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Novel tandem reaction of benzyne with cyclic ethers and active methines: synthesis of ω-trichloroalkyl phenyl ethers

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Abstract

The reaction of benzenediazonium carboxylate with chloroform in refluxing tetrahydrofuran afforded 5,5,5-trichloropentyl phenyl ether in 61% yield along with benzoic acid (7%). When dichloroacetonitrile was used as a reactant, 5,5-dichloro-5-cyanopentyl phenyl ether was obtained in 65% yield. Reactive benzyne derived from diazonium carboxylate initially reacted with THF to give a dipole intermediate, which further reacted with chloroform or dichloroacetonitrile to give ring opened products.

1. Introduction

Arynes are widely used as reactive intermediates and react with many dienes to afford corresponding cycloadducts.[1] Recent reports on the formation of arynes illustrate the continued interest in this area.[2] Recently, many insertion reaction of benzyne with single bonds containing Sn–Sn, Sn–C, N–C, C–C using *o*-trimethylsilylphenyl triflate (**1**) as a benzyne precursor has been reported.[3] Due to our ongoing interest in the exploration of reactive benzyne for the synthesis of functionalized S-heterocycles, we have also investigated the synthesis of benzothietes, benzothianes, and 1,3-benzodithioles by using **1**, benzenediazonium carboxylate (**2**), or phenyl[*o*-trimethylsilylphenyl]iodonium triflate as benzyne precursors.[4,5] Although the insertion reaction of benzyne with THF and water was reported to produce δ-phenoxybutyl-*N*-phenylanthranilic acid (17%), and 1,4-diphenoxybutane (4%) by Wolthuis et al.,[6] another type of insertion reaction of arynes with styrene oxide was recently reported.[7] These results prompted us to investigate further precise reaction of benzyne with cyclic ethers. In this Letter, we would like to describe novel tandem reaction of benzyne with cyclic ethers and active methines.

Birkett et al. reported the formation of ω-iodoalkyl *o*-iodophenyl ethers by tandem reaction of benzyne with cyclic ethers and *N*-iodosuccinimide, while the yields were only 24–35%.[8] If more reactive nucleophile is formed in the reaction, yields of tandem reaction products will be improved. To confirm this possibility, we first tried the reaction of benzyne with THF in refluxing chloroform. The treatment of isolated benzenediazonium carboxylate **2**, prepared from anthranilic acid and isoamyl nitrite, with 3 equiv of THF in refluxing chloroform resulted in the formation of 5,5,5-trichloropentyl phenyl ether (**3a**) and benzoic acid (**4**) in 21% and 11% yields, respectively. When a mixture of **2** and chloroform (5 equiv) was refluxed in THF, **3a** was obtained in 52% yield along with **4** (8%) (Scheme 1). To optimize this novel tandem reaction, we varied the reaction conditions, including benzyne precursor, temperature, and equivalent of chloroform. The results are shown in Table 1.

When 20 equiv of chloroform was used in refluxing THF, 5,5,5-trichloropentyl phenyl ether **3a** was obtained in 61% yield along with acid **4** (8%) (entry 1), whereas the reaction of 3 equiv of chloroform with **2** gave **3a** in 42% yield (entry 2). When in situ formed benzenediazonium carboxylate was

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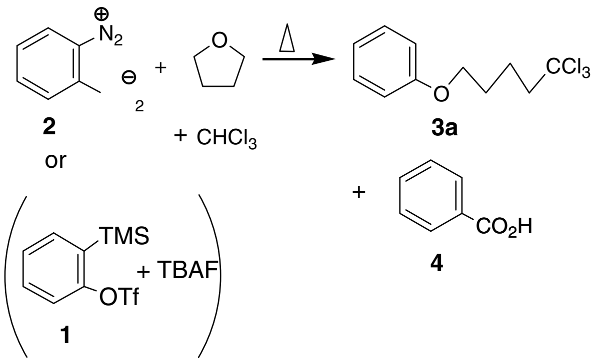


Scheme 1.

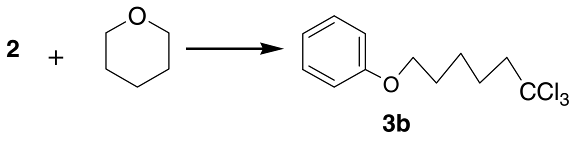
Table 1
Reaction of benzyne with THF followed by the addition of chloroform

Entry	Precursor	Chloroform (equiv)	Temperature	Time (h)	Products	
					3a	**4**
1	**2**	20	Reflux	2	61	8
2	**2**	3	Reflux	3	42	10
3	**2**	1	Reflux	3	18	13
4	**2**[a]	5	Reflux	3	8	15
5	**1**	5	rt	12	—	—
6	*o*-Carboxybenzene-diazonium chloride	5	Reflux	12	—	38

[a] Benzenediazonium carboxylate **2** was used without isolation.

reacted with chloroform in refluxing THF, **3a** was obtained in only 8% yield (entry 4). By using *o*-trimethylsilylphenyl triflate **1** as a benzyne precursor, unidentified complex mixture was produced (entry 5). Additionally, when *o*-carboxybenzenediazonium chloride was used as a benzyne precursor, ether **3a** was not obtained (entry 6). Thus, isolation of **2** must be required for the completion of the reaction.

The reaction of **2** with chloroform in tetrahydropyran (THP) gave 6,6,6-trichlorohexyl phenyl ether (**3b**) in 40% yield (Scheme 2). Fortunately, single crystals were obtained, thus the structure of **3b** was confirmed by X-ray crystallographic analysis[9] (Fig. 1).



Scheme 2.

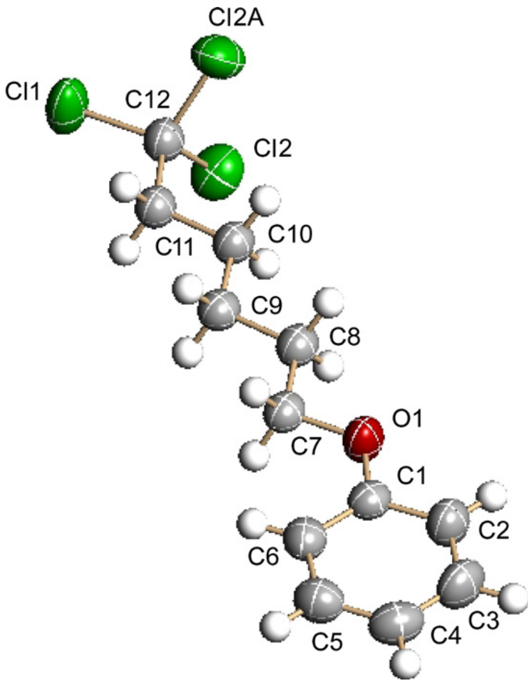
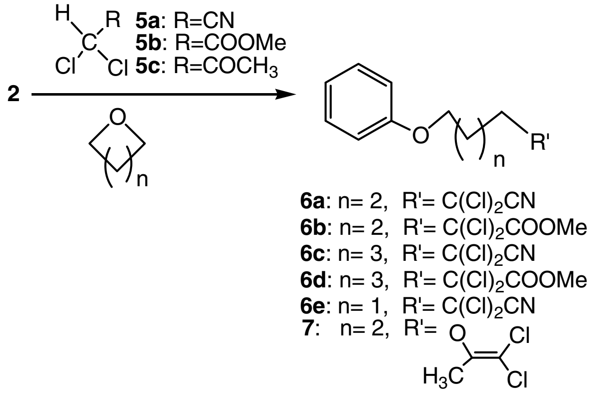


Fig. 1. Ortep drawing of 6,6,6-trichlorohexyl phenyl ether **3b**. Selected bond lengths: C(1)–O(1) 1.364(4), C(7)–(1) 1.441, C(10)–C(11) 1.515(4). Bond angles: C(1)–O(1)–C(7) 119.0(3), C(11)–C(12)–Cl(1) 110.1(2).

To investigate the scope and limitation of this novel tandem reaction, we then tried the reaction of benzyne with other active methylenes and methines. Unfortunately, active methylenes such as dichloromethane, malononitrile, and methyl acetoacetate did not afford the corresponding tandem reaction products. Then **2** was added to a refluxing solution of dichloroacetonitrile **5a** (5 equiv) in THF, the corresponding ether (**6a**) was obtained in 65% yield along with benzoic acid (8%). Similarly, methyl dichloroacetate (**5b**) gave **6b** in 34% yield. Interestingly, when **2** was added to a refluxing solution of dichloroacetone (**5c**) (3 equiv) in THF, the corresponding O-attacked ether (**7**) was obtained in 27% yield (Scheme 3). The results are shown in Table 2.

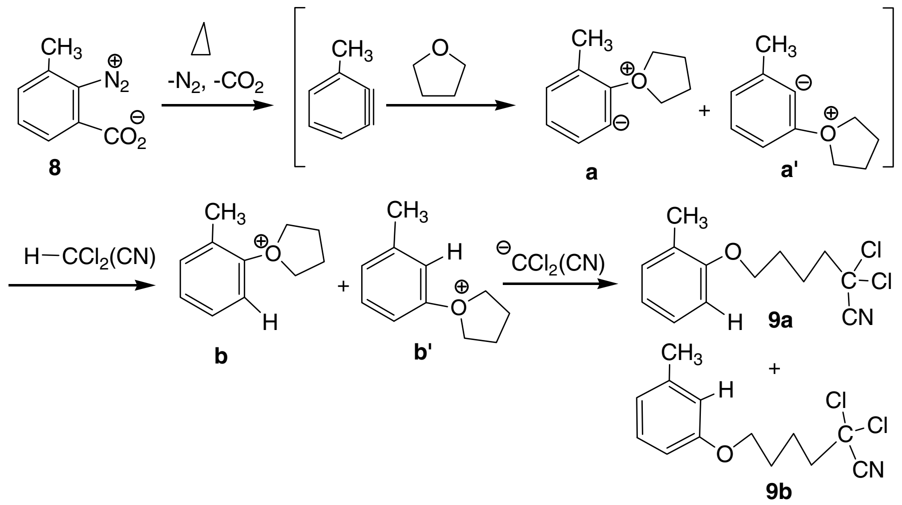


Scheme 3.

Table 2
Reaction of 2 with active methines in refluxing cyclic ether[a]

Substrate **5**	Cyclic ether	Time (h)	Product	Yield (%)
5a	THF	5	**6a**	65
5a	THP	3	**6c**	52
5a	Oxetane	6	**6e**	48
5b	THF	5	**6b**	34
5b	THP	5	**6d**	28
5c	THF	5	**7**	27

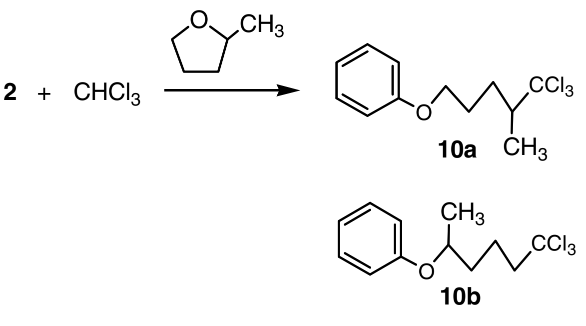
[a] Conditions: 1 mmol of **2**, 5 mmol of **5**, and 10 mmol of cyclic ether were used.



Scheme 4.

When 6-methylbenzenediazonium 2-carboxylate (**8**) was treated with dichloroacetonitrile, 5,5-dichloro-5-cyanopentyl *o*-methylphenyl ether (**9a**) and 5,5,5-trichloropentyl *m*-methylphenyl ether (**9b**) were obtained in 25% and 17% yields, respectively. Thus, the reaction might proceed as follows. Carboxylate **5** initially extruded nitrogen and carbon dioxide to afford benzyne, which reacted with THF to give THF-stabilized dipole intermediates (**a** and **a**′). These dipoles abstracted the hydrogen of dichloroacetonitrile to afford oxonium ions (**b** and **b**′) and dichlorocyanomethyl anion. When cations **b** and **b**′ were finally attacked by methyl anion, the corresponding ethers **9a** and **9b** were formed (Scheme 4). The reason that complex mixture was obtained by using **1** as a benzyne precursor might be the existence of ammonium salt, which prevented the formation of oxonium ion intermediate **b**.

Since Birkett et al. denied the existence of initially formed dipole intermediate **a** in the reaction of benzyne prepared from 1-aminobenzotriazole with *N*-iodosuccinimide in THF,[8] reaction of benzyne with THF (5 equiv) was carried out in refluxing $CDCl_3$. The corresponding *o*-deuterated 5,5,5-trichloropentyl phenyl ether (95% deuterated) was obtained in 32% yield, which clearly showed the hydrogen abstraction of chloroform by intermediate **a**. Interestingly, when carboxylate **2** was treated with chloroform in refluxing 2-methyltetrahydrofuran (10 equiv), two isomers (**10a**,**b**) were obtained in 51% yield (**10a**:**10b** = 2:5), suggesting that trichloromethyl carbanion attacked to the less bulky carbon (Scheme 5).



Scheme 5.

Thus, this method provides a new route to ω-chlorinated alkyl phenyl ethers. The extension of this novel tandem reaction and the application of the ω-chlorinated ethers are in progress.

2. Typical experiment

2.1. Reaction of benzenediazonium carboxylate with chloroform in THF

A mixture of benzenediazonium carboxylate **2** (1 mmol), chloroform (20 mmol), molecular sieves 3 Å (0.2 g) in THF (3 mL) was stirred for 2 h then refluxed for 1 h. The reaction mixture was evaporated to give a brown oil, which was chromatographed over silica gel by elution with hexane:ethyl acetate (10:1) to give 5,5,5-trichloropentyl phenyl ether **3a** (0.61 mmol) and benzoic acid (0.08 mmol). Compound **3a**: colorless oil ^{1}H NMR ($CDCl_3$) δ 1.84–2.10 (m, 4H, CH_2), 2.77 (dd, 2H, $J = 7.0$ Hz and 7.2 Hz, CH_2), 4.01 (t, 2H, $J = 5.6$ Hz, OCH_2), 6.90 (d, 2H, $J = 8.0$ Hz, *o*-Ph), 6.95 (t, 1H, $J = 7.2$ Hz, *p*-Ph), 7.24–7.32 (m, 2H, *m*-Ph). ^{13}C NMR ($CDCl_3$) δ 24.05 (CH_2), 28.65 (CH_2), 55.37 (CH_2), 67.64 (OCH_2), 100.28 (q-C), 114.84 (Ph), 121.10 (Ph), 129.76 (Ph), 159.02 (Ph).

X-ray crystallographic data for **3b**: crystal data for $C_{12}H_{15}Cl_3O$. Mp 50–51 °C. crystallized from dichloromethane–hexane. FW 281.59, Monoclinic, space group = $C2/m$, $a = 21.1430(8)$ Å, $b = 7.3410(3)$, $c = 8.8680(3)$ Å, $\alpha = 90.00°$, $\beta = 98.181(3)°$, $\gamma = 90.00°$, $V = 1362.40(9)$ Å^3, $Z = 4$, $D_x = 1.373$ Mg m^{-3}, the final R and wR were 0.0867 and 0.2006, respectively, using 1316 reflections.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.058.

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