$FeCl_3$-Catalyzed Coupling of Propargylic Acetates with Alcohols

Zhuang-Ping Zhan,* Hui-Juan Liu

Department of Chemistry and The Key Laboratory for Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, P. R. of China
Fax +86(592)2185780; E-mail: zpzhan@xmu.edu.cn

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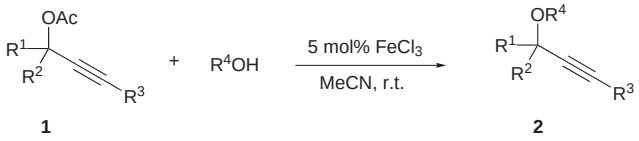
Abstract: A new method for the synthesis of propargylic ethers by $FeCl_3$-catalyzed alcoholysis of propargylic acetates was developed. The reaction was carried out at room temperature in acetonitrile without exclusion of moisture or air. High product yields were obtained with excellent reaction regioselectivity.

Key words: propargylic ethers, propargylic esters, alcohols, etherification



Scheme 1

The acetylenic carbon–carbon triple bond plays a pivotal role in a variety of functional group transformations,[1] which has resulted in the steady growth in the synthesis of propargylic derivatives. The Nicholas reaction has been widely accepted as a powerful tool for propargylic substitution reactions[2] but has some drawbacks, for example, a stoichiometric amount of $[Co_2(CO)_8]$ is required and several steps are necessary to obtain the required propargylic substances from propargylic alcohols via cationic propargylic complexes $[Co_2(CO)_6(propargyl)]^+$.[2,3] Recently, several transition-metal-catalyzed propargylic substitution reactions have been reported. Among them, a ruthenium-catalyzed process is a direct and versatile method.[4] Nevertheless, with this method, the substrate is limited to propargylic alcohols bearing terminal alkyne groups.[5] Recently, Toste[6] and Campagne[7] described efficient rhenium [(dppm)$ReOCl_3$] and gold [$NaAuCl_4 \cdot 2H_2O$]-catalyzed nucleophilic substitution of propargylic alcohols, respectively, but the high cost of such catalysts is a barrier to their large-scale use. Remarkably, Mahrwald et al. found that propargylic etherification was an attractive method for the preparation of propargylic ethers in the presence of $TiCl_4$[8] or Ti(*i*-PrO)$_4$.[9] However, the catalyst loading was relatively high (10 mol%) and the reaction scope was somewhat narrow. Furthermore, the catalysts were moisture sensitive, less environmentally friendly, and difficult to handle. Therefore, the development of a general, efficient, inexpensive, and commercially available catalyst for propargylic substitution reactions is highly desirable.[10]

Herein, we described an efficient $FeCl_3$-catalyzed nucleophilic substitution reaction of propargylic acetates with alcohols, giving an sp^3 C–O bond after etherification. The reaction was carried out at room temperature in the presence of a catalytic amount of $FeCl_3$ in acetonitrile. High yields were obtained with excellent regioselectivity and the reaction proceeded smoothly without exclusion of moisture or air (Scheme 1).[11]

In order to determine the scope and limitation of this reaction, various propargylic acetates and various alcohols were investigated (Table 1).[12] We found that during etherification propargylic acetates bearing an internal alkyne group proceeded rapidly at room temperature to give the corresponding ethers in excellent yields (Table 1, entries 1–11). Variations in the alkyne substituent from alkyl to aryl or to trimethylsilyl (**1a**–**c**) were well tolerated, without noticeable differences observed in the reaction temperature, time, or yields. In the case of 1-phenylhept-2-ynyl acetate (**1b**) with ethanol and isopropanol as the nucleophile, the corresponding ethers were obtained in 89% and 91% yields, respectively (Table 1, entries 5 and 6). In the $TiCl_4$-catalyzed reaction, only 68% and 42% of the desired products were obtained.[8] Therefore, our procedure was more efficient for the propargylic substitution. Gratifyingly, non-benzylic propargylic acetate **1d** also participated in the substitution reaction, and the etherification proceeded rapidly as well to give the corresponding products in high yields (Table 1, entries 10 and 11). In contrast, reactions of propargylic acetate bearing a terminal alkyne group **1e** were sluggish under identical conditions; a prolonged reaction time and higher temperature (60 °C) were required to produce the corresponding ether in good yield (Table 1, entry 12).

Different alcohols were also tested and the corresponding propargylic ethers were obtained in good yields with complete regioselectivity. Not only primary alkyl alcohols reacted with propargylic esters rapidly, secondary alkyl alcohols also underwent propargylic etherification to afford the propargyl adducts in excellent yields (Table 1, entries 2 and 6). Primary as well as secondary alcohols participated in the reaction without noticeable differences. Alcohols with other functional groups such as alkenyl, phenyl, and chloro substituents were also readily reacted (Table 1, entries 3, 4, 7–9, and 11), allowing the subsequent elaboration of the products after propargylic etherification.

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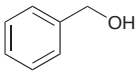
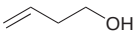
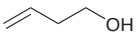
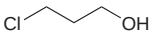
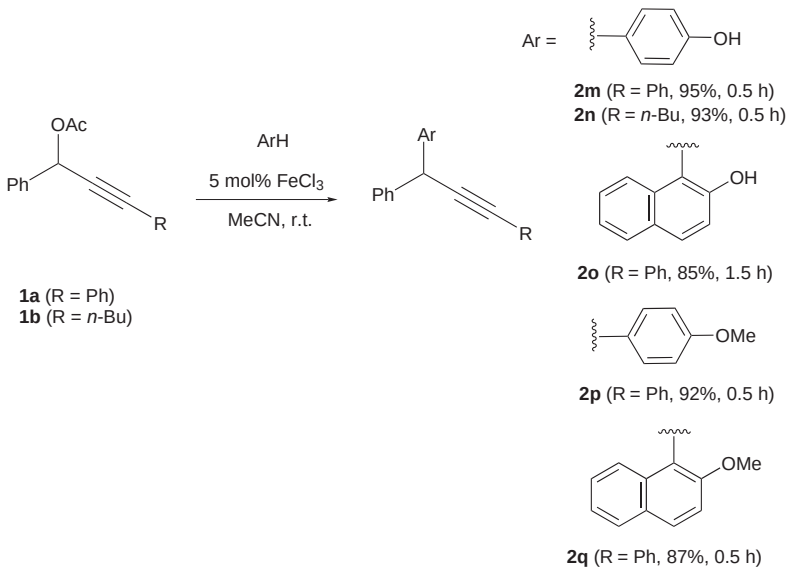
Table 1 $FeCl_3$-Catalyzed Coupling of Propargylic Acetates with Alcohols[a]

Entry	Acetate	R^1	R^2	R^3	R^4OH	Time (h)	Product	Yields of **2** (%)[c]
1	**1a**	Ph	H	Ph	*n*-BuOH	2.5	**2a**	92
2	**1a**	Ph	H	Ph		1.0	**2b**[6b]	93
3	**1a**	Ph	H	Ph		0.5	**2c**[8a]	92
4	**1a**	Ph	H	Ph		1.5	**2d**[6b]	95
5	**1b**	Ph	H	*n*-Bu	EtOH	1.0	**2e**[8a]	89
6	**1b**	Ph	H	*n*-Bu		1.0	**2f**[8a]	91
7	**1b**	Ph	H	*n*-Bu		0.5	**2g**[6b]	90
8	**1c**	Ph	H	TMS		0.5	**2h**[6b]	95
9	**1c**	Ph	H	TMS		1.5	**2i**[2b]	90
10	**1d**	Me	Me	Ph	EtOH	1.0	**2j**[14]	94
11	**1d**	Me	Me	Ph		0.5	**2k**[6b]	90
12	**1e**	Ph	H	H	EtOH	5.0	**2l**[4a]	80[b]

[a] The reactions of **1** (1 mmol) with R^4OH (3 mmol) were carried out in the presence of $FeCl_3$ (0.05 mmol) in MeCN (2 mL) at r.t.
[b] The reaction was carried out at 60 °C.
[c] Isolated yields.

Similarly, reactions of propargylic esters with phenols were also investigated.[12] Surprisingly, contrary to previous reports, the corresponding ethers were not detected.[13] Instead the Friedel–Crafts C-arylated products **2m** and **2n** were obtained in excellent yields with excellent regioselectivity (Scheme 2). β-Naphthol also reacted smoothly with 1,3-diphenylprop-2-ynyl acetate **1a** to afford the corresponding C–C coupling product **2o** in good yield. Other electron-rich aromatics such as methoxybenzene and β-methoxynaphthalene were also investigated, and the corresponding propargyl adducts **2p** and **2q** were obtained in good yields. In all cases, propargylation occurred selectively at the most electron rich position of the aromatic compounds. The results indicated that the reaction proceeded via an electrophilic aromatic substitution mechanism.

In conclusion, we have developed a general and efficient $FeCl_3$-catalyzed substitution reaction of propargylic esters



Scheme 2

with alcohols, leading to the construction of C–O bonds. However, phenolic compounds such as phenol, β-naphthol, methoxybenzene, and β-methoxynaphthalene reacted with propargylic esters to form C–C bonds under similar reaction conditions. In comparison to cobalt, rhenium, ruthenium, titanium, and gold complexes, our reported catalyst $FeCl_3$ offers several advantages such as cheaper cost, commercial availability, and milder reaction conditions. Further investigations on the elucidation of the detailed reaction mechanism and broadening the scope of this methodology are currently ongoing in our laboratory.

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References and Notes

(1) (a) Hudrlik, P. F.; Hudrlik, A. M. In *The Chemistry of the Carbon-Carbon Triple Bond*; Patai, S., Ed.; John Wiley & Sons: Chichester, **1978**, Chap. 7, 199. (b) Trost, B. M. *Comprehensive Organic Synthesis*, Vol. 4; Fleming, I., Ed.; Pergamon Press: Oxford, **1991**.

(2) Review articles: (a) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207. (b) Caffyn, A. J. M.; Nicholas, K. M. In *Comprehensive Organometallic Chemistry II*, Vol. 12; Abel, E. W.; Stone, F. G. A.; Wilkinson, J., Eds.; Pergamon Press: Oxford, **1995**, Chap. 7.1, 685. (c) Green, J. R. *Curr. Org. Chem.* **2001**, *5*, 809. (d) Teobald, B. J. *Tetrahedron* **2002**, *58*, 4133. (e) Kuhn, O.; Rau, D.; Mayr, H. *J. Am. Chem. Soc.* **1998**, *120*, 900.

(3) Nicholas, K. M.; Mulvaney, M.; Bayer, M. *J. Am. Chem. Soc.* **1980**, *102*, 2508.

(4) (a) Nishibayashi, Y.; Wakiji, I.; Hidai, M. *J. Am. Chem. Soc.* **2000**, *122*, 11019. (b) Nishibayashi, Y.; Wakiji, I.; Ishii, Y.; Uemura, S.; Hidai, M. *J. Am. Chem. Soc.* **2001**, *123*, 3393. (c) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 11846. (d) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 2681. (e) Milton, M. D.; Inada, Y.; Nishibayashi, Y.; Uemura, S. *Chem. Commun.* **2004**, 2712. (f) Nishibayashi, Y.; Milton, M. D.; Inada, Y.; Yoshikawa, M.; Wakiji, I.; Hidai, M.; Uemura, S. *Chem. Eur. J.* **2005**, *11*, 1433. (g) Nishibayashi, Y.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 7900.

(5) The ruthenium-catalyzed propargylic substitution was reported to run via allenylidene complex intermediates which can be produced only from the propargylic alcohols bearing terminal alkyne group see ref. 4. On the other hand ruthenium-catalyzed substitution of propargylic alcohols bearing an internal alkyne group were also investigated, see: (a) Nishibayashi, Y.; Inada, Y.; Yoshikawa, M.; Hidai, M.; Uemura, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1495. (b) Inada, Y.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 15172.

(6) (a) Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 15760. (b) Sherry, B. D.; Radosevich, A. T.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 6076. (c) Kennedy-Smith, J. J.; Young, L. A.; Toste, F. D. *Org. Lett.* **2004**, *6*, 1325.

(7) Georgy, M.; Boucard, V.; Campagne, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 14180.

(8) (a) Mahrwald, R.; Quint, S. *Tetrahedron* **2000**, *56*, 7463. (b) Bartels, A.; Mahrwald, R.; Quint, S. *Tetrahedron Lett.* **1999**, *40*, 5989.

(9) Mahrwald, R.; Quint, S.; Scholtis, S. *Tetrahedron* **2002**, *58*, 9847.

(10) Very recently new methodologies employing Brønsted acids as the catalysts have been developed although a higher temperature was needed or the reaction scope is somewhat narrow, see: (a) Sanz, R.; Martínez, A.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Eur. J. Org. Chem.* **2006**, 1383. (b) Liu, J. H.; Muth, E.; Flörke, U.; Henkel, G.; Merz, K. *Adv. Synth. Catal.* **2006**, *348*, 456.

(11) We suppose that HCl (from the reaction of water with $FeCl_3$) might be the actual catalyst, therefore a control experiment was done but no reaction occurred in a model reaction between **1a** and 1-butanol in the presence of 10% HCl.

(12) (a) Preparation of propargylic acetates: Bartels, A.; Mahrwald, R.; Müller, K. *Adv. Synth. Catal.* **2004**, *346*, 483. (b) **Propargylic Ethers; Typical Procedure**
1,3-Diphenylprop-2-ynyl acetate (**1a**) (0.250 g, 1 mmol), *n*-BuOH (0.222 g, 3.0 mmol), MeCN (2 mL), and anhyd $FeCl_3$ (0.008 g, 0.05 mmol) were successively added to a 5-mL flask, and then the mixture was stirred magnetically at r.t. for 2.5 h. The solution was concentrated under reduced pressure by an aspirator and then the residue was purified by silica gel column chromatography to afford 3-butoxy-1,3-diphenylprop-1-yne (**2a**) as a clear colorless oil (0.243 g, 92%).
The ^1H NMR and ^{13}C NMR spectra of known compounds **2b**, **2d**, **2g**, **2h**, **2i**, **2k**,[6b] **2c**, **2e**, **2f**,[8a] **2j**,[14] **2l**,[4a] **2m**, **2o**, **2p**,[6c] and **2q**[5a] are in accordance with those previously reported.
Compound **2a**: Pale yellow oil. IR (film): 3063, 3032, 2229, 1597, 1493, 1452 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, 3 H, *J* = 7.2 Hz), 1.39–1.50 (m, 2 H), 1.62–1.71 (m, 2 H), 3.55–3.62 (m, 1 H), 3.72–3.80 (m, 1 H), 5.39 (s, 1 H), 7.24–7.63 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 19.8, 32.0, 68.3, 72.0, 87.1, 87.2, 122.3, 127.0, 127.8, 128.0, 128.1, 131.3, 138.5. Anal. Calcd for $C_{19}H_{20}O$ (264.36): C, 86.32; H, 7.63. Found: C, 86.03; H, 7.42.
Compound **2n**: Yellow oil. IR (film): 3387, 1598, 1510, 1452cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, 3 H, *J* = 7.2 Hz), 1.38–1.59 (m, 4 H), 2.27 (td, 2 H, *J* = 7.2, 2.0 Hz), 4.66–4.76 (br s, 1 H), 4.91 (s, 1 H), 6.72–6.77 (m, 2 H), 7.16–7.25 (m, 3 H), 7.29 (t, 2 H, *J* = 7.6 Hz), 7.32–7.37 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 18.7, 22.1, 31.1, 42.5, 80.8, 85.0, 115.3, 126.6, 127.8, 128.5, 129.1, 135.0, 142.8, 154.2. Anal. Calcd for $C_{19}H_{20}O$ (264.36): C, 86.32; H, 7.63. Found: C, 86.51; H, 7.35.

(13) In $TiCl_4$-catalyzed nucleophilic substitution of 1-phenylhept-2-ynyl acetate(**1b**) with phenol the ether was obtained in moderate yield, see: (a) Mahrwald, R.; Quint, S. *Tetrahedron* **2000**, *56*, 7463. (b) Bartels, A.; Mahrwald, R.; Quint, S. *Tetrahedron Lett.* **1999**, *40*, 5989.

(14) Henseling, K.-O. *Chem. Ber.* **1977**, *110*, 1027.