Expedient Synthesis of 1-Hydroxy-4- and 1-Hydroxy-6-nitroindoles

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Abstract: Reaction of α-chloroalkyl ketones with 1,3-dinitrobenzenes provides 2,4-dinitrobenzyl ketones which when reduced with tin(II) chloride form 6-nitro derivatives of 1-hydroxyindoles. An alternative approach is the condensation of 2,4- and 2,6-dinitrotoluenes with diethyl oxalate or ethyl trifluoroacetate provides dinitrobenzyl ketones which leads after reduction with tin(II) chloride to nitro derivatives of 1-hydroxyindol-2-carboxylates or 1-hydroxy-2-(trifluoromethyl)indoles, respectively.

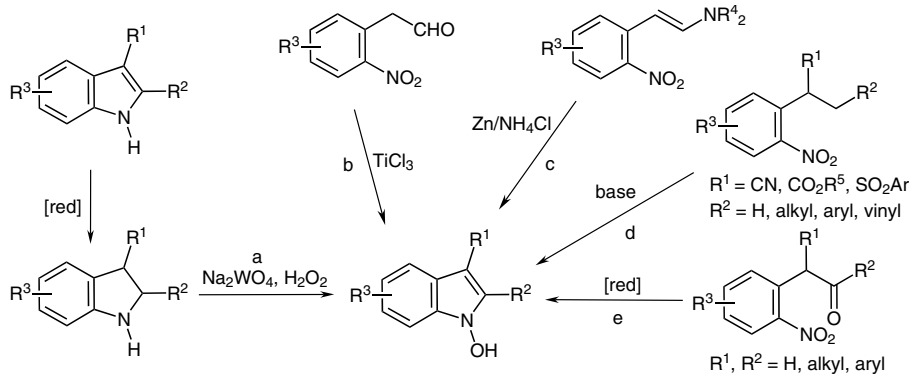
Key words: indoles, acylation, reduction, nucleophilic aromatic substitution, tin, ketones

Discovery of *N*-hydroxy- and *N*-methoxy-indole framework in numerous natural products such as aplicyanins,[1a] birnbaumins,[1b] nocathiacin I,[1c] phytoalexin,[1d] paniculidine B,[1d] stephacidin B[1e] and potential application of *N*-hydroxyindoles as therapeutic agents[2] spurred on the development of the synthetic methods leading to 1-hydroxy and alkoxyindoles as well as prompted the studies on this rather unknown part of indole chemistry.[3]

Some of general approaches to 1-hydroxyindoles are depicted in the Scheme 1. The path a known as Somei's tungstate method[3] deals with an oxidation of indolines with hydrogen peroxide in the presence of sodium tungstate or phosphotungstate as catalyst. This approach requires a reduction of the indole nucleus to indoline prior to the oxidation. In Acheson's method (path b) the 2-nitrophenylacetaldehydes were reduced with titanium(III) chloride or with zinc–ammonium chloride system.[4] The major drawback of this approach is a troublesome synthesis of the starting nitroaldehydes. A complementary method (path c) developed by Somei employed as starting material 2-(nitrophenyl)acetaldehyde enamines prepared from 2-nitrotoluene derivatives and DMF–DMA (Leimgruber–Batcho reaction).[5] Path d deals with an interaction of the nitro group with a carbanion generated at the β-position in a side chain located *ortho* to the nitro group. The older examples of this type of reaction were reviewed by Preston and Tennant in 1972.[6] We have found that this approach can be used for the synthesis of *N*-hydroxyindoles starting from allyl derivatives of *ortho*-nitroaryl acetonitriles.[7] A similar approach has been used recently by Selvakumar as a key step in the synthesis of phytoalexin and paniculidines.[1d] Following the path e variously substituted 1-hydroxy-indoles are formed from 2-nitrobenzyl ketones upon reduction with tin(II) chloride[8] or lead with triethylammonium formate.[9]

Classic methods for the synthesis of nitrobenzyl ketones deal with a nucleophilic aromatic substitution (S_NAr) of halogen in 2-nitro- and 2,4-dinitro-1-fluoro-benzenes with enolate anions of 1,3-dicarbonyl compounds or alkyl β-ketoalkanoates.[10a] In the latter case the S_NAr is followed by hydrolysis of the ester group and decarboxylation. Recently, the synthesis of nitrobenzyl ketones via S_NAr in fluoronitrobenzenes with carbanions of α-(benzothiazole-2-sulfonyl) ketones has been described.[10b]

One of the general methods for the introduction of substituents into nitroarenes is the vicarious nucleophilic substitution (VNS)[11] enabling replacement of hydrogen in the position *ortho* and/or *para* to the nitro group by carbanions bearing a leaving group at the α-position. The obtained *ortho*-nitrobenzyl derivatives are well suited as



Scheme 1 Selected methods of synthesis of *N*-hydroxyindoles

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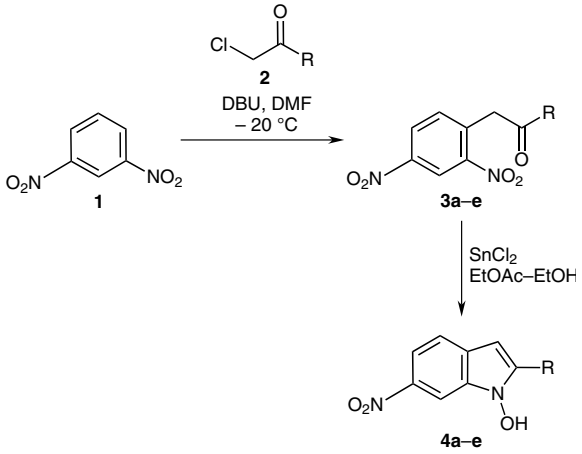
starting materials for the synthesis of heterocycles, particularly indoles[11b,c] and quinolines.[11b,c]

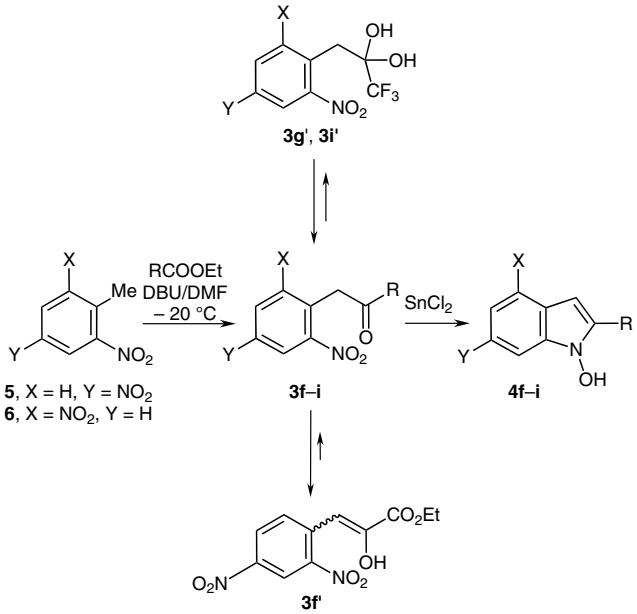
In one of our previous papers[12] we described the synthesis of nitrobenzyl ketones via the VNS of hydrogen in nitroarenes by α-chloromethyl ketone enolates. In this paper we present a simple two-step approach to 1-hydroxy-6-nitroindoles starting from 1,3-dinitro-benzene and chloromethyl ketones. The reaction of 1,3-dinitrobenzene (**1**) with α-chloromethyl ketones **2** proceeds smoothly in the presence of DBU in DMF giving the expected 2,4-dinitrobenzyl ketones **3** in good yields (Scheme 2).[13] The obtained ketones were then reduced with tin(II) chloride under mild conditions in an ethyl acetate–ethanol mixture to form 2-substituted 1-hydroxy-6-nitroindoles **4** (Table 1).[14]



Scheme 2 1-Hydroxyindoles via VNS of hydrogen in 1,3-nitrobenzene

One of the general methods for the preparation of indole-2-carboxylic esters is the Reissert synthesis dealing with the condensation of *ortho*-nitrotoluenes with dialkyl oxalates followed by a reductive cyclization of the intermediate 2-nitrophenyl pyruvates.[15] In contrast, reports concerning such a reaction of dinitrotoluenes with diethyloxalate are scarce.[16] We have found that the reaction of 2,4-dinitrotoluene (**5**) with diethyl oxalate in the presence of DBU proceeds slowly (3 d at –15 °C) giving the product in 78% yield. The ^{1}H NMR spectrum revealed that this product exist in the form of an enol **3f′**.[17] The reduction of 2,4-dinitrophenyl pyruvate with tin(II) chloride leads to a mixture of 1-hydroxy-6-nitroindole-2-carboxylate (**4f**) and its dexydroxylated analogue **8f**. In a similar reaction 2,6-dinitrotoluene (**6**) was transformed into ethyl (2,6-dinitrophenyl)pyruvate (**3h**) in 85% yield that upon reduction gave ethyl 1-hydroxy-4-nitro-indole-2-carboxylate (**4h**) in 75% yield.

Recent interest in the synthesis of 2-(trifluoromethyl)indoles[18] prompted us to employ this approach to the synthesis of this rather underdeveloped class of indole derivatives. Thus the condensation of 2,4-dinitrotoluene (**5**) with ethyl trifluoroacetate gave the expected trifluoromethyl 2,4-dinitrobenzyl ketone (**3g**) in 95% yield.[19] This compound was accompanied with variable amounts of its hydrate **3g′** formed during aqueous workup. Similar addition of water, but at lesser extent, was observed in the case of trifluoromethyl 2,6-dinitrobenzyl ketone (**3i**) obtained from 2,6-dinitrotoluene (**6**). These hydrates did not have an influence on the further reduction step.



Scheme 3 1-Hydroxyindoles via acylation of dinitrotoluenes

The reduction of the ketone **3g** with tin(II) chloride gave 1-hydroxy-6-nitro-2-(trifluoromethyl)indole (**4g**) in 50% yield. In a similar reaction sequence 2,6-dinitrotoluene (**6**) was transformed into the corresponding 2-trifluoromethyl derivative **4i** (Scheme 3, Table 2). 1-Hydroxyindoles can be easily transformed into indoles. Somei transformed the

Table 1 Dinitrobenzyl Ketones **3a**–**e** and 1-Hydroxyindoles **4a**–**e** via VNS of Hydrogen in 1,3-Dinitrobenzene

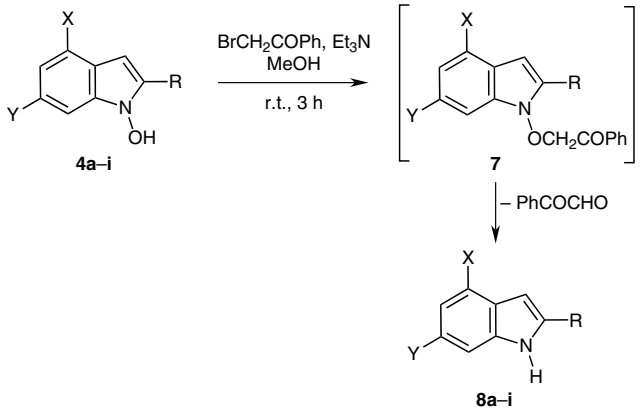
Entry		X	R	Yield of ketone **3** (%)	Yield of 1-hydroxyindole **4** (%)
1	**a**	H	Me	84	68
2	**b**	H	*t*-Bu	74	57
3	**c**	H	Ph	89	61
4	**d**	H	4-ClC_6H_4	81	60
5	**e**	H	4-MeOC_6H_4	86	60

Table 2 *N*-Hydroxynitroindoles **4f–i** via Acylation of Dinitrotoluenes

Entry		X	Y	R	Yield of ketone **3** (%)	Yield of 1-hydroxyindole **4** (%)
1	**f**	H	NO_2	CO_2Et	78[a]	25[b]
2	**g**	H	NO_2	CF_3	95	50
3	**h**	NO_2	H	CO_2Et	85	65
4	**i**	NO_2	H	CF_3	79	74

[a] Isolated as enol **3f′**.
[b] Also 20% of indole **8f** were isolated.

1-hydroxyindoles into *N*-methoxy[20a] or *N*-(ethoxycarbonyl)methyl[20b] derivatives which when treated with a base gave indoles. We have reported previously[21] that N-dehydroxylation can be performed under mild conditions with ethyl bromoacetate in the presence of triethylamine. We have found that for the compound **4a** the dehydroxylation using ethyl bromoacetate proceeds slowly and is complete within four days at room temperature giving the product **8a** in 51% yield. Now we have found that a much more effective alkylating reagent for this purpose is α-bromoacetophenone. Thus alkylation of *N*-hydroxy-indoles **4a–i** with α-bromoacetophenone proceeded smoothly giving after elimination of phenylglyoxal moiety[22] from the intermediate **6** the expected nitroindoles **8a–i** in high yields (Scheme 4, Table 3).[23]



Scheme 4 Dehydroxylation of 1-hydroxyindoles

In summary, we have developed a simple method for the synthesis of nitroderivatives of *N*-hydroxyindoles from dinitrobenzyl ketones easily available via vicarious nucleophilic substitution of hydrogen in 1,3-dinitrobenzene or via an acylation of 2,4- and 2,6-dinitrotoluenes. These *N*-hydroxyindoles can be easily dehydroxylated into indoles.

Acknowledgment

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Table 3 Dehydroxylation of *N*-Hydroxyindoles

Entry	*N*-Hydroxyindole **4**	Indole **8**	Yield (%)
1	**4a**	**8a**	83
2	**4b**	**8b**	90
3	**4c**	**8c**	99
4	**4d**	**8d**	87
5	**4e**	**8e**	87
6	**4f**	**8f**	81
7	**4g**	**8g**	99
8	**4h**	**8h**	94
9	**4i**	**8i**	98

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(13) **General Procedure for the Synthesis of Dinitrobenzyl Ketones 4a–f**

To a stirred solution of 1,3-dinitrobenzene (10 mmol) and α-chloromethyl ketone (**2**, 10 mmol) in DMF (25 mL) cooled to –20 °C was added DBU (5.32 g, 5.2 mL, 35 mmol). The stirring was continued for 40 min allowing the reaction mixture to reach r.t. Then the reaction mixture was stirred for additional 20 min and poured into diluted HCl (100 mL). The precipitate was filtered, diluted with EtOAc (50 mL), washed with brine, and dried with Na_2SO_4. After evaporation of the solvent the residue was chromatographed on silica gel with EtOAc–hexane (2:1). The following compounds were obtained.

1-(2,4-Dinitrophenyl)-propan-2-one (3a)

Pale yellow crystals, mp 65–67 °C (lit.[12] 66–67 °C).

1-(2,4-Dinitrophenyl)-3,3-dimethylbutan-2-one (3b)

Orange crystals, mp 60–62 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (s, 9 H), 4.24 (s, 2 H), 7.47 (d, *J* = 8.3 Hz, 1 H), 8.40 (dd, *J* = 8.3, 2.3 Hz, 1 H), 8.94 (d, *J* = 2.3 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.59, 42.70, 44.45, 120.54, 127.09, 128.86, 134.69, 137.92, 147.14, 149.25, 209.54. ESI-MS: *m/z* = 555 [2M + Na^+], 289 [M + Na^+]. ESI-HRMS: *m/z* calcd for $C_{12}H_{14}N_2O_5Na$: 289.0795; found: 289.0786.

1-(2,4-Dinitrophenyl)-2-phenylethanone (3c)

Pale yellow crystals, mp 133–135 °C (lit.[12] 136–137 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.87 (s, 2 H), 7.51–7.55 (m, 2 H), 7.59 (d, *J* = 8.5 Hz, 1 H), 7.63–7.68 (m, 2 H), 8.01–8.04 (m, 2 H), 8.46 (dd, *J* = 8.5, 2.2 Hz, 1 H), 8.98 (d, *J* = 2.2 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 44.14, 120.68, 127.32, 128.27, 128.92, 134.01, 134.93, 135.87, 137.56, 147.37, 149.23, 193.86. ESI-MS: *m/z* = 309 [M + Na^+]. ESI-HRMS: *m/z* calcd for $C_{14}H_{10}N_2O_5Na$: 309.0482; found: 309.0497.

1-(4-Chlorophenyl)-2-(2,4-dinitrophenyl)-ethanone (3d)

Yellow crystals, mp 145–147 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.83 (s, 2 H), 7.50–7.53 (m, 2 H), 7.59 (d, *J* = 8.4 Hz, 1 H), 7.95–7.99 (m, 2 H), 8.47 (dd, *J* = 8.4, 2.4 Hz, 1 H), 9.00 (d, *J* = 2.4 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 44.09, 120.75, 127.42, 129.28, 129.66, 134.18, 134.94, 137.17, 140.60, 147.47, 149.09, 192.75. ESI-HRMS: *m/z* calcd for $C_{14}H_9N_2O_5ClNa$: 343.0092; found: 343.0106.

1-(2,4-Dinitrophenyl)-2-(4-methoxyphenyl)ethanone (3e)

Yellow crystals, mp 102–103 °C (lit.[10b] 102–105 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.90 (s, 3 H), 4.82 (s, 2 H), 6.97–7.01 (m, 2 H), 7.58 (d, *J* = 8.4 Hz, 1 H), 7.98–8.02 (m, 2 H), 8.43 (dd, *J* = 8.4, 2.3 Hz, 1 H), 8.97 (d, *J* = 2.3 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 43.70, 55.58, 114.06, 120.57, 127.19, 128.86, 130.62, 134.88, 137.86, 147.25, 149.30, 164.19, 192.21. MS (EI, 70 eV): *m/z* (%) = 316 (2) [M^+], 152 (1), 135 (100), 107 (4), 92 (7), 77 (10). ESI-HRMS: *m/z* calcd for $C_{15}H_{12}N_2O_6Na$: 339.0588; found: 339.0590.

(14) **1-Hydroxy-nitroindoles from Dinitrobenzyl Ketones – General Procedure**

To dinitrobenzyl ketone (2 mmol) dissolved in EtOAc (10 mL) and EtOH (1 mL) $SnCl_2$ (1.44 g, 7.6 mmol) was added in one portion. The reaction mixture was stirred overnight at r.t. The reaction mixture was then evaporated, and the residue was subjected to column chromatography on silica gel. The product was eluted with EtOAc–hexane (4:1). The following compounds were obtained.

1-Hydroxy-2-methyl-6-nitroindole (4a)

Orange crystals, mp 153–155 °C. ^{1}H NMR [500 MHz, $(CD_3)_2CO$]: δ = 2.51 (d, *J* = 1.0 Hz, 3 H), 6.32 (q, *J* = 1.0 Hz, 1 H), 7.58 (d, *J* = 8.8 Hz, 1 H), 7.89 (dd, *J* = 8.8, 2.2 Hz, 1 H), 8.28 (d, *J* = 2.2 Hz, 1 H), 10.49 (br s, 1 H). ^{13}C NMR [125 MHz, $(CD_3)_2CO$]: δ = 11.34, 97.21, 105.24, 115.22, 120.36, 129.22, 133.19, 142.35, 142.98. IR (KBr): ν = 3261, 1609, 1583, 1505, 1458, 1392, 1365, 1326, 1276, 1220, 1134, 865, 762 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 192 (100) [M^+], 191 (10), 176 (22), 162 (7), 146 (32), 145 (15)130 (12), 129 (23), 128 (16), 117 (23), 103 (16), 102 (17). HRMS (EI): *m/z* calcd for $C_9H_8N_2O_3$: 192.0535; found: 192.0541.

2-*tert*-Butyl-1-hydroxy-6-nitroindole (4b)

Orange crystals, mp 147–149 °C. ^{1}H NMR [500 MHz, $(CD_3)_2CO$]: δ = 1.51 (s, 9 H), 6.32 (d, *J* = 0.9 Hz, 1 H), 7.61 (dd, *J* = 8.6, 0.6 Hz, 1 H), 7.89 (dd, *J* = 8.7, 2.1 Hz, 1 H), 8.26 (br d, *J* = 2.2 Hz, 1 H), 10.64 (br s, 1 H). ^{13}C NMR [125 MHz, $(CD_3)_2CO$]: δ = 29.23, 33.33, 95.00, 96.62, 105.29, 115.19, 120.78, 128.44, 134.52, 143.20, 153.52. MS (EI, 70 eV): *m/z* (%) = 234 (71) [M^+], 219 (100), 203 (12), 202 (13), 201 (17), 173 (13), 172 (12), 156 (13), 155 (15). HRMS (EI): *m/z* calcd for $C_{12}H_{14}N_2O_3$: 234.1004, found: 234.0997.

1-Hydroxy-2-phenyl-6-nitroindole (4c)

Red-orange crystals, mp 158–160 °C. ^{1}H NMR [500 MHz, $(CD_3)_2CO$]: δ = 6.84 (s, 1 H), 7.45–7.50 (m, 1 H), 7.51–7.56 (m, 2 H), 7.74 (d, *J* = 8.7 Hz, 1 H), 7.95–7.99 (m, 3 H), 8.41 (d, *J* = 2.1 Hz, 1 H), 10.72 (br s, 1 H). ^{13}C NMR [125 MHz, $(CD_3)_2CO$]: δ = 97.52, 105.31, 115.06, 120.57, 128.11, 128.36, 128.72, 128.94, 129.94, 134.13, 143.03, 143.08. IR (KBr): ν = 3247, 1607, 1501, 1478, 1467, 1316, 1273, 1081, 818, 763 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 254 (100) [M^+], 238 (25), 225 (11), 224 (10), 208 (24), 207 (17), 191 (23), 190 (38), 180 (17), 179 (50), 165 10), 164 (10), 163 (11), 152 (10). HRMS (EI): *m/z* calcd for $C_{14}H_{10}N_2O_3$: 254.0691; found: 254.0695.

2-(4-Chlorophenyl)-1-hydroxy-6-nitroindole (4d)

Orange crystals, mp 201–203 °C. ^{1}H NMR [500 MHz, $(CD_3)_2CO$]: δ = 6.86 (d, *J* = 1.0 Hz, 1 H), 7.54–7.58 (m, 2 H), 7.73 (d, *J* = 8.7 Hz, 1 H), 7.96 (dd, *J* = 8.7, 2.1 Hz, 1 H), 7.97–8.00 (m, 2 H), 8.38 (br d, 2.1 Hz, 1 H), 10.81 (br s, 1 H). ^{13}C NMR [125 MHz, $(CD_3)_2CO$]: δ = 98.70, 106.24, 116.01, 121.61, 128.81, 129.58, 129.73, 130.72, 135.06, 135.26, 142.48, 144.09. IR (KBr): ν = 3278, 1608, 1536, 1506, 1479, 1336, 1286, 1279, 1084, 813, 773, 761, 726 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 280 (57) [M^+], 270 (100), 258 (20), 242 (35), 213 (36), 206 (15), 191 (45), 190 (60), 178 (22). HRMS (EI): *m/z* calcd for $C_{14}H_9{}^{35}ClN_2O_3$: 288.0302; found: 288.0299.

1-Hydroxy-2-(4-methoxyphenyl)-6-nitroindole (4e)

Red-orange crystals, mp 183–185 °C. ^{1}H NMR [500 MHz, $(CD_3)_2CO$]: δ = 3.88 (s, 3 H), 6.74 (d, *J* = 1.0 Hz, 1 H), 7.07–7.11 (m, 2 H), 7.69 (d, *J* = 8.7 Hz, 1 H), 7.90–7.94 (m, 2 H), 7.96 (dd, *J* = 8.5, 2.0 Hz, 1 H), 8.37 (br d, *J* = 2.0 Hz, 1H), 10.70 (s, 1 H). ^{13}C NMR [125 MHz, $(CD_3)_2CO$]: δ = 54.84, 96.44, 105.10, 114.17, 115.04, 120.11, 122.26, 128.31,

129.76, 133.95, 142.62, 143.20, 150.50. MS (EI, 70 eV): *m/z* (%) = 284 (15) [M^+], 268 (100), 254 (14), 238 (29), 223 (13), 222 (44), 209 (13), 208 (9), 207 (20), 206 (10), 191 (9), 190 (7). HRMS (EI): *m/z* calcd for $C_{15}H_{12}N_2O_4$: 284.0797; found: 284.0805.

Ethyl 1-Hydroxy-6-nitroindole-2-carboxylate (4f)

Yellow crystals, mp 160–161 °C. ^{1}H NMR [500 MHz, $(CD_3)_2CO$]: δ = 1.40 (t, *J* = 7.0 Hz, 3 H), 4.41 (q, *J* = 7.0 Hz, 2 H), 7.22 (br s, 1 H), 7.90 (d, *J* = 8.8 Hz, 1 H), 7.98 (dd, *J* = 8.8, 1.9 Hz, 1 H), 8.43 (br s, 1 H), 10.92 (br s, 1 H). ^{13}C NMR [125 MHz, $(CD_3)_2CO$]: δ = 13.61, 61.04, 105.08, 106.29, 115.24, 123.20, 125.60, 131.12, 134.52, 145.45, 159.29. IR (KBr): ν = 3077, 1687, 1620, 1589, 1525, 1505, 1466, 1407, 1337, 1286, 1258, 1218, 1055, 1010, 826, 752, 726 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 250 (33) [M^+], 234 (8), 222 (6), 205 (14), 204 (100), 188 (10), 158 (9). HRMS (EI): *m/z* calcd for $C_{11}H_{10}N_2O_5$: 250.0590; found: 250.0596.

1-Hydroxy-6-nitro-2-(trifluoromethyl)indole (4g)

Yellow crystals, mp 113–115 °C. ^{1}H NMR [500 MHz, $(CD_3)_2CO$]: δ = 7.12 (dq, *J* = 1.2, 1.0 Hz, 1 H), 7.95 (d, *J* = 8.8 Hz, 1 H), 8.04 (dd, *J* = 8.8, 2.1 Hz, 1 H), 8.45 (br d, *J* = 2.1 Hz, 1 H), 11.39 (s, 1 H). ^{13}C NMR [125 MHz, $(CD_3)_2CO$]: δ = 101.16 (q, *J* = 3.4 Hz), 106.79, 116.41, 120.96 (q, *J* = 268.4 Hz), 124.10, 126.48, 130.06 (q, *J* = 38.9 Hz), 134.87, 146.78. ^{19}F NMR [470 MHz, $(CD_3)_2CO$]: δ = –61.83 (d, *J* = 1.2 Hz). IR (KBr): ν = 3245, 1559, 1511, 1338, 1290, 1244, 1173, 1148, 1132, 1040, 827, 729 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 246 (100) [M^+], 245 (23), 230 (60), 227 (13), 226 (41), 200 (32), 199 (12), 184 (42), 183 (35), 164 (12), 163 (17), 157 (10), 152 (20), 144 (15). HRMS (EI): *m/z* calcd for $C_9H_5F_3N_2O_3$: 246.0252; found: 246.0246.

Ethyl 1-Hydroxy-4-nitroindole-2-carboxylate (4h)

Yellow crystals, mp 108–110 °C. ^{1}H NMR [500 MHz, $(CD_3)_2CO$]: δ = 1.41 (t, *J* = 7.4 Hz, 3 H), 4.43 (q, *J* = 7.4 Hz, 2 H), 7.58 (dd, *J* = 8.2, 7.8 Hz, 1 H), 8.03 (br d, *J* = 8.2 Hz, 1 H), 8.19 (br d, *J* = 7.8 Hz, 1 H), 10.89 (br s, 1 H). ^{13}C NMR [125 MHz, $(CD_3)_2CO$]: δ = 13.62, 61.07, 103.83, 114.73, 117.11, 118.71, 124.14, 129.35, 137.49, 141.04, 159.40. IR (KBr): ν = 3259, 1706, 1529, 1334, 1289, 1245, 1147, 1025, 751, 733 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 250 (26) [M^+], 234 (24), 205 (14), 204 (100), 188 (26), 158 (10), 142 (11), 114 (27), 102 (14). HRMS (EI): *m/z* calcd for $C_{11}H_{10}N_2O_5$: 250.0590; found: 250.0587.

1-Hydroxy-4-nitro-2-(trifluoromethyl)indole (4i)

Yellow crystals, mp 159–161 °C. ^{1}H NMR [500 MHz, $(CD_3)_2CO$]: δ = 7.46 (br s, 1 H), 7.63 (dd, *J* = 8.0, 8.0 Hz, 1 H), 8.07 (br d, *J* = 8.0 Hz, 1 H), 8.23 (br d, *J* = 8.0 Hz, 1 H), 11.37 (br s, 1 H). ^{13}C NMR [125 MHz, $(CD_3)_2CO$]): δ = 99.09 (q, *J* = 4.0 Hz), 114.70, 116.95, 118.80, 120.21 (q, *J* = 268.0 Hz), 124.31, 127.70 (q, *J* = 38.4 Hz), 136.97, 141.12. ^{19}F NMR [470 MHz, $(CD_3)_2SO$]: δ = –61.22 s). IR (KBr): ν = 3216, 1556, 1513, 1331, 1289, 1234, 1145, 799, 737 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 246 (100) [M^+], 245 (31), 230 (63)227 (17), 226 (43), 200 (40), 199 (30), 184 (51), 183 (11), 172 (13), 164 (15), 163 (23), 152 (22), 144 (18), 133 (12), 130 (14), 114 (22), 102 (44). HRMS (EI): *m/z* calcd for $C_9H_5F_3N_2O_3$: 246.0252; found: 246.0256.

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(17) **Reaction of Dinitrotoluenes with Diethyl Oxalate – Synthesis of Ethyl 3-(2,4-Dinitrophenyl)-2-hydroxyacrylate (3f′) – Typical Procedure**

2,4-Dinitrotoluene (5, 6.1 g, 33.5 mmol) in DMF (25 mL) was added dropwise to a cooled solution (–22 °C) of diethyl oxalate (23.7 g, 162 mmol) and DBU (12.2 g, 88 mmol) in DMF (100 mL). The reaction mixture was kept at –15 °C for 3 d and then poured into H_2O (150 mL) and acidified with diluted HCl. The product was extracted with EtOAc (3 × 100 mL), washed with H_2O, and dried with Na_2SO_4. After evaporation of the solvent the product was purified chromatographically on silica gel with hexane–EtOAc (4:1, to remove remaining diethyl oxalate – then 2:1); yield 7.25 g (78%); orange solid, mp 78–83 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.43 (t, *J* = 7.1 Hz, 3 H), 4.44 (q, *J* = 7.1 Hz, 2 H), 6.96 (s, 1 H), 7.13 (d, *J* = 1.3 Hz, 1 H), 8.42 (dd, *J* = 8.8, 2.3 Hz, 1 H), 8.52 (d, *J* = 8.8 Hz, 1 H), 9.02 (d, *J* = 2.3, 1 H). ^{13}C NMR (125 MHz, ($CDCl_3$): δ = 14.09, 63.85, 101.10, 120.09, 126.63, 132.68, 134.56, 144.18, 145.84, 147.95, 164.87. IR (KBr): ν = 3410, 3090, 1712, 1660, 1651, 1600, 1592, 1535, 1413, 1351, 1331, 1261, 1012, 864, 836, 773 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{11}H_{10}N_2O_7Na$: 305.0380; found: 305.0387. Compound **3h** was obtained analogously from 2,6-dinitrotoluene.

Ethyl 2,6-Dinitrophenyl-glyoxalate (3h)

Yellow semi-solid; yield 85%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (t, *J* = 7.1 Hz, 3 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 4.72 (s, 2 H), 7.71 (t, *J* = 8.2 Hz, 1 H), 8.25 (d, *J* = 8.2 Hz, 2 H).). ^{13}C NMR (125 MHz, ($CDCl_3$): δ = 13.95, 38.97, 63.25, 124.14, 129.10, 129.41, 150.96, 159.60, 187.10.

(18) For a review on (trifluoromethyl)indoles, see: Muzalevskiy, V. M.; Shastin, A. V.; Balenkova, E. S.; Haufe, G.; Nenajdenko, V. G. *Synthesis* **2009**, 3905.

(19) **Reaction of 2,4-Dinitrotoluene with Ethyl Trifluoroacetate – Synthesis of 1,1,1-Trifluoro-3-(2,4-dinitrophenyl)propan-2-one (3g) – Typical Procedure**

2,4-Dinitrotoluene (**5**, 1.20 g, 6.6 mmol) in DMF (5 mL) was added dropwise to a cooled solution (–22 °C) of ethyl trifluoroacetate (6.55 g, 46 mmol) and DBU (2.54 g, 16.7 mmol) in DMF (15 mL). The reaction mixture was kept at –15 °C for 3 h and then poured into H_2O (100 mL) and acidified with diluted HCl. The product was extracted with EtOAc (3 × 20 mL), washed with H_2O, and dried with Na_2SO_4. After evaporation of the solvent the product was purified chromatographically on silica gel with hexane–EtOAc (2:1); yield 1.74 g (95%); yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.58 (s, 3 H), 7.61 (d, *J* = 8.2 Hz, 1 H), 8.53 (dd, *J* = 8.2, 2.3 Hz, 1 H), 9.07 (d, *J* = 2.3 Hz, 1 H); for hydrate **3g′**: δ = 3.59 (s, 2 H), 7.80 (d, *J* = 8.6 Hz, 1 H), 8.44 (dd, *J* = 8.6, 2.4 Hz, 1 H), 8.77 (d, *J* = 2.4 Hz, 1 H). ^{19}F NMR (470 MHz, $CDCl_3$): δ (hydrate **3g′**) = –78.50, –86.30. ESI-HRMS: *m/z* calcd for $C_9H_4N_2O_5F_3$: 277.0067; found: 277.0064. 1,1,1-Trifluoro-3-(2,6-dinitrophenyl)propan-2-one (**3i**) and its hydrate **3i′** were obtained analogously from 2,6-dinitrotoluene and ethyl trifluoroacetate.

1,1,1-Trifluoro-3-(2,6-dinitrophenyl)propan-2-one (3i) and Hydrate 3i′

Yellow oil. For **3i**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.61 (s, 2 H), 7.78 (t, *J* = 8.3 Hz, 1 H), 8.33 (d, *J* = 8.3 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.90, 115.42 (q, *J* = 292.5 Hz), 122.00, 129.51, 130.12, 150.84, 185.24 (q, *J* = 37.2 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ = –78.27. MS (FD): *m/z* = 278 [M^+].

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(22) GC analysis of the reaction mixture revealed the presence of a peak that matched the peak of phenylglyoxal standard.
(23) **Dehydroxylation of 1-Hydroxyindoles – General Procedure**

To a solution of 1-hydroxynitroindole (1 mmol) and α-bromoacetophenone (1 mmol) in MeOH (5 mL) Et_3N (0.23 g, 2.3 mmol) was added in one portion at r.t. The reaction mixture was stirred for 3 h (TLC control). Then the reaction mixture was evaporated under vacuum, and the residue was chromatographed on silica gel with EtOAc–hexane (2:1). The following compounds were obtained.

2-Methyl-6-nitroindole (8a)

Yellow crystals, mp 116–118 °C (lit.[24] 118–119 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.52 (s, 3 H), 6.34 (s, 1 H), 7.51 (d, *J* = 8.6 Hz, 1 H), 7.98 (dd, *J* = 8.6, 1.8 Hz, 1 H) 8.26 (d, *J* = 1.8 Hz, 1 H), 8.45 (br s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.99, 101.77, 107.22, 115.47, 119.13, 134.31, 134.45, 142.14, 142.22. MS (EI, 70 eV): *m/z* (%) = 176 (100) [M^+], 146 (35), 130 (58), 118 (13), 103 (44). HRMS (EI): *m/z* calcd for $C_9H_8N_2O_2$: 176.0586; found: 176.0589.

2-*tert*-Butyl-6-nitroindole (8b)

Yellow crystals; mp 125–127 °C. ^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 1.39 (s, 9 H), 6.40 (dd, *J* = 2.0, 0.8 Hz, 1 H), 7.59 (d, *J* = 8.7 Hz, 1 H), 7.87 (dd, *J* = 8.7, 2.0 Hz, 1 H), 8.23 (br d, *J* = 2.0 Hz, 1 H), 11.71 (s, 1 H). ^{13}C NMR [125 MHz, $(CD_3)_2SO$]: δ = 29.67, 32.16, 97.47, 107.24, 114.13, 119.29, 133.20, 134.53, 141.03, 156.61. MS (EI, 70 eV): *m/z* (%) = 218 (48) [M^+], 203 (100), 173 94), 158 (12), 157 (47), 142 (5), 130 (5), 129 (4), 128 (5). HRMS (EI): *m/z* calcd for $C_{12}H_{14}N_2O_2$: 218.1055; found: 218.1059.

6-Nitro-2-phenylindole (8c)

Orange crystals, mp 213–215 °C (lit.[24] 214–216 °C). ^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 7.42–7.47 (m, 1 H), 7.52–7.57 (m, 2 H), 7.72 (d, *J* = 8.7 Hz, 1 H), 7.92 (dd, *J* = 8.7, 2.2 Hz, 1 H), 7.93–7.97 (m, 2 H), 8.31 (d, *J* = 2.2 Hz, 1 H), 12.34 (s, 1 H). ^{13}C NMR [125 MHz, $(CD_3)_2SO$]: δ = 99.82, 107.76, 114.78, 120.09, 125.74, 128.92, 129.14, 130.82, 133.67, 135.44, 141.88, 144.15. MS (EI, 70 eV): *m/z* (%) = 238 (100) [M^+], 208 (29), 192 (36), 191 (27), 190 (14), 165 (22). HRMS (EI): *m/z* calcd for $C_{14}H_{10}N_2O_2$: 238.0742; found: 238.0743.

2-(4-Chlorophenyl)-6-nitroindole (8d)

Orange crystals, mp >280 °C (lit.[25] 260–261 °C). ^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 7.15 (br s, 1 H), 7.57–7.61 (m, 2 H), 7.71 (d, *J* = 8.9 Hz, 1 H), 7.89 (dd, *J* = 8.9, 2.0 Hz, 1 H), 7.92–7.96 (m, 2 H), 8.27 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR [125 MHz, $(CD_3)_2SO$]: δ = 100.35, 107.82, 114.85, 120.29, 127.41, 129.18, 129.73, 133.43, 133.54, 135.52, 142.10, 142.82. MS (EI, 70 eV): *m/z* (%) = 274 (33) [M^+ + 2], 272 (100) [M^+], 244 (9), 242 (29), 228 (11), 226 (32), 214 (7), 199 (7), 191 (39), 190 (31), 164 (8), 163 (10). HRMS (EI): *m/z* calcd for $C_{14}H_9{}^{35}ClN_2O_2$: 272.0353; found: 272.0350.

2-(4-Methoxyphenyl)-6-nitroindole (8e)

Yellow crystals, mp 235–237 °C (lit.[26] 233–234 °C). ^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 3.83 (s, 3 H), 7.00 (s, 1 H), 7.07–7.11 (m, 2 H), 7.65 (d, *J* = 8.7 Hz, 1 H), 7.85–7.89 (m, 2 H), 7.89 (dd, *J* = 8.7, 2.1 Hz, 1 H), 8.25 (d, *J* = 2.1 Hz, 1 H), 12.21 (s, 1 H). ^{13}C NMR [125 MHz, $(CD_3)_2SO$]: δ = 55.30, 98.64, 107.49, 114.60, 114.82, 119.55, 123.35, 127.26, 134.02, 135.28, 141.42, 144.47, 159.93. MS (EI, 70 eV): *m/z* (%) = 268 (100) [M^+], 253 (6), 252 (5), 238 (20), 222 (35), 207 (19), 191 (9), 179 (6), 178 (11), 152 (8). HRMS (EI): *m/z* calcd for $C_{15}H_{12}N_2O_3$: 268.0848; found: 268.0841.

Ethyl 6-Nitroindole-2-carboxylate (8f)

Orange crystals, mp 193–195 °C (lit.[27] 195–197 °C). ^{1}H NMR [500 MHz, $(CD_3)_2CO$]: δ = 1.39 (t, *J* = 7.0 Hz, 3 H), 4.42 (q, *J* = 7.0 Hz, 2 H), 7.32 (s, 1 H), 7.90 (d, *J* = 8.8 Hz, 1 H), 7.99 (dd, *J* = 8.8, 2.2 Hz, 1 H), 8.48 (br s, 1 H), 11.58 (br s, 1 H). ^{13}C NMR [125 MHz, $(CD_3)_2CO$]: δ = 13.66, 61.09, 107.65, 109.06, 114.99, 122.79, 131.76, 133.11, 135.71, 145.20, 160.55. MS (EI, 70 eV): *m/z* (%) = 234 (95) [M^+], 206 (5), 189 (22), 188 (100), 143 (11), 142 (32), 130 (13). HRMS (EI): *m/z* calcd for $C_{11}H_{10}N_2O_4$: 234.0641; found: 234.0645.

6-Nitro-2-(trifluoromethyl)indole (8g)

Yellow crystals, mp 143–145 °C. ^{1}H NMR [500 MHz, $(CD_3)_2CO$]: δ = 7.22 (dq, *J* = 1.0, 0.9 Hz, 1 H), 7.94 (d, *J* = 8.7 Hz, 1 H), 8.05 (dd, *J* = 8.7, 2.1 Hz, 1 H), 8.47 (ddd, *J* = 2.1, 0.8, 0.8 Hz, 1 H), 12.06 (br s, 1 H).^{19}F NMR (470 MHz, $[CD_3)_2CO$]: δ = –61.80 (d, *J* = 2.4 Hz). MS (EI, 70 eV): *m/z* (%) = 230 (100) [M^+], 214 (7), 211 (11), 200 (27), 184 (71), 172 (13), 164 (913), 157 (17), 152 (13), 137 (12). HRMS (EI): *m/z* calcd for $C_9H_5N_2O_2F_3$: 230.0303; found: 230.0300.

Ethyl 4-Nitroindole-2-carboxylate (8h)

Yellow solid, mp 224–226 °C (lit.[28] 227–229 °C). ^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 1.39 (t, *J* = 7.1 Hz, 3 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 7.50 (dd, *J* = 8.0, 8.0 Hz, 1 H), 7.95 (br d, *J* = 8.0 Hz, 1 H), 8.15 (br d, *J* = 8.0 Hz, 1 H), 12.77 (br s, 1 H). ^{13}C NMR [(125 MHz, $(CD_3)_2SO$]: δ = 14.15, 61.13, 106.31, 118.36, 119.87, 120.59, 123.77, 131.23, 138.88, 141.42, 160.59. MS (EI, 70 eV): *m/z* (%) = 234 (85) [M^+], 206 (5), 189 (24), 188 (100), 158 (14), 143 (13), 142 (36), 130 (12), 115 (14), 114 (47). HRMS (EI): *m/z* calcd for $C_{11}H_{10}N_2O_4$: 234.0641; found: 234.0643.

4-Nitro-2-(trifluoromethyl)indole (8i)

Yellow crystals, mp 219–221 °C. ^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 7.50 (dq, *J* = 0.9, 0.8 Hz, 1 H), 7.55 (dd, *J* = 8.2, 7.9 Hz, 1 H), 8.01 (ddd, *J* = 8.2, 0.8, 0.8 Hz, 1 H), 8.20 (dd, *J* = 7.9, 0.8 Hz, 1 H), 13.25 (s, 1 H). ^{13}C NMR [125 MHz, $(CD_3)_2SO$]: δ = 102.39 (q, *J* = 3.4 Hz), 118.48, 119.20, 120.49, 120.81 (q, *J* = 268.5 Hz), 123.81, 128.82 (q, *J* = 38.6 Hz), 138.41, 140.41. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –54.86 (d, *J* = 1.1 Hz). MS (EI, 70 eV): *m/z* (%) = 230 (100) [M^+], 211 (11), 200 (21), 184 (71), 172 (19), 164 (11), 157 (15), 152 (15), 144 (17), 137 (11). HRMS (EI): *m/z* calcd for $C_9H_5F_3N_2O_2$: 230.0303; found: 230.0297.

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