A Practical Synthesis of 1-N-SEM-Protected 3-Iodo-7-methyl-2-piperidin-3-ylindole

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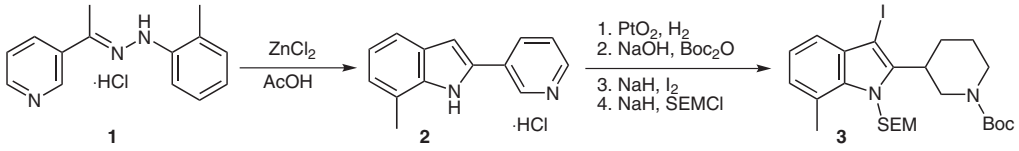
Received 31 August 2009; revised 30 September 2009

PSP No 178

Abstract: A convenient procedure for the preparation of the 1-N-SEM-protected 3-iodo-7-methyl-2-piperidin-3-ylindole **3** is described. This scaffold provides access to unique and diverse 7-methyl-substituted indole libraries.

Key words: 7-methylindoles, Fischer cyclization, 3-iodoindoles, 1,2,3,7-substituted indoles



1 **2** **3**

Scheme 1

Introduction

Methodology for the preparation of N-protected 3-haloindoles is a topic of much interest because cross-coupling reactions provide direct access to a variety of substances with significant biological activity.[1] N-Protection is an important aspect for reactions of 3-haloindoles due to the instability of the parent compounds, and the influence of the protecting group on subsequent chemistry. The most commonly employed indole N-protecting groups are arylsulfonyl derivatives (e.g., tosyl), carbamates (e.g., Boc), trialkylsilyl groups (e.g., triisopropylsilyl), *N*,*O*-acetals (e.g., SEM), and some alkyl groups (e.g., benzyl).[2]

On initial inspection, the synthesis of 2-substituted 3-halo-7-methylindoles presents several obstacles. Due to the presence of 2,7-disubstitution, steric hindrance in these indoles excludes the use of many common N-protecting groups. Most methods for synthesizing N-protected 2- and 3-haloindoles usually use electron-withdrawing groups with a preference in many instances for the phenylsulfonyl group.[3] Attempts to prepare 1-(trialkylsilyl)-7-methoxyindoles have been shown to be unsuccessful due to the steric hindrance of the 7-methoxy substituent.[4]

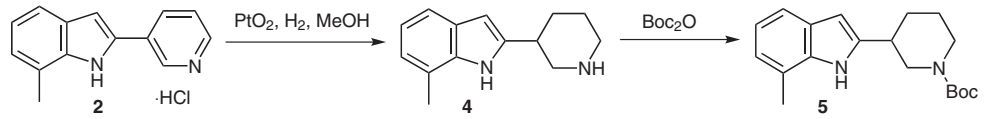
A review of literature revealed a paucity of reliable information regarding the use of Fischer cyclizations to prepare 2-heterocyclic-substituted 7-methylindoles. Only recently have there been reports of useful Fischer cyclizations of aromatic heterocyclic ketones to form 2-(2-pyridyl) indole.[5] Appropriate hydrogenation reaction conditions also needed to be considered to effect only the saturation of the 2-pyridin-3-yl substituent in preference to the pyrrole or benzene ring of the indole. Best conditions regarding the use of solvent, catalyst, temperature, and H_2 pressure needed to be explored.[6]

Scope and Limitations

It is important to emphasize that most of the methods and reaction conditions reported to yield successful Fischer indole cyclizations between phenylhydrazines and aromatic methyl ketones do not work to any appreciable extent for the preparation of 2-heteroaryl-substituted 7-methylindoles. Furthermore, Fischer cyclizations using 2-methylphenylhydrazine are best carried out using the hydrochloride since the free base is not stable.[7] We have found an efficient method to prepare pure *N*-(1-pyridin-3-ylethylidine)-*N*-*o*-tolylhydrazine hydrochloride (**1**) by the dropwise addition of 3-acetylpyridine into a methanol solution of commercially available 2-methylphenylhydrazine hydrochloride at room temperature followed by heating at reflux for one hour. Compound **1** precipitates from solution upon cooling and is collected by filtration in 89% yield. Methanol is the solvent of choice allowing for complete reaction and easy isolation.

A variety of common procedures and usual conditions for the Fischer cyclization of **1** to 7-methyl-2-pyridin-3-yl-1*H*-indole (**2**) have proven to be problematic. Heating **1** in polyphosphoric acid (PPA) at 180 °C or using Eaton's

SYNTHESIS 2010, No. 4, pp 0714–0717
Advanced online publication: 13.11.2009
DOI: 10.1055/s-0029-1217110; Art ID: M05109SS



Scheme 2

acid (3% P_2O_5 in methanesulfonic acid–dichloromethane, 1:2) at 45 °C provided little product and led to formation of intractable tars.[8,9] Treatment of hydrazine **1** with ethanolic hydrogen chloride at reflux or with five equivalents of zinc(II) chloride in dimethoxyethane at reflux or in glacial acetic acid at 70 °C returned mostly starting material after 24 hours.[10,11] However, treatment of compound **1** with five equivalents of zinc(II) chloride in glacial acetic acid at reflux for 17 hours provided the free base **2** in 40–50% reproducible yields after a convenient workup by precipitation directly in water followed by a simple purification protocol (Scheme 1).

Our attempts to reduce the pyridine ring of the free base **2** by catalytic hydrogenation using 5% palladium on carbon in acetic acid at room temperature at 50 psi as described for 2-pyridin-3-yl-1*H*-indole gave no reaction after 48 hours.[8] The toluenesulfonate salt of **2** was prepared, but was very insoluble in methanol, and underwent very little reduction using platinum(IV) oxide at room temperature at 50 psi after 24 hours. The hydrochloride of compound **2** was readily soluble in anhydrous methanol and underwent selective hydrogenation using platinum(IV) oxide at room temperature at 50 psi after 24 hours and afforded a 95% yield of 7-methyl-2-piperidin-3-yl-1*H*-indole (**4**). Boc protection of the piperidinyl nitrogen of **4** in aqueous sodium hydroxide and *tert*-butyl alcohol using di-*tert*-butyl dicarbonate proceeded in 72% isolated yield to afford indole **5** (Scheme 2).

The C-3 iodination of **5** in *N*,*N*-dimethylformamide at room temperature using potassium hydroxide and iodine appears to proceed quantitatively (TLC analysis), but attempted isolation of **6** leads to a mixture of products due to decomposition.[1] We therefore considered the preparation of the *N*-phenylsulfonyl derivative **7** following the well-established procedure by Gribble.[12] Treatment of indole **5** at –78 °C in anhydrous tetrahydrofuran under nitrogen with *n*-butyllithium followed by an iodine quench appeared to give the C-3 derivative **6**, but subsequent treatment with lithium diisopropylamide at –78 °C followed by quenching with benzenesulfonyl chloride gave a complex mixture of products. We rationalized this result as due to the failed *N*-phenylsulfonyl protection due to the steric hindrance of the 7-methyl and 2-piperidin-3-yl substituents and subsequent decomposition of the 3-iodoindole **6** (Figure 1). A followup experiment in which *N*-phenylsulfonyl protection of indole **5** was attempted prior to C-3 iodination, but failed to effect the desired protection to afford **8** (Figure 1).

Our observations suggested that we attempt the preparation of indole **3** by C-3 iodination of indole **5** followed by subsequent *N*-SEM protection of indole **6** without prior workup and isolation of **6**. *N*-SEM protection was proposed since SEMCl [2-(trimethylsilyl)ethoxymethyl chloride] is a reactive alkylating agent and introduces minimal steric interactions in a congested environment. A preliminary experiment showed that treatment of indole **5** in *N*,*N*-dimethylformamide at 0 °C with 1 equivalent of sodium hydride followed by quenching with SEMCl produced the *N*-SEM derivative **9** (Figure 1) in 85% isolated yield. Following this result, treatment of indole **5** in *N*,*N*-dimethylformamide at –10 °C with one equivalent of sodium hydride for 30 minutes and then dropwise addition of a *N*,*N*-dimethylformamide solution of one equivalent of iodine afforded the intermediate C-3 iodoindole **6**. This intermediate was directly treated with another equivalent of sodium hydride at –10 °C for 30 minutes followed by quenching with SEMCl to afford the desired scaffold **3** in 70% isolated yield after purification by chromatography and subsequent recrystallization (Scheme 1). This modification of the established Gribble procedure works efficiently, is less involved experimentally as only –10 to 0 °C temperatures are required, and conveniently uses sodium hydride as base. The introduction of these techniques provides synthetic flexibility and enables the use of other compatible protecting groups besides Boc on the piperidinyl nitrogen.

In conclusion, we have developed an efficient, flexible, and convenient procedure for the preparation of 1-*N*-SEM-protected 3-iodo-7-methyl-2-piperidin-3-ylindole. This scaffold provides access to a host of diverse indole libraries through subsequent chemistries at C-3 and the piperidinyl nitrogen.

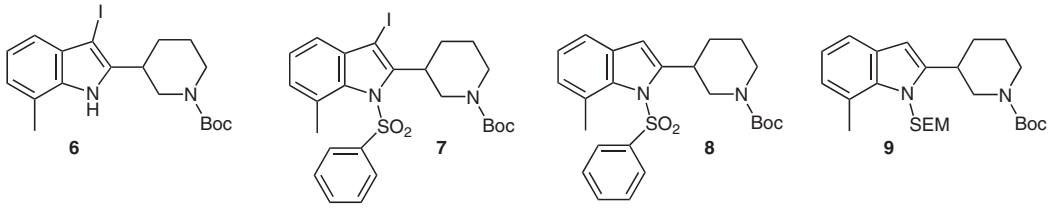


Figure 1 Compounds **6–9**

Mps were determined using an Electrothermal capillary melting point apparatus and are uncorrected. NMR spectra were recorded on either a Varian Inova 300 or 400 operating at 300 and 400 MHz for ^{1}H, respectively. Chemical shifts are reported in ppm relative to either residual $CHCl_3$ (δ = 7.24 ppm) in $CDCl_3$, HOD (δ = 4.67 ppm) in D_2O, or $CHD_2S(O)CD_3$ (δ = 2.49 ppm) in DMSO-d_6. TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck). Column chromatography was carried out on SiO_2 (silica gel 60, 230–400 microns). All reagents were purchased from Aldrich and were used without further purification. Solvents for chromatography and recrystallization were all ACS grade. HRMS analyses were performed at the chemistry department at the University of Akron. Microanalyses were performed at Galbraith Laboratories.

_N_-(1-Pyridin-3-ylethylidene)-_N_-_o_-tolylhydrazine Hydrochloride (1)

3-Acetylpyridine (16.43 g, 0.135 mol) was added dropwise in 25 min to a MeOH solution (250 mL) of 2-methylphenylhydrazine hydrochloride (21.0 g, 0.132 mol) at r.t. After the addition was complete, the mixture was heated at reflux for 1 h and then allowed to cool to r.t. with stirring. The mixture was cooled further to 0 °C with an ice bath, the precipitate was collected by filtration, the solid washed with MeOH (2 × 20 mL), and dried under high vacuum for several hours to give 30.9 g of a yellow solid (89%); mp 231–235 °C (dec.).

^{1}H NMR (300 MHz, D_2O): δ = 1.82 (s, 3 H), 1.91 (s, 3 H), 6.60 (t, *J* = 6.9 Hz, 1 H), 6.74 (d, *J* = 6.9 Hz, 1 H), 6.92 (t, *J* = 7.8 Hz, 1 H), 7.04 (d, *J* = 6.9 Hz, 1 H), 7.59 (dt, *J* = 1.5, 7.8 Hz, 1 H), 8.16 (d, *J* = 5 Hz, 1 H), 8.43 (d, *J* = 5 Hz, 1 H), 8.45 (s, 1 H).

HRMS: *m*/*z* calcd for (M + H)$^+$: 226.1344; found: 226.1341.

7-Methyl-2-pyridin-3-yl-1*H*-indole (2)

Compound **1** (10.16 g, 0.038 moles) and anhydrous $ZnCl_2$ (26 g, 0.19 mol) in glacial AcOH (100 mL) were heated at reflux under N_2 for 17 h. The reaction mixture was cooled to r.t. and added to ice water (600 g). After stirring for 2 h, the solids were filtered and washed with H_2O (50 mL). The solids were suspended in 1 N aq NaOH (100 mL, pH 11–12), extracted with EtOAc (2 × 150 mL), the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give a solid. Trituration with MTBE followed by filtration gave 3.56 g of a tan solid; mp 194–196 °C. Average yields over 3 runs were 40–50%. Additional product (approximately 5–10%) could be obtained from the aqueous filtrate by neutralization with NaOH and extraction with EtOAc, but this protocol was not optimized.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.52 (s, 3 H), 6.90 (m, 2 H), 7.0 (d, *J* = 2.15 Hz, 1 H), 7.35 (m, 1 H), 7.46 (ddd, *J* = 0.87, 4.75, 8.01 Hz, 1 H), 8.27 (ddd, *J* = 1.61, 2.37, 8.01 Hz, 1 H), 8.47 (dd, *J* = 1.61, 4.75 Hz, 1 H), 9.14 (ABq, *J* = 0.87, 2.37 Hz, 1 H).

HRMS: *m*/*z* calcd for (M + H)$^+$: 209.1078; found: 209.1196.

Anal. Calcd for $C_{14}H_{12}N_2 \cdot 0.2\ H_2O$: C, 79.37; H, 5.91; N, 13.22. Found: C, 79.66; H, 5.71; N, 13.11.

7-Methyl-2-piperidin-3-yl-1*H*-indole (4)

7-Methyl-2-pyridin-3-yl-1*H*-indole hydrochloride (**2**·HCl; 2.11 g, 8.65 mmol) was dissolved in anhydrous MeOH (200 mL) at r.t. The solution was degassed, $PtO_2 \cdot H_2O$ (0.20g) was added and the mixture hydrogenated at 35 psi at r.t. for 18 h. The catalyst was removed by filtration through Celite and the filtrate concentrated. The dry foam was dissolved in CH_2Cl_2 (30 mL), was washed with 10% aq Na_2CO_3 (30 mL), the organic layer separated, dried (Na_2SO_4), filtered, and concentrated to give 1.75 g of a tan foam (95%). This material was not further purified, but used directly.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52 (m, 1 H), 1.70 (m, 2 H), 2.01 (m, 1 H), 2.48 (s, 3 H), 2.60 (m, 2 H), 3.20 (m, 2 H), 3.68 (m, 1 H), 5.20 (br s, 1 H), 6.18 (s, 1 H), 6.87 (d, *J* = 7.16 Hz, 1 H), 6.96 (t, *J* = 7.16 Hz, 1 H), 7.35 (d, *J* = 7.87 Hz, 1 H), 9.37 (br s, 1 H).

HRMS: *m*/*z* calcd for (M + H)$^+$: 215.1548; found: 215.1733.

3-(7-Methyl-1*H*-indol-2-yl)piperidine-1-carboxylic Acid *tert*-Butyl Ester (5)

Boc_2O (1.79 g, 8.20 mmol) was added portionwise to a suspension of **4** (1.75 g, 8.194 mmol) in *t*-BuOH (6.2 mL) and aq NaOH (0.36 g NaOH, 9 mmol, in 8.2 mL of H_2O) which had been cooled to 5 °C. The mixture was allowed to warm to r.t., stirred for 1 h, and then extracted with EtOAc (50 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated. Purification of the residue obtained by flash silica chromatography using CH_2Cl_2–EtOAc followed by recrystallization from Et_2O–hexanes gave 1.85 g of white crystals (72%); mp 190–191 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 9 H), 1.43 (m, 2 H), 1.70 (m, 2 H), 2.07 (m, 1 H), 2.54 (s, 3 H), 2.83 (m, 2 H), 3.90 (m, 1 H), 4.10 (m, 1 H), 6.30 (d, *J* = 2 Hz, 1 H), 6.97 (d, *J* = 7.08 Hz, 1 H), 7.00 (t, *J* = 7.08 Hz, 1 H), 7.40 (d, *J* = 7.57 Hz, 1 H), 8.70 (br s, 1 H).

HRMS: *m*/*z* calcd for (M + Na)$^+$: 337.1891; found: 337.2131.

Anal. Calcd for $C_{19}H_{26}N_2O_2$ (314.42): C, 72.58; H, 8.33; N, 8.91. Found: C, 72.29; H, 8.22; N, 8.85.

3-[3-Iodo-7-methyl-1-(2-trimethylsilylethoxymethyl)-1*H*-indol-2-yl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (3)

To a suspension of NaH (60% dispersion, 0.66 g, 0.0165 mol) in anhydrous DMF (30 mL) cooled to –10 °C under N_2 was added a DMF (5 mL) solution of **5** (4.78 g, 0.0152 mol) dropwise in 5 min. Stirring was continued for 30 min and then a DMF (10 mL) solution of I_2 (3.84 g, 0.0151 mol) was added in 5 min. After 30 min at –10 °C, NaH (60% dispersion, 0.66 g, 0.0165 mol) was added portionwise. After stirring for an additional 30 min, 2-(trimethylsilyl)ethoxymethyl chloride (90%, 3.1 g, 0.0167 mol) was added via a syringe. The reaction was allowed to warm to 0 °C and after 1 h, quenched by the addition of aq NH_4Cl (100 mL). Extraction with EtOAc (2 × 60 mL), washing of the combined organic layers with 10% aq $Na_2S_2O_3$ (50 mL), followed by washing with brine (3 × 50 mL), drying (Na_2SO_4), and concentration gave the crude product. Purification by flash silica gel chromatography using EtOAc–hexanes, followed by recrystallization from Et_2O–hexanes (10:90) gave 6.06 g of white crystals (70%); mp 90–91 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.0 (s, 3 H), 0.96 (m, 2 H), 1.46 (s, 9 H), 1.62 (m, 2 H), 1.90 (m, 2 H), 2.60 (m, 1 H), 2.77 (s, 3 H), 2.85 (m, 1 H), 3.16 (m, 1 H), 3.58 (t, *J* = 7.57 Hz, 2 H), 4.18 (m, 2 H), 5.60 (ABq, *J* = 11.48 Hz, 2 H), 7.02 (d, *J* = 6.84 Hz, 1 H), 7.10 (t, *J* = 7.81 Hz, 1 H), 7.36 (d, *J* = 7.81 Hz, 1 H).

HRMS: *m*/*z* calcd for (M + Na)$^+$: 593.1672; found: 593.1842.

Anal. Calcd for $C_{25}H_{39}IN_2O_3Si$ (570.58): C, 51.89; H, 6.53; N, 5.04. Found: C, 52.10; H, 6.67; N, 4.89.

Acknowledgment

The authors would like to thank Professor Gribble for helpful suggestions and encouragement. We would also like to thank Dr. Dale Ray (Department of Chemistry at Case Western Reserve University) for NMR assistance.

References

(1) Li, J. J.; Gribble, G. W. In *Palladium in Heterocyclic Chemistry*; Pergamon: London, **2000**, 73–181.

(2) (a) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Thieme Verlag: Stuttgart, **2004**. (b) Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*, 3rd ed.; Wiley-Interscience: New York, **1999**, 615–631.
(3) (a) Illi, V. O. *Synthesis* **1979**, 136. (b) Conway, S. C.; Gribble, G. W. *Heterocycles* **1990**, *30*, 627.
(4) Amat, M.; Seffar, F.; Lior, N.; Bosch, J. *Synthesis* **2001**, 267.
(5) Lipinska, T.; Guibe-Jampel, E.; Petit, A.; Loupy, A. *Synth. Commun.* **1999**, *29*, 1349.
(6) Augustine, R. L. *Catalytic Hydrogenation*; Marcel Dekker: New York, **1965**, 104–109.
(7) (a) Hunsberger, I. M.; Shaw, E. R.; Fugger, J.; Ketcham, R.; Lednicer, D. *J. Org. Chem.* **1956**, *21*, 394. (b) Clasen, H. US Patent 4 066 698, **1978**; *Chem. Abstr.* **1976**, 164393.
(8) Jennings, L. D.; Foreman, K. W.; Rush, T. S.; Tsao, D. H. H.; Mosyak, L.; Kincaid, S. L.; Sukhdeo, M. N.; Sutherland, A. G.; Ding, W.; Kenny, C. H.; Sabus, C. L.; Liu, H.; Dushhin, E. G.; Moghazeh, S. L.; Labthavikul, P.; Peterse, P. J.; Tuckman, M.; Ruzin, A. V. *Bioorg. Med. Chem.* **2004**, *12*, 5115.
(9) Zhao, D.; Hughes, D. L.; Bender, D. R.; DeMarco, A. M.; Reider, P. J. *J. Org. Chem.* **1991**, *56*, 3001.
(10) Pfenninger, H. A. US Patent 3 468 894, **1969**; *Chem. Abstr.* **1969**, 77795.
(11) Hutchins, S. M.; Chapman, K. T. *Tetrahedron. Lett.* **1996**, *37*, 4869.
(12) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757.