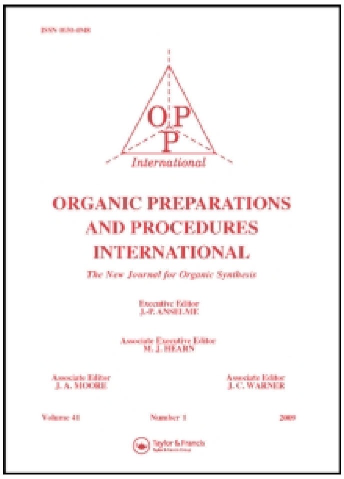

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A CONVENIENT PREPARATION OF 4-(*t*-BUTYLOXYCARBONYLAMINO)ANILINE

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OPPI BRIEFS

A CONVENIENT PREPARATION
OF 4-(*t*-BUTYLOXYCARBONYLAMINO)ANILINE

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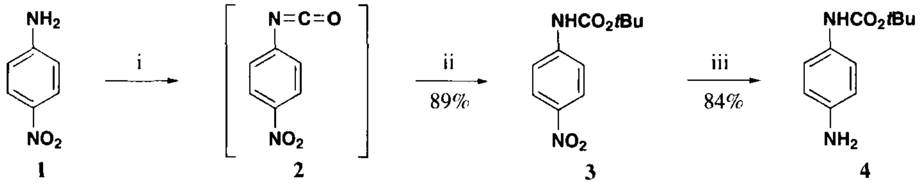
4-(*t*-Butyloxycarbonylamino)aniline (**4**) is an intermediate for the preparation of various compounds.[1-8] We needed multigram quantities of **4** for which a number of approaches have been reported. Compound **4** has been obtained by reduction of N-(*t*-butyloxycarbonyl)-4-nitroaniline (**3**) prepared by addition of *t*-butanol to 4-nitrophenylisocyanate (**2**); the isocyanate itself (**2**) has been generated by Hoffmann rearrangement of 4-nitrobenzamide with lead tetraacetate,[9] by reaction of 4-nitroaniline with methyl chloroformate (to give methyl-4-nitrophenylcarbamate, followed by *in situ* treatment with phosphorous oxychloride[10]), with phosgene[11] and diphosgene.[12] Unfortunately, phosgene and diphosgene are dangerous, especially when handled in large quantities and lead tetraacetate and phosphorous oxychloride generate undesirable effluents. Although it was reported that the reaction of *t*-butanol with **2** often leads to dehydration of the alcohol,[13] the reaction had no major side products when carried out *in situ*. Compound **3** has also been prepared by reaction of 4-nitroaniline with *t*-butyloxycarbonyl azide,[4] which is not safe to handle on a large scale due to its explosive properties.

A previous report described the preparation of N-(*t*-butyloxycarbonyl)-4-nitroaniline (**3**) from isocyanate (**2**) in 90% yield in presence of organotin catalysts.[13] Herein we report a safe and practical route using *bis*(trichloromethyl) carbonate (triphosgene) and 4-nitroaniline under mild conditions to generate the isocyanate (**2**), followed by addition of *t*-butanol *without* catalyst to afford compound **3** in 89% yield.



i) *bis*(Trichloromethyl) carbonate, EtOAC; ii) *t*-BuOH; iii) Raney-nickel, H_2, MeOH

Hydrogenation of **3** in the presence of Raney-nickel catalyst at 50 psi at ambient temperature gave 84% yield of **4** (overall yield of 75%). In comparison, compound **4** was obtained in an overall yield of 63% from 4-nitroaniline,[4] *via* reduction with Pd/C after N-carbo-t-butoxylation of the amino group with *t*-butyloxycarbonyl azide.

The advantages of this route are a) the use of *bis*(trichloromethyl) carbonate, a solid which can be handled safely on a large-scale b) the reaction of *t*-butanol with isocyanate proceeds without the necessity of a catalyst c) the replacement of expensive palladium-carbon catalyst for the reduction by a Raney-nickel catalyst. This procedure appears to possess generality and applicability to large-scale preparation.

EXPERIMENTAL SECTION

All chemicals and solvents were obtained from commercial sources and purified before use. Proton NMR spectra were recorded at 200 MHz in $CDCl_3$ solvent. Melting points were determined with a Veego digital automatic melting point apparatus and are uncorrected.

Preparation of N-(*t*–butyloxycarbonyl)-4-nitroaniline (3).- A 2-L 4-necked round bottomed flask equipped with mechanical stirrer, reflux condenser, calcium chloride guard tube, pressure equalizing dropping funnel and thermometer, was charged with *bis*(trichloromethyl) carbonate (50 g, 0.168 mol) and anhydrous ethyl acetate (250 mL). The reaction mixture was stirred at 60° for 1hr. Then 4-nitroaniline (50 g, 0.361 mol) in ethyl acetate (KF moisture content <0.1%; 400 mL) was added to the reaction mixture dropwise over 5 hr at 30°. After complete addition, the reaction mixture was heated to 70° for 2 hr followed by concentration under vacuum. To the resulting brown residue, carbon tetrachloride (200 mL) was added at 75° to precipitate the by-product, *bis*-N,N'-(4-nitrophenyl)urea (2.5g, mp. 358-360°., *lit.*[14] mp. 360°) which was removed by filtration. To the filtrate, t-butanol (55 g, 0.742 mol) was added dropwise at 30° over 30 min and then the mixture was heated to 80° for 5 hr or until TLC indicated the absence of starting material [mobile phase: benzene/ethyl acetate 4:1]. The reaction mixture was then cooled to 30°. A second crop of *bis*-N,N'-(4-nitrophenyl)urea (2.0 g) was removed by filtration. The filtrate was concentrated under reduced pressure to a volume of 135 mL and further cooled to 20-25°. Filtration gave light yellow crystals (77 g, 89% yield of **3**, mp. 90-92°) which was sufficiently pure to proceed to next stage. A sample was chromatographed on silica gel using an 8:2 dichloromethane-petroleum ether mixture as the mobile phase to yield an analytically pure sample, mp. 109-110°, *lit.*[9] mp. 109°. ^1H NMR: δ 1.55 (s, 9H, t-butyl), δ 7.05 (s, broad, 1H, NH), δ 7.55 (d, 2H, aromatic), δ 8.20 (d, 2H, aromatic).

Preparation of 4-(*t*-Butyloxycarbonylamino)aniline (4).- A 1-L stainless steel flask fitted on a Parr-hydrogenation apparatus, was charged with N-(*t*-butyloxycarbonyl)-4-nitroaniline (65 g, 0.273 mol), Raney-nickel (6.5 g) and methanol (350 mL). The reaction mixture was hydrogenated at 50-psi hydrogen at 25°. The reaction was monitored by TLC (benzene-ethyl acetate, 4:1) and upon completion of hydrogen uptake (10 hr), the catalyst was filtered off and the filtrate concentrated under reduced pressure, the resulting semi-solid was crystallized from methanol-water (350 mL, 70:30) to give **4** as an off-white powder (48 g, 84%, mp. 111-113°, *lit.*[4] mp. 112-114°. ^{1}H NMR ($CDCl_3$, 200 MH_Z): δ 1.5 (s, 9H, *t*-butyl), δ 3.45 (b, 2H, NH_2), δ 6.32(s, b, 1H, - NHCO-), δ 6.60 and δ 7.20 (d, 4H, aromatic).

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