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A Domino Process for Benzyne Preparation: Dual Activation of *o*-(Trimethylsilyl)phenols by Nonafluorobutanesulfonyl Fluoride

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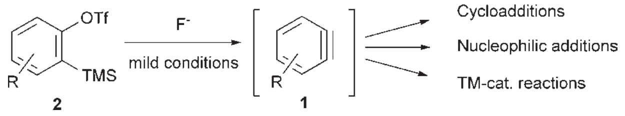
ABSTRACT

Benzynes were generated from *o*-(trimethylsilyl)phenols using nonafluorobutanesulfonyl fluoride (NfF) by a domino process, i.e., the nonaflation of the phenolic hydroxyl group of *o*-(trimethylsilyl)phenols by NfF followed by the attack of the produced fluoride ion on the trimethylsilyl group. The generated benzyne immediately underwent various reactions to give polysubstituted benzenes.

Benzynes **1** are one of the most valuable reaction intermediates for constructing polysubstituted aromatic compounds through cycloaddition, nucleophilic addition, and transition-metal (TM)-catalyzed reactions.[1] Various precursors have already been reported, and each of them is converted into **1** under different conditions.[2] Among them, the *o*-(trimethylsilyl)aryl triflates **2** are recently the most widely used benzyne precursors because of the easy preparation of **2** from phenol derivatives and the very mild reaction conditions for the generation of **1** (Scheme 1).[3]

Scheme 1. *o*-(Trimethylsilyl)aryl Triflates **2** As Useful Benzyne Precursors



Although the emergence of **2** has led to the development of various new benzyne reactions,[4] the use of unstable and/or expensive triflating reagents, such as triflic anhydride (Tf_2O), $PhNTf_2$, and Comins' reagent, for the synthesis of **2** has remained a critical issue.[5,6] The low hydrolytic

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(1) For recent reviews, see: (a) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701–730. (b) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502–528. (c) Dyke, A.; Hester, A.; Lloyd-Jones, G. *Synthesis* **2006**, 4093–4112. (d) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 215–291. (e) Yoshida, H.; Ohshita, J.; Kunai, A. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 199–219.

(2) (a) Kitamura, T.; Yamabe, M.; Inoue, K.; Todaka, M.; Fukatsu, N.; Meng, Z.; Fujiwara, Y. *J. Am. Chem. Soc.* **1999**, *121*, 11674–11679. (b) Kitamura, T. *Aust. J. Chem.* **2010**, *63*, 987–1001.

(3) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211–1214.

(4) For recent examples, see: (a) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558–1559. (b) Tadross, P. M.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1612–1614. (c) Morishita, T.; Yoshida, H.; Ohshita, J. *Chem. Commun.* **2010**, *46*, 640–642. (d) Yoshida, H.; Okada, K.; Kawashima, S.; Tanino, K.; Ohshita, J. *Chem. Commun.* **2010**, *46*, 1763–1765.

(5) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299–6302.

(6) Comins' reagent[5] and $PhNTf_2$ have been used as alternatives to Tf_2O for the substrates having labile functional groups; however, they are much more expensive and have a lower atom economy than NfF. For the synthesis of Tf_2O and $ArNTf_2$, see: JP Pat., 119355, 2007.

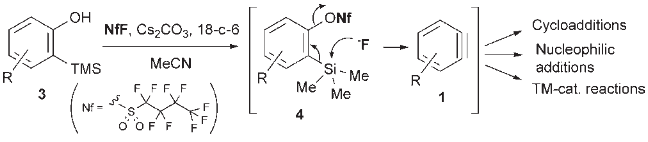
$$4\,CH_3SO_2Cl \xrightarrow{NaF} 4\,CH_3SO_2F \xrightarrow[\text{HF (excess)}]{\text{electrolysis}} 4\,CF_3SO_2F\ (TfF)$$

$$\xrightarrow{KOH} 4\,TfOH \xrightarrow{P_2O_5} 2\,Tf_2O \xrightarrow{ArNH_2} ArNTf_2$$

10.1021/ol200252c

stability of aryl triflates also sometimes causes crucial problems during their chemical transformations.[7] Therefore, an alternative method for the generation of **1** under mild conditions has been necessary for the further development of the benzyne chemistry. In this communication, we describe a novel preparation of benzynes **1** from *o*-(trimethylsilyl)phenols **3** by the domino process using nonafluorobutanesulfonyl fluoride (NfF) (Scheme 2).

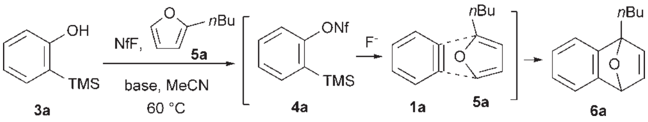
Scheme 2. *o*-(Trimethylsilyl)phenols **3** As New, Easy-to-Handle Benzyne Precursors



We anticipated that the use of perfluoroalkanesulfonyl fluorides, instead of the above-mentioned triflating reagents, would be more beneficial because they could directly generate the benzynes from more primitive and easy-to-handle *o*-(trimethylsilyl)phenols **3** via the nonaflation of the hydroxyl group of **3** followed by the immediate desilylation by the produced fluoride ion. This method does not need the isolation of the unstable intermediates, the *o*-(trimethylsilyl)aryl perfluoroalkanesulfonates, and is therefore much more convenient and useful compared to the known method shown in Scheme 1. It is also attractive from the viewpoint of atom economy because both components, the perfluoroalkanesulfonyl and fluoride moieties, are effectively utilizable. Among a variety of the perfluoroalkanesulfonyl fluorides, we chose NfF,[8,9] which is an air stable and less expensive reagent and has been used for the synthesis of the C4 homologues of the triflates.[10]

First, we examined the feasibility of this domino process using *o*-(trimethylsilyl)phenol **3a** as a test substrate. Thus, **3a** was reacted with NfF (4.0 equiv) at 60 °C in the presence of a base and 2-butylfuran **5a** (10 equiv) to trap the generated benzyne **1a** as the Diels–Alder adduct **6a** (Table 1). The use of NaH as a base for 4.5 h only gave the nonaflate **4a** (entry 1), which showed that the in situ benzyne generation was not easy.[11] On the other hand, the use of K_2CO_3 produced a small amount of the desired **6a** (entry 2, **4a**:**6a** = 70:30). After extensive optimization of the reaction conditions, Cs_2CO_3 was found to enhance the desilylation to give a better ratio of **6a** to **4a** (entry 3).

Table 1. Optimization of Reaction Conditions of Domino Nonaflation, Benzyne Generation, and Diels–Alder Reaction[a]



entry	base	(equiv)	additive	(equiv)	**4a**:**6a**[b]
1	NaH	(3.0)	-	-	100:0
2	K_2CO_3	(3.0)	-	-	70:30
3	Cs_2CO_3	(3.0)	-	-	30:70
4	Cs_2CO_3	(1.5)[c]	18-c-6	(0.6)	0:100[d]

[a] Conditions: With 1.0 equiv of **3a**, 4.0 equiv of NfF, and 10 equiv of **5a** in MeCN (0.10 M). **3a** was completely consumed in every case. [b] Determined by ^1H NMR. [c] With 1.5 equiv of NfF and 3.0 equiv of **5a**. [d] 86% isolated.

Finally, we were delighted to find that the reaction of **3a** with NfF (1.5 equiv), Cs_2CO_3 (1.5 equiv), and 18-crown-6 (18-c-6) (0.6 equiv) in MeCN[12] achieved the complete conversion of **4a** into **6a** (86% isolated yield) (entry 4). As a control experiment, the isolated **4a** was treated with $CsHCO_3$ (1.0 equiv), Cs_2CO_3 (0.5 equiv), and 18-c-6 (0.6 equiv) in MeCN at 60 °C for 7.5 h to provide **6a** in 45% yield. These reaction conditions corresponded to those after the nonaflation, except for the presence of the fluoride ion. This result suggests that the combination of Cs_2CO_3 and 18-c-6 may have played a role in the generation of **1a** from **3a**. More importantly, this result also reveals that the fluoride ion liberated from NfF plays a crucial role in the prompt and complete generation of the benzyne (for details, see Supporting Information).

We then applied our optimized conditions in Table 1 to the reactions of the precursors **3b**–**g** (Table 2). Our experience and literature search[13] have shown that the triflation of electron-rich substrates causes some problems. For instance, the triflation of **3b** with Tf_2O and Cs_2CO_3 mainly resulted in the formation of the desilylated product, 3,4-dimethoxyphenol (61%),[14] while the reaction of **3b** with NfF, Cs_2CO_3, 18-c-6, and **5a** gave the Diels–Alder product **6b** in 86% isolated yield (entry 1). A similar product **6c** was also obtained from **3c** (entry 2). Our method was similarly applicable to other precursors (**3d** and **3e**) possessing electron-withdrawing group(s) and provided adducts (**6d** and **6e**) in good yields (entries 3 and 4). It is worth noting that the TBDMS group of

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(7) Choy, P. Y.; Chow, W. K.; So, C. M.; Lau, C. P.; Kwong, F. Y. *Chem.—Eur. J.* **2010**, *16*, 9982–9985.

(8) NfF is less expensive than any of the common triflating reagents because it can be easily generated. For the synthesis of NfF, see: Zimmer, R.; Webel, M.; Reissig, H.-U. *J. Prakt. Chem.* **1998**, *340*, 274–277.

(9) Trifluoromethanesulfonyl fluoride (TfF) is another candidate of the dual activation reagent; however, it requires special care due to its low boiling point (−22 °C).

(10) For a recent review, see: Högermeier, J.; Reissig, H.-U. *Adv. Synth. Catal.* **2009**, *351*, 2747–2763.

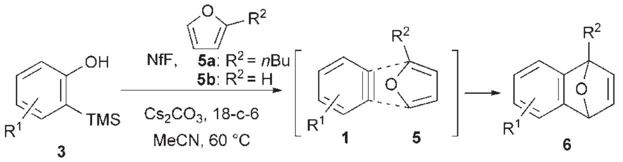
(11) The use of nonaflates **4** as benzyne precursors has never been reported.

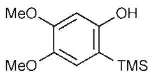
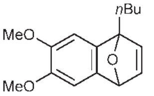
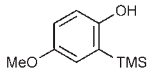
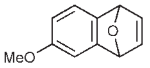
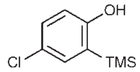
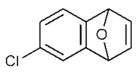
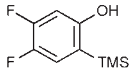
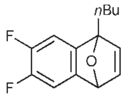
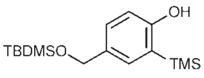
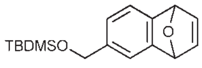
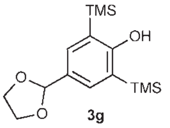
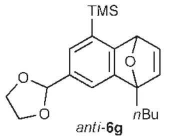
(12) For an example of the activation of CsF with 18-c-6 and MeCN, see: Nishikawa, T.; Shibuya, S.; Isobe, M. *Synlett* **1994**, 482–484. For the complexation of CsF with 18-c-6, see: Takeda, Y.; Kawarabayashi, A.; Endo, K.; Yahata, T.; Kudo, Y.; Katsuta, S. *Anal. Sci.* **1998**, *14*, 215–223.

(13) Tadross, P. M.; Gilmore, C. D.; Bugga, P.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1224–1227.

(14) The use of *n*BuLi as a base would be a solution; however, careful control of the reaction temperature at −100 °C was essential, and such harsh reaction conditions hamper their application to functionalized compounds; see: Peña, D.; Cobas, A.; Pérez, D.; Guitián, E. *Synthesis* **2002**, 1454–1458.

Table 2. Generation of Functionalized Benzynes **1** and Their Diels–Alder Reactions with Furans **5**[a]



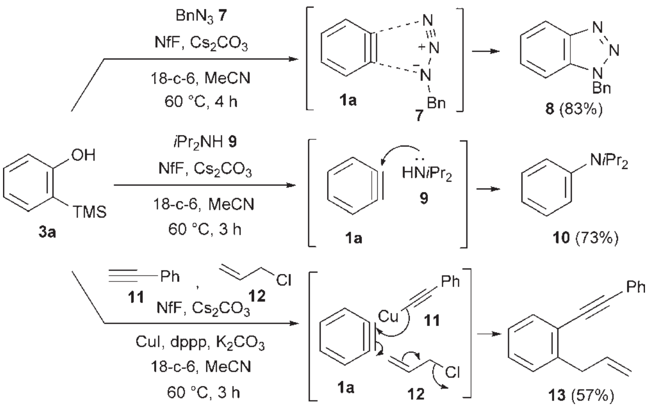
entry	substrate **3**	time (h)	product **6**	yield (%)
1	 **3b**	29	 **6b**	86[b]
2[c]	 **3c**	29	 **6c**	81
3[c]	 **3d**	29	 **6d**	81
4	 **3e**	3.5	 **6e**	72
5	 **3f**	12	 **6f**	86
6	 **3g**	11	 *anti*-**6g** *anti*-**6g**:*syn*-**6g** = 73:27	92[d]

[a] Unless otherwise specified, all reactions were carried out using **3** (1.0 equiv), **5** (3.0 equiv), NfF (1.5 equiv), Cs_2CO_3 (1.5 equiv), and 18-c-6 (0.6 equiv) in MeCN (0.10 M) at 60 °C. [b] Isolated as 4-butyl-6,7-dimethoxynaphthalen-1-ol **6b′** [c] With 18-c-6 (1.0 equiv). [d] With NaH (3.0 equiv), NfF (3.0 equiv), and Cs_2CO_3 (3.0 equiv).

Diels–Alder product **6f**, obtained from **3f** and **5b**, has not been deprotected although the fluoride ion should be produced by the nonaflation of **3f** (entry 5). On the other hand, the reaction of **6f** with CsF (1.0 equiv) and 18-c-6 (0.6 equiv) in MeCN at 50 °C for 2.5 h resulted in complete desilylation to give the corresponding alcohol (for details, see Supporting Information). These contrasting results suggest that, in the reaction of **3** and NfF, the fluoride ion generated from NfF was preferentially utilized for benzyne generation. This is the first time that the benzyne with a silyl protecting group has been prepared using a fluoride ion. Moreover, 5-(1,3-dioxolan-2-yl)-3-(trimethylsilyl)benzyne **1g**[15] was generated from **3g** to give the Diels–Alder adducts (*anti*- and *syn*-**6g**) (entry 6), which indicated that the acid labile cyclic acetal group was tolerant under the stated reaction conditions.[16]

This domino process was successfully applied to the [3 + 2] dipolar cycloaddition with an azide **7**[17] under the same reaction conditions. The nucleophilic addition reaction of diisopropylamine **9**[18] to **1a** took place with a minor alteration of the addition procedure.[19] Our benzyne generation was also availabe for the copper-catalyzed three-component coupling reaction.[20] Thus, in the presence of the acetylene **11**, allyl chloride **12**, dppp, and K_2CO_3, **1a** was generated by the NfF treatment and directly gave the disubstituted benzene **13** in 57% yield, in which four different reactions successively proceeded in a single pot (Scheme 3).

Scheme 3. Application of **1a** Generated from **3a** Using NfF



Next, the one-pot benzyne preparation from 2-bromophenol **14** has been accomplished (Scheme 4). The treatment of **14** with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) gave the TMS ether **15**. Without isolation of **15**, the halogen-lithium exchange reaction by *n*BuLi followed by the *retro*-Brook rearrangement formed lithium *o*-(trimethylsilyl)-phenolate **16**. The furan **5a**, Cs_2CO_3, 18-c-6, and NfF were then added to the reaction mixture to successively undergo the nonaflation, benzyne generation, and Diels–Alder reaction to produce **6a** in a 43% overall yield from **14**.

Finally, we examined the reactivity and stability differences between the triflate **2a** and the nonaflate **4a** (Table 3). In the presence of 2-butylfuran **5a** (3.0 equiv), the reaction of **2a** or **4a** with CsF (2.5 equiv) in MeCN at room temperature for 8.5 h gave **6a** along with the recovery of **2a** or **4a**. The fact that **4a** gave a slightly higher yield of **6a**

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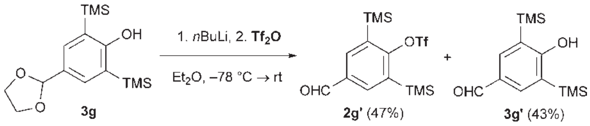
[15] Akai, S.; Ikawa, T.; Takayanagi, S.; Morikawa, Y.; Mohri, S.; Tsubakiyama, M.; Egi, M.; Wada, Y.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 7673–7676.

[16] The triflation of **3g** using Tf_2O and *n*BuLi predominantly gave the deacetalized products (**2g′** and **3g′**).



[17] Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409–2412.

[18] Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198–3209.

[19] 18-c-6 was added after the consumption of **3a**.

[20] Xie, C.; Liu, L.; Zhang, Y.; Xu, P. *Org. Lett.* **2008**, *10*, 2393–2396.

Scheme 4. One-Pot Benzyne Preparation from *o*-Bromophenol **14** and Its Diels−Alder Reaction

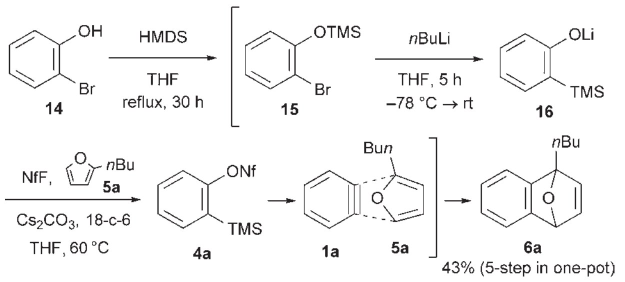
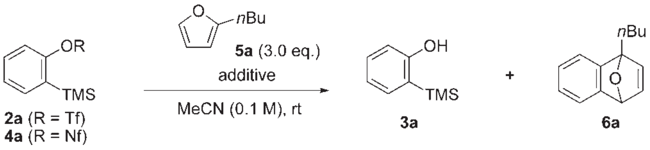


Table 3. Reactivity and Stability Difference between Precursors (**2a** and **4a**)



entry	R	additive (equiv)	time (h)	yield (%)[a]		
				2a or **4a**	**3a**	**6a**
1	Tf (**2a**)	CsF (2.5)	8.5	14	0	80
2	Nf (**4a**)	CsF (2.5)	8.5	7	0	84
3	Tf (**2a**)	NaOH (1.0)	5.0	0	84	1
4	Nf (**4a**)	NaOH (1.0)	5.0	69	25	4

[a] Determined by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard.

(84%) with its recovery in a lower yield (7%) (entry 2) than **2a** (**6a**, 80% yield and recovered **2a**, 14% yield) (entry 1) means that **4a** exhibits slightly higher reactivity than **2a** for benzyne generation.[21] Additionally, it was revealed that **4a** was much more stable than **2a** against alkaline hydrolysis using NaOH (1.0 equiv) in MeCN because **2a** was completely hydrolyzed (entry 3) while 69% of **4a** was recovered (entry 4).

In conclusion, we have developed a domino process for benzyne preparation from *o*-(trimethylsilyl)phenols **3** using NfF, which is one of the most stable and least expensive perfluoroalkanesulfonylating reagents.[10] The single reagent, NfF, promotes benzyne generation through two successive steps: the activation of the phenolic hydroxyl group of **3** by the formation of the nonaflate and the elimination of the trimethylsilyl group of **3** via nucleophilic attack by its fluoride moiety. Acid and/or fluoride ion labile functional groups, such as a cyclic acetal and an *O*-TBDMS group, were compatible under the developed conditions.

Acknowledgment. We are grateful to KAKENHI (No. 19890182) and a Grant-in-Aid for the Global COE Program from MEXT. Prof. Dr. Philip Hawke is acknowledged for assistance in preparation of this manuscript.

Supporting Information Available. Experimental procedures for the benzyne preparation and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[21] Bříza, T.; Král, V.; Martásek, P.; Kaplánek, R. *J. Fluorine Chem.* **2008**, *129*, 235–247.