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Preparation of F_2MCPGs via selenoxide elimination

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Dedicated to Prof. Yoshiro Kobayashi on the occasion of his 75th birthday

Abstract

2-(2,2-Difluoro-3-methylenecyclopropyl)glycine derivatives were prepared through selenoxide elimination of **3**, in which a competitive intramolecular substitution reaction proceeded depending on the steric environment.

Keywords: Methylenedifluorocyclopropane; Selenoxide derivative; Glycine derivative

1. Introduction

Methylenecyclopropane derivatives (MCPs) are known as useful intermediates in synthetic organic chemistry [1–4] and are also found in bioactive natural substances such as MCPG and its metabolite MCPF-CoA which show highly inhibitory activity against enoyl-CoA hydratase (crotonase) responsible for fatty acid metabolism [5,6]. It would be expected that introduction of fluorine on the ring of such MCPs alters the chemical reactivities due to the strong electron-withdrawing nature of fluorine as we have recently showed that methylene-*gem*-difluorocyclopropane (F_2MCP) acts as a good Michael acceptor in the reaction with thiol or amine nucleophile [7]. For the synthesis of F_2MCPs [8], we reported that selenoxide elimination of cyclopropylmethyl selenoxide works quite well, while this method cannot be applicable to nonfluorinated counter part due to a facile formation of the cyclopropylmethyl cation prior to methylenation (*syn*-elimination) [7]. In this paper, we describe the preparation of 2-(2,2-difluoro-3-methylenecyclopropyl)glycine (F_2MCPG) derivatives applying the selenoxide methodology and show a limitation of this method based on a competitive intramolecular substitution reaction in these particular cases (see Fig. 1).

2. Results and discussion

We have already reported the preparation of the cyclopropylmethanol derivatives (**1**), the precursors in the present study, in optically pure forms which were converted to the conformationally restricted glutamate analogs (F_2CCGs) [9]. Both isomers of **1** could be converted to the corresponding selenide (**2**) by treating **1** with 2-nitrophenyl selenocyanate and tributylphosphine without the formation of the pyrrolidine derivative (**5**) at this stage. The selenide (**2**) was oxidized by 30% H_2O_2 at 0°C to the selenoxide (**3**), which, without purification, was submitted to thermal reaction. Thus, upon heating in toluene at 80°C for 12–18 h, the selenoxide (**3**) derived from (2*R*,1′*S*,2′*R*)-**1** gave the desired methylenecyclopropane (2*R*,1′*S*)-**4** in 42% yield without the formation of the pyrrolidine compound (**5**), while the selenoxide (**3**) derived from (2*S*,1′*S*,2′*R*)-**1** gave a mixture of the desired methylenecyclopropane (2*S*,1′*S*)-**4** and the pyrrolidine compound (2*S*,3*S*,4*R*)-**5** in 18% and 17% yield, respectively (Scheme 1). In both cases, the yields of the isolated products were low mainly due to the removal of the Boc group during the reaction and due to the decomposition to a complex mixture, but we could not find out by-products derived from skeletal rearrangement or ring-opening of the difluorocyclopropane ring.

The formation of the pyrrolidine (**5**) from one of the diastereomers is possibly explained by considering a steric factor. In the pyrrolidine compound (2*S*,3*S*,4*R*)-**5** possibly formed through an intramolecular displacement of selenoxide by the amide group, the stereochemistry between the ester group and the cyclopropane moiety was *trans*, for

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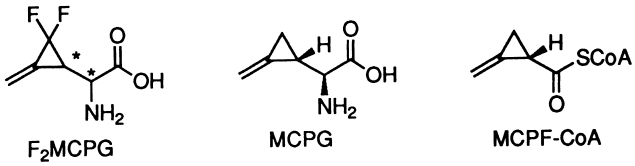
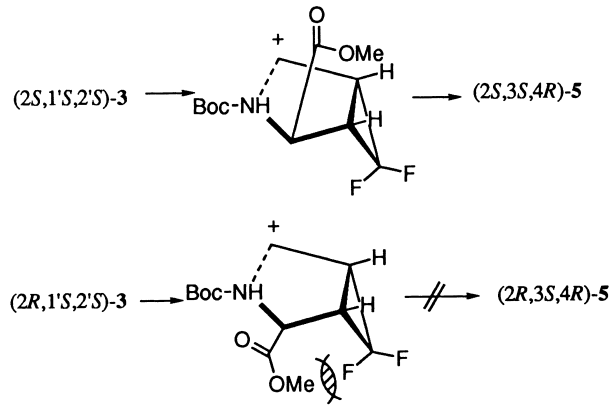


Fig. 1.

which sterically favorable reaction pathway was involved. On the other hand, in the case of the other diastereomer such an intramolecular substitution would be disfavorable due to the steric repulsion between the ester group and the cyclopropane moiety having *cis* relationship as shown in Scheme 2. This result indicated that a competitive reaction to cyclopropylmethyl cation versus *syn*-elimination cannot be excluded in the thermal reaction of difluorocyclopropylmethyl selenoxide, when there exists an efficient intramolecular participation of a nucleophilic center to the carbon atom attached the selenoxide group.



Scheme 2.

3. Experimental details

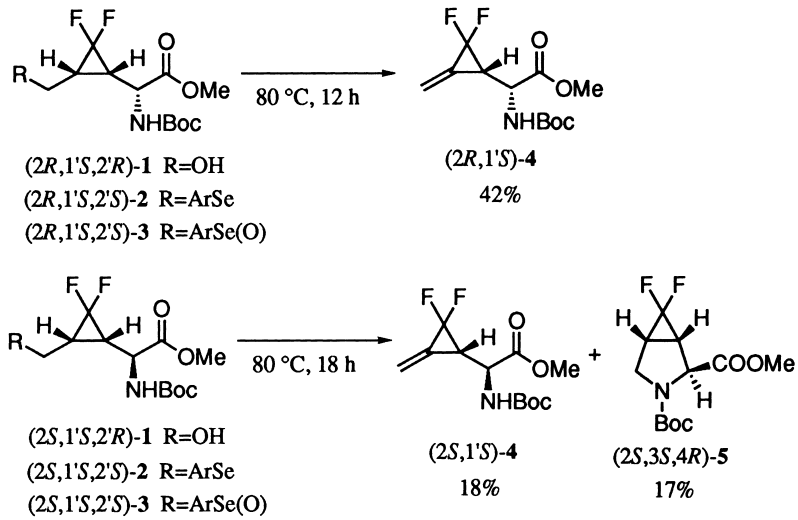
General ^{1}H- and ^{13}C-NMR spectra were taken on a Brucker AM400 or a Varian Gemini-300 spectrometer, and chemical shifts were reported in parts per million (ppm) using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for ^{1}H-NMR, and $CDCl_3$ (77.01 ppm) for ^{13}C-NMR as an internal standard, respectively. ^{19}F-NMR spectra were taken on a Brucker AM400 spectrometer, and chemical shifts were reported in parts per million (ppm) using benzotrifluoride as a standard. Infrared spectra (IR) were recorded on a Perkin-Elmer FTIR-1710 infrared spectrophotometer. Mass spectra (MS) were obtained on a Hitachi M-80 or VG Auto spec. Medium pressure liquid chromatography (MPLC) was performed using prepacked column (silica gel, 50 μm) with UV detector.

3.1. Methyl (2S,1′S,2′S)-N-tert-butyloxycarbonyl-2[-2-(2-nitrophenyl)selenylmethyl-3,3-difluorocyclopropyl]glycinate (2S,1′S,2′S)-2

A mixture of (2*S*,1′*S*,2′*R*)-**1** [9] (407 mg, 1.4 mmol), 2-nitrophenyl selenocyanate (470 mg, 2.1 mmol) and tributylphosphine (0.52 ml, 2.3 mmol) in THF (20 ml) was stirred at room temperature for 2 h. After the reaction mixture was concentrated under reduced pressure, the residue was purified by silica gel column chromatography (hexane: AcOEt=1:1) to give (2*S*,1′*S*,2′*S*)-**2** (537 mg, 79%) as a yellow oil. (2*S*,1′*S*,2′*S*)-**2**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.43 (9 H, s), 2.00 (2 H, dd, *J*=12.36, 7.69 Hz), 3.09 (2 H, m), 3.81 (3 H, s), 4.41 (1 H, t, *J*=9.39 Hz), 5.25 (1 H, d, *J*=9.39 Hz), 7.34 (1 H, ddd, *J*=8.27, 6.46, 1.95 Hz), 7.54 (2 H, ddd, *J*=15.78, 7.99, 1.66 Hz), 8.30(1 H, dd, *J*=8.30, 1.23 Hz).

3.2. Preparation of selenoxide from (2S,1′S,2′S)-2 and its thermal reaction

After a mixture of (2*S*,1′*S*,2′*S*)-**2** (537 mg, 1.1 mmol) and 30% H_2O_2 (1 ml) in THF (10 ml) was stirred for 2 h at 0°C



Scheme 1.

(ice bath), the reaction mixture was diluted with H_2O (30 ml) and extracted with AcOEt (30 ml × 2). The organic extracts were successively washed with $NaHCO_3$ aq and brine, and dried over $MgSO_4$. Removal of solvent under reduced pressure gave the crude selenoxide, which was heated in toluene at 80°C for 18 h. Purification by silica gel column (hexane: AcOEt=3:1) gave (2*S*,1′*S*)-**4** (L-F_2MCPG-I *N*-Boc Me ester) (52.3 mg, 18%) and (2*S*,3*S*,4*R*)-**5** (50.4 mg, 17%), respectively. (2*S*,1′*S*)-**4**: colorless needles; m.p. 48.5–50°C; $[\alpha]_D^{25.6}$ 97.9 (*c* 0.67, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.45 (9 H, s), 2.56 (1 H, m), 3.80 (3 H, s), 4.33 (1 H, brs), 5.15 (1 H, brs), 5.81 (1 H, s), 6.11 (1 H, d, *J*=3.2 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 28.2, 30.9 (t, *J*=12.4 Hz), 50.7, 52.8, 80.5, 105.8 (t, *J*=292.7 Hz), 114.1, 128.3 (t, *J*=7.5 Hz), 154.9, 170.7. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; –64.31 (1 F, dd, *J*=178.8, 5.5 Hz), –75.49 (1 F, d, *J*=178.8 Hz). IR (KBr): 1744, 1681 cm^{-1}. MS(EI) *m/z*; 278 (M+1), 221, 178, 162, 118. Anal. Calcd. for $C_{12}H_{17}F_2NO_4$: C, 51.98; H, 6.18; N, 5.05. Found: C, 52.21; H, 6.30; N, 4.73. (2*S*,3*S*,4*R*)-**5**: yellow oil; $[\alpha]_D^{25.6}$ –103.9 (c 1.80, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.40 (5 H, s), 1.44 (4 H, s), 2.24–2.39 (2 H, m), 3.72–3.96 (2 H, m), 3.78 (3 H, s), 4.52 (0.55 H, s), 4.66 (0.45 H, s). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 25.4 (t, *J*=12.0 Hz), 26.2 (t, *J*=11.9 Hz), 28.2, 28.3, 28.6 (t, *J*=12.8 Hz), 29.4 (t, *J*=12.6 Hz), 45.8, 52.5, 52.6, 58.7, 59.0, 80.8, 112.0 (dd, *J*=297.4, 277.9 Hz), 152.9, 153.5, 170.9, 171.1. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; –66.25 (0.45 F, dt, *J*=164.9, 11.7 Hz), –66.44 (0.55 F, dt, *J*=164.6, 12.1 Hz), –92.16 (0.55 F, d, *J*=164.6 Hz), –92.19 (0.45 F, d, *J*=164.9 Hz). IR (neat): 1756, 1707 cm^{-1}. MS(EI) *m/z*; 278 (M+1), 222, 176. Anal. Calcd. for $C_{12}H_{17}F_2NO_4$: C, 51.98; H, 6.18; N, 5.05. Found: C, 52.59; H, 6.26; N, 4.96.

3.3. D-F_2MCPG-II N-Boc Me ester (2*R*,1′*S*)-**4**

In a similar procedure as above, reaction of (2*R*,1′*S*,2′*R*)-**1** (114 mg, 0.39 mmol) with 2-nitrophenyl selenocyanate (131 mg, 0.59 mmol) and tributylphosphine (0.14 ml, 0.59 mmol) gave the selenide (2*R*,1′*S*,2′*S*)-**2** (153 mg, 79%), which was treated with 30% H_2O_2 (0.5 ml) in THF at 0°C for 2 h to give the crude selenoxide. Upon heating the selenoxide (161 mg) in toluene at 80°C for 12 h and subsequent purification by silica gel column (hexane: AcOEt=1: 1) afforded (2*R*,1′*S*)-**4** (D-F_2MCPG-II *N*-Boc Me ester, 35.7 mg, 42%). (2*R*,1′*S*)-**4**: colorless needles; m.p. 59–60°C; $[\alpha]_D^{25.4}$ 27.5 (*c* 1.79, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.44 (9 H, s), 2.58 (1 H, brs), 3.81 (3 H, s), 4.33 (1 H, brs), 5.08 (1 H, brs), 5.82 (1 H, s), 6.12 (1 H, d, *J*=3.2 Hz). ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ; 28.2, 30.4 (t, *J*=12.3 Hz), 50.7, 52.7, 80.4, 105.9 (dd, *J*=294.3, 291.0 Hz), 114.8, 127.7 (t, *J*=7.4 Hz), 154.8, 170.8. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; –64.70 (1 F, d, *J*=180.4 Hz), –77.3 (1 F, d, *J*=180.4 Hz). MS(EI) *m/z*; 278 (M+1), 221, 178, 162, 118. Anal. Calcd. for $C_{12}H_{17}F_2NO_4$: C, 51.98; H, 6.18; N, 5.05. Found: C, 52.24; H, 6.22; N, 4.81.

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