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CONVENIENT SYNTHESIS OF MASKED AMINOINDOLES BY INDIUM MEDIATED ONE-POT REDUCTIVE ACYLATION OF 3- AND 2-NITROINDOLES †

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Abstract – Unstable 3- and 2-aminoindoles are generated *in situ* by indium mediated reduction of 3- and 2-nitroindoles and capped as the stable amides (or carbamate) in moderate to high yields under mild conditions in a one-pot procedure.

As a class of indoles, both 3- and 2-aminoindoles are virtually unexplored as novel heterocyclic enamines. They could be useful precursors for the other important classes of indoles and novel fused heterocycles. 1-Methyl-3-aminoindole, generated *in situ* by deacetylation of 1-methyl-3-acetylaminoindole, has been shown to react with 1,3-dicarbonyl compounds in an easy one-pot process to yield δ-carbolines.[1] These δ-carbolines were subsequently used to synthesize annelated pyridoindole NADH models. In these syntheses, 3-acetylaminoindoles were prepared via the Beckmann rearrangement of the corresponding oximes which in turn were made from the 3-acetylindoles.[1-2] In fact, efficient synthesis of 3-aminoindoles are scarce due to their known instability.[3] Kurilo and co-workers had reported the synthesis of 3-acetylaminoindoles from 2-carbethoxyindoles. In their synthesis, the diazo coupling of 2-carbethoxyindoles with benzene diazonium chloride gave 2-carbethoxy-3-phenylazoindoles which were treated with Zn and acetic acid in the presence of acetic anhydride to produce 2-carbethoxy-3-acetamidoindoles. Basic hydrolysis of 2-carbethoxy-3-acetamidoindoles followed by thermal decarboxylation of carboxylic acid gave 3-acetylaminoindoles.[3] Recently, an *N*-substituted-3-acetylaminoindole was tested as a potential inhibitor against type 2 diabetes; however, the synthesis of 3-acetylaminoindole was not described.[4]

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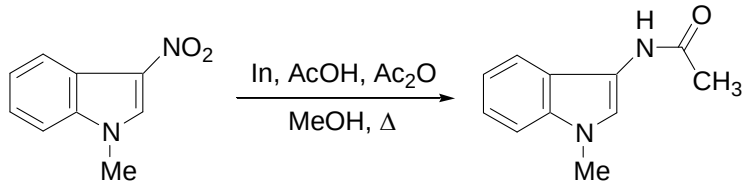
† Dedicated to Professor Steven M. Weinreb in celebration of his 65th birthday and his many outstanding contributions to synthetic organic chemistry.

Our research group has long been interested in the synthesis of the 3- and 2-aminoindoles. Since we have already reported several synthesis of 3- and 2-nitroindoles from indole,[5,6] the reduction of these nitroindoles would be the straightforward way to furnish the corresponding aminoindoles. In this direction, we have made several attempts (H_2, 10% Pd-C/ EtOH;[7] $Na_2S_2O_4$;[8] In, NH_4Cl/EtOH[9]) to reduce nitroindoles to the corresponding amines, but without success. Due to this lack of success to obtain free aminoindoles and because of the known instability of the aminoindoles, we decided to protect the amino group of the aminoindoles by acylation *in situ* as they form in the reaction.

In an initial study, inspired by the reported indium mediated conversion of nitroarenes to *N*-arylacetamides,[10] 1-methyl-3-nitroindole **(1)** was treated with indium in the presence of acetic acid and acetic anhydride in methanol. To our delight, the desired acetamide **(2)** was obtained in excellent yield **(Scheme 1)**.[11] Compound **(2)** is stable and can be stored indefinitely, but can be readily converted *in situ* to the 3-aminoindole by methanolic HCl when required for the reaction.[1]

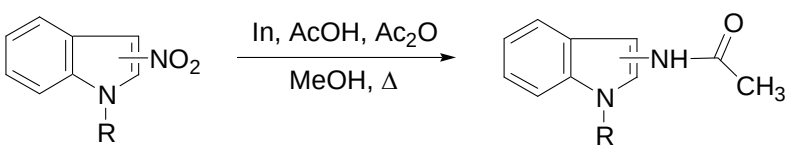


1 **2** (88%)

Scheme 1.

We have chosen to use indium as a reducing agent because it is a non-toxic metal and highly suitable for green chemistry processes. Moreover, it does not readily form oxides when exposed to air and most importantly, it is insensitive to moisture which provides greater operational simplicity in the indium mediated reaction.[12]

After this initial success, we subjected different *N*-protected 3-nitroindoles **(3-5)** to the same reaction conditions (**Scheme 2**). To our satisfaction, the corresponding protected amines **(9-11)** were obtained in good to excellent yield from the corresponding 3-nitroindoles **(Table 1)**.[13] Also, (*NH)*-free nitroindole **(6)** furnished the desired product **(12)** in excellent yield.[14] However, lower yields of **(13)** and **(14)** were obtained from 2-nitroindoles **(7)** and **(8)**, respectively.[15]



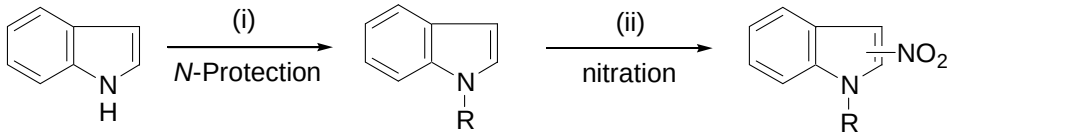
3-8 **9-14**

Scheme 2.

Table 1. Synthesis of acetylaminoindoles **(9-14)** from nitroindoles **(3-8)** with In, AcOH, Ac_2O.

Entry	Nitroindole	R	Product	Yield
3	3-NO_2	Bn	**9**	86%
4	3-NO_2	SO_2Ph	**10**	68%
5	3-NO_2	Boc	**11**	71%
6	3-NO_2	H	**12**	82%
7	2-NO_2	SO_2Ph	**13**	30%
8	2-NO_2	Boc	**14**	33%

The required nitroindoles for reduction were prepared from indole by *N*-protection followed by nitration **(Scheme 3)**.[16] The parent 3-nitroindole **(6)** was prepared from 3-nitro-1-(phenylsulfonyl)indole **(4)** by deprotection with 10% ethanolic NaOH solution in 71% yield.

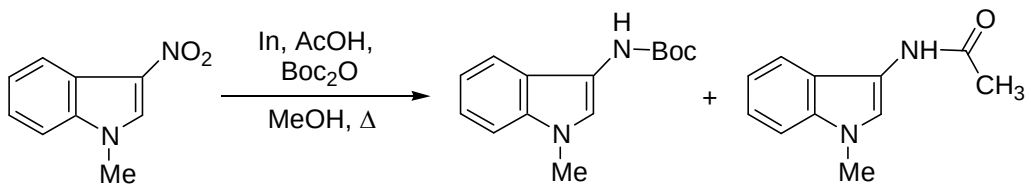


15 (R = Me, 90%)
16 (R = Bn, 80%)
17 (R = SO_2Ph, 89%)
18 (R = Boc, 98%)

1 (3-NO_2, R = Me, 38%)
3 (3-NO_2, R = Bn, 71%)
4 (3-NO_2, R = SO_2Ph, 83%)
5 (3-NO_2, R = Boc, 70%)
7 (2-NO_2, R = SO_2Ph, 51%)
8 (2-NO_2, R = Boc, 60%)

Scheme 3. i) for **15**: KOH, MeI, THF; for **16**: NaH, BnBr, DMF; for **17**: Boc_2O, DMAP (cat), THF; for **18**: NaOH, *n*-Bu_4HSO_4 (cat), $PhSO_2Cl$, CH_2Cl_2.
ii) for **1, 3-5**: $AcONO_2$ (from Ac_2O and HNO_3); for **7-8**: *t*-BuLi, N_2O_4.

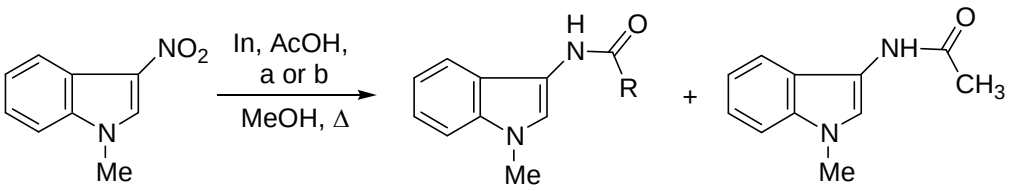
Reduction of 1-methyl-3-nitroindole **(1)** by indium in acetic acid in the presence of Boc-anhydride furnished the Boc-protected amine **(19)** in 66% yield.[17] A small amount of compound **2** (16%) was obtained as a byproduct in this reaction **(Scheme 4)**.



1 **19** (66%) **2** (16%)

Scheme 4.

Similarly, in the presence of hexanoic and benzoic anhydrides, 1-methyl-3-nitroindole **(1)** furnished the corresponding amides **(20)** and **(21) (Scheme 5)**.[18] In both cases, *N*-acetylaminoindole **(2)** was also obtained as a byproduct.



1

a) Hexanoic anhydride : (R=C_5H_{11}) **20** (75%) **2** (12%)
b) Benzoic anhydride : (R= Ph) **21** (56%) **2** (41%)

Scheme 5.

In conclusion, we have described a method to reduce 3- and 2-nitroindoles to the corresponding *N*-acylated aminoindoles. The desired products are obtained in moderate to excellent yield. The chemistry involving these aminoindoles is ongoing in our laboratory and will be reported in due course.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. C. Papamicaël, G. Quéguiner, J. Bourguignon, and G. Dupas, *Tetrahedron*, 2001, **57**, 5385.
2. F. M. Albini, R. Oberti, and P. Caramella, *J. Chem. Res. (M)*, 1983, 147.
3. G. N. Kurilo, O. N. Boyarintseva, and A. N. Grinev, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1975, 579; V. S. Velezheva, A. V. Yarosh, T. A. Kozik, and N. N. Suvorov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1978, 1217; V. S. Velezheva, A. V. Yarosh, T. A. Kozik, and N. N. Suvorov, *J. Org. Chem. USSR (Engl. Transl.)*, 1978, 1596.
4. F. Lehmann, S. Haile, E. Axen, C. Medina, J. Uppenberg, S. Svensson, T. Lundbaeck, L. Rondahl, and T. Barf, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4445.
5. E. T. Pelkey and G. W.Gribble, *Synthesis*, 1999, 1117.
6. S. Roy and G. W. Gribble, *Tetrahedron Lett.*, 2005, **46**, 1325; J. Jiang and G. W. Gribble, *Tetrahedron Lett.*, 2002, **43**, 4115; E. T. Pelkey and G. W. Gribble, *Tetrahedron Lett.*, 1997, **38**, 5603.
7. D. L. Boger and H. Zarrinmayeh, *J. Org. Chem.*, 1990, **55**, 1379; M. G. Ferlin, B.Gatto, G. Chiarelotto, and M. Palumbo, *Bioorg. Med. Chem.*, 2000, **8**, 1415; P. A. Ple, T. P.Green, L. F.

Hennequin, J. Curwen, M. Fennell, J. Allen, C. Lambert, and G. Costello, *J. Med. Chem.*, 2004, **47**, 871; Y. K. Yee, P. R. Bernstein, E. J. Adams, F. J. Brown, L. A. Cronk, K. C. Hebbel, E. P. Vacek, R. D. Krell, and D. W. Snyder, *J. Med. Chem.*, 1990, **33**, 2437.

8. R. A. Scheuerman and D. Tumelty, *Tetrahedron Lett.*, 2000, **41**, 6531.
9. M. R. Pitts, J. R. Harrison, and C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 2001, 955; C. J. Moody and M. R. Pitts, *Synlett*, 1998, 1028.
10. B. H. Kim, R. Han, F. Piao, Y. M. Jun, W. Baik, and B. M. Lee, *Tetrahedron Lett.*, 2003, **44**, 77.
11. **Representative Procedure: Compound (2):** AcOH (0.17 mL, 3 mmol) was added to a mixture of In powder (172 mg, 1.5 mmol), 1-methyl-3-nitroindole (53 mg, 0.3 mmol) and Ac_2O (77 mg, 0.75 mmol) in MeOH (1.5 mL). The reaction mixture was stirred at rt for 2 h and then at 45 ^oC for 5 min. The progress of the reaction was monitored by TLC. The reaction mixture was cooled, poured into saturated aqueous $NaHCO_3$ solution and extracted with AcOEt (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The solid residue was purified by flash column chromatography (hexanes : AcOEt = 1:3) to give the desired product (50 mg, 88%) as white crystals: mp 189-191 ^oC (lit.,[2] 191-192 ^oC); ^1H NMR (DMSO-d_6) δ 9.87 (br s, 1H), 7.81-7.79 (m, 1H), 7.72 (s, 1H), 7.37 (d, 1H, *J* = 8 Hz), 7.18-7.13 (m, 1H), 7.06-7.00 (m, 1H), 3.73 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.8, 133.8, 121.5, 120.5, 119.4, 118.1, 118.0, 114.6, 109.4, 32.3, 23.0.
12. C. J. Li and T. H. Chan, 'Organic Reactions in Aqueous Media' Wiley-Interscience, New York, 1997; C. J. Li, *Tetrahedron*, 1996, **52**, 5643; A. Lubineau, J. Augé, and Y. Queneau *Synthesis*, 1993, 741.
13. **Compound (9):** mp 174-175 ^oC; ^1H NMR (DMSO-d_6) δ 9.94 (s, 1H), 7.89 (s, 1H), 7.83 (d, 1H, *J* = 7.9 Hz), 7.42 (d, 1H, *J* = 8.2 Hz), 7.28 (t, 2H, *J* = 7.5 Hz), 7.21-7.24 (m, 1H), 7.17 (d, 2H, *J* = 7.3 Hz), 7.12 (t, 1H, *J* = 7.6 Hz), 7.03 (t, 1H, *J* = 7.5 Hz), 5.37 (s, 2H), 2.11 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.9, 138.4, 133.3, 128.5, 127.3, 127.0, 121.8, 120.7, 118.6, 118.3, 118.2, 115.2, 109.9, 109.3, 48.9, 23.0; LRMS (EI) *m*/*z* 264 (M^+), 221, 149, 131, 91 (100%); HRMS (EI) calcd for $C_{17}H_{16}N_2O$: 264.1263, found: 264.1256. **Compound (10):** mp 218-220 ^oC; ^1H NMR (DMSO-d_6) δ 10.24 (br s, 1H), 8.11 (s, 1H), 7.98 (d, 1H, *J* = 8.2 Hz), 7.93 (d, 1H, *J* = 7.9 Hz), 7.89-7.87 (m, 2H), 7.67-7.64 (m, 1H), 7.57-7.54 (m, 2H), 7.42-7.39 (m, 1H), 7.33-7.30 (m, 1H), 2.14 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 168.4, 136.7, 134.5, 132.4, 129.8, 126.5, 125.7, 124.5, 123.4, 122.0, 119.3, 113.4, 113.3, 23.1; LRMS (EI) *m*/*z* 314 (M^+), 173, 131 (100%), 103, 77; HRMS (EI) calcd for $C_{16}H_{14}N_2O_3S$: 314.0725, found: 314.0727. **Compound (11):** mp 163-165 ^oC; ^1H NMR (DMSO-d_6) δ 10.11 (brs, 1H), 8.09-8.06 (m, 2H), 7.96 (d, 1H, *J* = 7.8 Hz), 7.38-7.25 (m, 2H), 2.15 (s, 3H), 1.60 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 168.0, 149.2, 132.5, 124.9, 124.0, 122.3, 119.7, 118.6, 114.7, 113.3,

83.4, 27.7, 23.0; LRMS (EI) *m*/*z* 274 (M^+), 218, 174, 132 (100%), 103, 77; HRMS (EI) calcd for $C_{15}H_{18}N_2O_3$: 274.1317, found: 274. 1320.

14. **Compound (12):** mp 159-161 °C (lit.[3] 162-163 °C); ^{1}H NMR (acetone-d_6) δ 10.05 (br s, 1H), 9.32 (br s, 1H), 7.90 (d, 1H, *J* = 2.4 Hz), 7.74 (d, 1H, *J* = 8.1 Hz), 7.38 (d, 1H, *J* = 8.3 Hz), 7.13-7.10 (m, 1H), 7.02-6.99 (m, 1H), 2.17 (s, 3H); ^{13}C NMR (acetone-d_6) δ 168.1, 135.0, 122.6, 121.7, 119.3, 118.2, 116.7, 116.1, 112.2, 23.3.
15. **Compound (13):** oil; ^{1}H NMR ($CDCl_3$) 8.09 (br s, 1H), 7.83-7.80 (m, 1H), 7.60-7.40 (m, 5H), 7.31-7.26 (m, 1H), 7.19-7.16 (m, 2H), 3.74 (s, 3H). **Compound (14):** mp 132-134 °C**;** ^{1}H NMR ($CDCl_3$) δ 10.65 (s, 1H), 7.85 (d, 1H, *J* = 8.2 Hz), 7.46-7.47 (m, 1H), 7.16-7.23 (m, 3H), 2.26 (s, 3H), 1.74 (s, 9H); LRMS (EI) *m*/*z* 274 (M^+), 218, 174, 132 (100%); HRMS (EI) calcd for $C_{15}H_{18}N_2O_3$: 274.1318, found: 274. 1320.
16. All compounds were characterized and NMR data are identical to the literature values.[5,6]
17. **Compound (19):** mp 96-98 °C**;** ^{1}H NMR ($CDCl_3$) δ 7.50 (d, 1H, *J* = 7.8 Hz), 7.42 (s, 1H), 7.24-7.31 (m, 2H), 7.13 (t, 1H, *J* = 7.4 Hz), 6.54 (br s, 1H), 3.75 (s, 3H), 1.58 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 153.7, 134.8, 122.1, 121.3, 119.2, 118.8, 116.9, 114.0, 109.4, 80.3, 32.8, 28.6; LRMS (EI) *m*/*z* 246 (M^+), 190 (100%), 173, 146, 131, 103, 77; HRMS (EI) calcd for $C_{14}H_{18}N_2O_2$: 246.1368, found: 246.1373.
18. **Compound (20):** mp 91-93 °C**;** ^{1}H NMR ($CDCl_3$) δ 7.74 (br s, 1H), 7.69 (s, 1H), 7.56 (d, 1H, *J* = 7.8 Hz), 7.24-7.31 (m, 2H), 7.09-7.12 (m, 1H), 3.72 (s, 3H), 2.44 (t, 2H, *J* = 7.6 Hz), 1.75-1.81 (m, 2H), 1.36-1.39 (m, 2H), 0.93 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 171.1, 134.5, 122.2, 121.1, 120.6, 118.9, 116.9, 113.7, 109.5, 37.1, 32.8, 31.7, 25.8, 22.6, 14.1; LRMS (EI) *m*/*z* 244 (M^+), 191, 146 (100%); HRMS (EI) calcd for $C_{15}H_{20}N_2O$: 244.1576, found: 244.1571. **Compound (21):** mp 159-161 °C; ^{1}H NMR ($CDCl_3$) δ 8.16 (brs, 1H), 7.93-7.95 (m, 2H), 7.84 (s, 1H), 7.61 (d, 1H, *J* = 7.9 Hz), 7.54-7.57 (m, 1H), 7.47-7.51 (m, 2H), 7.34 (d, 1H, *J* = 8.2 Hz), 7.27-7.30 (m, 1H), 7.14-7.17 (m, 1H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.0, 134.8, 134.6, 131.7, 128.9, 127.2, 122.3, 121.1, 120.8, 119.1, 116.8, 113.8, 109.7, 32.9; LRMS (EI) *m*/*z* 250 (M^+), 244, 145 (100%), 105, 77; HRMS (EI) calcd for $C_{16}H_{14}N_2O$: 250.1106, found: 250.1110.