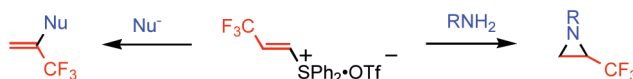


Preparation and Reactions of
(β -Trifluoromethyl)vinyl Sulfonium SaltRyoko Maeda, Kyoko Ooyama, Ryoko Anno, Masahiro Shiosaki, Takayuki Azema,
and Takeshi Hanamoto*Department of Chemistry and Applied Chemistry, Saga University, Honjyo-machi 1,
Saga 840-8502, Japan

hanamoto@cc.saga-u.ac.jp

Received April 2, 2010

ABSTRACT



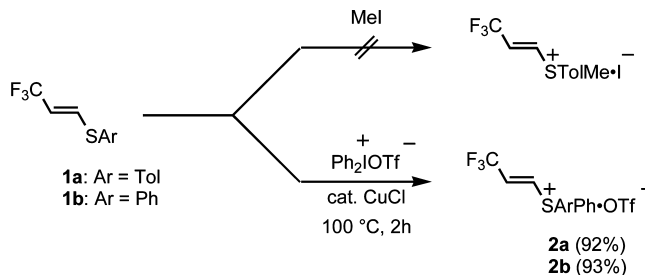
(β -Trifluoromethyl)vinyl sulfonium salt as a novel three-carbon fluorinated building block was conveniently prepared from easily available (β -trifluoromethyl)vinyl sulfide and diphenyl iodonium salt in excellent yield. This easily handled crystalline reagent displayed two types of useful transformation involving aziridination and vinylation to afford the corresponding trifluoromethylated compounds in excellent yields.

Vinyl sulfonium salts¹ and vinyl phosphonium salts² are conventional yet very useful synthetic intermediates for the preparation of functionalized complex molecules. They are well-recognized to behave as good Michael acceptors, mainly providing the corresponding reactive ylides. One of the potential advantages of these reagents should stem from findings that three-component coupling reactions have also been performed. For instance, Aggarwal and co-workers recently reported the synthesis of nitrogen-containing heterocycles using vinyl sulfonium salts.³ However, the expansion of fluorinated vinyl sulfonium and phosphonium salts has received less attention so far. We have been working on the development of versatile fluorine-containing building blocks prepared from easily available fluorinated molecules.⁴ These reports inspired us to investigate an efficient prepara-

tion and useful synthetic applications of the corresponding fluorinated vinyl sulfonium salts. In fact, working with our previous findings containing the preparation of α -fluorovinyl phosphonium salts⁵ and (β -trifluoromethyl)vinyl sulfides^{4b} should allow us to achieve this fascinating task. Herein, we disclose our preliminary results on the first preparation of (β -trifluoromethyl)vinyl sulfonium salt and the facile synthesis of (α -trifluoromethyl)aziridines, *N*-[(α -trifluoromethyl)vinyl]phthalimide, and (α -trifluoromethyl)vinylphosphonate in high yields under mild conditions.

Our simple route for the preparation of (β -trifluoromethyl)vinyl sulfonium salts is illustrated in Scheme 1. First, we confirmed that no quaternization of the sulfide **1a** and

Scheme 1. Preparation of (β -Trifluoromethyl)vinyl Sulfonium Salt



(1) (a) Yamanaka, H.; Matsuo, J.; Kawana, A.; Mukaiyama, T. *Arkivoc* **2004**, 42. (b) Kim, K.; Jimenez, L. S. *Tetrahedron: Asymmetry* **2001**, 12, 999. (c) Wang, Y.; Zhang, W.; Colandrea, V. J.; Jimenez, L. S. *Tetrahedron* **1999**, 55, 10659.

(2) (a) Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2000**, 122, 2387. (b) Hinkel, R. J.; Stang, P. J.; Kowalski, M. H. *J. Org. Chem.* **1990**, 55, 5033. (c) Zbiral, E. *Synthesis* **1974**, 775–797. (d) Schweizer, E. E.; Bach, R. D. *J. Org. Chem.* **1964**, 29, 1746.

(3) (a) Kokotos, C. G.; McGarrigle, E. M.; Aggarwal, V. K. *Synlett* **2008**, 2191. (b) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2008**, 47, 3784. (c) Unthank, M. G.; Hussain, N.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2006**, 45, 7066.

(4) (a) Hanamoto, T.; Yamada, K. *J. Org. Chem.* **2009**, 74, 7559. (b) Hanamoto, T.; Anno, R.; Yamada, K.; Ryu, K.; Maeda, R.; Aoi, K.; Furuno, H. *Tetrahedron* **2009**, 65, 2757. (c) Hanamoto, T.; Hashimoto, E.; Miura, M.; Furuno, H.; Inanaga, J. *J. Org. Chem.* **2008**, 73, 4736.

iodomethane occurred. The second quaternization of **1a** and diphenyliodonium triflate in the presence of a catalytic amount of CuCl(I) successfully proceeded to furnish the corresponding (β -trifluoromethyl)vinyl phenyl tolyl sulfonium triflate **2a** in 92% yield.⁶ Although this method itself is highly effective and efficient, it suffers from the need to isolate the sensitive, oily vinyl sulfonium salt **2a**. To overcome this shortcoming, we further searched for a corresponding crystalline alternative of **2a**. As a result, we found the beneficial (β -trifluoromethyl)vinyl diphenyl sulfonium triflate **2b**, a free-flowing, shelf-stable, and easy to handle crystalline material.

With a facile preparation of crystalline **2b** in hand, we next paid attention to the synthetic approach to (α -trifluoromethyl)aziridine.⁷ Nonfluorinated aziridine rings have recently received great attention due to their biological activity and/or versatile synthetic intermediates.⁸ We expected that a variety of (α -trifluoromethyl)aziridines should give the opportunity to develop new designed trifluoromethylated pharmaceuticals and agrochemicals.⁹ According to a reported procedure, we initially examined the preparation of the corresponding (α -trifluoromethyl)aziridine from the sulfonium salt **2b** and benzylamine.^{1a,10} The reaction smoothly proceeded to provide the *N*-benzyl-(α -trifluoromethyl)aziridine **4a** in 90% yield (Table 1, entry 1).^{7g} Compared to a

to give the corresponding (α -trifluoromethyl)aziridine **4** in good to excellent yields. It is noteworthy that amino- or ester-substituted primary amines were also employed in this reaction to afford the corresponding functionalized aziridines (entries 6 and 7). In addition, the sodium salt of the less nucleophilic *p*-toluenesulfonamide (TsNH₂) also participated in this reaction to give the *N*-tosyl-(α -trifluoromethyl)aziridine in excellent yield (entry 8).^{7b}

When we performed the aziridination with the optically active primary amine (*S*)-1-phenethylamine **5**, a mixture of diastereomers **6a** and **6b** was obtained with a ratio of 54:46 in 82% combined yield. These diastereomers could be cleanly separated by silica gel column chromatography. As one of the diastereomers was known in the literature,^{7g} we compared the ¹H NMR data to determine their stereochemistry. The ¹H NMR spectrum of the more polar diastereomer was identical with that of (*R*)-1-[(*S*)-1-phenethylamino]-2-trifluoromethylaziridine **6a**. Thus, the stereochemistry of the less polar diastereomer was assigned to (*S*)-1-[(*S*)-1-phenethylamino]-2-trifluoromethylaziridine **6b** (Scheme 2).

Scheme 2. Reaction of Optically Active Amine with **2b**

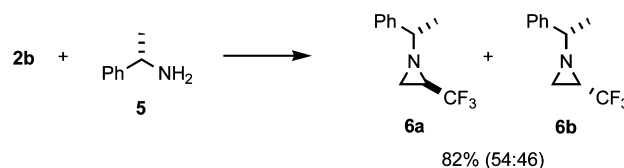


Table 1. Substrate Scope^a

entry	primary amine	product	yield (%) ^b
1	benzylamine	4a	90
2	2-phenylethylamine	4b	96
3	3,5-dimethylbenzylamine	4c	94
4	3,5-bis(trifluoromethyl)benzylamine	4d	91
5	1-naphthylmethylamine	4e	86
6	2-diethylaminoethylamine	4f	63 ^c
7 ^d	glycine ethyl ester hydrochloride	4g	78
8 ^e	<i>p</i> -toluenesulfonamide	4h	91

^a Unless otherwise noted, the reaction of **2b** (1.05 equiv) with **3** (1 equiv) was carried out in the presence of ^tBuNH₂ (3 equiv). ^b Isolated yield. ^c Percent yield including a small amount of unidentified product. ^d The reaction of **2b** (1 equiv) with **3** (2 equiv) was conducted in the presence of TEA (1.5 equiv). ^e Reaction performed in the presence of NaH (1.2 equiv) in THF.

previous method for the preparation of related (α -trifluoromethyl)aziridines,⁷ this simple method should be more convenient and practical. To explore the generality and scope of the aziridination with **2b**, representative primary amines were examined. The results are summarized in Table 1. A variety of primary amines **3** were smoothly reacted with **2b**

We next envisioned that using an appropriate nucleophile instead of the primary amines would create an alternative to the aziridine synthesis mode, and such a nucleophile, phthalimide **7**, was initially chosen. Thus, the reaction of **2b** with **7** in the presence of triethylamine smoothly proceeded to afford the corresponding *N*-[(α -trifluoromethyl)vinyl]phthalimide **8** in 98% yield.¹¹ Accomplishment of this transformation suggests that a wide range of 3,3,3-trifluoro-2-substituted propenes may be synthesized depending on choice of nucleophile under modified conditions. To test our hypothesis, we next examined

(7) For the preparation of trifluoromethylated aziridines, see: (a) Yamauchi, Y.; Kawate, T.; Katagiri, T.; Uneyama, K. *Tetrahedron* **2003**, *59*, 9839. (b) Yamauchi, Y.; Kawate, T.; Itahashi, H.; Katagiri, T.; Uneyama, K. *Tetrahedron Lett.* **2003**, *44*, 6319. (c) Akiyama, T.; Ogi, S.; Fuchibe, K. *Tetrahedron Lett.* **2003**, *44*, 4011. (d) Volonterio, A.; Bravo, P.; Panzeri, W.; Pesenti, C.; Zenda, M.; Eur, J. *Org. Chem.* **2002**, 3336. (e) Crousse, B.; Narizuka, S.; Bonnet-Delpon, D.; Bégué, J.-P. *Synlett* **2001**, 679. (f) Katagiri, T.; Takahashi, M.; Fujiwara, Y.; Ihara, H.; Kenji, U. *J. Org. Chem.* **1999**, *64*, 7323. (g) Katagiri, T.; Ihara, H.; Takahashi, M.; Kashino, S.; Furuhashi, K.; Uneyama, K. *Tetrahedron: Asymmetry* **1997**, *8*, 2933. (h) Quinze, K.; Laureny, A.; Mison, P. *J. Fluorine Chem.* **1989**, *44*, 233. (i) Tanaka, K.; Ohsuga, M.; Sugimoto, Y.; Okafuji, Y.; Mitsuhashi, K. *J. Fluorine Chem.* **1988**, *39*, 39.

(8) (a) Dauban, P.; Malik, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 9026. (b) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194.

(9) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (c) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303.

(10) Matsuo, J.; Yamanaka, H.; Kawana, A.; Mukaiyama, T. *Chem. Lett.* **2003**, *32*, 392.

(11) (a) Ishihara, K.; Nakano, K.; Akakura, M. *Org. Lett.* **2008**, *10*, 2893. (b) Yamanaka, H.; Mukaiyama, T. *Chem. Lett.* **2003**, *32*, 1192.

(5) Hanamoto, T.; Shindo, K.; Matuoka, M.; Kiguchi, Y.; Kondo, M. *J. Chem. Soc., Perkin Trans.1* **2000**, 103.

(6) Kitamura, T.; Yamane, M.; Zhang, B. X.; Fujiwara, Y. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1215.

the reaction of **2b** with diethylphosphonate **9** as a nitrogen homologous series. Unlike in the case of **7**, we had some difficulty in determining the optimized reaction conditions. Finally, the desired [(α -trifluoromethyl)vinyl]diethylphosphonate **10** was obtained in 85% yield (Scheme 3).¹² Since each new

are difficult to construct without use of these trifluoromethylated building blocks.¹³

In summary, we have developed an efficient method for the synthesis of (β -trifluoromethyl)vinyl diphenyl sulfonium triflate **2b** and have illustrated its high performance. Further studies on synthetic applications of trifluoromethylated aziridines **4**, **6**, *N*-[(α -trifluoromethyl)vinyl]phthalimide **8**, and [(α -trifluoromethyl)vinyl]diethylphosphonate **10** are underway in our laboratory.

Acknowledgment. We greatly thank F-Tech Co., Ltd. for a gift of 2-bromo-3,3,3-trifluoropropene and Central Glass Co., Ltd. for a gift of trifluoromethanesulfonic acid. We also thank Prof. Hiroshi Furuno at Kyushu University for valuable discussion and experimental support.

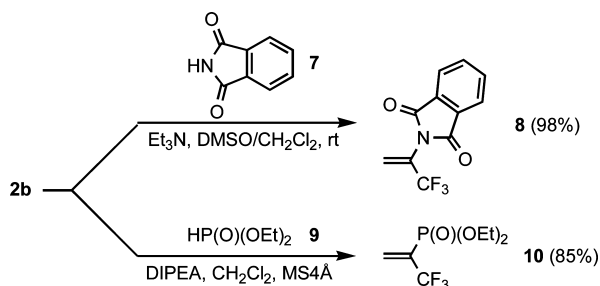
Supporting Information Available: Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL100768S

(13) Although we attempted the relevant cyclopropanation reaction using dimethyl malonate and the salt **2a**, the reaction did not work well to give the complex mixtures.¹⁴

(14) (a) Wang, Y.; Zhao, X.; Li, Y.; Lu, L. *Tetrahedron Lett.* **2004**, 45, 7775. (b) Jiang, B.; Zhang, F.; Xiong, W. *Chem. Commun.* **2003**, 536.

Scheme 3. Synthesis of (α -Trifluoromethyl)vinyl Compounds



trifluoromethylated molecule has an important functional group, we believe that they would play a significant role in the preparation of novel trifluoromethylated organic molecules that

(12) (a) Janecki, T.; Kedzia, J.; Wasek, T. *Synthesis* **2009**, 1227. (b) Minami, T.; Okauchi, T.; Kouno, R. *Synthesis* **2001**, 349. (c) Minami, T.; Motoyoshiya, J. *Synthesis* **1992**, 333.