

Communications to the Editor

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STEREOSELECTIVE SYNTHESIS OF
gem-BISTRIFLUOROMETHYLCYCLOPROPANE DERIVATIVES

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gem-Bistrifluoromethylcyclopropanecarboxylic acids were synthesized through the inter- and intramolecular cyclopropanation of bistrifluoromethylethylenic compounds with sulfonium ylids. The trans-cyclopropane (10) was converted to the hexafluorocypermethrin (13).

KEYWORDS— cyclopropane; trifluoromethyl; sulfonium ylid; cypermethrin

Introduction of fluorine into bioactive compounds has attracted attention because of the augmented activity or selectivity of their functions compared with those of the parent compound. A number of chemical modifications of chrysanthemic acid and related compounds have been synthesized and their structure-activity relationship has been investigated.^{1,2)} Some of the fluorine-modified analogs were highly active.^{3,4)}

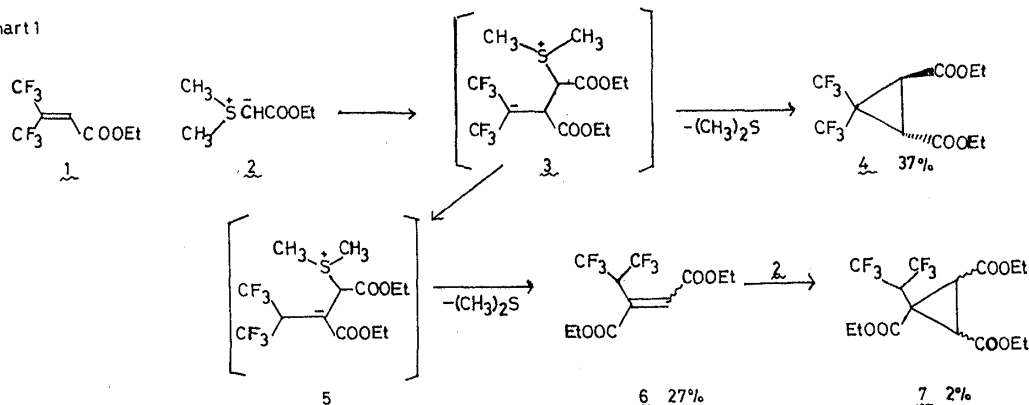
In this paper we report the synthesis of gem-bistrifluoromethylcyclopropane derivatives through the cyclopropanation of bistrifluoromethylethylenic compounds with sulfonium ylid in a stereoselective manner,⁵⁾ and the conversion of the trans-isomer to the hexafluorocypermethrin (13).

Owing to the electron-withdrawing character of the trifluoromethyl group, bistrifluoromethylethylenic compounds were reported to react as a Michael acceptor with amines⁶⁾ and as a 1,3-dipolarophile with diazo or azide compounds.⁷⁾

The reaction of ethyl hexafluorosenecionate (1)⁸⁾ with sulfonium ylid (2) was investigated under a variety of reaction conditions, but gave the desired trans-cyclopropane (4)⁹⁾ in relatively low yield accompanied by the olefinic compounds (6) and the cyclopropane derivative (7). The formation of 6 may be explained by the proton transfer from the initial adduct 3 to the carbanion (5) stabilized by the ester group, followed by the β -elimination of dimethylsulfide (Chart 1).

To avoid the competitive proton transfer the ester group of 1 was converted to a hydroxyl group. The allyl alcohol (8) was obtained by treatment of 1 with DIBAL-H in 70-80% yield. As expected, the reaction of the benzoate (9) with 2 (DMF, r.t., 16h) gave the trans-cyclopropane (10) in 44% yield as the only product isolated. The trans-stereochemistry of 10 was confirmed by the following transformation to the

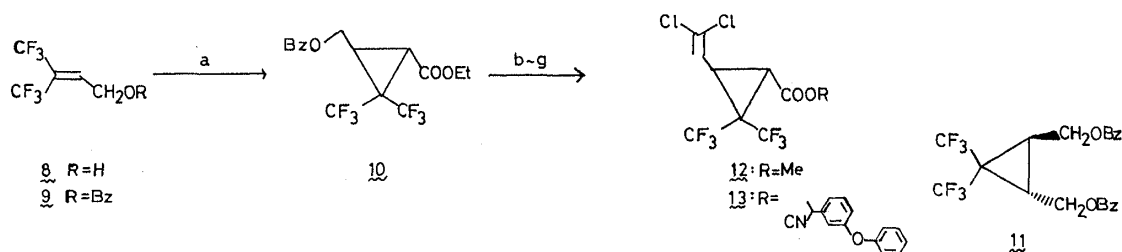
Chart 1



diol derivative (11). Reduction of the ester group of 10 (DIBAL-H, ether) and the subsequent esterification (PhCOCl, Py) afforded the dibenzoate [11, $^1\text{H-NMR}(\text{CDCl}_3)\delta$ 2.43 (2H, m), 4.53 (4H, m). $^{19}\text{F-NMR}(\text{CDCl}_3)\delta$ -3.3 (s)],¹⁰ whose physical data are identical with those of the dibenzoate derived from the diester (4) (DIBAL-H then PhCOCl, Py). $^{19}\text{F-NMR}$ of either 4 or 11 showed one single peak due to their C_2 -symmetrical structure.

The trans-cyclopropane (10) was converted to the hexafluorocypermethrin (13). Thus, the Swern oxidation¹¹ (step d in Chart 2) of the hydroxy ester afforded an unstable aldehyde, which was subjected to the Wittig reaction to form the dichloride (12, 51% yield from the hydroxy ester). Saponification of 12 to the acid (mp 85.8°C, 92% yield) and the subsequent reaction with the bromonitrile gave the hexafluorocypermethrin (13) as a diastereomeric mixture [13, 59% yield. $^1\text{H-NMR}(\text{CDCl}_3)\delta$ 2.83 (1H, dm, $J=7.2$ Hz), 3.27 (1H, tm, $J=7.2$ Hz), 5.75 (1H, dm, $J=7.2$ Hz), 6.31 and 6.35 (1H, each s), 6.88-7.50 (9H, m). $^{19}\text{F-NMR}(\text{CDCl}_3)\delta$ +2.0 (qm, $J=8.5$ Hz), +1.4 (qm, $J=8.5$ Hz)]¹² (Chart 2).

Chart 2

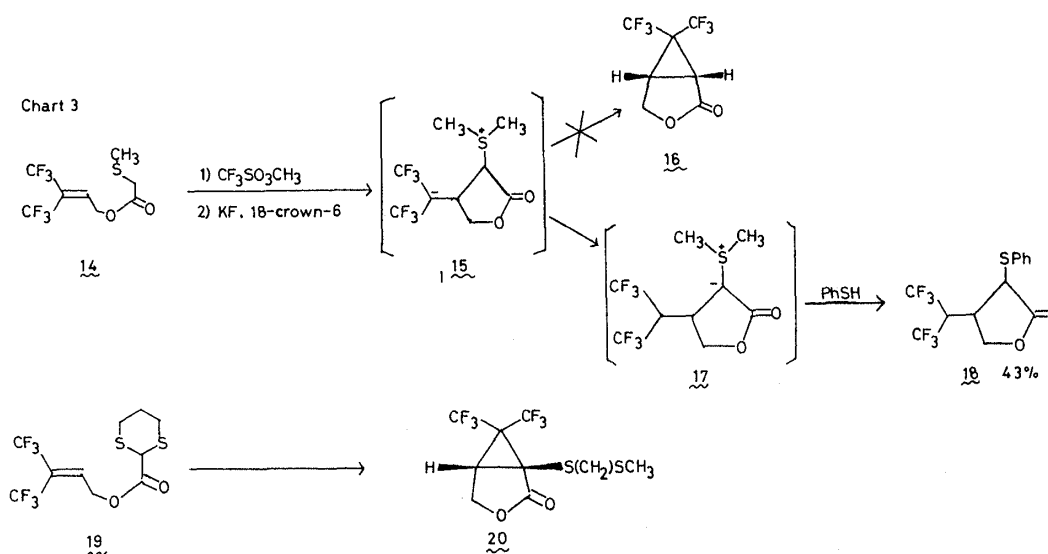


a) 2. DMF b) KOH, MeOH c) CH_2N_2 d) DMSO, $(\text{COCl})_2$, Et_3N , CH_2Cl_2 e) CBrCl_3 , $(\text{Me}_2\text{N})_3\text{P}$, CH_2Cl_2 , -100°C

f) KOH, MeOH g) $\text{BrCH}(\text{CN})\text{C}_6\text{H}_4\text{-OC}_6\text{H}_5$, Et_3N , acetone

For the synthesis of cis-isomer (16) intramolecular cyclopropanation to form a [3,1,0] ring system was examined.¹³ First, the methylthioacetate (14) was used as starting material. Thus, S-methylation ($\text{CF}_3\text{SO}_3\text{CH}_3$, 0°C , 1h) followed by the subsequent treatment with base (KF or Et_3N eg) gave no cyclopropane (16), but in the presence of benzenethiol (KF, 18-crown-6, CH_2Cl_2 then PhSH, CH_2Cl_2) the phenylsulfide (18) was obtained in 43% yield. This suggests the initial formation of the adduct (15), which was easily transformed to the sulfonium ylid (17). To prevent the ylid formation through the proton-transfer, the α -hydrogen atom was replaced with a sulfur atom. Indeed the 1,3-dithiane-2-carboxylate (19) was found to give the cyclopropane (20) by the similar reaction [a) $\text{CF}_3\text{SO}_3\text{CH}_3$, 0°C , b) KF, 18-crown-6, CH_2Cl_2 -

DMF, r.t.] in 43% yield. Several attempts were made to convert 20 to 16, but failed. Thus, instead of the dithiane derivative another functional group should be used (Chart 3).



In conclusion, using γ,γ -bistrifluoromethylallyl alcohol (8) as the starting material gem-bistrifluoromethylcyclopropane derivatives are synthesized in stereo-selective manner through inter- and intramolecular cyclopropanation with sulfonium ylid.

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- 9) $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 1.28 (6H, t, $J=7.5$ Hz), 3.10 (2H, s), 4.27 (4H, q, $J=7.5$ Hz). $^{19}\text{F-NMR}(\text{CDCl}_3)\delta$: 10 +0.27 (6F, s).
- 10) Benzotrifluoride was used as internal standard. + means high field.
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