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Convenient Preparation of N-Substituted Indoles by Modified Leimgruber-Batcho Indole Synthesis

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Abstract: *A modified reductive alkylation of pre-indole 3, prepared from readily available Leimgruber-Batcho indole synthesis derived intermediates, followed by acidic methanolysis generates 6-carbomethoxy-N-substituted indoles. The three step preparation of pre-indole 3 from substituted 2-nitrotoluene I in 66% yield and conversion to a variety of N-substituted indoles is presented.* Copyright © 1996 Elsevier Science Ltd

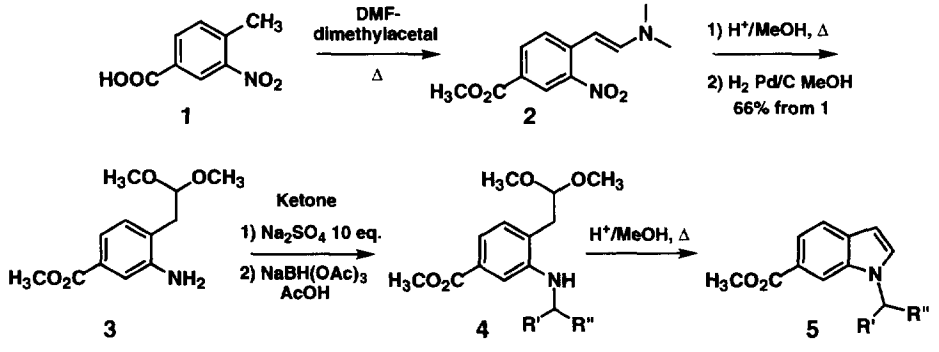
In connection with medicinal chemistry studies we required a flexible and convergent entry into a variety of N-alkylated 6-carboxy indoles. The nitrogen substituents in question were chosen to survey the relationship between 6-carboxy substituents, the indole nucleus and an amine appended at the indole nitrogen in hopes of identifying necessary features for receptor binding. Attachment of the indole N-substituent to a preformed 6-substituted indole ring would be the most efficient route to these analogues. However, the ambident nucleophilic character of the indole ring system precludes simple N-alkylation of indoles lacking C-3 substitution,[1] except for the reaction of primary electrophiles at N-1 under alkylation,[2] Mitsunobu[3] or Michael addition[4] conditions. A limited number of examples have been reported that accomplish alkylation on the indole nitrogen with branched substrates.[5,6] As a result, approaches to N-substituted indoles with branched substituents generally rely on building the indole nucleus after the introduction of the nitrogen substituent.

The most versatile approach of this type has been described by Sugasawa and co-workers,[7] wherein the indole nucleus is generated in two steps after reductive alkylation of anilines with ketones.[7,8] Lewis acid mediated ortho acylation of the substituted aniline with chloroacetonitrile,[7,9] followed by reduction of the resulting ketone and subsequent closure generates the indole nucleus. Early commitment to the N-substituent requires each product to be generated in a multistep process involving Lewis acid-mediated chemistry. This represents a potentially problematic situation in our case with electron withdrawing groups at the pro-6-position of the indole nucleus.[7b] Herein we describe a complementary and convergent method that allows rapid analog preparation by introduction of a variety of N-1 substituents late in a generic indole synthesis.

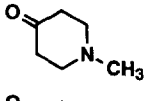
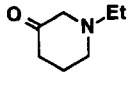
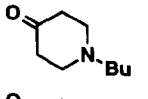
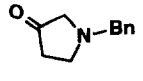
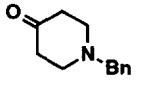
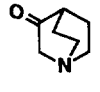
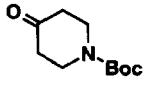
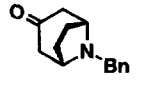
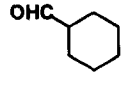
The cornerstone of this approach relies on alkylation of the pre-indole, **3**, prepared by a modified Leimgruber-Batcho indole synthesis. As illustrated below, aniline **3** was prepared from nitrotoluene **1** *via* simultaneous esterification[10] and enamine formation,[11] acetalization[12] and reduction in 66% overall yield.[13]

Reductive alkylation conditions have been successfully applied to anilines,[7a,b] and a general procedure for weakly basic anilines is known.[8c,d] The mild acidic conditions required for imine formation and reduction, however, raised the specter of premature acid catalyzed indole formation and subsequent reduction to indolines which has been observed under similar conditions.[8a] Furthermore, we sought products derived from cyclic tertiary-aminoketones which, as the ammonium salt in AcOH, would resist imine formation and subsequent

reduction. The reaction of **3** with 1-methyl-4-piperidone under the conditions described by Maryanoff[8c] ($NaBH(OAc)_3$/AcOH (6 eq.)/ DCE) produced alkylated aniline **4a**, but did not proceed to completion. Carrying out the reaction with either excess anhydrous sodium sulfate powder (10 eq.) as dehydrating agent or in neat AcOH failed to drive the reaction to completion.[14] Ultimately, the combination of dehydrating agent and AcOH provided the best results, fully consuming aniline **3** with no observed indole formation (**5a**, GCMS). The optimal conditions consisted of aging for 15 min. at room temperature a combination of pre-indole **3** (1 eq.), 1-methyl-4-piperidone (2 eq.) and excess anhydrous sodium sulfate powder (10 eq.) in AcOH (0.2 M) followed by addition of $NaBH(OAc)_3$ (3.0 eq.). These conditions resulted in full consumption of starting aniline **3** and produced **4a** in quantitative yield. Indole **5a** was not detected during the reductive amination step. After workup, indole **5a** was formed in acidic methanol (1N HCl/MeOH, Δ, <1 h) in 96% isolated yield.[15]



Table

	Ketone	yield of 4	yield of 5 (overall yield)		Ketone	yield of 4	yield of 5 (overall yield)
a		96	100% (96%)	f		48	62% (30%)
b		63	45% (28%)	g		–	70% (70%)
c		80	87% (70%)	h		64	54% (35%)
d		—	75% (75%)	i		51	48% (25%) (4/1 α/β)
e		—	67% (67%)	j		—	66% (66%)

The stubborn reactivity of **3** under standard reductive alkylation conditions[8] presumably arises from a combination of steric hindrance and electronic factors[16] which is readily overcome under the new conditions reported here. N-Alkylated indoles can easily be prepared from a range of amino substituted cyclic ketones in good to excellent yields. Acyclic ketones (**e**) and α-branched aldehydes (**j**) are equally suited to this transformation.[17] Pre-indoles such as **3** are easily prepared[11,16] allowing a convenient stockpile of late-stage synthetic indole precursors. These results demonstrate functional group compatibility with numerous potential substrates in a facile approach to N-alkylated indoles.

References and Notes

1. Cardillo, B.; Casnati, G.; Pochini, A.; Ricca, A. *Tetrahedron* **1967**, *23*, 3771. For a general discussion of indole chemistry see "Indoles," Parts I - IV in A. Weissberger and E. C. Taylor *The Chemistry of Heterocyclic Compounds*; John Wiley & Sons, Inc. New York; 1972 - 1983. For a discusion of indole alkylation, see Part I Section IVC.

2. For leading references, see Bourak, M.; Gallo, R. *Heterocycles* **1990**, *31*, 447.

3. Indole N-substitution *via* Mitsunobu reaction requires electron-withdrawing group activation. See Bhagwat, S. S.; Gude, C. *Tetrahedron Lett.* **1994**, *35*, 1847.

4. a) Allen, G. R.; Poletto, J. F.; Weiss, M. J. *J. Org. Chem.* **1965**, *30*, 2897. b) Remers, W. A.; Roth, R. A.; Weiss, M. J. *J. Org. Chem.* **1965**, *30*, 2910.

5. a) De Angelis, F.; Grasso, M.; Nicoletti, R. *Synthesis* **1977**, 335. b) Botta, M.; De Angelis, F.; Nicoletti, R. *J. Heterocyclic Chem.* **1979**, *16*, 501.

6. Gifford, M.; Garbrecht, W. L. *Synthesis* **1987**, 651.

7. a) Sasakura, K.; Adachi, M.; Sugasawa, T. *Synth. Commun.* **1988**, *18*, 265. b) Adachi, M.; Sasakura, K.; Sugasawa, T. *Chem. Pharm. Bull.* **1985**, *33*, 1826. c) Sugasawa, T.; Adachi, M.; Sasakura, K.; Kitagawa, A. *J. Org. Chem.* **1979**, *44*, 578. d) Sugasawa, T.; Toyoda, T.; Adachi, M.; Sasakura, K. *J. Am. Chem. Soc.* **1978**, *100*, 4842.

8. a) Gribble, G. W.; Lord, P. D.; Skotnicki, J.; Dietz, S. E.; Eaton, J. T.; Johnson, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 7812. Also see b) Gribble, G. W.; Jasinski, J. M.; Pellicone, J. T.; Panetta, J. A. *Synthesis* **1978**, 766. c) Abdel-Magid, A.; Maryanoff, C. A. *Synlett* **1990**, 537. d) Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595. e) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah R. D. *J. Org. Chem.* **1996**, *61*, 3849.

9. For recent studies exploiting the Sugasawa reaction conditions, see: a) Douglas, A. W.; Abramson, N. L.; Houpis, I. N.; Karady, S.; Molina, A.; Xavier, L. C.; Yasuda, N. *Tetrahedron Lett.* **1994**, *35*, 6807. b) Houpis, I. N.; Molina, A.; Douglas, A. W.; Xavier, L. C.; Lynch, J.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1994**, *35*, 6811.

10. For leading references with DMF/DMA see Fitt, J. J.; Gschwend, H. W. *J. Org. Chem.* **1977**, *42*, 2639. and Widmer, U. *Synthesis* **1983**, 135.

11. a) Leimgruber, W.; Batcho, A. D.; Abstracts of Papers, Third International Congress of Heterocyclic Chemistry, Tohoku University, Sendai, Japan, Aug. 1971. b) A. D. Batcho and W. Leimgruger, U. S. Patent 3,976,639, (1976); *Chem. Abstr.*, 86, 29624t (1977). c) Clark, R. D.; Repke, D. B. *Heterocycles*, **1984**, *22*, 195. d) For the preparation of other enamines see, Vetelino, M. G.; Coe, J. W. *Tetrahedron Lett.* **1994**, *35*, 219.

12. For a discussion of enamine hydrolysis, see E. J. Stamhuis, "Hydrolysis of Enamines," Ch. 3, in A. G. Cook *Enamines*; Marcel Dekker, New York, 1969; Ch. 3. Also see reference 16.

13. For an alternative preparation of aniline **3**, see a) Tischler, A. N.; Lanza, T. J. *Tetrahedron Lett.* **1986**, *27*, 1653. b) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles*, **1988**, *27*, 2225.

14. Gribble, G. W.; Nutaitis, C. F. *Org. Prep. Proc. Int.* **1985**, *17*, 317.

15. **Experimental Details**

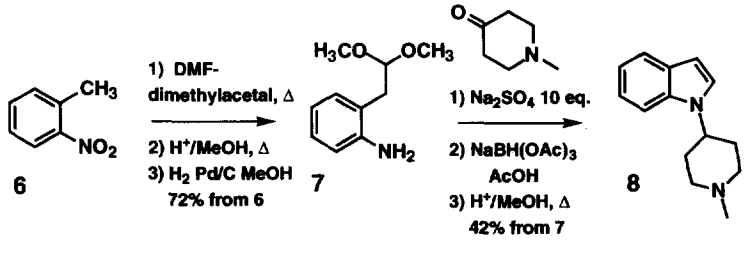
Preparation of enamine **2**: A solution of 4-methyl-3-nitrobenzoic acid (3.62 g, 20 mmol) and *N,N*-dimethylformamide dimethyl acetal (5.48 g, 46 mmol) in DMF (40 mL) was warmed to 140 °C under nitrogen for 18 h. Concentration *in vacuo* (80 °C, 20 mm) provides a dark purple oil which was diluted in hot MeOH (25 mL) and allowed to crystallize (0 °C) providing 4.04 g (81% yield) of **2** as purple crystals (mp 76-77 °C).

Preparation of pre-indole **3**: Enamine **2** (6.0 g, 24 mmol) in MeOH (100 mL) was treated with chlorotrimethylsilane (6.5 g, 59 mmol) and refluxed for 18 h. The reaction was concentrated *in vacuo* then partitioned between EtOAc and saturated aqueous $NaHCO_3$ solution. The EtOAc layer was washed with brine, dried (Na_2SO_4) and evaporated to afford 6.05 g of a yellow oil which crystallized on standing. (recryst. Et_2O, mp 63-65 °C). The nitro acetal was reduced (H_2, 50 psi, 5% wt. of 10% Pd/C, MeOH), the catalyst filtered off through a Celite pad and the filtrate concentrated to a white solid. Recrystallization from ether/hexanes affords pre-indole **3**, as a white crystalline solid (4.7 g, 82%, mp 59-61 °C).

Preparation of indole **5a**: Pre-indole **3** (1.19 g, 5.0 mmol) and 1-methyl-4-piperidone (1.13 g, 10 mmol) were magnetically stirred in AcOH (25 mL) and treated with anhydrous sodium sulfate powder (7.4 g, 50 mmol, Aldrich Chemical Co., cat.# 23,859-7). After aging 10 - 15 min., $NaHB(OAc)_3$ (3.16 g, 15 mmol) was added in portions over 2 min. and the resulting mixture was stirred 15 min. to 1 h then poured carefully into saturated aqueous $NaHCO_3$ solution (75 mL). Aniline **4** was extracted with EtOAc/ Hexanes (8/1), dried over Na_2SO_4, and concentrated *in vacuo*. This material was dissolved in dry 1N HCl/MeOH, refluxed 1 h, concentrated *in vacuo* to a white solid **5a** as the HCl salt (1.54 g, 100%, mp 229-231 °C, dec.) The sample was free based and chromatographed on silica gel to provide homogeneous material in 96% yield.

Preparation of indoles **5**: The other examples were prepared as described for **5a** using fresh ketone precursors and conversion of aniline **3** to alkylated intermediate **4** monitored by TLC (5 min. to 24 h). Products **5 a-j** were chromatographed on silica gel or, in the case of **5b** and **d**, crystallized directly from the acidic methanolysis as HCl salts. Melting points (°C) as HCl salts: **5b** 269-271 (Et_2O/Hex); **5c** 255-256 (Et_2O); **5d** 265-266 (MeOH/Et_2O); **5f** 125-127 (Et_2O); **5g** 95-97 (EtOAc/Hex); **5h** 179-180 (Et_2O); **5i** 105-107 (EtOAc/Hex; 4/1 α/β mixture of isomers). Neutral products **5e** (oil) and **5j** (mp 70-71 ° C) were chromatographed on silica gel. 1.5 eq of aldehyde and 2 eq. of $NaHB(OAc)_3$ were used in example **j**. All compounds exhibited satisfactory NMR and mass spectral data.

16. We have found pre-indole **7**[11d,15] is converted to N-alkylated indole **8** in 42% yield.



17. The reaction of unbranched aldehydes ($OHCCH_2R$) takes an unexpected course which is currently under investigation.

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