lett.* **2010**, *12*, 372. (m) Yan, R.-L.; Luo, J.; Wang, C.-X.; Ma, C.-W.; Huang, G.-S.; Liang, Y.-M. *J. Org. Chem.* **2010**, *75*, 5395.

10.1021/ol201054z

These strategies generally rely on noble metal catalysis, multiple synthetic steps, or highly functionalized substrates. As a result, the development of efficient synthetic routes allowing the facile assembly of polysubstituted furans and pyrroles from readily available precursors is still of special interest.

Herein, we report a novel efficient synthetic method: under different conditions, propargyl alcohols and terminal alkynes were selectively transformed into 1,4-diynes and polysubstituted furans/pyrroles.

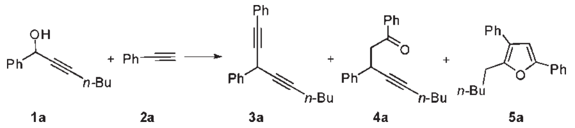
Scheme 1. Proposed Reaction Pathways



On the basis of our and others' previous work,[5] activation of propargyl alcohol **1** by Lewis or Brønsted acid was presumed to afford carbocation **A** (Scheme 1). We anticipated that a nucleophilic attack of alkyne **2** would lead to the formation of alkenyl cation **B**.[6] Two competitive pathways, proton elimination (path I) and hydrolysis (path II), could occur subsequently, leading to the formation of 1,4-diynes **3** and γ-alkynyl ketones **4**, respectively. Our continuous interest in heterocycle chemistry prompted us to explore the possibility of using **4** as the precursor for the synthesis of polysubstituted furans **5** and pyrroles **7**.[5b−e] Obviously, the search for different reaction conditions, which would allow the selective synthesis of 1,4-diynes and furans/pyrroles, was the major challenge posed for us.

With this hypothesis in mind, we set out to examine the reaction of propargyl alcohol **1a** and ethynylbenzene (**2a**) using Cu(OTf)$_2$ as the catalyst. Our results indicated that both the yield and selectivity of this reaction showed remarkable sensitivity to solvents (Table 1, entries 1−6). To our delight, **3a** was obtained in 76% yield without any competitive formation of **4a** and **5a** when 1,2-dichloroethane (DCE) was used as the solvent (Table 1, entry 6). Notably, removal of H$_2$O using 4 Å molecular sieves resulted in an improved yield (81%; Table 1, entry 7). Catalyst screening revealed that Cu(OTf)$_2$ was still the preferential catalyst for 1,4-diyne synthesis (Table 1, entries 8−12).

Table 1. Optimization of Reaction Conditions [a]



entry	catalyst (mol %)	solvent	time	yield (%)[b] of **3a/4a/5a**
1	Cu(OTf)$_2$ (10)	MeNO$_2$	5 min	35/45/0
2	Cu(OTf)$_2$ (10)	PhMe	5 min	64/0/0
3	Cu(OTf)$_2$ (10)	THF	5 h	41/0/0
4	Cu(OTf)$_2$ (10)	MeCN	5 min	18/62/0
5	Cu(OTf)$_2$ (10)	DMF	5 min	0/0//0 [c]
6	Cu(OTf)$_2$ (10)	DCE	5 min	76/0/0
7[d]	**Cu(OTf)$_2$(10)**	**DCE**	**5 min**	**81/0/0**
8	Bi(OTf)$_3$ (10)	DCE	20 min	70/0/0
9	Sc(OTf)$_3$ (10)	DCE	5 h	59/0/0
10	Zn(OTf)$_2$ (10)	DCE	12 h	19/0/0
11	AgOTf (10)	DCE	30 min	71/0/0
12	HOTf (10)	DCE	5 min	58/13/0
13	HOTf (10)	MeCN	5 min	7/67/0
14	HOTf (20)	MeCN	5 min	4/76/0
15	TFA (20)	MeCN	2 h	3/41/0
16	*p*-TSA (20)	MeCN	5 min	3/56/0
17	**HOTf (20)**	**MeCN/ PhMe**	**5 min/ 30 min**	**4/0/71**

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.55 mmol), catalyst, solvent (2 mL), reflux. [b] Isolated yields refer to **1a**. [c] **2a** underwent a self-coupling reaction, affording 1,4-diphenylbuta-1,3-diyne as the main product in 67% yield. [d] 4 Å MS (200 mg) was added.

Our next investigation indicated that acetonitrile favored the formation of γ-alkynyl ketone **4a**, and **4a** could be obtained with high selectivity when trifluoromethanesulfonic acid (HOTf, 20 mol %) was used as the catalyst (Table 1, entry 14).

Inspired by our previous work on furan synthesis,[5b] we supposed that **4a** might undergo a cycloisomerization to afford furan **5a** in the presence of a catalytic amount of TfOH. To evaluate this concept, MeCN was removed under reduced pressure after **4a** was obtained,

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(5) (a) Zhan, Z.; Yu, J.; Liu, H.; Cui, Y.; Yang, R.; Yang, W.; Li, J. *J. Org. Chem.* **2006**, *71*, 8298. (b) Zhan, Z.; Cai, X.; Wang, S.; Yu, J.; Liu, H.; Cui, Y. *J. Org. Chem.* **2007**, *72*, 9838. (c) Liu, X.; Huang, L.; Zheng, F.; Zhan, Z. *Adv. Synth. Catal.* **2008**, *350*, 2778. (d) Pan, Y.; Zheng, F.; Lin, H.; Zhan, Z. *J. Org. Chem.* **2009**, *74*, 3148. (e) Hao, L.; Pan, Y.; Wang, T.; Lin, M.; Chen, L.; Zhan, Z. *Adv. Synth. Catal.* **2010**, *352*, 3215. (f) Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180.

(6) The catalytic nucleophilic attack of terminal alkynes to unsaturated electrophiles (C=O, C=N, and C≡N bonds) has been largely developed; see: (a) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963. (b) Li, C.-J. *Acc. Chem. Res.* **2010**, *43*, 581. (c) Shen, Q.; Huang, W.; Wang, J.; Zhou, X. *Organometallics* **2008**, *27*, 301. (d) Chen, Z.; Yang, X.; Wu, J. *Chem. Commun.* **2009**, 3469. (e) Li, P.; Zhang, Y.; Wang, L. *Chem.—Eur. J.* **2009**, *15*, 2045. (f) Han, J.; Xu, B.; Hammond, G. B. *J. Am. Chem. Soc.* **2010**, *132*, 916. The nucleophilic attack of a terminal alkyne to a cabocation to afford a vinyl cation has also been reported, see: (g) Liu, Z.; Wang, J.; Zhao, Y.; Zhou, B. *Adv. Synth. Catal.* **2009**, *351*, 371.

and toluene (2 mL) was added. Pleasingly, without employment of any other catalyst, the cycloisomerization of **4a** readily provided **5a** in 71% yield in one pot (Table 1, entry 17).[7] Significantly, this furan synthesis from a propargyl alcohol and a terminal alkyne is of 100% atom economy.[8]

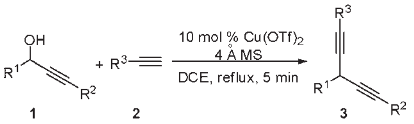
With the optimal reaction conditions identified (Table 1, entry 7), attention was focused on the selective synthesis of 1,4-diynes. A wide range of propargyl alcohols underwent this reaction, offering a facile access to 1,4-diynes (Table 2). The alkyne terminus of **1** could accommodate different substituted groups (R^2 = *n*-butyl, phenyl and TMS). The alkynylation of **1d** containing a terminal alkyne moiety also proceeded readily (R^2 = H; Table 2, entries 4 and 12). While an electron-donating substituent had no observable influence on this reaction (Table 2, entry 5 vs 3), the presence of a strong electron-withdrawing group had an adverse impact (Table 2, entry 6 vs 2). Treatment of aliphatic propargyl alcohol **1g** with **2a** in the presence of $Cu(OTf)_2$ led to the formation of **3g** in a fair yield (Table 2, entry 7). This result could be attributed to the instability of the cationic intermediate **A**.

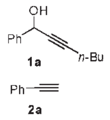
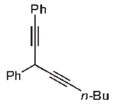
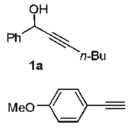
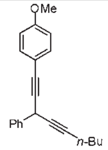
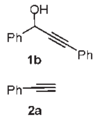
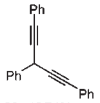
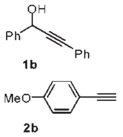
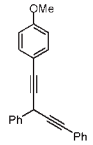
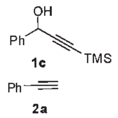
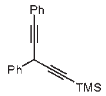
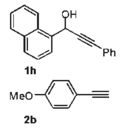
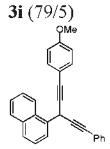
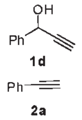
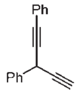
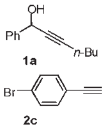
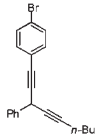
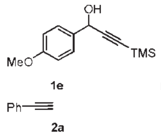
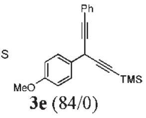
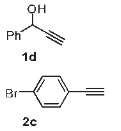
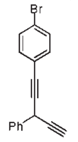
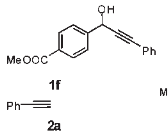
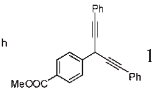
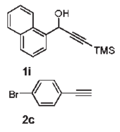
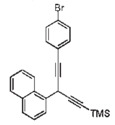
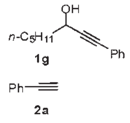
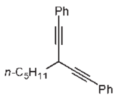
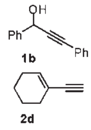
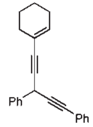
The scope of terminal alkyne **2** was subsequently examined. Both electron-rich and electron-poor aromatic alkynes reacted smoothly with propargyl alcohols (Table 2, entries 8–13). Nonaromatic alkyne **2d** also participated in the alkynylation of **1b**, generating **3n** in 68% yield with a prolonged reaction time (Table 2, entry 14). Notably, small amounts of γ-alkynyl ketones **4** were observed in the alkynylation of propargyl alcohols with **2b** (Table 2, entries 8–10). We reasoned that the electron-donating group (R^3 = 4-MeO-C_6H_4) might stabilize alkenyl cation **B**, facilitating the nucleophilic attack of water.

Next, we focused our efforts on the selective synthesis of furans (Table 3). The reaction occurred with a wide variety of propargyl alcohols. Alkyl or strong electron-withdrawing substituents at the propargylic position led to decreased efficiency (Table 3, entries 3 and 9). The TMS group was not tolerated under these conditions and fell off during workup (Table 3, entries 2, 6, and 13). Although the same product was obtained in the examples involving **1c** and **1d**, the employment of a TMS group led to an improved yield in a shorter duration (Table 3, entry 6 vs 7), providing an valuable alternative route to 2-methyl-substituted furans.

Small amounts of 1,4-diynes were observed while alkynes **2a** and **2c**,**d** were employed as substrate. The reaction of **1b** and nonaromatic alkyne **2d** afforded γ-alkynyl ketone **4b** in 65% yield. The subjection of **4b** to cyclization conditions failed to afford the desired furan (Table 3, entry 14). The reaction of substrate **1a** and an internal alkyne (prop-1-ynylbenzene) has also been tested; however, the reaction led to a complex mixture and no desired tetrasubstituted furan was observed.

Table 2. Selective Synthesis of 1,4-Diynes [a]



entry	substrates	product yield[b] (%) 3/4	entry	substrates	product yield[b] (%) 3/4
1	 1a 2a	 **3a** (81/0)	8	 1a 2b	 **3h** (76/5)
2	 1b 2a	 **3b** (87/0)	9	 1b 2b	 **3i** (79/5)
3	 1c 2a	 **3c** (84/0)	10	 1h 2b	 **3j** (70/4)
4	 1d 2a	 **3d** (79/0)	11	 1a 2c	 **3k** (74/0)
5	 1e 2a	 **3e** (84/0)	12	 1d 2c	 **3l** (72/0)
6	 1f 2a	 **3f** (72/0)	13	 1i 2c	 **3m** (80/0)
7 [c,d]	 1g 2a	 **3g** (47/0)	14 [d]	 1b 2d	 **3n** (68/0)

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.55 mmol), $Cu(OTf)_2$ (0.05 mmol), 4 Å MS (200 mg), DCE (2 mL), reflux, 5 min. [b] Isolated yields refer to **1**. [c] 5 equiv of **2a** was employed. [d] Reaction ran for 1 h.

As a demonstration of the synthetic utility of this methodology, several polysubstituted pyrroles were prepared in a one-pot procedure (Scheme 2). After the

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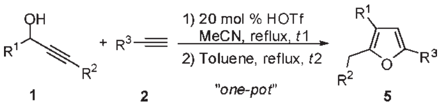
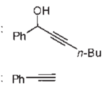
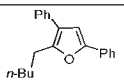
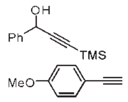
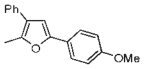
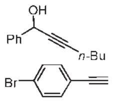
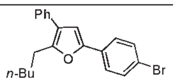
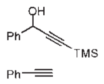
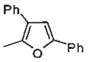
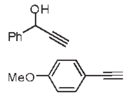
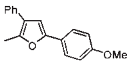
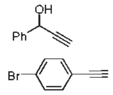
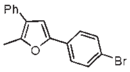
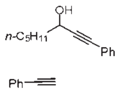
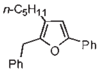
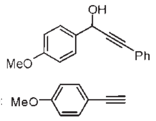
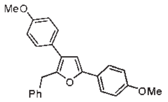
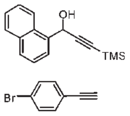
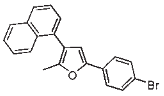
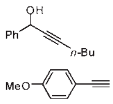
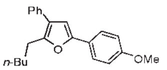
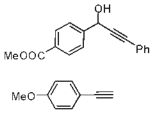
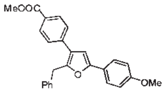
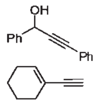
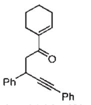
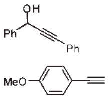
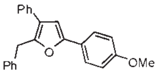
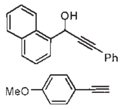
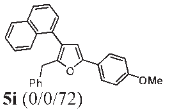
(7) When 1/1 mixed acetonitrile/toluene was used as the solvent, the reaction proceeded with low selectivity (**3a**/**4a**/**5a** = 43%/12%/18%).

(8) Cao, H.; Jiang, H.; Mai, R.; Zhu, S.; Qi, C. *Adv. Synth. Catal.* **2010**, *352*, 143.

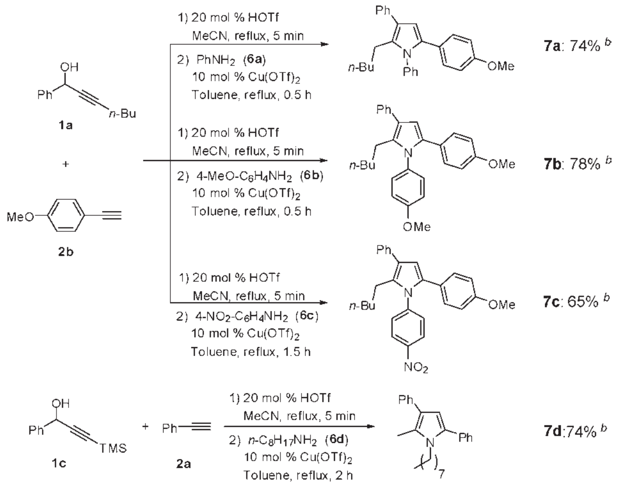
Table 3. Selective Synthesis of Furans[a]



entry	substrates	product yield (%)[b] 3/4/5 time: t1/t2	entry	substrates	product yield (%)[b] 3/4/5 time: t1/t2	entry	substrates	product yield (%)[b] 3/4/5 time: t1/t2
1	1a, 2a 	 **5a** (4/0/71) 5 min/30 min	6	1c, 2b 	 **5f** (0/0/80) 5 min/15 min	11	1a, 2c 	 **5j** (3/0/68) 5 min/30 min
2	1c, 2a 	 **5b** (3/0/75) 5 min/15 min	7	1d, 2b 	 **5f** (0/0/73) 5 min/40 min	12	1d, 2c 	 **5k** (3/0/64) 5 min/40 min
3[c]	1g, 2a 	 **5c** (3/0/31) 2 h/1 h	8	1j, 2b 	 **5g** (0/0/79) 5 min/40 min	13	1i, 2c 	 **5l** (4/0/72) 5 min/20 min
4	1a, 2b 	 **5d** (0/0/78) 5 min/20 min	9	1f, 2b 	 **5h** (0/0/61) 5 min/1 h	14	1b, 2d 	 **4b** (4/65/0) 1 h/0 min
5	1b, 2b 	 **5e** (0/0/74) 5 min/40 min	10	1h, 2b 	 **5i** (0/0/72) 5 min/40 min			

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.55 mmol), HOTf (0.1 mmol), CH_3CN (2 mL), reflux, t1. CH_3CN was then removed under reduced pressure, followed by the addition of toluene (2 mL), reflux, t2. [b] Isolated yields refer to **1**. [c] 5 equiv of **2a** was employed.

Scheme 2. One-Pot Synthesis of Pyrroles[a]



[a] Reaction conditions: **1** (0.5 mmol), **2** (0.55 mmol), HOTf (0.1 mmol), CH_3CN (2 mL), reflux, 5 min; CH_3CN was then removed, amines **6** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), and toluene (2 mL) were added, reflux, t. [b] Isolated yields refer to **1**.

γ-alkynyl ketones were obtained, various amines **6** were subjected to the $Cu(OTf)_2$-catalyzed consendation–cycloisomerization tandem reaction, readily affording polysubstituted pyrroles **7**.[9]

In summary, starting from propargyl alcohols and terminal alkynes, 1,4-diynes and polysubstituted furans/pyrroles have been prepared with high selectivity. Three attractive features of this methodology are readily available starting materials, high selectivity, and high atom economy.

Acknowledgment. We thank the National Nature Science Foundation of China (No. 21072159) for financial support.

Supporting Information Available. Detailed experimental procedure and copies of ^1H NMR and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] In the absence of $Cu(OTf)_2$, the reactions provided pyrroles **7** in low yields.