Mendeleev Commun., 2003, 13(2), 80–81

Unusual cascade heterocyclization of substituted *m*-xylenes, isobutyraldehyde and nitriles

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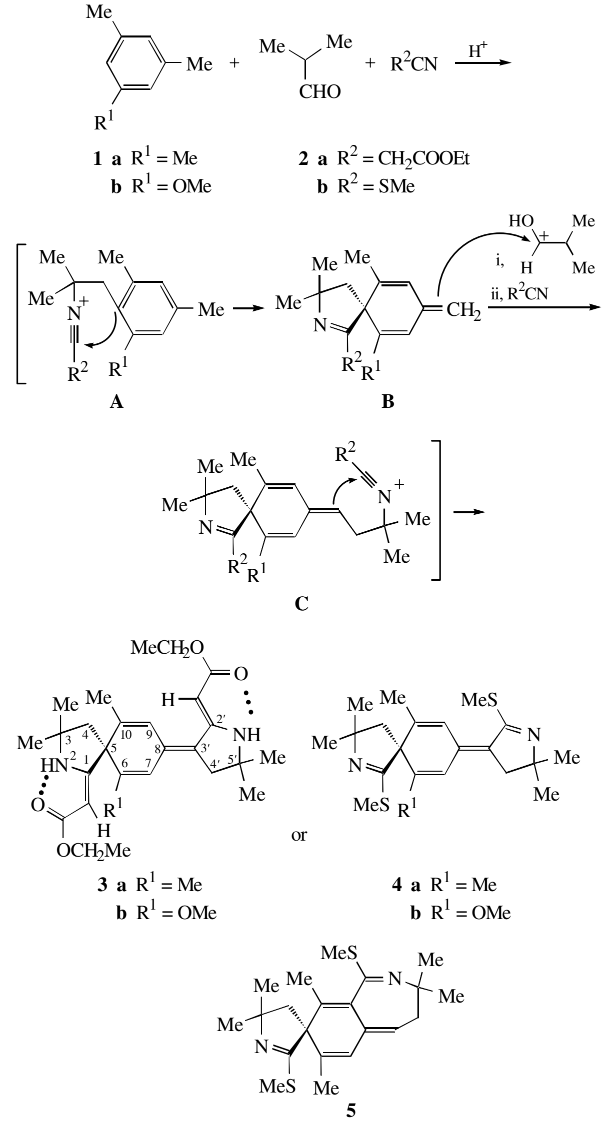
10.1070/MC2003v013n02ABEH001697

Mesitylene and 3,5-dimethylanisole underwent an unusual cascade condensation with isobutyraldehyde and nitriles in concentrated sulfuric acid to form substituted 2-azaspiro[4,5]deca-1,6,9-trienes.

Recently, we described the acid-induced three-component condensation of *ortho*- or *para*-xylene with isobutyraldehyde and nitriles RCN leading to 1-R-6,7-(or 5,8)-dimethoxy-3,4-dihydroisoquinolines.[1] Here, we report on the condensation of mesitylene and 3,5-dimethylanisole, which gave rise to unexpected products. First, we found that the reaction of *m*-xylene, isobutyraldehyde and ethyl cyanoacetate in the presence of concentrated sulfuric acid yielded a yellow compound with the double set of signals due to CH_2COOEt and CH_2Me_2 groups in the ^1H NMR spectrum. When we applied this reaction to mesitylene, we also obtained a yellow compound with a similar ^1H NMR spectrum. In both cases, the mass spectra indicated that two aldehyde and nitrile molecules react with one molecule of the arene. Obviously, mesitylene could not yield any isoquinoline derivative, as was reported for *ortho*- or *para*-xylene; thus, we supposed the mode of condensation shown in Scheme 1.

In this route, intermediate nitrilium ion **A** was stabilised by an *ipso*-attack, as in the similar reaction of anisole.[2,3] However, intermediate **B** with an *exo*-methylene group was formed, which was exposed to the next electrophilic attack at this *exo*-methylene group with the stabilization of intermediate **C** by formation of a five-membered pyrrolidine ring. In this reaction pathway, a double electrofilic attack at the *exo*-CH_2-group is supposed. We failed to isolate intermediate **B**, although some relative structures are reported in literature. For instance, 5-methylene-1,3-cyclohexadiene, an alicyclic isomer of toluene, was obtained earlier by the thermolysis of (cyclohexa-1,4-dien-1-yl)methylcarbonate.[4]

Note that even when we took equimolar quantities of starting compounds, cascade heterocyclization took place, *i.e.*, an electrophilic attack of the second molecule of protonated isobutyraldehyde at an *exo*-methylene group is preferential to other possible ways of stabilization of **B**.



Scheme 1

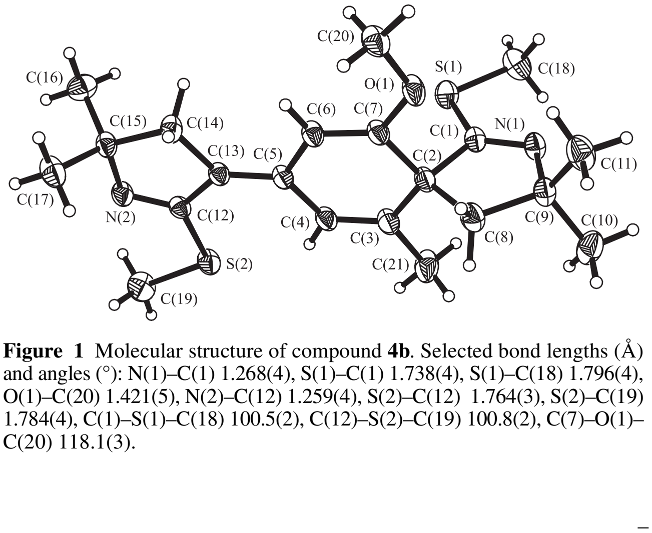


Figure 1 Molecular structure of compound **4b**. Selected bond lengths (Å) and angles (°): N(1)–C(1) 1.268(4), S(1)–C(1) 1.738(4), S(1)–C(18) 1.796(4), O(1)–C(20) 1.421(5), N(2)–C(12) 1.259(4), S(2)–C(12) 1.764(3), S(2)–C(19) 1.784(4), C(1)–S(1)–C(18) 100.5(2), C(12)–S(2)–C(19) 100.8(2), C(7)–O(1)–C(20) 118.1(3).

Other structures, originated from different ways of the initial attack at **B** and cyclization, for instance, condensed azepine **5**, were excluded according to the ^1H and ^{13}C NMR data. Thus, this process can be regarded as a double electrophilic attack on an *exo*-methylene group and is a characteristic feature of *m*-xylene and its derivatives: mesitylene (compounds **3a**, **4a**) and 3,5-dimethylanisole (**3b**, **4b**) in this reaction.

Here, we disclose an easy route to compounds **3a**,**b**, **4a**,**b** with the original structure.† Compounds **3a**,**b**, **4a**,**b** are characterised by elemental analysis, IR, ^{1}H and ^{13}C NMR (for **3b**) spectroscopy and mass spectrometry.[‡] Signals of protonated atoms in **3b** were assigned using 2D hetero-nuclear correlation experiments HETCOR. Structure of **4b** was confirmed by X-ray diffraction analysis.[§]

The molecular structure of **4b** is given in Figure 1. Compound **4b** was found to have *E*-configuration of the C=C bridge between two heterocycles. Configurations of compounds **3a**,**b**, **4a** are unknown, although ^{1}H NMR data indicate the existence of **3a**,**b**, **4a** in one form, probably, *E*-configuration. Compounds **3a**,**b** exist as enamines with intramolecular hydrogen bonds between NH and C=O groups in both pyrrolidine rings, as was described for congener spiro-compounds[3] and 3,4-dihydroisoquinoline derivatives.[5,6]

Poor yields in the cases of **3b**, **4b** are due to competitive reactions: condensation of isobutyraldehyde with two of arene molecules[1] and a *para*-attack to substituted anisole with formation of corresponding 2-azaspiro[4.5]deca-1,6,9-trien-8-ones,[3] although these oily by-products were only detected by TLC but not isolated.

This work was supported by the Russian Foundation for Basic Research (grant no. 01-03-96479).

References

1 Yu. V. Shklyaev and Yu. V. Nifontov, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 780 (*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, 844).

2 (*a*) V. A. Glushkov, Yu. V. Shklyaev, V. I. Sokol, V. S. Sergienko and V. V. Davidov, *Mendeleev Commun.*, 1998, **227**; (*b*) V. A. Glushkov, Yu. V. Shklyaev, V. I. Sokol, V. S. Sergienko and V. V. Davidov, *Mendeleev Commun.*, 1999, 170.

3 V. A. Glushlov, 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).

4 W. J. Bailey and R. A. Baylouny, *J. Org. Chem.*, 1962, **27**, 3476.

5 B. B. Alexandrov, M. S. Gavrilov, M. I. Vakhrin and V. S. Shklyaev, *Khim. Geterotsikl. Soedin.*, 1985, 794 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1985, **21**, 662].

6 O. Barum, P. K. Mohanta, H. Ila and H. Junjappa, *Synlett.*, 2000, 653.

7 G. M. Sheldrick, *SHELXL-97, Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.

Received: 9th December 2002; Com. 02/2023

[†] *A typical experimental procedure*: a mixture of 6.8 g (50 mmol) of 3,5-dimethylanisole (or 6.0 g, 6.93 ml of mesitylene), 3.6 g (4.5 ml, 50 mmol) of isobutyraldehyde and an appropriate nitrile (50 mmol) were added dropwise with vigorous stirring to concentrated sulfuric acid (12 ml, 0.225 mol), at 0–5 °C (in the case of 3,5-dimethylanisole, all components were dissolved in 50 ml of CH_2Cl_2). After stirring for 0.5–1 h, the reaction mixture was poured onto the slush of 400 g of crushed ice and 40 ml of 25% ammonium hydroxide solution (pH ~7–8). Dichloromethane (70 ml) was added. The organic layer was separated, washed with 50 ml of water, the combined aqueous layers were extracted with dichloromethane (twice by 30 ml), the combined organic layers were washed with brine and dried over $MgSO_4$. After removing the solvent, the products were recrystallised.

[‡] *8-(2'-Carbethoxymethylene-5',5'-dimethylpyrrolidin-3'-ylidene)-1-carbethoxymethylene-3,3,6,10-tetramethyl-2-azaspiro[4,5]deca-6,9-diene* **3a**: yield 71%, mp 195–197 °C (from ethanol–MeCN). ^{1}H NMR (300 MHz, [$^{2}H_6$]DMSO) δ: 1.14 (t, 3H, Me), 1.20 (t, 3H, Me), 1.25 [s, 3H, C(5′)-Me], 1.28 [s, 3H, C(5′)-Me], 1.43 [s, 6H, C(3)-Me], 1.85 (s, 3H, Me), 1.89 (s, 3H, Me), 2.00 [s, 2H, C(4)H_2], 2.66 [q, 2H, C(4′)H_2], 3.83 (s, 1H, CH=), 3.95 (q, 2H, OCH_2), 4.02 (q, 2H, OCH_2), 4.77 (s, 1H, CH=), 6.19 [s, 1H, H(7)], 6.75 [s, 1H, H(9)], 8.25 (s, 1H, NH), 8.40 (s, 1H, NH). IR (Nujol, ν/cm^{-1}): 3355 (N–H), 3335 (N–H), 1735 (O–C=O), 1725 (O–C=O), 1660 (C=N), 1595 (C=N), 1580 (C=C). MS (EI, 70 eV) *m*/*z* (%): 454 [M$^+$] (100), 439 (24), 409(21), 381 (30), 341 [M$^+$ – – $NCCH_2COOEt$] (100), 326 (100), 300 (89), 280 (22), 268 (43), 238 (25), 224 (19), 210 (20), 196 (26). Found (%): C, 71.19; H, 8.50; N, 6.12. Calc. for $C_{27}H_{38}N_2O_4$ (%): C, 71.34; H, 8.42; N, 6.16.

8-(2'-Carbethoxymethylene-5',5'-dimethylpyrrolidin-3'-ylidene)-1-carbethoxymethylene-6-methoxy-3,3,10-trimethyl-2-azaspiro[4,5]deca-6,9-diene **3b**: yield 6%, mp 204–206 °C (from ethanol). ^{1}H NMR (500 MHz, [$^{2}H_6$]DMSO) δ: 1.15 (t, 3H, Me), 1.20 (t, 3H, Me), 1.28 [d, 6H, 2C(5′)–Me], 1.39 [s, 3H, C(3)–Me], 1.41 [s, 3H, C(3)–Me], 1.82 (s, 3H, Me), 2.05 [q, 2H, C(4)H_2], 2.66 [q, 2H, C(4′)H_2], 3.68 (s, 3H, OMe), 3.85 (s, 1H, CH=), 3.92 (q, 2H, OCH_2), 4.00 (q, 2H, OCH_2), 4.75 (s, 1H, CH=), 5.47 [s, 1H, H(7)], 6.76 [s, 1H, H(9)], 8.17 (s, 1H, NH), 8.45 (s, 1H, NH). ^{13}C NMR (75.47 MHz, [$^{2}H_6$]DMSO) δ: 169.59 (C=O), 169.28 (C=O), 165.35 [C(1)], 162.36 [C(2′)], 159.22 [C(6)], 140.19 [C(10)], 131.35* [C(8)], 125.98* [C(3′)], 118.94 [C(9)], 95.99 [C(7)], 76.95 [CH=], 73.79 [CH=], 61.74 [C(3) and C(5′)], 57.90 [C(5)], 57.65 [OCH_2], 57.52 [OCH_2], 55.30 [OMe], 45.30 [C(4)], 43.48 [C(4′)], 30.06 [C(5′)–*Me*], 29.72 [C(5′)–*Me*], 29.00 [C(3)*Me*$_2$], 19.06 [C(10)–*Me*], 14.60 [Me], 14.44 [Me]. IR (Nujol, ν/cm^{-1}): 3360 (N–H), 3320 (N–H), 1735 (O–C=O), 1720 (O–C=O), 1655 (C=N), 1600 (C=N), 1585 (C=C). MS (EI, 70 eV) *m*/*z* (%): 470 [M$^+$] (67), 455 (20), 425 (11), 397 (18), 357 [M$^+$ – $NCCH_2COOEt$] (100), 342 (63), 326 (42), 316 (48), 284 (28), 268 (32), 212 (21). Found (%): C, 68.89; H, 8.28; N, 5.77. Calc. for $C_{27}H_{38}N_2O_5$ (%): C, 68.91; H, 8.14; N, 5.95.

8-(2'-Methylthio-5',5'-dimethylpyrrolin-1-ylidene-3')-1-methylthio-3,3,6,10-tetramethyl-2-azaspiro[4,5]deca-1,6,9-triene **4a**: yield 67%, mp 143–144 °C (from hexane). ^{1}H NMR (500 MHz, [$^{2}H_6$]DMSO) δ: 1.18 [s, 3H, C(5′)Me], 1.21 [s, 3H, C(5′)Me], 1.35 [s, 6H, C(3)Me], 1.60 [s, 6H, C(7)Me, C(9)Me], 2.00 [s, 2H, C(4)H_2], 2.32 (s, 3H, SMe), 2.43 (s, 3H, SMe), 2.68 [q, 2H, C(4′)H_2], 6.15 (s, 1H, CH=), 7.09 (s, 1H, CH=). IR (Nujol, ν/cm^{-1}): 1660 (C=N), 1600 (C=N), 1580 (C=C). MS (EI, 70 eV) *m*/*z* (%): 374 [M$^+$] (6), 301 [M$^+$ – MeSCN] (100), 286 (48), 259 (23). Found (%): C, 67.18; H, 8.17; N, 7.37. Calc. for $C_{21}H_{30}N_2S_2$ (%): C, 67.33; H, 8.07; N, 7.48.

8-(2'-Methylthio-5',5'-dimethylpyrrolin-1-ylidene-3')-1-methylthio-6-methoxy-3,3,10-trimethyl-2-azaspiro[4,5]deca-1,6,9-triene **4b**: yield 0.8%, mp 207–210 °C (from ethanol). ^{1}H NMR (500 MHz, [$^{2}H_6$]DMSO) δ: 1.21 [s, 3H, C(5′)Me], 1.24 [s, 3H, C(5′)Me], 1.30 [s, 3H, C(3)Me], 1.35 [s, 3H, C(3)Me], 1.79 [s, 3H, C(10)Me], 1.97 [d, 1H, C(4)H], 2.07 [d, 1H, C(4)H], 2.32 (s, 3H, SMe), 2.45 (s, 3H, SMe), 2.65 [q, 2H, C(4′)H_2], 3.67 (s, 1H, MeO), 5.32 [s, 1H, C(7)H], 7.07 [s, 1H, C(9)H]. IR (Nujol, ν/cm^{-1}): 1725 (C=C), 1655 (C=N), 1595 (C=N), 1235, 1160, 1130, 1080, 1055, 995, 940. MS (EI, 70 eV) *m*/*z* (%): 390 [M$^+$] (2), 318 (20), 317 [M$^+$ – MeSCN] (100), 302 (60), 260 (10). Found (%): C, 64.48; H, 7.87; N, 7.05. Calc. for $C_{21}H_{30}N_2OS_2$ (%): C, 64.57; H, 7.74; N, 7.17.

[§] *Crystallographic data for* **4b**: $C_{21}H_{30}N_2OS_2$, triclinic, space group $P\bar{1}$, $a = 7.789(1)$, $b = 11.093(1)$, $c = 12.957(1)$ Å, $\alpha = 75.65(1)°$, $\beta = 81.54(1)°$, $\gamma = 82.11(1)°$, $V = 1066.8(2)$ Å^3, $Z = 2$, $d_{calc} = 1.216$ g cm^{-3}, λ(MoKα) = 0.7107 Å, μ(MoKα) = 2.62 cm^{-1}, $F(000) = 420$, $T = 293(2)$ K. Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer using the ω scan method (2θ from 2 to 56°). The structure was solved by the direct method and refined by a full-matrix least-squares procedure (SHELXL-97[7]) in an anisotropic approximation for all non-hydrogen atoms. The coordinates and thermal parameters of the hydrogen atoms were fixed (U_H 0.08 Å^2, C–H 0.96 Å). Final $R_1 = 0.073$, $wR_2 = 0.213$ for 3156 observed reflections with $I > 2\sigma(I)$.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 199456. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2003.