



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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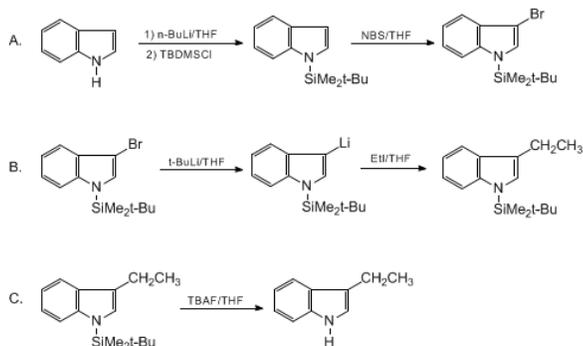
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

REGIOSELECTIVE SYNTHESIS OF 3-SUBSTITUTED INDOLES: 3-ETHYLINDOLE

[1H-Indole, 3-ethyl-]



Submitted by Mercedes Amat, Sabine Hadida, Swargam Sathyanarayana, and Joan Bosch¹.
Checked by Ji Liu, Chris H. Senanayake, and Ichiro Shinkai.

1. Procedure

Caution! *tert*-Butyllithium is extremely pyrophoric and must not be allowed to come into contact with the atmosphere. This reagent should only be handled by individuals trained in its proper and safe use. It is recommended that transfers be carried out by using a 20-mL or smaller glass syringe filled to no more than 2/3 capacity, or by cannula. For a discussion of procedures for handling air-sensitive reagents, see *Aldrich Technical Bulletin AL-134*. [Note added August 2009].

A. **3-Bromo-1-(tert-butyl(dimethylsilyl)indol-1-yl)indole**. An oven-dried, 500-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, 100-mL pressure-equalizing addition funnel, and an argon inlet and outlet, is charged with **indole** (8.0 g, 0.068 mol) (Note 1) and **tetrahydrofuran** (200 mL) (Note 2). The solution is stirred and cooled to -78°C with a dry ice/acetone bath, and a solution of **butyllithium** in **hexane** (47 mL of a 1.6 M solution, 0.075 mol) (Note 3) is added dropwise via cannula. The mixture is warmed to -10°C , stirred for 15 min, and cooled to -50°C . A solution of **tert-butyl(dimethylsilyl) chloride** (11.6 g, 0.077 mol) (Note 3) in **tetrahydrofuran** (60 mL) is added dropwise to this mixture. The temperature is raised to 0°C and after 3 hr the reaction mixture is cooled to -78°C . Freshly crystallized **N-bromosuccinimide** (12.18 g, 0.0684 mol) (Note 4) is added via a solid-addition funnel and the resulting mixture is stirred in the dark at -78°C for 2 hr and allowed to warm to room temperature. **Hexane** (100 mL) and **pyridine** (1 mL) are added and the resulting suspension is filtered through a Celite pad. The filtrate is evaporated under reduced pressure. The crude residue is purified (Note 5) by flash chromatography on silica gel (Note 6) (350 g, 30 cm \times 6 cm) (100% **hexane**) to give 17.8 g (84%) of **3-bromo-1-(tert-butyl(dimethylsilyl)indol-1-yl)indole** as a colorless solid (Note 7).

B. **1-(tert-Butyl(dimethylsilyl)indol-1-yl)indole**. An oven-dried, 500-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, 50-mL pressure-equalizing addition funnel, and an argon inlet and outlet, is charged with **3-bromo-1-(tert-butyl(dimethylsilyl)indol-1-yl)indole** (10 g, 0.032 mol) and **tetrahydrofuran** (100 mL). The mixture is stirred and cooled to -78°C with a dry ice/acetone bath. A solution of **tert-butyllithium** (Note 8) (41.7 mL of a 1.7 M solution in **pentane**, 0.071 mol) is transferred slowly to the above mixture from a graduated tube via a stainless steel cannula under positive argon pressure. The reaction mixture becomes yellow. Stirring is continued at -78°C for 10 min. A solution of **ethyl iodide** (5.2 mL, 0.065 mol) (Note 9) in **tetrahydrofuran** (20 mL) is added dropwise over 15 min to the resulting **1-(tert-butyl(dimethylsilyl)indol-1-yl)indole**. The reaction mixture becomes colorless, and after 15 min it is allowed to reach room temperature, poured into a cold saturated **sodium carbonate** solution (200 mL), and extracted with **methylene chloride** (3 \times 100 mL). The combined organic layers are washed with water (100 mL), dried over **sodium sulfate**, and evaporated under reduced pressure to give 8.0 g (96%) of **1-(tert-butyl(dimethylsilyl)indol-1-yl)indole** as a light pink oil (Note 10).

C. **3-Ethylindole**. An oven-dried, 250-mL, round-bottomed flask, equipped with a magnetic stirring bar, rubber septum, and an argon inlet and outlet, is charged with **1-(tert-butyl(dimethylsilyl)indol-1-yl)indole** (8 g, 0.031 mol) and **tetrahydrofuran** (100 mL). The mixture is stirred and a 1 M solution of **tetrabutylammonium fluoride** (TBAF) in **tetrahydrofuran** (31 mL, 0.031 mol) (Note 11) is added. After the solution is stirred for 10 min at room temperature, it is poured into a saturated solution of **sodium carbonate** (200 mL) and extracted with **dichloromethane** (3 \times 100 mL). The combined organic layers are washed with water (100 mL), dried over **sodium sulfate**, and evaporated under reduced pressure. The residue is subjected to flash chromatography on silica gel (175 g, 32 cm \times 4.5 cm) (25% **dichloromethane-hexane**, v/v) to give 4.1 g (92%) of **3-ethylindole** as colorless plates (Note 12).

2. Notes

- Indole** was obtained from Fluka Chemie AG, and was crystallized from **hexane** and dried over **phosphorus pentoxide** (P_2O_5) before use.
- Tetrahydrofuran** was distilled from sodium benzophenone ketyl immediately before use.
- Butyllithium** and **tert-butyl(dimethylsilyl) chloride** were obtained from Fluka Chemie AG and used as received.
- N-Bromosuccinimide** was obtained from Fluka Chemie AG, and crystallized from water and dried over P_2O_5 before use.
- Chromatographic purification of the reaction mixture must be effected as soon as possible after workup in order to separate traces of contaminating **3-bromoindole**, which promotes rapid decomposition.
- 3-bromo-1-(tert-butyl(dimethylsilyl)indol-1-yl)indole** can be stored under argon at 4°C without appreciable decomposition.
- Silica gel** (35–70 mesh) was used as received.
- The spectral properties for **3-bromo-1-(tert-butyl(dimethylsilyl)indol-1-yl)indole** are as follows: ^1H NMR (300 MHz, CDCl_3) δ : 0.60 (s, 6 H), 0.93 (s, 9 H), 7.17 (s, 1 H), 7.20 (m, 2 H), 7.48 (m, 1 H), 7.54 (m, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ : -4.0 (CH_3Si), 19.3 [$\text{C}(\text{CH}_3)_3$], 26.2 [$\text{C}(\text{CH}_3)_3$], 93.6 (C-3), 114.0 (C-7), 119.1 (C-4), 120.5 (C-5), 122.5 (C-6), 129.6 (C-2), 129.8 (C-3a), 140.2 (C-7a). Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{BrNSi}$: C, 54.18; H, 6.50; Br, 25.75; N, 4.51. Found: C, 54.21; H, 6.60; Br, 25.52; N, 4.62. Attempts to crystallize **3-bromo-1-(tert-butyl(dimethylsilyl)indol-1-yl)indole** were unsuccessful.
- tert-Butyllithium** (1.7 M solution in **pentane**) was obtained from Aldrich Chemical Company, Inc., and used as received.
- Ethyl iodide** was obtained from Fluka Chemie AG and distilled prior to use.
- NMR spectrum shows the presence of less than 3% of **1-(tert-butyl(dimethylsilyl)indol-1-yl)indole**. Crude **1-(tert-butyl(dimethylsilyl)indol-1-yl)indole** can be purified by flash column chromatography on silica gel (35–70 mesh) (350 g, 30 cm \times 6 cm) (100% **hexane**) to give pure **1-(tert-butyl(dimethylsilyl)indol-1-yl)indole** as a colorless oil in about 90% yield. The spectral properties are as follows: ^1H NMR (300 MHz, CDCl_3) δ : 0.57 (s, 6 H), 0.92 (s, 9 H), 1.32 (t, 3 H, $J = 7.5$), 2.76 (g, 2 H, $J = 7.5$), 6.92 (s, 1 H), 7.12 (m, 2 H), 7.47 (m, 1 H), 7.58 (m, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ : -3.9 (CH_3Si), 14.5 (CH_2CH_3), 18.4 (CH_2CH_3), 19.5 [$\text{C}(\text{CH}_3)_3$], 26.3 [$\text{C}(\text{CH}_3)_3$], 113.8 (C-7), 118.8 (C-4), 119.2 (C-5), 119.8 (C-3), 121.3 (C-6), 126.9 (C-2), 130.9 (C-3a), 141.6 (C-7a). Anal. Calcd for $\text{C}_{16}\text{H}_{25}\text{NSi}$: C, 74.06; H, 9.71; N, 5.40. Found: C, 74.18; H, 9.73; N, 5.46.
- Tetrabutylammonium fluoride** in **tetrahydrofuran** (1 M solution) was obtained from Fluka Chemie AG and used as received.
- The spectral properties for **3-ethylindole** are as follows: ^1H NMR (200 MHz, CDCl_3) δ : 1.37 (t, 3 H, $J = 7.5$), 2.82 (q, 2 H, $J = 7.5$), 6.98 (br s, 1 H), 7.18 (m, 2 H), 7.37 (d, 1 H, $J = 7.5$), 7.66 (d, 1 H, $J = 7.8$), 7.85 (br s, 1 H); ^{13}C NMR (50 MHz, CDCl_3) δ : 15.0 (CH_2CH_3), 18.9 (CH_2CH_3), 111.6 (C-7), 119.3 (C-3), 119.5 (C-4), 119.6 (C-5), 121.1 (C-6), 122.4 (C-2), 128.0 (C-3a), 136.9 (C-7a).

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

Although there are many studies about the preparation and synthetic applications of N-protected 2-lithioindoles,² their isomers, the 3-lithioindoles, have received little attention. Thus, the only indole protecting group used for the preparation of simple 3-lithioindoles is the benzenesulfonyl group. **1-(Benzenesulfonyl)indole** is prepared at -100°C by halogen-metal exchange with **tert-butyllithium** from the corresponding **3-iodo**-³ or **3-bromoindole**.⁴ At higher temperatures it rearranges to the thermodynamically more stable 2-lithio isomer. On the other hand, some 2-substituted **1-(benzenesulfonyl)indole** 3-lithioindoles undergo ring fragmentation to give 2-aminophenylacetylene derivatives.⁵ The change of the benzenesulfonyl protecting group for a trialkylsilyl group allows the preparation of 3-lithioindoles that are relatively stable species even at room temperature.

In the present procedure, **indole** is protected with a **tert-butyl(dimethylsilyl)** group and further brominated with **N-bromosuccinimide** in a one-pot reaction. **3-Bromo-1-(tert-butyl(dimethylsilyl)indol-1-yl)indole** readily undergoes halogen-lithium exchange with **tert-butyllithium** at -78°C . Subsequent reaction with an electrophile is exemplified by the reaction with **ethyl iodide** to give **1-(tert-butyl(dimethylsilyl)indol-1-yl)indole**. Other electrophiles such as alkyl or allyl halides, ethylene oxide, acylating reagents, carbon dioxide, aromatic aldehydes, and trimethyltin chloride have also been employed successfully in a 500 mg scale (see Table).⁶ The reactions regioselectively lead to 3-substituted indoles. 2-Substituted indoles were not detected, indicating that **1-(tert-butyl(dimethylsilyl)indol-1-yl)indole** (**1**) does not undergo rearrangement to the 2-lithio isomer. Products arising from a ring fragmentation were not detected either. When the reactions of **1** with **ethyl iodide** and **methyl iodide** were carried out at room temperature, the yields of the respective 3-alkylindoles were similar to those obtained when operating at -78°C . Finally, the **1-(tert-butyl(dimethylsilyl)indol-1-yl)indole** protecting group can be readily removed by treatment with TBAF under mild conditions.

TABLE
SYNTHESIS OF 3-SUBSTITUTED INDOLES

Entry	Electrophile	R	2 Yield(%)	3 Yield(%) ^a	
a	MeI	Me	<p>90</p>	85	
b	BuBr	Bu	<p>64</p>	61	
c	(CH ₂ CH ₂)O	CH ₂ CH ₂ OH	<p>63</p>	62	
d	Me ₂ C=CHCH ₂ Br ^b	CH ₂ CH=CMe ₂	<p>69^c</p>		
e	HCONMe ₂ ^d	CHO	e	<p>94</p>	
f	C ₆ H ₅ COCl ^d	COC ₆ H ₅	e	<p>84</p>	
g	C ₆ H ₅ CO ₂ CH ₃ ^d	COC ₆ H ₅	<p>69</p>	58	
h	ClCO ₂ CH ₃ ^d	CO ₂ CH ₃	<p>84</p>	80	
i	CO ₂	CO ₂ H	<p>94</p>	70 ^f	
j	C ₆ H ₅ CHO	CHOHC ₆ H ₅	<p>67</p>	g	
k	4-CHO-C ₃ H ₄ N	4-CHOH-C ₃ H ₄ N	<p>55</p>	g	

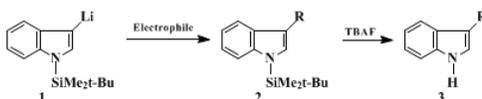
^aOverall yield after purification by column chromatography. ^bThe 3-lithioindole **1** was converted into a cuprate by addition of 1 equiv of CuBr·SMe₂. ^cAn 85:15 mixture of **3d** and the isomer in which R is CMe₂C obtained. ^dThe best yields were obtained by reverse addition of the lithium derivative **1** to a THF solution of the electrophile at -78°C. ^eThe corresponding 3-acyl derivatives undergo partial desilylation during desilylation was best effected by using CsF instead of TBAF. ^fThese carbinols were obtained as pink oils, which partially decomposed during purification by column chromatography. ^gAttempts to deprotect the triethylsilyl group were unsuccessful.

Entry	Electrophile	R	2 Yield(%)	3Yield(%) ^a
1	ClSnMe ₃	SnMe ₃	<p style="text-align: center;">94</p>	h

^aOverall yield after purification by column chromatography. ^bThe 3-lithioindole **1** was converted into a cuprate by addition of 1 equiv of CuBr·SMe₂. ^cAn 85:15 mixture of **3d** and the isomer in which R is CMe₂C obtained. ^dThe best yields were obtained by reverse addition of the lithium derivative **1** to a THF solution of the electrophile at -78°C. ^eThe corresponding 3-acyl derivatives undergo partial desilylation during desilylation was best effected by using CsF instead of TBAF. ^fThese carbinols were obtained as pink oils, which partially decomposed during purification by column chromatography. ^hAttempts to deprotect the tin only indole.

The triisopropylsilyl group gave comparable satisfactory results.⁷

As a further synthetic application, 3-lithioindole **1** was converted to 1-(tert-butyl(dimethyl)silyl)-3-indolylzinc chloride, which has been successfully employed in the heteroarylation of the indole 3-position by a palladium(0)-catalyzed cross-coupling reaction.⁸



References and Notes

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

silica gel
P₂O₅
sodium benzophenone ketyl
sodium carbonate (497-19-8)
sodium sulfate (7757-82-6)
carbon dioxide (124-38-9)
pyridine (110-86-1)
palladium (7440-05-3)
Ethylene oxide (75-21-8)
Methyl iodide (74-88-4)
Pentane (109-66-0)
methylene chloride,
dichloromethane (75-09-2)
Ethyl iodide (75-03-6)
butyllithium (109-72-8)
Tetrahydrofuran (109-99-9)
N-bromosuccinimide (128-08-5)
Indole (120-72-9)
hexane (110-54-3)
argon (7440-37-1)
Tetrabutylammonium fluoride (429-41-4)
phosphorus pentoxide (1314-56-3)
tert-Butyllithium (594-19-4)
trimethyltin chloride (1066-45-1)
tert-butyl(dimethyl)silyl chloride (18162-48-6)
3-Ethylindole,
1H-Indole, 3-ethyl- (1484-19-1)
3-Bromo-1-(tert-butyl(dimethyl)silyl)indole (153942-69-9)
1-(tert-butyl(dimethyl)silyl)-3-ethylindole (153942-71-3)
1-(tert-butyl(dimethyl)silyl)-3-lithioindole
3-bromoindole
1-(tert-butyl(dimethyl)silyl)indole
1-(Benzenesulfonyl)-3-lithioindole
3-lithioindole
1-(tert-butyl(dimethyl)silyl)-3-indolylzinc chloride