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Three-Component Condensation of Methoxyarenes with Isobutyraldehyde and α-Substituted Benzyl Cyanides

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Abstract—Three-component condensation of anisole with isobutyraldehyde and substituted benzyl cyanides gives 1-benzyl-3,3-dimethyl-2-azaspiro[4.5]deca-6,9-dien-8-ones which undergo dienone–phenol rearrangement during the reaction. Analogous condensation of 1-methoxynaphthalene leads to the formation of 2′-benzyl-5′,5′-dimethyl-4′,5′-dihydro-4*H*-spiro[naphthalene-1,3′-pyrrol]-4-ones.

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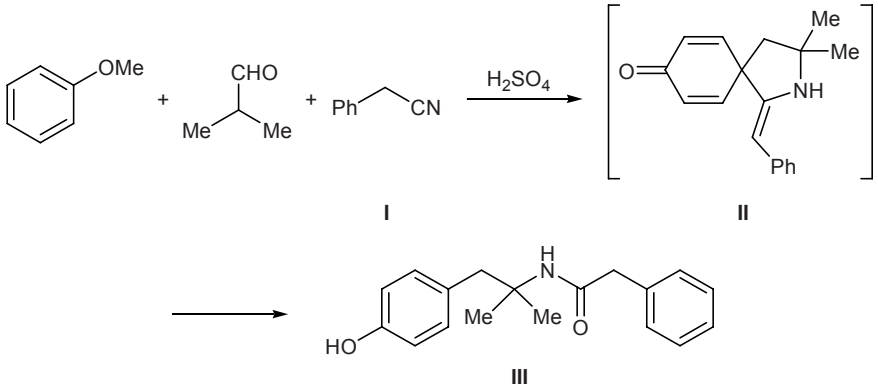
We previously showed that anisole reacts with isobutyraldehyde or 1,2-epoxy-2-methylpropane and methyl or benzyl thiocyanate to give spiro-fused dihydropyrrole derivatives [1–3] and that analogous reactions with acetonitrile and ethyl cyanoacetate are accompanied by dienone–phenol rearrangement of the primary spiro-fused pyrroles [4, 5]. It is also known that steric load at the cyano group does not affect the formation of 1-benzyl-3,4-dihydroisoquinolines [6]. It was interesting to study the behavior in analogous reaction of benzyl cyanide and its α-substituted derivatives.

Three-component reaction of anisole with benzyl cyanide (**I**) and isobutyraldehyde led to the formation of *N*-[1-(4-hydroxyphenyl)-2-methylpropan-2-yl]phenylacetamide (**III**) in a satisfactory yield (Scheme 1). In keeping with the results of our previous studies, the reaction involves intermediate formation of (1*Z*)-1-benzylidene-3,3-dimethyl-2-azaspiro[4.5]deca-6,9-dien-8-one (**II**) which then undergoes dienone–phenol rearrangement.

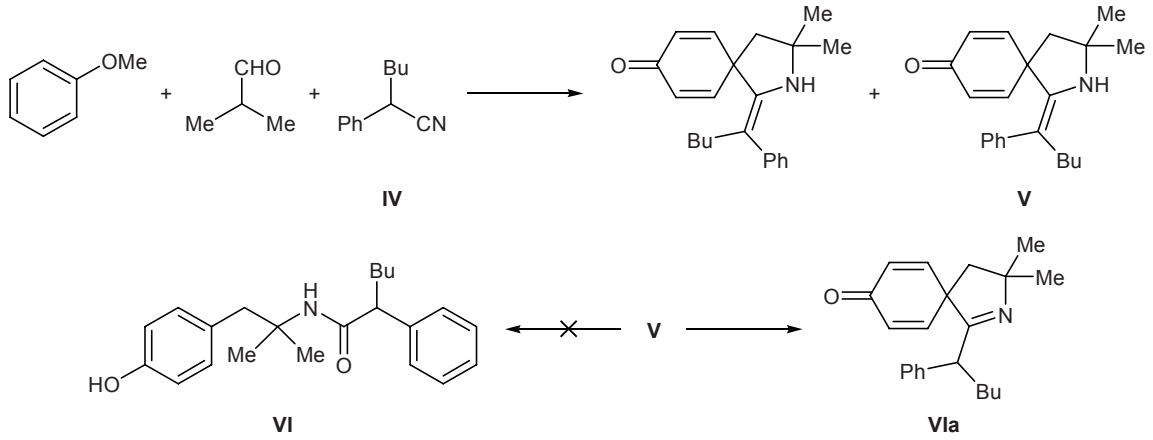
As we showed previously [7], if the α-position in the nitrile component is occupied by an alkyl group larger than ethyl, the resulting 3,4-dihydroisoquinoline derivatives exist exclusively in the imino form; therefore, their protonation and subsequent dienone–phenol rearrangement should occur *in statu nascendi*, as was reported in [4]. With a view to elucidate the possibility for isolating spiro-fused products from α-substituted benzyl cyanides, we examined the reaction of anisole with butyraldehyde and 2-phenylhexanenitrile (**IV**). We succeeded in isolating 3,3-dimethyl-1-(1-phenylpentylidene)-2-azaspiro[4.5]deca-6,9-dien-8-one (**V**) as an inseparable mixture of isomers at the exocyclic

Scheme 1.



I **II** **III**

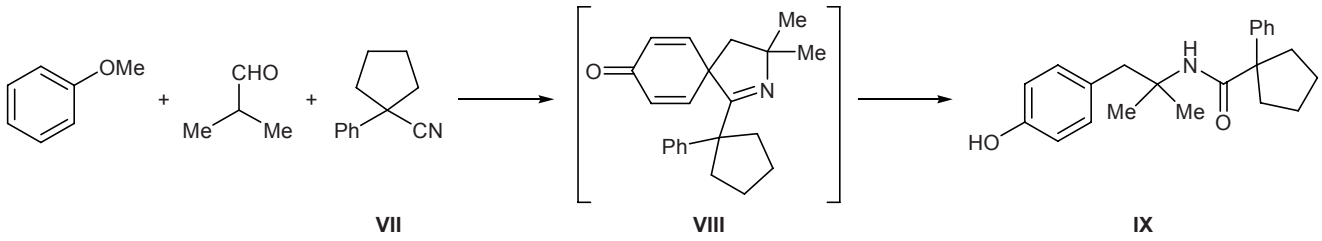
Scheme 2.



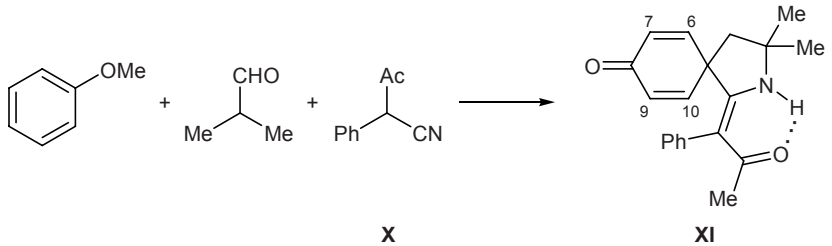
double bond at a ratio of 3:2 (according to the ^{1}H NMR data; Scheme 2). In the IR spectrum of **V** we observed an absorption band at 3350 cm^{-1}, which corresponds to stretching vibrations of the NH bond, and carbonyl absorption at 1650 cm^{-1}. The ^{1}H NMR spectrum of **V** contained four signals from methyl groups at δ 1.11, 1.18, 1.20, and 1.24 ppm (intensity ratio 2:3:2:3), the methylene protons on C^4 gave rise to a typical *AB* system (δ 2.69, 2.90 ppm; ^2J = 12 Hz), methyl protons in the butyl group resonated as a triplet at δ 0.79 ppm, the α-methylene group in the butyl radical gave a signal at δ 3.07 ppm, and signals from the other methylene protons were complex multiplets at δ 1.67 and 2.07 ppm. Protons of the NH group resonated at δ 4.86 and 4.96 ppm (intensity ratio 2:3), and protons in the cyclohexadiene fragment also appeared as a double set of almost indistinguishable signals at δ 6.23 and 6.26 ppm with a coupling constant *J* of 10 Hz. A complex multiplet in the region δ 7.18–7.29 ppm was assigned to the aromatic protons. Quantum-chemical calculation (AM1, Hyperchem 6.0) of the enthalpies of formation of the two possible isomers gave a difference of 4.3 kcal/mol (187.3387 and 182.9905 kcal/mol), which is consistent with the experimentally observed isomer ratio. Treatment of isomer mixture **V** with sulfuric acid in acetic acid resulted in tautomeric transformation to dihydropyrrole **VIa** instead of the expected dienone–phenol rearrangement into amide **VI** (Scheme 2).

Compound **VIa** displayed in the ^{1}H NMR spectrum signals from two methyl groups at δ 0.97 and 1.17 ppm, while neither triplet signal from the α-methylene group in the butyl radical (δ 3.07 ppm in the spectrum of **V**) nor NH proton signal (δ ~5 ppm) were

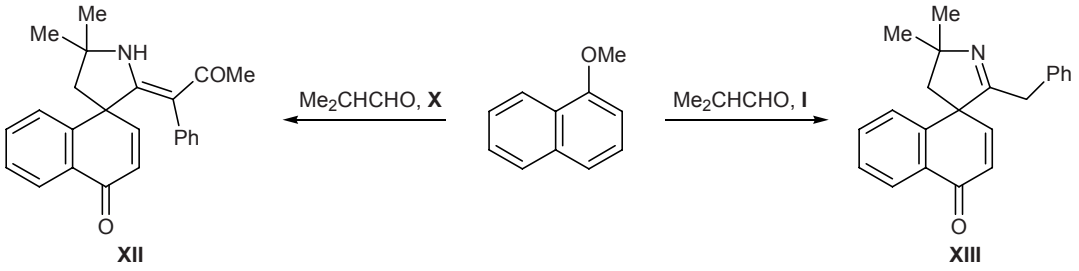
Scheme 3.



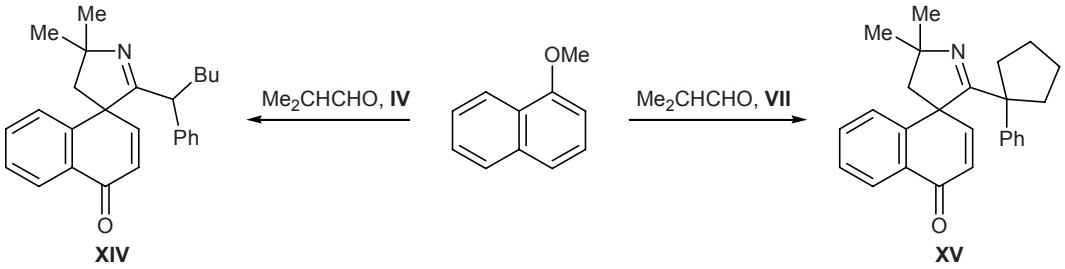
Scheme 4.



Scheme 5.



Scheme 6.



present. The benzylic proton resonated as a triplet at δ 3.37 ppm, and signals from the 4-H protons constituted a typical *AB* system (δ 2.56, 2.89 ppm; J = 12 Hz). The α-methylene protons in the butyl group gave two complex multiplets at δ 1.52 and 1.90 ppm each having an intensity corresponding to one proton; this may be due to anisotropic effect of the lone electron pair on the nitrogen atom. Protons in the cyclohexadiene fragment appeared as doublets of doublets at δ 6.38 and 6.57 ppm (J = 10 Hz), and aromatic proton signals were observed in the region δ 7.18–7.26 ppm.

The reaction of anisole with isobutyraldehyde and 1-phenylcylopentanecarbonitrile (**VII**) [8] gave a product whose ^{1}H NMR spectrum lacked signal from methoxy group, while signals in the aromatic region corresponded to a *para*-substituted benzene ring rather than to cyclohexadienone fragment. The IR spectrum of this compound contained absorption bands assignable to a phenolic hydroxy group (3220 cm^{-1}) and amide carbonyl (1640 cm^{-1}). These data led us to identify the product as *N*-[1-(4-hydroxyphenyl)-2-methylprop-2-yl)-1-phenylcyclopentane-1-carboxamide (**IX**) formed via dienone–phenol rearrangement of intermediate 1-(1-phenylcyclopentyl)-3,3-dimethyl-2-azaspiro-[4.5]deca-1,6,9-trien-8-one (**VIII**) (Scheme 3).

As shown in [9], 3-oxo-2-phenylbutanenitrile (**X**) can also be used as nitrile component in the Ritter reaction. By reaction of anisole with isobutyraldehyde and nitrile **X** [10] we obtained spriocyclic compound **XI**. The relative stability of the latter may be rationalized in terms of considerable reduction of basicity of the nitrogen atom due to formation of intramolecular hydrogen bond; as a result, its protonation is hampered (Scheme 4).

According to our previous data [11], spirocyclic systems obtained by three-component condensation with methoxynaphthalenes are considerably more stable toward dienone–phenol rearrangement. In fact, 1-methoxynaphthalene reacted with isobutyraldehyde and nitrile **X** to give (2′*Z*)-5′,5′-dimethyl-2′-(2-oxo-1-phenylpropylidene)-4*H*-spiro[naphthalene-1,3′-pyrrolidin]-4-one (**XII**) (Scheme 5). The reaction of 1-methoxynaphthalene with isobutyraldehyde and benzyl cyanide produced 2′-benzyl-5′,5′-dimethyl-4′,5′-dihydro-4*H*-spiro[naphthalene-1,3′-pyrrol]-4-one (**XIII**), and the corresponding spiro-fused compounds **XIV** and **XV** were formed from substituted benzyl cyanides **IV** and **VII** (Scheme 6).

Our results showed that the presence of an electron-withdrawing group in the α-position of benzyl cyanide is favorable for the formation of spiro-fused systems; such systems are also formed on the basis of 1-methoxynaphthalene; however, in all the examined reactions, the size of the nitrile component is not significant for the *ipso* attack to occur.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Varian Mercury

Plus 300 instrument at (300 MHz) using DMSO-d_6 as solvent and tetramethylsilane as internal reference. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using chloroform–acetone (9:1) as eluent; spots were visualized by treatment with a 0.5% solution of chloranil in toluene. The mass spectra (electron impact, 70 eV) were obtained on an Agilent GC 6890N–MSD 5975B system. The elemental compositions were determined on a LECO CHNS-932 analyzer.

***N*-[1-(4-Hydroxyphenyl)-2-methylpropan-2-yl]-phenylacetamide (III).** A mixture of 10.8 g (0.1 mol) of anisole, 7.2 g (0.1 mol) of isobutyraldehyde, and 11.7 g (0.1 mol) of benzyl cyanide was added dropwise under stirring over a period of 15–20 min to 50 ml of 96% sulfuric acid cooled to 0–5°C. The mixture was stirred for 30 min, poured into 300 ml of water, and extracted with 100 ml of toluene, the extract was washed with aqueous ammonium carbonate and dried over sodium sulfate, the solvent was removed on a rotary evaporator, and the residue was recrystallized from alcohol. Yield 25%, mp 195–197°C. IR spectrum, ν, cm^{-1}: 1550, 1640, 3360. ^{1}H NMR spectrum, δ, ppm: 1.11 s (6H, Me), 2.75 s (2H, CH_2), 6.52 d (2H, 6-H, 10-H, J = 10 Hz), 6.68 d (2H, 7-H, 9-H, J = 10 Hz), 7.15–7.29 m (5H, Ph), 7.34 s (1H, OH), 9.07 s (1H, NH). Found, %: C 76.43; H 7.38; N 4.81. $C_{18}H_{21}NO_2$. Calculated, %: C 76.30; H 7.47; N 4.94.

3,3-Dimethyl-1-[(1*E*)-1-phenylpentylidene]-2-azaspiro[4.5]deca-6,9-dien-8-one (V) was synthesized in a similar way from 17.3 g (0.1 mol) of 2-phenylhexanenitrile, 7.3 g (0.1 mol) of isobutyraldehyde, and 10.8 g (0.1 mol) of anisole. Yield 57%, mp 186–188°C (from ethyl acetate). The spectral parameters of compound **V** are given in text. Found, %: C 82.34; H 8.49; N 4.41. $C_{22}H_{27}NO$. Calculated, %: C 82.20; H 8.47; N 4.36.

3,3-Dimethyl-1-(1-phenylpentyl)-2-azaspiro[4.5]-deca-1,6,9-trien-8-one (VIa). Compound **V**, 0.5 g (1.6 mmol), was dissolved in 15 ml of acetic acid, one drop of concentrated sulfuric acid was added, and the mixture was heated to the boiling point and was kept boiling for 3 min. It was then poured into 100 ml of water and adjusted to pH 8 with aqueous ammonia, and the precipitate was filtered off, dried, and recrystallized from ethyl acetate. mp 179–181°C. The spectral parameters of compound **VIa** are given in text. Found, %: C 82.23; H 8.40; N 4.51. $C_{22}H_{27}NO$. Calculated, %: C 82.20; H 8.47; N 4.36.

***N*-[1-(4-Hydroxyphenyl)-2-methylprop-2-yl]-1-phenylcyclopentane-1-carboxamide (IX)** was synthesized as described above for compound **III** from 10.8 g (0.1 mol) of anisole, 7.2 g (0.1 mol) of isobutyraldehyde, and 17.1 g (0.1 mol) of 1-phenylcyclopentanecarbonitrile. Yield 63%, mp 118–119°C. IR spectrum, ν, cm^{-1}: 1520, 1540, 1600, 1640, 3220, 3400. ^{1}H NMR spectrum, δ, ppm: 1.13 s (6H, Me); 1.55 m, 1.73 m, 1.93 m, and 1.91 m [2H each, $(CH_2)_4$], 2.71 s (2H, CH_2), 4.95 s (1H, NH), 6.65–6.71 m (4H, C_6H_4), 6.80 s (1H, OH), 7.12–7.24 m (5H, Ph). Found, %: C 78.43; H 8.18; N 4.10. $C_{22}H_{27}NO_2$. Calculated, %: C 78.30; H 8.06; N 4.15.

(1*Z*)-3,3-Dimethyl-1-(2-oxo-1-phenylpropylidene)-2-azaspiro[4.5]deca-6,9-dien-8-one (XI). A mixture of 10.8 g (0.1 mol) of anisole, 7.3 g (0.1 mol) of isobutyraldehyde, and 15.9 g (0.1 mol) of 3-oxo-2-phenylbutanenitrile in 30 ml of methylene chloride was added dropwise under stirring over a period of 15–20 min to 50 ml of 96% sulfuric acid cooled to 0–5°C. The mixture was stirred for 30 min, poured into 300 ml of water, and neutralized to pH 8–9 with aqueous ammonium carbonate. The precipitate was filtered off, washed with water, dried, and recrystallized from propan-2-ol. Yield 32%, mp 168–170°C. IR spectrum, ν, cm^{-1}: 1550, 1600, 1660, 3300. ^{1}H NMR spectrum, δ, ppm: 1.43 s (6H, Me), 1.76 s (3H, MeCO), 1.97 s (2H, CH_2), 5.72 d (2H, 6-H, 10-H, J = 10 Hz), 6.68 d (2H, 7-H, 9-H, J = 10 Hz), 6.93–7.12 m (5H, H_{arom}), 10.87 s (1H, NH). Found, %: C 78.10; H 6.98; N 4.67. $C_{20}H_{21}NO_2$. Calculated, %: C 78.15; H 6.89; N 4.56.

(2*Z*)-5,5-Dimethyl-2′-(2-oxo-1-phenylpropylidene)-4*H*-spiro[naphthalene-1,3′-pyrrolidin]-4-one (XII) was synthesized in a similar way from 1.58 g (0.01 mol) of 1-methoxynaphthalene, 0.73 g (0.01 mol) of isobutyraldehyde, and 1.59 g (0.01 mol) of 3-oxo-2-phenylbutanenitrile using 30 ml of methylene chloride. Yield 30%, mp 220–222°C. IR spectrum, ν, cm^{-1}: 1550, 1600, 1660, 3300. ^{1}H NMR spectrum, δ, ppm: 1.49 s (3H, Me), 1.53 s (3H, Me), 1.62 s (3H, MeCO), 2.25 d.d (2H, CH_2, J = 12 Hz), 5.83 d (1H, 2-H, J = 10 Hz), 5.96 d (1H, 3-H, J = 10 Hz), 6.46–7.89 m (5H, Ph), 7.20–7.76 m (4H, H_{arom}), 11.33 s (1H, NH). Found, %: C 80.76; H 6.40; N 4.07. $C_{24}H_{23}NO_2$. Calculated, %: C 80.64; H 6.49; N 3.92.

2′-Benzyl-5′,5′-dimethyl-4′,5′-dihydro-4*H*-spiro-[naphthalene-1,3′-pyrrol]-4-one (XIII) was synthesized in a similar way from 1.17 g (0.01 mol) of benzyl cyanide. Yield 27%, mp 141–142°C (from hexane). IR spectrum, ν, cm^{-1}: 1590, 1650. ^{1}H NMR spectrum, δ, ppm: 1.78 s (3H, Me), 1.87 s (3H, Me), 2.53 s

(2H, PhC**H**$_2$), 3.61 d and 4.24 d (1H each, 4′-H, J = 12 Hz), 6.17 d (1H, 2-H, J = 10 Hz), 6.39 d (1H, 3-H, J = 10 Hz), 6.85–7.12 m (6H, H$_{arom}$), 7.51 m (2H, H$_{arom}$), 8.17 m (1H, H$_{arom}$). Found, %: C 83.82; H 6.83; N 4.55. $C_{22}H_{21}NO$. Calculated, %: C 83.78; H 6.71; N 4.44.

5′,5′-Dimethyl-2′-(1-phenylpentyl)-4′,5′-dihydro-4*H*-spiro[naphthalene-1,3′-pyrrol]-4-one (XIV) was synthesized in a similar way from 1.73 g (0.01 mol) of 2-phenylhexanenitrile. The product was identified as the corresponding hydrobromide (the free base was dissolved in diethyl ether, and dry gaseous hydrogen bromide was passed through the solution until it became perfectly transparent). Yield 60%, mp 101–103°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 1590, 1650. ^{1}H NMR spectrum of the free base, δ, ppm: 0.65 t (3H, C**H**$_3$CH$_2$), 0.72–1.17 m (4H, CH$_2$), 1.80 s (3H, Me), 2.02 s (3H, Me), 2.17–2.38 m (2H, PhCHC**H**$_2$), 2.53 d.d (2H, 4′-H, J = 12 Hz), 3.11 t (1H, PhC**H**), 6.11 d (1H, 2-H, J = 12 Hz), 6.17 d (1H, 3-H, J = 10 Hz), 6.99–8.29 m (9H, H$_{arom}$). Found, %: C 84.17; H 7.99; N 3.70. $C_{26}H_{29}NO$. Calculated, %: C 84.06; H 7.87; N 3.77.

5′,5′-Dimethyl-2′-(1-phenylcyclopentyl)-4′,5′-dihydro-4*H*-spiro[naphthalene-1,3′-pyrrol]-4-one (XV) was synthesized in a similar way from 17.1 g (0.1 mol) of 1-phenylcyclopentane-1-carbonitrile. Yield 57%, mp 137–139°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 1590, 1620, 1650. ^{1}H NMR spectrum, δ, ppm: 1.18–2.31 m (8H, CH$_2$), 1.39 s (3H, Me), 1.48 s (3H, Me), 2.13–2.20 d.d (2H, 4′-H, J = 12 Hz), 5.80 d (1H, 2-H, J = 10 Hz), 6.27 d (1H, 3-H, J = 10 Hz), 6.89–7.29 m (8H, H$_{arom}$), 8.03–8.06 m (1H, H$_{arom}$). Found, %: C 84.13; H 8.01; N 3.75. $C_{27}H_{31}NO$. Calculated, %: C 84.11; H 8.10; N 3.63.

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