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Intermolecular Reductive Radical Addition to 2-(2,2,2-Trifluoroethylidene)-1,3-dithiane 1-Oxide: Experimental and Theoretical Studies

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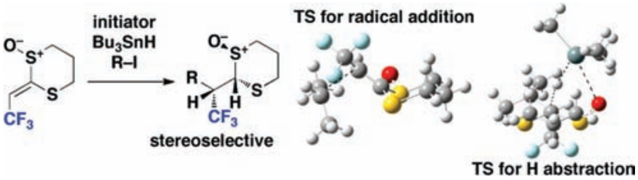
ABSTRACT



Tin hydride mediated radical addition of organic halide to 2-(2,2,2-trifluoroethylidene)-1,3-dithiane 1-oxide has been devised. The reaction is equivalent to an unrealizable radical addition to trifluoromethylketene, providing useful α-trifluoromethyl carbonyl equivalents. The trifluoromethyl and the sulfoxide groups of the substrate play key roles for the success of the radical addition, lowering the barrier of the radical addition step and controlling the stereoselectivity of the reaction, which DFT calculations have elucidated.

Trifluoromethylated compounds have found many important applications because of their characteristic biological and physical properties.[1] A variety of trifluoromethyl-containing building blocks have been widely used for the synthesis of trifluoromethylated compounds.[2] We recently devised a trifluoromethylketene dithioacetal derivative, 2-(2,2,2-trifluoroethylidene)-1,3-dithiane 1-oxide (**1**), of interesting reactivity and developed new Pummerer-type reactions for efficient synthesis of trifluoromethylated compounds.[3]

Radical addition to ketene dithioacetals and their derivatives seems useful, as the reaction provides an alternative route to various carbonyl compounds via radical pathways. While tin hydride mediated intramolecular radical cyclization onto a ketene dithioacetal moiety has been reported,[4] its intermolecular variant is limited.[5,6] Our previous investiga-

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(1) (a) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley-Interscience: NJ, 2008. (b) Hiyama, T. *Organofluorine Compounds: Chemistry and Applications*; Springer: Berlin, 2000. (c) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004. (d) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, 2006. (e) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1–16. (f) Iseki, K. *Tetrahedron* **1998**, *54*, 13887–13914.

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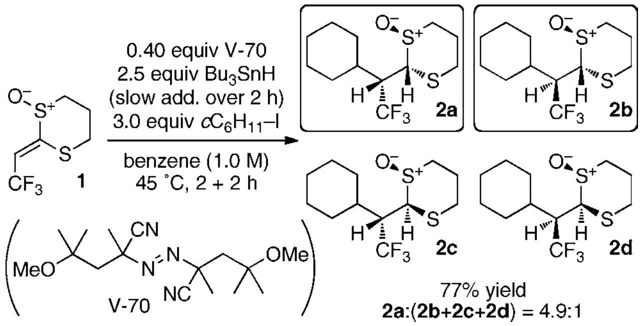
tions disclosed that 2-methylene-1,3-dithiane 1-oxide, which bears no trifluoromethyl group, is an excellent radical acceptor in tin hydride mediated intermolecular radical addition.[7] We next envisioned intermolecular radical addition to **1** since the expected adducts are synthetically equivalent to α-trifluoromethyl carbonyl compounds, which are difficult to synthesize.[8]

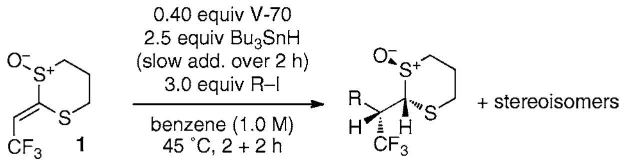
Addition of an alkyl radical to **1** should be slow owing to the sterically hindered double bond of **1**. Our initial attempts indeed failed to achieve efficient Bu$_3$SnH-mediated radical addition of alkyl halides to **1**. After extensive screening, we finally found efficient reaction conditions. Neat tributyltin hydride (2.5 equiv) was added slowly over 2 h to a benzene solution of **1**, cyclohexyl iodide (3 equiv), and V-70[9] (0.40 equiv) at 45 °C (Scheme 1). The resulting mixture was stirred for an additional 2 h to afford the corresponding adduct **2** in 77% yield.

Scheme 1. Radical Addition of Cyclohexyl Iodide to **1**



The addition reaction was stereoselective, and one of the four possible stereoisomers, **2a**, was mainly formed. We were able to separate **2a** easily by using silica gel column chromatography. The relative stereochemistry of the major isomer **2a** was clearly determined by X-ray crystallographic analysis. Among the three minor isomers, one isomer was predominantly formed although we could not unambiguously determine the stereochemistry of the isomer at present. Considering that the signals of the methyne protons of the 1,2-*trans*-2-alkyl-1,3-dithiane 1-oxide derivatives characteristically appear at 3.6−3.9 ppm,[10] we assume that the isomer would be **2b**, which showed the corresponding signal at 3.7 ppm. The formation of **2b** is also supported by the fact that the hydride transfer from Bu$_3$SnH to 2-alkyl-1-oxo-1,3-dithian-2-yl radical provided the corresponding 1,2-*trans* product almost exclusively.[7b]

Table 1. Scope of Organic Iodides



entry	R	product	yield /%	major/others[a]
1	*i*Pr	**3**	68	4.6:1
2	C$_6$H$_{13}$	**4**	76	3.0:1
3	C$_{12}$H$_{25}$	**5**	76	2.3:1
4	*t*Bu	**6**	39[b]	10:1
5	EtO$_2$C(CH$_2$)$_5$	**7**	85	2.1:1
6	MeSO$_2$HN(CH$_2$)$_5$	**8**	79	2.4:1
7	TBDMSO(CH$_2$)$_6$	**9**	64	6.8:1
8	HO(CH$_2$)$_6$	**10**	85	8.1:1
9[c]	Ph	**11**	74	3.9:1
10	*c*C$_6$H$_{11}$[d]	**2**	61	4.9:1

[a] Isomer ratio of the major isomer to other three isomers. [b] NMR yield. [c] Bu$_3$SnH was added over 5 h, and the total reaction time was 7 h. V-70 (0.20 equiv) was placed at the beginning of the reaction, and additional V-70 was added at 2.5 and 5.0 h (0.20 equiv each) after the reaction started. [d] Cyclohexyl bromide was used.

The scope of alkyl iodide was surveyed (Table 1). Primary alkyl iodides participated in the addition reaction as efficiently as secondary ones although the addition of primary alkyl groups was less stereoselective (entries 2 and 3). The steric hindrance of a *tert*-butyl group seemed to retard the addition reaction albeit with highest stereoselectivity (entry 4). Ester, methanesulfonamide, siloxy, and unprotected hydroxy groups were compatible under the reaction conditions (entries 5−8). The stereoselectivities of the additions of 6-iodo-1-hexanol and of its TBDMS ether are high although the reason for the high stereoselectivities is not clear at this stage. It is worth noting that iodobenzene was available for radical phenylation under modified reaction conditions to yield **11** in 74% yield (entry 9). Cyclohexyl bromide was converted with less efficiency than the iodo analogue (entry 10). Cyclohexyl chloride resisted the reaction.

The products **2**−**11** are synthetic equivalents to α-trifluoromethyl aldehyde and might undergo a variety of trans-

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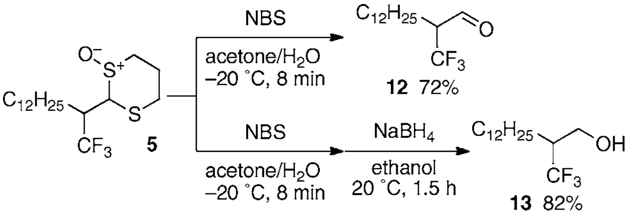
formations. For instance, **5** was converted to the corresponding aldehyde **12** by treatment with *N*-bromosuccinimide in aqueous acetone for 8 min[11,12] although α-trifluoromethyl aldehydes are generally unstable (Scheme 2). Aldehyde **12** was isolable by silica gel column chromatography in 72% yield although **12** was partly decomposed during the purification. Reduction of crude **12** by sodium borohydride afforded 2-trifluoromethyl-1-tetradecanol (**13**) in a higher yield.[13]

Scheme 2. Transformation of Adduct

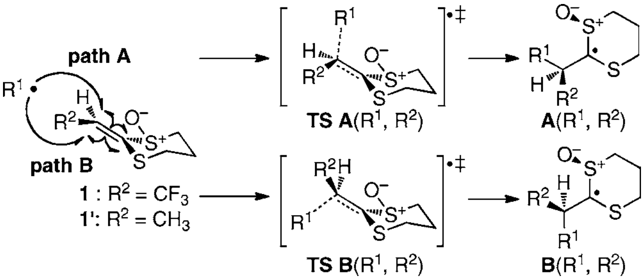


The radical reaction consists of two chain-propagation steps, addition of an alkyl radical to **1** and abstraction of the hydrogen from Bu_3SnH by the resulting 2-alkyl-1-oxo-1,3-dithian-2-yl radical. We performed *ab initio* and DFT calculations of each step to rationalize the stereoselectivity of the radical addition reaction and the high reactivity of **1**.[14]

The first step determines the relative stereochemistry between the oxygenated sulfur atom and the trifluoromethylated carbon atom. Additions of a methyl, an ethyl, and an isopropyl radical (R^1•) to **1** were investigated through the use of calculations at the BHandHLYP/DZP level of theory[15] (Table 2). The calculations reveal that the alkyl radicals approach **1** preferably from the opposite side of the sulfoxide oxygen to yield **B**(R^1, CF_3) via **TS B**(R^1, CF_3) (**path B**). As R^1• becomes larger, **path B** becomes more favorable than **path A** (Table 2, entries 1−3), which is consistent with the results in Scheme 1 and Table 1.

It is worth noting that addition of an isopropyl radical to the defluorinated analogue of **1**, 2-ethylidene-1,3-dithiane 1-oxide (**1′**), is calculated to have a much higher barrier than the addition to **1** (Table 2, entry 4). Our experimental attempts to perform radical addition to **1′** indeed failed. The electron-withdrawing trifluoromethyl group would promote the radical addition of electron-rich alkyl radicals. Notably, the addition to **1′** is calculated not to be stereoselective by judging from the small ΔΔ*E* of 1.9 kJ•mol^{-1}. The trifluoromethyl group of **1** thus plays an important role for the stereoselection.

Table 2. Calculated Energy Barriers for Addition of Alkyl Radical R^1• to **1** and Its Methyl Analog **1′**



entry	R^1	R^2	Δ*E*(**TS A**)[a]	Δ*E*(**TS B**)[a]	ΔΔ*E*[a,b]
1	Me	CF_3	19.9	18.2	1.7
2	Et	CF_3	20.5	14.4	6.1
3	*i*Pr	CF_3	24.6	13.1	11.5
4	*i*Pr	CH_3	34.7	32.8	1.9

[a] Energies in kJ•mol^{-1}. [b] Δ*E*(**TS A**) − Δ*E*(**TS B**).

As depicted in Figure 1, an isopropyl radical should approach **1** to minimize steric repulsion. In **TS A**(*i*Pr, CF_3) ([a] and [e]), both the trifluoromethyl group and the dithiane skeleton can cause strong steric repulsion toward the isopropyl radical. On the other hand, in the preferable **TS B**(*i*Pr, CF_3) ([b] and [f]), the isopropyl group can avoid interaction with the trifluoromethyl group because the dithiane ring does not provide strong repulsion. The calculated radical addition to **1′** would not be stereoselective because of the smaller methyl group of **1′**, which does not induce steric repulsion in both of the transition states ([c], [d], [g], and [h]).

The stereoselectivity of the abstraction of the hydrogen from tin hydride would originate from the directing effect of the sulfoxide oxygen (Figure 2).[16,17] In the model reaction of **B**(*i*Pr, CF_3) with Me_3SnH, the sulfoxide-directed approach of Me_3SnH (**TS B1**) is calculated to have a lower barrier than undirected **TS B2** by 14.9 kJ•mol^{-1} at the BHandHLYP/DZP level of theory. In **TS B1**, the distance between the oxygen and the tin is predicted to be 3.206 Å, which is much shorter than the sum of the van der Waals radii of oxygen and tin (4.0 Å).[18] The favorable base−acid interaction would lead to the selective formation of **2a**. The case is also

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(11) (a) Tanaka, K.; Fujimoto, Y.; Saikawa, Y.; Nakata, M. *J. Org. Chem.* **2008**, *73*, 6292–6298. (b) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553–3560.

(12) The reaction should be terminated within 8 min. A prolonged reaction resulted in affording a complex mixture.

(13) We believe that enantiomerically enriched **12** and **13** could be obtained if one of the enantiomers of **1** was used.

(14) Stereoelectronic effects of similar ketene dithioacetal monoxides were investigated: Ulshöfer, R.; Podlech, J. *J. Am. Chem. Soc.* **2009**, *131*, 16618–16619.

(15) BHandHLYP performs as well as higher correlation techniques such as CCSD(T) or QCISD for calculating radical processes. See: (a) Kyne, S. H.; Schiesser, C. H.; Matsubara, H. *J. Org. Chem.* **2008**, *73*, 427–434. (b) Matsubara, H.; Ryu, I.; Schiesser, C. H. *Org. Biomol. Chem.* **2007**, *5*, 3320–3324. (c) Matsubara, H.; Falzon, C. T.; Ryu, I.; Schiesser, C. H. *Org. Biomol. Chem.* **2006**, *4*, 1920–1926. (d) Matsubara, H.; Ryu, I.; Schiesser, C. H. *J. Org. Chem.* **2005**, *70*, 3610–3617. (e) Matsubara, H.; Schiesser, C. H. *Org. Biomol. Chem.* **2003**, *1*, 4335–4341.

(16) Oxygen-directed hydrostannylation reactions of alkenes and alkynes were reported: (a) Miura, K.; Wang, D.; Hosomi, A. *Synlett* **2005**, 406–410. (b) Miura, K.; Wang, D.; Hosomi, A. *J. Am. Chem. Soc.* **2005**, *127*, 9366–9367. (c) Dimopoulos, P.; George, J.; Tocher, D. A.; Manaviazar, S.; Hale, K. J. *Org. Lett.* **2005**, *7*, 5377–5380, and references cited therein.

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(18) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441–451.

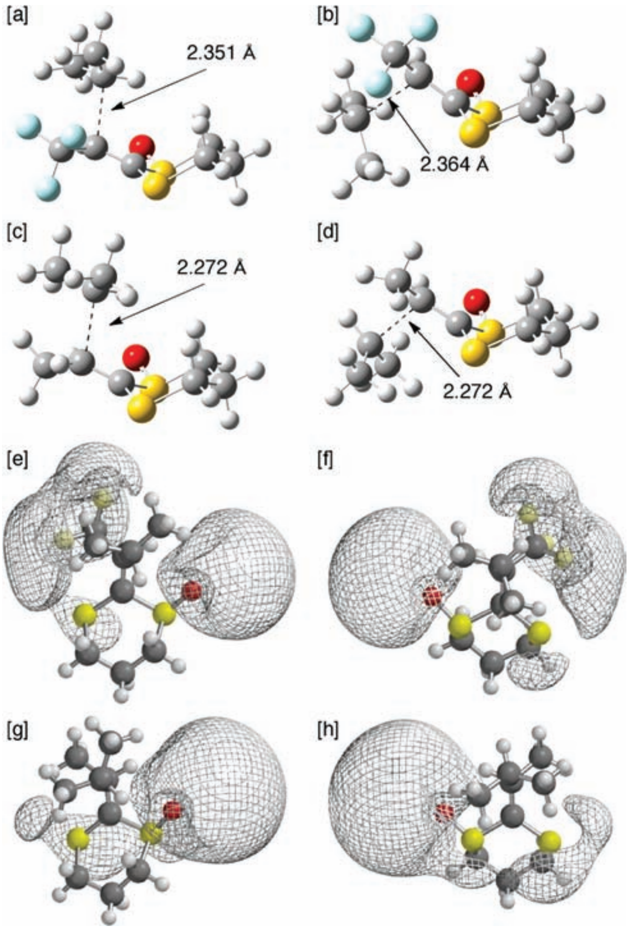

Figure 1. Structures [a−d] and potential surfaces (isosurface value: 63 kJ•mol^{-1}) [e−h] of transition states: [a and e] **TS A**(*i*Pr, CF_3); [b and f] **TS B**(*i*Pr, CF_3); [c and g] **TS A**(*i*Pr, CH_3); [d and h] **TS B**(*i*Pr, CH_3). Potential surfaces are views from the sides of an isopropyl radical. Atom colors: C, gray; H, white; O, red; S, yellow; F, aqua.

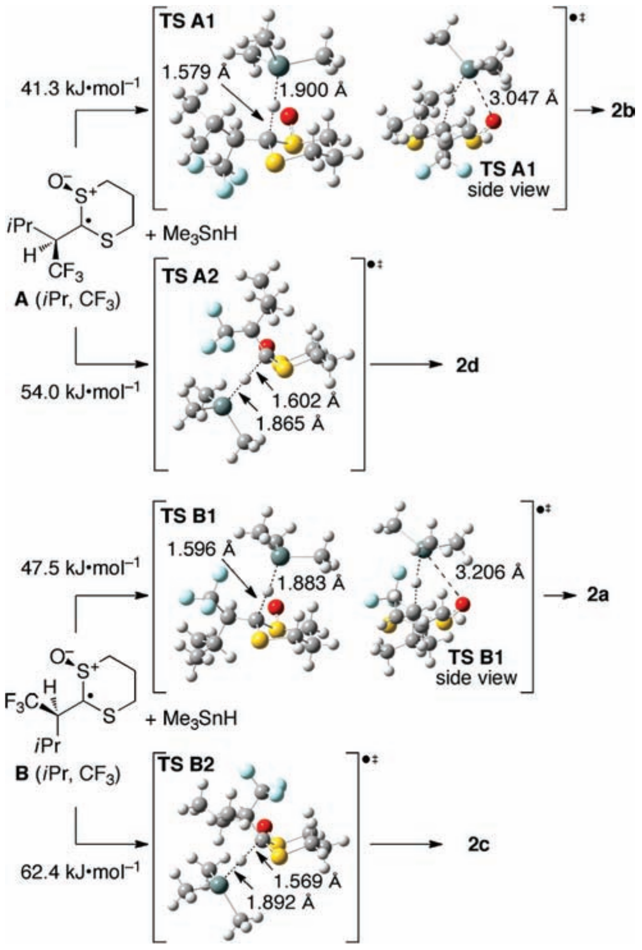

Figure 2. Calculated reaction mechanism of abstraction of hydrogen from Me_3SnH by intermediary radicals **A**(*i*Pr, CF_3) and **B**(*i*Pr, CF_3). Atom colors: C, gray; H, white; O, red; S, yellow; F, aqua; Sn, bluish gray.

applicable to the hydrogen abstraction by the minor radical intermediate **A**(*i*Pr, CF_3).

In summary, we have developed a tin hydride mediated radical addition reaction of organic halides with 2-(2,2,2-trifluoroethylidene)-1,3-dithiane 1-oxide (**1**). The reaction is equivalent to the difficult radical addition to trifluoromethylketene, providing useful α-trifluoromethyl carbonyl equivalents. The radical addition is high-yielding and stereoselective, the reason for which DFT calculations clearly elucidated. The electron-withdrawing nature of both the trifluoromethyl and the sulfoxide groups of the substrate lower the barrier of the radical addition step. The steric hindrance of the trifluoromethyl group and the directing nature of the sulfoxide group have proven to control the stereoselectivity of the reaction.

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Supporting Information Available: Characterization data of the products and experimental and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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