Russian Journal of Organic Chemistry, Vol. 39, No. 10, 2003, pp. 1489–1492. Translated from Zhurnal Organicheskoi Khimii, Vol. 39, No. 10, 2003, pp. 1558–1560.

Prostanoids: LXXXVI.* Synthesis and Reductive Transformations of 2-Chloro-4,4-ethylenedioxy-3-phenylsulfanyl-2-cyclopentenone

N. A. Ivanova, A. A. Khusainova, F. G. Shangiraeva, R. R. Akhmetvaleev, and M. S. Miftakhov

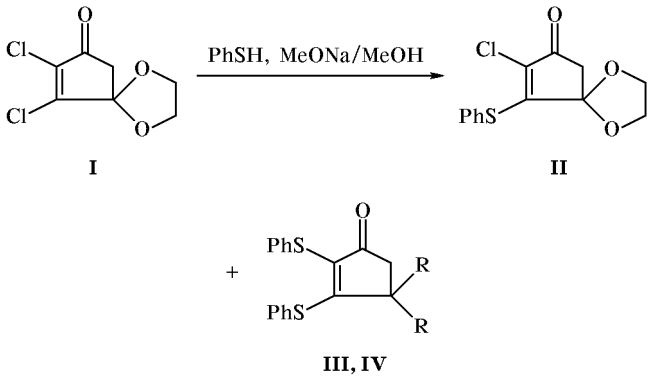
Institute of Organic Chemistry, Ufa Research Center, Russian Academy of Sciences, pr. Oktyabrya 71, Ufa, 450054 Bashkortostan, Russia
e-mail: bioreg@anrb.ru

Received April 17, 2002

Abstract—The reduction of 2-chloro-4,4-ethylenedioxy-3-phenylsulfanyl-2-cyclopentenone with sodium tetrahydridoborate in ethanol yields 3-chloro-4-hydroxy-2-phenylsulfanyl-2-cyclopentenone, while with the use of lithium aluminum hydride in tetrahydrofuran or the system Zn/NH_4Cl in methanol products of more profound reduction are obtained.

Oxygenated cyclopentenes having a phenyl vinyl sulfone fragment attract interest as central cyclopentenone building blocks in the synthesis of prostanoids according to the triple convergent coupling scheme [2–4]. With the goal of developing approaches to such compounds on the basis of hexachloropentadiene derivatives, in the present work we examined the reduction of phenylsulfanylcyclopentenone **II** under various conditions. Compound **II** was synthesized in more than 80% yield by reaction of previously reported 2,3-dichloro-4,4-ethylenedioxy-2-cyclopentenone (**I**) [5] with sodium benzenethiolate in methanol (Scheme 1). The minor product of this reaction was 2,3-bis(phenylsulfanyl) derivative **III** (~10%) which can readily be converted into symmetric diketone **IV** by acid hydrolysis (yield (87%).

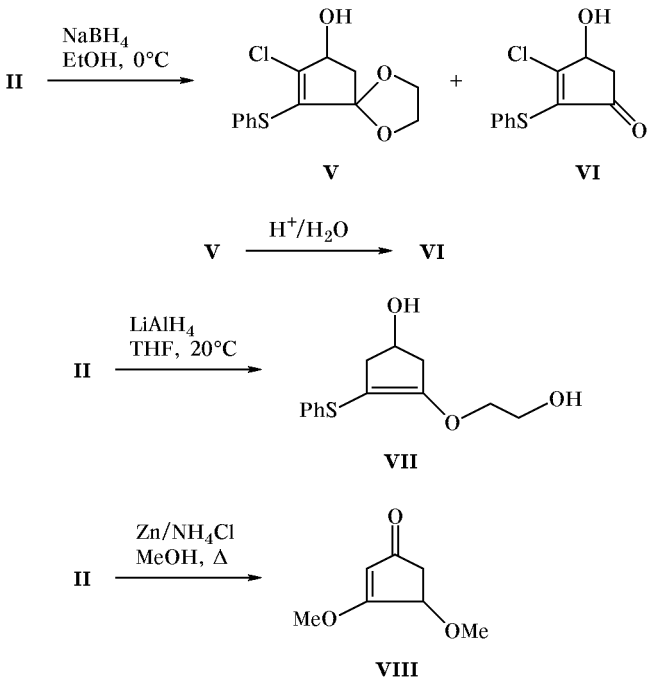
Scheme 1.



III, R = OCH_2CH_2O; **IV**, RR = O.

We examined the reduction of cyclopentenone **II** with the use of $NaBH_4$ in ethanol, $LiAlH_4$ in THF,

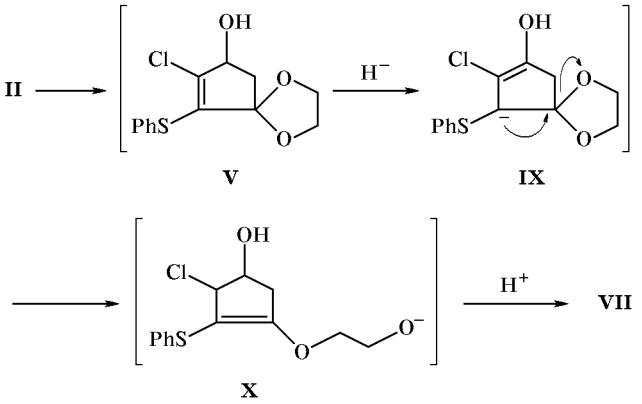
Scheme 2.



* For communication LXXXV, see [1].

1070-4280/03/3910-1489 $25.00 © 2003 MAIK "Nauka / Interperiodica"

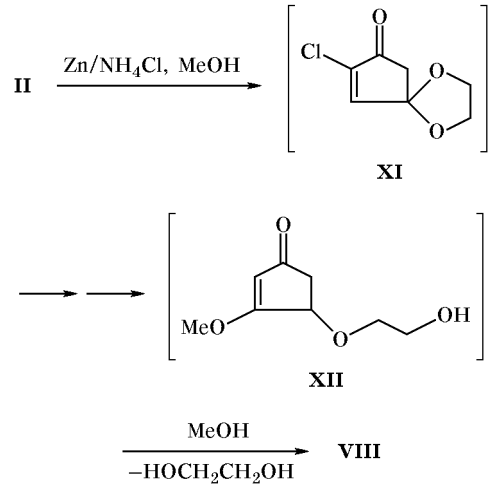
Scheme 3.



and Zn/NH_4Cl in MeOH. The hydride reducing agents were found to afford different reduction products. In the reduction with sodium tetrahydridoborate, followed by treatment of the reaction mixture with acetone, we isolated expected alcohol **V** and hydroxycyclopentenone **VI** (Scheme 2). The latter was the only product when the reaction mixture was subjected to acid hydrolysis. Ready hydrolysis of related acetals in neutral media was also observed by us previously [6, 7]; this process is favored by intramolecular assistance by the existing hydroxy group.

The reduction of compound **II** with $LiAlH_4$ in tetrahydrofuran gave an anomalous product, hydroxycyclopentene **VII**. Unusual reduction product, dimethoxy derivative **VIII**, was also obtained by heating of cyclopentenone **II** with Zn/NH_4Cl in MeOH (Scheme 2). Probable mechanisms of formation of anomalous reduction products **VII** and **VIII** are of undoubted interest. The transformation **II** → **VII** was presumed to involve intermediate **X** which is likely to result from successive reduction of the ketone group in **II** to hydroxy, saturation of the double bond in **V** via hydride transfer, and stabilization of anion **IX** by opening of the dioxolane ring. Reductive elimination of the chlorine atom and subsequent protonation of enolate **X** lead to formation of final product **VII** (Scheme 3).

Scheme 4.



Presumably, the initial stage in the reaction of sulfide **II** with Zn/NH_4Cl in MeOH is reductive elimination of the phenylsulfanyl group. Next follows Michael addition of methanol to enone **XI** and synchronous elimination of the chlorine atom from sp^2-hybridized carbon atom and opening of the dioxolane ring. Transetherification of enol ether **XII** with MeOH yields 3,4-dimethoxycyclopentenone **VIII** (Scheme 4).

3-Chloro-4-hydroxy-2-phenylsulfanyl-2-cyclopentenone (**VI**) obtained by reduction of ketone **II** with sodium tetrahydridoborate is promising as intermediate product in the syntheses of prostanoids, which we plan to perform.

EXPERIMENTAL

The IR spectra were recorded on UR-20 and Specord M-80 spectrometers from samples prepared as thin films or suspensions in mineral oil. The ^1H and ^{13}C NMR spectra were obtained on a Bruker AM-300 spectrometer (300.13 and 75.47 MHz, respectively) using $CDCl_3$ as solvent and reference (δ 7.27 ppm, δ_C 77.00 ppm). The mass spectra (electron impact, 20 and 70 eV) were run on an MKh-1306 instrument (ion source temperature 75–100°C). The progress of reactions was monitored by TLC using Silufol plates (eluent hexane–ethyl acetate); spots were visualized by treatment with an alkaline solution of potassium permanganate [8].

Reaction of 2,3-dichloro-2-cyclopentenone (I) with sodium benzenethiolate. Benzenethiol, 1.1 g (10 mmol), was added with stirring to a solution of 0.54 g (10 mmol) of sodium methoxide in 10 ml of methanol, and a solution of 1.4 g (6.7 mmol) of ketone **I** in 15 ml of methanol was added dropwise. The mixture was stirred for 1 h, an equal volume of water was added, and the mixture was extracted with chloroform (3 × 30 ml). The combined extracts were washed with a saturated aqueous solution of sodium chloride (3 × 10 ml) and dried over $MgSO_4$, and the solvent was distilled off. Recrystallization of the residue from petroleum ether–ethyl acetate (1 : 1) gave 1.71 g (85%) of sulfide **II**. The mother liquor was evaporated, and the residue was subjected to chromatography to isolate 0.2 g (10%) of bis-sulfide **III**. Compound **III** was kept for 2 h in a 1 : 1 mixture

of methanol with 10% hydrochloric acid at room temperature. We thus isolated diketone **IV** in 87% yield.

2-Chloro-4,4-ethylenedioxy-3-phenylsulfanyl-2-cyclopentenone (II). mp 65°C. IR spectrum, ν, cm^{-1}: 1580, 1732. ^1H NMR spectrum, δ, ppm: 2.75 s (2H, 5-H), 3.72 m (2H, CH_2O), 3.91 m (2H, CH_2O), 7.35–7.58 m (5H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 47.02 (C^5), 65.74 (CH_2O), 110.54 (C^4), 126.82 (C^2), 128.79 (C^o), 129.50 (C^p), 132.14 (C^i), 135.18 (C^m), 163.43 (C^3), 192.19 (C^1). Mass spectrum: *m*/*z* 282. Found, %: C 55.41; H 3.83; Cl 12.38; S 11.24. $C_{13}H_{11}ClO_3S$. Calculated, %: C 55.22; H 3.92; Cl 12.54; S 11.34.

4,4-Ethylenedioxy-2,3-bis(phenylsulfanyl)-2-cyclopentenone (III). Colorless oily substance. IR spectrum, ν, cm^{-1}: 1575, 1730. ^1H NMR spectrum, δ, ppm: 2.70 s (2H, CH_2), 3.61 m (2H, CH_2O), 3.75 m (2H, CH_2O), 7.10–7.40 m (10H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 47.77 (C^5), 65.58 (CH_2O), 111.17 (C^4), 126.64 and 128.88 (C^p), 128.29 and 129.49 (C^i), 128.68 and 128.79 (C^o), 129.49 and 132.12 (C^m), 132.10 (C^2), 169.52 (C^3), 195.53 (C^1). Found, %: C 64.10; H 4.69; S 18.17. $C_{19}H_{16}O_3S_2$. Calculated, %: C 64.02; H 4.52; S 17.99.

2,3-Bis(phenylsulfanyl)-2-cyclopentene-1,4-dione (IV). Colorless oily substance. IR spectrum, ν, cm^{-1}: 1745. ^1H NMR spectrum, δ, ppm: 3.05 s (2H, CH_2), 7.22–7.35 m (10H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 42.64 (C^5), 128.45 (C^i), 128.65 (C^i), 128.68 (C^p), 128.91 (C^o), 132.51 (C^m), 152.54 (C^2, C^3), 192.43 (C^1, C^4). Found, %: C 65.12; H 3.79; S 20.63. $C_{17}H_{12}O_2S_2$. Calculated, %: C 65.25; H 3.87; S 20.52.

Reduction of ketone II with $NaBH_4$. Sodium tetrahydridoborate, 0.03 g (0.8 mmol) was added at 0°C to a solution of 0.56 g (2 mmol) of ketone **II** in 10 ml of methanol. The mixture was stirred for 1 h, 3 ml of acetone was added, and the mixture was evaporated. Water, 10 ml, was added to the residue, the product was extracted into methylene chloride, the extract was dried over $MgSO_4$ and evaporated, and the residue was subjected to chromatography on silica gel using petroleum ether–ethyl acetate (8:2) as eluent. We isolated 0.47 g (82%) of hydroxy acetal **V** and 0.06 g (13%) of enone **VI**. Compound **VI** was obtained in 89% yield when the reaction mixture was treated with 5 ml of 5% hydrochloric acid.

2-Chloro-4,4-ethylenedioxy-3-phenylsulfanyl-2-cyclopenten-1-ol (V). Yellow oily substance. IR spectrum, ν, cm^{-1}: 1615, 3400. ^1H NMR spectrum, δ, ppm: 2.11 d (1H, 5-H_A, J = 4, 16 Hz), 2.6 d.d (1H, 5-H_B, J = 4, 16 Hz), 3.70–3.90 m (4H, CH_2O), 4.60 br.s (1H, 4-H), 7.10–7.3 m (5H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 45.22 (C^5), 66.13 and 65.76 (CH_2O), 70.96 (C^1), 115.20 (C^4), 146.88 (C^2), 130.14 (C^3), 128.01 (C^p), 129.09 (C^o), 129.95 (C^m), 132.19 (C^i). Found, %: C 54.74; H 4.53; Cl 12.28; S 11.18. $C_{13}H_{13}ClO_3S$. Calculated, %: C 54.83; H 4.61; Cl 12.45; S 11.26.

3-Chloro-4-hydroxy-2-phenylsulfanyl-2-cyclopenten-1-one (VI). Yellow oily substance. IR spectrum, ν, cm^{-1}: 1590, 1630, 3400. ^1H NMR spectrum, δ, ppm: 2.50 d.d (1H, 5-H, J = 3, 18 Hz), 2.90 d.d (1H, 5-H, J = 6, 18 Hz), 3.44 br.s (1H, OH), 4.77 br.s (1H, 4-H), 7.10–7.40 m (5H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 44.42 (C^5), 73.50 (C^4), 126.83 (C^p), 128.09 (C^o), 131.81 (C^i), 134.82 (C^m), 146.88 (C^2), 167.31 (C^3), 197.36 (C^1). Found, %: C 55.02; H 3.92; Cl 14.95; S 13.41. $C_{11}H_9ClO_2S$. Calculated, %: C 54.89; H 3.77; Cl 14.73; S 13.32.

3-(2-Hydroxyethoxy)-4-phenylsulfanyl-3-cyclopenten-1-ol (VII). A solution of 0.2 g (0.7 mmol) of ketone **II** in 2 ml of anhydrous THF was added dropwise to a suspension of 0.03 g (0.84 mmol) of $LiAlH_4$ in 5 ml of anhydrous diethyl ether, while stirring at room temperature under argon. The mixture was stirred for 3 h, 3 ml of water was added, and the product was extracted into chloroform (3 × 10 ml). The combined organic extracts were washed with a saturated solution of sodium chloride, dried over $MgSO_4$, and evaporated. The residue was subjected to chromatography on silica gel using chloroform–methanol (40:1) as eluent. Yield 0.10 g (56%). Colorless oily substance. IR spectrum, ν, cm^{-1}: 1590, 1740. ^1H NMR spectrum, δ, ppm: 2.20 d (1H, 2-H, J = 15.4 Hz), 2.72 d.d (1H, 2-H, J = 15.4, 6.3 Hz), 2.43 d (1H, 4-H, J = 16.7 Hz), 2.75 d.d (1H, 4-H, J = 16.7, 6.6 Hz), 3.60 br.s (4H, CH_2O, OH), 3.91 br.s (2H, CH_2O), 4.30 m (1H, 1-H), 7.01–7.23 m (5H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 40.51 (C^2); 42.90 (C^5); 60.24 (CH_2OH); 67.15 (C^1); 71.15 (CH_2O); 97.79 (C^3); 125.26, 127.37, 128.67, 135.46 (C_6H_5); 158.45 (C^4). Found, %: C 62.01; H 6.55. $C_{13}H_{16}O_3S$. Calculated, %: C 61.89; H 6.39; S 12.71.

3,4-Dimethoxy-2-cyclopentenone (VIII). A mixture of 0.20 g (0.7 mmol) of ketone **II** and 0.5 g (7.7 mmol) of zinc dust in 5 ml of anhydrous MeOH was heated under reflux until the conversion of the initial ketone was complete (3 h, TLC). The mixture was diluted with chloroform, filtered from zinc, washed with a saturated solution of sodium chloride, dried over $MgSO_4$, and evaporated. The residue was subjected to chromatography on silica gel using

benzene–methanol (9 : 1) as eluent. Yield 0.11 g (59%). IR spectrum, ν, cm^{-1}: 1605, 1740. ^1H NMR spectrum, δ, ppm: 2.40 d.d (1H, 5-H, J = 2.4, 17.7 Hz), 2.72 d.d (1H, 5-H, J = 6.6, 17.7 Hz), 3.47 s (3H, OMe), 3.92 s (3H, OMe), 4.45 d.d (1H, 4-H, J = 2.4, 6.6 Hz), 5.37 s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 41.35 (C^5), 57.74 (OMe), 59.02 (OMe), 77.04 (C^4), 105.77 (C^2), 186.95 (C^3), 201.12 (C^1). Found, %: C 88.67; H 11.33. C_8H_{12}. Calculated, %: C 88.82; H 11.18.

This study was financially supported by the Russian Foundation for Basic Research (project no. 99-03-32915a) and by the "Integration" Federal Special-Purpose Program (project no. 30344).

REFERENCES

1. Akhmetvaleev, R.R., Bikbulatov, R.V., Belogaeva, T.A., Akbutina, F.A., and Miftakhov, M.S., *Russ. J. Org. Chem.*, 2003, vol. 39, p. 658.
2. Donaldson, R.E. and Fuchs, P., *J. Am. Chem. Soc.*, 1981, vol. 103, no. 8, p. 2108.
3. Saddler, J.C. and Fuchs, P.L., *J. Am. Chem. Soc.*, 1981, vol. 103, no. 8, p. 2112.
4. Donaldson, R.E., Saddler, J.C., Burn, S., Mckenzie, A.T., and Fuchs, P.L., *J. Org. Chem.*, 1983, vol. 48, no. 13, p. 2167.
5. Akhmetvaleev, R.R., Imaeva, L.R., Belogaeva, T.A., and Miftakhov, M.S., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 1997, no. 9, p. 1699.
6. Tolstikov, G.A., Ismailov, S.A., Vel'der, Ya.L., and Miftakhov, M.S., *Zh. Org. Khim.*, 1991, vol. 27, p. 90.
7. Akhmetvaleev, R.R., Imaeva, L.R., Belogaeva, T.A., and Miftakhov, M.S., *Russ. J. Org. Chem.*, 1999, vol. 35, p. 238.
8. Kirchner, J.G., *Thin-Layer Chromatography*, Perry, E.S., Ed., New York: Wiley, 1978, 2nd ed. Translated under the title *Tonkosloinaya khromatografiya*, Moscow: Mir, 1981, vol. 1, p. 269.