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Synthesis of 1-substituted (*R,S*)-8-(2-methoxy-5-methylphenyl)-3,3,9-trimethyl-2-azaspiro[4.5]deca-1,7-dien-6-ones

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Reactions between *p*-methylanisole, isobutyraldehyde, and nitriles (acetonitrile, methyl thiocyanate, or ethyl cyanoacetate) in conc. H_2SO_4 yield 1-substituted (*R,S*)-8-(2-methoxy-5-methylphenyl)-3,3,9-trimethyl-2-azaspiro[4.5]deca-1,7-dien-6-ones.

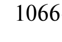
Key words: nitrogen-containing spiroheterocycles, *p*-methylanisole, isobutyraldehyde, nitriles, Ritter reaction, *ortho*-spiroheterocyclization, alkylation.

Earlier,[1—4] it was shown that a three-component condensation of anisole, isobutylene oxide, and nitriles (acetonitrile, methyl thiocyanate, or ethyl cyanoacetate) affords 2-substituted 5,5-dialkyl-4´-oxospiro(pyrroline-3,1´-cyclohexadienes), while *p*-dimethoxybenzene reacts with isobutylene oxide and nitriles to give the corresponding 3,4-dihydroisoquinolines.[5] It was of interest to study the reaction direction for arenes bearing two different substituents, *e.g.*, for *p*-methylanisole.

In this work, isobutyraldehyde was used instead of isobutylene oxide since the products of successive Baeyer and Ritter reactions remain the same.[6]

The aforementioned reagents were found to undergo *ortho*-spiroheterocyclization into 1,3,3,9-tetramethyl-2-azaspiro[4.5]deca-1,7,9-trien-6-one (**A**), which then changes (for R = Me) to (*R,S*)-8-(2-methoxy-5-methylphenyl)-1,3,3,9-tetramethyl-2-azaspiro[4.5]deca-1,7-dien-6-one (**1a**) (Scheme 1). In the case of ethyl cyanoacetate, the reaction products were a mixture of *E*- and *Z*-isomers of ethyl (*R,S*)-8-(2-methoxy-5-methylphenyl)-3,3,9-trimethyl-6-oxo-2-azaspiro[4.5]dec-7-en-1-ylideneacetate (**2**).

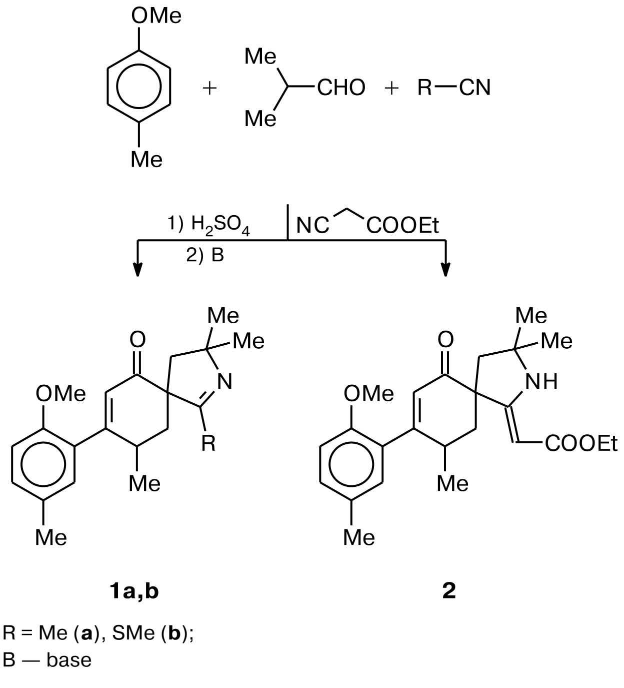
Scheme 1



A

It should be noted that spirotrienone **A** was not isolated; for any reagent ratio, nitrile used, and reaction duration, the reaction products were compounds **1a,b** or **2** (Scheme 2).

Scheme 2



1a,b **2**

R = Me (**a**), SMe (**b**);
B — base

The initial reaction step is analogous to that described previously,[3] except that the carbonyl group occupies the *ortho*- rather than *para*-position.

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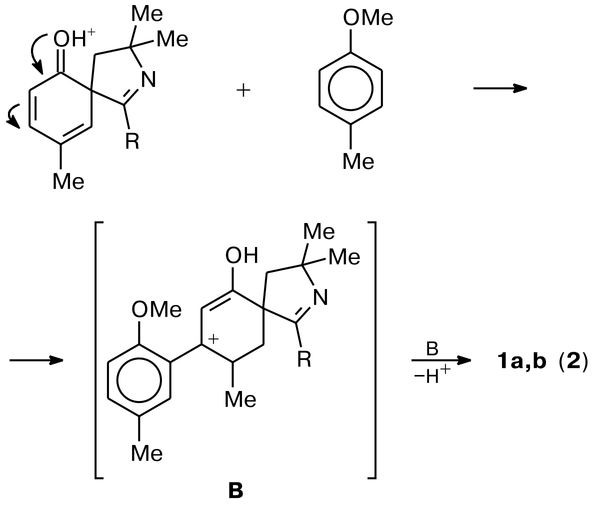
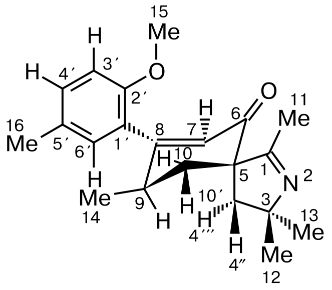
Scheme 3



It can be assumed from the final products that spirotrienone **A** is then protonated and attacks a *p*-methylanisole molecule to give intermediate **B**. Base treatment of the latter affords compounds **1a,b** or **2** (Scheme 3). As a result, isobutyraldehyde and nitrile remain in excess; their reaction yields a normal product, namely, bisamide, detected by TLC with a special marker.[6]

Such a reaction was not observed for anisole, methyl thiocyanate, and isobutylene oxide[1] (or isobutyraldehyde), probably because of steric hindrances presented by the orthogonal pyrroline ring.

^{1}H and ^{13}C NMR spectra (Table 1) were solved using two-dimensional homonuclear COSY and ROESY and heteronuclear HSQC and HMBC spectroscopy techniques. Addition of the phenyl ring to the cyclohexene ring at the doubly bonded C atom was confirmed by the three-bond coupling between the H(3´) and C(8) atoms (HMBC data), as well as by the vicinity of the H(15) protons of the methoxy group and the H(7) proton at the double bond (ROESY data). A high coupling constant $J_{9,10}$ (9 Hz) indicates their pseudodiaxial arrangement in the flattened cyclohexenone ring. Spiro union between the five-membered and cyclohexenone rings in compound **1a** is evident from spatial H(10)—H(11) and H(4″)—H(9) contacts (ROESY data).



1a

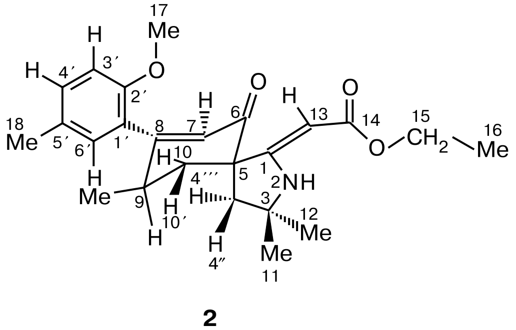
Table 1. ^{1}H and ^{13}C NMR data for compound **1a**

Atom	δ		*J*/Hz	Nuclear Overhauser effect (ROESY)	Proton/carbon correlation for $^2J_{H,C}$ and $^3J_{H,C}$ (HMBC)
	^{13}C	^{1}H			
1	168.9	—	—	—	—
3	70.8	—	—	—	—
4″	45.3	2.04	$J_{4'',4'''} = 13.4$	4″/4‴; 4″/9	4″/6; 4″/5; 4″/10
4‴	—	1.77	—	—	4″/3; 4″/12; 4‴/13; 4‴/10; 4‴/13
5	65.45	—	—	—	10/9; 10/4″; 10´/8
6	199.2	—	—	—	—
7	125.7	5.80	$J_{7,9} = 2.4$	7/15; 7/16	7/1´; 7/5; 7/9
8	166.0	—	—	—	—
9	30.5	3.26	$J_{9,10} = 9.0$, $J_{9,10'} = 4.5$	9/14; 9/10´	—
10	40.7	2.05	$J_{10,10'} = 13.3$	10/10´; 10/11	10/9; 10/4″; 10´/8; 10´/6;
10´	—	1.91	—	—	10´/5; 10´/9; 10´/4″
11	16.0	1.78	—	11/10	11/5; 11/3; 11/1
12	30.9	1.23	—	12/4″; 12/13	12/4″; 12/3; 12/13
13	29.7	1.08	—	13/4‴	13/4″; 13/3; 13/12
14	19.5	0.85	$J_{14,9} = 7.0$	14/10; 14/10´	14/8; 14/10; 14/9
15	55.7	3.77	—	—	15/2´
16	19.9	2.25	—	—	16/6´; 16/5´; 16/4´
1´	127.7	—	—	—	6´/4´; 6´/2´; 6´/8; 6´/16
2´	153.4	—	—	—	—
3´	111.2	6.95	—	3´/15	3´/2´; 3´/5´
4´	130.3	7.17	$J_{3',4'} = 8.4$	4´/16; 4´/6´	4´/6´; 4´/2´; 4´/16
5´	129.4	—	—	—	—
6´	129.1	6.97	$J_{4',6'} = 2.0$	6´/16; 6´/7	6´/4´; 6´/2´; 6´/8; 6´/16

Table 2. ^{1}H and ^{13}C NMR data (δ) for compound **2**

Atom	*Z*-Isomer		*E*-Isomer	
	^{13}C	^{1}H	^{13}C	^{1}H
1	166.1	—	163.6	—
2	—	8.22	—	8.18
3	60.7	—	60.0	—
4″	44.6	2.15	45.8	2.69
4‴	—	1.98	—	1.60
5	58.2	—	57.4	—
6	198.3	—	195.8	—
7	125.3	5.80	127.1	5.94
8	165.5	—	167.1	—
9	30.2	3.28	30.5	3.49
10	42.8	2.03	43.5	2.13
10′	—	2.03	—	1.89
11	30.6	1.35	30.4	1.31
12	28.8	1.19	30.2	1.35
13	75.3	4.16	75.3	4.65
14	169.5	—	169.5	—
15	57.5	4.00	57.7	4.00
16	14.6	1.17	14.5	2.16
17	55.7	3.73	55.5	3.76
18	19.7	2.25	19.7	2.25
1′	127.6	—	128.0	—
2′	153.5	—	153.4	—
3′	111.2	6.95	111.1	6.96
4′	130.3	7.17	130.2	7.17
5′	129.4	—	129.4	—
6′	129.2	6.96	128.7	6.92

Two-dimensional (homonuclear COSY and ROESY and heteronuclear HSQC and HMBC) spectroscopy was also used to interpret the ^{1}H and ^{13}C NMR spectra of ethyl (*R*,*S*)-8-(2-methoxy-5-methylphenyl)-3,3,9-trimethyl-6-oxo-2-azaspiro[4.5]dec-7-en-1-ylideneacetate (**2**) (Table 2). It was found that compound **2** exists in the enamine form as a mixture of *Z*- and *E*-isomers (1 : 1). Linking of the phenyl ring to the cyclohexenone ring at the doubly bonded C atom was confirmed by the three-bond coupling between the H(3′) and C(8) atoms (HMBC data) and the vicinity of the H(17) protons of the methoxy group and the H(7) proton at the double bond (ROESY data). A high coupling constant $J_{9,10}$ (9 Hz) indicates their pseudodiaxial arrangement in the flattened cyclohexene ring. Spiro union between the five-membered and cyclohexenone rings in compound **2** is evident from spatial H(13)—H(10) and H(4″)—H(9) contacts (ROESY data).



2

Experimental

Melting points were determined on a PTP instrument and are given noncorrected. IR spectra were recorded on a UR-20 spectrophotometer (Vaseline oil). ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d$_6$ at 303 K on Bruker DRX-500 (500.13 MHz) and Bruker AM-300 instruments (75.470 MHz), respectively. The residual signal for protons in DMSO-d$_6$ was used as a standard for ^{1}H NMR spectra (δ 2.50). The chemical shift of a signal for DMSO-d$_6$ was taken to be δ 39.5 in the ^{13}C NMR spectra. Two-dimensional spectra were recorded according to a standard procedure (Bruker Co.). The mixing time in the NOESY spectra was 500 ms. The HBMC experiment was optimized for a coupling constant of 8 Hz. Mass spectra were obtained with a Finnigan MAT instrument (EI, 70 eV). The course of the reaction was monitored and the purity of the compounds obtained was checked by TLC on Silufol UV-254 plates in chloroform—acetone (9 : 1); spots were visualized with 0.5% chloranil in toluene.

Synthesis of compounds 1a,b and 2 (general procedure). A mixture of *p*-methylanisole (12.2 g, 0.1 mol), freshly distilled isobutyraldehyde (7.2 g, 0.1 mol), and a corresponding nitrile (0.1 mol) was added dropwise at 0—10 °C (cooling with ice water) to vigorously stirred conc. H_2SO_4 (50 mL). Stirring was continued for 30 min. Then the resulting solution was poured into 300 mL of water, and the product was extracted from the aqueous layer with toluene, and the organic layer was separated. The residue was alkalified with aqueous ammonia to pH 9—10. The precipitate that formed was filtered off, washed with water, dried, and crystallized from hexane. Analogously, compounds **1a,b** and **2** were obtained from 2 equiv. of *p*-methylanisole, the yields (in %) of products **1a,b** and **2** being virtually the same (from the arene).

(*R*,*S*)-8-(2-Methoxy-5-methylphenyl)-1,3,3,9-tetramethyl-2-azaspiro[4.5]deca-1,7-dien-6-one (1a). Yield 72%, m.p. 129—130 °C. Found (%): C, 77.39; H, 8.45; N, 4.40. $C_{21}H_{27}NO_2$. Calculated (%): C, 77.50; H, 8.36; N, 4.30. IR, ν/cm^{-1}: 1600 (C=N); 1650 (C=O). MS, *m*/*z* (I_{rel} (%)): 325 $[M]^+$ (23), 284 [M – MeC≡N] (100), 228 [M – MeCN – $(CH_3)_2C=CH_2]^+$.

(*R*,*S*)-8-(2-Methoxy-5-methylphenyl)-3,3,9-trimethyl-1-methylthio-2-azaspiro[4.5]deca-1,7-dien-6-one (1b). Yield 79%, m.p. 180—181 °C. Found (%): C, 70.41; H, 7.8; N, 4.03; S, 9.10. $C_{21}H_{27}NO_2S$. Calculated (%): C, 70.55; H, 7.61; N, 3.92; S, 8.97. IR, ν/cm^{-1}: 1595 (C=N); 1650 (C=O). ^{1}H NMR, δ: 7.14 (s, 1 H, H(6′)); 6.95 (d, 1 H, H(6′)); 6.90 (d, 1 H, H(3′)); 5.76 (s, 1 H, H(7)); 3.77 (s, 3 H, OMe); 3.24 (m, 1 H, Me—C(9)); 2.40 (s, 3 H, SMe); 2.26 (s, 3 H, Me arom.); 2.15—1.95 (m, 4 H, HC(9), HC(10)); 1.31 (s, 3 H, HC(10′)); 1.16 (s, 3 H, HC(10)); 0.80 (d, 3 H, MeC(9)). MS, *m*/*z* (I_{rel} (%)): 357 $[M]^+$ (100), 342 $[M – Me]^+$ (22), 284 $[M – MeSC≡N]^+$ (40), 228 [M – MeSC≡N – $Me_2C=CH_2]^+$ (20).

Ethyl (*R*,*S*)-8-(2-methoxy-5-methylphenyl)-3,3,9-trimethyl-6-oxo-2-azaspiro[4.5]dec-7-en-1-ylideneacetate (2). Yield 84%, m.p. 160—161 °C (hexane). Found (%): C, 72.33; H, 7.66; N, 3.41. $C_{24}H_{30}NO_4$. Calculated (%): C, 72.54; H, 7.56; N, 3.53. IR, ν/cm^{-1}: 3275 (NH); 1730 (COOEt); 1650 (C=O); 1600 (C=C). MS, m/z (I_{rel} (%)): 397 $[M]^+$ (100); 368 $[M - Et]^+$ (70); 352 $[M - OEt]^+$ (30); 341 $[M - Me_2{=}CH_2]^+$ (10).

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