Russian Journal of Organic Chemistry, Vol. 38, No. 4, 2002, pp. 491–493. Translated from Zhurnal Organicheskoi Khimii, Vol. 38, No. 4, 2002, pp. 515–517.

Prostanoids: LXXXIV.* Synthons for New Halochlorvulones II from 6,7-Dichloro-1,4-dioxaspiro[4.4]non-6-en-8-one

N. A. Ivanova, A. M. Shainurova, A. A. Khusainova, O. V. Shitikova, R. R. Akhmetvaleev, and M. S. Miftakhov

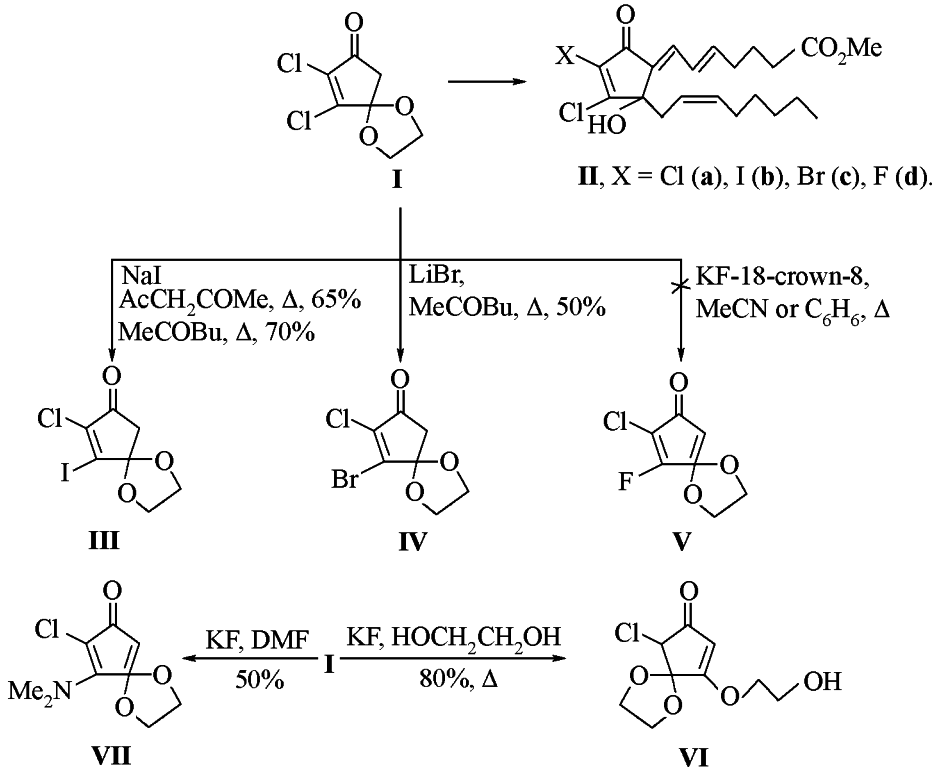
Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, Ufa, 450054 Russia

Received April 6, 2001

Abstract—By reaction of 6,7-dichloro-1,4-dioxaspiro[4.4]non-6-en-8-one with NaI and LiBr in boiling acetylacetone or methyl butyl ketone the corresponding 3-iodo and 3-bromo derivatives of cyclopentenone were prepared.

We formerly reported on the synthesis of pharmaceutically promising modified derivative of "sea prostanoids", 11-chlorochlorvulone **II** (**IIa**) [2] proceeding from dichlorocyclopentenone (**I**) [3]. Aiming at preparation of fundamental for compounds **IIb–d** synthons **III–V** we investigated the possibility of their synthesis by *trans*-halogenation at the C^3 atom in dichlorocyclopentenone **I** along Finkelstein reaction.

It turned out that under standard conditions [5] (5 equiv of anhydrous NaI, boiling in acetone) the desired 3-iodocyclopentenone (**III**) did not form in 48 h. The latter was obtained in good yield on applying higher boiling solvents, butyl methyl ketone (128°C, 24 h, yield 65%) or acetylacetone (158°C, 12 h, yield 70%). We successfully prepared 3-bromocyclopentenone (**IV**) in 50% yield at boiling dichloro-



* For communication LXXXII see [1].

** The study was carried out under financial support from the Russian Foundation for Basic Research (grant no. 99-03-32916a).

1070-4280/01/3804-491$27.00 © 2002 MAIK "Nauka/Interperiodica"

ketone **I** with 5 equiv of anhydrous LiBr in butyl methyl ketone for 6 h.

The attempts to synthesize fluoro derivative **V** even at the use of one among the most efficient fluorinating agents, KF–18-crown-6 [6, 7] (in benzene or acetonitrile) were unsuccessful. The reaction carried out in ethylene glycol [8] or DMF [9] gave rise to products consisting of uncommonly protected derivative of cyclopentane-1,3,4-trione (**VI**) and enaminoketone **VII** respectively. Here the fluoride ion that is known to act as a strong base [7] plays the role of catalyst in the concurrent reaction of the conjugate 1,4-addition of O- and N-nucleophiles.

EXPERIMENTAL

IR spectra were recorded on spectrophotometers UR-20 and Specord M-80 from films or mulls in mineral oil. ^{1}H and ^{13}C NMR spectra were registered on Bruker AM-300 instrument at operating frequencies 300.13 and 75.47 MHz respectively from solutions in $CDCl_3$. As internal reference served chloroform signals (δ 7.27, δ_C 77.0 ppm). Mass spectra were measured on MKh-1306 instrument, ionizing electrons energy 20 and 70 eV, ionizing chamber temperature 75–100°C. The reactions progress was monitored by TLC on Silufol plates, eluent hexane–ethyl acetate, development with alkaline solution of $KMnO_4$ [10]. In experiments were used anhydrous solvents [11] and anhydrous NaI, LiBr, and KF [12].

6-Iodo-7-chloro-1,4-dioxaspiro[4.4]non-6-en-8-one (III). A mixture of 0.5 g (2.39 mmol) of ketone **I**, 1.90 g (12.6 mmol) of anhydrous NaI in 30 ml of acetylacetone (*a*) or methyl butyl ketone (*b*) was boiled for 12 h at vigorous stirring. The reaction mixture was evaporated, to the residue 10 ml of water was added, and the reaction product was extracted into ethyl acetate (3 × 10 ml). The combined organic extracts were washed with water, with saturated water solution of NaCl, dried with $MgSO_4$, evaporated till 5 ml volume, 10 ml of petroleum ether was added thereto, and the separated precipitate was filtered off and recrystallized from ethyl acetate. As a result 0.47 g (65%, *a*) or 0.5 g (70%, *b*) of chloroiodocyclopentenone **III** was obtained. mp 195–197°C. IR spectrum, ν, cm^{-1}: 1448, 1568, 1712. ^{1}H NMR spectrum, δ, ppm: 2.90 s (2H, CH_2), 4.1 m (2H, OCH_2CH_2O), 4.3 m (2H, OCH_2CH_2O). ^{13}C NMR spectrum, δ, ppm: 46.99 (C^9), 66.66 (C^2, C^3), 110.32 (C^5), 133.94 (C^7), 146.16 (C^6), 192.06 (C^8). Mass spectrum, *m/z*: 300 $[C_7H_6ICIO_3]^+$, 113 $[M–IC_2H4O_2]^+$ (I_{max}), 270 $[M–CH_2]^+$, 265 $[M–Cl]^+$, 173 $[M–I]^+$. Found, %: C 28.13; H 2.19. $C_7H_6ClIO_3$. Calculated, %: C 27.98; H 2.01.

6-Bromo-7-chloro-1,4-dioxaspiro[4.4]non-6-en-8-one (IV). A mixture of 0.5 g (2.39 mmol) of ketone **I**, 1.04 g (11.96 mmol) of anhydrous LiBr in methyl butyl ketone was boiled for 6 h at vigorous stirring. The reaction mixture was evaporated, to the residue 10 ml of water was added, and the reaction product was extracted into ethyl acetate. The combined organic extracts were washed with saturated water solution of NaCl, dried with $MgSO_4$, evaporated, and the crystalline residue was recrystallized from ethyl acetate. Yield of chlorobromocyclopentenone **IV** 0.3 g (50%), light yellow crystals, mp 114–114.5°C. IR spectrum, ν, cm^{-1}: 1448, 1600, 1724. ^{1}H NMR spectrum, δ, ppm: 2.97 s (2H, CH_2), 4.08 m (2H, OCH_2), 4.18 (2H, OCH_2). ^{13}C NMR spectrum, δ, ppm: 47.04 (C^9), 66.69 (C^2, C^3), 109.15 (C^5), 138.93 (C^7), 152.09 (C^6), 191.76 (C^8). Mass spectrum, *m/z*: 252–256 $[M]^+$, 217–219 $[\mu–Cl]^+$, 173–175 $[M–Br]^+$, 131–133 $[BrC≡CCO]^+$, 113 $[M–C_2ClBr–H]^+$, 87–89 $[ClC≡CCO]^+$. Found, %: C 32.81; H 2.57. $C_7H_6BrClO_3$. Calculated, %: C 33.17; H 2.39.

6-(2-Hydroxyethyloxy)-9-chloro-1,4-dioxaspiro-[4.4]non-6-en-8-one (VI). A mixture of 0.5 g (2.39 mmol) of ketone **I**, 1.03 g (5.98 mmol) of anhydrous KF in 10 ml of anhydrous ethylene glycol was stirred for 1 h at 130°C. The reaction mixture was cooled, diluted with 10 ml of water, and the reaction product was extracted into ethyl acetate. The combined organic extracts were washed with saturated NaCl solution in water, and dried with $MgSO_4$. The solvent was evaporated, and the residue (0.49 g) was subjected to column chromatography on SiO_2 (eluent chloroform–MeOH, 20 : 1). Yield of compound **VI** 0.45 g (80%), colorless crystals, mp 105–107°C. IR spectrum, ν, cm^{-1}: 1520, 1620, 1724. ^{1}H NMR spectrum, δ, ppm: 3.69–3.72 m (2H, $C^{1'}H_2$), 3.95–4.14 m (5H, OCH_2CH_2O, OH), 4.14–4.24 m (2H $C^{2'}H_2$), 4.85 s (1H, C^9H), 5.72 C (1H, C^7H). ^{13}C NMR spectrum, δ, ppm: 50.01 (C^1), 62.62 (C^9), 66.57 (C^3), 66.95 (C^2), 74.65 ($C^{2'}$), 105.01 (^{7}), 107.03 (C^5), 180.17 (C^6), 192.08 (C^8). Mass spectrum, *m/z*: 234 $[M]^+$, 199 $[M–Cl]^+$, 155 $[M–Cl– C_2H_4O]^+$, 113 $[C_5H_5O_3]^+$, 120 $[C_4H_5ClO_2]^+$, 89 $[M–C_2H_5OH]^+$, 45 $[M–C_2H_5OH]^+$, 31 $[M–CH_2OH]^+$. Found, %: C 46.54; H 4.48; Cl 15.43. $C_9H_{10}ClO_5$. Calculated, %: C 46.34; H 4.31; Cl 15.23.

6-Dimethylamino-7-chloro-1,4-dioxaspiro[4.4]-non-6-en-8-one (VII). A mixture of 0.5 g (2.39 mmol)

of ketone **I**, 1.03 g (5.98 mmol) of anhydrous KF in 10 ml of anhydrous DMF glycol was stirred for 3 h at boiling. The reaction mixture was cooled, diluted with water, and the reaction products were extracted into ethyl acetate. The combined organic extracts were washed with saturated NaCl solution in water, and dried with $MgSO_4$. The solvent was evaporated, and the residue (0.31 g) was subjected to column chromatography on SiO_2 (eluent hexane–ethyl acetate, 1 : 9). Yield of compound **VII** 0.26 g (50%), light-yellow crystals, mp 92–94°C. IR spectrum, ν, cm^{-1}: 1600, 1705. ^1H NMR spectrum, δ, ppm: 2.47 s (2H, C^5H_2), 3.20 s (6H, $2CH_3$), 3.95–4.20 m (4H, $2CH_2O$). ^{13}C NMR spectrum, δ, ppm: 41.52 (CH_3), 45.76 (C^5), 64.02 (CH_2O), 104.78 (C^3), 109.12 (C^4), 159.65 (C^2), 189.55 (C^8). Found, %: C 49.47; H 5.55; Cl 16.43; N 6.29. $C_9H_{11}ClNO_3$. Calculated, %: C 49.67; H 5.56; Cl 16.29; N 6.44.

REFERENCES

1. Akhmetvaleev, R.R., Bikbulatov, R.V., Akbutina, F.A., Belogaeva, T.A., Shitikova, O.V., and Miftakhov, M.S., *Zh. Org. Khim.*, 2002, vol. 38, no. 4, pp. 487–490.
2. Miftakhov, M.C., Adler, M.E., Akbutina, F.A., and Tolstikov, G.A., *Usp. Khim.*, 1994, vol. 63, no. 6, pp. 543–555.
3. Baibulatova, G.M., Akhmetvaleev, R.R., and Vasil'eva, E.V., Abstracts of Papers, *XIII Mezhdunarodnaya nauchno-tekhn. konf. "Khimicheskie reaktivy, reagenty i protsessy malotonnazhnoi khimii"* (13th Int. Conf. "Chemicals, Reagents, and Pilot Plant Chemistry Processes"), Tula, 2000, p. 75.
4. Akhmetvaleev, R.R., Imaeva, L.R., Belogaeva, T.A., and Miftakhov, M.S., *Izv. Russian Akad. Nauk, Ser. Khim.*, 1997, no. 9, pp. 1699–1701.
5. Kochetkov, N.K., *Usp. Khim.*, 1955, vol. 24, no. 1, pp. 32–51.
6. Rybinskaya, M.I., Nesmeyanov, A.N., and Kochetkov, N.K., *Usp. Khim.*, 1969, vol. 38, no. 6, pp. 962–1008.
7. Clark, J.H., *Chem. Rev.*, 1980, vol. 80, no. 5, pp. 429–452.
8. Liotta, C.L. and Harris, H.P., *J. Am. Chem. Soc.*, 1974, vol. 96, no. 7, pp. 2250–2253.
9. Akhmetvaleev, R.R., *Doctoral Sci. (Chem.) Dissertation*, Ufa, 2000.
10. Kirchner, J.G., *Thin Layer Chromatography*, New York: Wilei Interscience, 1978.
11. Gordon, A.J. and Ford, R.A., *The Chemist's Companion*, New York: Wiley–Interscience, 1972; Translated under the title *Sputnik khimika*, Moscow: Mir, 1976, p. 319.
12. Weygang–Hilgetag, *Organisch-chemische Experimentierkunst*, Leipzig: Verlag, 1964. Translated under the title *Metody eksperimenta v organicheskoi khimii*, Moscow: Khimiya, 1968, 950 p.