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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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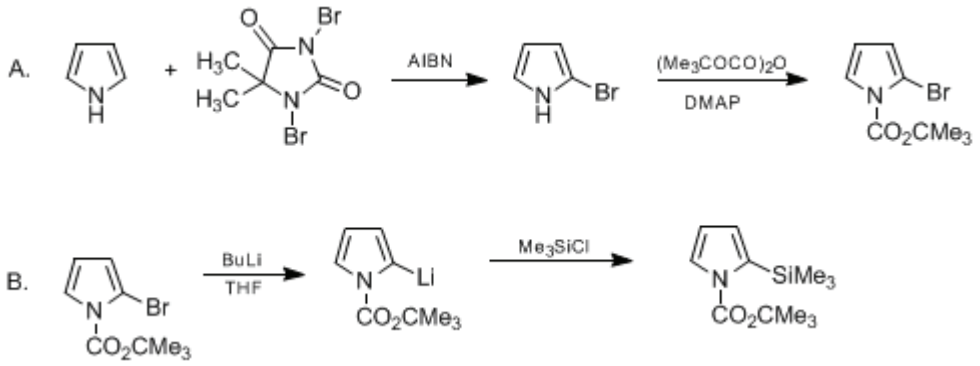
2-SUBSTITUTED PYRROLES FROM N-tert-BUTOXYCARBONYL-2-BROMOPYRROLE: N-tert-BUTOXYCARBONYL-2-TRIMETHYLSILYLPYRROLE



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1. Procedure

A. *N-tert-Butoxycarbonyl-2-bromopyrrole*. A dry, 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, two solid addition funnels, and a three-way stopcock attached to a balloon filled with nitrogen. To the flask are added 4.5 g (67.2 mmol) of pyrrole (Note 1) and 180 mL of tetrahydrofuran (Note 2). The flask is evacuated and purged with nitrogen (Note 3). The stirred solution is cooled to −78°C with a dry ice-acetone bath (Note 4) and a catalytic amount (ca. 0.1 g) of azoisobutyronitrile (AIBN) (Note 5) is added via a solids addition funnel. After 5 min, 9.57 g (33.6 mmol) of 1,3-dibromo-5,5-dimethylhydantoin (Note 6) is added over a 20-min period via a solids addition funnel. The light-green mixture is stirred for an additional 10 min, then allowed to stand for 2 hr, keeping the temperature below −50°C. The solution is filtered by suction into a dry, 500-mL, round-bottomed flask that has been cooled to −78°C in a dry ice-acetone bath. The flask is equipped with a magnetic stirring bar and a three-way stopcock attached to a balloon filled with nitrogen. To the stirred dark-green solution is added 2.71 g (26.9 mmol) of triethylamine followed immediately by addition of 20.4 g (93.9 mmol) of di-tert-butyl dicarbonate and a catalytic amount (ca. 0.1 g) of 4-dimethylaminopyridine (Note 7). The flask is evacuated and purged with nitrogen (Note 3). The mixture is stirred for 8 hr while it is allowed to warm to room temperature (Note 8). The solvent is removed under reduced pressure at room temperature and 100 mL of hexane is added to the crude product, which is washed with deionized water (3 × 100 mL), dried over sodium sulfate, and concentrated under reduced pressure at room temperature. The crude product is purified by chromatography on amine-treated neutral silica (270 g) using hexane as the eluent (Note 9). The fractions containing the product are identified by TLC, combined, and concentrated under reduced pressure at room temperature to yield compound **1** as a colorless oil (13.5–14.7 g, 82–89%) (Note 10).

B. *N-tert-Butoxycarbonyl-2-trimethylsilylpyrrole*. A solution of N-tert-butoxycarbonyl-2-bromopyrrole (13.5 g, 54.9 mmol) in 40 mL of hexane is added to 200 mL of tetrahydrofuran (Note 2) in a dry, 500-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and a three-way stopcock attached to a balloon of nitrogen. The flask is evacuated and purged with nitrogen (Note 3). The stirred mixture is cooled to −78°C and 34.3 mL of 1.6 M butyllithium in hexane (Note 10) is added slowly via syringe over a 10-min period, during which time the colorless solution becomes brown. After an additional 10 min, 13.4 g (124 mmol) of chlorotrimethylsilane (Note 11) in 10 mL of tetrahydrofuran (Note 3) is added via syringe over a 10-min period. Stirring is continued and the mixture is allowed to warm to −30°C over a 1-hr period. The reaction mixture is quenched with saturated aqueous sodium bicarbonate (10 mL) at which point a dark red-purple color develops. After warming to 0°C, the solvent is removed under reduced pressure and the product is

extracted into 300 mL of hexane. The organic layer is washed twice with 150 mL of water and then dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure, and the residue is distilled twice using a Kugelrohr oven at 85°C and 0.15 mm to give the pure product **2** (10.5–11.1 g, 80–85%) (Note 12).

2. Notes

1. Pyrrole (Aldrich Chemical Company, Inc.) was freshly distilled before use.
2. Tetrahydrofuran was distilled from sodium benzophenone ketyl.
3. The apparatus is maintained under a nitrogen atmosphere during the course of the reaction.
4. The level of the reaction mixture must remain below the level of the cooling bath to avoid partial decomposition of the bromination product.
5. Azoisobutyronitrile (AIBN) (Fluka) was used as received.
6. Commercial 1,3-dibromo-5,5-dimethylhydantoin (Aldrich Chemical Company, Inc.) (22.0 g) was stirred for 12 hr at room temperature with 400 mL of 5% aqueous sodium bicarbonate, then stirred with 400 mL of deionized water for 8 hr, filtered, washed with 500 mL of deionized water and dried over phosphorus pentoxide to constant weight. The checkers used the commercial brominating agent as received from Aldrich Chemical Company, Inc.
7. Di-tert-butyl dicarbonate (Aldrich Chemical Company, Inc.) and 4-dimethylaminopyridine (Aldrich Chemical Company, Inc.) were used as received.
8. The checkers found that the reaction mixture must be stirred at room temperature for at least 2 hr prior to workup. It is advisable to monitor the progress of reaction by TLC.
9. The column is packed with hexane and pretreated with 500 mL of 5% triethylamine in hexane, then washed with 700 mL of hexane before addition of the compound.
10. Although this N-Boc derivative is far more stable than 2-bromopyrrole, it is best stored as a 20–25% solution in hexane at −10°C. Under these conditions, solutions show no sign of decomposition after many months. The product shows the following spectrum: ^{1}H NMR ($CDCl_3$) δ: 1.61 (s, 9 H), 6.14 (t, 1 H, J = 3.5), 6.29 (dd, 1 H, J = 2.0, 3.5), 7.30 (dd, 1 H, J = 2.0, 3.5).
11. Butyllithium solution (Aldrich Chemical Company, Inc.) and chlorotrimethylsilane (Aldrich Chemical Company, Inc.) were used as received.
12. The spectral properties for 2-trimethylsilyl-N-Boc pyrrole are as follows: ^{1}H NMR ($CDCl_3$) δ: 0.27 (s, 9 H), 1.60 (2, 9 H), 6.21 (t, 1 H, J = 3.0), 6.46 (dd, 1 H, J = 1.5, 3.0), 7.38 (dd, 1 H, J = 1.5, 3.0).

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

Whereas 2-lithiothiophene and 2-lithiofuran are readily prepared from butyllithium and the parent heterocycles by lithium-hydrogen exchange, a similar exchange with pyrrole affords only N-lithiopyrrole. A study of the lithium-hydrogen exchange of several N-blocked pyrroles with strong bases concluded that synthetically useful lithium-hydrogen exchange at the 2-position could best be effected using as the substrate N-tert-butoxycarbonylpyrrole, but only in conjunction with the very hindered and costly base lithium tetramethylpiperidide.[3]

In the present procedure, pyrrole is brominated under mild conditions to the very labile 2-bromopyrrole using 1,3-dibromo-5,5-dimethylhydantoin: the latter reagent gives better results than the previously employed N-bromosuccinimide.[4] Direct conversion of 2-bromopyrrole to its more stable N-tert-butoxycarbonyl derivative (**1**) affords a substrate which readily undergoes lithium-halogen exchange with butyllithium at −78°C. Subsequent reaction with an electrophile is exemplified by the reaction with chlorotrimethylsilane to give N-tert-butoxycarbonyl-2-trimethylsilylpyrrole (**2**). Other electrophiles (e.g., dimethyl disulfide, methyl chloroformate) have also been employed successfully.[5] In addition, a similar procedure has been used to convert pyrrole into N-tert-butoxy-2,5-disubstituted pyrroles.[5]

The N-tert-butoxycarbonyl protecting group of substituted pyrroles can be removed readily by methoxide ion[3] or, when electron-withdrawing substituents are present, by mild thermolysis.[6]

References and Notes

1. Department of Chemistry, The University of Alabama, P.O. Box 870336, Tuscaloosa, AL 35487–0336.
2. Department of Chemistry, University of the West Indies, Mona, Kingston 7, Jamaica, West Indies.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

sodium benzophenone ketyl

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Pyrrole (109-97-7)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

methyl chloroformate (79-22-1)

N-bromosuccinimide (128-08-5)

hexane (110-54-3)

triethylamine (121-44-8)

dimethyl disulfide (624-92-0)

CHLOROTRIMETHYLSILANE (75-77-4)

2-lithiothiophene

N-lithiopyrrole

4-dimethylaminopyridine (1122-58-3)

phosphorus pentoxide (1314-56-3)

N-tert-Butoxycarbonyl-2-bromopyrrole (117657-37-1)

1,3-dibromo-5,5-dimethylhydantoin (77-48-5)

N-tert-Butoxycarbonyl-2-trimethylsilylpyrrole,
2-trimethylsilyl-N-Boc pyrrole (75400-57-6)

2-bromopyrrole

N-tert-butoxycarbonylpyrrole (5176-27-2)

lithium tetramethylpiperidide

2-Lithiofuran

azoisobutyronitrile (78-67-1)

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