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Spirocyclohexadienones: IX.* Synthesis of 1-Alkoxycarbonylmethylidene-6,10-dimethoxy-8-[(alkoxycarbonyl)cyanomethylidene]-3,3-R_2-2-azaspiro[4.5]deca-6,9-dienes by Four-Component Condensation of 1,3,5-Trimethoxybenzene with α-Branched Aldehydes and Alkyl Cyanoacetates

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Abstract—Four-component condensation of 1,3,5-trimethoxybenzene, a C_2-synton, and alkyl cyanoacetate in the presence of concentrated sulfuric acid gave the corresponding 1-alkoxycarbonylmethylidene-6,10-dimethoxy-8-[(alkoxycarbonyl)cyanomethylidene]-3,3-R_2-2-azaspiro[4.5]deca-6,9-dienes.

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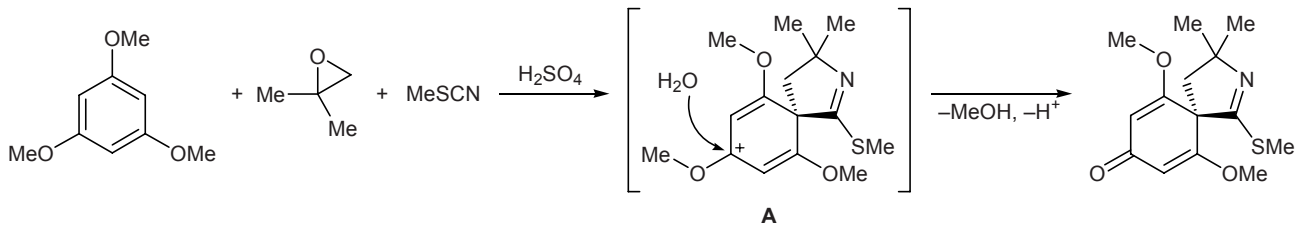
Multicomponent reactions are widely used in the chemistry of nitrogen-containing heterocyclic compounds due to their practicability, simplicity, and short reaction time [2]. We previously described three-component electrophilic condensation of 1,3,5-trimethoxybenzene with 1,2-epoxy-2-methylpropane and methyl thiocyanate in the presence of concentrated sulfuric acid, which led to the formation of 6,10-dimethoxy-3,3-dimethyl-1-methylsulfanyl-2-azaspiro[4.5]deca-1,6,9-trien-8-one [3] (Scheme 1). The reaction involved intermediate formation of resonance-stabilized carbocation **A** which reacted with water during the isolation procedure [4, 5].

We found that analogous reaction with methyl or ethyl cyanoacetate instead of methyl thiocyanate occurs as four-component condensation in which intermediate carbocatione **A** reacts with the second alkyl cyanoacetate molecule to give 3,3-disubstituted 1-alkoxycarbonylmethylidene-6,10-dimethoxy-8-[(alkoxycarbonyl)cyanomethylidene]-2-azaspiro[4.5]deca-6,9-dienes **I**–**IV** (Scheme 2). Here, alkyl cyanoacetate acts as both C^1–N^2 synthon and nucleophile which attacks carbocation **A**. The yields of condensation products **I**–**IV** were fairly poor (14–24%). The optimal reactant ratio (arene–aldehyde–alkyl cyanoacetate) was 1:1:2; however, even at an equimolar ratio of the reactants, compounds **I**–**IV** were formed as the major products. Among by-products we identified by ^{1}H NMR spectroscopy 1,1-bis(2,4,6-trimethoxyphenyl)-2-methylpropane; the other by-products were unidentified low-melting oligomeric compounds.

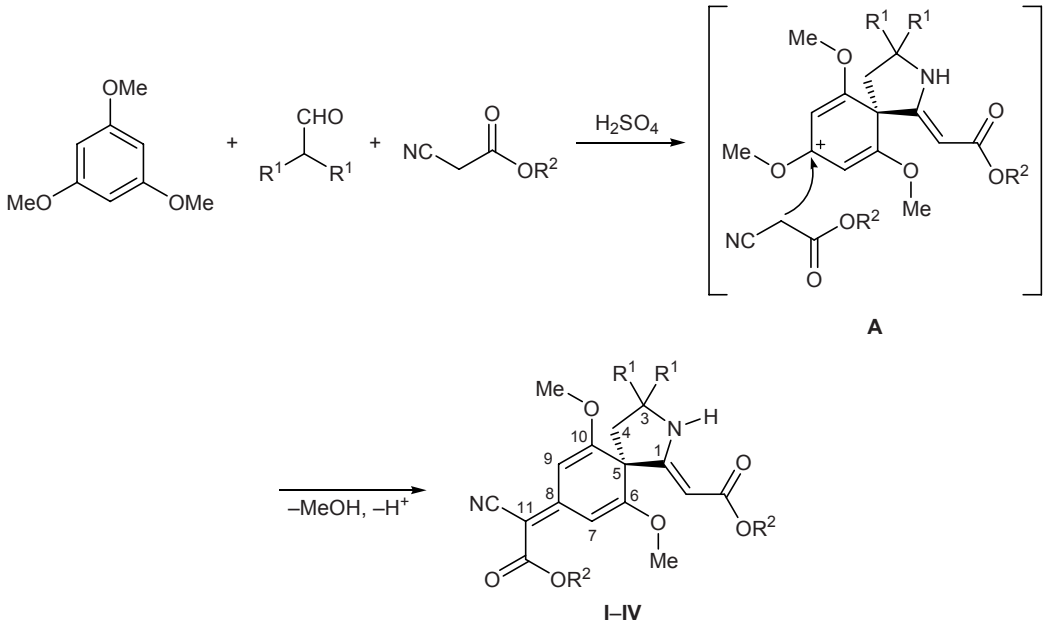
The reactions were carried at room temperature (0.5–1 h), and the mixture was then neutralized with aqueous ammonia to avoid hydrolytic dienone–phenol

Scheme 1.



* For communication VIII, see [1].

Scheme 2.



I, $R^1 = R^2 = Me$; **II**; $R^1 = Me$, $R^2 = Et$; **III**, $R^1R^1 = (CH_2)_5$, $R^2 = Me$; **IV**, $R^1R^1 = (CH_2)_5$, $R^2 = Et$.

rearrangement of substituted 2-azaspiro[4.5]deca-1,6,9-trien-8-ones, which is known to occur in dilute acids [6]. In the condensation with cyclohexanecarbaldehyde we obtained dispiro compounds **III** and **IV**.

No analogous products were detected in analogous three-component condensations with anisole [7] and 1,3-dimethoxybenzene [8]. Presumably, the observed four-component condensation is favored by increased ability of 1,3,5-trimethoxybenzene to undergo dearomatization [9]. On the other hand, capture of carbocationic intermediates by the initial arene was reported by us previously in three-component reactions with substituted anisoles [10].

Alternatively, compounds **I**–**IV** could be synthesized by Knoevenagel condensation. However, our attempts to obtain analogous products by Knoevenagel condensation of 3,3-dimethyl-1-ethoxycarbonylmethylidene-2-azaspiro[4.5]deca-6,9-dien-8-one [7] and ethyl cyanoacetate were unsuccessful despite variation of the reaction conditions. We also failed to trap intermediate cation **A** with such 1,3-dicarbonyl compounds as diethyl malonate and dimedone.

The structure of compounds **I**–**IV** was confirmed by elemental analyses and IR, ^{1}H and ^{13}C NMR, and mass spectra. The products were isolated as mixtures of *E* and *Z* isomers with respect to the exocyclic double bond C=C(CN)COOAlk; their ^{13}C NMR spectra contained double sets of signals from the ester group. After recrystallization, only one isomer was obtained, but we failed to determine its configuration on the basis of the NMR data. The configuration of the other exocyclic double bond in **I**–**IV** is fixed due to formation of intramolecular hydrogen bond between the ester carbonyl oxygen atom and proton of the endocyclic NH group (*Z* configuration), as reported previously for spirocyclohexadienones derived from anisole [7]. This structure is also confirmed by the IR (reduced ester carbonyl vibration frequency, 1650–1670 cm^{-1}, and NH absorption at 3310–3355 cm^{-1}) and ^{1}H NMR data (olefinic proton signal at δ 3.79–3.83 ppm and NH signal at δ 8.30–8.37 ppm). In the ^{13}C NMR spectra of **I**–**IV**, the spiro carbon atom (C^5) resonated at δ_C 57.75–58.59 ppm, and signal from the β-carbon atom with respect to the NH group appeared in a fairly strong field, δ_C 73.00–73.71 ppm. Stretching vibrations of the cyano group in molecules **I**–**IV** gave rise to a weak band at 2155–2175 cm^{-1} in the IR spectra. The mass spectra of compounds **I**–**IV** lacked molecular ion peaks, but their fragmentation pattern involved successive elimination of the alkyl cyanoacetate residue and hydrocarbon fragment on C^3.

EXPERIMENTAL

The elemental compositions were determined on a Leco CHNS analyzer. The IR spectra were recorded on a Specord M80 spectrometer from samples dis-

persed in mineral oil. The ^{1}H and ^{13}C NMR spectra were obtained from solutions in DMSO-d_6 on a Varian Mercury Plus instrument (300 and 75 MHz, respectively); the chemical shifts were measured relative to HMDS as internal reference (^{1}H) or solvent signal (^{13}C). Analytical thin-layer chromatography was performed on Sorbfil plates using chloroform–acetone (9:1) as eluent; spots were detected by spraying with a 1% solution of chloranil in toluene. The mass spectra (electron impact, 70 eV) were recorded on an Agilent 6890N–5975B GC–MS system.

Methyl cyano[6,10-dimethoxy-1-(2-methoxy-2-oxoethylidene)-3,3-dimethyl-2-azaspiro[4.5]deca-6,9-dien-8-ylidene]acetate (I). A mixture of 1.68 g (10 mmol) of 1,3,5-trimethoxybenzene, 0.95 g (1.2 ml, 13.2 mmol) of freshly distilled isobutyraldehyde, 1.98 g (1.76 ml, 20 mmol) of methyl cyanoacetate, and 3 ml of methylene chloride was added dropwise to 6 ml of 96% sulfuric acid on cooling with water. The mixture was stirred for 0.5 h and poured into a mixture of 200 g of ice and 20 ml of 25% aqueous ammonia (pH ~7–8), the organic layer was separated, and the aqueous layer was extracted with methylene chloride (3×20 ml). The extracts were combined with the organic phase, washed with 30 ml of water and 20 ml of a saturated solution of sodium chloride, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel using chloroform as eluent. Yield 0.81 g (18%), pale yellow crystals, mp 185.5–187.0°C, R_f 0.57. IR spectrum, ν, cm^{-1}: 3320 (NH); 2155 (C≡N); 1690, 1660 (C=O); 1630, 1580 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.38 s (6H, Me); 2.17 s (2H, 4-H); 3.45 s, 3.74 s, and 3.78 s (3H each, OCH_3); 3.81 m (4H, OCH_3, CH=); 5.94 s and 7.35 s (1H each, 7-H, 9-H); 8.36 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 29.97 (3-CH_3), 45.46 (C^4), 49.58 (OCH_3), 51.93 (OCH_3), 56.75 (OCH_3), 56.79 (OCH_3), 58.59 (C^5), 62.70 (C^3), 73.25 (CH=), 88.96 (C^{11}), 93.70 (C^7), 95.36 (C^9), 117.52 (C≡N), 158.25 (C^6), 161.97 (C^{10}), 164.00 (C^8), 169.46 (C^1), 170.01 (C=O), 170.07 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 289 (95) [M – $NCCH_2CO_2Me$]$^+$, 247 (100) [M – $NCCH_2CO_2Me$ – C_3H_6]$^+$, 230 (15), 216 (18). Found, %: C 61.20; H 6.10; N 7.21. $C_{20}H_{24}N_2O_6$. Calculated, %: C 61.85; H 6.23; N 7.21.

Ethyl cyano[1-(2-ethoxy-2-oxoethylidene)-6,10-dimethoxy-3,3-dimethyl-2-azaspiro[4.5]deca-6,9-dien-8-ylidene]acetate (II) was synthesized in a similar way from 4.2 g (25 mmol) of 1,3,5-trimethoxybenzene, 1.90 g (2.4 ml, 26.4 mmol) of isobutyraldehyde, and 5.60 g (2.13 ml, 50 mmol) of ethyl cyanoacetate using 20 ml of methylene chloride and 15 ml of concentrated sulfuric acid. After removal of the solvent, the residue was recrystallized from methanol. Yield 1.95 g (24%), bright yellow crystals, mp 167–169°C, R_f 0.64. IR spectrum, ν, cm^{-1}: 3310 (NH); 2175 (C≡N); 1700 sh, 1670 (C=O); 1600 (C=C); 1265, 1170, 1075, 860. ^{1}H NMR spectrum, δ, ppm: 1.12 t and 1.27 t (3H each, Me, J = 7.8 Hz), 1.38 s (6H, Me), 2.18 s (2H, CH_2), 3.79 s (4H, OMe, CH=), 3.82 s (3H, OMe), 3.93 q and 4.21 q (2H each, OCH_2, J = 7.8 Hz), 5.95 s and 7.33 s (1H each, 7-H, 9-H), 8.30 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 14.12 ($CH_2\mathbf{C}H_3$), 14.45 ($CH_2\mathbf{C}H_3$), 29.79 (3-CH_3), 45.14 (C^4), 56.71 (OCH_3), 57.80 (OCH_3), 58.40 (C^5), 60.70 (OCH_3), 62.72 (OCH_3, C^3), 73.00 (CH=), 88.88 (C^{11}), 93.44 (C^7), 95.09 (C^9), 117.55 (C≡N), 158.00 (C^6), 161.77 (C^{10}), 163.44 (C^8), 168.94 (C^1), 169.87 (C=O), 169.94 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 416 (15) [M]$^+$, 303 (100) [M – $NCCH_2CO_2Et$]$^+$, 261 (46), 189 (15), 114 (14). Found, %: C 63.22; H 6.64; N 6.75. $C_{22}H_{28}N_2O_6$. Calculated, %: C 63.45; H 6.78; N 6.73.

Methyl cyano[1,5-dimethoxy-15-(2-methoxy-2-oxoethylidene)-14-azadispiro[5.1.5.2]pentadeca-1,4-dien-3-ylidene]acetate (III) was synthesized in a similar way from 0.59 g (3.5 mmol) of 1,3,5-trimethoxybenzene, 0.42 ml (0.39 g, 3.5 mmol) of cyclohexanecarbaldehyde, and 0.66 ml (0.75 g, 7 mmol) of methyl cyanoacetate using 2 ml of concentrated sulfuric acid. After removal of the solvent, the residue was recrystallized from ethanol. Yield 0.22 g (14%), pale yellow crystals, mp 208–209°C, R_f 0.62. IR spectrum, ν, cm^{-1}: 3355 (NH); 2155 (C≡N); 1690, 1650 (C=O); 1625, 1595 (C=C). ^{1}H NMR spectrum,** δ, ppm: 1.29–1.69 m (10H, CH_2); 2.14 s (2H, 4-H); 3.46 s, 3.74 s, 3.77 s, and 3.80 s (3H each, OCH_3); 3.83 s (1H, CH=); 5.95 s and 7.35 s (1H each, 7-H, 9-H); 8.37 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 23.45 ($C^{3'}$, $C^{5'}$), 24.59 ($C^{4'}$), 38.22 ($C^{2'}$, $C^{6'}$), 42.52 (C^4), 49.70 (OCH_3), 51.96 (OCH_3), 56.80 (OCH_3), 56.84 (OCH_3), 57.82 (C^5), 65.18 (C^3), 73.52 (CH=), 88.82 (C^{11}), 93.65 (C^7), 95.31 (C^9), 117.54 (C≡N), 158.22 (C^6), 162.05 (C^{10}), 163.97 (C^8), 169.67 (C^1), 169.93 (C=O), 169.99 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 329 (50) [M – $NCCH_2CO_2Me$]$^+$, 247 (100) [M – $NCCH_2CO_2Me$ – C_6H_{10}]$^+$, 216 (10). Found, %: C 64.40; H 6.51; N 6.54. $C_{23}H_{28}N_2O_6$. Calculated, %: C 64.47; H 6.59; N 6.54.

** For atom numbering in the NMR spectra of **III** and **IV**, see Scheme 2.

Ethyl cyano[15-(2-ethoxy-2-oxoethylidene)-1,5-dimethoxy-14-azadispiro[5.1.5.2]pentadeca-1,4-dien-3-ylidene]acetate (IV) was synthesized in a similar way from 1.68 g (10 mmol) of 1,3,5-trimethoxybenzene, 1.2 ml (1.12 g, 10 mmol) of cyclohexanecarbaldehyde, and 2.12 ml (2.26 g, 20 mmol) of ethyl cyanoacetate using 8 ml of concentrated sulfuric acid. After removal of the solvent, the residue was recrystallized from ethanol. Yield 0.94 g (21%), yellow crystals, mp 138–139°C, R_f 0.66. IR spectrum, ν, cm^{-1}: 3350 (NH); 2170 (C≡N); 1700, 1660 (C=O); 1640, 1605 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.06 t and 1.21 t (3H each, CH_2CH_3, J = 6.9 Hz), 1.26–1.63 m (10H, CH_2), 2.09 s (2H, 4-H), 3.72 s and 3.75 s (3H each, OCH_3), 3.78 s (1H, CH=), 3.88 q and 4.15 q (2H each, OCH_2, J = 6.9 Hz), 5.90 s and 7.30 s (1H each, 7-H, 9-H), 8.33 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 14.17 (CH_2CH_3), 14.49 (CH_2CH_3), 23.48 ($C^{3'}$, $C^{5'}$), 24.60 ($C^{4'}$), 38.22 ($C^{2'}$, $C^{6'}$), 42.46 (C^4), 56.77 (OCH_3), 56.82 (OCH_3), 57.75 (C^5), 58.02 (OCH_2), 60.75 (OCH_2), 65.16 (C^3), 73.71 (CH=), 89.28 (C^{11}), 93.68 (C^7), 95.32 (C^9), 117.55 (C≡N), 157.98 (C^6), 162.04 (C^{10}), 163.54 (C^8), 169.41 (C^1), 169.78 (C=O), 169.83 (C=O). Mass spectrum, m/z (I_{rel}, %): 343 (28) [M – $NCCH_2CO_2Et]^+$, 262 (20), 261 (100) [M – $NCCH_2CO_2Et$ – $C_6H_{10}]^+$, 216 (12), 189 (17). Found, %: C 65.71; H 7.02; N 6.10. $C_{25}H_{32}N_2O_6$. Calculated, %: C 65.77; H 7.07; N 6.14.

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