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Synthesis, Properties and Use of Nitridotricarbonic Acid Tri-*tert*-Butyl Ester

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Exhaustive *tert*-butoxycarbonylation of Boc_2NH with Boc_2O-DMAP furnishes Boc_3N in nearly quantitative yield. This stable compound is susceptible to nucleophiles and affords Boc_2NH upon aminolysis. The properties of Boc_3N have been exploited in a practical one-pot procedure for the synthesis of Boc_2NH from NH_4Cl, which is particularly economical in the preparation of $Boc_2{}^{15}NH$.

In connection with efforts to optimize our earlier synthesis of Boc_2NH (Boc = *tert*-butoxycarbonyl), originally prepared by Carpino,[1] we observed that the crude product always contained minor amounts of $BocNH_2$ together with traces of a hitherto unknown compound.[2,3] After isolation and purification, spectroscopic evidence indicated that this new compound was nitridotricarbonic acid tri-*tert*-butyl ester, Boc_3N. This substance is a white crystalline solid and is perfectly stable under ordinary conditions. Scattered information about nitridotricarbonic acid trialkyl esters is available in the literature. The only derivative described hitherto appears to be the triethyl ester.[4]

Synthesis of Boc_3N. Larger amounts of pure Boc_3N were conveniently accessible by exhaustive *tert*-butoxycarbonylation of Boc_2NH with Boc_2O in dry acetonitrile in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP), as depicted in eqn. (1).[5] The yield in this conversion was essentially quantitative and the

$$Boc_2NH \underset{DEAEA/CH_3CN}{\overset{Boc_2O,\ DMAP/CH_3CN}{\rightleftharpoons}} Boc_3N \qquad (1)$$

desired product of excellent purity was obtained by a simple work-up.

Nucleophilic cleavage of Boc_3N. Although Boc_3N was sufficiently stable under neutral conditions, it seemed to be rather labile in alkaline or acidic media. Thus Boc_3N readily underwent nucleophilic displacement in the presence of various amines, thereby smoothly reverting to Boc_2NH. Evidently, the third Boc function is considerably more unstable to such aminolytic conditions than are the remaining Boc groups.[6] This cleavage could also be readily accomplished with the strong base 1,1,3,3-tetramethylguanidine (TMG) in methanol but a preliminary NMR study indicated that this selective deblocking was at least five times faster when a small excess of 2-diethylaminoethylamine (DEAEA) was used with acetonitrile as the reaction medium. This latter deprotection reagent also provided a more practical work-up since all of the reagent was readily removed by a simple acidic extraction.[2] It is surprising that no trace of $BocNH_2$ was detected in the crude cleavage mixture even after prolonged treatment with an excess of strong bases such as TMG or hydrazine.[6] We have also confirmed that the potassium salt of Boc_2NH was stable for several months when stored under normal laboratory conditions. Obviously the Boc_2N^- anion is an electronically stabilized species under these conditions.

One-pot preparation of Boc_2NH via Boc_3N. The properties of this novel compound were further exploited in a new convenient one-pot procedure for the efficient synthesis of the very useful amine precursor Boc_2NH using NH_4Cl as the starting material. Thus, powdered NH_4Cl was suspended in a solution of excess Boc_2O in dry acetonitrile. Upon slow addition of an excess of DMAP, the $BocNH_2$ initially formed was subsequently converted via Boc_2NH into Boc_3N. This intermediate was then aminolysed with DEAEA to furnish essentially pure Boc_2NH in excellent overall yield. In this context it is also worth mentioning that a stepwise approach using other bases such as triethylamine or TMG to liberate ammonia from NH_4Cl, together with DMAP, furnished mainly $BocNH_2$. This intermediate species could not readily be converted into the desired Boc_3N using a large excess of Boc_2O in the presence of catalytic amounts of DMAP following the one-pot strategy. Presumably DMAP is partly protonated by the hydrochloride present, thereby inhibiting its catalytic activity.

Attempted selective acidolysis of Boc_3N. Preliminary experiments aimed at the selective removal of one Boc function from Boc_3N under acidic conditions have given less encouraging results. Normally, Boc derivatives are deprotected with mild acid[7] and it has also proved possible to split off one Boc group selectively from the Boc_2N moiety using a small excess of trifluoroacetic acid (TFA) in a dilute solution.[8–11] However, attempted removal of one Boc group from Boc_3N using a small excess of TFA in dilute dichloromethane solution gave a mixture of Boc_3N, Boc_2NH and $BocNH_2$. A further investigation revealed that excess trichloroacetic acid rapidly and non-selectively removed all Boc groups, whereas Boc_3N was largely uneffected by formic acid and chloroacetic acid under comparable conditions. A somewhat slower deprotection occurred in the presence of dichloroacetic acid but even in this case the removal of one Boc moiety could not be achieved in a selective manner.

Concluding remarks

This new procedure provides a viable alternative for the synthesis of ^{15}N-labelled Boc_2NH from the less expensive $^{15}NH_4Cl$. The previously published procedure[12] utilized $HCO^{15}NH_2$ as the starting material, thus mimicking the synthesis of unlabelled Boc_2NH.[2] In recent years $Boc_2{}^{15}NH$ has found interesting applications in the preparation of various ^{15}N-labelled amino acids.[8–10] The increased accessibility of $Boc_2{}^{15}NH$ afforded by this method will no doubt render this important amine precursor a convenient starting material for the synthesis of various other ^{15}N-labelled amino derivatives.

Experimental

All melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. All solvents used as reaction media were of analytical grade and were dried over molecular sieves (4 Å). DMAP was recrystallized from EtOAc (4 ml g^{-1}, decolourizing carbon) and dried meticulously under high vacuum before use. TLC analyses were performed on 0.25 mm thick precoated UV-sensitive silica plates (Merck DC-Fertigplatten Kieselgel 60 F_{254}) and the mobile phases used were petroleum ether (b.p. 40–65°C)–Et_2O 2 : 1 (A) and toluene–MeCN 2 : 1 (B). TLC spots were visualized, after brief heating, by exposure to Cl_2 followed by dicarboxidine spray (violet–blue spots).[13] ^1H and ^{13}C NMR spectra were recorded on a JEOL JMN-EX 270 instrument at 270 MHz and 67.9 MHz, respectively, and ^{15}N NMR spectra were measured on a JEOL FX 90Q at 9.03 MHz, all in $CDCl_3$. The NMR data are compiled in Table 1. FT-IR spectra were recorded for KBr disks at 4 cm^{-1} resolution on a Mattson Polaris spectrometer equipped with software for conversion to % transmission and unbiased determinations of positions and intensities of bands. Pertinent peaks are summarized in Table 2. (For comparison, $BocNH_2$ and its ^{15}N labelled analogue are also included in Tables 1 and 2). Elemental analyses (CHN) were carried out by Mikro Kemi AB, Uppsala, Sweden.

*Nitridotricarbonic acid tri-*tert*-butyl ester (Boc_3N).* Recrystallized Boc_2NH (2.17 g, 10.0 mmol) and Boc_2O (2.40 g, 11.0 mmol) were dissolved in dry CH_3CN (10 ml) and treated with DMAP (122 mg, 1.00 mmol) in small portions with rapid stirring at room temperature under dry argon. After 1 h, TLC indicated complete reaction and after a further 2 h the solvent was stripped off at reduced pressure. The oily brownish residue was partitioned between ether (80 ml) and 0.2 M citric acid (40 ml) and the colourless organic extract was washed successively with 0.2 M citric acid, 1 M $NaHCO_3$ and saturated NaCl (3 × 20 ml each) and dried over $MgSO_4$. After treatment with decolourizing carbon, the solvent was evaporated off to furnish a white solid weighing 3.11 g (98%). TLC (A,B) on the crude product gave one spot. Recrystallization of this material from light petroleum (10 ml g^{-1}, decolourizing carbon) afforded white crystals m.p. 66–66.5°C after seeding and chilling to 0°C overnight. Found: C, 56.8; H, 8.6; N, 4.6. $C_{15}H_{27}NO_6$ requires C, 56.8; H, 8.6; N, 4.6.

*[^{15}N]Nitridotricarbonic acid tri-*tert*-butyl ester ($Boc_3{}^{15}N$).* Prepared from $Boc_2{}^{15}NH$[12] on a 5 mmol scale by analogy with the unlabelled analogue above in 99% crude yield. Recrystallization furnished white crystals m.p. 66–66.5°C.

*Di-*tert*-Butyl imidodicarbonate (Boc_2NH) by DEAEA-mediated aminolysis of Boc_3N.* Recrystallized Boc_3N (1.59 g, 5.00 mmol) was dissolved in dry CH_3CN (10 ml) under dry nitrogen and treated dropwise with DEAEA

Table 1. NMR data of Boc amides in $CDCl_3$ (δ).

Comp. (5% soln.)	^1H NMR ($\delta_{TMS}=0$)		^{13}C NMR ($\delta_{CDCl_3}=77.0$)			^{15}N NMR ($\delta_{HCO^{15}NH_2}=113.2$)
	CH_3	NH ($J_{^{15}N^1H}$/Hz)	CH_3	Me_3C	CO ($J_{^{13}C^{15}N}$/Hz)	
$BocNH_2$	1.45	4.61	28.2	79.6	156.4	—
$Boc^{15}NH_2$	1.45	4.74 (88.8)	28.2	79.5	156.5 (25.7)	73.5
Boc_2NH	1.48	6.81	28.0	81.9	149.7	—
$Boc_2{}^{15}NH$	1.48	6.82 (90.8)	28.0	81.9	149.7 (25.6)	119.4
Boc_3N	1.51	—	27.7	83.9	148.9	—
$Boc_3{}^{15}N$	1.51	—	27.6	83.9	148.8 (22.0)	158.6

Table 2. FT-IR data on Boc_3N and related substances.[a]

Compound	NH	CO	Amide-II	Other strong bands
$BocNH_2$	3449 $(s)_2$ 3261 (m)	1686 $(s)_1$	1608 $(m)_5$	1393_4, 1366_3
$Boc^{15}NH_2$	3438 $(s)_2$ 3247 (m)	1679 $(s)_1$	1603 $(m)_5$	1392_4, 1366_3
Boc_2NH	3270 (m)	1762 $(s)_3$[b]	1529 $(s)_4$	1146_2, 1102_1
$Boc_2{}^{15}NH$	3260 (m)	1760 $(s)_3$[c]	1513 $(s)_4$	1140_1, 1097_2
Boc_3N	—	1799 $(s)_3$ 1757 (s) 1723 (s)	—	1284_2, 1261, 1158_4, 1103_1
$Boc_3{}^{15}N$	—	1799 $(s)_3$ 1756 (s) 1723 (s)	—	1275_5, 1257_4, 1151_2, 1099_1

[a]Bands are characterized as s(trong), m(edium) and w(eak) and/or by subscripts according to decreasing intensity. [b]Weak bands visible also at 1799 and 1775 cm^{-1}. [c]Weak bands also at 1798 and 1774 cm^{-1}.

(871 mg, 7.50 mmol) with rapid stirring at room temperature over a period of 30 min. The pale yellow solution was stirred overnight after which TLC (A) confirmed that all Boc_3N had been consumed. The solvent was stripped off at reduced pressure and the brownish syrupy residue was partitioned between ether (80 ml) and 1 M $KHSO_4$ (40 ml). The colourless extract was washed in turn with 1 M $KHSO_4$, 1 M $NaHCO_3$ and sat. NaCl (3 × 20 ml each), dried over $MgSO_4$ and treated with decolourizing carbon. The yield of pure Boc_2NH was 1.04 g (96%) and the recrystallized sample was identical in all respects with an authentic specimen.[2]

*Di-*tert*-Butyl imidodicarbonate (*Boc_2NH*). One-pot procedure from* NH_4Cl. Well-dried, finely ground NH_4Cl (535 mg, 10.0 mmol) was suspended in a solution of Boc_2O (10.9 g, 50.0 mmol) in dry CH_3CN (30 ml) under dry argon at ambient temperature. The resulting slurry was then treated dropwise with DMAP (2.45 g, 20.0 mmol) dissolved in dry CH_3CN (20 ml) with rapid stirring over a period of 1 h. The initially vigorous evolution of gas gradually subsided after a few hours and the stirring was continued overnight (23 h) with exclusion of moisture. TLC (A,B) confirmed that the reaction mixture contained Boc_3N together with traces of the desired end product Boc_2NH. The resulting clear yellow solution was treated dropwise with vigorous agitation with DEAEA (4.65 g, 40.0 mmol) over a period of 1 h and the reaction mixture was stirred at room temperature overnight with exclusion of atmospheric moisture. Removal of the solvent at reduced pressure left a brownish thick oil which was partitioned between ether (200 ml) and 1 M $KHSO_4$ (100 ml). The ethereal extract was washed in turn with 1 M $KHSO_4$, 1 M $NaHCO_3$ and saturated NaCl (3 × 50 ml each), dried over $MgSO_4$ and treated with decolourizing carbon. Evaporation afforded 2.09 g (96%) of essentially pure product and the recrystallized sample was identical in all respects with an authentic specimen.[2]

*Di-*tert*-Butyl [*^{15}N*]imidodicarbonate (*$Boc_2{}^{15}NH$*). One-pot procedure from* $^{15}NH_4Cl$. $Boc_2{}^{15}NH$ was synthesized in 94% yield on a 5 mmol scale by the procedure detailed above for the unlabelled analogue. The properties of the recrystallized sample agreed in all respects with those reported earlier.[7]

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