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Spirocyclohexadienones

7*. Three-component condensation of 1- or 2-methoxynaphthalene with isobutyraldehyde and nitriles

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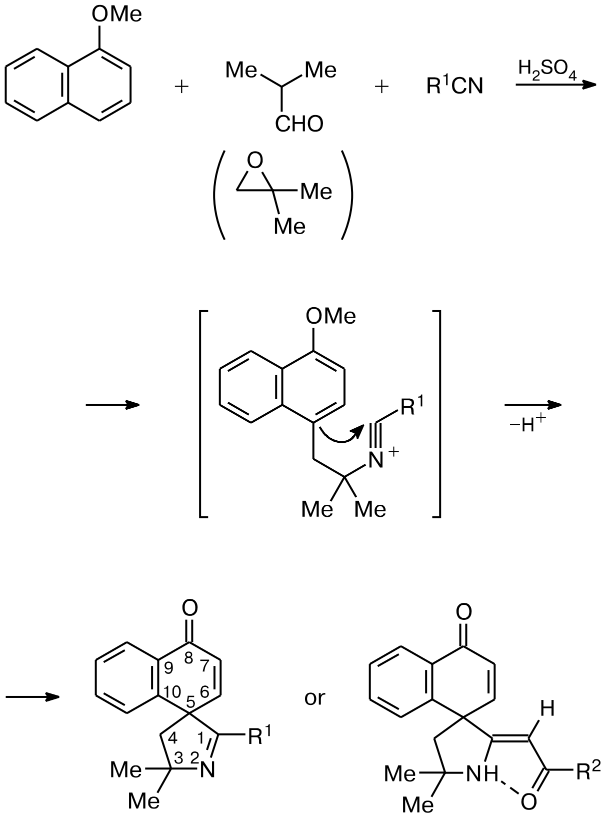
1-R-3,3-Dimethylbenzo[*i*]-2-azaspiro[4.5]deca-1,6-dien-8-ones or 1-R-3,3-dimethylbenzo[*i*]-2-azaspiro[4.5]deca-1,7-dien-6-ones were synthesized by three-component condensation of 1- or 2-methoxynaphthalene, isobutyraldehyde (or isobutylene oxide), and nitrile RCN in concentrated sulfuric acid.

Key words: spiro compounds, pyrroles, naphthalene, isobutyraldehyde, isobutylene oxide, nitriles, cascade heterocyclization.

Only few naphthalene derivatives spiro-coupled with residues of heterocycles, for example, isoxazole[2] or pyrrolidine,[3] have been described in the literature. Spiro compounds of this type sometimes serve as intermediates in ring closure of carbocyclic[4,5] or heterocyclic[6] compounds. Researchers are interested in studying heterocyclic spirocyclohexadienones because fragments of similar structures compose the molecular frameworks of some condensed nitrogen-containing heterocycles commonly found in nature, for example, discorhabdins[7] isolated from marine sponges of the genus *Latrunculia du Bocage*, which inhabit in New Zealand waters. In this work we propose a method for synthesis of substituted benzo[*i*]-2-azaspiro[4.5]deca-1,6-dien-8-ones (**1**, **2**) and benzo[*i*]-2-azaspiro[4.5]deca-1,7-dien-6-ones (**3**, **4**) by three-component condensation of 1- or 2-methoxynaphthalene, dicarbon synthon, and corresponding nitrile R^1CN (R^1 = Me, SMe, CH_2CO_2Et, CH_2CONH_2) in concentrated H_2SO_4.

We used[8] this methodology for synthesis of 1-substituted 3,3-dimethyl-2-azaspiro[4.5]deca-1,6,9-trien-8-ones by the reaction of anisole with nitriles and isobutylene oxide (as a dicarbon synthon) in the presence of H_2SO_4. Further it has been shown[1] that isobutyraldehyde can act as a dicarbon synthon. In this work we used both isobutyraldehyde (Table 1, method *A*) and isobutylene oxide (see Table 1, method *B*) as dicarbon precursors of the C(3)—C(4) atoms in the pyrroline cycle. In the second case, lower yields can be explained by side processes of isobutylene oxide and 1-methoxynaphthalene condensation in concentrated H_2SO_4.

Scheme 1



1a,b **2a,b**

1: R^1 = Me (**a**), SMe (**b**); **2:** R^2 = OEt (**a**), NH_2 (**b**)

No dienone-phenol rearrangement, which is characteristic[9] of 1-R-3,3-dialkyl-2-azaspiro[4.5]deca-1,6,9-trien-8-ones, is observed under the reaction conditions and during isolation of compounds **1a,b** and **2a,b**. Probably, a higher stability of these compounds against

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* For Part 6, see Ref. 1.

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Table 1. Yields, melting points, and elemental analysis data for compounds **1—4** synthesized by methods *A* and *B*

Compound	Yield (*A*/*B*) (%)	M.p.* /°C	Found / Calculated (%) C	H	N	Molecular formula
1a	69/68	104—105	80.21	7.19	5.96	$C_{16}H_{17}NO$
			80.30	7.16	5.85	
1b	71/48	146—147	71.00	6.20	5.04	$C_{16}H_{17}NOS$
			70.81	6.31	5.16	
2a	74/33	174—177	73.25	6.99	4.63	$C_{19}H_{21}NO_3$
			73.29	6.80	4.50	
2b	79/53	242—243	72.43	6.31	9.85	$C_{17}H_{18}N_2O_2$
			72.32	6.43	9.92	
3	63/52	100—101	70.74	6.33	5.07	$C_{16}H_{17}NOS$
			70.81	6.31	5.11	
4	68/56	220—221	72.39	6.45	9.85	$C_{17}H_{18}N_2O_2$
			72.32	6.43	9.92	

* Solvents for crystallization: hexane (**1a**, **3**), EtOH—water (**1b**, **2a**), and EtOH (**2b**, **4**).

hydrolysis is caused by the presence of the annealated benzene ring.

Both possible directions of the *ipso*-attack occur in this reaction to form a mixture of enantiomers relative to the spiro-C(5) atom in compounds **1a,b** and **2a,b**. The ^{1}H NMR spectra of compounds **1a,b** and **2a,b** (Table 2) are characterized by magnetic nonequivalence of the diastereotopic C(4)H$_2$ protons and *gem*-methyl groups at the C(3) atom of the pyrroline cycle. The latter is a consequence of the influence of the aryl ring. The nonequivalence of these protons could also be attributed to the nonplanar structure of this molecular fragment and, hence, to their pseudoaxial and pseudoequatorial arrangement. However, a computer model constructed for compound **1a** (AM1 method, Hyperchem 5.01 program package) has shown that the pyrroline ring is planar and orthogonal to the plane of the tetralone fragment.

2-Methoxynaphthalene reacts similarly with isobutyraldehyde and nitriles (Scheme 2, see Table 1) to form spirans **3** or **4**. Note that compounds **3** and **4** demonstrate the formation of *ortho*-spiroenones, which is rather rare for this type of reactions.

The IR and ^{1}H NMR spectroscopic data for compounds **1—4** are presented in Table 2. The data for the ^{13}C NMR and mass spectra of compounds **1—3** are given in Table 3.

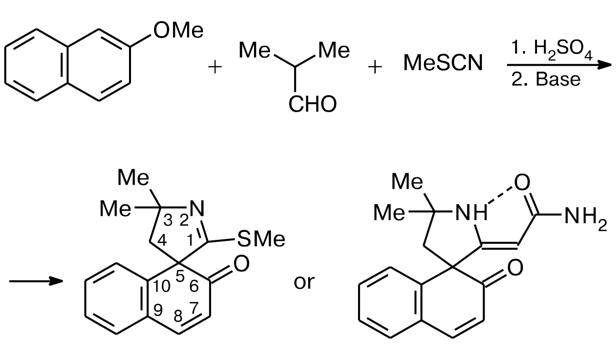
Compounds **2a,b** and **4** in Schemes 1 and 2 are presented separately from compounds **1a,b** and **3** because analysis of their IR, ^{1}H and ^{13}C NMR spectra (see Tables 2 and 3) show that in the crystalline state and in solutions they exist in the enamine form with the intramolecular

Table 2. IR and ^{1}H NMR spectroscopic data of spiro compounds **1a,b**, **2a,b**, **3**, and **4**

Compound	IR*, ν/cm^{-1}	^{1}H NMR, δ (*J*/Hz)
1a	1655 (C=O), 1605 (C=N), 1580, 1500	1.40 (s, 3 H, C(1)Me); 1.44 (s, 3 H, C(3)Me); 1.48 (s, 3 H, C(3)Me); 2.25 (d, 1 H, HC(4), *J* = 12.0); 2.42 (d, 1 H, HC(4), *J* = 12.0); 6.43 (d, 1 H, H(7), *J* = 10.0); 7.01 (d, 1 H, H(6), *J* = 10.0); 7.27 (d, 1 H, H arom., *J* = 7.5); 7.50 (t, 1 H, H arom., *J* = 7.5); 7.70 (t, 1 H, H arom., *J* = 7.5); 8.10 (d, 1 H, H arom., *J* = 7.5)
1b	1655 (C=O), 1605 (C=N), 1585, 1540	1.44 (s, 3 H, C(3)Me); 1.53 (s, 3 H, C(3)Me); 2.30 (s, 3 H, SMe); 2.40 (d, 1 H, HC(4), *J* = 12.0); 2.55 (d, 1 H, HC(4), *J* = 12.0); 6.39 (d, 1 H, H(7), *J* = 10.0); 7.05 (d, 1 H, H(6), *J* = 10.0); 7.32 (d, 1 H, H arom., *J* = 8.0); 7.48 (t, 1 H, H arom., *J* = 8.0); 7.69 (t, 1 H, H arom., *J* = 8.0); 8.01 (d, 1 H, H arom., *J* = 8.0)
2a	3350 (N—H), 1660 (C=O), 1600 (C=C), 1500	1.10 (t, 3 H, Me, *J* = 7.6); 1.49 (s, 3 H, C(3)Me); 1.56 (s, 3 H, C(3)Me); 2.38 (d, H, H—C(4), *J* = 12.0); 2.43 (d, H, H—C(4), *J* = 12.0); 3.63 (s, 1 H, =CH); 3.93 (q, 2 H, OCH$_2$, *J* = 7.6); 6.34 (d, 1 H, H(7), *J* = 10.0); 7.16 (d, 1 H, H(6), *J* = 10.0); 7.42 (d, 1 H, H arom., *J* = 7.5); 7.47 (t, 1 H, H arom., *J* = 7.5); 7.67 (t, 1 H, H arom., *J* = 7.5); 7.98 (d, 1 H, H arom., *J* = 7.5); 8.44 (s, 1 H, NH)
2b	3400, 3310, 3135 (N—H), 1660 (C=O), 1640 (C=O), 1580, 1500	1.47 (s, 3 H, C(3)Me); 1.54 (s, 3 H, C(3)Me); 2.28 (d, 1 H, HC(4), *J* = 12.0); 2.33 (d, 1 H, HC(4), *J* = 12.0); 3.81 (s, 1 H, =CH); 6.05 (br.s, 2 H, NH$_2$); 6.32 (d, 1 H, H(7), *J* = 10.0); 7.17 (d, 1 H, H(6), *J* = 10.0); 7.45 (m, 2 H, H arom.); 7.65 (t, 1 H, H arom., *J* = 7.5); 7.97 (d, 1 H, H arom., *J* = 7.5); 8.61 (s, 1 H, NH)
3	1655 (C=O), 1605 (C=N), 1580, 1500	1.45 (s, 3 H, C(3)Me); 1.49 (s, 3 H, C(3)Me); 2.08 (d, 1 H, HC(4), *J* = 12.0); 2.27 (s, 3 H, SMe); 2.58 (d, 1 H, HC(4), *J* = 12.0); 6.14 (d, 1 H, H(7), *J* = 10.0); 7.18 (d, 1 H, H(6), *J* = 10.0); 7.37 (d, 1 H, H arom., *J* = 8.0); 7.48 (t, 2 H, H arom., *J* = 8.0); 7.72 (d, 1 H, H arom., *J* = 8.0)
4	3280, 3200 (br, NH), 1655 (C=O), 1640 (C=O), 1600 (C=C), 1580, 1500	1.49 (s, 3 H, C(3)Me); 1.52 (s, 3 H, C(3)Me); 2.08 (d, 1 H, HC(4), *J* = 12.0); 2.48 (d, 1 H, HC(4), *J* = 12.0); 3.78 (s, 1 H, =CH); 5.95 (br.s, 2 H, NH$_2$); 6.12 (d, 1 H, H(7), *J* = 10.0); 7.32 (m, 2 H, H(6) + H arom.); 7.45 (m, 2 H, H arom.); 7.69 (d, 1 H, H arom., *J* = 7.5); 8.60 (s, 1 H, NH)

* For suspensions in Nujol.

Scheme 2



3 **4**

hydrogen bond, as it has previously been found for 3,3-dialkyl-1-ethoxycarbonyl-2-azaspiro[4.5]deca-1,6,9-trien-8-one.[1] For example, the IR spectrum of ester **2a** contains the band of the NH group (3350 cm^{-1}), and the band of the ester group shifts to 1660 cm^{-1} due to the formation of an intramolecular hydrogen bond. The ^{1}H NMR spectrum of compound **2a** in DMSO-d_6 exhibits signals from the =CH (δ 3.62) and NH groups (δ 8.44), that of compound **2b** contains signals at δ 3.81 and 8.60 (NH), and signals at δ 3.80 and 8.60 (NH) appear in the spectrum of compound **4**; in addition, the ^{1}H NMR spectra of amides **2b** and **4** demonstrate broadened signals from the NH_2 groups at 6.05 and 5.97 ppm, respectively. Due to the anisotropic influence of the benzoannelated ring, the signals from the olefinic C atom in the =CHCO group in the ^{13}C NMR spectra of compounds **2a,b** demonstrate the upfield shift and lie at 77.2 and 81.5 ppm, respectively. It is also probable that the signals from the spiro-C(5) atom in compounds **2a,b** also manifest the upfield shift and appear at 53.9 and 53.5 ppm under the anisotropic effect of the C=C and C=O double bonds of the enamine form of the orthogonal pyrrolidine fragment. This is contrary to compounds **1a,b** and **3**, whose spiro atoms in the ^{13}C NMR spectra appear at 73.3—75.3 ppm, as it has already been described for similar compounds.[9]

The mass spectra of compounds **1—3** (see Table 3) confirm their structure. Elimination of the methyl groups and the group originated from the initial nitrile is the characteristic route of fragmentation under electron impact.

Experimental

Melting points were determined on a PTP instrument and were not corrected. IR spectra were recorded on a UR-20 spec-

Table 3. ^{13}C NMR spectroscopic and mass spectrometric data of spiro compounds **1a,b**, **2a,b**, and **3**

Compound	^{13}C NMR, δ										MS, m/z (I_{rel} (%))
	C(5)	C(6)	C(7)	C(8)	C(1)	C(4)	C(3)	C(3)Me	Ar	R^1, R^2	
1a	73.3	150.7	131.0	183.1	166.7	51.2	63.1	30.6, 30.9	125.8, 127.1, 127.3, 127.5, 133.4 (C(9)), 144.9 (C(10))	14.9 (Me)	240 [M + 1]$^+$ (10), 199 (60), 198 [M – MeCN]$^+$ (100), 183 [M – MeCN – Me]$^+$ (62), 155 (27), 128 (17)
1b	74.3	150.8	131.0	183.4	168.7	53.7	62.7	31.3, 31.4	125.8, 126.9, 128.0, 128.3, 133.6 (C(9)), 144.6 (C(10))	13.9 (SMe)	271 [M]$^+$ (8), 199 [M – MeSCN – H]$^+$ (15), 198 [M – MeSCN]$^+$ (100), 183 (83), 155 (31), 128 (20), 115 (13), 100 (20)
2a	53.9	151.1	130.5	183.2	165.2	51.0	61.7	30.6, 30.9	125.0, 125.3, 127.4, 128.2, 133.3 (C(9)), 146.5 (C(10))	14.4 (Me); 77.2 (C(O)CH=); 57.7 (OCH_2); 168.8 (OC=O)	311 [M]$^+$ (100), 296 [M – Me]$^+$ (43), 266 [M – OEt]$^+$ (23), 250 (98), 238 (42), 224 (39), 198 (75), 183 (85), 165 (17), 155 (39), 128 (27), 115 (18)
2b	53.5	152.1	130.4	183.5	161.8	51.2	60.6	30.9, 31.4	124.6, 125.2, 127.2, 128.3, 133.3 (C(9)), 147.4 (C(10))	81.5 (C(O)CH=); 171.4 (C=O)	282 [M]$^+$ (100), 267 (14), 250 (15), 238 (14), 198 (65), 183 (85), 155 (29), 128 (28), 115 (17)
3	75.3	197.83	131.1	146.4	166.8	54.8	72.8	30.5, 31.6	124.6, 128.1, 128.2, 129.2, 129.9, 142.4 (C(10))	14.0 (SMe)	271 [M]$^+$ (5), 199 (15), 198 [M – MeSCN]$^+$ (100), 183 (65), 166 (16), 155 (11), 128 (14), 100 (12)

trophotometer in Nujol. ^{1}H NMR spectra were measured on a Bruker DRX-500 instrument (500.13 MHz), and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument (75.470 MHz) in DMSO-d$_6$ using Me$_4$Si as internal standard. Mass spectra were measured on a Finnigan MAT instrument under standard conditions (EI, 70 eV). The reaction course and purity of the compounds were monitored by TLC on Silufol UV-254 plates in a chloroform—acetone (9 : 1) mixture using a 0.5% solution of chloranil in toluene for visualization.

1,3,3-Trimethylbenzo[*i*]-2-azaspiro[4.5]deca-1,6-dien-8-one (1a), 3,3-dimethyl-1-methylthiobenzo[*i*]-2-azaspiro[4.5]deca-1,6-dien-8-one (1b), and 3,3-dimethyl-1-methylthiobenzo[*i*]-2-azaspiro[4.5]deca-1,7-dien-6-one (3) (general procedure). A mixture of 1- or 2-methoxynaphthalene (15.8 g, 0.1 mol), isobutyraldehyde (7.2 g, 0.1 mol) (or isobutylene oxide (4.5 mL, 3.6 g, 0.1 mol)), and the corresponding nitrile (0.1 mol) were added dropwise with stirring to 96% H$_2$SO$_4$ (50 mL) for 15—20 min at 0—5 °C (when synthesizing compound **3**, the added mixture was diluted with toluene (30 mL)). The mixture was stirred for 30 min, poured into water (300 mL), and extracted with toluene (2×50 mL). A toluene layer was separated, and an aqueous layer was brought to pH 8—9 by ammonium carbonate. A precipitate was separated, washed with water, dried in air, and recrystallized.

1-Ethoxycarbonylmethylene-3,3-dimethylbenzo[*i*]-2-azaspiro[4.5]dec-6-en-8-one (2a) was synthesized similarly from 1-methoxynaphthalene (15.8 g, 0.1 mol), isobutyraldehyde (7.2 g, 0.1 mol) (or isobutylene oxide (4.5 mL, 3.6 g, 0.1 mol)), and ethyl cyanoacetate (10.6 mL, 11.3 g, 0.1 mol). After the first extraction with toluene, the precipitate formed from the extract was washed with water, added to the main portion of the substance prepared by the general procedure, and recrystallized.

1-Carbamoylmethylene-3,3-dimethylbenzo[*i*]-2-azaspiro[4.5]dec-6-en-8-one (2b) and 1-carbamoylmethylene-3,3-dimethylbenzo[*i*]-2-azaspiro[4.5]dec-7-en-6-one (4). Cyanacetamide (8.4 g, 0.1 mol) was dissolved in 96% H$_2$SO$_4$ (60 mL) and added dropwise by a mixture of 1- or 2-methoxynaphthalene (15.8 g, 0.1 mol) and isobutyraldehyde (7.2 g, 0.1 mol) (or isobutylene oxide (4.5 mL, 3.6 g, 0.1 mol)) for 15—20 min at 0—5 °C (in the case of 2-methoxynaphthalene, the added mixture was diluted with toluene (30 mL)). Further the reaction mixture was treated according to the general procedure, and the product was recrystallized.

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References

1. V. A. Glushkov, O. G. Ausheva, S. N. Shurov, and Yu. V. Shklyaev, *Izv. Akad. Nauk*, *Ser. Khim.*, 2002, 822 [*Russ. Chem. Bull.*, *Int. Ed.*, 2002, **51**, 894].
2. S. Hirotani and E. Kaji, *Tetrahedron*, 1999, **55**, 4255.
3. J. Boivin, M. Yousfi, and S. Z. Zard, *Tetrahedron Lett.*, 1997, **38**, 5985.
4. J. J. Sepiol, M. Gora, and M. K. Luczynski, *Synlett*, 2001, 1383.
5. I. A. Blair, L. N. Mander, and P. H. C. Mundill, *Austr. J. Chem.*, 1981, **34**, 1235.
6. S. Doi, N. Shirai, and Y. Sato, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 2217.
7. B. R. Copp, K. F. Fulton, N. B. Perry, J. W. Blunt, and M. H. G. Munro, *J. Org. Chem.*, 1994, **59**, 8233.
8. V. A. Glushkov, G. A. Postanogova, and Yu. V. Shklyaev, *Khim. Geterotsikl. Soedin.*, 2000, 1559 [*Chem. Heterocycl. Compd.*, 2000 (Engl. Transl.)].
9. V. A. Glushkov, O. G. Ausheva, S. N. Shurov, and Yu. V. Shklyaev, *Izv. Akad. Nauk*, *Ser. Khim.*, 2001, 1571 [*Russ. Chem. Bull.*, *Int. Ed.*, 2001, **50**, 1648].

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