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Cascade Approach to Trichloroalkyl Phenyl Ethers from Benzyne, Epoxides, and Chloroform

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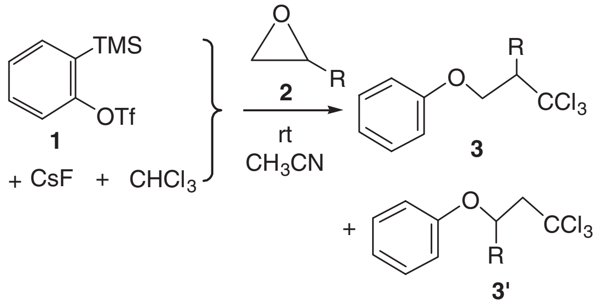
The reaction of *o*-(trimethylsilyl)phenyl triflate with CsF and propene oxide in the presence of chloroform gave an isomeric mixture of trichloroalkyl phenyl ethers in 72% yield. The reaction of 1,2-epoxy-5-hexene with benzyne afforded 1,2-epoxy-6-phenyl-3-hexene in 66% yield. Thus, single bond insertion of one of the C–O bonds of epoxides and ene reaction proceeded chemoselectively.

Arynes are very useful intermediates for their insertion ability to carbon–carbon and carbon–heteroatom double and single bonds.[1] Recently, many insertion reactions of benzyne with Sn–Sn, Sn–C, N–C, and C–C single bonds using *o*-(trimethylsilyl)phenyl triflate (**1**) as a benzyne precursor have been reported.[2] However, there are very few reports on the reaction of benzyne with epoxides **2**. Ghosh et al. reported the formation of *N*-(9-carbazoyl)-2-chloroaniline (1.3%) by the reaction of 2-carboxybenzene diazonium chloride with propene oxide (**2a**).[3] Nakayama et al. also reported the reaction of benzyne with 1,3-benzodithiole-2-thione in the presence of propene oxide (**2a**) to give tetracyclic sulfonium chloride.[4] While **2a** was only used as a proton trapping reagent in these reactions, one true example to react an epoxide with benzyne was reported by Peña et al.[5] Benzyne inserts into one of the C–O bonds of styrene oxide to form 2,3-dihydrobenzofuran (32%) as the major product together with five other reaction products. Very recently, palladium-catalyzed three component coupling reaction of allylic epoxides with benzyne was reported.[6] We have reported the reaction of benzyne prepared from benzenediazonium carboxylate with THF in the presence of chloroform, which produced novel phenyl ethers in moderate yields.[7] These results prompted us to investigate the reaction of benzyne with epoxides. Herein, we report a simple cascade approach for the synthesis of chlorinated alkyl phenyl ethers from benzyne, epoxides, and chloroform.

We first investigated the reaction of **2a** with benzyne. Treatment of **2a** with benzenediazonium carboxylate in refluxing chloroform resulted in the formation of biphenylene in 12% yield. No product relating to **2a** was obtained. However, when 10 equivalents of **2a** was treated with triflate **1**, CsF, and chloroform in CH_3CN at rt, an isomeric mixture of 3,3,3-trichloro-2-methylpropyl phenyl ether (**3a**) and 3,3,3-trichloro-1-methylpropyl phenyl ether (**3a′**) was obtained in 48 and 24% yields, respectively (Scheme 1). When tetrabutylammonium fluoride (TBAF) was used as a fluoride source, phenyl ethers **3a** and **3a′** were obtained in 2 and 1% yields, respectively.[8] In the absence of chloroform, phenyl ethers **3** or products relating **2a** were not obtained.



2a: R= Me
2b: R= Et
2c: R= *n*-Bu
2d: R= *n*-hexyl

3a: R= Me
3b: R= Et
3c: R= *n*-Bu
3d: R= *n*-hexyl

Scheme 1.

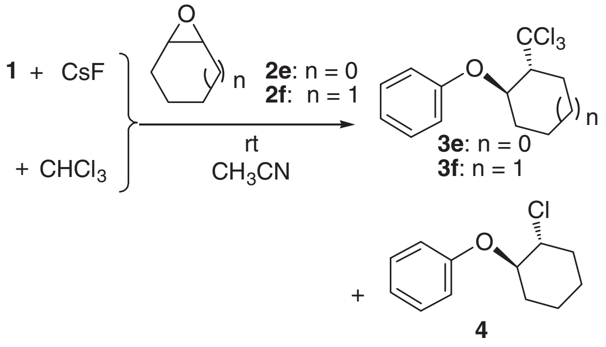
Table 1. Reaction of **2** with benzyne and $CHCl_3$

2	equiv	Time/h	Products **3**	(Yield/%) **3′**
2a	10	16	48	24
2a	5	24	43	21
2b	10	24	39	26
2c	10	16	37	25
2d	10	24	19	6

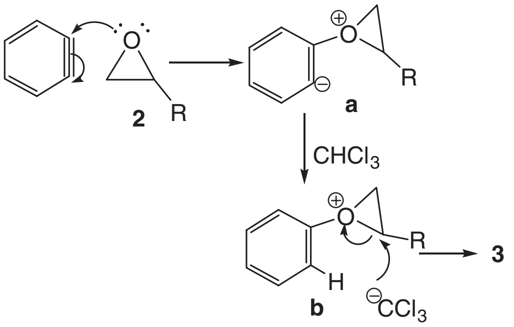
Since CsF was found to be a good fluoride source, we then investigated the other epoxides under these conditions. Treatment of 1,2-butene oxide (**2b**) (10 equiv) with triflate **1**, CsF, and chloroform at rt resulted in the formation of 2-(trichloromethyl)butyl phenyl ether (**3b**) and 3,3,3-trichloro-1-ethylpropyl phenyl ether (**3b′**) in 39 and 26% yields, respectively. Similarly, 1,2-hexene oxide (**2c**) or 1,2-octene oxide (**2d**) afforded **3c** and **3c′** in 37 and 25% yields, or **3d** and **3d′** in 19 and 6% yields, respectively (Table 1).

When cyclopentene oxide (**2e**) was allowed to react with triflate at rt in acetonitrile, *trans*-1-phenoxy-2-(trichloromethyl)cyclopentane (**3e**) was obtained in 32% yield (Scheme 2). Similarly, cyclohexene oxide (**2f**) was allowed to react with benzyne and chloroform to afford *trans*-1-phenoxy-2-(trichloromethyl)cyclohexane (**3f**) and *trans*-1-chloro-2-phenoxycyclohexane (**4**) in 28 and 6% yields, respectively. These results suggested that the intermediate for this reaction would be not carbocation but oxonium ion. Thus, tandem reaction of benzyne, epoxides **2**, and chloroform to give phenyl ethers **3** was achieved.

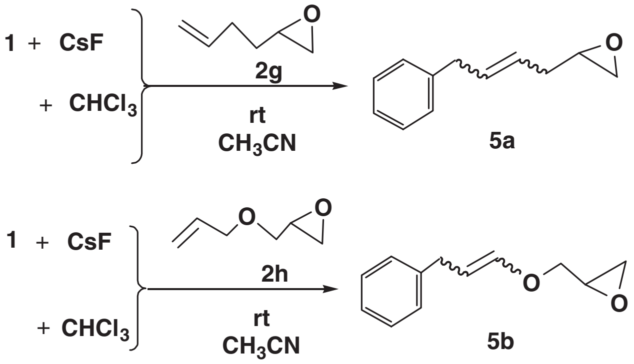
When deuteriochloroform was used instead of chloroform, ortho deuterated **3a** and **3a′** were obtained. Thus, the reaction might proceed as follows: Epoxide **2** reacts with benzyne to give the corresponding betaines **a**, which abstract a proton of chloroform to give oxonium ions **b**. Trichloromethyl anion attacks the α-carbon of oxygen to afford final ethers **3** (Scheme 3).



Scheme 2.



Scheme 3.



Scheme 4.

Interestingly, when 1,2-epoxy-5-hexene (**2g**) was used as a substrate, a mixture of (*E*)- and (*Z*)-1,2-epoxyy-6-phenyl-4-hexene (**5a**) was obtained in 68% yield (E:Z = 65:35). Similarly, allyl glycidyl ether (**2h**) reacted with triflate to give 3-phenylprop-1-enyl glycidyl ether (**5b**) in 65% yield (E:Z = 60:40), suggesting that the ene reaction proceeded predominantly (Scheme 4). Previously, many authors reported the ene reaction of benzyne with alkenes, however many gave [2 + 2] or [4 + 2] adducts as side products.[9] The present reaction provided ene reaction products exclusively.

Thus, a cascade approach to trichloroalkyl phenyl ethers from epoxides, benzyne, and chloroform was achieved. The presents result opened a door to the reaction of benzyne with epoxides.

References and Notes

1 a) H. Yoshida, M. Watanabe, H. Fukushima, J. Ohshita, A. Kunai, *Org. Lett.* **2004**, *6*, 4049. b) K. Okuma, K. Shiki, K. Shioji, *Chem. Lett.* **1998**, 79. c) K. Okuma, A. Okada, Y. Koga, Y. Yokomori, *J. Am. Chem. Soc.* **2001**, *123*, 7166; For a recent review: D. Peña, D. Pérez, E. Guitián, *Angew. Chem., Int. Ed.* **2006**, *45*, 3579.

2 a) H. Yoshida, Y. Honda, T. Hiyama, E. Shirakawa, *Chem. Commun.* **2001**, 1880. b) H. Yoshida, K. Tanino, J. Ohshita, A. Kunai, *Angew. Chem., Int. Ed.* **2004**, *43*, 5052. c) U. K. Tambar, B. M. Stoltz, *J. Am. Chem. Soc.* **2005**, *127*, 5340. d) W. Lin, I. Sapountzis, P. Knochel, *Angew. Chem., Int. Ed.* **2005**, *44*, 4258. e) H. Yoshida, M. Watanabe, T. Morishita, J. Ohshita, A. Kunai, *Chem. Commun.* **2007**, 1505. f) Y.-Y. Yang, W.-G. Shou, Y.-G. Wang, *Tetrahedron Lett.* **2007**, *48*, 8163. g) I. Larrosa, M. I. Da Silva, P. M. Gomez, P. Hannen, E. Ko, S. R. Lenger, S. R. Linke, A. J. P. White, D. Wilton, A. G. M. Barrett, *J. Am. Chem. Soc.* **2006**, *128*, 14042.

3 R. Ghosh, E. B. Sheinin, C. L. Bell, L. Bauer, *J. Heterocycl. Chem.* **1975**, *12*, 203.

4 J. Nakayama, A. Kimata, H. Taniguchi, F. Takahashi, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2349.

5 S. Beltrán-Rodil, D. Peña, E. Guitián, *Synlett* **2007**, 1308; also see: R. W. Hoffmann, *Dehydrobenzene and Cycloalynes*, Academic Press, New York, **1967**, p. 178.

6 M. Jeganmohan, S. Bhuvaneswari, C.-H. Cheng, *Angew. Chem., Int. Ed.* **2009**, *48*, 391.

7 K. Okuma, K. Fukuzaki, A. Nojima, K. Shioji, Y. Yokomori, *Tetrahedron Lett.* **2008**, *49*, 3063.

8 Typical reaction: To a dried mixture of triflate **1** (1.0 mmol) and CsF (3.0 mmol) was added a solution of propene oxide (**2a**) (10 mmol) and chloroform (10 mmol) in acetonitrile (3.0 mL). After stirring for 16 h at rt, the reaction mixture was evaporated and added water (15 mL). The reaction mixture was extracted with ether (5 mL × 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to give a pale brown oil, which was chromatographed over silica gel by elution with hexane:ethyl acetate (5:1) to give phenyl ether **3a** (0.48 mmol) and **3a′** (0.24 mmol). Compound **3a**: colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.53 (d, 3H, $J = 5.6$ Hz, CH_3), 3.06 (m, 1H, CH), 3.94 (dd, 1H, $J = 9.2$ and 8.8 Hz, OCHH), 4.58 (dd, 1H, $J = 9.2$ and 3.2 Hz, OCHH), 6.85–6.99 (m, 3H, Ph), 7.30 (t, 2H, $J = 7.6$ Hz, Ph). ^{13}C NMR ($CDCl_3$): δ 15.33 (CH_3), 54.50 (CH), 69.39 (OCH_2), 103.20 (CCl_3), 114.85, 121.48, 129.81, 158.56 (Ph). HRMS: (m/z): Calcd for $C_{10}H_{11}Cl_3O$; 251.9875. Found 251.9867 (M^+). Compound **3a′**: colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.46 (d, 3H, $J = 5.6$ Hz, CH_3), 2.93 (dd, 1H, $J = 15.2$ and 3.6 Hz, CHH), 3.30 (dd, 1H, $J = 15.2$ and 6.0 Hz, CHH), 4.80 (m, 1H, OCH), 6.88–7.02 (m, 3H, Ph), 7.32 (dd, 2H, $J = 8.0$ and 7.6 Hz, Ph). ^{13}C NMR ($CDCl_3$): δ 20.87 (CH_3), 60.95 (CH_2), 71.78 (OCH), 97.60 (CCl_3), 116.32, 121.53, 129.84, 157.35 (Ph). HRMS: (m/z): Calcd for $C_{10}H_{11}Cl_3O$; 251.9875. Found 251.9840 (M^+).

9 a) G. Friedrichs, E. Goos, J. Gripp, H. Nicken, J.-B. Schonborn, H. Vogel, F. Temps, *Z. Phys. Chem.* **2009**, *223*, 387. b) L. Lombardo, D. Wege, *Tetrahedron* **1974**, *30*, 3945.