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SHORT COMMUNICATIONS

# Retropinacol Rearrangement in the Synthesis of 3,3,4-Trimethyl-2-azaspiro[4.5]deca-1,6,9-trien-8-one Derivatives

**Yu. V. Shklyaev, O. G. Stryapunina, and O. A. Maiorova**

*Institute of Technical Chemistry, Ural Division, Russian Academy of Sciences, ul. Akademika Koroleva 3, Perm, 614013 Russia*
*e-mail: shklyaev@itch.perm.ru*

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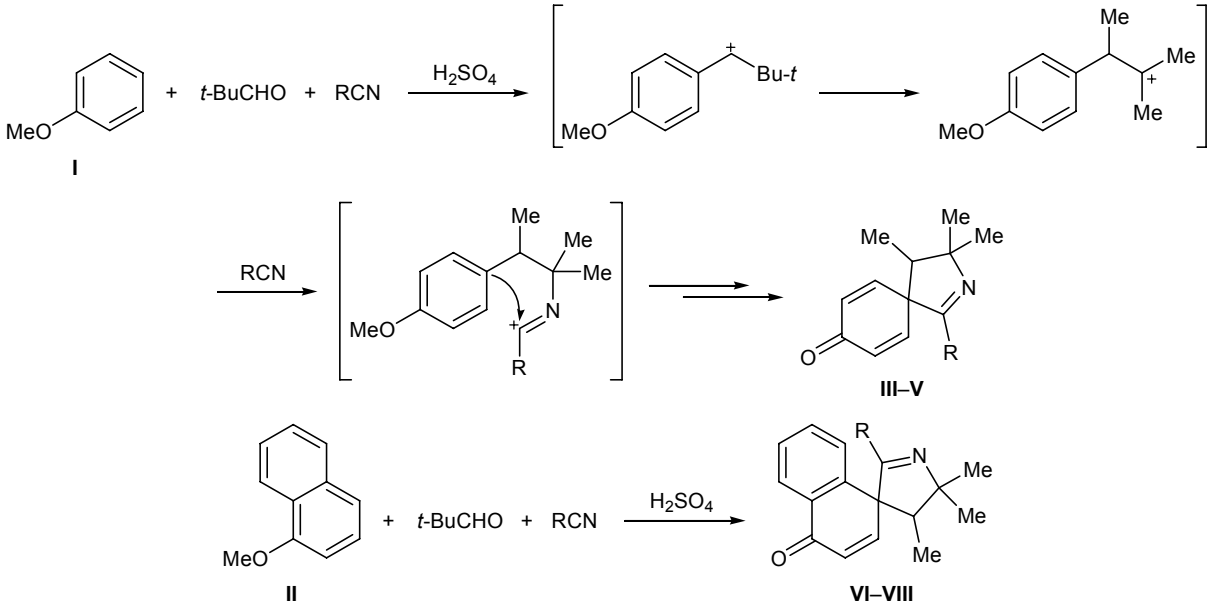
In the recent years 2-azaspiro[4.5]deca-1,6,9-trien-8-one derivatives have attracted researchers' attention due to their biological activity [1, 2]. These compounds may be synthesized in different ways; for example, 7-methoxy-2-methyl-2-azaspiro[4.5]deca-6,9-diene-3,8-dione was obtained by heating 2-[(3,4-dimethoxybenzyl)(methyl)amino]-2-oxoethyldiazonium salt for a short time [3]. The simplest procedure for the synthesis of 2-azaspiro[4.5]deca-1,6,9-trien-8-one derivatives is based on three-component condensation of substituted anisole with isobutyraldehyde and nitrile in concentrated sulfuric acid [4–7]. Generation of carbenium ion as key intermediate in the Ritter heterocyclization is also possible via retropinacol rearrangement of the corresponding alcohol [8]; in this way, 3,3,4-trimethyl-3,4-dihydroisoquinoline derivatives can be obtained.

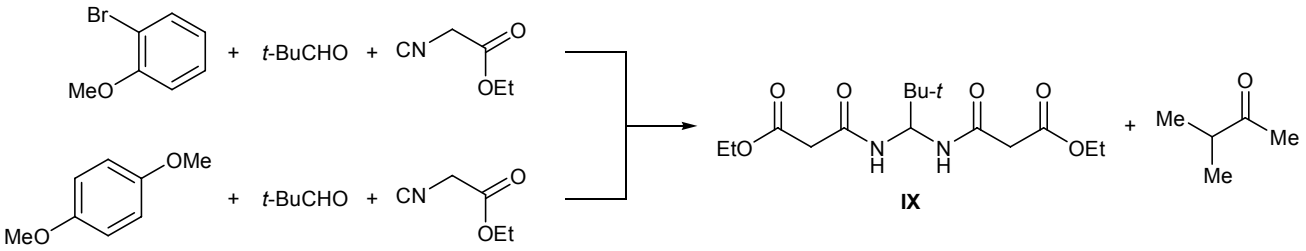
In fact, by reaction of anisole (**I**) or 1-methoxynaphthalene (**II**) with pivalaldehyde and nitriles (such as methyl thiocyanate and methyl and ethyl cyanoacetates) under the conditions described in [8] we obtained the corresponding 2-azaspiro[4.5]deca-1,6,9-trien-8-one derivatives **III**–**VIII** in 28–49% yield (Scheme 1). The reaction was accompanied by concurrent Danilov rearrangement [9], so that 2 equiv of pivalaldehyde was necessary.

**Scheme 1.**




**III**, **VI**, R = MeS; **IV**, **VII**, R = $MeOCOCH_2$; **V**, **VIII**, R = $EtOCOCH_2$.

**Scheme 2.**




The described reaction is sensitive to electronic and steric factors. Analogous condensations with *ortho*-bromoanisole and *p*-dimethoxybenzene afforded only bisamide **IX** and methyl isopropyl ketone (Scheme 2); the latter was identified by GC–MS.

**3,3,4-Trimethyl-1-methylsulfanyl-2-azaspiro-[4.5]deca-1,6,9-trien-8-one (III).** A mixture of 0.54 g (5 mmol) of anisole (**I**), 0.86 g (10 mmol) of pivalaldehyde, and 0.36 g (5 mmol) of methyl thiocyanate was added dropwise to 3 ml of concentrated sulfuric acid on cooling with ice. The mixture was stirred for 40–45 min, poured into a mixture of 150 g of crushed ice and 9 ml of concentrated aqueous ammonia (to pH ~8), and extracted with methylene chloride (3× 20 ml). The extracts were combined, washed with water, and dried over $MgSO_4$, the solvent was distilled off, and the residue was recrystallized from aqueous ethanol. Yield 0.36 g (31%), mp 111–112°C. IR spectrum, ν, $cm^{-1}$: 1658 (C=O), 1617 (C=N), 1577 (C=C). $^1H$ NMR spectrum ($CDCl_3$), δ, ppm: 0.85 d (3H, 4-$CH_3$, $J$ = 7.2 Hz), 1.23 s and 1.40 s (3H each, 3-$CH_3$), 2.38–2.45 m (4H, 4-H, $SCH_3$), 6.34 d.d (1H, 9-H, $J$ = 8.5, 1.8 Hz), 6.38 d.d (1H, 7-H, $J$ = 8.5, 1.8 Hz), 6.64 d.d (1H, 6-H, $J$ = 10.0, 2.7 Hz), 6.78 d.d (1H, 10-H, $J$ = 10.3, 2.4 Hz). $^{13}C$ NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 9.72 (4-$CH_3$), 13.50 ($SCH_3$), 24.72 and 30.16 (3-$CH_3$), 54.20 ($C^4$), 65.13 ($C^5$), 75.11 ($C^3$), 130.45 ($C^9$), 130.61 ($C^7$), 146.40 ($C^{10}$), 149.87 ($C^6$), 167.59 ($C^1$), 185.14 (C=O). Found, %: C 65.57; H 7.33; N 5.85. $C_{13}H_{17}NOS$. Calculated, %: C 66.34; H 7.28; N 5.95.

**Methyl (*Z*)-2-(3,3,4-trimethyl-8-oxo-2-azaspiro-[4.5]deca-1,6,9-trien-1-yl)acetate (IV)** was synthesized from 0.54 g (5 mmol) of anisole, 0.86 g (10 mmol) of pivalaldehyde, and 0.49 g (5 mmol) of methyl cyanoacetate in 3 ml of concentrated sulfuric acid. After removal of the solvent, the residue was recrystallized from aqueous ethanol. Yield 0.37 g (28%), mp 159–160°C. IR spectrum, ν, $cm^{-1}$: 3319, 3285 (NH); 1659 (C=O, ester); 1621 (C=O); 1603 (C=C). $^1H$ NMR spectrum (DMSO-$d_6$), δ, ppm: 0.74 d (3H, 4-$CH_3$, $J$ = 7.2 Hz), 1.24 s and 1.36 s (3H each, 3-$CH_3$), 2.43 q (1H, 4-H, $J$ = 7.2 Hz), 3.48 s (3H, $OCH_3$), 3.97 s (1H, =CH), 6.21 d.d (1H, 9-H, $J$ = 9.9, 1.8 Hz), 6.30 d.d (1H, 7-H, $J$ = 9.9, 1.8 Hz), 6.89 d.d (1H, 6-H, $J$ = 9.9, 2.7 Hz), 7.02 d.d (1H, 10-H, $J$ = 10.2, 3.0 Hz), 8.33 br.s (1H, NH). $^{13}C$ NMR spectrum (DMSO-$d_6$), $\delta_C$, ppm: 8.99 (4-$CH_3$), 24.99 and 29.31 (3-$CH_3$), 49.37 ($OCH_3$), 49.73 ($C^4$), 57.07 ($C^5$), 63.42 ($C^3$), 76.40 (=CH), 128.69 ($C^9$), 129.28 ($C^7$), 148.34 ($C^{10}$), 151.24 ($C^6$), 160.88 ($C^1$), 168.95 (OC=O), 184.84 ($C^8$=O). Found, %: C 68.35; H 7.33; N 5.35. $C_{15}H_{19}NO_3$. Calculated, %: C 68.40; H 8.04; N 5.32.

**Ethyl (*Z*)-2-(3,3,4-trimethyl-8-oxo-2-azaspiro-[4.5]deca-1,6,9-trien-1-yl)acetate (V)** was synthesized from 0.54 g (5 mmol) of anisole, 0.86 g (10 mmol) of pivalaldehyde, and 0.56 g (5 mmol) of ethyl cyanoacetate in 3 ml of concentrated sulfuric acid. After removal of the solvent, the residue was recrystallized from aqueous ethanol. Yield 0.52 g (38%), mp 195–196°C. IR spectrum, ν, $cm^{-1}$: 3305 (NH), 1659 (C=O, ester), 1621 (C=O), 1604 (C=C), 1595. $^1H$ NMR spectrum ($CDCl_3$), δ, ppm: 0.85 d (3H, 4-$CH_3$, $J$ = 7.2 Hz), 1.22 t (3H, $CH_2C\mathbf{H}_3$, $J$ = 7.5 Hz), 1.29 s and 1.39 s (3H each, 3-$CH_3$), 2.37 q (1H, 4-H, $J$ = 7.5 Hz), 4.07 q (2H, $OCH_2$, $J$ = 7.2 Hz), 4.29 s (1H, =CH), 6.28 d.d (1H, 9-H, $J$ = 10.2, 1.5 Hz), 6.34 d.d (1H, 7-H, $J$ = 9.9, 1.5 Hz), 6.67 d.d (1H, 6-H, $J$ = 10.2, 2.7 Hz), 6.86 d.d (1H, 10-H, $J$ = 10.2, 3.0 Hz), 8.01 br.s (1H, NH). $^{13}C$ NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 9.02 (4-$CH_3$), 14.30 ($CH_2\mathbf{C}H_3$), 25.82 and 29.88 (3-$CH_3$), 50.51 ($C^4$), 56.79 ($C^5$), 58.60 ($OCH_2$), 62.72 ($C^3$), 78.37 (=CH), 129.24 ($C^9$), 129.84 ($C^7$), 146.74 ($C^{10}$), 149.98 ($C^6$), 160.96 ($C^1$), 170.15 (OC=O), 185.11 ($C^8$=O). Found, %: C 69.78; H 7.60; N 5.06. $C_{16}H_{21}NO_3$. Calculated, %: C 69.79; H 7.69; N 5.09.

**4′,5′,5′-Trimethyl-2′-methylsulfanyl-4′,5′-dihydro-4*H*-spiro[naphthalene-1,3′-pyrrol]-4-one (VI)** was synthesized in a similar way from 0.79 g (5 mmol) of 1-methoxynaphthalene, 0.86 g (10 mmol) of pivalaldehyde, and 0.36 g (5 mmol) of methyl thiocyanate in

3 ml of concentrated sulfuric acid. After removal of the solvent, the residue was recrystallized from methylene chloride–hexane (1:1). Yield 0.57 g (43%), mp 117–118°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 0.73 d (3H, 4′-$CH_3$, $J$ = 6.9 Hz), 1.24 s and 1.45 s (3H each, 5′-$CH_3$), 2.31 s (3H, $SCH_3$), 2.63 q (1H, 4′-H, $J$ = 7.5 Hz), 6.52 d (1H, 3-H, $J$ = 10.8 Hz), 7.07 d (1H, 2-H, $J$ = 10.8 Hz), 7.41 d (1H, 8-H, $J$ = 8.1 Hz), 7.50 t (1H, 7-H, $J$ = 7.5 Hz), 7.70 t (1H, 6-H, $J$ = 7.5 Hz), 8.02 d (1H, 5-H, $J$ = 8.1 Hz). $^{13}$C NMR spectrum (DMSO-$d_6$), $\delta_C$, ppm: 10.01 (4′-$CH_3$), 13.23 ($SCH_3$), 25.04 and 30.51 (5′-$CH_3$), 59.34 ($C^{4'}$), 65.54 ($C^1$), 74.57 ($C^{5'}$), 125.42 ($C^5$), 127.87 ($C^8$), 128.60 ($C^7$), 129.27 ($C^3$), 131.59 ($C^{4a}$), 133.21 ($C^6$), 143.96 ($C^{1a}$), 148.29 ($C^2$), 169.21 ($C^{2'}$), 183.27 (C=O). Found, %: C 71.53; H 6.62; N 4.91; S 11.25. $C_{17}H_{19}NOS$. Calculated, %: C 71.54; H 6.71; N 4.91; S 11.23.

**Methyl (*Z*)-(4′,5′,5′-trimethyl-4-oxo-4′,5′-dihydro-4*H*-spiro[naphthalene-1,3′-pyrrol]-2′-yl)acetate (VII)** was synthesized from 0.79 g (5 mmol) of 1-methoxynaphthalene, 0.86 g (10 mmol) of pivalaldehyde, and 0.49 g (5 mmol) of methyl cyanoacetate in 3 ml of concentrated sulfuric acid. After removal of the solvent, the residue was recrystallized from ethanol. Yield 0.76 g (49%), mp 187–188°C. IR spectrum, ν, $cm^{-1}$: 3350 (NH), 1671 (C=O, ester), 1663 (C=O), 1602 (C=C). $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 0.67 d (3H, 4′-$CH_3$, $J$ = 7.5 Hz), 1.30 s and 1.47 s (3H each, 5′-$CH_3$), 2.58 q (1H, 4′-H, $J$ = 7.5 Hz), 3.44 s (3H, $OCOCH_3$), 3.62 s (1H, =CH), 6.45 d (1H, 3-H, $J$ = 10.5 Hz), 7.11 d (1H, 2-H, $J$ = 10.8 Hz), 7.45 d (1H, 8-H, $J$ = 7.8 Hz), 7.48 t (1H, 7-H, $J$ = 7.8 Hz), 7.66 t (1H, 6-H, $J$ = 7.5 Hz), 7.99 d (1H, 5-H, $J$ = 8.1 Hz), 8.55 br.s (1H, NH). $^{13}$C NMR spectrum (DMSO-$d_6$), $\delta_C$, ppm: 9.18 (4′-$CH_3$), 25.24 and 29.79 (5′-$CH_3$), 49.60 ($OCOCH_3$), 55.39 ($C^{4'}$), 58.22 ($C^1$), 63.20 ($C^{5'}$), 77.25 (=CH), 125.16 ($C^5$), 127.72 ($C^8$), 127.84 ($C^7$), 128.81 ($C^3$), 131.62 ($C^{4a}$), 133.26 ($C^6$), 145.55 ($C^{1a}$), 148.62 ($C^2$), 165.21 ($C^{2'}$), 169.11 (OC=O), 183.47 (C=O). Found, %: C 73.36; H 6.71; N 4.48. $C_{19}H_{21}NO_3$. Calculated, %: C 73.29; H 6.80; N 4.50.

**Ethyl (*Z*)-(4′,5′,5′-trimethyl-4-oxo-4′,5′-dihydro-4*H*-spiro[naphthalene-1,3′-pyrrol]-2′-yl)acetate (VIII)** was synthesized in a similar way from 0.79 g (5 mmol) of 1-methoxynaphthalene, 0.86 g (10 mmol) of pivalaldehyde, and 0.56 g (5 mmol) of ethyl cyanoacetate in 3 ml of concentrated sulfuric acid. After removal of the solvent, the residue was recrystallized from ethanol. Yield 0.66 g (40%), mp 206–207°C. IR spectrum, ν, $cm^{-1}$: 3340 (NH), 1667 (C=O, ester), 1656 (C=O), 1602 (C=C). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.74 d (3H, 4′-$CH_3$, $J$ = 7.5 Hz), 1.16 t (3H, $CH_2C\mathbf{H}_3$, $J$ = 7.5 Hz) 1.24 s and 1.45 s (3H each, 5′-$CH_3$), 2.62 q (1H, 4′-H, $J$ = 7.5 Hz), 3.99–4.06 m (2H, $OCH_2$), 4.01 s (1H, =CH), 6.48 d (1H, 3-H, $J$ = 10.5 Hz), 6.90 d (1H, 2-H, $J$ = 10.2 Hz), 7.38 d (1H, 8-H, $J$ = 7.8 Hz), 7.38 t (1H, 7-H, $J$ = 7.8 Hz), 7.55 t (1H, 6-H, $J$ = 7.8 Hz), 8.11 d (1H, 5-H, $J$ = 7.8 Hz), 8.28 br.s (1H, NH). $^{13}$C NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 9.26 (4′-$CH_3$), 14.30 ($CH_2\mathbf{C}H_3$), 26.22 and 30.38 (5′-$CH_3$), 56.30 ($C^{4'}$), 58.23 ($C^1$), 58.55 ($OCH_2$), 62.55 ($C^{5'}$), 79.11 (=CH), 125.81 ($C^5$), 127.42 ($C^8$), 128.28 ($C^7$), 128.54 ($C^3$), 132.01 ($C^{4a}$), 132.85 ($C^6$), 145.30 ($C^{1a}$), 147.10 ($C^2$), 165.66 ($C^{2'}$), 170.59 (OC=O), 184.03 (C=O). Found, %: C 73.82; H 6.90; N 4.29. $C_{20}H_{23}NO_3$. Calculated, %: C 73.82; H 7.12; N 4.30.

**Diethyl 3,3′-[(2,2-dimethylpropane-1,1-diyl)diimino]bis(3-oxopropanoate) (IX)** was obtained in a similar way by reaction of 0.93 g (5 mmol) of 2-bromoanisole with 0.86 g (10 mmol) of pivalaldehyde and 0.56 g (5 mmol) of ethyl cyanoacetate in 3 ml of concentrated sulfuric acid. After removal of the solvent, the residue was recrystallized from ethanol. Yield 0.21 g (13%), mp 149–150°C. IR spectrum, ν, $cm^{-1}$: 3276, 3127 (NH); 1732 (C=O, ester); 1653 (C=O). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.96 s (9H, *t*-Bu), 1.24 t (6H, $CH_2C\mathbf{H}_3$, $J$ = 6.9 Hz), 2.34 q (4H, $CH_2$, $J$ = 16.2 Hz), 4.14 q (4H, $OCH_2$, $J$ = 7.5 Hz), 5.77 t (1H, CH, $J$ = 9.3 Hz), 8.05 s and 8.08 s (1H each, NH). $^{13}$C NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 13.95 ($CH_2\mathbf{C}H_3$), 25.20 [$C(\mathbf{C}H_3)_3$], 35.61 [$\mathbf{C}(CH_3)_3$], 41.87 ($CH_2$), 61.18 ($OCH_2$), 62.19 (CH), 165.21 (C=O), 168.21 (OC=O). Mass spectrum, $m/z$ ($I_{rel}$, %): 315 (0.6) $[M - Me]^+$, 274 (12.9), 273 (100) $[M - t\text{-Bu}]^+$, 200 (25.8), 159 (93.5), 115 (47.9), 113 (24.1), 88 (17.1), 86 (26.2), 71 (13.3), 70 (15.9), 69 (14.2), 57 (12.6), 45 (27.8), 43 (28.9), 42 (14.8), 41 (15.0), 29 (28.1). Found, %: C 55.21; H 7.55; N 8.37. $C_{15}H_{26}N_2O_6$. Calculated, %: C 54.53; H 7.93; N 8.48.

The mass spectra were obtained on an Agilent Technologies 6890N/5975B GC–MS system (HP-5MS column, 30 m × 0.25 mm, film thickness 0.25 μm, carrier gas helium; electron impact, 70 eV). The $^1$H and $^{13}$C NMR (DEPT) spectra were recorded on a Varian Mercury Plus instrument at 300.06 and 75.46 MHz, respectively, using hexamethyldisiloxane as internal reference. The IR spectra were measured on a Bruker IFS-66 spectrometer from samples dispersed in mineral oil. The elemental compositions were determined on a Leco CHNS-932 analyzer. The progress of reactions and the purity of products were monitored by TLC on Silufol plates using ethyl acetate–hexane (1:1)

as eluent; spots were visualized by treatment with a 0.5% solution of tetrachloro-1,4-benzoquinone in toluene. The melting points were determined on a PTP melting point apparatus and were not corrected.

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