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Mendeleev Commun., 2015, **25**, 315–317

Mendeleev Communications

Synthesis of 3-acyl-1-hydroxy-1*H*-indole-5,6-dicarbonitriles

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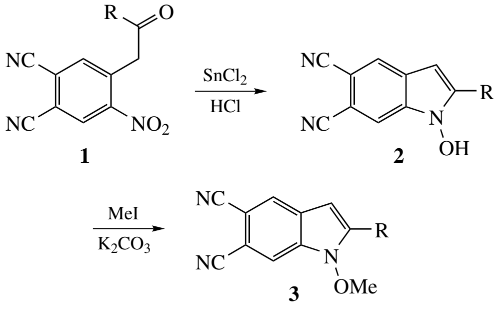
DOI: 10.1016/j.mencom.2015.07.030

The Vilsmeier–Haack formylation of 4-(2-aryl-2-oxoethyl)-5-nitrophthalonitriles followed by reduction affords 3-acyl-1-hydroxy-1*H*-indole-5,6-dicarbonitriles.

3-Acyl-1*H*-indoles can serve as starting components for biologically active compounds[1] and pharmaceutical substances possessing antifungal and analgesic activity.[2,3] *N*-Hydroxy-1*H*-indoles exert bactericidal[4,5] and antitumor[6] activity. Therefore, 3-acyl-1-hydroxy-1*H*-indoles can be of this 'joint' interest.

Usually, 3-acylindoles are prepared by Friedel–Crafts acylation[7,9] or Vilsmeier–Haack formylation[10] of the already existing indole cycle. Recently, Pd- and Rh-based catalysts were used for the synthesis of substituted 3-acylindoles from *o*-(alkynyl)-anilines.[11–13] Metal-based catalysis is employed for addition of nitriles to 3-unsubstituted indoles,[14,15] formylation,[16] or cyclization of ethenyl substrates with a nitro group in *ortho*-position[4] and aminoacetylation using *N*-sulfonyltriazole intermediates.[17]

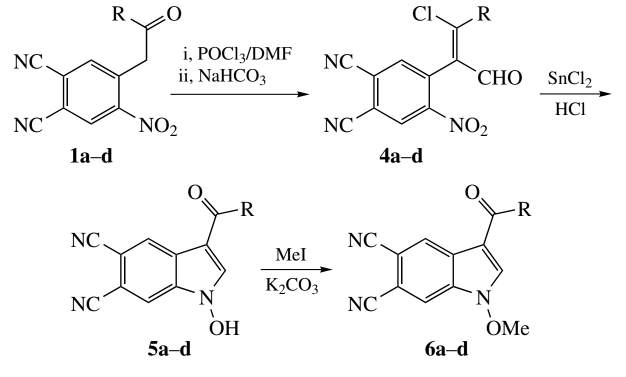
Earlier we reduced 4-(2-oxo-2-R-ethyl)-5-nitrophthalonitriles **1** into 1-hydroxy-2-R-1*H*-indole-5,6-dicarbonitriles **2** which were further O-methylated to the corresponding 1-methoxy derivatives **3**[18] (Scheme 1). Such compounds with a phthalonitrile motif are of interest, in particular, in the synthesis of macroheterocycles and polymer chemistry (see ref. 18 and references therein).



Scheme 1

Here, this strategy was developed for a synthesis of 3-acyl-1-hydroxy-1*H*-indole-5,6-dicarbonitriles (Scheme 2). Noteworthy, the examples of the 1-hydroxy-3-acyl-1*H*-indoles synthesis *via* reductive cyclization are scarce,[19–21] and there are no data on preparation of 3-acyl-substituted 1-hydroxyindole-5,6-dicarbonitriles. First, formyl derivatives **4a–d** were prepared by the Vilsmeier–Haack reaction[22] (yields up to 72%). Using 3-fold excess of $POCl_3$ resulted in formylation with concomitant replacement of enol hydroxyl group by chlorine atom.

Compounds **4a–d** were formed as *E*/*Z*-isomeric mixtures with predominant *E*-isomer (81–98%), in accordance with published data for similar compounds.[23] Their structure was proved by IR and NMR spectroscopy (including 2D NMR) and mass spectrometry. The NOESY spectrum of compound **4d** featured a key cross-peak of formyl proton with an H-5′ proton of thiophene ring, thus supporting the *E*-configuration of the major isomer. Based on the HMBC spectrum of compound **4c**, full assignment of hydrogen and carbon atoms was fullfilled. Mass spectra of compounds **4a–d** feature molecular ion peak of low abundance as two signals (3 : 1) according to the isotope composition of Cl.



a R = Ph
b R = 4-MeC_6H_4
c R = 4-$MeOC_6H_4$
d R = 2-thienyl

Scheme 2

Treatment of compounds **4a–d** with $SnCl_2$ in HCl[18] resulted in reduction of the nitro group along with replacement of the chlorine atom by the hydroxyl group and cyclization to the corresponding 3-acyl-1-hydroxy-1*H*-indole-5,6-dicarbonitriles **5a–d** in yields up to 80% (Scheme 2).[†] Reduction of the compounds like **4** was not previously described in literature. Reductive cyclization of unsymmetrical 2-(*o*-nitrophenyl)-1,3-dicarbonyl

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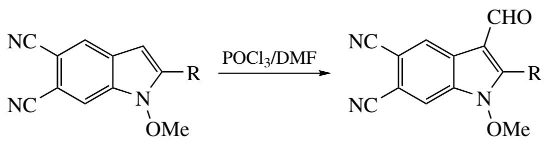
[†] IR spectra were measured on a Perkin-Elmer RX-1 spectrometer in the range of 700–4000 cm^{-1} using suspensions of substances in Nujol. Mass spectra were obtained using a FINNIGAN MAT INCOS 50 mass spectrometer; the ionization energy was 70 eV. NMR spectra were recorded on a Bruker DRX-500 instrument at 30 °C for solutions in DMSO-d_6. Signals of residual protons of the solvent in ^1H NMR spectra (δ_H 2.50) or the signal of DMSO-d_6 in ^{13}C spectra (δ_C 39.5) were used as references for chemical shift measurements. Two-dimensional spectra were recorded using standard Bruker techniques. The mixing time in NOESY spectra was 0.3 s. Elemental analysis was carried out on a Perkin Elmer 2400 instrument.

Synthesis of compounds **1**–**3** was described earlier.[18]

compounds was reported[20] to produce a mixture of isomers. However, in the present work due to the use of β-chlorovinylcarbonyl compounds **4a–d** the problem of regioselectivity was solved leading exclusively to **5a–d**. To prove the structure of compounds **5a–d**, they were converted to *N*-methoxy-1*H*-indoles **6a–d** by methylation with MeI in the presence of K_2CO_3. Such *N*-methoxy derivatives are more stable under EI mass spectrometry conditions thus enabling the observation of molecular ion peaks.

The structure of products **5** and **6** was proved by IR and NMR spectroscopy and mass spectrometry. On the basis of 2D NMR ^{1}H and ^{13}C HSQC and HMBC of compound **5b** the exact structures of **5a–d**, **6a–d** were established and all the signals of H and C atoms were assigned. Singlets of methoxy group were observed at 4.0–4.3 ppm in ^{1}H NMR spectra of **6a–d**. Mass spectra of the compounds **5a–d** are characterized by low abundance of the molecular ion peaks, $[M^+ - O]$ being one of the main fragment ions.[24] On the contrary, for compounds **6a–d** molecular ion is one of the most abundant ones and $[M^+ - OMe]$ is the main fragment ion.



3a–d **7a–d**

a R = Ph **c** R = 4-$MeOC_6H_4$
b R = 4-MeC_6H_4 **d** R = 2-thienyl

Scheme 3

If the reaction sequence is changed, the reductive cyclization of nitro ketones **1a–d** carried out first, the resulting 1-hydroxy-1*H*-indoles **2** methylated (see Scheme 1) and 1-methoxy-1*H*-indoles **3** then treated with a Vilsmeier reagent, 2-substituted-3-formyl-1*H*-indoles **7a–d** are obtained instead of isomeric 3-acylindoles **6a–d** (Scheme 3).[‡] Note that treatment of *N*-hydroxy-1*H*-indoles with chlorinating agents was reported[25,26] to produce 3-chloroindoles with elimination of hydroxyl group. Similarly, formylation of 2-aryl-1-hydroxy-1*H*-indoles was also accompanied by elimination of OH group and furnished 2-aryl-1*H*-indoles.[27] Thus, formylation at the 3-position with the retention of N-substituent proceeds smoothly for O-methylated *N*-hydroxy-1*H*-indoles only.

The structure of compounds **7a–d** was established by IR and NMR spectroscopy and mass spectrometry and confirmed by X-ray diffraction data for **7b**. ^{1}H NMR spectra of indoles **7a–d** feature a low-field singlet corresponding to the formyl proton at 9.80–10.12 ppm.

An asymmetric unit cell contains one molecule of **7b** (Figure 1).[§] The *p*-tolyl and methoxy substituents are out of

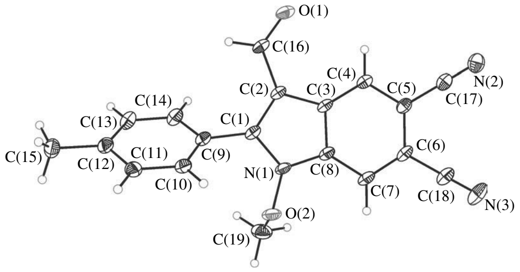


Figure 1 Molecular structure of compound **7b**. Displacement ellipsoids are drawn at the 50% probability level.

4-(2-Aryl-1-chloro-3-oxoprop-1-en-2-yl)-5-nitrophthalonitriles **4a–d** *(general procedure).* Compound **1a–d** (6 mmol) was added to a solution of $POCl_3$ (18 mmol) in DMF (3 ml). The mixture was stirred at 80–90 °C for 2 h, cooled and poured into cold 5% aq. $NaHCO_3$ solution. The resulting precipitate was filtered, thoroughly washed with water and recrystallized from EtOH.

4-[1-Chloro-1-(4-methoxyphenyl)-3-oxoprop-1-en-2-yl]-5-nitrobenzene-1,2-dicarbonitrile **4c**: yield 66%, mp 191–193 °C (ethanol). IR (ν/cm^{-1}): 2241 (C≡N), 1664 (C=O), 1600 (Ar), 1531, 1349 (NO_2). ^{1}H NMR (DMSO-d_6) δ: *E*-isomer >98%, 3.88 (s, 3H, OMe), 7.18 (d, 2H, H-3′, H-5′, *J* 8.7 Hz), 7.66 (d, 2H, H-2′, H-6′, *J* 8.7 Hz), 8.60 (s, 1H, H-3), 9.03 (s, 1H, H-6), 9.44 (s, 1H, COH). ^{13}C NMR (DMSO-d_6) δ: 187.07, 162.42, 155.29, 150.05, 138.39, 134.39, 134.15, 132.42 (2C), 130.19, 125.95, 119.48, 116.76, 114.60 (2C), 114,58 114.42, 55.73. MS, *m/z* (%): 367 [M^+] (21), 338 [M–COH] (11), 303 (56), 294 (57), 259 (50), 251 (49), 233 (53), 215 (42), 202 (68), 189 (74), 165 (86), 169 (34), 155 (52), 142 (41), 135 (51), 119 (48), 107 (51), 92 (80), 76 (39), 64 (100). Found (%): C, 58.52; H, 2.65; N, 11.34. Calc. for $C_{18}H_{10}ClN_3O_4$ (%): C, 58.79; H, 2.74; N, 11.43.

*3-Acyl-1-hydroxy-1*H*-indole-5,6-dicarbonitriles* **5a–d** *(general procedure).* Compound **4a–d** (3 mmol) was added to a solution of $SnCl_2$ (0.01 mol) in conc. HCl (2 ml) and EtOH (2 ml), and the mixture was stirred at 50 °C for 0.5–1 h. The precipitate formed upon cooling of the solution was filtered and recrystallized from EtOH.

*1-Hydroxy-3-(4-methylbenzoyl)-1*H*-indole-5,6-dicarbonitrile* **5b**: yield 79%, mp 272–273 °C (ethanol). IR (ν/cm^{-1}): 3561 (OH), 2230 (C≡N), 1635 (C=O), 1585 (Ar). ^{1}H NMR (DMSO-d_6) δ: 2.42 (s, 3H, Me), 7.38 (d, 2H, H-3′, H-5′, *J* 8.0 Hz), 7.77 (d, 2H, H-2′, H-6′, *J* 8.0 Hz), 8.44 (s, 1H, H-4), 8.61 (s, 1H, H-2), 8.80 (s, 1H, H-7), 12.87 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ: 188.26 (C=O), 142.46 (C-1′), 137.61 (C-2), 136.05 (C-4′), 133.73 (C-7a), 129.26 (C-3′, C-5′), 128.92 (C-2′, C-6′), 128.52 (C-7), 124.72 (C-3), 117.11 (6-CN), 116.91 (C-4), 116.82 (5-CN), 110.70 (C-3a), 107.46 (C-5), 106.81 (C-6), 21.16 (Me). MS, *m/z* (%): 301 (1), 285 [M^+–O] (6), 154 (11), 139 (15), 119 (100), 91 (97). Found (%): C, 71.53; H, 3.52; N, 13.88. Calc. for $C_{18}H_{11}N_3O_2$ (%): C, 71.75%; H, 3.68; N, 13.95.

*3-Acyl-1-methoxy-1*H*-indole-5,6-dicarbonitriles* **6a–d** *(general procedure).* MeI (1.1 mmol) and K_2CO_3 (1.3 mmol) were added to a solution of compounds **5a–d** (1 mmol) in DMF (5 ml) and the mixture was stirred at 30–40 °C for 1–2 h. Then it was cooled, the resulting precipitate was filtered and recrystallized from EtOH.

*3-Benzoyl-1-methoxy-1*H*-indole-5,6-dicarbonitrile* **6a**: yield 78%, mp 251–253 °C (ethanol). IR (ν/cm^{-1}): 2237 (C≡N), 1659 (C=O), 1615 (Ar). ^{1}H NMR (DMSO-d_6) δ: 4.26 (s, 3H, OMe), 7.60 (t, 2H, H-3′, H-5′, *J* 7.7 Hz), 7.69 (t, 1H, H-4′, *J* 7.7 Hz), 7.90 (d, 2H, H-2′, H-6′, *J* 7.7 Hz), 8.65 (s, 1H, H-4), 8.84 (s, 1H, H-2), 8.91 (s, 1H, H-7). ^{13}C NMR (DMSO-d_6) δ: 188.66, 138.39, 137.08, 132.26 (2C), 128.71 (2C), 128.67 (2C), 128.49, 124.59, 116.81, 116.79, 116.53, 111.22, 108.08, 107.42, 68.00. MS, *m/z* (%): 301 [M^+] (13), 224 (25), 215 (15), 165 (26), 105 (44), 77 (100). Found (%): C, 71.52; H, 3.57; N, 13.89. Calc. for $C_{18}H_{11}N_3O_2$ (%): C, 71.75; H, 3.68; N, 13.95.

For characteristics of compounds **4a**,**b**,**d**, **5a**,**c**,**d** and **6b–d**, see Online Supplementary Materials.

[‡] *3-Formyl-1-methoxy-2-R-1*H*-indole-5,6-dicarbonitriles* **7a–d** *(general procedure).* Compound **3a–d** (1 mmol) was added to a solution of $POCl_3$ (0.279 ml, 460 mg, 3 mmol) in DMF (5 ml). The reaction mixture was stirred at 80–90 °C for 2 h. The solution was cooled and poured into 10-fold excess of ice water. The resulting precipitate was filtered, washed with 1% $NaHCO_3$ solution and crystallized from EtOH.

*3-Formyl-1-methoxy-2-phenyl-1*H*-indole-5,6-dicarbonitrile* **7a**: yield 53%, mp 236–238 °C (decomp.). IR (ν/cm^{-1}): 2227 (C≡N), 1664 (C=O), 1607 (Ar). ^{1}H NMR (DMSO-d_6) δ: 3.93 (s, 3H, OMe), 7.68 (m, 3H, H-3′, H-4′, H-5′), 7.87 (d, 2H, H-2′, H-6′, *J* 7.4 Hz), 8.71 (s, 1H, H-4), 8.81 (s, 1H, H-7), 9.81 (s, 1H, COH). ^{13}C NMR (DMSO-d_6) δ: 185.35, 149.12, 132.09, 131.31, 130.88 (2C), 129.09 (2C), 127.45, 124.49, 122.90, 116.92, 116.69, 116.56, 110.74, 108.65, 108.20, 67.19. MS, *m/z* (%): 301 [M^+] (30), 270 [M^+–OMe] (100), 241 (13), 215 (36), 77 (11). Found (%): C, 71.62; H, 3.76; N, 13.89. Calc. for $C_{18}H_{11}N_3O_2$ (%): C, 71.75; H, 3.68; N, 13.95.

For characteristics of compounds **7b–d**, see Online Supplementary Materials.

[§] *Crystal data for* **7b**. Crystals of $C_{19}H_{13}N_3O_2$ are triclinic, space group $P\bar{1}$: $a = 8.5169(4)$, $b = 8.6573(4)$ and $c = 12.2902(6)$ Å, $\alpha = 103.3990(10)°$, $\beta = 97.4720(10)°$, $\gamma = 109.8100(10)°$, $V = 807.54(7)$ Å^3, $Z = 2$, $M = 315.32$, $d_{calc} = 1.297$ g cm^{-3}, $\mu = 0.087$ mm^{-1}, $wR_2 = 0.1286$ calculated on F^2_{hkl} for 5135 independent reflections ($R_{int} = 0.0237$) with $2\theta < 62°$ [GOF = 1.010, $R = 0.0451$ calculated on F_{hkl} for 4283 reflections with $I > 2\sigma(I)$].

CCDC 1037901 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

the plane of the indole cycle due evidently to sterical reasons while the formyl substituent is coplanar to the cycle. It should be noted that in spite of the absence of the acidic H-atoms in molecule **7b**, the O(1) atom of the formyl group forms relatively strong hydrogen bond C(7)–H(7A)···O(1) [C···O 3.1694(13) Å, H···O 2.25 Å, ∠CHO 162°], that links molecules into chains along crystallographic axis *a*. All the other intermolecular interactions are of ordinary van-der-Waals type.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.07.030.

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Received: 18th December 2014; Com. 14/4535