Russian Journal of Organic Chemistry, Vol. 38, No. 9, 2002, pp. 1386–1387. Translated from Zhurnal Organicheskoi Khimii, Vol. 38, No. 9, 2002, pp. 1437–1438.

SHORT COMMUNICATIONS

Synthesis and Rearrangement of 1-Substituted 3,3,7-Trimethyl-2-azaspiro[4.5]deca-1,6,9-trien-8-ones*

Yu. V. Nifontov, V. A. Glushkov, O. G. Ausheva, and Yu. V. Shklyaev

Institute of Technical Chemistry, Ural Division, Russian Academy of Sciences, ul. Lenina 13, Perm, 614600 Russia
e-mail: cheminst@mpm.ru

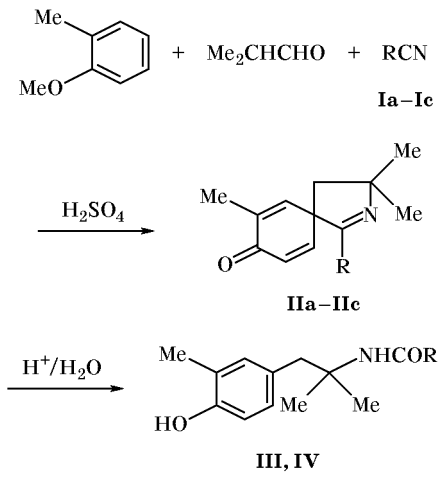
Received July 31, 2001

We previously synthesized 3,3-dimethyl-1-methylthio-2-azaspiro[4.5]deca-1,6,9-trien-8-one by three-component condensation of anisole, 1,2-epoxy-2-methylpropane, and nitriles in the presence of concentrated sulfuric acid [1]. An analogous result was obtained in the reaction of anisole with isobutyraldehyde and nitriles [2]. Taking into account that the product composition strongly depends on the nature and position of substituents in the aromatic ring [3], we thought it reasonable to examine the same transformation of anisole homologs, in particular of methyl *o*-tolyl ether.

We have fount that introduction of a methyl group into the *ortho*-position of anisole does not change the reaction direction. Addition of an equimolar mixture of methyl *o*-tolyl ether, isobutyraldehyde, and methyl thiocyanate to concentrated sulfuric acid at 0–5°C, followed by dilution of the reaction mixture with cold water and neutralization of the aqueous phase with ammonium carbonate, leads to formation of 3,3,7-trimethyl-1-methylthio-2-azaspiro[4.5]deca-1,6,9-trien-8-one (**IIa**) in 67% yield. The isolated product was a single enantiomer whose configuration was not determined. The presence of an asymmetric spiro-carbon atom in molecule **IIa** is confirmed by the ^{1}H NMR spectrum, where splitting of signals from diastereotopic protons of the C^4H_2 and 3-CH_3 groups is observed.

Spiro compounds **IIb** and **IIc**, formed in the reactions with ethyl cyanoacetate and cyanoacetamide, undergo dienone–phenol rearrangement during isolation. As a result, amides **III** and **IV** were obtained. The relatively ready hydrolysis of structurally related spiro compounds with carbonyl-containing groups (derived from anisole) was noted by us previously [4].

3,3,7-Trimethyl-1-methylthio-2-azaspiro[4.5]-deca-1,6,9-trien-8-one (IIa). A mixture of 12.2 g (0.1 mol) of methyl *o*-tolyl ether, 7.2 g (0.1 mol) of isobutyraldehyde, and 7.3 g (0.1 mol) of methyl thiocyanate was added dropwise over a period of 15–20 min to 50 ml of 96% sulfuric acid stirred at 0–5°C. The mixture was stirred for 30 min, poured into 300 ml of water, and extracted with 50 ml of toluene. The aqueous phase was separated and neutralized with $(NH_4)_2CO_3$ to pH 8–9. The precipitate was filtered off, washed with water, dried, and recrystallized twice from methanol. Yield 15.75 g (67%), mp 63–64°C. IR spectrum, ν, cm^{-1}: 1660 (C=O), 1630 (C=C), 1605 (C=N), 1580. ^{1}H NMR spectrum, δ, ppm: 1.36 s and 1.39 s (6H, 3-CH_3), 1.82 s (3H, 7-CH_3), 2.18 s and 2.20 s (2H, 4-H),



I, **II**, R = SCH_3 (**a**), $CH_2COOC_2H_5$ (**b**), CH_2CONH_2 (**c**); **III**, R = $CH_2COOC_2H_5$; **IV**, R = CH_2CONH_2.

* This study was financially supported by the Russian Foundation for Basic Research (project no. 01-03-96479).

2.33 s (3H, SCH_3), 6.20 d (1H, 9-H, ^3J = 10 Hz), 6.67 d (1H, 6-H, ^4J = 2 Hz), 6.85 d.d (1H, 10-H, ^3J = 10, ^4J = 2 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 235 $[M]^{+\cdot}$ (14), 220 $[M-CH_3]^+$ (30), 162 $[M-CH_3SCN]^+$ (84), 147 $[M-CH_3SCN-CH_3]^+$ (100), 121 (83), 91 (47). Found, %: C 66.50; H 7.16; N 6.10. $C_{13}H_{17}NOS$. Calculated, %: C 66.35; H 7.28; N 5.95.

Ethyl *N*-[2-(4-hydroxy-3-methylphenyl)-1,1-dimethylethyl]malonamate (III) was obtained by reaction of 12.2 g (0.1 mol) of methyl *o*-tolyl ether, 7.2 g (0.1 mol) of isobutyraldehyde, and 11.3 g (0.1 mol) of ethyl cyanoacetate in 50 ml of 96% sulfuric acid, according to the above procedure. Yield 20.3 g (69%), mp 84–86°C (from benzene). IR spectrum, ν, cm^{-1}: 3380 (OH), 3260 br (NH), 1720 (C=O, ester), 1660 (C=O, amide), 1605 ($C=C_{arom}$), 1550. ^1H NMR spectrum, δ, ppm: 1.17 s (6H, CH_3), 1.23 t (3H, $CH_2C\mathbf{H}_3$, *J* = 7 Hz), 2.09 s (3H, CH_3), 2.80 s (2H, CH_2), 3.15 s (2H, $COCH_2$), 4.12 q (2H, OCH_2, *J* = 7 Hz), 6.63 d (1H, 5-H, *J* = 8 Hz), 6.73 d (1H, 6-H, *J* = 8 Hz), 6.80 s (1H, 2-H), 7.30 s (1H, OH), 8.75 s (1H, NH). Found, %: C 65.55; H 7.96; N 4.91. $C_{16}H_{23}NO_4$. Calculated, %: C 65.51; H 7.90; N 4.77.

***N*-[2-(4-Hydroxy-3-methylphenyl)-1,1-dimethylethyl]malonamide (IV).** A mixture of 12.2 g (0.1 mol) of methyl *o*-tolyl ether and 7.2 g (0.1 mol) of isobutyraldehyde was added dropwise with stirring over a period of 15–20 min to a solution of 8.4 g (0.1 mol) of cyanoacetamide in 50 ml of 96% sulfuric acid. The mixture was stirred for 30 min, poured into 300 ml of water, and treated with 50 ml of toluene. The aqueous phase was separated and neutralized with ammonium carbonate to pH 8–9. The precipitate was filtered off, washed with water, dried, and recrystallized from ethanol. Yield 17.20 g (65%), mp 189–190°C. IR spectrum, ν, cm^{-1}: 3370 (OH), 3260 br (NH, NH_2), 1670 (C=O). ^1H NMR spectrum, δ, ppm: 1.19 s (6H, CH_3), 2.09 s (3H, CH_3), 2.80 s (2H, CH_2), 2.95 s (2H, $COCH_2$), 6.62 d (1H, 5-H, *J* = 8 Hz), 6.70 d (1H, 6-H, *J* = 8 Hz), 6.79 s (1H, 2-H), 6.90 br.s (1H, NH), 7.36 br.s (1H, NH), 7.40 s (1H, OH), 8.78 s (1H, NH). Found, %: C 63.70; H 7.66; N 10.52. $C_{14}H_{20}N_2O_3$. Calculated, %: C 63.62; H 7.63; N 10.60.

The IR spectra were obtained on a UR-20 spectrometer from samples dispersed in mineral oil. The ^1H NMR spectra were recorded on a Bruker AM-300 spectrometer (300 MHz) in DMSO-d_6 using TMS as internal reference. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using chloroform–acetone (9:1) as eluent; spots were developed with a 0.5% solution of chloranil in toluene.

REFERENCES

1. Glushkov, V.A., Shklyaev, Yu.V., Sokol, V.I., Sergienko, V.S., and Davidov, V.V., *Mendeleev Commun.*, 1998, no. 6, pp. 227–228; *ibid.*, 1999, no. 4, p. 170.
2. Glushkov, V.A., Ausheva, O.G., Shurov, S.N., and Shklyaev, Yu.V., Abstracts of Papers, *Tretii Vserossiiskii simpozium "Strategiya i taktika organicheskogo sinteza"* (IIIrd All-Russian Symp. "Strategy and Tactics of Organic Synthesis"), Yaroslavl, 2001, p. 38.
3. Shklyaev, Yu.V., Nifontov, Yu.V., and Glushkov, V.A., Abstracts of Papers, *Konferentsiya "Nauchno-tekhnicheskii potentsial Zapadnogo Urala v oblasti konversii voenno-promyshlennogo kompleksa"* (Conf. "Scientific and Technical Potential of the West Ural in the Field of Conversion of the Military–Industrial Establishment"), Perm, 2001, p. 38.
4. Ausheva, O.G., Glushkov, V.A., Shurov, S.N., and Shklyaev, Yu.V., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 2001, no. 9, pp. 1571–1579.