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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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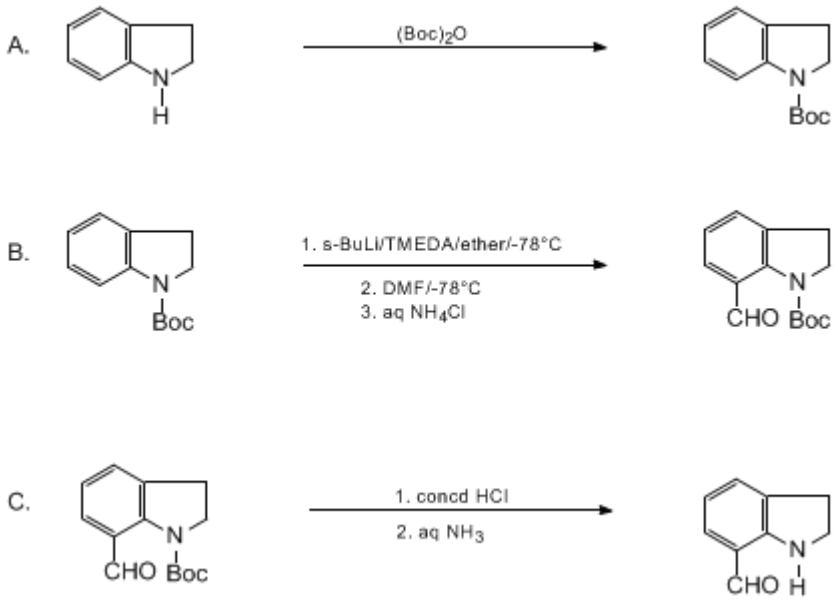
SYNTHESIS OF 7-SUBSTITUTED INDOLINES via DIRECTED LITHIATION OF 1-(tert-BUTOXYCARBONYL)INDOLINE: 7-INDOLINECARBOXALDEHYDE



Submitted by Masatomo Iwao and Tsukasa Kuraishi[1].
Checked by Jeff Crowley and Stephen F. Martin.

1. Procedure

Caution! Part C of this procedure should be carried out in an efficient hood to avoid exposure to noxious vapors (hydrogen chloride and ammonia).

A. *1-(tert-Butoxycarbonyl)indoline.* A 1-L, two-necked, round-bottomed flask, equipped with a reflux condenser fitted with a calcium chloride-filled drying tube, a pressure-equalizing addition funnel, and a magnetic stirring bar, is charged with 113.5 g (0.52 mol) of di-tert-butyl dicarbonate (Note 1) and 200 mL of tetrahydrofuran. Through the dropping funnel, 59.6 g (0.50 mol) of indoline is added to the reaction mixture with stirring over 30 min which maintains a steady evolution of carbon dioxide(Note 2). The reaction mixture is stirred at room temperature for an additional 3 hr followed by removal of the solvent with a rotary evaporator. The residual liquid is distilled under reduced pressure to give 107.6–107.8 g of 1-(tert-butoxycarbonyl)indoline (98% yield) as a colorless oil, bp 83–84°C at 0.1 mm, which on standing solidifies, mp 42–45°C (Note 3).

B. *1-(tert-Butoxycarbonyl)-7-indolinecarboxaldehyde.* An oven-dried, 2-L, three-necked, round-bottomed flask, equipped with an argon inlet, 200-mL pressure-equalizing dropping funnel fitted with a rubber septum, a low temperature thermometer, and a 4.5-cm egg-shaped magnetic stirring bar (Note 4), is flushed with argon and charged with 32.9 g (0.15 mol) of 1-(tert-butoxycarbonyl)indoline, 27.2 mL (0.18 mol) of N,N,N',N'-tetramethylethylenediamine (TMEDA) (Note 5), and 750 mL of anhydrous ether (Note 6). The dropping funnel is charged with 167 mL (0.18 mol) of a 1.08 M solution of sec-butyllithium in cyclohexane via syringe (Note 7). Under a positive pressure of argon, the flask is immersed in a dry ice-acetone bath. When the internal temperature has reached ca. −70°C, a white precipitate of the starting material appears. The solution of sec-butyllithium is added dropwise to this suspension with rapid stirring over 30 min while keeping the internal temperature below −70°C. The dropping funnel is rinsed with 10 mL of anhydrous ether. The light brown mixture is stirred for an

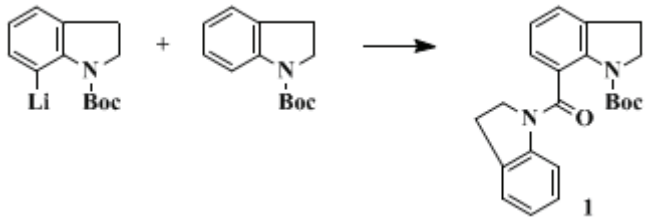
additional 2 hr at −78°C, during which time the precipitate completely dissolves and the color of the reaction mixture becomes deep brown. After the 2 hr has elapsed, 17.0 mL (0.22 mol) of N,N-dimethylformamide (DMF) is added dropwise through the addition funnel over a 10-min period (Note 8). After stirring the resulting mixture for 30 min at −78°C, 50 mL of saturated aqueous ammonium chloride solution is added through the dropping funnel over 15 min, and the cooling bath is removed (Note 9). When the internal temperature of the reaction mixture has reached −50°C, 50 mL of water is added dropwise, whereupon the deep orange color becomes light yellow. The reaction mixture is allowed to warm to 0°C and then poured into a 2-L separatory funnel containing water (200 mL). After thorough mixing, the layers are separated, and the aqueous phase is extracted with two 200-mL portions of ether. The combined organic layers are washed twice with 200 mL of saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated under reduced pressure on a rotary evaporator followed by exposure to oil pump vacuum to remove as much of the volatiles as possible. The residue is chromatographed on 750 g of silica gel (Note 10), using a carefully packed 8-cm diameter glass column, and a mixture of toluene and ethyl acetate (30:1) as the eluent (Note 11). The appropriate fractions are combined and concentrated to give crude 1-(tert-butoxycarbonyl)-7-indolinecarboxaldehyde (23.6–25.5 g, 64–69% yield) as a light yellow solid. Recrystallization of this solid from a mixture of ethyl acetate and hexane affords the pure aldehyde (20.5–21.1 g, 55–57% yield in two crops) as practically colorless needles, mp 86.5–87.5°C (Note 12).

C. *7-Indolinecarboxaldehyde*. A 300-mL Erlenmeyer flask fitted with a magnetic stirring bar is charged with 150 mL of concentrated (36%) hydrochloric acid. To this magnetically stirred solution, 19.8 g (0.08 mol) of finely powdered 1-(tert-butoxycarbonyl)-7-indolinecarboxaldehyde is added portionwise over 15 min at room temperature. The starting material gradually dissolves accompanied by gas evolution. After 2 hr, the resulting orange-colored solution is poured into a 2-L beaker containing crushed ice (500 g). To this mixture, 120 mL of 28% aqueous ammonia solution is added slowly with stirring, and the resulting mixture containing a yellow precipitate is transferred to a 2-L separatory funnel and extracted with four 100-mL portions of dichloromethane. The combined extracts are washed with 100 mL of saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. The resulting yellowish brown oil is passed through 300 g of silica gel (Note 10) packed in an 8-cm diameter glass column using a mixture of toluene and ethyl acetate (30:1) as an eluent. The yellow eluates are combined, and the solvent is removed to give pure 7-indolinecarboxaldehyde (10.6–11.2 g, 90–95% yield) as a yellow solid, mp 48.5–49°C (Note 13).

2. Notes

1. Di-tert-butyl dicarbonate was purchased from Wako Pure Chemical Industries, Ltd. and used without further purification.
2. Indoline was purchased from Tokyo Kasei Kogyo Co., Ltd. and distilled under reduced pressure before use.
3. The spectral data for 1-(tert-butoxycarbonyl)indoline are as follows: IR (KBr) cm^{-1}: 1700 (C=O); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.56 (s, 9 H), 3.07 (t, 2 H, J = 8.5), 3.96 (t, 2 H, J = 8.5), 6.91 (dt, 1 H, J = 7.5, 1.0), 7.11–7.17 (m, 2 H), 7.4–8.0 (extremely broad, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.3, 28.5, 47.6, 80.8, 114.7, 122.1, 124.7, 127.4, 131.1, 142.8, 152.7.
4. For efficient stirring, a powerful magnetic stirrer should be used. The submitters employed Super Stirrer Model MS-2 manufactured by Ishii Laboratory Works Co., Ltd.
5. N,N,N',N'-Tetramethylethylenediamine was distilled from powdered calcium hydride and stored under argon.
6. Ether was distilled from sodium benzophenone ketyl under nitrogen.
7. sec-Butyllithium was purchased from Kanto Chemical Co., Inc. and used after titration with 2,5-dimethoxybenzyl alcohol.[2]
8. N,N-Dimethylformamide was distilled from powdered calcium hydride and stored over 3 Å molecular sieves under argon.
9. When the reaction mixture was warmed to room temperature (4 hr – stirring after removal of cooling bath) before quenching with aqueous ammonium chloride solution, 7-indolinecarboxaldehyde (9.8–10.1 g, 44–46%) was obtained directly after silica gel column chromatography (SiO_2, 750 g, toluene elution).[3] However, the product was contaminated by small amounts of impurities, and attempted purification by recrystallization (ether-pentane) caused considerable loss of the main product.

10. Merck silica gel 60 (230–400 mesh) (No. 9385) was used.
11. Compound **1**, a major by-product of this reaction, was eluted after 1-(tert-butoxycarbonyl)-7-indolinecarboxaldehyde on chromatography (ca. 10% yield). This compound could be formed by condensation of the C-7 lithiated 1-(tert-butoxycarbonyl)indoline with the non-lithiated starting material. Compound **1** has mp 192–195°C (decomp.) after recrystallization from ethyl acetate.



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The submitters attempted inverse addition of 1-(tert-butoxycarbonyl)indoline to the ether solution of sec-BuLi-TMEDA complex at −78°C in order to suppress this side reaction. Formation of **1** was certainly decreased, but C-2 lithiation was observed as the other side reaction.
12. Spectral data of 1-(tert-butoxycarbonyl)-7-indolinecarboxaldehyde are as follows: IR (KBr) cm^{-1}: 1700, 1675 (C=O); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 9 H), 3.07 (t, 2 H, J = 8.0), 4.17 (t, 2 H, J = 8.0), 7.10 (t, 1 H, J = 7.5), 7.36 (dq, 1 H, J = 7.5, 1.0), 7.64 (dd, 1 H, J = 7.5, 1.0), 10.11 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.2, 49.9, 82.5, 124.0, 125.0, 126.1, 129.2, 134.5, 143.7, 153.9, 189.6.
13. Spectral data of 7-indolinecarboxaldehyde are as follows: IR (KBr) cm^{-1}: 1650 (C=O); ^1H NMR (400 MHz, $CDCl_3$) δ: 3.05 (t, 2 H, J = 8.5), 3.78 (t, 2 H, J = 8.5), 6.60 (dd, 1 H, J = 8.0, 7.0), 7.17 (dq, 1 H, J = 7.0, 1.0), 7.27 (dd, 1 H, J = 8.0, 1.0), 9.82 (s, 1 H) (NH absorption not observed); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 27.8, 47.1, 116.0, 116.1, 129.2, 130.7, 131.1, 153.5, 192.4.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described here offers a general route to 7-substituted indolines.[3] The method is based on the directed ortho-lithiation of N-(tert-butoxycarbonyl)aniline derivatives.[4 5 6 7] The tert-butoxycarbonyl group seems to be essential for C-7 selective lithiation, since other directing groups so far reported promote C-2 or C-3 metalation on the indoline ring.[8 9 10] The C-7 selective lithiation of 1-(tert-butoxycarbonyl)indoline is in contrast to the C-2 selective lithiation of 1-(tert-butoxycarbonyl) indole.[11]

The C-7 lithio species reacts successfully with a wide range of electrophiles (chlorotrimethylsilane, tributyltin chloride, diphenyl disulfide, iodine, 1,2-dibromoethane, hexachloroethane, iodomethane, carbon dioxide, DMF, aromatic and aliphatic aldehydes).[3] Lithiation occurs selectively at C-7 even in the presence of moderately ortho-directing methoxy or chloro groups on the aromatic ring.[3] The tert-butoxycarbonyl group is a well-established protective group for amine functionality and can be easily removed under a variety of reaction conditions.[12] Since indolines are readily oxidized to indoles,[13 14] this method should be useful for the preparation of 7-substituted indoles, which are not readily prepared by using conventional methodologies.[15 16 17 18 19]

Two other methods for the C-7 selective functionalization of indoline have been reported. Somei developed C-7 selective thallation of 1-acetylindoline and applied it to the synthesis of 7-substituted indoles.[20 21 22 23] Lo reported a synthesis of 7-benzoylindoline[24] by using Sugasawa's boron trichloride-mediated ortho-acylation of aniline derivatives.[25] The present method is superior to these procedures since a greater diversity of functionality can be introduced, the metalation exhibits high regioselectivity, and the use of highly toxic reagents such as thallium tris(trifluoroacetate) can be avoided.

References and Notes

1. Department of Chemistry, Nagasaki University, 1–14 Bunkyo-machi, Nagasaki 852, Japan.
2. Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87.
3. Iwao, M.; Kuraishi, T. *Heterocycles* **1992**, *34*, 1031.
4. Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798;
5. Stanetty, P.; Koller, H.; Mihovilovic, M. *J. Org. Chem.* **1992**, *57*, 6833;
6. Beak, P.; Lee, W.-K. *Tetrahedron Lett.* **1989**, *30*, 1197;
7. Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.
8. Meyers, A. I.; Hellring, S. *Tetrahedron Lett.* **1981**, *22*, 5119;
9. Meyers, A. I.; Milot, G. *J. Org. Chem.* **1993**, *58*, 6538;
10. Alhbrecht, H.; Konetzky, D.; Purder, T.; Katritzky, A. R.; Ghivirga, I.; Levell, J. *Synthesis* **1997**, 171.
11. Hasan, I.; Marinelli, E. R.; Lin, L.-C. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157.
12. Greene, T. W.; Wuts, P. G. M. "Protective Groups in Organic Synthesis", 2nd ed.; John Wiley & Sons: New York, 1991; p. 327.
13. Inada, A.; Nakamura, Y.; Morita, Y; *Chem. Lett.* **1980**, 1287;
14. Ketcha, D. M. *Tetrahedron Lett.* **1988**, *29*, 2151.
15. For recent approaches to the preparation of 7-substituted indoles, see: (a) Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106;
16. Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, *30*, 2129;
17. Dobson, D.; Todd, A.; Gilmore, J. *Synth. Comm.* **1991**, *21*, 611;
18. Dobson, D. R; Gilmore, J.; Long, D. A. *Synlett* **1992**, 79;
19. Kondo, Y.; Kojima, S.; Sakamoto, T. *Heterocycles* **1996**, *43*, 2741.
20. Somei, M.; Saida, Y. *Heterocycles* **1985**, *23*, 3113;
21. Somei, M.; Saida, Y.; Funamoto, T.; Ohta, T. *Chem. Pharm. Bull.* **1987**, *35*, 3146;
22. Somei, M.; Funamoto, T.; Ohta, T. *Heterocycles* **1987**, *26*, 1783;
23. Somei, M.; Kawasaki, T.; Ohta, T. *Heterocycles* **1988**, *27*, 2363.
24. Lo, Y. S.; Walsh, D. A.; Welstead, Jr., W. J.; Mays, R. P.; Rose, E. K.; Causey, D. H.; Duncan, R. L. *J. Heterocycl. Chem.* **1980**, *17*, 1663.
25. Sugasawa, T.; Toyoda, T.; Adachi, M.; Sasakura, K. *J. Am. Chem. Soc.* **1978**, *100*, 4842.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

sodium benzophenone ketyl

lithiated 1-(tert-butoxycarbonyl)indoline

TMEDA

hydrogen chloride,
hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

cyclohexane (110-82-7)

iodine (7553-56-2)

toluene (108-88-3)

1,2-dibromoethane (106-93-4)

iodomethane (74-88-4)

Pentane (109-66-0)

dichloromethane (75-09-2)

Tetrahydrofuran (109-99-9)

N,N-dimethylformamide,
DMF (68-12-2)

hexane (110-54-3)

argon (7440-37-1)

calcium hydride (7789-78-8)

diphenyl disulfide (882-33-7)

hexachloroethane (67-72-1)

CHLOROTRIMETHYLSILANE (75-77-4)

thallium tris(trifluoroacetate) (23586-53-0)

sec-butyllithium,
sec-BuLi (598-30-1)

indoline (496-15-1)

2,5-dimethoxybenzyl alcohol (33524-31-1)

tributyltin chloride (1461-22-9)

1-(tert-Butoxycarbonyl)indoline (143262-10-6)

7-Indolinecarboxaldehyde (143262-21-9)

1-(tert-Butoxycarbonyl)-7-indolinecarboxaldehyde (174539-67-4)

N,N,N',N'-tetramethylethylenediamine (110-18-9)

1-(tert-butoxycarbonyl)indole (75400-67-8)

1-acetylindoline (16078-30-1)

7-benzoylindoline

Di-tert-butyl dicarbonate (24424-99-5)