ISSN 1070-4280, Russian Journal of Organic Chemistry, 2016, Vol. 52, No. 7, pp. 1050–1053. © Pleiades Publishing, Ltd., 2016.
Original Russian Text © D.N. Nikolaev, P.B. Davidovich, L.B. Piotrovskii, 2016, published in Zhurnal Organicheskoi Khimii, 2016, Vol. 52, No. 7, pp. 1056–1059.

Synthesis of Fullerene C_{60} Monoadducts. Cyclopropanation of C_{60} with Sulfonium Ylides

D. N. Nikolaev[a],* P. B. Davidovich[b], and L. B. Piotrovskii[a]

[a] *Institute of Experimental Medicine, ul. Akad. Pavlova 12, St. Petersburg, 197376 Russia*
**e-mail: pp225@yandex.ru*
[b] *St. Petersburg State Institute of Technology, Moskovskii pr. 26, St. Petersburg, 190013 Russia*

Received April 6, 2016

Abstract—3′*H*-Cyclopropa[1,9](C_{60}-I_h)[5,6]fullerene-3′-carboxylic acid can be synthesized in a good yield by cyclopropanation of fullerene C_{60} with 2-(dimethyl-λ^4-sulfanylidene)acetates provided that the ester residue is readily hydrolyzable in acid medium.

DOI: 10.1134/S107042801607023X

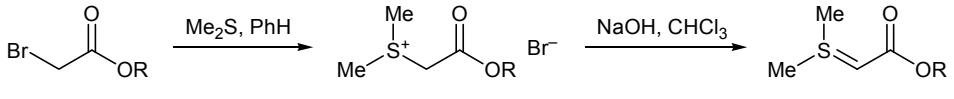
An important problem in the chemistry of medicines is related to the necessity of controlled variation of lipophilicity of biologically active molecules. This goal may be achieved with the use of various monoadducts of fullerene C_{60}. Such adducts are currently synthesized by the Bingel [1] and Prato reactions [2], as well as by cyclopropanation with sulfonium ylides [3]. The Bingel reaction gives cyclopropane-fused C_{60} with two carboxy groups, which is not always convenient for further transformations. The Prato reaction product is a pyrrolidinofullerene whose further transformations may involve both side-chain carboxy group and nitrogen atom. Therefore, one of these functionalities should be protected. Cyclopropanation of C_{60} with sulfonium ylides leads to cyclopropafullerenes having one carboxy group [3].

3′*H*-Cyclopropa[1,9](C_{60}-I_h)[5,6]fullerene-3′-carboxylic acid (**1**) obtained by cyclopropanation of C_{60} with sulfonium ylides is a monoadduct convenient for subsequent modifications. We previously described cyclopropanation of fullerene C_{60} with a sulfonium ylide immobilized on 2-chlorotrityl chloride resin. As might be expected, the solid-phase reaction was regioselective, and only one monoadduct was obtained; however, the yield was low [4]. In continuation of this study, in the present work we examined the effect of different alkyl groups in the ester moiety of (2-alkoxy-2-oxoethyl)(dimethyl)sulfanium bromide on the cyclopropanation of C_{60} in solution and on the overall yield of 3′*H*-cyclopropa[1,9](C_{60}-I_h)[5,6]fullerene-3′-carboxylic acid (**1**).

Alkyl 2-(dimethyl-λ^4-sulfanylidene)acetates **4a**–**4d** were synthesized as shown in Scheme 1. Initial alkyl bromoacetates **2a**–**2d** and (2-alkoxy-2-oxoethyl)(dimethyl)sulfanium bromides **3a**–**3d** were prepared as described in [5–8]. Compounds **3a**–**3d** showed in the ^{1}H NMR spectra signals from methyl and methylene protons at δ 2.6–3.4 (s, Me_2S) and 4–5 ppm (s, SCH_2). In the ^{13}C NMR spectra of **3a**–**3d**, the methyl, methylene, and carbonyl carbon atoms resonated at δ_C 25–26, 35–37, and 163–166 ppm, respectively. A strong ester carbonyl stretching band was observed in the IR spectra of **3a**–**3d** at 1719–1737 cm^{-1}; and their mass spectra contained ion peaks with *m*/*z* values corresponding to the cation.

Alkyl 2-(dimethyl-λ^4-sulfanylidene)acetates **4a**–**4d** were synthesized according to the procedure described in [8], by treatment of a solution of **3a**–**3d** in chloroform with a 12.5 N alkali solution on cooling. Compounds **4a**–**4d** are unstable at room temperature, and

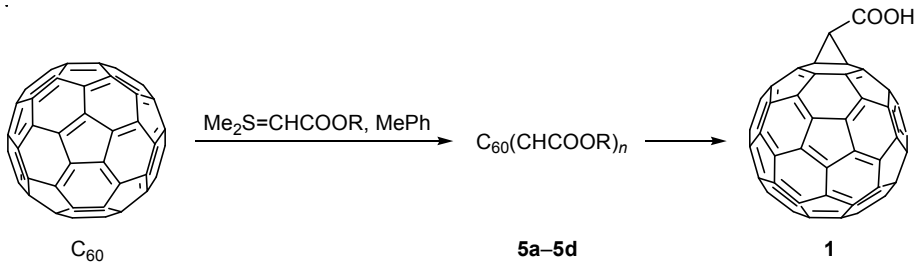
Scheme 1.



2a–2d **3a–3d** **4a–4d**

R = Et (**a**), *t*-Bu (**b**), $PhCH_2$ (**c**), Ph_2CH (**d**).

Scheme 2.



R = Et (**a**), *t*-Bu (**b**), $PhCH_2$ (**c**), Ph_2CH (**d**); $n = 1$.

they should be stored in a tightly closed vessel in a freezing chamber at –16°C. Compounds **4b**–**4d** are white solids, and **4a** is a yellowish oil. The ^1H NMR spectra of **4a**–**4d** contained signals from methyl and CH protons (Me_2S=CH) as an unresolved broadened singlet at δ 2.5–3.0 ppm. In the ^{13}C NMR spectra of **4b**–**4d**, signals from the CH_3, =CH, and C=O carbon atoms were located at δ_C 30, 32, and 169–170 ppm, respectively. The IR spectra of **4b**–**4d** displayed a strong ester carbonyl stretching band at 1610–1626 cm^{-1}. Despite ~100-cm^{-1} low-frequency shift relative to reference values, the position of this band is consistent with published data for structurally related compounds [8].

The cyclopropanation of fullerene C_{60} with ylides **4b**–**4d** was carried out according to Scheme 2. Cyclopropanation of C_{60} always leads to the formation of mixtures of mono- and polyaddition products. Monoadducts **5a**–**5d** were isolated by column chromatography. In enlarged syntheses, compounds **5c** and **5d** were easiest to isolate, whereas the isolation of **5a** was the most difficult, and double chromatography was necessary to purify it from unreacted C_{60} and polyadducts.

All monoadducts **5a**–**5d** are black solids. They showed in the ^1H NMR spectra a singlet at δ 4.5–5.0 ppm due to CH proton in the cyclopropane fragment. The corresponding carbon signal was observed in the ^{13}C NMR spectra of **5a**–**5d** at δ_C 39–41 ppm, and signals from the fullerene core and carbonyl carbon atom were located at δ_C 35–37 and 164–166 ppm, respectively. A strong absorption band at 1710–1735 cm^{-1} in the IR spectra was assigned to the ester carbonyl group. The molecular weights of **5a**–**5d** determined from the MALDI mass spectra confirmed the formation of monoadducts. The UV spectra of **5a**–**5d** displayed a strong absorption maximum at λ 327 nm, a weak narrow band with its maximum at λ 427 nm, and a weak broadened band centered at 493 nm, which are typical of methanofullerenes [9].

The ester group in **5a**–**5d** was converted into carboxy by different methods, depending on the ester alkyl group. When a solution of **5a** in toluene was treated with sodium hydride, followed by addition of methanol (according to Hirsch [10]), most part of the substrate remained unchanged. Esters **5b** and **5d** were successfully hydrolyzed with *p*-toluenesulfonic acid monohydrate and aqueous trifluoroacetic acid. The use of *p*-toluenesulfonic acid monohydrate is more economic. To remove the benzyl group from **5c** we initially tried classical atmospheric pressure hydrogenation over 5% Pd/C; however, the desired product was not obtained. Acid hydrolysis of **5c** with aqueous trifluoroacetic acid was also unsuccessful. Alkaline hydrolysis of ester group is inapplicable to fullerene derivatives because of formation of fullerenols [11]. Development of methods for removal of benzyl protection from fullerene derivatives is important from the practical viewpoint, in particular for the synthesis of fullerene-containing peptides.

Thus, we succeeded in obtaining 3′*H*-cyclopropa[1,9](C_{60}-I_h)[5,6]fullerene-3′-carboxylic acid (**1**) in a good yield (85–90%) only from monoadducts **5b** and **5d**. The spectral and analytical data of **1** coincided with those reported in [4]. Taking into account easy isolation by column chromatography and mild removal of the benzhydryl protecting group, compound **5d** was found to be the most convenient monoadduct for scaling up of the cyclopropanation reaction from 1 to 2 mmol of initial C_{60}. Benzhydryl bromoacetate is readily available by acid-catalyzed esterification of bromoacetic acid with benzhydrol with azeotropic removal of water [7].

EXPERIMENTAL

The UV spectra were measured on a Beckman Coulter DU 800 spectrophotometer (USA) in the range λ 240–640 nm using decane as solvent. The IR spectra (400–4000 cm^{-1}) were recorded on a Schimadzu FTIR

8400S spectrometer from samples pressed with KBr. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer at 400 and 100 MHz, respectively. The mass spectra (MALDI) were obtained on a Bruker Daltonics UltrafleXtreme MALDI TOF/TOF instrument, and the ESI mass spectra were taken on a Bruker Maxis 4G spectrometer (Germany).

Fullerene C_{60} with a purity of 99.7–99.8% (*NeoTekProdakt*, St. Petersburg, Russia), bromoacetic acid, benzhydrol, methylene chloride, ethanol, *tert*-butyl alcohol, benzyl alcohol, acetonitrile, chloroform, hexane, dimethyl sulfide, *o*-dichlorobenzene, *p*-toluenesulfonic acid monohydrate, sodium hydroxide, potassium carbonate, toluene, pyridine, dioxane, and silica gel (grain size 0.06–0.2 mm, pore diameter 60 Å; Acros) were commercial products.

Alkyl bromoacetates **2a** [5], **2b**, **2c** [6], and **2d** [7] were synthesized by known methods. IR spectrum: ν 1742 cm^{-1} (C=O). ^{1}H NMR spectrum of **2d** ($CDCl_3$), δ, ppm: 3.97 s (2H), 7.09 s (1H), 7.40–7.54 m (10H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 26.20 (CH_2), 78.81 (CH), 127.30–128.79 (C^o, C^m, C^p), 139.57 (C^i), 166.29 (C=O).

Compounds **3a**–**3d** and **4a**–**4d** were synthesized according to the procedures described in [8].

(2-Ethoxy-2-oxoethyl)(dimethyl)sulfanium bromide (3a). Yield 60%, white crystals, mp 82–84°C; published data [12]: mp 85–87°C. IR spectrum: ν 1730 cm^{-1} (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.16 t (3H, C**H**$_3$CH$_2$), 3.33 s [6H, $(CH_3)_2$S], 4.12 q (2H, C**H**$_2$CH$_3$), 4.93 s (2H, SCH_2). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.21 (**C**H$_3$CH$_2$), 25.20 [$(CH_3)_2$S], 36.51 (SCH_2), 63.43 (OCH_2), 163.76 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 149.0630 (100) $[M - Br]^+$, 374.0778 (60) $[M + Br + M]^+$.

(2-*tert*-Butoxy-2-oxoethyl)(dimethyl)sulfanium bromide (3b). Yield 75%, white crystals, mp 112–114°C. IR spectrum: ν 1719 cm^{-1} (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.45 s [9H, $(CH_3)_3$C], 3.44 s [6H, $(CH_3)_2$S], 5.00 s (2H, SCH_2). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 25.25 [$(CH_3)_2$S], 27.97 [(**C**H$_3$)$_3$C], 36.97 (SCH_2), 85.88 [O**C**$(CH_3)_3$], 163.31 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 177.0946 (100) $[M - Br]^+$, 433.1075 (60) $[M + Br + M]^+$.

(2-Benzyloxy-2-oxoethyl)(dimethyl)sulfanium bromide (3c). Yield 82%, white crystals, mp 78–80°C. IR spectrum: ν 1737 cm^{-1} (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.36 s [6H, $(CH_3)_2$S], 5.18 s (2H, SCH_2), 5.23 s (2H, OCH_2), 7.33 m (5H, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 25.27 [$(CH_3)_2$S], 35.69 (SCH_2), 67.91 (OCH_2), 128.00–129.00 (C^o, C^m, C^p), 134.97 (C^i), 164.35 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 211.0789 (100) $[M - Br]^+$, 501.0766 (60) $[M + Br + M]^+$.

[2-(Diphenylmethoxy)-2-oxoethyl](dimethyl)-sulfanium bromide (3d). Yield 70%, white crystals, mp 111–113°C. IR spectrum: ν 1736 cm^{-1} (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.15 s, 2.17 s, and 2.67 s [6H, $(CH_3)_2$S]; 3.30 s and 3.95 s (2H, SCH_2), 6.94 s (1H, OCH), 7.39 m (10H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 25.97 [$(CH_3)_2$S], 35.95 (SCH_2), 77.70–78.72 (CH), 127.12–128.61 (C^o, C^m, C^p), 139.34–139.88 (C^i), 166.19 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 287.1100 (100) $[M - Br]^+$, 653.1389 (60) $[M + Br + M]^+$.

Ethyl 2-(dimethyl-λ^4-sulfanylidene)acetate (4a). Yield 90%, yellowish oil. IR spectrum: ν 1626 cm^{-1} (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.01 t (3H, C**H**$_3$CH$_2$), 3.76 q (2H, C**H**$_2$CH$_3$), 2.56 s [7H, $(CH_3)_2$SCH]. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.45 (**C**H$_3$CH$_2$), 30.80 [$(CH_3)_2$S], 32.76 (SCH), 59.72 (OCH_2), 170.13 (C=O).

***tert*-Butyl 2-(dimethyl-λ^4-sulfanylidene)acetate (4b).** Yield 92%, white amorphous solid. IR spectrum: ν 1610 cm^{-1} (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.30 s [9H, $(CH_3)_3$C], 2.60 s [7H, $(CH_3)_2$SCH]. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 28.95 [(**C**H$_3$)$_3$C], 30.69 [$(CH_3)_2$S], 33.00 (SCH), 76.55 [**C**$(CH_3)_3$], 170.42 (C=O).

Benzyl 2-(dimethyl-λ^4-sulfanylidene)acetate (4c). Yield 96%, white amorphous solid. IR spectrum: ν 1620 cm^{-1} (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.50 s [6H, $(CH_3)_2$S], 2.90 s (1H, SCH), 5.00 s (2H, OCH_2), 7.24 m (5H, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 30.37 [$(CH_3)_2$S], 32.68 (SCH), 63.71 (OCH_2), 127.30–128.30 (C^o, C^m, C^p), 138.51 (C^i), 169.67 (C=O).

Diphenylmethyl 2-(dimethyl-λ^4-sulfanylidene)-acetate (4d). Yield 96%, white amorphous solid. IR spectrum: ν 1620 cm^{-1} (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.70 s [6H, $(CH_3)_2$S], 3.10 s (1H, SCH), 6.89 s (1H, OCH), 7.30–7.40 m (10H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 30.40 [$(CH_3)_2$S], 32.61 (SCH), 74.29 (OCH), 127.12–128.27 (C^o, C^m, C^p), 142.52 (C^i), 169.18 (C=O).

Alkyl 3′*H*-cyclopropa[1,9][C_{60}-I_h][5,6]fullerene-3′-carboxylates 5a–5d (*general procedure*). A 2-L

flask was charged with 900 mL of toluene and 720 mg (1 mmol) of C_{60}, and the mixture was stirred until it became homogeneous. A solution of 1.8 mmol of compound **4a**–**4d** in chloroform was added dropwise, and the mixture was stirred for 3 h (TLC, toluene–hexane, 1:3). The originally violet solution turned dark red. The mixture was evaporated under reduced pressure, the black solid residue was dissolved in a minimum amount of *o*-dichlorobenzene, 1/2 to 1/3 of the solution was mixed with 5–6 g of silica gel (40–60 μm, 60 Å), and the mixture was evaporated under reduced pressure; the remaining part of the solution was applied to silica gel in a similar way. Monoadducts **5a**–**5d** were isolated by column chromatography using 120–130 or 250–270 g of the sorbent for the adduct obtained, respectively, from 1 or 2 mmol of C_{60}. Pure monoadduct **5a** was isolated by repeated chromatography; unreacted C_{60} was eluted with hexane, and compound **5a**, with toluene–hexane (1:3 to 1:2).

Ethyl 3′*H*-cyclopropa[1,9](C$_{60}$-*I*$_h$)[5,6]fullerene-3′-carboxylate (5a). Yield 30%. IR spectrum: ν 1734 cm^{-1} (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.00 t (3H, C**H**$_3$CH$_2$), 4.21–4.26 q (2H, OCH$_2$), 4.50 s (3′-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.30 (**C**H$_3$CH$_2$), 40.40 (C$^{3'}$), 70.40 (C_{sp^3} in C_{60}), 83.8 (OCH$_2$), 140.00–147.00 (C_{sp^2} in C_{60}), 165.40 (C=O). Mass spectrum: *m*/*z* 806.0375 (I_{rel} 70%).

***tert*-Butyl 3′*H*-cyclopropa[1,9](C$_{60}$-*I*$_h$)[5,6]fullerene-3′-carboxylate (5b).** Yield 45%. IR spectrum: ν 1734 cm^{-1} (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.52 s [9H, (CH$_3$)$_3$C], 4.49 s (1H, 3′-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 28.40 [(**C**H$_3$)$_3$C], 40.90 (C$^{3'}$), 71.40 (C_{sp^3} in C_{60}), 83.40 [**C**(CH$_3$)$_3$], 140.00–147.00 (C_{sp^2} in C_{60}), 164.80 (C=O). Mass spectrum: *m*/*z* 834.0673 (I_{rel} 40%).

Benzyl 3′*H*-cyclopropa[1,9](C$_{60}$-*I*$_h$)[5,6]fullerene-3′-carboxylate (5c). Yield 55%. IR spectrum: ν 1734 cm^{-1} (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.85 s (1H), 5.52 s (2H), 7.20–7.55 m (5H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 39.02 (C$^{3'}$), 69.70 (OCH$_2$), 70.60 (C_{sp^3} in C_{60}), 127.30–128.30 (C^o, C^m, C^p), 140.00–147.00 (C^i, C_{sp^2} in C_{60}), 166.30 (C=O). Mass spectrum: *m*/*z* 868.0540 (I_{rel} 70%).

Diphenylmethyl 3′*H*-cyclopropa[1,9](C$_{60}$-*I*$_h$)-[5,6]fullerene-3′-carboxylate (5d). Yield 55%. IR spectrum: ν 1734 cm^{-1} (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.91 s (1H), 7.19–7.54 m (10H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 39.10 (C$^{3'}$), 70.5 (C_{sp^3} in C_{60}), 79.10 (OCH), 127.20–128.70 (C^o, C^m, C^p), 140.00–147.00 (C^i, C_{sp^2} in C_{60}), 164.70 (C=O). Mass spectrum: *m*/*z* 944.0825 (I_{rel} 30%).

3′*H*-Cyclopropa[1,9](C$_{60}$-*I*$_h$)[5,6]fullerene-3′-carboxylic acid (1). Monoadduct **5b** or **5d**, 0.45–0.55 mmol, was dissolved in 100–120 mL of *o*-dichlorobenzene under stirring. *p*-Toluenesulfonic acid monohydrate, 3 equiv, was added, and the mixture was stirred at a bath temperature of 90°C until the initial compound disappeared (TLC, *o*-dichlorobenzene–pyridine, 3:1). The mixture was cooled and extracted with two 20–30-mL portions of water. The organic phase was evaporated under reduced pressure, and the black solid residue was dispersed in 80–100 mL of ethanol, separated by centrifugation, washed with acetone (20 mL), diethyl ether (20 mL), and hexane (20 mL) (each time by grinding and subsequent centrifugation), and dried in a vacuum desiccator. Yield 85–90%.

The authors thank Marie Curie FP7-PEOPLE-2010-IRSES (project no. 269138 MC-IRSES) for financial support and Prof. B.L. Mil'man for recording and discussing the mass spectra.

REFERENCES

1. Bingel, C., *Chem. Ber*., 1993, vol. 126, p. 1957.
2. Prato, M. and Maggini, M., *Acc. Chem. Res*., 1998, vol. 31, p. 519.
3. Wang, Y., Cao, J., Schuster, D.I., and Wilson, S.R., *Tetrahedron Lett*., 1995, vol. 36, p. 6843.
4. Nikolaev, D.N., Klimenicheva, Yu.S., Davidovich, P.B., and Piotrovskii, L.B., *Russ. Chem. Bull., Int. Ed*., 2012, vol. 61, p. 853.
5. Natelson, S. and Gottfried, S., *Organic Syntheses*, Smith, L.I., Ed., New York: Wiley, 1943, vol. 23, p. 37.
6. Shchukina, L.A. and Zhuze, A.L., *Zh. Obshch. Khim*., 1967, vol. 37, p. 1980.
7. Paredes, R., Agudelo, F., and Taborda, G., *Tetrahedron Lett*., 1996, vol. 37, p. 1965.
8. Payne, G.B., *J. Org. Chem*., 1967, vol. 32, p. 3351.
9. Isaacs, L., Wehwig, A., and Diederich, F., *Helv. Chim. Acta*, 1993, vol. 76, p. 1231.
10. Lamparth, I. and Hirsch, A., *J. Chem. Soc., Chem. Commun*., 1994, p. 1727.
11. Li, J., Takeuchi, A., Ozawa, M., Li, X., Saigo, K., and Kitazawa, K., *J. Chem. Soc., Chem. Commun*., 1993, p. 1784.
12. Speziale, A.J., Tung, C.C., Ratts, K.W., and Yao, A., *J. Am. Chem. Soc*., 1965, vol. 87, p. 3460.