

Synthesis of 2,5-cyclohexadien-4-one-spiro-3'-(2'-R-5',5'-dimethyl-1'-pyrrolines) by the Ritter reaction

Vladimir A. Glushkov,^{*a} Yuri V. Shklyayev,^a Valentina I. Sokol,^b Vladimir S. Sergienko^{*b} and Victor V. Davidov^c

^a Institute of Technical Chemistry, Ural Branch of the Russian Academy of Sciences, 614600 Perm, Russian Federation.

Fax: +7 3422 12 4375; e-mail: cheminst@mpm.ru

^b N. S. Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, 117907 Moscow, Russian Federation.

Fax: +7 095 954 1279; e-mail: sokol@ionchran.msk.ru

^c Peoples' Friendship University of Russia, 117198 Moscow, Russian Federation. Fax: +7 095 433 1511;

e-mail: v davidov@mx.pfu.edu.ru

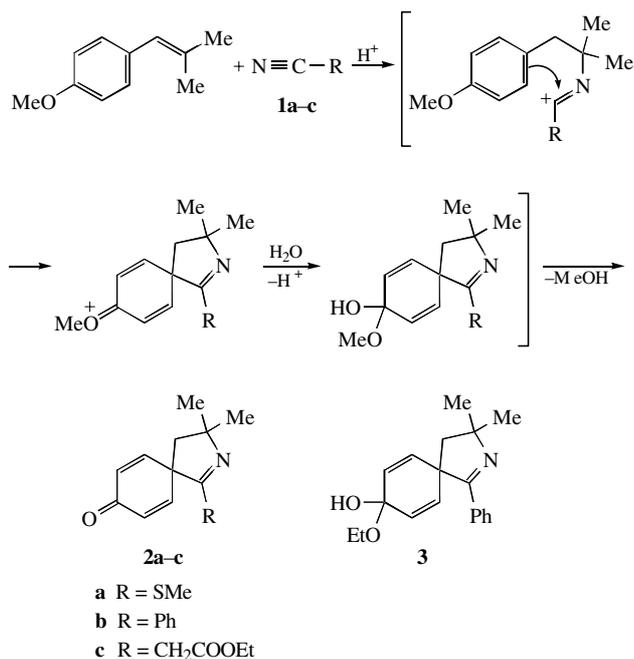
Reactions of 1-(4'-methoxyphenyl)-2-methylpropene with nitriles RCN in concentrated sulfuric acid give 2,5-cyclohexadien-4-one-spiro-3'-(2'-R-5',5'-dimethyl-1'-pyrrolines) in good yields.

In recent years, several methods to synthesise substituted 1-spiro-2,5-cyclohexadien-4-ones have been described. These methods are based on an intramolecular electrophilic *ipso*-attack of *para*-substituted anisoles^{1,2} in the presence of Lewis acids. However, preparation of heterocyclic 1-spiro-2,5-cyclohexadienones has not yet been reported. In this work we present a simple synthesis of 2,5-cyclohexadien-4-one-spiro-3'-(2'-R-5',5'-dimethyl-1'-pyrrolines) based on the Ritter reaction.

Recently, we described the reaction of aromatic compounds activated by two methoxy groups with 1,1-dimethyloxirane and nitriles (tandem alkylation-cyclization procedure) leading to the substituted 3,3-dimethyl-6,7-(or 5,8-)dimethoxy-3,4-dihydroisoquinolines.³ In the cyclisation stage, the carbimmonium ion is formed as an intermediate. Using anisole in the reaction with 1,1-dimethyloxirane and methyl thiocyanate, we expected to obtain substituted 7-methoxyisoquinoline, but to our surprise, only the corresponding 1-spiro-2,5-cyclohexadienone **2a** was isolated in ~40% yield.

Obviously, the *para*-methoxy group hinders *ortho*-attack that should lead to isoquinoline in the cyclisation stage. In fact, *ipso*-attack is favoured giving 2,5-cyclohexadien-4-one-spiro-3'-(2'-R-5',5'-dimethyl-1'-pyrrolines).

In this work, we used 1-(4'-methoxyphenyl)-2-methylpropene as a carbocation source to avoid the first stage of the tandem reaction — alkylation by a tertiary oxirane — and to increase the yield. The yields of products **2a–c** were 58–82%. Methyl isothiocyanate, benzonitrile or cyanoacetic ester were used as



Scheme 1

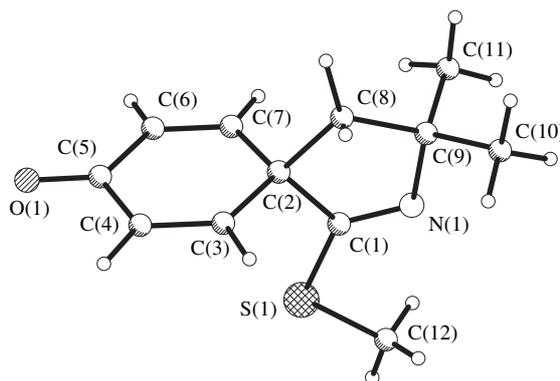


Figure 1 The structure of compound **2a**. Selected bond lengths (Å): C(1)–N(1) 1.264(3), C(9)–N(1) 1.493(3), C(1)–S(1) 1.757(2), C(12)–S(1) 1.789(3), C(5)–O(1) 1.230(2). (The averaged values for two independent molecules.)

nitrile components.[†] The reaction proceeds according to Scheme 1. The corresponding 7-methoxyisoquinolines were formed only in trace amounts (TLC data).

The structures of the compounds obtained **2a–c** and **3**[‡] were confirmed by elemental analysis, IR and ¹H NMR spectroscopy, and compound **2a** was studied additionally by mass spectrometry and X-ray diffraction.[§] The general view of molecule **2a** is given in Figure 1.

In the course of the reaction, semiketal **3** was isolated, which can be converted to **2b**. Compounds **2b,c** were isolated as semihydrates; in these compounds water molecules apparently bridge the carbonyl groups at two cyclohexadiene rings by forming hydrogen bonds.

Thus, by changing the substituents in the aromatic ring, we changed the reaction of the carbimmonium ion, and an easy and

[†] A typical experimental procedure is given below. A mixture of 1-(4-methoxyphenyl)-2-methylpropene (16.2 g, 0.1 mol) and an appropriate nitrile (0.1 mol) in 100 ml of toluene was added dropwise to concentrated sulfuric acid (50 ml, 0.94 mol) during 30 min with vigorous stirring (the temperature was maintained in the range 20–50 °C; for **2a**, in the range 20–25 °C). The reaction mixture was stirred for 1 h, poured into 300 ml of cold water, and stirred again. The resulting water layer was quickly separated. The organic layer was washed with 150 ml of water. In the case of **2a**, the combined water layers were washed with 40 ml of toluene and then basified with ammonium carbonate to pH 8. Compound **2a** was filtered off, dried in air and recrystallised first from 50% aqueous ethanol and then from a hexane-*n* chloroform mixture. Compounds **2b,c** precipitated as colourless crystals (**2b**) or a yellowish tar (**2c**) from the organic layer 3–15 min after washing it with water. Recrystallisation of **2b** first from toluene and then from ethanol afforded compound **3**. Refluxing semiketal **3** with 200 mg of *p*-toluenesulfonic acid in toluene (1 h), distilling off the solvent and recrystallising the precipitate from toluene gave **2b** semihydrate. The tar of compound **2c** was dissolved in CHCl₃, washed with aqueous NaHCO₃ and water, and dried with anhydrous magnesium sulfate; after removing the solvent, the substance was then recrystallised from acetone-water and hexane-CH₂Cl₂ mixtures.

convenient synthesis of 2,5-cyclohexadiene-4-one-spiro-3'-(2'-R-5',5'-dimethyl-1'-pyrrolines) was thereby achieved.

‡ **2a**: yield 82%, mp 95–97 °C. ¹H NMR (80 MHz, CDCl₃) δ: 1.38 (s, 6H, 5'-Me), 2.18 (s, 2H, 4'-CH₂), 2.33 (s, 3H, SMe), 6.22 (d, 2H, 3-H and 5-H, *J* 10.2 Hz), 6.71 (d, 2H, 2-H and 6-H, *J* 10.0 Hz). IR (Nujol, ν/cm⁻¹): 1700 (weak), 1660 (s), 1625, 1585 (s), 1375, 1325, 1255, 1225, 1170, 1130, 1070 (s), 955 (s), 860 (s). MS, *m/z*: 221 [M⁺].

2b: yield 58%, mp 145–146 °C (semihydrate). ¹H NMR (80 MHz, CDCl₃) δ: 1.37 (s, 6H, 5'-Me), 2.98 (s, 2H, 4'-CH₂), 5.72 (br. s, 1H, H₂O), 6.65 (d, 2H, 3-H and 5-H), 6.92 (d, 2H, 2-H and 6-H), 7.25–7.60 (m, 5H, H_{arom}). IR (Nujol, ν/cm⁻¹): 3400 (OH), 3200 (br., OH), 1630, 1610, 1590, 1540, 1315, 1255, 1230, 1175, 950.

2c: yield 64%, mp 100–103 °C (semihydrate). ¹H NMR (80 MHz, CDCl₃) δ: 1.18 (t, 3H, Me), 1.26 (s, 6H, 5'-Me), 2.87 (s, 2H, -CH₂), 3.16 (s, 2H, 4'-H), 4.03 (q, 2H, OCH₂), 6.54–6.68 (m, 3H, 3-H, 5-H and OH), 6.79 (d, 2H, 2-H and 6-H). IR (Nujol, ν/cm⁻¹): 3390 (OH), 3260 (br., OH), 1730 (O=C=O), 1640, 1615, 1590, 1545, 1510, 1280, 1270, 1255, 1230, 1175, 1155, 1175, 1155, 1100, 1045, 955.

3: yield 55%, mp 154–157 °C. ¹H NMR (80 MHz, CDCl₃) δ: 1.13 (t, 3H, Me), 1.37 (s, 6H, 5'-Me), 2.98 (s, 2H, 4'-H), 3.46 (q, 2H, OCH₂), 5.75 (s, 1H, OH), 6.65 (d, 2H, 3-H and 5-H), 6.90 (d, 2H, 2-H and 6-H), 7.25–7.50 (m, 5H, H_{arom}). IR (Nujol, ν/cm⁻¹): 3410 (OH), 3200 (br., OH), 1635, 1610 (shoulder), 1535, 1260, 1230, 1180, 1135, 840.

§ *Crystallographic data for 2a*: C₁₂H₁₅NOS, monoclinic, space group *P*₂₁/*a*, *a* = 13.404(3), *b* = 11.303(2), *c* = 17.086(3) Å, β = 105.47(3)°, *V* = 2494.8(8) Å³, *Z* = 8, *D*_x = 1.326 g cm⁻³, λ(MoKα) = 0.7107 Å (MoKα) = 2.64 cm⁻¹, *F*(000) = 1062, *T* = 294 K. Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer using the θ/2θ scan method (2θ_{max} = 54°). The structure was solved by the direct method (SHELXS-88⁴) and refined by the full-matrix least-squares procedure (SHELXL-93⁵) in an anisotropic approximation for all non-hydrogen atoms. The coordinates and thermal parameters of the hydrogen atoms were fixed (*U*_H 0.08 Å², C–H 0.096 Å). Final *R*₁ = 0.052, *wR*₂ = 0.137 and *S* = 1.071 for 3933 observed reflections with *I* > 2σ(*I*). Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, 1998, Issue 1. Any request to CCDC for data should quote the full literature citation and the reference number 1135/33.

This study was supported by the Russian Foundation for Basic Research (grant no. 98-03-32689a) and the Special Federal Program 'Integratsiya' (grant no. K0512).

References

- 1 A. M. Fivush and S. R. Strunk, *Synth. Commun.*, 1996, **26**, 1623.
- 2 Y. Nagao, W. S. Lee, I. Y. Jeong and M. Shiro, *Tetrahedron Lett.*, 1995, **36**, 2799.
- 3 V. A. Glushkov and Yu. V. Shklyayev, *Mendeleev Commun.*, 1998, 17.
- 4 G. M. Sheldrick, *Acta Crystallogr.*, 1990, **46A**, 467.
- 5 G. M. Sheldrick, *SHELXL-93, Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.

Received: Moscow, 3rd July 1998

Cambridge, 30th September 1998; Com. 8/05570J