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A new synthesis of 2-nitroindoles

Jun Jiang and Gordon W. Gribble*

Department of Chemistry, Dartmouth College, Hanover, NH 03755, USA

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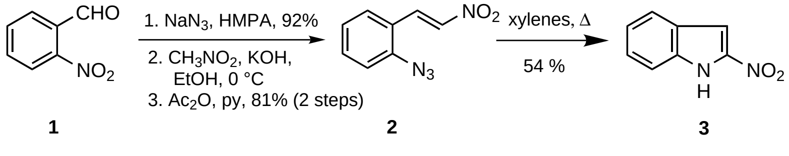
Abstract—The C-2 lithiation of *N*-Boc- and *N*-(phenylsulfonyl)indoles (**4**–**7**) followed by reaction with dinitrogen tetroxide at low temperature affords the corresponding 2-nitroindoles **10**–**13** in 63–78% yields. Deprotection of the *N*-Boc-2-nitroindoles (**10**, **11**) with trifluoroacetic acid gives 2-nitroindole (**3**) and 3-methyl-2-nitroindole (**14**) in essentially quantitative yields. © 2002 Elsevier Science Ltd. All rights reserved.

Both 2- and 3-nitroindoles have provided novel routes to pyrrolo[2,3-*b*]indoles and pyrrolo[3,4-*b*]indoles, via both the Barton–Zard pyrrole synthesis[1] and Münchnone cycloaddition reactions.[2] Moreover, these electron-deficient indoles undergo both nucleophilic addition reactions[3] and normal Diels–Alder cycloaddition reactions.[4] Whereas 3-nitroindoles are easily prepared by nitration of *N*-protected indoles,[5] the synthesis of 2-nitroindoles (**3**), which were essentially unknown when we began our investigations, require a four-step synthesis from 2-nitrobenzaldehyde (**1**) (Scheme 1).[6] Furthermore, an intermediate, *o*-azido-β-nitrostyrene (**2**), in this synthesis is a powerful skin and eye irritant, not unlike 'pepper spray' ('CS', *o*-chlorobenzalmalonitrile). In addition, we found that for best results the carcinogenic solvent HMPA was necessary in this synthesis. Recently, an *ipso*-nitration reaction of 2-stannylindoles to make 2-nitroindoles was reported, but with only moderate yields (30–48%).[7]

To circumvent these problems, we now describe a direct lithiation–nitration sequence from the readily available *N*-protected indoles[8] (Scheme 2). Thus, using Eaton's method,[9] C-2 lithiation of indoles **4**–**7** followed by adding dinitrogen tetroxide (N_2O_4) onto the frozen reaction mixture and then a facile melt-and-react process affords the corresponding 2-nitroindoles **10**–**13** in good yields. [10] Our results are summarized in Table 1.

This method is superior in the nitration of 2-lithioindoles to other obvious electrophilic nitration reagents such as nitronium triflate,[15] nitronium boron tetrafluoride, acetyl nitrate or pivaloyl nitrate. These reactions always resulted in either recovered starting materials or 2-acylindoles, and a similar observation was described before in other systems.[16] Low temperature (−120°C) is necessary to maximize the yields by reducing the possible oxidation of 2-lithioindoles to C-2 radicals by N_2O_4.

The *N*-Boc or phenylsulfonyl protecting groups are necessary in this reaction not only in directing metalation at the C-2 position but also in stabilizing the indole ring from the powerful oxidative property of N_2O_4. For example, both 1-methylindole (**8**) and indole are decomposed by treating with N_2O_4 on the melting surface of their THF solutions to give an intractable mixture. This could explain why the attempted N_2O_4 nitrations of lithioindoles **8** and **9** were unsuccessful and led to decomposition.



Scheme 1.

Keywords: N_2O_4; 2-lithioindoles; nitration; 2-nitroindoles; dinitrogen tetroxide.

* Corresponding author. Tel.: 1-603-646-3118; fax: 1-603-646-3946; e-mail: grib@dartmouth.edu

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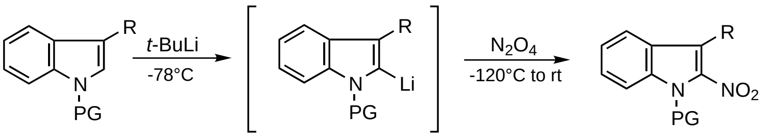


4-9 **10-13**

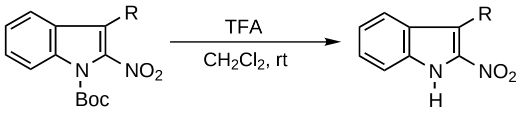
Scheme 2.

Table 1. Synthesis of 2-nitroindoles **10**–**13** from **4**–**7**

Indole	PG	R	Product	Yield (%)
4	Boc	H	**10**	78
5	Boc	CH_3	**11**[11]	74
6	$PhSO_2$	H	**12**[12]	67
7	$PhSO_2$	CH_3	**13**[13]	63
8	Me	H	–	0
9	CO_2Li[a]	H	–	0

[a] This was generated by bubbling CO_2 into 1-lithioindole (known as Katritzky's method).[14]

Although the synthesis of 2-nitroindole (**3**) via Katritzky's method[14] was unsuccessful, **3** was readily made by deprotection of its *N*-Boc derivative **10** in almost quantitative yield.[17] Thus, we have synthesized 2-nitroindole (**3**) from indole in three steps in 76% overall yield (compared to our previous four-step synthesis in 40% yield). The known 3-methyl-2-nitroindole[6,19] (**14**), whose prior synthesis was not practical, was also made in a similar way[18] with an overall yield of 74% (Scheme 3).



10 R=H
11 R=CH₃

3 R=H (98%)
14 R=CH₃ (100%)

Scheme 3.

Acknowledgements

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8. Compounds **4** and **5** were made in quantitative yields by stirring indole or 3-methylindole (100 mmol) with di-*t*-butyl-dicarbonate (100 mmol) and 4-dimethylaminopyridine (DMAP, 0.5 mmol) in THF (200 mL) for 12 h. Removal of solvent and drying under vacuum of the resulting oil gave pure sample which was used without further purification.
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10. Compound **10** (general procedure for 2-nitration): To a –78°C stirred solution of **4** (4.0 mmol) in dry THF under nitrogen was added *t*-butyllithium (4.4 mmol) dropwise and the mixture was stirred at –78°C for 1 h before it was frozen by external liquid nitrogen. Liquid N_2O_4 (1.6 g, 17 mmol, condensed from commercial cylinder) was allowed to evaporate slowly and condensed onto the frozen surface of the reaction mixture. Liquid nitrogen bath was removed and the reaction mixture was allowed to melt and warm up to rt over 45 min before it was poured into aqueous $NaHCO_3$ and extracted by ethyl acetate. The organic phase was dried (Na_2SO_4) and purified by flash chromatography to give yellowish solid **10** (3.13 mmol, 78%) mp 98–99°C, IR (KBr) ν_{max} 1747, 1512, 1446, 1296, 1159 cm^{-1}; UV (EtOH) λ_{max} 216, 326 nm; ^1H NMR ($CDCl_3$) δ 8.07 (m, 1H), 7.69 (m, 1H), 7.56 (m, 1H), 7.37 (m, 2H), 1.62 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 148.0, 137.0, 129.5, 124.9, 124.7, 123.7, 114.9, 111.4, 86.6, 27.8 ppm. MS *m*/*z* 262 (M^+), 162, 57 (100%); HRMS *m*/*z* calcd for $C_{13}H_{14}N_2O_4$ (M^+): 262.0955; found: 262.0955. Anal. calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.24; H, 5.36; N, 10.73.
11. Compound **11**: mp 63.5–65°C, IR (KBr) ν_{max} 1748, 1517, 1447, 1372, 1156 cm^{-1}; UV (EtOH) λ_{max} 220, 328 nm; ^1H NMR ($CDCl_3$) δ 8.06 (m, 1H), 7.64 (m, 1H), 7.55 (m, 1H), 7.36 (m, 2H), 2.52 (s, 3H), 1.60 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 148.2, 135.8, 129.6, 126.8, 124.2, 121.9, 121.7, 114.9, 86.1, 27.8, 9.8 ppm. MS *m*/*z* 276 (M^+), 176, 57 (100%); HRMS *m*/*z* calcd for $C_{14}H_{16}N_2O_4$ (M^+): 276.1110; found: 276.1108. Anal. calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.74; H, 5.82; N, 10.20.

12. Compound **12**: mp 167.5–169°C (lit.[6] 157–160°C); NMR data is identical to the literature values.[6]
13. Compound **13**: mp 154.5–156°C, IR (KBr) v_{max} 1506, 1367, 1180, 944 cm^{-1}; UV (EtOH) λ_{max} 207, 318 nm; ^{1}H NMR ($CDCl_3$) δ 8.09 (m, 1H), 7.95 (m, 2H), 7.58 (m, 4H), 7.50 (m, 2H), 7.38 (m, 1H), 2.45 (s, 3H), ppm; ^{13}C NMR ($CDCl_3$) δ 137.4, 136.4, 134.5, 129.8, 129.2, 128.1, 127.5, 125.3, 124.5, 122.1, 116.3, 9.92 ppm. MS m/z 316 (M^+, 100%), 300, 175, 141, 77; HRMS m/z calcd for $C_{15}H_{12}N_2O_4S$ (M^+): 316.0518; found: 316.0519. Anal. calcd for $C_{15}H_{12}N_2O_4S$: C, 56.95; H, 3.82; N, 8.86, S, 10.13. Found: C, 57.10; H, 3.89; N, 9.04; S, 10.14.
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17. Compound **3** (general procedure for *N*-Boc deprotection): To a rt stirred solution of **10** (1.00 mmol) in CH_2Cl_2 (20 mL) was added trifluoroacetic acid (0.5 mL) and the mixture was stirred at rt for 48 h. The solvent and acid was removed under reduced pressure to gave an TLC and NMR pure compound. Flash chromatography gave pure **3** (0.98 mmol, 98%): mp 115–116.5°C, (lit.[6] 116–118°C), NMR data identical to the literature.[6]
18. Compound **14**: mp 139–140°C, (lit.[19] 140–141.5°C); NMR data is identical to the literature values[19]
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