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Nucleophilic amination of 2-iodo-3-nitro-1-(phenylsulfonyl)indole

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Abstract—The reaction of 2-iodo-3-nitro-1-(phenylsulfonyl)indole (**2**) with amines affords the corresponding 2-amino-3-nitroindoles in excellent yields via nucleophilic aromatic substitution.

Indoles and fused indoles that contain a nitrogen atom at C-2 both occur naturally and are potential useful synthetic intermediates for pharmacologically important compounds.[1,2] For example, the anticholinesterase alkaloid physostigmine has a long and rich history and clinical utility,[1a] the structurally related bromine-containing flustramine marine indoles continue to be of interest,[1b] the novel pyrrolo[2,3-*b*]indole alkaloids pyrroindomycins A and B have powerful antibiotic activity against drug-resistant bacteria,[1c] and other natural products embodied with a C-2 nitrogen are known.[1d,e] Certain synthetic 2-aminoindole derivatives are both anti-hypertensive agents and potent inhibitors of blood platelet aggregation and thromboxane synthetase,[2a] pyrimidino[1,2-*a*]indoles are 5HT4-receptor antagonists,[2b] and indolo[2,1-*d*][1,2,3,5]tetrazines are used for the treatment of melanoma, mycosis fungoides, and brain tumors.[2c,d] Whereas the π-excessive indole ring readily reacts with electrophiles at C-3,[3] it is much less prone to undergo reaction with nucleophiles,[4] and C-2 substitution is especially difficult, except for metalation techniques such as α-lithiation[5] and α-palladation[6] followed by the addition of electrophiles. For example, Witulski et al. have recently reported a palladium catalyzed synthesis of 3-substituted 2-aminoindoles by a heteroannulation reaction.[7]

Traditional syntheses of 2-aminoindoles and protected derivatives include reductive cyclization of (2-nitrophenyl)acetonitriles,[8] reaction of indoles with arylsulfonyl azides,[9] amination of 2-indolinethiones,[10] Curtius degradation of indole-2-carboxylic acid azides,[11] cyclization of 1-aryl-2-acylhydrazines[12] and 1-arylamino-1-acylhydrazones,[13] and heating *N*-methyloxindole with hexamethylphosphoramide.[14] In addition, we recently reported the reductive acylation of 2-(and 3-)nitroindoles.[15]

Despite these known routes to 2-aminoindoles, their extreme sensitivity to oxidation[16] has thwarted more direct syntheses and studies of simple 2-aminoindoles. Moreover, the obvious S_NAr nucleophilic displacement of an activated C-2 haloindole has only been reported a few times,[1c,2a,17] although such displacements are well known with other π-excessive heterocycles.[18–22]

Our earlier work demonstrating nucleophilic addition reactions of 2- and 3-nitroindoles[23] suggested that an S_NAr displacement reaction with 2-halo-3-nitroindoles would offer a simple route to 2-amino-3-nitroindoles. Indeed, we now report that 2-iodo-3-nitro-1-(phenylsulfonyl)indole (**2**) undergoes a S_NAr reaction with secondary amines to give the corresponding 2-amino-3-nitroindoles. Initially, we treated the previously unknown 2-iodo-3-nitro-1-(phenylsulfonyl)indole (**2**) with dimethylamine (40 wt % solution in water). To our delight, the desired C-2 substituted product **3** was obtained in excellent yield (Scheme 1).[24,25] Compound **2** is very reactive toward this S_NAr reaction under mild conditions, as no heat or external base is necessary. However, reactions of **2** with sodium azide, ammonia (both in methanol and dioxane), and phenol in the presence of triethyl amine were unsuccessful. Nitroindole **2** is conveniently prepared in gram amounts in 78% yield by the nitration of 2-iodoindole **1**[26] with acetyl nitrate (3.5 equiv) at 0° C.[23b,27]

Likewise, treatment of **2** with diethylamine gives aminoindole **4**[28] in 76% yield, and dibenzylamine affords **5**[29] in

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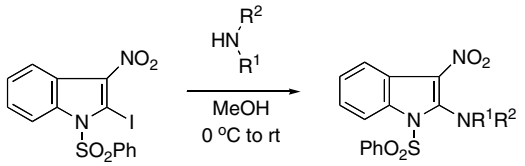

2

3 (R^1, R^2 = Me; 90%)
4 (R^1, R^2 = Et; 76%)
5 (R^1, R^2 = Bn; 91%)
6 (R^1, R^2 = -$(CH_2)_4$-; 83%)
7 (R^1, R^2 = -$(CH_2)_5$-; 81%)
8 (R^1, R^2 = -$(CH_2)_2O(CH_2)_2$-; 96%)
9 (R^1, R^2 = -$(CH_2)_2N(CH_3)(CH_2)_2$-; 80%)
10 (R^1 = H, R^2 = cyclohexyl; 43%)

Scheme 1.

91% yield under the same reaction conditions. Reaction of **2** with pyrrolidine gives 2-pyrrolidinylindole **6**[30] in very high yield, and a similar reaction with piperidine furnishes **7**[31] in 81% yield. Morpholine and *N*-methylpiperazine also provide the expected 2-aminoindoles **8**[32] and **9**,[33] respectively. However, treatment of **2** with cyclohexylamine under the usual conditions gives 2-aminoindole **10**[34] only in 43% yield (Scheme 1).

In summary, we have described a S_NAr reaction on the readily available 2-iodo-3-nitroindole **2** that gives 2-amino-3-nitroindoles in good to excellent yields. This route should provide a simple and versatile entry to a wide variety of C-2, C-3 difunctionalized indoles and related polycyclic systems, and we are pursuing these ideas.

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24. *Representative procedure*: To a stirred suspension of **2** (0.2 mmol) in methanol (1.5 mL) at 0 °C was added dropwise the corresponding amine (0.6 mmol). The mixture was stirred at rt for 3 h and then poured into ice-cold water (30 mL) and extracted with ethyl acetate (2×25 mL). The combined organic extract was washed with brine and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column chromatography on silica gel to yield the desired product.
25. *N,N-Dimethyl-3-nitro-(1-phenylsulfonyl)-1H-indol-2-amine* (**3**): mp 110–112 °C; ^{1}H NMR (acetone-d_6): δ 8.09–8.11 (m, 1H), 7.87–7.89 (m, 1H), 7.63–7.69 (m, 3H), 7.51–7.54 (m, 2H), 7.38–7.43 (m, 2H), 3.13 (s, 3H); ^{13}C NMR (acetone-d_6): δ 152.2, 137.1, 135.8, 132.4, 130.4, 128.1, 127.4, 126.3, 125.7, 120.4, 118.2, 44.6; LRMS (EI): *m*/*z* 345 (M^+), 300, 204 (100%), 157, 144, 131, 117, 77; HRMS (EI): calcd for $C_{16}H_{15}N_3O_4S$: 345.0783, found: 345.0782.
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27. *2-Iodo-3-nitro-1-(phenylsulfonyl)indole* (**2**): mp 197–199 °C; ^{1}H NMR ($CDCl_3$): δ 8.46 (d, 1H, $J = 7.6$ Hz), 8.21 (d, 1H, $J = 8.5$ Hz), 8.02 (d, 2H, $J = 7.6$ Hz), 7.68 (t, 1H, $J = 7.6$ Hz), 7.55 (t, 2H, $J = 7.9$ Hz), 7.44–7.48 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 135.4, 129.8, 127.9, 127.3, 126.0, 120.8, 115.7; LRMS (EI): *m*/*z* 428 (M^+), 271, 141, 77 (100%); HRMS (EI): calcd for $C_{14}H_9IN_2O_4S$: 427.9328, found: 427.9331.
28. *N,N-Diethyl-3-nitro-(1-phenylsulfonyl)-1H-indol-2-amine* (**4**): mp 104–106 °C; ^{1}H NMR (acetone-d_6): δ 8.03–8.05 (m, 1H), 7.87–7.89 (m, 1H), 7.62–7.66 (m, 3H), 7.48–7.52 (m, 2H), 7.33–7.36 (m, 2H), 3.64 (m, 4H), 1.17–1.20 (m, 6H); ^{13}C NMR (acetone-d_6): δ 150.9, 137.5, 135.7, 132.5, 130.4, 127.9, 127.2, 126.1, 125.6, 120.4, 117.9, 49.2, 13.4; LRMS (EI): *m*/*z* 373 (M^+), 328, 232, 198, 187, 171, 144 (100%), 130, 117, 77; HRMS (EI): calcd for $C_{18}H_{19}N_3O_4S$: 373.1096, found: 373.1095.
29. *3-Nitro-2-[bis(phenylmethyl)amino]-(1-phenylsulfonyl)-1H-indole* (**5**): mp 171–173 °C; ^{1}H NMR (DMSO-d_6): δ 7.80 (d, 1H, $J = 7.6$ Hz), 7.71 (d, 1H, $J = 7.9$ Hz), 7.56 (t, 1H, $J = 7.3$ Hz), 7.32–7.37 (m, 14H), 7.24–7.27 (m, 1H), 7.19–7.22 (m, 1H), 4.76 (s, 4H); ^{13}C NMR (DMSO-d_6): δ 149.5, 135.8, 135.7, 134.9, 130.7, 129.5, 129.2, 128.5, 128.1, 126.5, 126.4, 125.1, 124.1, 121.5, 119.3, 116.3, 58.5; LRMS (EI): *m*/*z* 497 (M^+), 392. 356, 310, 235, 219, 105, 91 (100%), 77; HRMS (EI): calcd for $C_{28}H_{23}N_3O_4S$: 497.1409, found: 497.1402.
30. *3-Nitro-(1-phenylsulfonyl)-2-(1-pyrrolidinyl)-1H-indole* (**6**): mp 109–111 °C; ^{1}H NMR (acetone-d_6): δ 8.05–8.07 (m, 1H), 7.85–7.88 (m, 1H), 7.64–7.67 (m, 1H), 7.60–7.62 (m, 2H), 7.49–7.52 (m, 2H), 7.35–7.40 (m, 2H), 3.57–3.59 (m, 4H), 2.07–2.10 (m, 4H); ^{13}C NMR (acetone-d_6): δ 149.4, 137.1, 135.7, 132.7, 130.6, 130.3, 128.1, 127.4, 126.1, 120.4, 117.9, 54.1, 26.4; LRMS (EI): *m*/*z* 371 (M^+), 326, 288, 230, 213, 185 (100%), 158.143, 130, 117, 77; HRMS (EI): calcd for $C_{18}H_{17}N_3O_4S$: 371.0940, found: 371.0936.
31. *3-Nitro-(1-phenylsulfonyl)-2-(1-piperidinyl)-1H-indole* (**7**): mp 145–147 °C; ^{1}H NMR (acetone-d_6): δ 8.12–8.14 (m, 1H), 7.85–7.87 (m, 1H), 7.64–7.69 (m, 3H), 7.51–7.55 (m, 2H), 7.39–7.43 (m, 2H), 3.40–3.42 (m, 4H), 1.79–1.83 (m, 4H), 1.72 (m, 2H); ^{13}C NMR (acetone-d_6): δ 151.3, 137.5, 135.7, 132.7, 130.4, 127.8, 127.3, 126.4, 125.4, 120.3, 118.0, 54.0, 26.1, 24.4; LRMS (EI): *m*/*z* 385 (M^+), 340, 244 (100%), 224, 199, 144, 115, 77 (100%); HRMS (EI): calcd for $C_{19}H_{19}N_3O_4S$: 385.1096, found: 385.1094.
32. *3-Nitro-2-morpholino-(1-phenylsulfonyl)-1H-indole* (**8**): mp 125–127 °C; ^{1}H NMR (DMSO-d_6): δ 8.04–8.06 (m, 1H), 7.85–7.87 (m, 1H), 7.66–7.70 (m, 1H), 7.60–7.62 (m, 2H), 7.51–7.54 (m, 2H), 7.39–7.45 (m, 2H), 3.78 (t, 4H, $J = 4.6$ Hz); ^{13}C NMR (DMSO-d_6): δ 148.9, 135.7, 135.2, 131.1, 130.2, 129.8, 127.0, 126.7, 126.0, 123.5, 122.7, 120.7, 119.4, 116.7, 65.7, 51.6; LRMS (EI): *m*/*z* 387 (M^+), 342, 246 (100%), 201, 144, 77; HRMS (EI): calcd for $C_{18}H_{17}N_3O_5S$: 387.0889, found: 387.0888.
33. *3-Nitro-2-(4-methyl-1-piperazinyl)-(1-phenylsulfonyl)-1H-indole* (**9**): oil; ^{1}H NMR (DMSO-d_6): δ 8.03 (d, 1H, $J = 7.0$ Hz), 7.82–7.84 (m, 1H), 7.77–7.69 (m, 1H), 7.57 (d, 2H, $J = 7.3$ Hz), 7.52 (t, 2H, $J = 7.6$ Hz), 7.38–7.43 (m, 2H), 3.41 (s, 8H), 2.31 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 149.3, 135.2, 131.1, 129.7, 129.4, 127.5, 126.6, 125.8, 119.3, 116.8, 53.8, 51.3, 45.7; LRMS (EI): *m*/*z* 400 (M^+), 383, 368, 288, 258, 240, 229, 214, 141, 99 (100%), 77; HRMS (EI): calcd for $C_{19}H_{20}N_4O_4S$: 400.1205, found: 400.1206.
34. *N-Cyclohexyl-3-nitro-(1-phenylsulfonyl)-1H-indol-2-amine* (**10**): mp 107–109 °C; ^{1}H NMR (DMSO-d_6): δ 8.82 (d, 1H, $J = 9.5$ Hz), 7.86–7.88 (m, 1H), 7.75–7.77 (m, 1H), 7.65–7.68 (m, 1H), 7.60–7.62 (m, 2H), 7.48–7.51 (m, 2H), 7.27–7.33 (m, 2H), 4.11–4.17 (m, 1H), 2.04–2.07 (m, 2H), 1.70–1.73 (m, 2H), 1.48–1.58 (m, 2H), 1.20–1.36 (m, 4H); ^{13}C NMR (DMSO-d_6): δ 151.8, 135.6, 134.2, 131.1, 129.7, 127.0, 124.9, 124.0, 118.8, 116.9, 60.1, 33.0, 24.8, 24.4; LRMS (EI): *m*/*z* 399 (M^+), 368, 354, 258 (100%), 176, 143, 77; HRMS (EI): calcd for $C_{20}H_{21}N_3O_4S$: 399.1253, found: 399.1246.