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New simple synthesis of *N*-acylpyrazolidines and *N*-arylsulfonyl-2-pyrazolines

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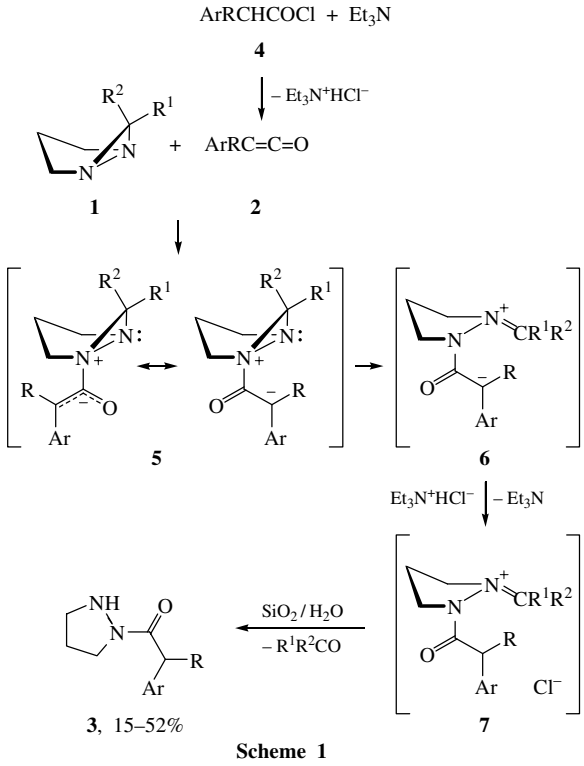
New simple methods for the synthesis of 1-mono- and 1,2-diacylpyrazolidines as well as 1-arylsulfonyl-2-pyrazolines, based on the interaction of 1,5-diazabicylo[3.1.0]hexanes with acyl- or arylsulfonyl chlorides, have been proposed.

Pyrazolidine derivatives exhibit a broad spectrum of biological activity. The pyrazolidine ring is a constituent part of 1,5-diazabicyclo[3.3.0]octan-2-one derivatives – γ-lactam antibacterial agents against a variety of clinically important pathogens.[1,2] 1-Acylpyrazolidines are used as initial compounds in the synthesis of inhibitors of the tumor necrosis factor α (TNF-α).[3,4] Cathepsin C inhibitors containing a 1-acylpyrazolidine fragment have been recently synthesised.[5] However, in contrast to pyrazoles and pyrazolines for which the methods of synthesis are well developed,[6] pyrazolidines are more difficult to achieve. Therefore, a search of new preparative methods for their synthesis remains desirable. Classical approaches to the synthesis of pyrazolidines are based on the reduction of pyrazolines[7] or pyrazole salts,[7,8] as well as on the interaction of hydrazine with 1,3-dibromides[9,10] or phenylhydrazones with electron-deficient alkenes.[11] Two 1,2-bis(phenylcarbamoyl)pyrazolidines were obtained in small yields (5–31%) by the interaction of 6-monoalkyl-1,5-diazabicyclo[3.1.0]hexanes with phenylisocyanate.[12] In the alkylation of analogous bicyclic structures with alkyl halides under phase-transfer conditions, the reaction products were 1-alkyl-2-pyrazolines.[13]

Recently,[14] we found that 1-(arylacetyl)pyrazolidines **3** were formed under the interaction of 1,5-diazabicyclo[3.1.0]hexanes **1** with arylketenes **2** at –30 °C in diethyl ether and at 20 °C in benzene (Scheme 1). Arylketenes **2** were generated from arylacetyl chlorides **4** and TEA. Here, we studied a new approach to the preparation of pyrazolidine derivatives on the basis of readily accessible 1,5-diazabicyclo[3.1.0]hexanes **1**. (The synthesis of compounds **1** is based on the action of alkaline metal hypochlorites on an equimolar mixture of a carbonyl compound and 1,3-diaminopropane).[15]

The following mechanism was proposed[14] for the formation of 1-(arylacetyl)pyrazolidines **3**. At the first stage, zwitterion intermediate **5** is formed. Then, the C–N bond cleavage is performed with the formation of another zwitterion intermediate **6**. The enolate ion in this intermediate is a rather strong base, which can remove the HCl molecule from triethylammonium chloride giving salts **7**, the analogues of α-halogen alkylamines.[16] The latter are hydrolysed to corresponding pyrazolidines **3** and carbonyl compounds during the isolation by column chromatography on SiO_2 (Scheme 1).



Scheme 1

The assumed mechanism of the transformation of compounds **1** (Scheme 1) could be formally considered as a succession of acylation and hydrolysis steps. If that is true, this reaction could be modified by a removal of the conjugated anion in intermediate **6** using acyl chlorides instead of ketenes as acylating reagents. To examine this assumption, 1,5-diazabicyclo[3.1.0]-hexane **1a** was treated with equimolar amounts of arylacetyl chlorides **4a**,**e** in the methylene chloride–aqueous NaOH solution two-phase system at room temperature. Indeed, under these conditions, compound **1a** was transformed to pyrazolidine derivatives; however, desirable 1-(arylacetyl)pyrazolidines **3a**,**e**

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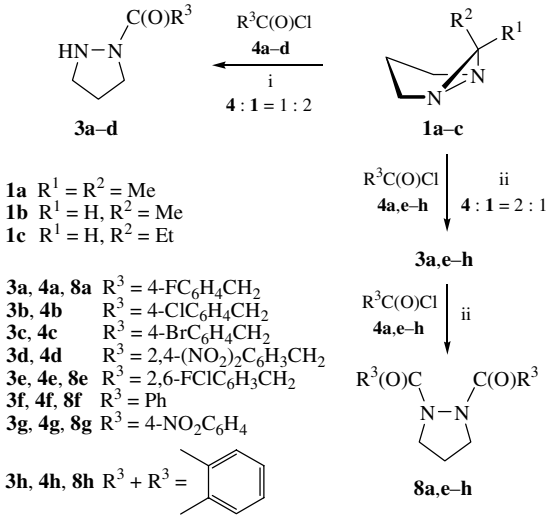
were obtained in insignificant amounts (TLC control) and the main reaction products were 1,2-bis(arylacetyl)pyrazolidines **8a**,**e**, which were isolated in low yields. Evidently, formed compounds **3a**,**e** entered the acylation reaction more quickly than initial bicycle **1a**. The use of two equivalents of arylacetyl chlorides **4a**,**e** resulted in compounds **8a**,**e** in 53–91% yields. For the preparation of 1-(arylacetyl)pyrazolidines **3a–d**, the preferable conditions proved to be: a double excess of initial bicycles **1**, a temperature of –15 °C and toluene as a solvent (Scheme 2).‡

To extend a scope of such an approach over the synthesis of 1,2-disubstituted pyrazolidines, different aroyl chlorides **4f–h**, as well as arylsulfonyl chlorides **9a–c**, were used in the reaction with 1,5-diazabicyclo[3.1.0]hexanes **1** in the presence of inorganic bases in the methylene chloride–water system at room temperature. In all cases, a 2:1 molar ratio of compounds **4f–h** or **9a–c** to initial compounds **1** was used. Reactions with aroyl chlorides resulted in expected 1,2-bis(aroyl)pyrazolidines **8f–h** with preparative yields. Another result was obtained in reactions with arylsulfonyl chlorides **9a–c**: 1-arylsulfonylpyrazolines **10a–c** were isolated as reaction products (Scheme 3).‡ It could be assumed that, at the first step, the reaction would proceed by

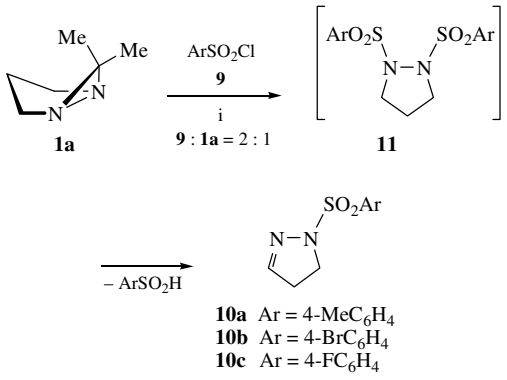


Scheme 2 *Reagents and conditions*: i, toluene, –15 °C → 20 °C, 3 h; ii, CH_2Cl_2/H_2O, NaOH, –5 °C → 20 °C, 5 h.

analogy with the formation of 1,2-bis(arylsulfonyl)pyrazolidines **11**. However, under the action of inorganic bases, arylsulfinic acids split off as sodium salts resulting in pyrazoline derivatives **10** (Scheme 3). The similar splitting of arylsulfinic acids is known in the synthesis of other heterocycles, for example 1,2,3-triazol-4-ine derivatives.[17]

The structures of the previously unknown compounds were established using elemental analysis and standard spectroscopy characteristics (IR, ^{1}H, ^{13}C NMR and mass spectra). For compound **10a**, it was supplemented by X-ray diffraction analysis.§

According to XRD, the five-membered ring in **10a** has an envelope conformation with the deviation of the C(5) atom from the plane of the rest ring atoms by 0.41 Å (Figure 1). The N(1) atom is characterised by a pyramidal configuration with the sum of bond angles equal to 341.6(1)°. Note that the electron lone pair (Lp) of the N(1) atom is antiperiplanar to the S(1)–C(6) bond [the pseudotorsion angle LpN(1)S(1)C(6) is 174.6°]. Thus, we can assume the presence of anomeric interaction of N(1) Lp with S(1)–C(6) σ-antibonding orbital (Lp-σ* interaction). The plane of a phenyl ring is almost perpendicular to the S(1)–N(1) bond with the torsion angle N(1)S(1)C(6)C(11) equal to 83.3°. The high resolution of experimental data makes it possible to perform a detailed analysis of charge denstiy distribution [$\rho(r)$] in the crystal of **10a**. As one can see from the deformation electron density (DED) map in the plane of N(1)S(1)C(6) atoms the Lp [the maxima of DED in the vicinity of the N(1) atom] is almost parallel to the area of DED depletion in the vicinity of the C(6)–C(11) bond. Thus, the presence of the Lp-σ* interaction in **10a** was demonstrated independently. To investigate the charge distribution in the



Scheme 3 *Reagents and conditions*: i, CH_2Cl_2/H_2O, NaOH, –5 °C → → 20 °C, 5 h.

‡ All new compounds exhibited satisfactory elemental analysis. IR spectra were measured on a UR-20 spectrometer; ^{1}H and ^{13}C NMR spectra were recorded on Bruker WM-250 (250 MHz) and Bruker AM-300 (75.5 MHz) spectrometers, respectively ($CDCl_3$ was used as an internal standard). Mass spectra were measured on a Finnigan MAT INCOS-50 instrument. TLC was carried out on Silufol UV-254 plates. Isolation of new compounds was performed on Kieselgel 60 F_{254} (Merk). Melting points were measured on a Gallenkamp instrument (Sanyo).

1-[(4-Fluorophenyl)acetyl]pyrazolidine **3a**: yield 52% (from **1c**), R_f 0.29 [ethyl acetate–*n*-heptane, 1:1 (v/v)], mp 76–77.5 °C (lit.,[14] mp 76–77 °C).

1-[(4-Chlorophenyl)acetyl]pyrazolidine **3b**: yield 41% (from **1a**), mp 104–105 °C (lit.,[14] mp 104–105 °C).

1-[(4-Bromophenyl)acetyl]pyrazolidine **3c**: yield 45% (from **1c**), mp 103–104 °C (lit.,[14] mp 102–104 °C).

1-[(2,4-Dinitrophenyl)acetyl]pyrazolidine **3d**: yield 37% (from **1b**), mp 118–120 °C (lit.,[14] mp 119–125 °C).

1,2-Bis[(4-fluorophenyl)acetyl]pirazolidine **8a**: yield 53% (from **1a**), R_f 0.34 (EtOAc), mp 127–128 °C. ^{1}H NMR ($CDCl_3$) δ: 1.87 (q, 2H, CCH_2C, ^2J 18 Hz, ^3J 9 Hz), 2.67 (m, 2H, NCH_2), 3.63 (m, 4H, CH_2CO), 4.15 (m, 2H, NCH_2), 6.99–7.25 (m, 8H, Ar).

1,2-Bis[(2-fluoro-6-chlorophenyl)acetyl]pyrazolidine **8e**: yield 91% (from **1a**), R_f 0.36 (ethyl acetate), mp 111–112 °C. ^{1}H NMR ($CDCl_3$) δ: 2.12 (q, 2H, CCH_2C, ^2J 18 Hz, ^3J 9 Hz), 3.13 (m, NCH_2), 4.05 (m, 4H, CH_2CO), 4.38 (m, 2H, NCH_2), 7.02 (t, 2H, Ar), 7.22 (d, 4H, Ar).

1,2-Dibenzoylpyrazolidine **8f**: yield 84% (from **1a**), mp 145–146 °C (lit.,[18] mp 146–147 °C).

1,2-Bis(4-nitrobenzoyl)pyrazolidine **8g**: yield 76% (from **1a**), R_f 0.48 (ethyl acetate–*n*-heptane, 5:1), mp 241–243 °C. ^{1}H NMR ($CDCl_3$) δ: 2.35 (m, 2H, CCH_2C), 3.55 (br. s. 4H, NCH_2), 7.1, 8.5 (2d, 8H, Ar). ^{13}C NMR ($CDCl_3$) δ: 24.3 (C*C*C), 48.5 (br. s, NCH_2), 123, 129, 140, 148 (Ar), 167 (CO). IR (ν/cm^{-1}): 708, 720, 840, 860, 1012, 1112, 1144, 1240, 1292, 1316, 1396, 1492, 1604, 1648. MS, *m*/*z*: 370 (M^+), 220, 150, 104.

*2,3-Dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione* **8h**: yield 26% (from **1a**), mp 206–208 °C (lit.,[19] mp 205–206 °C).

1-(4-Methylphenylsulfonyl)-2-pyrazoline **10a**: yield 23% (from **1a**), R_f 0.5 (ethyl acetate–*n*-heptane, 3:5), mp 167–168 °C. ^{1}H NMR ($CDCl_3$) δ: 2.4 (s, 3H, Me), 2.75 (t, 2H, $=CCH_2C$), 3.5 (t, 2H, NCH_2), 7.0 (s, =CH), 7.3, 7.75 (2d, Ar). ^{13}C NMR ($CDCl_3$) δ: 21.5 (Me), 34.13 (=C*C*C), 45.49 (NC), 128, 129.5, 131.0, 144.5 140, 148 (Ar), 150.2 (=C). IR (ν/cm^{-1}): 708, 732, 824, 928, 980, 1100, 1164, 1292, 1352, 1596.

1-(4-Fluorophenylsulfonyl)-2-pyrazoline **10b**: yield 78% (from **1a**), R_f 0.21 (ethyl acetate–*n*-heptane, 1:5), mp 161–162 °C. ^{1}H NMR ($CDCl_3$) δ: 2.75 (t, 2H, $=CCH_2C$), 3.5 (t, 2H, NCH_2), 7.0 (s, =CH), 7.2, 7.9 (2d, Ar). IR (ν/cm^{-1}): 708, 732, 824, 928, 980, 1100, 1164, 1292, 1352, 1596.

1-(4-Bromophenylsulfonyl)-2-pyrazoline **10c**: yield 22% (from **1a**), R_f 0.82 (ethyl acetate–*n*-heptane, 2:3), mp 169–171 °C. ^{1}H NMR ($CDCl_3$) δ: 2.78 (t, 2H, $=CCH_2C$), 3.5 (t, 2H, NCH_2), 7.0 (s, =CH), 7.7, 7.85 (2d, Ar). IR (ν/cm^{-1}): 704, 748, 828, 928, 980, 1008, 1168, 1280, 1356, 1572, 1596.

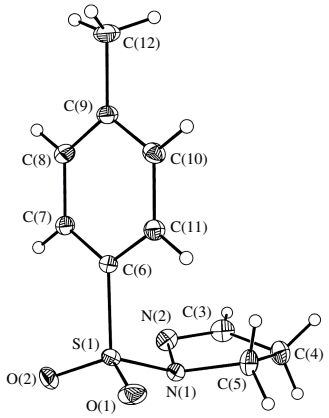


Figure 1 The general view of a molecule of **10a**. Selected bond lengths (Å): S(1)–O(2) 1.4327(5), S(1)–O(1) 1.4386(5), S(1)–N(1) 1.6608(4), S(1)–C(6) 1.7544(4), N(1)–N(2) 1.4218(6), N(1)–C(5) 1.4864(6), N(2)–C(3) 1.2837(8), C(3)–C(4) 1.4959(9); bond angles (°): O(2)–S(1)–O(1) 119.99(3), O(2)–S(1)–N(1) 107.02(3), O(1)–S(1)–N(1) 103.82(2), O(2)–S(1)–C(6) 109.07(3), O(1)–S(1)–C(6) 108.72(2), N(1)–S(1)–C(6) 107.49(2), N(2)–N(1)–C(5) 109.19(4), N(2)–N(1)–S(1) 113.69(3), C(5)–N(1)–S(1) 118.75(3), C(3)–N(2)–N(1) 106.93(5).

crystal of **10a**, we determined the atomic basins (Ω) surrounded by a zero-flux surface and integrated $\rho(r)$ over Ω. The charges obtained according to this procedure were 1.62, –0.75 and –0.28 e for S(1), N(1) and N(2), respectively.

Thus, a new simple approach to the synthesis of 1-mono- and 1,2-diacylpyrazolidines, **3** and **8**, respectively, was offered based on the interaction of easy-to-synthesise 1,5-diazabicyclo[3.1.0]-hexanes **1** with 0.5 or 2 mol of arylacetyl or aroyl chlorides **4**. The reaction of compounds **1** with 2 mol of arylsulfonyl chlorides resulted in 1-arylsulfonyl-2-pyrazolines **10**.

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§ *X-ray diffraction analysis*. Crystals of **10a** ($C_{10}H_{12}N_2O_2S$, $M = 224.29$) are monoclinic, space group $P2_1/c$, at 100(2) K: $a = 7.4472(10)$, $b = 17.8933(4)$ and $c = 8.3936(2)$ Å, $\beta = 112.4550(7)°$, $V = 1033.68(4)$ Å^3, $Z = 4$, $d_{calc} = 1.441$ g cm^{-3}, μ(MoKα) = 0.294 cm^{-1}, $F(000) = 472$. Intensities of 47405 reflections were measured with a Bruker AXS Smart 1000 CCD diffractometer and 8380 independent reflections [$R_{int} = 0.0248$] were used in further refinement. The refinement converged to $wR_2 = 0.0923$ and GOF = 1.000 for all independent reflections [$R_1 = 0.0335$ was calculated against F for 7062 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.

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 638459. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2007.

The multipole refinement was carried out for **1** within the Hansen–Coppens formalism[20] using the XD program package.[21] Before the refinement, C–H were normalised to 1.08 Å. The level of multipole expansion was octopole for carbon, nitrogen, oxygen and sulfur atoms and dipole for hydrogen atoms. The refinement was carried out against F and converged to $R = 0.0251$, $wR = 0.0244$ and GOF = 1.1431 for 7266 merged reflections with $I > 3\sigma(I)$. All bonded pairs of atoms satisfy the Hirshfeld rigid-bond criteria.[22] The average difference of the mean square displacement amplitudes along the bond was 6×10^{-4} Å^2. The residual electron density was no more than 0.135 eÅ^{-3}. Analysis of topology of the $\rho(r)$ function was carried out using the WINXPRO program package.[23]

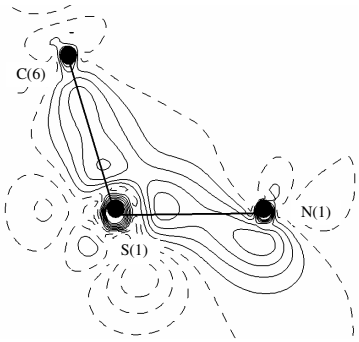

Figure 2 A section of DED in the N(1)S(1)C(6) plane. The contours are drawn with a 0.1 eÅ^{-3} step; the negative contours are dashed.

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