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A convenient synthesis of 2-nitroindoles

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Abstract—The reaction of 2-iodo- and 2-bromoindoles with silver nitrite in aqueous acetone affords the corresponding 2-nitroindoles in modest to good yields.

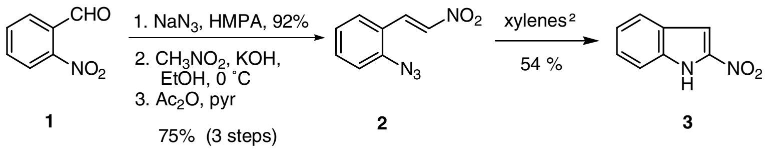
Both 2- and 3-nitroindoles are important building blocks for the synthesis of pyrrolo[2,3-*b*]indoles and pyrrolo[3,4-*b*]indoles, via the Barton–Zard pyrrole synthesis[1] and 1,3-dipolar cycloaddition reactions with mesoionic münchnones.[2] These electron-deficient indoles also undergo normal–demand Diels–Alder reactions leading to carbazoles[3] and nucleophilic addition reactions.[4]

Whereas 3-nitroindoles are readily obtained by standard electrophilic nitration of *N*-protected indoles,[5] the synthesis of 2-nitroindoles is less straightforward. Indeed, 2-nitroindole was an unknown compound when we began our work in this area.[6]

Our original synthesis of 2-nitroindoles involved a four-step sequence from 2-nitrobenzaldehyde (**1**) (Scheme 1).[6] Unfortunately, the carcinogenic solvent HMPA is necessary for best results in the reaction of **1** with sodium azide, and the intermediate 2-azido-β-nitrostyrene (**2**) is a powerful skin and eye irritant not unlike 'pepper spray' ('CS', 2-chlorobenzalmalonitrile). Thermolysis of **2** in xylenes gives 2-nitroindole (**3**) in 54% yield. Quintard and co-workers have reported the *ipso*-nitration of 2-stannylindoles to afford 2-nitroindoles in moderate yields (30–48%).[7] In an alternative approach to 2-nitroindoles, we found that C-2 lithiated indoles **5** can be quenched with dinitrogen tetroxide (N_2O_4) to give 2-nitroindoles **6** in 63–78% yields (Scheme 2).[8] This 'melt-and-react' process is technically difficult to perform and dinitrogen tetroxide is a very expensive gas. Other potential sources of NO_2^+ failed to yield 2-nitroindoles.

Prompted by an early report on the conversion of 2-bromofurans to 2-nitrofurans with silver nitrite,[9] we now describe a new synthesis of 2-nitroindoles using silver nitrite that avoids the above problems. Thus, the reaction of 2-haloindoles with silver nitrite in aqueous acetone gives the corresponding 2-nitroindoles in variable yield (Scheme 3 and Table 1).[10] The products obtained are highly pure and the recovered starting materials can be recovered and reused.

The reaction works best for *N*-ethoxycarbonyl-substituted indoles **7** and **11**, but less well for the more



Scheme 1.

Keywords: 2-Nitroindole; Silver nitrite; 2-Haloindoles.

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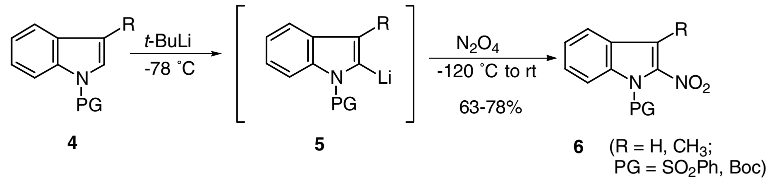
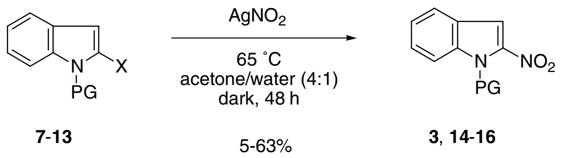


Scheme 2.



Scheme 3.

Table 1. Synthesis of 2-nitroindoles from 2-haloindoles with silver nitrite

2-Haloindole	X	PG	Product	Yield (%)
7	I	CO_2Et	**14**[10]	52[a]
8	I	SO_2Ph	**15**[11]	10[b]
9	I	Me	**16**[12]	5[c]
10	I	Boc	**3**[13]	57[c]
11	Br	CO_2Et	**14**	63[d]
12	Br	SO_2Ph	**15**	5[e]
13	Br	Boc	—	0[c]

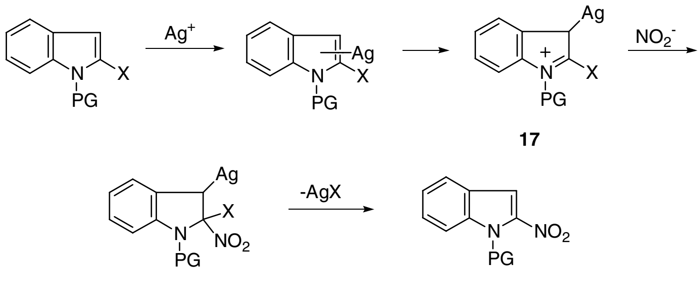
[a] 33% of **7** was recovered.
[b] 80% of **8** was recovered.
[c] No starting material was recovered.
[d] 20% of **11** was recovered.
[e] 80% of **12** was recovered.

electron-withdrawing *N*-phenylsulfonyl-substituted indoles **8** and **12**. The *N*-Boc-substituted 2-iodoindole **10** gives *N*-deprotected 2-nitroindole (**3**) in 57% yield, representing a superior synthesis of 2-nitroindole. The reaction of 2-iodo-1-methylindole (**9**) affords only a low yield of 1-methyl-2-nitroindole (**16**) because of the extreme instability of this particular 2-iodoindole. Likewise, attempted reaction of *N*-Boc-2-bromoindole **13** under the usual conditions leads to decomposition of labile 2-bromoindole. The *N*-ethoxycarbonyl group possesses the ideal blend of providing stability for the 2-haloindole and reactivity for the replacement reaction.[14] The reaction of 3-bromo- and 3-iodoindoles with silver nitrite does not give the corresponding 3-nitroindoles and starting materials are recovered. Likewise, the reactions of **8** with both sodium nitrite in place of silver nitrite and sodium nitrite/silver nitrate return only starting material. Likewise, there was no reaction of **8** with silver cyanide.

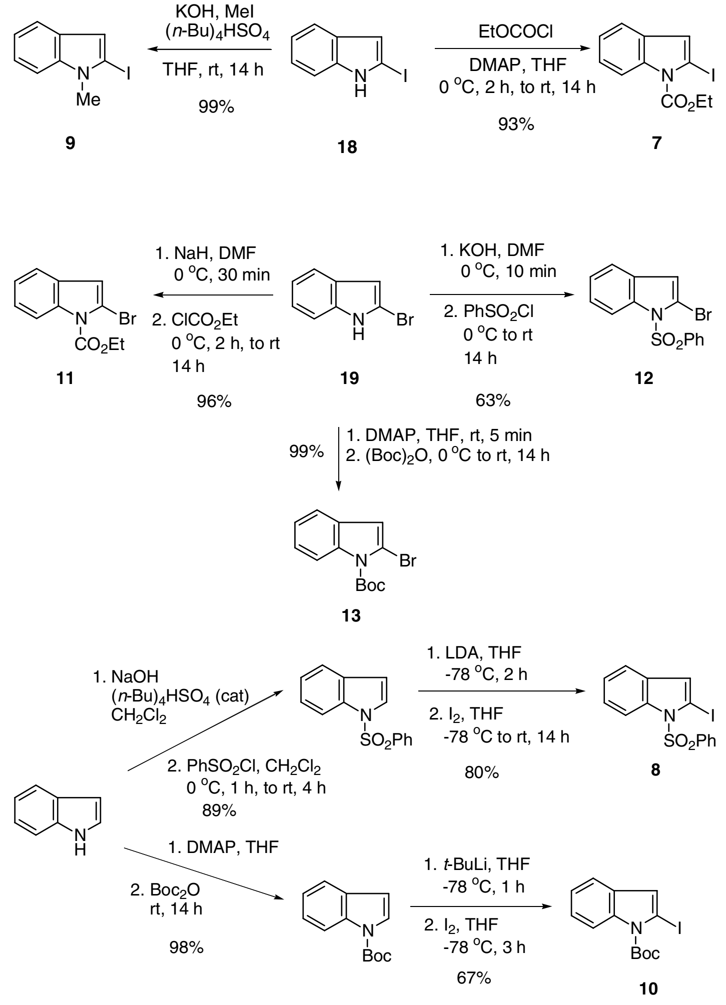
A possible mechanism for this reaction is shown in Scheme 4. Initial π-complexation is followed by formation of the C-3 silver σ-complex **17**. Addition of nitrite to C-2 and loss of silver halide affords the 2-nitroindole. Some related chemistry is worth noting. The formation of 1-nitroisoquinoline from the reaction of isoquinoline with acetic anhydride, DMSO, and potassium nitrite has been reported,[15] and the reaction of 3-iodoindole with silver acetate in acetic acid affords indoxyl acetate.[16] The use of silver(I) to induce cyclizations of amino allenes and amino alkynes to form nitrogen heterocycles has been described,[17] and the silver(I)-induced rearrangements of strained sigma bonds is well known.[18] Noteworthy is that a pyrrole iminium ion analogous to **17** has been proposed recently.[17f] Moreover, silver nitrite in aqueous acetone converts primary alkyl halides to nitroalkanes.[19]

The requisite 2-haloindoles **7**–**13** were prepared as summarized in Scheme 5.[20] All are known compounds except 2-bromo-1-ethoxycarbonylindole (**11**). The excellent Katritzky–Bergman method for synthesizing 2-iodoindole (**18**) and 2-bromoindole (**19**)[21] was used to prepare **7**, **9**, **11**–**13**, and 2-haloindoles **8** and **10** were synthesized from the corresponding *N*-protected indoles.

In summary, 2-nitroindoles **3** and **14** are conveniently synthesized from suitable 2-haloindoles (**7**, **10**, and **11**) by reaction with silver nitrite in aqueous acetone.



Scheme 4.



Scheme 5.

Acknowledgements

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10. Compound **14**: To a stirred solution of **7** (315 mg, 1.00 mmol) in 4:1 acetone–water (20 mL) was added silver nitrite (923 mg, 6.00 mmol). The mixture was stirred in the dark for 48 h at 65 °C. Ether (30 mL) was added, the solution was filtered to remove insoluble material, and the filtrate was washed with water. The organic phase was dried (Na_2SO_4) and the residue was purified by flash column chromatography (4:1 hexanes–ethyl acetate) to yield **14** (122 mg, 52%) as a yellow solid: mp 47–49 °C (lit.[2b] mp 55–57 °C); ^1H NMR ($CDCl_3$) δ 8.05–8.03 (m, 1H), 7.70–7.68 (m, 1H), 7.58–7.55 (m, 1H), 7.43 (s, 1H), 7.38–7.35 (m, 1H), 4.50 (q, 2H, $J = 7$ Hz), 1.43 (t, 3H, $J = 7$ Hz). During column chromatography, 33% (104 mg) of the starting material was also recovered, which eluted before the product.

11. Compound **15**: mp 158–159 °C (lit.[6] mp 157–160 °C); ^{1}H NMR ($CDCl_3$) δ 8.19–8.17 (m, 1H), 8.09–8.07 (m, 2H), 7.69–7.66 (m, 2H), 7.63–7.56 (m, 3H), 7.45 (d, 1H, $J = 0.7$ Hz), 7.41–7.38 (m, 1H).
12. Compound **16**: mp 105–107 °C; NMR data is identical to the literature values.[7b]
13. Compound **3**: To a stirred solution of **10** (344 mg, 1.00 mmol) in 4:1 acetone–water (20 mL) was added silver nitrite (923 mg, 6.00 mmol). The mixture was stirred in the dark for 48 h at 65 °C. Ether (30 mL) was added, the solution was filtered to remove insoluble material, and the filtrate was washed with water. The organic phase was dried (Na_2SO_4) and the residue was purified by flash column chromatography (3:1 hexanes–ethyl acetate) to yield **3** (92 mg, 57%) as a yellow solid: mp 116–118 °C (lit.[6] mp 116–118 °C); ^{1}H NMR ($CDCl_3$) δ 9.27 (br s, 1H), 7.77–7.73 (m, 1H), 7.51–7.44 (m, 3H), 7.29–7.23 (m, 1H).
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20. Compound **7**: mp 65.5–66.5 °C (lit. mp 65–67 °C: Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312–2313). Compound **8**: mp 95–97 °C (lit. mp 96–98 °C: Ketcha, D. M.; Lieurance, B. A.; Homan, D. F. J.; Gribble, G. W. *J. Org. Chem.* **1989**, *54*, 4350–4356). Compound **9**: mp 75–77 °C (lit. mp 76–77 °C: Bergman, J.; Eklund, N. *Tetrahedron* **1980**, *36*, 1439–1443). Compound **10**: Colorless oil (lit. oil: Kline, T. *J. Heterocycl. Chem.* **1985**, *22*, 505–509); ^{1}H NMR ($CDCl_3$): δ 8.15–8.13 (m, 1H), 7.49–7.48 (m, 1H), 7.29–7.21 (m, 2H), 7.02 (s, 1H), 1.77 (s, 9H); LRMS (EI): *m*/*z* 343 (M^+), 287, 243, 217, 161, 117, 89, 57 (100%); HRMS (EI): Anal. Calcd for $C_{13}H_{14}NO_2I$: 343.0069. Found 343.0064. Compound **11**: mp 33–34 °C; ^{1}H NMR ($CDCl_3$): δ 8.14–8.11 (m, 1H), 7.53–7.49 (m, 1H), 7.37–7.24 (m, 2H), 6.80 (s, 1H), 4.59 (q, 2H, $J = 7.1$ Hz), 1.56 (t, 3H, $J = 7.1$ Hz); LRMS (EI): *m*/*z* 267 (M^+), 210, 195 (100%), 116, 89; HRMS (EI): Anal. Calcd for $C_{11}H_{10}NO_2Br$: 266.9895. Found: 266.9896; Anal. Calcd for $C_{11}H_{10}NO_2Br$: C, 49.90; H, 3.83; N, 5.33, Br, 28.11. Found: C, 49.28; H, 3.76; N, 5.22; Br, 29.80. Compound **12**: mp 50–51 °C (lit. mp 62–64 °C: Ketcha, D. M.; Lieurance, B. A.; Homan, D. F. J.; Gribble, G. W. *J. Org. Chem.* **1989**, *54*, 4350–4356). Compound **13**: reddish oil (lit. no data reported: Fiumana, A.; Jones, K. *Chem. Commun.* **1999**, 1761–1762); ^{1}H NMR ($CDCl_3$): δ 8.13 (d, 1H, $J = 8.3$ Hz), 7.52–7.49 (m, 1H), 7.35–7.23 (m, 2H), 6.78 (s, 1H), 1.75 (s, 9H); LRMS (EI): *m*/*z* 295 (M^+), 195 (100%), 115, 77; HRMS (EI): Anal. Calcd for $C_{13}H_{14}NO_2Br$: 295.0208. Found: 295.0201.
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