Selective Cleavage of Boc-acylamides. A Novel Approach to Deacylation of Carboxamides

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Boc (*tert*-butoxycarbonyl) derivatives were recently prepared from various amides. This paper describes some of their properties with particular attention to mild amide cleavage. Boc-protected carboxamides were cleaved by aminolysis with complete selectivity to give the corresponding *tert*-butyl carbamates. The amines used ranged from hydrazine to morpholine, but for preparative purposes 2-diethylaminoethylamine was preferred. A simple two-step one-pot procedure for *tert*-butoxycarbonylation followed by aminolysis was developed which could be used for removal of formyl, acetyl and benzoyl groups. In extreme cases, these derivatives were cleaved by alcoholysis. Upon addition of bases such as *N,N,N',N'*-tetramethylguanidine (TMG) this reaction became very fast. TMG-catalysed methanolysis gave 98 % cleavage in 30 min or less in two preparative experiments.

Amides are relatively stable compounds that are normally cleaved by heating in strongly acidic or alkaline media,[1] although a few milder, more specific cleavage methods have also been described.[2] We recently reported briefly on a novel, exceptionally mild procedure for the selective cleavage of such compounds[3] based on prior exhaustive *tert*-butoxycarbonylation of the starting amides,[4] and resulting in acid-labile *tert*-butoxycarbonyl (Boc) derivatives of the amino components. Below, we report in detail on this alternative approach, the potential of which is illustrated by the selective removal of the formyl, acetyl and benzoyl groups from the corresponding simple amides which were chosen as model compounds.

Deacylation by aminolysis. Recently the preparation and properties of miscellaneous Boc-acylamides were reported, and some general aspects of the scope and limitations of this novel synthetic method were also outlined.[4] Although these Boc-acylamides are essentially stable for months toward atmospheric moisture at room temperature, it was discovered that these compounds could be cleaved by certain nucleophilic bases under very mild conditions. For example, when Boc-acetamides *1a–1i* (Scheme 1) are treated with 2-diethylaminoethylamine (DEAEA) in acetonitrile solution, the acetyl groups are smoothly removed and the corresponding *tert*-butyl carbamates *2a–2i* are obtained in excellent yields. In this context, we must emphasize that the latter reaction is highly selective. In fact, no trace of the anomalous cleavage products (i.e., acetamides) can be detected in the crude reaction mixtures by TLC or ^{1}H NMR. This specific reaction has also been exploited in a new, efficient synthesis of di-*tert*-butyl iminodicarbonate, a useful Gabriel reagent.[5]

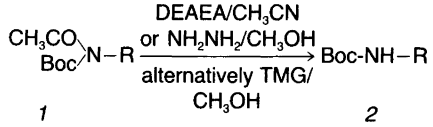
Boc-acylamides can also be cleaved by other amines, but DEAEA was chosen to facilitate work-up since the principal side products can be removed easily by acid extraction. It was also confirmed that acetamides in general are not sensitive to DEAEA under normal reaction conditions.

Influence of structure on aminolysis. The DEAEA-mediated aminolysis of *1a–1f* is reasonably fast and the reaction rate appears to be fur-

ther enhanced by electron-withdrawing substituents (cf. *1c* and *1e,* Table 1). It may also be worth mentioning that the ester group in *1c* remains intact under these circumstances. On the other hand, the cleavage of *1g–1i,* containing an aliphatic amide moiety, proceeds considerably more slowly, even in the presence of a large excess of DEAEA. The reaction is also influenced by steric factors, as could be judged from a semi-quantitative ^{1}H NMR experiment (see Experimental). As expected, the DEAEA-assisted cleavage of *1b* as well as its *meta* isomer parallels that of *1a,* whereas the removal of the acetyl group in the corresponding *ortho* isomer is considerably retarded. A rough estimate based on inspection of the ^{1}H NMR spectra indicated that the cleavage rate of the latter isomer is lower than that of the two former by a factor of at least fifty.

One-pot procedure for tert-*butoxycarbonylation and aminolysis.* By this strategy, a wide range of acetamides can be converted to the corresponding Boc analogues under unusually mild conditions. In addition, we have now also shown that this two-step transformation can be carried out by a convenient one-pot procedure. First, the acetamide derivatives were subjected to exhaustive *tert*-butoxycarbonylation using Boc_2O-DMAP (DMAP = 4-dimethylaminopyridine) in acetonitrile as described earlier.[4] When complete reaction had been attained, the subsequent aminolysis of the intermediate Boc-acetamide was achieved by direct addition of a slight excess of neat DEAEA to the reaction mixture. After a simple work-up, the desired *tert*-butyl carbamates were obtained in high overall yields (see Table 1). This one-pot procedure is equally applicable to both aromatic and aliphatic acetamides with only minor modifications, and provides a useful tool for the direct conversion of acetamides to the corresponding Boc analogues.

Alternative reaction conditions. Base-catalysed methanolysis. The aminolysis of the Boc-acetamides is facilitated slightly when methanol is exchanged for acetonitrile as reaction medium. In a study of the slow-reacting *1h,* the use of methanol as solvent seemed to increase the reaction rate approximately three-fold while maintaining high yield and selectivity. A similar enhancement of the reaction rate could, of course, be achieved



a: R=Ph
b: R=4-Bu^t-C_6H_4
c: R=4-EtO_2C-C_6H_4
d: R=2-Et-C_6H_4
e: R=4-Bu^t-2-NO_2-C_6H_3
f: R=2-thienyl
g: R=$PhCH_2$
h: R=$Ph(CH_2)_2$
i: R=$(EtO_2C)_2(Bu^tO_2C)C$

Scheme 1.

by raising the reaction temperature (see Experimental). We also found that the reaction time can be decreased ten-fold when the reaction is carried out using hydrazine hydrate in methanol. The difference in reaction rate is particularly evident for the more sluggish aliphatic derivatives. Even with this powerful reagent, the reaction displays the same remarkable specificity as usual and this modification thus provides a favourable alternative for resistant analogues lacking hydrazine- or hydroxyl-sensitive functions.

Among alternative nucleophiles investigated were thioglycolic acid and mercaptoethanol. Surprisingly, *1b* is completely inert toward treatment with excess thioglycolic acid in dimethylformamide or with mercaptoethanol in methanol overnight at ambient temperature. However, the latter partially converts the more reactive formyl derivative *3a* to *2a* (see under Scope and limitations). On the other hand, the analogue *3a,* in contrast to *1a,* slowly decomposes to *2a* in methanol alone, as judged from TLC, but is not affected by α-mercaptotoluene in acetonitrile. From these experiments, we conclude that thiol nucleophiles are not suitable for these deacylations, even after prolonged reaction times in polar solvents.

Previously, selective ring-opening of cyclic Boc lactams has been accomplished using an excess of lithium hydroxide in aqueous tetrahydrofuran or with sodium methoxide in methanol.[6] Since such powerful reagents are not always compatible with sensitive substrates, milder conditions using hydroxide as nucleophile were sought. Attempted cleavage of *1a* in buffered aqueous acetonitrile has not proved very successful, since only traces of *2a* are observed after standing at pH = 10 for several hours. On the other hand, when a benzene solution of *1a* is treated with an excess of

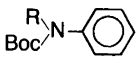
Table 1. Properties of Boc amides *2a–2i*.

Compound No.	R	Reaction conditions[a]	Yield[b]/%	Recrystallization solvent[c]	Mp/°C[d]	^{1}H NMR (CD_3CN, 90 MHz)/δ ppm rel. TMS
2a	Ph	DEAEA (24 h)	90	Heptane (100 ml/g)	136–137	7.06–7.40 (m, ~6H), 1.48 (s, 9H)
		Hydrazinolysis of *3b* (1 h)	88			
		Phase transfer conditions	95			
		TMG (0.2 h)	98			
		One-pot procedure: Boc_2O (8 h), DEAEA (8 h)	94			
2b	4-Bu^t-C_6H_4	Hydrazinolysis as described for *2h* (1 h)	100	Hexane (10 ml/g)	90–90.5	7.39 (br. s, ~1H), 7.30 (s, 4H), 1.47 (s, 9H), 1.27 (s, 9H)
2c	4-EtO_2C-C_6H_4	One-pot procedure: Boc_2O (2 h), DEAEA (2 h)	96	Hexane-EtOAc, 10/1, 200 ml/g	148–148.5	7.92 (d, 2H), 7.82 (br. s, ~1H), 7.51 (d, 2H), 4.30 (q, 2H, 1.49 (s, 9H), 1.33 (t, 3H)
2d	2-Et-C_6H_4	One-pot procedure: Boc_2O (3 h), DEAEA (10 h)	95	Petroleum ether (100 ml/g)	54.5–55	7.04–7.51 (m, 4H), 6.85 (br. s, ~1H) 2.59 (q, 2H), 1.47 (s, 9H), 1.15 (t, 3H)
2e	4-Bu^t-2-NO_2-C_6H_3	One-pot procedure: Boc_2O (2 h), DEAEA (2 h)	97	–	Oil	9.21 (br. s, ~1H), 8.28 (d, 1H, J=9 Hz), 8.12 (d, 1H, J=2 Hz), 7.75 (dd, 1H) 1.51 (s, 9H) 1.32 (s, 9H)
2f	2-Thienyl	One-pot procedure: Boc_2O (2 h), DEAEA (2 h)	98	Hexane (150 ml/g)	149.5–150	8.16 (br, s, ~1H), 6.81 (pert. d, 2H), 6.54 (q, 1H), 1.48 (s, 9H)
2g	$PhCH_2$	DEAEA, 3 equiv. (70 h)	96	Hexane (100 ml/g)	53.5–54	7.28 (s, 5H), 5.72 (br. s, ~1H), 4.20 (d, 2H), 1.40 (s, 9H)
		TMG (0.5 h)	98			
		One-pot procedure: Boc_2O, 1.9 equiv. (15 h), DEAEA, 2.5 equiv. (15 h).	92			
2h	$Ph(CH_2)_2$	DEAEA (150 h)	91	Hexane (20 ml/g)	54.5–55	7.19–7.29 (m, 5H), 5.25 (br. s, ~1H), 3.24 (pert. q, 2H), 2.73 (pert. t, 2H), 1.38 (s, 9H)
		Hydrazinolysis (1 h)	98			
		One-pot procedure: Boc_2O, 50 °C, 2.2 equiv. (6 h), DEAEA, 2.5 equiv. (15 h)	92			
2i	$(EtO_2C)_2$ $(Bu^tO_2C)C$	DEAEA (24 h)	92	Petroleum ether (10 ml/g)[e]	Oil	6.01 (br. s, ~1H), 4.23 (q, 4H), 1.45 (s, 9H), 1.41 (s, 9H), 1.25 (t, 6H)

[a]See Experimental. [b]Crude product. ^{1}H NMR indicated >99 % purity. Yields in one-pot experiments calculated from acetamide derivatives. [c]Decolourizing carbon added. [d]Uncorrected. [e]Cooling to −70 °C gave a white precipitate which melted below −20 °C.

solid potassium hydroxide, the conversion to *2a* is virtually complete within 24 h. We also discovered that the reaction rate is considerably enhanced in the presence of catalytic amounts of certain phase transfer reagents, such as 18-crown-6 or tetrabutylammonium hydrogen sulfate (see Experimental for a typical procedure). When a slight excess of the strong base *N,N,N',N'*-tetramethylguanidine (TMG) is added to a methanol solution of *1a,* the acetyl group is readily split off and, as indicated by ^{1}H NMR, *2a* is obtained as the sole product. Separate studies have also established that *2a* is stable toward treatment with TMG in methanol for several days. Extended ^{1}H NMR experiments comparing the reactivity of *1a, 1g* and *1h* have revealed that this base-induced methanolysis occurs considerably faster than the corresponding DEAEA-mediated cleavage in all of these cases. Thus, *1a* is completely converted to *2a* within 15 min under these conditions and, furthermore, the selectivity of this deacylation is retained entirely. Similarly, the more resistant substrates *1g* and *1h* are completely cleaved to the corresponding *tert*-butyl carbamates *2g* and *2h* after 30 and 60 min, respectively, under these conditions. The deacylation of sterically restricted Boc-acetamides is also greatly facilitated by this method. A ^{1}H NMR study confirmed that the acetyl group is removed completely from the *o*-Bu^t isomer of *1b* within 2 h under comparable conditions. In addition, preparative experiments demonstrated that *2a* and *2g* can be isolated in almost quantitative yields following brief treatment of *1a* and *1g,* respectively, with TMG in methanol (see Table 1 and Experimental for a representative procedure). Clearly, this TMG-assisted methanolysis offers an efficient alternative to aminolysis for the selective deacylation of slow-reacting substrates lacking base-vulnerable functions. We assert that this alcoholysis requires a strong assisting base, since the cleavage is retarded considerably when the weaker base triethylamine (TEA) is exchanged for TMG. Thus, when *1a* in methanol is treated with an excess of TEA, most of the starting material remains unchanged after one day.

Scope and limitations. A variety of Boc-acylamides with acyl components other than acetyl (Scheme 2, *3a–3g*) have also been screened for their ability to undergo the above DEAEA-induced cleavage. Thus, ^{1}H NMR experiments have revealed that the formyl analogue *3a* reacts about ten times more rapidly with DEAEA than the corresponding acetyl derivative *1a,* but still gives *2a* as the sole product. In addition, a preliminary experiment has shown that *3a* is smoothly cleaved by the much weaker base morpholine under similar conditions. The benzoyl group of *3b* is removed at a rate comparable to that of *1a* under similar conditions and also in this case, the reaction exhibits complete selectivity. On the other hand, the corresponding benzyloxycarbonyl (Z) analogue *3c* reacts at least ten times slower than *1a* with DEAEA. In addition, the ^{1}H NMR spectrum of the crude reaction mixture indicates that the selectivity of the reaction in this case is diminished. Thus, inspection of the spectrum shows a product ratio *2a:* benzyl *N*-phenyl carbamate ~6. Clearly, the retarded reaction together with the observed unspecific cleavage reflect the relative similarity between the Z and Boc groups. Accordingly, the splitting of *3d* with DEAEA occurs only very slowly and only a few per cent of this substrate is converted to *2a* after several weeks at room temperature.



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a: R=HCO
b: R=PhCO
c: R=PhCH$_2$OCO
d: R=Boc
e: R=4-Me-C$_6$H$_4$SO$_2$
f: R=2-NO$_2$-C$_6$H$_4$S
g: R=Ph$_2$P(=O)

Scheme 2.

Attempts to cleave the toluenesulfonyl (Tos) group by this approach have so far been unsuccessful. We found that *3e*[4] cannot be transformed to the desired *2a,* either by DEAEA or by sodium borohydride in various solvents. Instead, it slowly reverts to Tos-anilide after prolonged reaction times. As expected, hydrazine speeds up the reaction, but in this case the outcome is the same as with DEAEA.

The reactivity of the 2-nitrophenylsulfenyl (Nps) anilide *3f*[4] as well as the diphenylphosphinyl analogue *3g*[4] was studied by semiquantitative ^{1}H NMR experiments. When *3f* is allowed to react with DEAEA, a slow conversion to *2a* is observed. After one month maintaining standard

conditions, approximately one-half of the starting material has been consumed and the only detectable reaction product is *2a*. On the other hand, *3g* remains largely unchanged under these conditions and only traces of *2a* are detected after several weeks. Apparently, this new strategy offers little advantage for the deprotection of derivatives of this type.

In conclusion, using this two-step reaction sequence, Boc, which is readily removable by moderately strong acid at or below room temperature, can be exchanged smoothly for other acyl groups which are generally more resistant to deacylation. Furthermore, preparative experiments fully confirm that this conversion can also be accomplished in very satisfactory yields by a convenient one-pot procedure without isolating the intermediate Boc-acylamides. Although the full scope of this novel strategy remains to be explored, this method, at its present stage, might find promising applications in the chemistry of protective groups.

Experimental

Deacetylation of N-*Boc-acetamides* 1a–1i; *typical procedures*

Preparation of 2a. *DEAEA cleavage.* A solution of *1a* (235 mg, 1.00 mmol) in dry acetonitrile (5 ml) was treated with DEAEA (332 mg, 2.00 mmol) and left at room temperature. The reaction was monitored by TLC (toluene/acetonitrile, 2:1) and after 24 h, no starting material remained. Evaporation at reduced pressure gave a semi-solid residue which was partitioned between ether (40 ml) and 1 M aq. $KHSO_4$ (20 ml). The organic phase was thoroughly washed in turn with 1 M aq. $KHSO_4$, 1 M aq. $NaHCO_3$ and brine (3×10 ml each), dried over $MgSO_4$ and treated with decolourizing carbon. Removal of the solvent afforded crude *2a* as a white solid. For yield, recrystallization solvent and physical properties, see Table 1.

Direct conversion of 2-acetamidothiophene to Boc analogue 2f. *One-pot procedure.* To a vigorously stirred slurry of dry, pulverized 2-acetamidothiophene (705 mg, 5.00 mmol) in dry acetonitrile (5 ml) was added DMAP (61 mg, 0.5 mmol) followed by Boc_2O (1.20 g, 5.50 mmol) in one portion. All solid material dissolved completely after gentle heating for a few minutes. The reaction mixture was stirred at ambient temperature and after 2 h, TLC (system above) indicated that all starting material had been consumed. The mixture was then treated with DEAEA (725 mg, 6.25 mmol) under rapid stirring. Heat was evolved and after stirring for 2 h, TLC displayed only one spot. Most of the solvent was removed at room temperature and the oily residue was partitioned between ether (160 ml) and 1 M aq. $KHSO_4$ (80 ml). The yellow water phase was discarded and the almost colourless ether extract washed in turn with 1 M aq. $KHSO_4$. 1 M aq. $NaHCO_3$ and brine (3×40 ml each) and dried over $MgSO_4$. Evaporation of the extract and thorough drying in high vacuum afforded *2f* as a white crystalline solid. For yield, purification and physical properties, see Table 1.

Preparation of 2h. *Hydrazine cleavage of* 1h. A solution of *1h* (526 mg, 2.00 mmol) in methanol (5 ml) was carefully mixed with hydrazine hydrate (0.50 ml, 10 mmol). After 1 h at ambient temperature, TLC (system above) showed that no *1h* remained and the mixture was then evaporated at room temperature. The semi-solid residue was partitioned between ether (50 ml) and 1 M aq. $KHSO_4$ (25 ml), and the ethereal extract was washed according to the procedures described above. Removal of the solvent left a colourless viscous oil which soon solidified in the cold. For further details, see Table 1.

Hydrolysis of 1a *under phase transfer conditions.* To a well-stirred solution of dry *1a* (235 mg, 1.00 mmol) in dry benzene (10 ml) was added tetrabutylammonium hydrogen sulfate (71 mg, 0.2 mmol) followed by finely powdered KOH (123 mg, 2.2 mmol). After 6 h with rapid stirring at room temperature, TLC (system above) indicated complete reaction. The turbid mixture was then partitioned between ether (50 ml) and water (25 ml), and the ethereal extract worked up as described above. For further information, see Table 1.

Methanolysis of 1g *in the presence of TMG. Preparation of* 2g. To a solution of *1g* (229 mg, 0.920 mmol) in methanol (0.9 ml) was slowly added TMG (132 mg, 1.15 mmol) dissolved in methanol (0.9 ml) under vigorous stirring, and the reaction was allowed to proceed for 30 min at ambient

temperature. Most of the volatile components were rapidly removed at reduced pressure at room temperature and the residual viscous oil partitioned between ether (40 ml) and 1 M $KHSO_4$ (20 ml). The colourless ethereal extract was separated and worked up as usual. Evaporation to dryness afforded crude *2g*, pure by ^1H NMR, as soft white crystals. For additional information, see Table 1.

Semiquantitative ^1H NMR experiments. A 0.1–0.2 M solution of the substrate (*1* or *3*) in dry CD_3CN was treated with excess DEAEA (1.5–2 equiv.) in an NMR tube at room temperature. Spectra were recorded after appropriate reaction times and integrations carried out over Boc-, Ac- or other well-separated signals, preferably singlets.

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