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2-(2,2,2-Trifluoroethylidene)-1,3-dithiane Monoxide as a Trifluoromethylketene Equivalent

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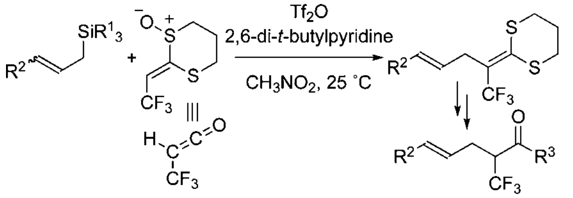
ABSTRACT



A method to prepare 2-(2,2,2-trifluoroethylidene)-1,3-dithiane monoxide has been developed, and its interesting reactivity under Pummerer-like conditions is disclosed. The products are useful synthetic intermediates for the synthesis of α-trifluoromethyl ketones.

Trifluoromethylated compounds have attracted much attention because of their important applications as biologically active agents and advanced organic materials that exhibit specific biological and physical properties.[1] Methods for introducing a trifluoromethyl group into an organic compound have thus been investigated extensively.[2] However, α-trifluoromethylation of carbonyl compounds has remained difficult.[3] Therefore, a novel trifluoromethylketene equivalent should be a useful building block for the synthesis of α-trifluoromethyl carbonyl compounds.[4]

Recently, we have been developing the synthetic utility of ketene dithioacetal monoxides as ketene equivalents.[5] Thus, we have been interested in the chemical behavior of trifluoromethylketene dithioacetal monoxide, 2-(2,2,2-trifluoroethylidene)-1,3-dithiane monoxide (**1a**). We anticipated that **1a** would react with nucleophile at C1 under extended Pummerer reaction conditions[5c,6] to yield ketene dithioacetal **2**, which might be a very attractive intermediate for further transformation (Scheme 1). Hydrolysis of ketene dithioacetal

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[1] (a) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, 2006. (b) Hiyama T.; Kanie, K.; Kusumoto, T.; Morizawa, Y.; Shimizu, M. *Organofluorine Compounds*; Springer-Verlag: Berlin, Heidelberg, 2000. (c) Ramachandran, P. V. *Asymmetric Fluoroorganic Chemistry: Synthesis, Applications, and Future Directions*; American Chemical Society: Washington, DC, 2000. (d) Soloshonok, V. A. *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedical Targets*; Wiley: Chichester, 1999. (e) Chambers, R. D. *Organofluorine Chemistry*; Springer: Berlin, 1997. (f) Ojima, I.; McCarthy, J. R.; Welch, J. T. *Biomedical Frontiers of Fluorine Chemistry*; American Chemical Society: Washington, DC, 1996. (g) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994. (h) Filler, R.; Kobayashi, Y; Yagupolskii, L. M. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: Amsterdam, 1993. (i) Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd ed.; Ellis Horwood: Chichester, 1976.

[2] (a) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214. (b) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6149. (c) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1. (d) Iseki, K. *Tetrahedron* **1998**, *54*, 13887.

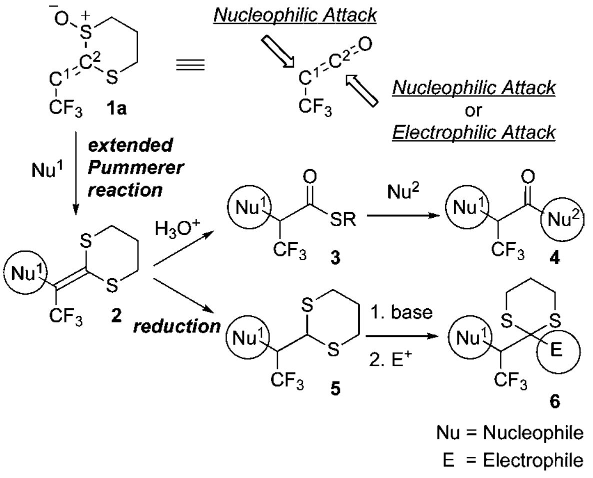
[3] Selected examples: (a) Miura, K.; Takeyama, Y.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1542. (b) Umemoto, T.; Adachi, K. *J. Org. Chem.* **1994**, *59*, 5692. (c) Sato, K.; Omote, M.; Ando, A.; Kumadaki, I. *Org. Lett.* **2004**, *6*, 4359. (d) Mikami, K.; Tomita, Y.; Ichikawa, Y.; Amikura, K.; Itoh, Y. *Org. Lett.* **2006**, *8*, 4671. (e) Eisenberger, P.; Gischig, S.; Togni, A. *Chem.*−*Eur. J.* **2006**, *12*, 2579.

[4] (a) Solberg, J.; Benneche, T.; Undheim, K. *Acta Chem. Scand.* **1989**, *43*, 69. (b) Huot, J.-F.; Muzard, M.; Portella, C. *Synlett* **1995**, 247. (c) Hanamoto, T.; Anno, R.; Yamada, K.; Ryu, K. *Tetrahedron Lett.* **2007**, *48*, 3727.

[5] (a) Yoshida, S.; Yorimitsu, H.; Oshima, K. *Synlett* **2007**, 1622. (b) Yoshida, S.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 5573. (c) Yoshida, S.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2008**, *37*, 786. (d) Yoshida, S.; Yorimitsu, H.; Oshima, K. *Heterocycles* **2008**, *76*, 679. (e) Yoshida, S.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2009**, *38*, 248. (f) Yoshida, S.; Yorimitsu, H.; Oshima, K. *Heterocycles*, in press, DOI: 10.3987/COM-09-S(S)6.

10.1021/ol9004883 CCC: $40.75

Scheme 1. Synthesis of α-Trifluoromethyl Ketone Using the Trifluoromethylketene Equivalent **1a**



2 could provide thiol ester **3**, which should react with nucleophile at C2 to give α-trifluoromethyl ketone **4**.[7] Alternatively, reduction of **2** could afford dithiane **5**, which can participate in the conventional dithiane chemistry.[8] The synthesis of **6** would provide another route to α-trifluoromethyl ketone. Here, we report the synthetic method for 2-(2,2,2-trifluoroethylidene)-1,3-dithiane monoxide (**1a**) and its interesting reactivity in extended Pummerer reaction.

2-(2,2,2-Trifluoroethylidene)-1,3-dithiane monoxide (**1a**) was prepared starting from 1,3-dithiane and ethyl trifluoroacetate as a stereoisomeric mixture ($E/Z = 4{:}1$) (Scheme 2). The method is facile and scalable. Trifluoroacetylation of 1,3-dithiane followed by reduction and tosylation afforded dithiane **7**. Oxidation of **7** to monoxide and subsequent treatment with potassium *tert*-butoxide yielded 2-(2,2,2-trifluoroethylidene)-1,3-dithiane monoxide (**1a**). The stereoisomers of **1a** were separated from each other by column chromatography on silica gel.

An interesting reactivity of 2-(2,2,2-trifluoroethylidene)-1,3-dithiane monoxide (**1a**) was observed in an extended Pummerer reaction with allylsilanes. Treatment of (*E*)-**1a** with allyltrimethylsilane (**8a**) in the presence of trifluoromethanesulfonic anhydride and 2,6-di-*tert*-butylpyridine in nitromethane provided the corresponding allylated ketene dithioacetal **9a** in high yield (Table 1, entry 1). A mixture of *E* and *Z* isomers of **1a** ($E/Z = 2{:}3$) reacted equally as (*E*)-**1a** to afford **9a**. Perfluoroalkylketene dithioacetal monoxide (*E*)-**1b** also reacted with allylsilane **8a** under the same reaction conditions (entry 2). On the other hand, the reactions of ethylidene and phenylmethylene 1,3-dithiane monoxide (*E*)-**1c** and (*E*)-**1d** gave complex mixtures (entries 3 and 4). Thus, the trifluoromethyl or perfluoroalkyl group played an important role for the successful reaction.

Scheme 2. Synthesis of 2-(2,2,2-Trifluoroethylidene)-1,3-dithiane Monoxide (**1a**)

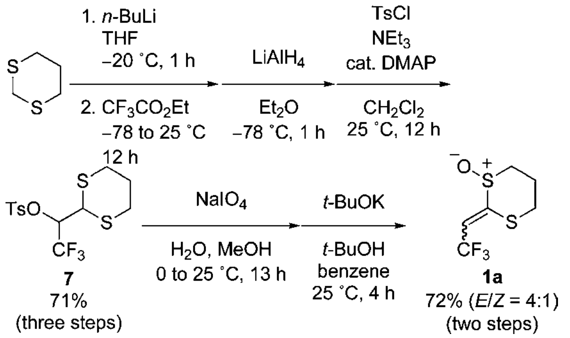
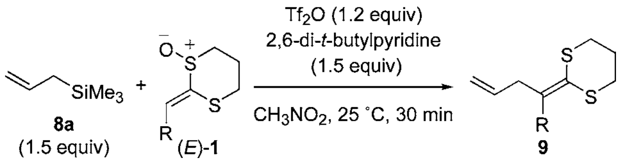


Table 1. Extended Pummerer Reaction of **1** with Allylsilane **8a**



entry	R	**1**	**9**	yield/%[a]
1	CF_3	**1a**	**9a**	86 (85)[b]
2	*n*-C_3F_7	**1b**	**9b**	84
3	Me	**1c**	**9c**	0
4	Ph	**1d**	**9d**	7

[a] Isolated yields. [b] An *E*/*Z* mixture (2:3) was used instead of pure *E* isomer.

Next we examined the scope and limitation using various allylsilanes or allylstannane **8** (Table 2). The reactions with allyl-*tert*-butyldimethylsilane (**8b**) and allyltriethoxylsilane (**8c**) also proceeded effectively to give allylated ketene dithioacetal **9a** in good yields (entries 2 and 3). On the other hand, allyltributylstannane (**8d**) failed to cause efficient allylation and afforded **9a** in only 29% yield (entry 4). The reactions with *β*-methyl- and *β*-phenyl-substituted allylsilanes **8e** and **8f** afforded the corresponding products **9e** and **9f**, respectively, in high yields (entries 5 and 6).

In the reactions with *γ*-substituted allylsilanes (entries 7−10), unusual regioselectivity was observed.[9] *γ*-(2-Phenylethyl)-substituted allylsilane **8g** reacted with **1a** to yield

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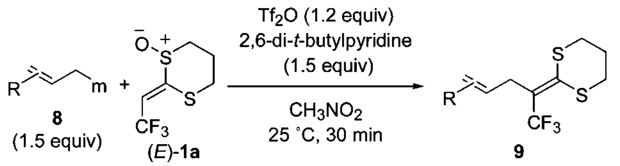
(6) Selected examples: (a) Craig, D.; Daniels, K. *Tetrahedron* **1993**, *49*, 11263. (b) Kita, Y.; Takeda, Y.; Matsugi, M.; Iio, K.; Gotanda, K.; Murata, K.; Akai, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1529. (c) Padwa, A.; Kuethe, J. T. *J. Org. Chem.* **1998**, *63*, 4256. (d) Akai, S.; Morita, N.; Iio, K.; Nakamura, Y.; Kita, Y. *Org. Lett.* **2000**, *2*, 2279. (e) Feldman, K. S.; Vidulova, D. B. *Org. Lett.* **2004**, *6*, 1869. (f) Akai, S.; Kawashita, N.; Satoh, H.; Wada, Y.; Kakiguchi, K.; Kuriwaki, I.; Kita, Y. *Org. Lett.* **2004**, *6*, 3793. (g) Padwa, A.; Nara, S.; Wang, Q. *Tetrahedron Lett.* **2006**, *47*, 595. (h) Feldman, K. S.; Karatjas, A. G. *Org. Lett.* **2006**, *8*, 4137. (i) Feldman, K. S.; Skoumbourdis, A. P.; Fodor, M. D. *J. Org. Chem.* **2007**, *72*, 8076.

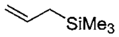
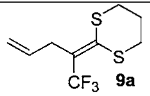
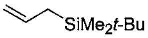
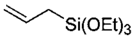
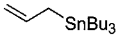
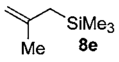
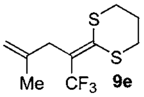
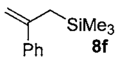
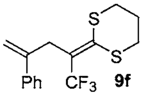
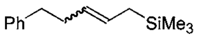
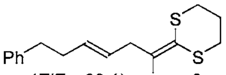
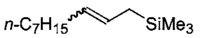
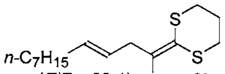
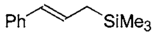
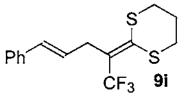
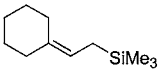
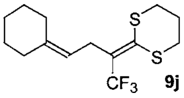
(7) Thiol esters are useful for synthesis of aldehydes or ketones. Selected examples: (a) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050. (b) Kuniyasu, H.; Ogawa, A.; Sonoda, N. *Tetrahedron Lett.* **1993**, *34*, 2491. (c) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189. (d) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260. (e) Ikeda, Z; Hirayama, H.; Matsubara, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 8200.

(8) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.

(9) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941.

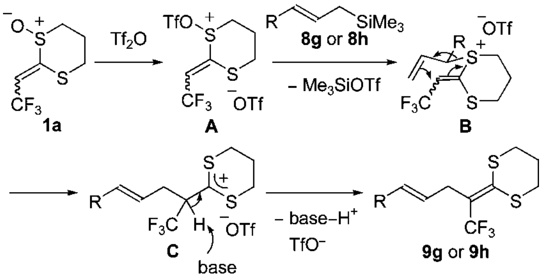
Table 2. Reactions of **1a** with Allylsilanes or Allylstannane **8** in the Presence of Tf_2O



entry	8	9	yield/%[a]
1	 **8a**	 **9a**	86
2	 **8b**	**9a**	78
3	 **8c**	**9a**	79
4	 **8d**	**9a**	29
5	 **8e**	 **9e**	86
6	 **8f**	 **9f**	87[b]
7	 (*E*/*Z* = 1:4) **8g**	 (*E*/*Z* > 99:1) **9g**	74
8	 (*E*/*Z* = 1:5) **8h**	 (*E*/*Z* > 99:1) **9h**	75[c]
9	 **8i**	 **9i**	0
10	 **8j**	 **9j**	19[d]

[a] Isolated yields. [b] 2.0 equiv of **8** was used, and the reaction was performed at 0 °C for 1 h. [c] CH_2Cl_2 was used as a solvent instead of CH_3NO_2. [d] CH_2Cl_2/CH_3NO_2 (1:1) was used as a solvent.

Scheme 3. Plausible Reaction Mechanism



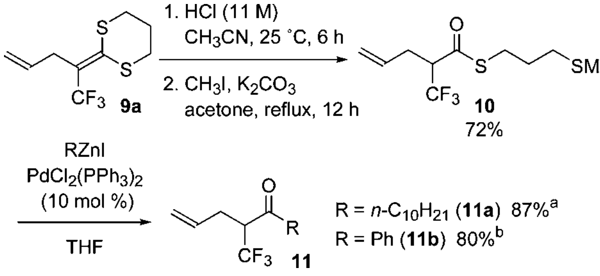
ketene dithioacetal **9g** stereo- and regioselectively (entry 7), which was produced via carbon−carbon bond formation at the α-position of **8g**. γ-Heptyl-substituted allylsilane **8h** also reacted at the α-position exclusively (entry 8).[10] Notably, **9g** and **9h** were formed with exclusive *E* selectivity. However, the reaction with cinnamylsilane **8i** gave a complex mixture with no trace amount of the expected product **9i** (entry 9). γ,γ-Disubstituted allylsilane **8j** was not a good allylating agent (entry 10).

A plausible reaction mechanism that rationalizes the stereo- and regioselectivity is shown in Scheme 3. Treatment of **1a** with trifluoromethanesulfonic anhydride gives sulfonium salt **A**.[5b,c] Allylsilane **8g** or **8h** then attacks the cationic sulfur along with liberation of trimethylsilyl triflate to afford sulfonium salt **B**.[11] Sulfonium salt **B** then undergoes [3,3]-sigmatropic rearrangement via a chairlike transition state, followed by deprotonation, to afford **9g** or **9h** with exclusive stereo- and regioselectivity.[11c,12,13] Although the role of the trifluoromethyl group is still unclear, the trifluoromethyl group might prevent generation of unstable dicationic species via cleavage of the S-OTf bond.[5b,c]

The products **9** are useful synthetic intermediates. We thus demonstrate two different approaches to synthesize α-trifluoromethylketones from ketene dithioacetal **9**.

Treatment of ketene dithioacetal **9a** with aqueous hydrochloric acid in acetonitrile followed by methylation yielded thiol ester **10**, which is a good electrophile in the reactions with various nucleophiles (Scheme 4).[7] For instance, palladium-catalyzed cross-coupling reactions of thiol ester **10** with organozinc reagents afforded α-trifluoromethyl ketones **11a** and **11b** in good yields.

Scheme 4. Synthesis of α-Trifluoromethyl Ketones **11**



[a] 50 °C, 6 h. [b] 0 °C, 1 h.

Reduction of ketene dithioacetal **9a** proceeded smoothly in the presence of $NaBH_4$ and hydrochloric acid to afford

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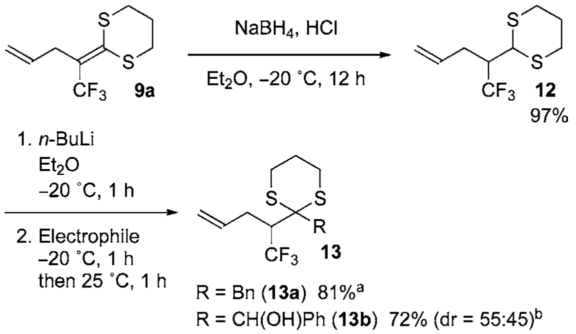
(10) Dichloromethane was used as a solvent instead of nitromethane. In the case of nitromethane, **9h** was obtained in low yield probably due to the poor solubility of **8h.**

(11) (a) Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S. *Tetrahedron* **2000**, *56*, 3077. (b) Nenajdenko, V. G.; Vertelezkij, P. V.; Balenkova, E. S. *Synthesis* **1997**, 351. (c) Harvey, J. N.; Viehe, H. G. *J. Chem. Soc., Chem. Commun.* **1995**, 2345.

(12) Thio-Claisen rearrangement of allyl vinyl sulfonium ion has been reported: (a) Bycroft, B. W.; Landon, W. *J. Chem. Soc., Chem. Commun.* **1970**, 967. (b) Tomita, K.; Terada, A.; Tachikawa, R. *Heterocycles* **1976**, *4*, 733.

(13) The reaction of (phenylsulfinyl)ethene with allyltrimethylsilane under the reaction conditions afforded a complex mixture.

Scheme 5. Synthesis of Dithiane **13**



[a] $PhCH_2Br$ was used as an electrophile.
[b] PhCHO was used as an electrophile.

trifluoromethylated dithiane **12**, which could be used further as an acyl anion equivalent (Scheme 5). Deprotonation of **12** with butyllithium followed by addition of electrophiles afforded dithianes **13a** and **13b** in good yields.

In conclusion, we have synthesized 2-(2,2,2-trifluoroethylidene)-1,3-dithiane monoxide and disclosed its interesting reactivity under Pummerer-like conditions. The trifluoromethyl group plays an important role for the extended Pummerer reaction. The product should provide a new entry to various trifluoromethylated compounds.

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Supporting Information Available: Experimental procedure and characterization data of **1**, **7**, **9**, **10**, **11**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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