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A facile synthesis of per(poly)fluoroalkyl-substituted electrophilic cyclopropane derivatives

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Abstract

Per(poly)fluoroalkyl-substituted electrophilic cyclopropane derivatives are readily prepared in good yields by the reaction of activated methylene compounds (**2**), such as CH_2E_2 (E=CO_2Et, $COCH_3$), with $R_FCH{=}C(I)CO_2Et$ (**1**). © Elsevier Science S.A.

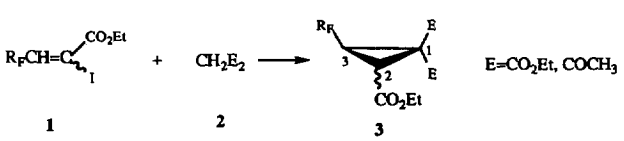
Keywords: Activated methylene compounds; Electrophilic cyclopropane derivatives; β-Per(poly)fluoroalkyl α-iodoacrylates

1. Introduction

Cyclopropane derivatives have attracted special attention because of their potential therapeutic and notable pesticidal activities [1]. In addition, they can also be considered as precursors of specific ring-opened derivatives [2]. Work concerning the synthesis and chemical properties of such cyclopropane derivatives has expanded rapidly in recent years [3]. The appearance of fluorine-containing pyrethroids has stimulated scientists to search for new ways to synthesize cyclopropane derivatives bearing a fluorine-containing group [4]. In this paper, we report a one-step synthetic route for the preparation of per(poly)fluoroalkyl-substituted electrophilic cyclopropane derivatives by the reaction of $R_FCH{=}C(I)CO_2Et$ (**1**) [5] with activated methylene compounds.

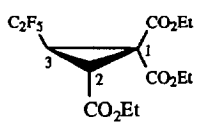
2. Experimental details and results

Methylene compounds (**2**) were treated with NaH; the nucleophile formed was then reacted with $R_FCH{=}C(I)$-CO_2Et (**1**), giving cyclopropane derivatives as the end products.

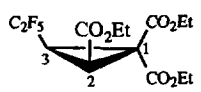


1 2 3

Such a synthesis is illustrated with $C_2F_5CH{=}C(I)CO_2Et$ and $CH_2(CO_2Et)_2$ (a similar result was obtained when (*Z*)-$C_2F_5CH{=}C(I)CO_2Et$ was used). In a typical experiment, 10 mmol of $CH_2(CO_2Et)_2$ (**2a**) in 15 ml of *N,N*-dimethylformamide (DMF) and 7.5 mmol of NaH (80%) were mixed and stirred at room temperature for 30 min. Then 7.5 mmol of $C_2F_5CH{=}C(I)CO_2Et$ (**1a**) was added dropwise into the mixture. The mixture was stirred for 1 h (monitored by gas chromatography (GC) and ^{19}F nuclear magnetic resonance (NMR)). Usual work-up and flash chromatography gave **3a** in 75% yield.



3a trans



3a cis

Compound **3a** (trans). Oil. IR ν_{max}: 1740 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.27 (m, 9H, 3×CH_3), 2.95 (td, *J*=13.2, 7.5 Hz, 1H, C^3-H), 3.10 (d, *J*=7.5 Hz, 1H, C^2-H), 4.24 (m, 6H, 3×CH_2) ppm. ^{19}F NMR (90 MHz, $CDCl_3$, CF_3COOH as standard) δ: 8.54 (s, 3F, CF_3), 40.07 (d, *J*=13.2 Hz, 2F, CF_2-ring) ppm. ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 13.82, 13.98, 14.10 (3×3, 3×CH_3), 28.10 (t, *J*=2.8 Hz, C^2), 29.01 (t, *J*=26.0 Hz, C^3), 40.75 (s, C^1), 62.38, 62.96, 63.10 (3×s, 3×OCH_2), 108.48–124.51 (m, CF_2CF_3), 163.64, 164.17, 166.67 (3×s, 3×CO) ppm. MS (*m/e*): 377 (M^++1, 59), 331 (M^+−EtO, 100), 303 (M^+−CO_2Et, 53), 275 (M^++1−CO_2Et−Et, 66), 185 (M^+−2CO_2Et−Et, 60). Compound **3a** (cis). Oil. IR ν_{max}: 1750 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.32 (m, 1H, 3×CH_3), 2.48 (td, *J*=14.4, 10.2 Hz, 1H, C^3-H), 2.73 (d,

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Table 1
Cyclopropanation of **1** with **2** [a]

Entry	1	2	3 (yield) (cis/trans) [b]
1	$C_2F_5CH=C(I)CO_2Et$ (**1a**)	$CH_2(CO_2Et)_2$ (**2a**)	**3a** (75%) (25/75)
2	$C_2F_5CH=C(I)CO_2Et$	$CH_2(COCH_3)CO_2Et$ (**2b**)	**3b** (70%) [c]
3	$C_2F_5CH=C(I)CO_2Et$	$CH_2(COCH_3)_2$ (**2c**)	**3c** (62%) (0/100) [d]
4	$C_4F_9CH=C(I)CO_2Et$ (**1b**)	$CH_2(CO_2Et)_2$ (**2a**)	**3d** (76%) (25/75)
5	$C_4F_9CH=C(I)CO_2Et$	$CH_2(COCH_3)_2$ (**2c**)	**3e** (68%) (0/100) [d]
6	$ClC_2F_4CH=C(I)CO_2Et$ (**1c**)	$CH_2(CO_2Et)_2$ (**2a**)	**3f** (80%) (24/76)
7	$ClC_2F_4CH=C(I)CO_2Et$	$CH_2(COCH_3)_2$ (**2c**)	**3g** (66%) (0/100) [d]
8	$ClC_4F_8CH=C(I)CO_2Et$ (**1d**)	$CH_2(CO_2Et)_2$ (**2a**)	**3h** (78%) (25/75)
9	$ClC_4F_8CH=C(I)CO_2Et$	$CH_2(COCH_3)_2$ (**2c**)	**3i** (65%) (0/100) [d]

[a] All reactions were run at room temperature for 1–4 h under nitrogen. The ratio of **1**:**2**:NaH = 1:1.25:1.
[b] Isolated yield. The ratio of cis/trans was estimated by GC.
[c] Mixture of four cis/trans isomers.
[d] Only trans isomer was obtained in the reaction. Satisfactory spectral and analytical data of all new compounds were obtained.

J = 10.2 Hz, 1H, C^2-H), 4.27 (m, 6H, 3×CH_2) ppm. ^{19}F NMR (90 MHz, $CDCl_3$, CF_3COOH as standard) δ: 8.19 (s, 3F, CF_3), 33.10 (AB, J = 295.2, 14.5 Hz, 1F, CF-ring), 37.33 (AB, J = 295.2, 14.4 Hz, 1F, CF-ring) ppm. ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 13.93, 14.11, 14.30 (3×3, 3×CH_3), 27.97 (t, J = 25.4 Hz, C^3), 29.71 (t, J = 2.9 Hz, C^2), 37.54 (s, C1), 62.13, 62.54, 63.68 (3×s, 3×OCH_2), 109.0–124.2 (m, CF_2CF_3), 162.54, 164.37, 167.71 (3×s, 3×CO) ppm. MS (m/e): 377 (M^+ + 1, 45), 331 (M^+ − EtO, 57), 303 (M^+ − CO_2Et, 100). Analysis: calculated for $C_{14}H_{17}F_5O_6$: C, 44.68%; H, 4.52%; F, 25.27%; found: C, 44.67%; H, 4.68%; F, 25.48%.

The configurations of the cis and trans isomers were determined by comparison of their proton coupling constants of ^2H–^3H [6]. The cis isomers have a larger $J(^2H–^3H)$ value (10.2 Hz in **3a**) than the trans isomers (7.5 Hz in **3a**). Similar results were obtained when other active methylene compounds, such as ethyl acetoacetate or acetoacetone, were used. The reactivity of the above-mentioned active methylene compounds decreased roughly in the order: $CH_2(CO_2Et)$ > $CH_2(COCH_3)CO_2Et$ > $CH_2(COCH_3)_2$. The length of the R_F chain had little effect on this reaction. β-Pentafluoroethyl α-iodoacrylate (**1a**) and β-nonafluorobutyl α-iodoacrylate (**1b**) gave similar results. Representative results are summarized in Table 1.

3. Conclusions

A versatile cyclopropane reaction is described. The ready availability of the materials, the simplicity of the procedure and the good yields make this approach a useful route to the synthesis of per(poly)fluoroalkyl-substituted cyclopropane derivatives.

Acknowledgements

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