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THREE-COMPONENT SYNTHESIS OF SUBSTITUTED 5,5-DIMETHYL-2-METHYLTHIO-4'-OXOSPIRO-(PYRROLIN-3,1'-CYCLOHEXADIENES) BY SPIROCYCLIZATION OF METHOXY-SUBSTITUTED BENZENES

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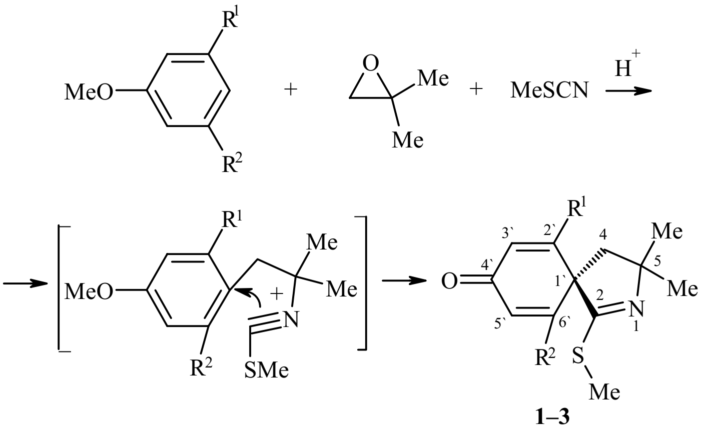
We described previously the three-component synthesis of substituted 3,3-dimethyl-1-methylthio-3,4-dihydroisoquinolines in Ritter reaction conditions (CH_2Cl_2, conc. H_2SO_4, 20-25°C), starting from veratrol (or 1,4-dimethoxybenzene), isobutene oxide, and methyl thiocyanate [1]. An attempt to extend this reaction to anisole, 1,3-dimethoxybenzene, or 1,3,5-trimethoxybenzene led unexpectedly to the formation of 5,5-dimethyl-2-methylthio-4'-oxospiro(1-pyrrolin-3,1'-cyclohexadienes) **1-3**. In the case of 1,3-dimethoxybenzene a mixture of the stereoisomers **2a**,**b** was obtained.

The corresponding 3,4-dihydroisoquinolines were not observed among the reaction products. The exclusive formation of the spirocompounds **1-3** may be explained by the fact that the positive mesomeric effect of the methoxy groups in the *para* and *ortho* positions of the benzene nucleus facilitate *ipso* attack in the key cyclization step:



1 $R^1 = R^2 = H$; **2 a** $R^1 = OMe$, $R^2 = H$; **b** $R^1 = H$, $R^2 = OMe$; **3** $R^1 = R^2 = OMe$

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Compound **1** [2] and the similar 2-alkylthio-5,5-pentamethylene-4'-oxospiro(1-pyrrolin-3,1'-cyclohexadienes) [3] have been obtained from the corresponding carbinols and thiocyanates, but we effected the one-pot strategy for the synthesis of compounds **1-3** by spiroheterocyclization from the three structural blocks for the first time.

5,5-Dimethyl-2-methylthio-4'-oxospiro(1-pyrrolin-3,1'-cyclohexadiene) (1). A solution of anisole (5.4 g, 50 mmol), isobutene oxide (3.6 g, 4.5 ml, 50 mmol), and methyl thiocyanate (3.45 ml, 50 mmol) in CH_2Cl_2 (50 ml) was added dropwise with intense stirring to 98% H_2SO_4 (12 ml, 220 mmol) at a temperature no higher than -15°C. Stirring was continued for 30 min and the mixture was then poured into a mixture of ice (250 g), NH_4Cl (75 g) and con. NH_4OH (75 ml) (pH 7-8). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 20 ml). The combined organic layers were dried with anhydrous $MgSO_4$, the solvent was removed, and the residue was crystallized from a hexane–CH_2Cl_2 mixture (-20°C). Yield 4.42 g (40%); mp 95-97°C. R_f 0.60 (6:1 $CHCl_3$–acetone, development with iodine vapor). The melting point, IR and ^1H NMR spectra corresponded with those of compound **1** obtained by another method [2].

2'-Methoxy-5,5-dimethyl-2-methylthio-4'-oxospiro(1-pyrrolin-3,1'-cyclohexadiene) (2a) and 6'-Methoxy-5,5-dimethyl-2-methylthio-4'-oxospiro(1-pyrrolin-3,1'-cyclohexadiene) (2b), mixture of isomers, was obtained analogously to compound **1** from dimethyl ether of resorcinol (6.55 ml, 6.91 g, 50 mmol), isobutene oxide (3.6 g, 4.5 ml, 50 mmol), and methyl thiocyanate (3.45 ml, 50 mmol) in CH_2Cl_2 (50 ml). After analogous workup and removal of the solvent the residue was chromatographed on silica gel (eluent 1:1 ethyl acetate–hexane) and crystallize from hexane in the cold. Yield 1.35 g (11%); mp 117-124°C. R_f 0.56. According to the ^1H NMR spectrum a 3:1 mixture of isomers **2a** and **2b** was formed which we were unable to separate. In view of the steric hindrance to *ipso*-attack, we assume that isomer **2a** is formed preferentially. IR spectrum (nujol mull), ν, cm^{-1}: 1660 (C=O), 1620 (shoulder, C=C), 1590 (C=N), 1235, 1220, 1190, 1080, 1015, 950, 890. ^1H NMR spectrum of the mixture of **2a** and **2b** (300 MHz, DMSO-d_6), δ, ppm: 1.38 (6H, s, Me_2); 2.32 (3H, s, SMe); 3.70 and 3.78 (total intensity 3H, two s, 2'-OMe and 6'-OMe); 5.63 (1H, s, 3'- or 5'-H); 6.08 (1H, d, 5'- or 3'-H); 6.64 (1H, d, 6'- or 2'-H). Found, %: C 62.98; H 7.09; N 5.42; S 12.67. $C_{13}H_{17}NO_2S$. Calculated, %: C 62.12; H 6.82; N 5.57; S 12.76.

2',6'-Dimethoxy-5,5-dimethyl-2-methylthio-4'-oxospiro(1-pyrrolin-3,1'-cyclohexadiene) (3). A mixture of 1,3,5-trimethoxybenzene (8.4 g, 50 mmol), isobutene oxide (3.6 g, 4.5 ml, 50 mmol), and methyl thiocyanate (3.65 g, 3.45 ml, 50 mmol) in CH_2Cl_2 (50 ml) was added dropwise with intense stirring to 98% H_2SO_4 (12 ml, 220 mmol) at a temperature of 0 to +5°C. After removing the solvent the oily residue was triturated with hexane, the crystals were filtered off, washed with cold ether (5 ml), and crystallized at -20°C from hexane–CH_2Cl_2 mixture to give compound **3** (3.30 g, 24%); mp 168-169°C, R_f 0.50. IR (nujol mull), ν, cm^{-1}: 1660 (C=O), 1620 (shoulder, C=C), 1600 (C=N), 1240, 1215, 1160, 1070, 1015, 950, 865. ^1H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm: 1.34 (6H, s, Me_2); 2.23 (2H, s, CH_2); 2.33 (3H, s, SMe); 3.70 (6H, s, $(OMe)_2$); 5.45 (2H, s, 3',5'-H). Found, %: C 59.91; H 7.03; N 5.05; S 11.38. $C_{14}H_{19}NO_3S$. Calculated, %: C 59.76; H 6.81; N 4.98; S 11.40.

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