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A Facile Synthesis of Primary and Secondary Amines*

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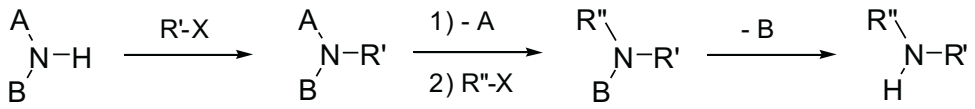
A facile synthesis of primary amines (R-CH_2-NH_2, where R = napht-2-yl, anthr-9-yl, phenyl, *p*-nitrophenyl) and secondary amines (R-NH-R', where R is as mentioned above for primary amines and R' = methyl) is described. The primary amines were obtained by alkylation of di-*tert*-butyl imidodicarbonate (Boc_2NH) under phase-transfer catalysis (PTC) conditions, followed by acidolytic removal of the amine protecting groups. The secondary amines were obtained from the appropriate primary amines by alkylation of their N-*tert*-butoxycarbonyl derivatives (Boc-NH-R), followed by Boc group acidolysis. It is worth emphasizing that the substrates for synthesis of secondary amines (Boc-NH-R) were obtained *via* selective removal of one of the *tert*-butoxycarbonyl groups from the alkylated di-*tert*-butyl imidodicarbonates (Boc_2N-R).

Key words: primary and secondary amine synthesis, di-*tert*-butyl imidodicarbonate, PTC catalysis

The classical method of the synthesis of primary amines involves the alkylation of the potassium salt of phthalimide, followed by acidic hydrolysis of the phthaloyl group was introduced by Gabriel [1] over 100 years ago. Subsequently, this method has been modified, *i.e*. both alkylation and hydrolysis steps have been changed and, as a result, less "drastic" conditions could be applied [2,3]. However, the Gabriel's method is not suitable for synthesis of secondary amines. Replacement of the phthaloyl group in the phthalimide moiety by two chemically different electron withdrawing groups, like some derivatives of carboxylic, phosphonic or sulphonic groups, leads to a new type of Gabriel's reagent, which is useful for synthesis of primary amines and also, after selective removal of one of the groups, for synthesis of secondary amines (Scheme below):



Scheme 1. Synthesis of primary and secondary amines (where: R'X and R''X – alkylating agents (chloro- or bromo-methylarenes), and A and B – electronwithdrawing groups (-CO-R, -CO-OR, -SO_2R or -$PO(OR)_2$).

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* Dedicated to Prof. E. Borowski on the occasion of his 75th birthday.

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RESULTS AND DISCUSSION

For our purpose, *i.e*. for syntheses of the primary and secondary amines, we have chosen Boc_2NH (di-*tert*-butyl imidodicarbonate) as a starting compound. This new Gabriel's type reagent has been used for the syntheses of primary amines and α-amino acids [4–7], but so far only in a classical methodology involving an alkylation of its potassium salt. In our work we have applied new conditions of Boc_2NH alkylation involving phase-transfer catalysis. We have also compared the results with those for classical alkylation of potassium salt of Boc_2NH. In our approach, instead classical KOH, weaker bases like K_2CO_3 can be employed. Additionally, usage of phase-transfer catalysts – tetrabutylammonium bromide (TBAB), increases solubility of ionic reagents in organic solvents and the rate of the reaction, thus the alkylation process can be performed at milder conditions (*e.g.* lower temperature).

We chose Boc_2NH due to simplicity of its synthesis involving either introduction of two Boc-protections on the nitrogen of formamide [4,8] followed by a nucleophilic removal of formyl group or by exhaustive acylation of the nitrogen atom in ammonium chloride with three Boc groups followed by partial deprotection with 2-diethylaminoethylenediamine yielding the desired product [9]. Other advantages of this compound are the relatively mild conditions of removal of *tert*-butoxycarbonyl group after the synthesis by means of acidolysis (50% trifluoroacetic acid in CH_2Cl_2 or HCl in dioxane at room temperature [10]). Additionally, two *tert*-butoxycarbonyl groups located on the same nitrogen are not chemically equivalent and it is possible to split selectively one of these groups from Boc_2N-R using the molar equivalent of trifluoroacetic acid [11]. The obtained N-*tert*-butoxycarbonyl-amine derivative (Boc-NH-R) can be alkylated at the nitrogen atom under the same PTC conditions as applied previously for alkylation of Boc_2NH. Liberation of secondary amines from Boc-N(R)R' can be accomplished by treatment with 50% TFA in CH_2Cl_2.

The alkylation of Boc_2NH proceeded smoothly and the best yield and purity of final product (Boc_2N-R) were obtained when tetrahydrofuran (THF) was used as the reaction solvent. Acetonitrile (CH_3CN) proved to be a less satisfying solvent, resulting in the formation of more side products. An application of other solvents like toluene or CH_2Cl_2 required higher reaction temperature, which resulted in decomposition of the substrate and products (the Boc group is unstable at higher temperatures) and yields in the range of 40÷50%. The application of NaH, powdered KOH or K_2CO_3 as a base gave comparable yields and purity of the alkylation products. During the optimization of the alkylation reaction conditions we applied the following two phase-transfer catalysts: benzyltriethylammonium chloride (TEBAC) and tetrabutylammonium bromide (TBAB). Better results were obtained for the former so the elaborated optimum reaction conditions are as follows: reactions are carried out in THF in the presence of K_2CO_3 or NaH as a base and TBAB as a phase-transfer catalyst. The yields of alkylation of Boc_2NH under PTC conditions were slightly higher (81÷96%) than those for the reaction carried out under classical alkylation conditions of potassium salt of Boc_2NH (79÷89%).

In order to obtain a substrate for the next alkylation reaction removal of one Boc group from Boc_2N-R was performed by means of trifluoroacetic acid according to the modified method of Connell *et al*. [11]. At this step the yields were almost quantitative.

The next step – alkylation of Boc-NH-R with an appropriate alkylating agent (dimethyl sulphate, diethyl sulphate, allyl bromide or benzyl bromide) was performed in THF using NaH as a base in the presence of TBAB at 35÷40°C temperature. Application of other bases necessitated higher reaction temperatures, which increased the amounts of side products formed due to decomposition of the substrate and the product. The optimization of reaction conditions was done for the reaction of Boc-NH-R (where R = napht-2-yl, anthr-9-yl, phenyl) with dimethyl sulphate. The yields of the methylation process were very satisfactory (87÷93%).

The prepared Boc-protected secondary amines served as precursors of final products since their treatment with 50% TFA in CH_2Cl_2 gives the respective amine trifluoroacetate with almost quantitative yields.

The described methodology of the amines preparation was elaborated by us because of the need of simple and efficient access to secondary amines containing aromatic chromophores that can be useful, after their incorporation into a peptide chain, in conformational analyses by means of fluorescence. The application of fluorescence methods for conformational studies of peptides requires the presence of appropriate chromophores (acceptor and/or donor of energy [12]). Usually aromatic amino acids, *i.e*. tyrosine and tryptophan, are used as the chromophores, but many peptides do not contain these aromatic amino acids. Simple modification of a studied peptide by transformation of its C-terminal carboxylic group into an amide, which can be achieved by reaction with an amine containing the appropriate chromophore (*e.g.* naphtylmethylamine), leads to a compound which can be a suitable substrate for conformational studies by means of fluorescence. Our methodology allows us to obtain different types of amine-derived chromophores with desired fluorescence parameters (long lifetime of excited state, high fluorescence quantum yield, *etc.*). However, the main advantage of the described method is the possibility of synthesis of both primary and secondary amine starting from one, easily accessible substrate – *tert*-butyl imidodicarbonate.

EXPERIMENTAL

General. All solvents and reagents were of analytical purity or were purified according to literature procedures [13]. The purity of compounds was assessed by thin layer chromatography and by spectroscopic (NMR, IR) methods. TLC was carried out on aluminium sheets precoated with SiO_2 60 F-254 (Merck), using the following solvent systems: A: AcOEt:petroleum ether (1:10, v/v) and B: $CHCl_3$:MeOH:AcOH (85:10:5, v/v). Individual spots were visualised using UV lamp ($\lambda_{obs.}$ = 254 nm) and/or revealed using ninhydrin reagent. IR spectra were recorded on a Bruker IFS 66 spectrometer (KBr pellets or nujol). NMR spectra were measured on Varian Mercury 400 MHz and Tesla BF-567A 100 MHz spectrometers. Mass spectra were obtained using VG Masslab Tri-3 spectrometer with quadrupole filter. Melting points are uncorrected.

General procedure of Boc_2NH alkylation (the PTC method). To a solution of Boc_2NH (10 mmoles, 2.17 g) in THF (20 ml) finely powdered K_2CO_3 (11 mmoles, 1.55 g), alkylating agent (an appropriate bromo-methylarene) (11 mmoles) and TBAB (1 mmole, 0.33 g) were added. The resulting mixture was stirred at room temperature till the time when TLC analysis (solvent system: diethyl ether/hexane = 1:1) revealed lack of Boc_2NH. The solvent was removed under reduced pressure and the residue was partitioned between diethyl ether and water. The organic phase was next washed with H_2O, 0.5M $NaHCO_3$, brine, 0.5M $KHSO_4$, brine, 0.5M $NaHCO_3$, brine and dried (anh. $MgSO_4$). Filtration of drying agent, followed by evaporation of the solvent yielded the product, which was used for the next steps. Crystallization (petroleum ether (fr. 45÷60°C) or hexane) or column chromatography on Merck Kieselgel 60 (70÷230 mesh, mobile phase: ethyl acetate/petroleum ether mixture) for oils was performed only for the analytical purposes.

N,N-Bis(*tert*-butoxycarbonyl)anthracen-9-ylmethylamine*:* Yield: 91%; M.p.: 55.5÷57.0°C; ^{1}H-NMR (400 MHz, DMSO-d_6, δ *vs* TMS, ppm): 1.15 (18 H, s, 2×Boc), 5.72 (2H, s, CH_2), 7.49–7.57 (4H, m, H-2, H-3, H-6, H-7 ar.), 8.08–8.10 (2H, m, H-4, H-5, ar.), 8.39–8.41 (2H, d, J = 8.8 Hz, H-1, H-8 ar.), 8.60 (1H, s, H-10 ar.); IR (KBr, ν, cm^{-1}): 1753, 1697 ($\nu_{C=O}$, urethane); TLC: R_f = 0.44^A; Anal. Calcd. for $C_{25}H_{29}NO_4$: C, 73.7; H, 7.2; N, 3.4. Found: C, 73.8; H, 7.1; N, 3.5.

N,N-Bis(*tert*-butoxycarbonyl)naphtalen-2-ylmethylamine: Yield: 93%; M.p.: 94÷96°C; ^{1}H-NMR (400 MHz, DMSO-d_6, δ *vs* TMS, ppm): 1.40 (18 H, s, 2×Boc), 4.85 (2H, s, CH_2), 7.38-7.41 (1H, dd, J = 8.4 Hz, J = 1.6 Hz, H-3 ar.), 7.47–7.53 (2H, m, H-6, H-7, ar.), 7.63 (1H, br. s, H-1 ar.), 7.87–7.91 (3H, m, H-4, H-5, H-8 ar.); IR (KBr, ν, cm^{-1}): 1776, 1694 ($\nu_{C=O}$, urethane); TLC: R_f = 0.47^A; Anal. Calcd. for $C_{21}H_{27}NO_4$: C, 70.6; H, 7.6; N, 3.9. Found: C, 70.4; H, 7.7; N, 4.0.

N,N-Bis(*tert*-butoxycarbonyl)benzylamine: Yield: 96%; M.p.: 30÷31°C (30÷31°C [4]); ^{1}H-NMR (400 MHz, DMSO-d_6, δ *vs* TMS, ppm): 1.39 (18 H, s, 2×Boc), 4.69 (2H, s, CH_2), 7.21–7.27 (3H, m, H-2, H-4, H-6 ar.), 7.32–7.37 (2H, m, H-3, H-5, ar.); IR (film, ν, cm^{-1}): 1748, 1701 ($\nu_{C=O}$, urethane); TLC: R_f = 0.52^A; Anal. Calcd. for $C_{17}H_{25}nO_4$: C, 66.4; H; 8.2; N, 4.6. Found: C, 66.6; H, 8.2; N, 4.6.

N,N-Bis(*tert*-butoxycarbonyl)-4-nitrobenzylamine*:* Yield: 81%; M.p.: 110÷112°C; ^{1}H-NMR (400 MHz, DMSO-d_6, δ *vs* TMS, ppm): 1.41(18 H, s, 2×Boc), 4.81 (2H, s, CH_2), 7.47–7.49 (2H, *AA'* XX', J = 8.8 Hz, H-2, H-6 ar.), 8.22–8.24 (2H, AA' *XX'*, J = 8.8 Hz, H-3, H-5 ar.); IR (KBr, ν, cm^{-1}): 1728, 1689 ($\nu_{C=O}$, urethane); TLC: R_f= 0.38^A; Anal. Calcd. for $C_{17}H_{24}N_2O_6$: C, 57.9; H, 6.9; N, 7.9. Found: C, 57.9; H, 6.8; N, 8.0.

General procedure of Boc_2NH alkylation (classical alkylation *via* potassium salt – Boc_2NK). To a stirred solution of freshly prepared potassium salt of Boc_2NH [5] (10 mmoles, 2.55 g) in DMF (10 ml) an alkylating agent (an appropriate bromo-methylarene) (11 mmoles) was added slowly. The resulting slurry was stirred till the time when TLC analysis (solvent system diethyl ether/hexane = 1:1) revealed lack of Boc_2NH. The solvent was stripped off under reduced pressure and the residue was worked-up as mentioned in the procedure described above.

General procedure for removal of one Boc group from Boc_2N-R. To an ice-cooled solution of Boc_2N-R (10 mmoles) in CH_2Cl_2 (50 ml) TFA (12.5 mmoles) was added and the resulting mixture was stirred at room temperature until the TLC analysis showed the absence of the substrate was (about 3 h). Then the mixture was washed with 0.5M $NaHCO_3$ (3×10 ml) and brine (1×10 ml). The organic phase was dried ($MgSO_4$) and the solvent was evaporated. Yield 98–100%. These BocN(R)H were pure enough for the second alkylation.

N-(*tert*-Butoxycarbonyl)anthracen-9-ylmethylamine: M.p.: 134÷135°C; ^{1}H-NMR (400 MHz, DMSO-d_6, δ *vs* TMS, ppm): 1.39 (9 H, s, Boc), 5.13–5.15 (2H, d, J = 5.2 Hz, CH_2), 7.39 (1H, br.s., N-H), 7.50–7.58 (4H, m, H-2, H-3, H-6, H-7 ar.), 8.08–8.10 (2H, m, H-4, H-5, ar.), 8.44–8.46 (2H, d, J = 8.8 Hz, H-1, H-8 ar.), 8.58 (1H, s, H-10 ar.); IR (KBr, ν, cm^{-1}): 3368 (ν_{N-H}), 1679 ($\nu_{C=O}$, urethane); TLC: R_f = 0.36^A. MS (FAB): 308 $(M+H)^+$.

N-(*tert*-Butoxycarbonyl)naphtalen-2-ylmethylamine: M.p.: 96÷98°C; ^{1}H-NMR (100 MHz, $CDCl_3$, δ *vs* TMS, ppm): 1.39 (9 H, s, Boc), 4.50–4.57 (2H, d, J = 7.5 Hz CH_2), 5.10 (1H, br. s., N-H), 7.45–7.65 (3H, m, H-3, H-6, H-7 ar.), 7.75–8.00 (4H, m, H-1, H-4, H-5, H-8 ar.); IR (KBr, ν, cm^{-1}): 3349 (ν_{N-H}), 1687 ($\nu_{C=O}$, urethane); TLC: R_f = 0.26^A. MS (FAB): 258 $(M+H)^+$.

N-(*tert*-Butoxycarbonyl)benzylamine: M.p.: 53÷54°C (54÷55°C [14]); ^{1}H-NMR (100 MHz, $CDCl_3$, δ *vs* TMS, ppm): 1.47 (9 H, s, Boc), 4.35–4.40 (2H, d, J = 6.5 Hz, CH_2), 4.95 (1H, br. s., N-H), 7.25 (5H, s, H-2, H-3, H-4, H-5, H-6 ar.); IR (film, ν, cm^{-1}): 3308 (ν_{N-H}), 1679 ($\nu_{C=O}$, urethane); TLC: R_f = 0.38^A. MS (FAB): 208 $(M+H)^+$.

N-(*tert*-Butoxycarbonyl)-4-nitrobenzylamine: M.p.: 105÷108°C (109÷110°C [15]); ^{1}H-NMR (100 MHz, $CDCl_3$, δ *vs* TMS, ppm): 1.47 (9 H, s, Boc), 4.42–4.50 (2H, d, J = 7.5 Hz, CH_2), 5.10 (1H, br.s., N-H), 7.50–7.60 (2H, *AA'* XX', J = 10.0 Hz, H-2, H-6 ar.), 8.25–8.35 (2H, AA' *XX'*, J = 10.0 Hz, H-3, H-5 ar.); IR (KBr, ν, cm^{-1}): 3325 (ν_{N-H}),1689 ($\nu_{C=O}$, urethane); TLC: R_f = 0.10^A. MS (FAB): 253 $(M+H)^+$.

General method of Boc-NH-R alkylation. To a suspension of NaH (7 mmoles, 55% in mineral oil) in dry THF (20 ml) Boc-NH-R (5 mmoles) and TBAB (0.5 mmoles, 0.16 g) were added and the resulting mixture was stirred at room temperature under argon atmosphere for 15 min. Then $(CH_3O)_2SO_2$ (7 mmoles) was added dropwise and temperature was kept at 40°C until TLC inspection showed lack of a substrate. The work-up was analogous to isolation of products of alkylation of Boc_2NH.

N-(*tert*-Butoxycarbonyl)(anthracen-9-ylmethyl)methylamine: M.p.: 279÷280°C; ^{1}H-NMR (100 MHz, DMSO-d_6, δ *vs* TMS, ppm): 1.52 (9 H, s, Boc), 3.45 (3H, s, CH_3), 5.00 (2H, s, CH_2), 7.57–7.75 (4H, m, H-2, H-3, H-6, H-7 ar.), 8.12–8.37 (2H, m, H-4, H-5, ar.), 8.5–8.77 (3H, H-1, H-8, H-10 ar.); IR (KBr, ν, cm^{-1}): 1675 ($\nu_{C=O}$, urethane); TLC: R_f = 0.38^A. MS (FAB): 322 $(M+H)^+$.

N-(*tert*-Butoxycarbonyl)(naphtalen-2-ylmethyl)methylamine: thick oil; ^{1}H-NMR (100 MHz, $CDCl_3$, δ *vs* TMS, ppm): 1.50 (9 H, s, Boc), 2.88 (3H, s, CH_3), 4.63 (s, 2H, CH_2), 7.33–7.95 (7H, m, naphthalene residue); IR (KBr, ν, cm^{-1}): 1694 ($\nu_{C=O}$, urethane); TLC: R_f = 0.28^A. MS (FAB): 272 $(M+H)^+$.

N-(*tert*-Butoxycarbonyl)benzylmethylamine: oil; ^{1}H-NMR (100 MHz, $CDCl_3$, δ *vs* TMS, ppm): 1.50 (9 H, s, Boc), 2.83 (3H, s, CH_3), 4.45 (2H, s, CH_2), 7.25–7.40 (5H, m, H-1, H-2, H-4, H-5, H-6 ar.); IR (film, ν, cm^{-1}): 1696 ($\nu_{C=O}$, urethane); TLC: R_f = 0.39^A. MS (FAB): 222 $(M+H)^+$.

General procedure for removal of Boc-group(s) from Boc-N(Me)R and Boc_2N-R; preparation of amines. To a solution of Boc-N(Me)R (or Boc_2N-R) (5 mmoles) in CH_2Cl_2 (15 ml) TFA (15 ml) was added dropwise and the resulting mixture was stirred at room temperature for 1 h. Then the solvents were evaporated under reduced pressure and the residue was treated with ethyl ether. The crystalline trifluoroacetates were isolated by filtration.

(Anthracen-9-ylmethyl)methylamine trifluoroacetate: M.p.: 210÷221°C (dec.); ^{1}H-NMR (400 MHz, $CDCl_3$, δ *vs* TMS, ppm): 2.46 (3H, s, CH_3), 4.75 (2H, s, CH_2), 7.49–7.57 (4H, m, H-2, H-3, H-6, H-7 ar.), 8.08–8.10 (2H, m, H-4, H-5, ar.), 8.39–8.41 (2H, d, J = 8.8 Hz, H-1, H-8 ar.), 8.60 (1H, s, H-10 ar.), 9.90 (2H, s, NH_2^+); IR (KBr, ν, cm^{-1}): 1665 ($\nu_{C=O}$, COO^-); TLC: R_f = 0.51^A. MS (FAB) 222 $[(M+H)^+$ -TFA].

(Naphtalen-2-ylmethyl)methylamine trifluoroacetate: M.p = 120÷121°C; ^{1}H-NMR (100 MHz, $CDCl_3$, δ *vs* TMS, ppm): 2.48 (3H, s, CH_3), 4.10 (2H, s, CH_2), 7.45–7.72 (3H, m, H-3H-6, H-7, ar.), 7.84–8.00 (4H, m, H-1, H-4, H-5, H-8H ar.), 9.80 (2H, br. s, NH_2^+) ; IR (KBr,ν, cm^{-1}): 1679 ($\nu_{C=O}$, COO^-); TLC: R_f = 0.38^B. MS (FAB): 172 $[(M+H)^+$ -TFA].

Benzylmethylamine trifluoroacetate: M.p.: 64÷65°C; ^{1}H-NMR (100 MHz, $CDCl_3$, δ *vs* TMS, ppm): 2.52 (3H, s, CH_3), 4.0 (2H, s, CH_2), 7.50 (5H, s, H-2, H-3, H-4, H-5, H-6 ar.), 9.76 (2H, br. s, NH_2^+); IR (film, ν, cm^{-1}): 1696 ($\nu_{C=O}$, COO^-); TLC: R_f = 0.40^B. MS (FAB): 122 $[(M+H)^+$ -TFA].

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