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Spirocyclohexadienones: X.* Three-Component Condesation of 1,2,3- and 1,2,4-Trimethoxybenzenes with Cyclohexanecarbaldehyde and Nitriles. Synthesis of 1,2- and 1,4-Dimethoxy-14-azadispiro[5.1.5.2]pentadeca-1,4-dien-3-ones

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Abstract—Substituted 1,2- and 1,4-dimethoxy-14-azadispiro[5.1.5.2]pentadeca-1,4-dien-3-ones and 1,2(1,4)-dimethoxy-14-azadispiro[5.1.5.2]pentadeca-1,4,14-trien-3-ones were synthesized by three-component condensation of cyclohexanecarbaldehyde with 1,2,3- or 1,2,4-trimethoxybenzene and the corresponding nitriles in the presence of concentrated sulfuric acid.

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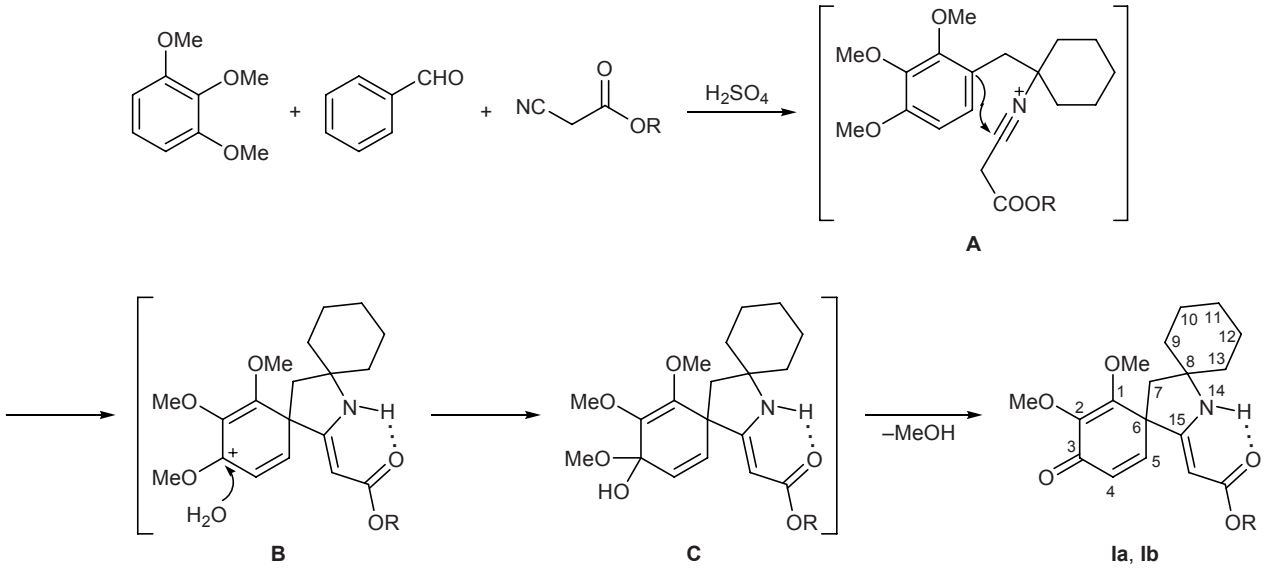
In the recent years interest in the synthesis of heterocyclic systems from aromatic precursors has increased considerably. We have developed a procedure for dearomatization of substituted arenes via three-component condensation with α-branched aldehydes and nitriles which ensured one-step preparation of 2-azaspiro[4.5]decanes. Some 2-azaspiro[4.5]decane derivatives were found in the nature; examples are antibiotic spirostaphylotrichin [2] and alkaloid annosqualine [3]. Among synthetic 2-azaspiro[4.5]decane derivatives, HIV-1 protease inhibitors [4] and compounds possessing anticarcinogenic [5], antiarthritic [6], and antigastric properties [7] were reported. In some cases 2-azaspiro[4.5]decanes are formed as intermediates in cyclizations and recyclizations of isoquinolines [8, 9]. Classical synthetic approaches to 2-azaspiro[4.5]decanes include radical cyclizations of haloacetamides [10, 11], *N*-allyl amides [12], and dithiocarbonates [13] and intramolecular Heck reactions [14]. In the recent time, new effective spirocyclization procedures have been reported, such as olefin metathesis [15], intramolecular cascade cyclization of iminium [16] and thionium salts [17], dearomatization of arene ruthenium complexes [18–23], and cyclization of diene iron complexes [24–26].

We previously proposed a procedure for the synthesis of 2-azaspiro[4.5]decane derivatives by three-component condensation of anisole [27] or *m*-xylene [28] with isobutyraldehyde and nitriles in the presence of concentrated sulfuric acid. With a few exceptions [29, 30], no data on analogous reactions with cyclohexanecarbaldehyde have been reported, although such reactions should obviously lead to the formation of dispiro compounds some of which were prepared by us previously by linear syntheses [31].

The goal of the present work was to examine the behavior of cyclohexanecarbaldehyde in three-component condensation of 1,2,3- and 1,2,4-trimethoxybenzenes with some nitriles. In the first step of our study, 1,2,3-trimethoxybenzene was reacted with cyclohexanecarbaldehyde and cyanoacetic acid esters in the presence of concentrated sulfuric acid (Scheme 1). As a result, we isolated the corresponding dispiro compounds, substituted 14-azadispiro[5.1.5.2]pentadeca-1,4-dien-3-ones **Ia** and **Ib**, whose structure was confirmed by IR and ^{1}H NMR spectroscopy. Compound **Ia** displayed in the ^{1}H NMR spectrum signals from three methoxy groups at δ 3.57, 3.69, and 3.99 ppm. In the ^{1}H NMR spectrum of **Ib** we observed a set of signals typical of ester ethoxy group (a triplet at δ 1.12 ppm and a multiplet at δ 3.96 ppm due to CH_3

* For communication IX, see [1].

Scheme 1.

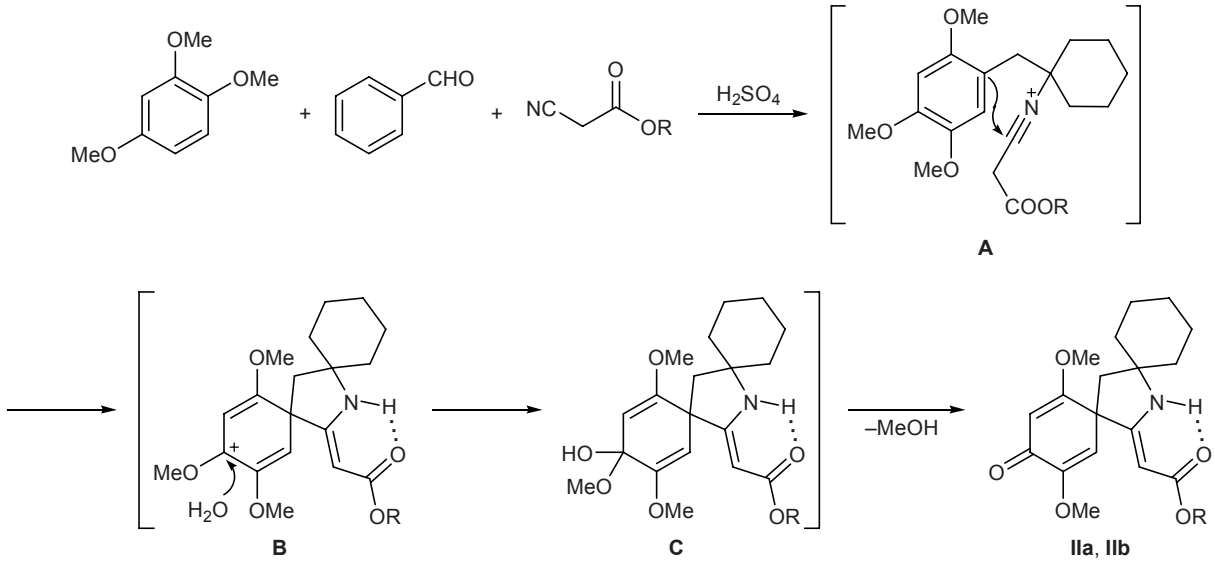


R = Me (**a**), Et (**b**).

and OCH_2 protons, respectively). The IR spectra of **Ia** and **Ib** contained absorption bands belonging to stretching vibrations of NH and C=O groups (3320 and 1652–1660 cm^{-1}, respectively); the latter was displaced toward lower frequencies due to formation of intramolecular hydrogen bond, as we observed previously for spiro compounds obtained from anisole [27]. Compounds **Ia** and **Ib** were isolated as mixtures of enantiomers with respect to the C^6 spiro-carbon atom; as a result, diastereotopic methylene protons on C^7 had different chemical shifts, and their signals were split into doublets (^2J = 13.5–13.8 Hz).

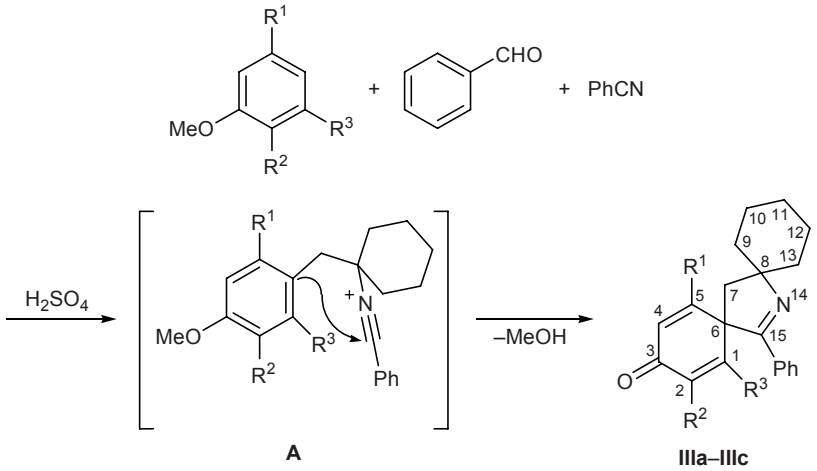
Analogous condensation was performed using 1,2,4-trimethoxybenzene as aromatic component. The reaction followed a similar path (Scheme 2) and resulted in the formation of dispiro compounds **IIa** and **IIb**. Like compounds **Ia** and **Ib**, 1,4-dimethoxy derivatives **IIa** and **IIb** had enamine structure. Their ^{1}H NMR spectra contained a singlet at δ 3.91–3.93 ppm from the olefinic proton (C^{15}=CH) and a broadened NH

Scheme 2.



R = Me (**a**), Et (**b**).

Scheme 3.



R^1 = H, R^2 = R^3 = MeO (**a**); R^1 = R^2 = MeO, R^3 = H (**b**); R^1 = R^3 = MeO, R^2 = H (**c**).

singlet at δ 8.37 ppm. In the IR spectra of **IIa** and **IIb**, NH absorption bands appeared at 3320–3330 cm^{-1}, stretching vibrations of the ester C=O group involved in intramolecular hydrogen bond had a frequency of 1640–1645 cm^{-1}, and the band at 1590–1625 cm^{-1} was assigned to vibrations of the endocyclic C=C bond. In the ^{13}C NMR spectra of these compounds, the spiro carbon atoms gave signals at δ_C 64.66–64.72 (C^8) 56.73–56.74 ppm (C^6), and the olefinic carbon nuclei (=CH) resonated at δ_C 74.16–74.38 ppm. The upfield position of the latter signal was also confirmed by the two-dimensional ^1H–^{13}C NMR spectrum. As in compounds **Ia** and **Ib**, the presence of a chiral spiro carbon atom (C^6) in molecules **IIa** and **IIb** makes methylene protons on C^7 diastereotopic, and their signals appear as two doublets with a ^2J value of 13.5–14.0 Hz.

We also examined three-component condensation of 1,2,3- and 1,2,4-trimethoxybenzenes with cyclohexanecarbaldehyde and benzonitrile. For comparison, analogous condensation was performed with 1,3,5-trimethoxybenzene. In all cases, the corresponding dispiro compounds **IIIa**–**IIIc** were smoothly obtained (Scheme 3). Anisotropic effect of the phenyl group induces downfield shift of the C^6 signal in the ^{13}C NMR spectra of **IIIa** and **IIIb** (δ_C 75–76 ppm) as compared to **I** and **II**; the second spiro carbon atom (C^8) gives a signal at δ_C 61–64 ppm.

The described three-component condensation of trimethoxybenzenes with cyclohexanecarbaldehyde and nitriles ensures preparation of dispiro compounds **I**–**III** in satisfactory yields (26–69%). We can conclude that the use of cyclohexanecarbaldehyde as two-carbon synthon gives essentially the same results as in the condensation with isobutyraldehyde.

EXPERIMENTAL

The IR spectra were recorded on a Specord M80 spectrometer from samples dispersed in mineral oil. The ^1H and ^{13}C NMR spectra were obtained on a Varian Mercury Plus instrument at 300 and 75 MHz, respectively; the chemical shifts were measured relative to hexamethyldisiloxane as internal reference (^1H) or solvent signal (^{13}C). The elemental compositions were determined on a Leco CHNS analyzer. Sorbfil plates were used for analytical thin-layer chromatography (eluent chloroform–acetone, 9:1; spots were visualized by treatment with a 3% solution of chloranil in toluene).

General procedure for three-component condensation of trimethoxybenzenes with cyclohexanecarbaldehyde and nitriles. A mixture of 5 mmol of 1,2,3-, 1,2,4-, or 1,3,5-trimethoxybenzene, 5 mmol of cyclohexanecarbaldehyde, 5 mmol of the corresponding nitrile, and 2 ml of methylene chloride was added dropwise under stirring to 3 ml of concentrated sulfuric acid on cooling on a water bath. The mixture was stirred for 20 min, poured into a mixture of 20 ml of 25% aqueous ammonia, 20 ml of a saturated solution of ammonium chloride, and 100 g of crushed ice, and extracted with methylene chloride (2×50 ml). The extracts were combined, washed with cold water and a saturated solution of sodium chloride, and dried over anhydrous $MgSO_4$. The solvent was distilled off, and the residue was subjected to column chromatography on silica gel (compounds **Ia** and **IIIa**; gradient elution with hexane–ethyl acetate, 5 to 50 vol % of the latter) or rerecrystallized from appropriate solvent (**Ib**, **IIa**, **IIb**, **IIIb**, **IIIc**).

Methyl [(6*RS*)-1,2-dimethoxy-3-oxo-14-azadispiro[5.1.5.2]pentadeca-1,4-dien-(15*Z*)-ylidene]acetate (Ia). Yield 40%, mp 103–104.5°C (from aqueous ethanol). IR spectrum, ν, cm^{-1}: 3320 (NH), 1746 (C=O), 1660 (C=O, ester), 1602 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.28–1.64 m (10H, CH_2), 1.92 d (1H, 7-H, *J* = 13.5 Hz), 2.26 d (1H, 7-H, *J* = 13.5 Hz), 3.57 s (3H, OCH_3), 3.69 s (3H, OCH_3), 3.99 s (3H, OCH_3), 4.2 s (1H, CH=), 6,02 d (1H, 4-H, *J* = 10.2 Hz), 6.40 d (1H, 5-H, *J* = 10.2 Hz), 8.24 br.s (1H, NH). Found, %: C 65.57; H 7.23; N 3.96. $C_{19}H_{25}NO_5$. Calculated, %: C 65.69; H 7.25; N 4.03.

Ethyl [(6*RS*)-1,2-dimethoxy-3-oxo-14-azadispiro-[5.1.5.2]pentadeca-1,4-dien-(15*Z*)-ylidene]acetate (Ib). Yield 55%, mp 95–97°C (from EtOH). IR spectrum, ν, cm^{-1}: 3320 (NH), 1716 (C=O), 1652 (C=O, ester), 1600 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.18 t (3H, $CH_2C\mathbf{H}_3$, *J* = 7.2 Hz), 1.39–1.64 m (10H, CH_2), 1.92 d (1H, 7-H, *J* = 13.8 Hz), 2.26 d (1H, 7-H, *J* = 13.8 Hz), 3.69 s (3H, OCH_3), 3.99 s (3H, OCH_3), 4.05 m (3H, CH=, OCH_2), 6.02 d (1H, 4-H, *J* = 9.6 Hz), 6.41 d (1H, 5-H, *J* = 9.6 Hz), 8.28 br.s (1H, NH). Found, %: C 66.32; H 7.35; N 3.88. $C_{20}H_{27}NO_5$. Calculated, %: C 66.46; H 7.53; N 3.88.

Methyl [(6*RS*)-1,4-dimethoxy-3-oxo-14-azadispiro[5.1.5.2]pentadeca-1,4-dien-(15*Z*)-ylidene]acetate (IIa). Yield 48%, mp 167.5–168.5°C (from EtOH). IR spectrum, ν, cm^{-1}: 3330 (NH); 1705 (C=O); 1640 (C=O, ester); 1600, 1585 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.46–1.69 m (10H, CH_2), 2.02 d (1H, 7-H, *J* = 13.5 Hz), 2.36 d (1H, 7-H, *J* = 13.5 Hz), 3.61 s (3H, OCH_3), 3.65 s (3H, OCH_3), 3.72 s (3H, OCH_3), 4.21 s (1H, CH=), 5.42 s (1H, 2-H), 5.63 s (1H, 5-H), 8.34 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 23.50, 24.63, 38.20 (CH_2); 43.45 (C^7); 49.72, 54.62, 54.89 (OCH_3); 56.74 (C^6); 64.72 (C^8); 74.16 (CH=); 101.92 (C^2); 115.53 (C^5); 148.35 (C^4); 163.56 (C^1); 169.86 (C^{15}); 174.46 (C=O); 180.97 (C^3). Found, %: C 65.48; H 7.22; N 3.95. $C_{19}H_{25}NO_5$. Calculated, %: C 65.69; H 7.25; N 4.03.

Ethyl [(6*RS*)-1,2-dimethoxy-3-oxo-14-azadispiro-[5.1.5.2]pentadeca-1,4-dien-(15*Z*)-ylidene]acetate (IIb). Yield 26%, mp 158–159°C (from EtOH). IR spectrum, ν, cm^{-1}: 3320 (NH); 1710 (C=O); 1645 (C=O, ester); 1625, 1590 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.23 t (3H, $CH_2C\mathbf{H}_3$, *J* = 7.2 Hz), 1.45–1.68 m (10H, CH_2), 2.00 d (1H, 7-H, *J* = 14.0 Hz), 2.36 d (1H, 7-H, *J* = 14.0 Hz), 3.65 s (3H, OCH_3), 3.72 s (3H, OCH_3), 4.07 q (2H, OCH_2, *J* = 6.9 Hz), 4.20 s (1H, CH=), 5.42 s (1H, 2-H), 5.63 s (1H, 5-H), 8.34 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.55 ($CH_2\mathbf{C}H_3$); 23.47, 24.60, 38.18 (CH_2); 43.44 (C^7); 54.57, 54.86 (OCH_3); 56.73 (C^6); 57.95 (OCH_2); 64.66 (C^8); 74.38 (CH=); 101.86 (C^2); 115.52 (C^5); 148.28 (C^4); 163.46 (C^1); 169.53 (C^{15}); 174.44 (C=O); 180.95 (C^3). Found, %: C 66.25; H 7.53; N 3.86. $C_{20}H_{27}NO_5$. Calculated, %: C 66.46; H 7.53; N 3.88.

(6*RS*)-1,2-Dimethoxy-15-phenyl-14-azadispiro-[5.1.5.2]pentadeca-1,4,14-trien-3-one (IIIa). Yield 62%, mp 110–111°C (from hexane). IR spectrum, ν, cm^{-1}: 1652 (C=O); 1636 (C=C); 1616 (C=N); 1594, 1532, 1496 ($C=C_{arom}$); 1322, 1288, 1204, 1156, 1100, 1054, 1012, 968, 870, 830. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.33–1.94 m (10H, CH_2), 2.13 d (1H, 7-H, *J* = 13.5 Hz), 2.30 d (1H, 7-H, *J* = 13.5 Hz), 3.69 s (3H, OCH_3), 3.90 s (3H, OCH_3), 6.24 s (1H, 4-H), 6.65 s (1H, 5-H), 7.28 pseudotriplet (2H, 3′-H, 5′-H, *J* = 7.5 Hz), 7.33 pseudotriplet (1H, 4′-H, *J* = 7.5 Hz), 7.68 pseudodublet (2H, 2′-H, 6′-H, *J* = 7.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 23.01, 23.36, 25.32, 38.88, 39.20 (CH_2); 46.98 (C^7); 60.34, 60.79 (OCH_3); 64.27 (C^8); 76.01 (C^6); 126.71** (C_{arom}); 127.18** (C^4); 128.13**, 130.29** (C_{arom}); 133.64 (C^2); 138.05 (C_{arom}); 146.65 (C^5); 162.36 (C^1); 163.97 (C^{15}); 184.09 (C^3). Found, %: C 75.55; H 6.91; N 3.93. $C_{20}H_{27}NO_5$. Calculated, %: C 75.19; H 7.17; N 3.99.

(6*RS*)-1,4-Dimethoxy-15-phenyl-14-azadispiro-[5.1.5.2]pentadeca-1,4,14-trien-3-one (IIIb). Yield 69%, mp 176–178°C (from hexane–CH_2Cl_2). IR spectrum, ν, cm^{-1}: 1645 (C=O), 1630 (C=C), 1580 (C=N). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.40–1.89 m (10H, CH_2), 2.17 d (1H, 7-H, *J* = 13.5 Hz), 2.36 d (1H, 7-H, *J* = 13.5 Hz), 3.64 s (6H, OCH_3), 5.56 s (1H, 7-H), 5.73 s (1H, 5-H), 7.30 m (3H, H_{arom}), 7.67 d (2H, H_{arom}, *J* = 7.8 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 22.90, 23.04, 25.26 (CH_2); 49.08 (C^7); 55.01, 56.69 (OCH_3); 61.28 (C^8); 75.36 (C^6); 102.27 (C^2); 115.53 (C^5); 127.10, 128.29, 130.23, 133.51 (C_{arom}); 149.18 (C^4); 163.97 (C^5); 175.41 (C^{15}); 180.65 (C^3). Found, %: C 75.01; H 7.07; N 3.95. $C_{22}H_{25}NO_3 \cdot 0.5H_2O$. Calculated, %: C 75.19; H 7.17; N 3.99.

(6*RS*)-1,5-Dimethoxy-15-phenyl-14-azadispiro-[5.1.5.2]pentadeca-1,4,14-trien-3-one (IIIc). Yield 51%, mp 177–179°C (from hexane–CH_2Cl_2). IR spectrum, ν, cm^{-1}: 1656 (C=O), 1624 (C=C), 1588 (C=N). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.32–1.86 m (10H, CH_2), 2.22 s (2H, 7-H), 3.63 s (6H, OCH_3),

** Alternative assignment is possible.

5.55 s (2H, 2-H, 4-H), 7.29 m (3H, H_{arom}), 7.67 d (2H, H_{arom}, J = 8.1 Hz). Found, %: C 75.02; H 6.97; N 3.86. $C_{22}H_{25}NO_3$. Calculated, %: C 75.19; H 7.17; N 3.99.

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