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SYNTHESIS OF 4-SUBSTITUTED INDOLES FROM o-NITROTOLUENES

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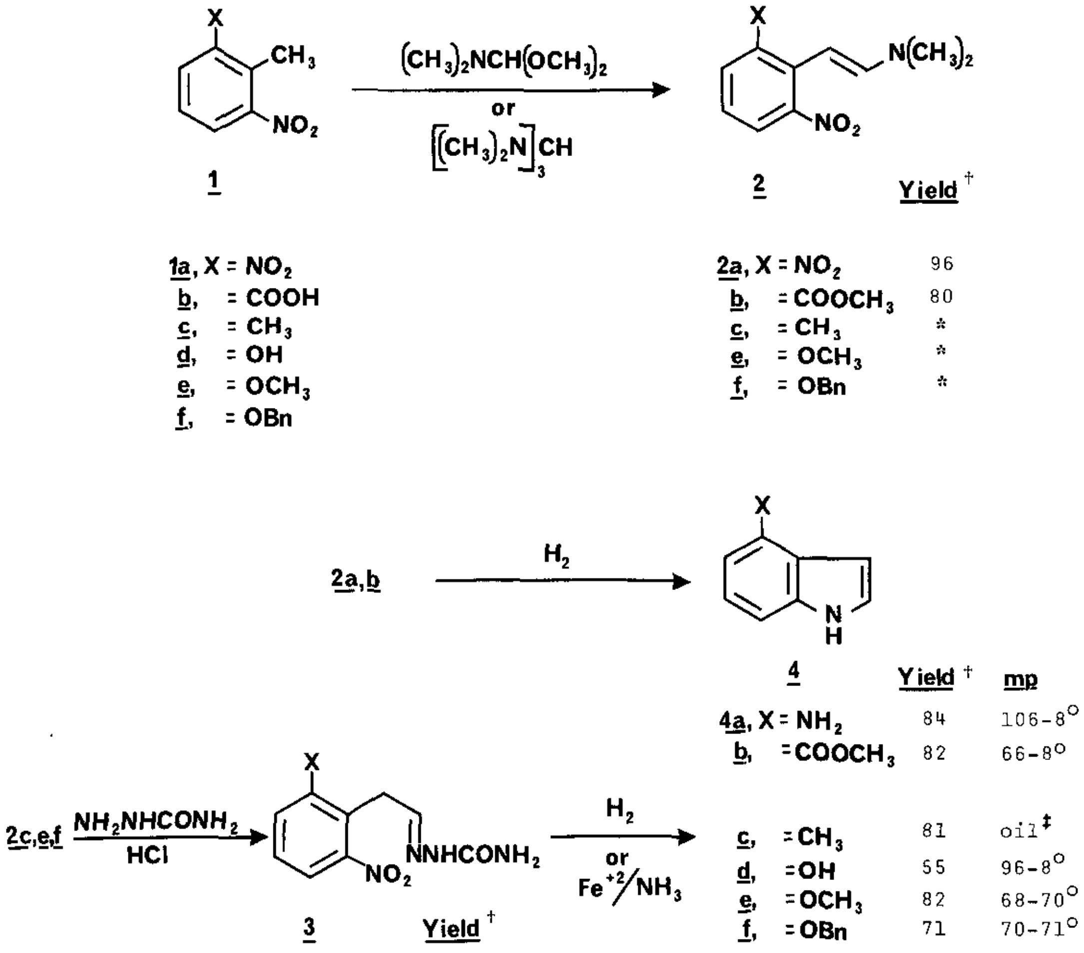
Abstract - A facile two- or three-step transformation of o-nitrotoluenes into 4-substituted indoles is described. Treatment of o-nitrotoluenes 1 with DMF acetal, or sometimes more advantageously with tris(N,N-dimethylamino)methane, affords β-(N,N-dimethylamino)styrenes 2 which are readily converted to o-nitrophenylacetaldehyde semicarbazones 3 without isolation. Reduction of either 2 or 3 affords 4-substituted indoles 4. Use of the very insoluble semicarbazones results in vastly superior yields of 4 by minimizing competing bimolecular condensation reactions during reduction. This new procedure has been applied to efficiently and conveniently prepare a series of 4-substituted indoles 4.

A wealth of naturally occurring compounds incorporate an indolic nucleus substituted at the 4 position with carbon (ergot),[1] oxygen (psilocin, psilocybin),[2] or nitrogen (dehydrobufotenine)[3] functional groups. The widespread natural abundance of 4-substituted indoles belies the difficulty of preparing this class of heterocycles by total synthesis.[4] A study of 5-hydroxytryptamine relatives has led to the development of the general method described in this paper for preparing these indoles.

In principle the substitution pattern present in commercially available o-nitrotoluenes makes them potentially useful precursors to indoles; only addition of a suitable one carbon fragment and reductive cyclization are required for conversion. Although this general transformation has been accomplished via the circuitous Reissert procedure,[5] low yields and length severely limit the utility of this sequence. A much more effective route, whose origin is based in the known reaction of nitrotoluenes with DMF acetal,[6] as illustrated in the Scheme, is described in this paper. Condensation of o-nitrotoluenes 1 with DMF acetal or aminal afforded β-dimethylaminostyrenes 2. Subsequent reductive cyclization of 2 or derived semicarbazones 3 gave 4-substituted indoles 4.

SCHEME



1	X
1a	NO$_2$
b	COOH
c	CH$_3$
d	OH
e	OCH$_3$
f	OBn

2	X	Yield†
2a	NO$_2$	96
b	COOCH$_3$	80
c	CH$_3$	*
e	OCH$_3$	*
f	OBn	*

4	X	Yield†	mp
4a	NH$_2$	84	106-8°
b	COOCH$_3$	82	66-8°
c	CH$_3$	81	oil‡
d	OH	55	96-8°
e	OCH$_3$	82	68-70°
f	OBn	71	70-71°

3	X	Yield†
3c	CH$_3$	93
e	OCH$_3$	82
f	OBn	84

* not isolated

† % yields are for isolated, analytically pure compounds

‡ picrate, mp 194-5° (methanol)

In an initial investigation of this pathway as a general route to 4-substituted indoles highly reactive 2,6-dinitrotoluene (1a) was condensed with DMF dimethyl acetal (3 equiv) in DMF (115°,6h) and the resulting (96%) β-dimethylaminostyrene 2a[7] was reduced (60 psi hydrogen, 10% palladium on carbon) in benzene giving 4-aminoindole (4a), mp 106-8°, in 84% yield. Similarly, 2-methyl-3-nitrobenzoic acid (1b) upon reaction with DMF dimethyl acetal (5 equiv) in DMF (115°, 24 h) provided the anticipated methyl ester 2b (80%).[8] Subsequent reduction (60 psi hydrogen, 10% palladium or charcoal) in benzene gave (82%) indole 4b, mp 66-68°, the key intermediate in a synthesis of a tricyclic ergot synthon, Uhles ketone.[9]

Attempts to apply this strategy as a general route to more interesting indoles bearing bulky or deactivating, electron donating groups met with only limited success. The hydroxynitrotoluene 1d rapidly reacted with DMF acetal to give the ether 1e, but conversion to 2e was extremely slow (48 h). In addition, hydrogenation of 2e gave 4-methoxyindole (4e) in erratic yields (22-63%) depending on concentration and the amount of catalyst used. Careful GC/MS analysis of the crude reaction mixture revealed considerable dimeric and trimeric material had formed along with intractable green polymer at the expense of desired indole. This enhanced tendency toward polymerization was generally observed with less reactive β-dimethylaminostyrenes and is possibly due to a slower rate of reduction of the hindered, electron rich nitroaromatic which allows competing condensations of the indole product with reduction intermediates to take place.[10]

After a detailed experimental study, these difficulties were resolved by two pivotal modifications: 1) use of the highly reactive tris(N,N-dimethylamino)-methane[11] which dissociates into a much stronger base (dimethylamide *vs* methoxide formed from DMF acetal) and gives a rapid homologation under mild conditions (typically 1-6 h at 100-110°), 2) reduction of the very insoluble phenylacetaldehyde semicarbazone derivatives 3 prepared *in situ* from the β-dimethylaminostyrenes 2 by treatment with acidic aqueous semicarbazide. Vastly superior yields of indole were obtained by reducing the semicarbazones, a result attributed to the very low solution concentration of starting semicarbazone and reduction intermediates which increases the *effective* catalyst loading ratio and minimizes the polymerization reactions while still using a reasonable amount of catalyst. The preparation of indoles 4c-f (Scheme) clearly demonstrates the utility of this new procedure for synthesizing 4-substituted indoles which have previously been prepared only in low yield or by lengthy routes.[2,4,5] Thus, as illustrated in the experiment, 1c was converted to 3c and reduced (60 psi hydrogen, 10% palladium on carbon, ethanol) to give indole 4c in excellent overall yield. A similar sequence enables the transformation of 1e and 1f (derived from 1d by in situ etherification with methyl iodide or benzyl bromide, respectively) to semicarbazones 3e and 3f. Subsequent catalytic hydrogenation of 3e gave indole 4e. Benzyl ether 3f underwent the expected reductive cyclization and debenzylation to give deprotected indole 4d in reasonable yield. The alternative reduction of 3f with ammoniacal ferrous sulfate[5] readily yields protected indole 4f. This mild chemical reduction complements catalytic hydrogenation as a means for converting 3 to 4 and is easily employed for semicarbazides 3 bearing functional groups sensitive to hydrogenation.

In summary, the ease of preparation and ready availability of these indoles will allow further transformation into naturally occurring materials. This is now underway and will be reported in due course.

Illustrative Experiment: 4-Methoxyindole (4e).

A. 2-Methoxy-6-nitrophenylacetaldehyde semicarbazone (3e).

A 1-l flask equipped with reflux condenser and magnetic stirrer was flushed with argon and charged with 50% sodium hydride dispersion (9.6 g, 0.2 mole). The dispersion was washed with two 100 ml portions of hexane, then suspended in dry DMF (100 ml) during the slow (foaming!) addition of 2-methyl-3-nitrophenol (30.62 g, 0.2 mole). The red solution was cooled, iodomethane (18.6 ml, 0.3 mole) was added rapidly, the solution was heated at 90° in an oil bath for 20 min, and tris(dimethylamino)methane (43.5 g, 0.3 mole) was added followed by heating at 115° for 3 h. The mixture was cooled and a solution of semicarbazide hydrochloride (23.4 g, 0.21 mole) and concentrated hydrochloric acid (18 ml, 0.22 mole) in water (250 ml) was added. The tan mixture was cooled, filtered, and the precipitate was washed sequentially with water (500 ml), ice-cold ethanol (150 ml), and ether (250 ml), then dried to give 41.08g (81.5%) of 3e as tan crystals, mp 205-7°(d).[7]

B. 4-Methoxyindole (4e).

A suspension of semicarbazone 3e (18 g, 0.071 mole) in ethanol (150 ml) was hydrogenated over 10% palladium on carbon (4 g)[13] for 6 h at 60 psi, then filtered and concentrated. The residue was triturated with water (100 ml), filtered and dried. The crude crystalline indole was purified in a sublimation apparatus equipped with a dry-ice cold trap (85°/0.3 mm) and the sublimate was recrystallized from boiling chloroform (30 ml) by the addition of hot hexane (150 ml) giving 8.6 g (82%) of 4-methoxyindole (4e) as pure white crystals, mp 68-70° (lit.[5] 69°).

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Notes and References

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2. A. Hofmann, A. Frey, H. Ott, Th. Petrzilka, and F. Troxler, *Experientia*, 1958, **14**, 397; A. Hofmann, R. Heim, A. Brack, H. Kobel, A. Frey, H. Ott, Th. Petrzilka, and F. Troxler, *Helv. Chim. Acta*, 1959, **42**, 1557.
3. B. Robinson, G. F. Smith, A. H. Jackson, D. Shaw, B. Frydman, and V. Deulofeu, *Proc. Chem. Soc.* (London), 1961, 310; F. Marki, A. V. Robertson, and B. Witkop, *J. Amer. Chem. Soc.*, 1961, **83**, 3341; W. F. Gannon, J. D. Benigni, J. Suzuki, and J. W. Daly, *Tetrahedron Lett.*, 1967, 1531.
4. Various indoles of this type have been prepared by different methods but no efficient, general route to these compounds has been described. For an excellent, if somewhat dated, review of indole syntheses, see R. J. Sundberg, 'The Chemistry of Indoles' in 'Organic Chemistry A Series of Monographs', Vol. 18, ed. A. T. Blomquist, Academic Press, New York, 1970, pp 142-213.
5. K. G. Blaikie and W. H. Perkin, Jr., *J. Chem. Soc.*, 1924, 296.
6. Meerwein first described the condensation of activated nitrotoluenes with amide acetals, H. Meerwein, W. Florian, N. Schön, and G. Stopp, *Ann. Chem.*, 1961, **641**, 1. This homologation was later applied to an elegant synthesis of a few indoles, A. D. Batcho and W. Leimgruber, U. S. Patent 3,976,639(1976), *Chem. Abstr.*, 1977, **86**, 29624t.
7. Compounds were characterized as follows: (2a), deep violet crystals, mp 90-93°; ir (nujol mull) 1630, 1600, 1530, 1400, 1300, cm^{-1}; nmr (CDCl$_3$) δ 2.9 (s, 6H), 5.3 (d, J = 14 Hz, 1H), 6.5 (d, J = 14 Hz, 1H), 7.1 (m, 1 H), 7.65 (d, J = 7 Hz, 2 H); MS *m/e* 237 (M+); (2b), red oil, bp(k) 150-158°/0.4 mm; ir (neat) 1720, 1600, 1530, 1260 cm^{-1}; nmr (CDCl$_3$) δ 2.8 (s, 6 H), 3.8 (s, 3 H), 5.6 (d, J = 14 Hz, 1 H), 6.3 (d, J = 14 Hz, 1 H), 7.02 (t, J = 8 Hz, 1 H), 7.6 (m, 2 H), MS *m/e* 250 (M+); (3c), light yellow crystals, mp 216-7° (d); ir (nujol mull) 3460, 3400-3000, 1700, 1590, 1530, 1140 cm^{-1}; nmr (DMSO-d$_6$) δ 2.3 (s, 3 H), 3.5 (d, J = 4 Hz, 2 H), 5.9 (br s, 3 H, exchanges with D$_2$O), 7.15 (t, J = 5 Hz, 1H), 7.5 (d of t, J = 2 Hz, 5 Hz, 2 H), 9.75 (br s, 1 H); chemical ionization (methane) MS *m/e* 194 (M + H$^+$); (3e), light tan crystals, mp 205-207°

(d); ir (nujol mull) 3500, 3400-3100, 1700, 1600, 1530, 1290 cm^{-1}; nmr (DMSO-d_6) δ 3.8 (d, J = 5 Hz, 2 H), 3.9 (s, 3 H), 5.9 (br s, 3 H, exchanges with D_2O), 7.2-7.6 (br m, 3 H), 9.9 (br s, 1H); MS *m/e* 252 (M^+); (*3f*), white crystals, mp 188-190° (d); ir (nujol mull) 3460, 3300-3000, 1700, 1580, 1540, 1290 cm^{-1}; nmr (DMSO - d_6) δ 3.5 (d, J = 3 Hz, 2 H), 5.05 (s, 2 H), 5.8 (br s, 3 H, exchanges with D_2O), 7.0 - 7.4 (br m, 8 H), 9.8 (br s, 1 H); chemical ionization (methane) MS *m/e* 329 ($M+H^+$).

8. The reaction of carboxylic acids and phenols with DMF acetals is known to give the corresponding ester or ether. See H. Büchi, K. Steen, and A. Eschenmoser, *Angew. Chem. Int. Ed.*, 1964, **3**, 62; H. Vorbrüggen, *ibid.*, 1963, **2**, 211; H. Brechbuhler, H. Büchi, E. Hatz, and A. Eschenmoser, *Helv. Chim. Acta*, 1965, **48**, 1746. Preformed methyl 2-methyl-3-nitrobenzoate also provides 4-carbomethoxyindole when subjected to Leimgruber's original procedure (Reference 6). See G. S. Ponticello and J. J. Baldwin, *J. Org. Chem.*, 1979, **44**, 4003; A. P. Kozikowski, H. Ishida, and Y. Y. Chen, *ibid.*, 1980, **45**, 3350.

9. F. C. Uhle, C. M. McEwan, Jr., H. Schröter, C. Yuan, and B. W. Baker, *J. Am. Chem. Soc.*, 1960, **82**, 1200. For more recent references to this compound, see T. Nagasaka and S. Ohki, *Chem. Pharm. Bull.*, 1977, *11*, 3023.

10. This interpretation is suggested by the known condensation of, e.g., nitrosoaromatics with pyrroles, M. A. T. Rogers, *J. Chem. Soc.*, 1943, 590, 593; and indole, W. Madelung and M. Tencer, *Chem. Ber.*, 1915, **48**, 953, which resembles the well known Ehrlich-Sachs reaction, D. M. W. Anderson and J. L. Duncan, *J. Chem. Soc.*, 1961, 1631 and references therein.

11. For a review of the chemistry of formamide acetals see R. F. Abdulla and R. S. Brinkmeyer, *Tetrahedron*, 1979, **35**, 1675.

12. Recently several other groups have described various new approaches to the synthesis of 4-substituted indoles. See M. Somei, Y. Karasawa, T. Shoda, and C. Kaneko, *Chem. Pharm. Bull.*, 1981, **29**, 249; M. Somei, Y. Karasawa, S. Tokutake, T. Shoda, F. Yamada, and C. Kaneko, *Heterocycles*, 1981, **16**, 139; M. Somei, Y. Karasawa, and C. Kaneko, *Chem. Lett.*, 1980, 813; M. Natsume and H. Muratake, *Tetrahedron. Lett.*, 1979, 3477; M. Somei, F. Yamada, and C. Kaneko, *Chem. Lett.*, 1979, 943; H. Plieninger, E. Meyer, F. Sharif-Nassirian, and E. Weidmann, *Ann. Chem.*, 1976, 1475.

13. A high quality catalyst is essential to the success of the reaction. Aldrich Chemical Company, Inc. catalyst was used.

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