Brief Communications

Spirocyclohexadienones. 6*. Three-component synthesis of 1-R-3,3-dimethyl-2-azaspiro[4.5]deca-1,6,9-trien-8-ones

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1-R-3,3-Dimethyl-2-azaspiro[4.5]deca-1,6,9-trien-8-ones were synthesized through three-component condensation of anisole, isobutyraldehyde, and a corresponding nitrile in dichloromethane in the presence of concentrated sulfuric acid.

Key words: spiro compounds, pyrroles, cyclohexa-2,5-dien-1-one, anisole, isobutyraldehyde, nitriles, the Ritter reaction, cascade heterocyclization.

Earlier,[2] we have synthesized 1-substituted 3,3-dimethyl-2-azaspiro[4.5]deca-1,6,9-trien-8-ones by the Ritter reaction. Later, a three-component synthesis of such compounds from anisole (or 1,3-dimethoxy- or 1,3,5-trimethoxybenzene), isobutylene oxide, and methyl thiocyanate in the presence of sulfuric acid has been described;[3] isobutylene oxide was used to construct the C(3)—C(4) fragment of the isoquinoline ring.

We found that isobutylene oxide can be successfully replaced by an aliphatic aldehyde branched at the α-carbon atom, in particular, isobutyraldehyde. In the present work, we propose a convenient preparative "one-pot" synthesis of 1-substituted 3,3-dimethyl-2-azaspiro[4.5]deca-1,6,9-trien-8-ones from anisole, isobutyraldehyde, and a corresponding nitrile RCN in methylene chloride in the presence of sulfuric acid at −15 to 15 °C.

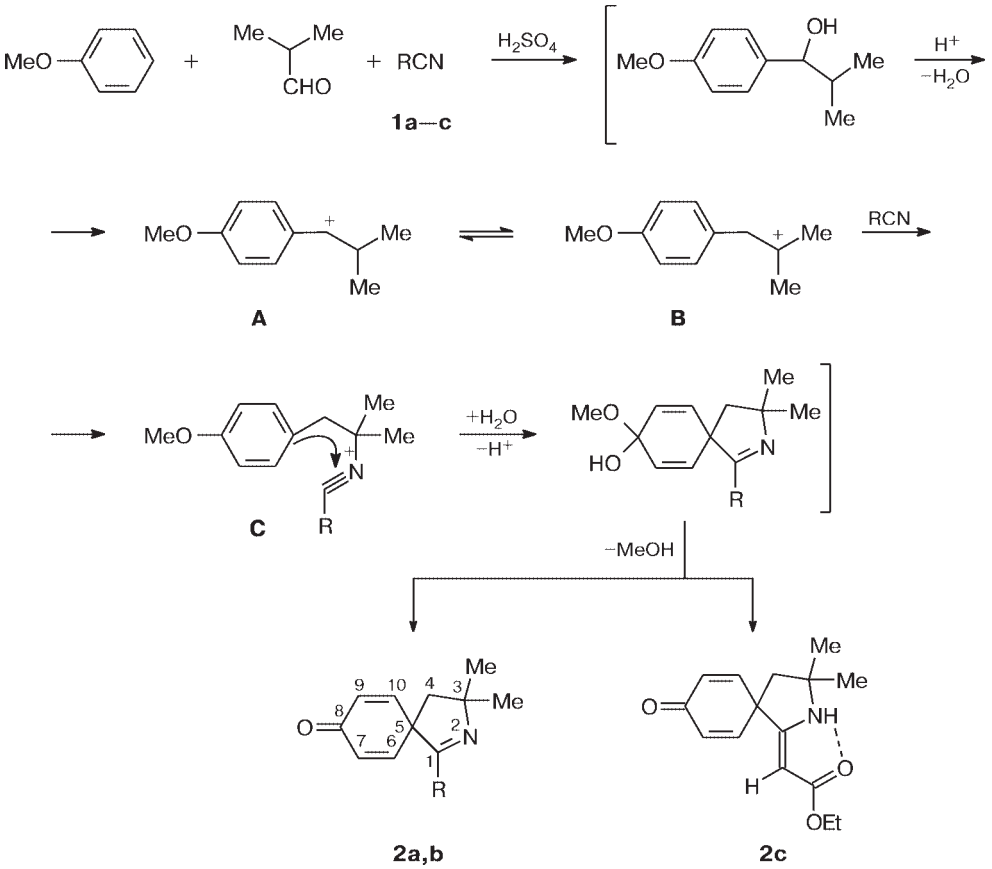
The process can be regarded as a combination of the known Baeyer[4] and Ritter[5] reactions finalized by intramolecular *ipso*-attack in an intermediate nitrilium ion **C** to form the azaspiro[4.5]deca-1,6,9-trien-8-one system (Scheme 1). As can be seen in the scheme, this reaction mechanism becomes possible because of equilibrium between carbenium ions **A** and **B**. The Baeyer reaction product, namely, 1,1-bis(*p*-anisyl)-2-methylpropane, was not isolated; apparently, the reaction of nitrile with the intermediate carbocation **B** is faster than

* For Part 5, see Ref. 1.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 5, pp. 822—824, May, 2002.

1066-5285/02/5105-894 $27.00

Scheme 1



1,2: R = SMe (**1a**, **2a**); Ph (**1b**, **2b**); CH_2COOEt (**1c**)

that of anisole with cation **A**. In addition, an equimolar ratio of anisole to a nitrile and an aldehyde should be taken into account.

This method was used to obtain spiran **2a** in 34% yield and previously[6] inaccessible compounds **2b,c** in 10 and 30% yields, respectively. The ^{1}H NMR spectrum of **2c** suggests that this compound in DMSO-d_6 exists entirely in the enamine form, as has been observed earlier for ethyl (3,4-dihydroisoquinolin-1-yl)acetates.[7,8] *Z*-Configuration of such compounds is due to an intramolecular hydrogen bond (IHB).[8,9] Indeed, the absorption band of the ester group in the IR spectrum of **2c** is shifted to the low-frequency region (1615 cm^{-1}), which indicates the formation of an IHB between the carbonyl and NH groups.

We performed quantum-chemical calculations for the enamine and imine forms of spiran **2c** using the semiempirical SCF MO LCAO method in the AM1 approximation.[10] The results obtained show that the *Z*-enamine form is more stable (the calculated enthalpy of its formation ΔH_f is 339.91 kJ mol^{-1}) than the *E*-enamine and imine forms (ΔH_f = 303.29 and 319.48 kJ mol^{-1}, respectively).

The ^{13}C NMR spectra of compounds **2a—c** contain a characteristic signal at δ 72.4—76.4 for the spiro carbon atom.

The structures of compounds **2b,c** were also confirmed by their mass spectra. No molecular ion peak appears in the mass spectrum of **2b**; compounds **2b,c** decompose through loss of benzonitrile or ethyl cyanoacetate (for **2b** and **2c**, respectively) and the methyl groups (see Experimental).

Compounds **2a—c** are rather stable and do not decompose under normal conditions for two to three months; however, in the presence of atmospheric moisture and acid traces, compound **2a** virtually quantitatively transforms (through dienone-phenol rearrangement) into the corresponding *p*-hydroxyphenylethyl amide.[2]

Experimental

IR spectra were recorded on a UR-20 instrument (Vaseline oil, paste). ^{1}H NMR spectra were recorded on Bruker AM-300 (300 MHz) and Tesla-BS 487C (80 MHz) instruments with HMDS as the internal standard. ^{13}C NMR spectra were taken

using a Bruker DRX 500 instrument (125.76 MHz). The mass spectra of compound **2b,c** were recorded on a Finnigan MAT instrument (EI, 70 eV). The course of the reaction was monitored and the purity of the products was checked by TLC on Silufol plates in chloroform—acetone (9 : 1); spots were visualized with a 3% solution of chloranil in toluene. Methylene chloride (Lancaster Co., Great Britain) was used. Quantum-chemical calculations were performed on a Pentium-133 PC with the MOPAC 7.0 program package.[11]

3,3-Dimethyl-1-methylthio-2-azaspiro[4.5]deca-1,6,9-trien-8-one (2a). A solution of anisole (5.4 mL, 0.05 mol), freshly distilled isobutyraldehyde (4.5 mL, 0.05 mol), and thiocyanate **1a** (3.5 mL, 0.05 mol) in 40 mL of CH_2Cl_2 was added dropwise at −15 °C to vigorously stirred 96% H_2SO_4 (12 mL, 0.22 mol). After 40 min, the reaction mixture was poured onto a mixture of ice (300 mL) and 20% NH_4OH (45 mL). The aqueous layer was separated, and the organic material was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were washed with water and dried over $MgSO_4$. The solvent was removed, and the residue was recrystallized from methanol with addition of water. The yield of compound **2a** was 3.7 g (34%), R_f 0.48. The melting point and spectroscopic characteristics of spiran **2a** are identical with those reported in Ref. 6.

3,3-Dimethyl-1-phenyl-2-azaspiro[4.5]deca-1,6,9-trien-8-one (2b) was obtained analogously from anisole (10.9 mL, 0.1 mol), isobutyraldehyde (9.1 mL, 0.1 mol), benzonitrile (10.0 mL, 0.1 mol), and 96% H_2SO_4 (24 mL, 0.44 mol) in 100 mL of CH_2Cl_2 at 10 to 15 °C. Removal of the solvent gave a partially crystallized residue; the crystals were filtered off and recrystallized from hexane (100 mL) to give compound **2b** (2.51 g, 10%), m.p. 130—132 °C, R_f 0.53. MS, m/z (I_{rel} (%)): 148 [M^+ − PhCN] (100); 133 (49); 104 (35); 77 (21). IR (Vaseline oil), ν/cm^{-1}: 1660 (C=O); 1625 (C=C); 1605 (C=N and $C=C_{arom}$); 1575 (C=N). ^1H NMR (300 MHz, DMSO-d_6), δ: 1.45 (s, 6 H, C(3)Me_2); 2.23 (s, 2 H, C(4)H_2); 6.28 (d, 2 H, C(7)H and C(9)H, J = 10.2 Hz); 7.15 (d, 2 H, C(6)H and C(10)H, J = 10.2 Hz); 7.32 (m, 2 H, H_{arom}); 7.40 (m, 1 H, H_{arom}); 7.64 (m, 2 H, H_{arom}). ^{13}C NMR (DMSO-d_6), δ: 30.22 (C(3)Me_2); 48.96 (C(4)); 60.71 (C(3)); 72.36 (C(5)); 127.26*, 127.83* (C(7), C(9)); 128.04, 130.27, 133.49 (Ph); 152.01 (C(6), C(10)); 164.02 (C(1)); 183.83 (C(8)). Found (%): C, 81.35; H, 6.90; N, 5.42. $C_{17}H_{17}NO$. Calculated (%): C, 81.24; H, 6.82; N, 5.57.

***Z*-1-Ethoxycarbonylmethylidene-3,3-dimethyl-2-azaspiro[4.5]deca-6,9-dien-8-one (2c).** A solution of anisole (5.4 mL, 0.05 mol), freshly distilled isobutyraldehyde (4.5 mL, 0.05 mol), and ethyl cyanoacetate (5.3 mL, 0.05 mol) in 30 mL of CH_2Cl_2 was added dropwise to vigorously stirred 96% H_2SO_4 (12 mL, 0.22 mol) while cooling it with water. After 40 min, the reaction mixture was poured onto a mixture of ice (150 mL) and aqueous 20% NH_4OH (45 mL). The aqueous layer was separated, and the organic material was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were washed with water and dried over $MgSO_4$. The solvent was removed, and the residue was recrystallized from ethanol. The yield of compound **1c** was 3.92 g (30%), colorless plates, m.p. 195.5—197 °C, R_f 0.62. MS, m/z (I_{rel} (%)): 261 [$M]^+$ (47); 246 [M − Me]$^+$ (16); 216 [M − OEt]$^+$ (22); 200 [M − Me − OEt − H]$^+$ (70); 188 [M − COOEt]$^+$ (21); 172 [M − Me − COOEt − H]$^+$ (28); 160 [M − C_4H_8 − OEt]$^+$ (43); 148 [M − $NCCH_2COOEt]^+$ (93); 133 [M − Me − $NCCH_2COOEt]^+$ (100); 120 (12); 107 (48). IR (Vaseline oil), ν/cm^{-1}: 3325 (NH), 1660 (C=O), 1615 (sh, O—C=O), 1600 (C=C). ^1H NMR (300 MHz, DMSO-d_6), δ: 1.15 (t, 3 H, Me, J = 7.0 Hz); 1.44 (s, 6 H, C(3)Me_2); 2.15 (s, 2 H, C(4)H_2); 3.97 (m, 3 H, OCH_2 + —CH=); 6.15 (d, 2 H, C(7)H and C(9)H, J = 10.1 Hz); 6.99 (d, 2 H, C(6)H and C(10)H, J = 10.1 Hz); 8.23 (s, 1 H, NH). ^1H NMR (80 MHz, $CDCl_3$), δ: 1.16 (t, 3 H, Me, J = 7.0 Hz); 1.40 (s, 6 H, C(3)Me_2); 2.11 (s, 2 H, C(4)H_2); 3.98 (q, 3 H, OCH_2, J = 7.0 Hz); 4.23 (s, 1 H, —CH=); 6.13 (d, 2 H, C(7)H and C(9)H, J = 10.1 Hz); 6.77 (d, 2 H, C(6)H and C(10)H, J = 10.1 Hz); 7.85 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 14.38 (Me); 30.18 (C(3)Me_2); 45.39 (C(4)); 52.76* (OCH_2); 57.62* (C(3)); 61.49* (—CH=); 76.39 (C(5)); 126.83 (C(7), C(9)); 150.77 (C(6), C(10)); 160.74 (C(1)); 168.56 (OC(=O); 184.09 (C(8)). Found (%): C, 69.02; H, 7.27, N, 5.49. $C_{15}H_{19}NO_3$. Calculated (%): C, 68.94; H, 7.33; N, 5.36.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 01-03-96479).

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Received April 24, 2001;
in revised form December 14, 2001

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