A Simple Method for *tert*-Butoxycarbonylation of Amides

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The *tert*-butoxycarbonyl (Boc) function was conveniently introduced onto the amide nitrogen in several secondary amides using di-*tert*-butyl dicarbonate in dry acetonitrile with 4-dimethylaminopyridine as catalyst. Carboxamides with different acyl groups such as formyl, acetyl and benzoyl are presented as well as derivatives of carbamic acid. Examples also include other amide types: sulfonamide, sulfenamide and phosphinamide which were all smoothly converted to the corresponding Boc derivatives under these conditions. The yields were generally excellent and the resulting Boc analogues stable compounds which could be stored for months under ordinary conditions. Some stereochemical and structural aspects of this acylation are also discussed. Bulky substituents in the proximity of the amide moiety significantly retarded the reaction and in some cases no product was detected. For one compound with an activated methine group, *C* acylation was observed.

The *tert*-butoxycarbonyl (Boc) group is one of the most valuable protecting groups for amino functions presently known.[1] It is stable in many synthetic routes but is conveniently removed by acid under mild conditions. The Boc group is nowadays widely used for amine protection in peptide synthesis. The synthesis of Boc derivatives is, in most cases, readily accomplished by treating the amine with Boc-N_3, Boc-F or Boc-OPh, often under aqueous conditions and the yield of the desired product is generally good. Lately, di-*tert*-butyl dicarbonate[2] (Boc_2O) has gained increasing popularity in this respect since it is both very efficient for introducing the Boc group and commercially available. Recently, it was also discovered that *tert*-butoxycarbonylations with Boc_2O are greatly facilitated by the powerful acylation catalyst 4-dimethylaminopyridine (DMAP). This feature enables the convenient preparation of several Boc derivatives which have not so far been easily accessible by other methods. Thus, in the last few years, the DMAP-catalyzed *tert*-butoxycarbonylation of lactams,[3] pyrroles and indoles[4] and various peptide nitrogens[5] has been reported. Therefore, we decided to explore the general applicability of Boc_2O/DMAP to the *tert*-butoxycarbonylation of various types of amides and to design a general preparative procedure. A brief account of the preparation and properties of some selected Boc-acylamides was recently given.[6]

Results and discussion

When the amides *1a–1q* were subjected to exhaustive acylation with Boc_2O in dry acetonitrile at ambient temperature using DMAP as catalyst, the corresponding new Boc analogues *2a–2q* (Scheme 1) could be isolated in excellent yields after a simple workup procedure. The Boc derivatives are stable compounds which can be handled under normal conditions without special precautions. To obtain a maximum yield it was important to use a dry solvent since moisture appears to consume the acylating agent. It was also shown that Boc-N_3 or Boc-OPh could not be exchanged for Boc_2O in this reaction (no trace of the desired Boc-acyl derivatives could be detected in these reaction mixtures either by TLC or ^{1}H NMR). Earlier investigators used dichloromethane as solvent in a similar Boc_2O/DMAP-mediated acylation of amide nitrogens.[3] We have now discovered that the acylation of amides proceeds smoothly in acetonitrile and that no extra

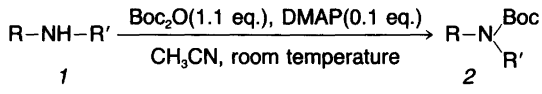
base is required for complete reaction. Obviously, the visible evolution of carbon dioxide from the reaction mixture is sufficient for shifting the equilibrium in the desired direction. In this context it should also be emphasized that only catalytic amounts of DMAP (0.05–0.1 equiv.) were required and, in most cases, only a small excess of Boc_2O (1.1 equiv.) was sufficient for complete reaction.

With respect to the mechanism of the reaction, it is generally accepted that an 1-acyl-4-dimethylaminopyridinium ion serves as the acylating agent[5,6,7] and the 1-Boc adduct has also been isolated as its tetrafluoroborate.[8] Although no active intermediate was isolated in this study, semiquantitative ^1H NMR measurements revealed that the ratio Boc/DMAP adduct: free DMAP is more than five times higher in acetonitrile than in dichloromethane under comparable conditions ($\delta(CH_3)_2N$ = 2.96 for DMAP in both solvents was shifted to δ = 3.36 and 3.47 for the complex in acetonitrile and dichloromethane respectively).

The formanilide *1a* was *tert*-butoxycarbonylated very rapidly under these circumstances and the conversion was virtually complete in less than 1 h. The acetyl and benzoyl derivatives, *1b* and *1c* respectively, reacted somewhat more slowly and in the case of the aliphatic analogues *1f–1i,* the reaction was further retarded. From a practical point of view it is interesting to note that *2g* could also be conveniently prepared in a one-pot procedure from benzylamine without prior isolation of the intermediate *1g*. Obviously this approach provides a useful method for the synthesis of di-Boc amides, which is of potential value when complete protection of amines is needed.

The presence of electron-withdrawing substituents in the benzene nucleus appears to enhance the reaction rate considerably as was observed for *1j* and especially for *1k*. Furthermore, this acylation reaction is by no means restricted to carboxyamides. Both the toluenesulfonanilide *1l* and the *o*-nitrobenzenesulfenanilide *1m* as well as the diphenylphosphinanilide *1n* all afforded the corresponding Boc analogues *2l, 2m* and *2n* respectively in very high yields.

Semiquantitative ^1H NMR experiments comparing the acylation rates of the isomeric *tert*-butylacetanilides have indicated that the steric parameters of this reaction are indeed important. Thus, the *para* and *meta* analogues *1o* and *1p* reacted readily with Boc_2O/DMAP, essentially parallelling the behaviour of the unsubstituted acetanilide *1b*. However, in the case of the *ortho* analogue *1q,* in which the amide function is shielded by the bulky *tert*-butyl group, the corresponding reaction is significantly retarded and a large excess of Boc_2O was required for complete conversion. In this context, it is worth mentioning that the use of 4-pyrrolidinopyridine, claimed to be even more efficient as acylation catalyst than DMAP, did not noticeably affect the *tert*-butoxycarbonylation rate of *1q* under comparable conditions. Moreover, pivalanilide failed to give the desired Boc analogue despite prolonged reaction times and a considerable excess of Boc_2O. This observation is also in agreement with earlier find-



1 *2*

a: R=Ph	R′=HCO	*j:* R=4–EtOCO–C_6H_4	R′=CH_3CO
b: R=Ph	R′=CH_3CO	*k:* R=4–NO_2–2–CF_3–C_6H_3	R′=CH_3CO
c: R=Ph	R′=PhCO	*l:* R=Ph	R′=4–Me–$C_6H_4SO_2$
d: R=Ph	R′=$PhCH_2OCO$	*m:* R=Ph	R′=2–NO_2–C_6H_4S
e: R=Ph	R′=Boc	*n:* R=Ph	R′=$Ph_2P(=O)$
f: R=$PhCH_2$	R′=CH_3CO	*o:* R=4–Bu^t–C_6H_4	R′=CH_3CO
g: R=$PhCH_2$	R′=Boc	*p:* R=3–Bu^t–C_6H_4	R′=CH_3CO
h: R=$Ph(CH_2)_2$	R′=CH_3CO	*q:* R=2–Bu^t–C_6H_4	R′=CH_3CO
i: R=$Ph(CH_2)_2$	R′=Boc	*r:* R=$(EtO_2C)_2(Bu^tO_2C)C$	R′=CH_3CO

Scheme 1.

Table 1. Properties of R-N(Boc)R′, *2a–q*.

Compound No.	R	R′	Reaction time/h[a]	Yield[b]/%	Recrystallization solvent[c]	M.p./°C[d]	^{1}H NMR (CD_3CN, 90 MHz)/δ ppm rel. TMS
2a	Ph	HCO	1	92	Heptane (10 ml/g)	69.5–70	9.32 (s, 1H), 7.35–7.50 (m, 3H), 7.11–7.24 (m, 2H), 1.46 (s, 9H)
2b	Ph	CH_3CO	8	99	Heptane (10 ml/g)	59.5–60	7.30–7.42 (m, 3H), 7.05–7.16 (m, 2H), 2.50 (s, 3H), 1.35 (s, 9H)
2c	Ph	PhCO	4	92	Heptane (50 ml/g)	98.5–99	7.21–7.78 (m, 10H), 1.19 (s, 9H)
2d	Ph	$PhCH_2OCO$	20	95	Hexane (40 ml/g)	70.5–71	7.15–7.42 (m, 10H), 5.14 (s, 2H), 1.36 (s, 9H)
2e	Ph	Boc	3	96	Hexane (20 ml/g)	82–82.5	7.09–7.40 (m, 5H), 1.40 (s, 18H)
2f	$PhCH_2$	CH_3CO	20	86	[e]	Oil	7.26 (pert. s, 5H), 4.84 (s, 2H), 2.46 (s, 3H), 1.40 (s, 9H)
2g	$PhCH_2$	Boc	[f]	[f]	Petroleum ether (5 ml/g)	30–31	7.29 (s, 5H), 4.73 (s, 2H), 1.42 (s, 18H)
2h	$Ph(CH_2)_2$	CH_3CO	20	97	[e]	Oil	7.16–7.29 (m, 5H), 3.84 (pert. t, 2H), 2.78 (pert. t, 2H), 2.37 (s, 3H), 1.46 (s, 9H)
2i	$Ph(CH_2)_2$	Boc	50[g]	94	Hexane (10 ml/g)	39–39.5	7.20–7.29 (m, 5H), 3.75 (pert. t, 2H), 2.83 (pert. t, 2H), 1.44 (s, 18H)
2j	4-EtOCO-C_6H_4	CH_3CO	2	85	Heptane	115–115.5	8.02 (d, 2H), 7.24 (d, 2H), 4.34 (q, 2H), 2.53 (s, 3H), 1.36 (s, 9H), 1.35 (t, 3H)
2k	4-NO_2-2-CF_3-C_6H_3	CH_3CO	1	83	Heptane (30 ml/g)[h]	124–125	8.55 (d, 1H), 8.44 (q, 1H), 7.64 (m, 1H), 2.58 (s, 3H), 1.34 (s, 9H)
2l	Ph	4-Me-C_6H_4-SO_2	1	94	Heptane: EtOAc = 6:1 (50 ml/g)	123–123.5	7.86 (d, 2H), 7.22–7.51 (m, 7H), 2.45 (s, 3H), 1.27 (s, 9H)
2m	Ph	2-NO_2-C_6H_4-S	1	96	Petroleum ether (60 ml/g)	80–80.5	8.31 (pert. d, 1H), 7.21–7.84 (m, 8H), 1.42 (s, 9H)
2n	Ph	$Ph_2P(=O)$	1	98	Petroleum ether: EtOAc 1:1 (80 ml/g)	174–175	7.11–7.94 (m, 15H), 1.18 (s, 9H)[i]
2o	4-Bu^t-C_6H_4	CH_3CO	6	98	Hexane (10 ml/g)	88.5–89	7.42 (d, 2H), 7.03 (d, 2H), 2.42 (s, 3H), 1.37 (s, 9H), 1.32 (s, 9H)
2p	3-Bu^t-C_6H_4	CH_3CO	20[j]	98	Petroleum ether (5 ml/g)	24–25	6.84–7.43 (m, 4H), 2.49 (s, 3H), 1.35 (s, 9H), 1.30 (s, 9H)
2q	2-Bu^t-C_6H_4	CH_3CO	50[g]	97	Hexane (30 ml/g)	84–84.5	6.86–7.59 (m, 4H), 2.52 (s, 3H), 1.36 (s, 9H), 1.28 (s, 9H)

(cont.)

Compound No.	R	R′	Reaction time/h[a]	Yield[b]/%	Recrystallization solvent[c]	M.p./°C[d]	^{1}H NMR (CD_3CN, 90 MHz)/δ ppm rel. TMS
1r	$(Bu^tO_2C)(EtO_2C)_2C$	CH_3CO	1	93	Petroleum ether: EtOAc 10:1 (40 ml/g)	55.5–56	9.34 (broad s, 1H), 4.22 (q, 4H), 1.97 (s, 3H), 1.45 (s, 9H), 1.24 (t, 6H)
2r	$(Bu^tO_2C)(EtO_2C)_2C$	CH_3CO	90[k]	88[l]	Hexane (8 ml/g)[m]	Oil	4.19 (q, 4H), 2.37 (s, 3H), 1.45 (s, 9H), 1.44 (s, 9H), 1.23 (t, 6H)

[a]Monitored by TLC to complete reaction. In most cases, it was advantageous to allow the reaction to proceed overnight to decompose excess Boc_2O which is difficult to remove from the reaction mixture. [b]Crude product. [c]Decolourizing carbon added. It was often necessary to cool the solution below −20 °C and seed to induce crystallization. [d]Uncorrected. [e]Purified by chromatography on silica gel with dichloromethane as eluent. [f]Prepared in one step from benzylamine and excess of Boc_2O (see Experimental). [g]An additional equivalent of Boc_2O was added after 24 h. [h]The crude product was intensely red but two recrystallizations using decolourizing carbon almost completely removed the colour. Traces of impurities remained, however, as judged from TLC. [i]^{31}P NMR (CD_3CN); δ = 23.24 ppm ($\delta_{(H_3PO_4)}$ = 0 ppm). [j]^{1}H NMR experiment indicated complete reaction after 6 h. [k]After 12 h, the mixture was taken to dryness. The oily residue was redissolved in acetonitrile and treated with more Boc_2O (1.5 equiv.). After a further 12 h, this procedure was repeated once and the mixture left for 3 d before conventional workup. [l]Yield after chromatography on silica gel using dichloromethane/acetone 10:1 as eluent. The crude product contained a minor quantity of *1r* (~10 %) together with Boc_2O (δ = 1.49 ppm) and $Bu^t_2CO_3$ (δ = 1.41 ppm). [m]Cooling to −70 °C afforded a solid precipitate which was collected in the cold. This material melted below room temperature.

ings concerning DMAP-mediated acetylations of miscellaneous sterically hindered substrates.[3,7,9,10]

In one case studied so far, the reaction course differed from that discussed above: when diethyl acetamidomalonate was allowed to react with Boc_2O in the presence of DMAP according to the usual conditions, it was preferentially acylated at the activated methine moiety and was rapidly converted to *1r* in excellent yield. Similar DMAP-catalyzed *C*-acylations have also been observed previously; examples include the modified Dakin-West reaction and the self-condensation of acetic anhydride.[7,9,10] Furthermore, a preliminary investigation has revealed that DMAP-mediated *C*-acylations may be of general utility. Thus, diethyl methylmalonate afforded *tert*-butyl diethyl ethane-1,1,1-tricarboxylate in good yield although, in this case, the reaction was much retarded and required a larger excess of Boc_2O in comparison with the synthesis of *1r*. The *tert*-butoxycarbonylation of the amide function in *1r* could also be accomplished but this reaction proceeded very sluggishly. Despite a considerable excess of Boc_2O in combination with a prolonged reaction time, the resulting crude product still contained some starting material (see footnotes, Table 1).

Attempts to use the structurally related dimethyl dicarbonate as acylating agent instead of Boc_2O gave rather discouraging results. This is probably due to the limited stability of this reagent in the presence of DMAP. Preliminary ^{1}H NMR experiments showed that dimethyl dicarbonate is almost instantaneously destroyed in acetonitrile solution containing 0.1 equiv. of DMAP whereas Boc_2O decomposes only slowly under these conditions. When *1b* was treated with a very large excess of dimethyl dicarbonate (5 equiv.!) according to the normal preparative procedure, some Ac(MeOCO)NPh could be detected as judged from the ^{1}H NMR spectrum of the crude mixture after conventional workup. However, attempts to chromatograph this mixture on silica gel afforded only an impure product and ^{1}H NMR indicated that the initially formed methoxycarbonyl analogue of *1b* was decom-

posed during the attempted purification step. Evidently, the acetyl group is split off under these circumstances and this feature is in striking contrast to the properties of compounds *2f* and *2h* which could be chromatographed on silica gel without noticeable deterioration.

In conclusion, this efficient *tert*-butoxycarbonylation method has proven useful for the conversion of various types of amides to the corresponding Boc analogues. Although there are some inherent steric limitations, the reaction with Boc_2O in combination with DMAP under anhydrous conditions represents a very mild procedure for introducing the Boc function into sluggishly reacting substrates also. The nucleophilic cleavage of these Boc-acylamides often exhibits a remarkable selectivity. This aspect of their chemistry will be dealt with separately.

The Boc derivatives described in this paper represent a novel type of protected amides in which weakly acidic hydrogens have been replaced by Boc. This is an expansion in the well established application of Boc to reduce the basicity and particularly the nucleophilicity of primary and secondary amines. We have also confirmed that the Boc function can be cleaved selectively in high yield from Boc amides under conventional deprotection conditions (CH_2Cl_2: TFA 2:1, 2h, RT). In its new context, Boc might supplement various *N*-alkyl and benzyl protecting groups preferred so far.[11]

Experimental

All melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. TLC analyses were performed on 0.25 mm thick, precoated UV sensitive silica gel plates (Merck DC-Fertigplatten, Kieselgel 60 F_{254}). Spots were visualized by inspection under UV light at 254 nm or after exposure to vapourized iodine. All compounds described or used were chromatographically pure and gave the expected ^1H NMR spectrum unless otherwise stated. The starting amides were prepared according to standard methods or, when possible, purchased, their melting points agreeing with those previously reported. All such substrates were finely ground and dried *in vacuo* at 40 °C overnight before use. Acetonitrile (analytical grade) was thoroughly dried over a molecular sieve (4Å) for several d. DMAP (Fluka) was recrystallized from dry ethyl acetate (4 ml/g, decolourizing carbon) and dried *in vacuo*. Boc_2O (Fluka, 97 %) was used without further purification. All glassware was dried in an open flame immediately before use. ^1H NMR spectra were recorded on a Jeol FX 90Q at 90 MHz. Elemental analyses of selected derivatives were carried out by Mikro Kemi AB, Uppsala, Sweden.

tert-*Butoxycarbonylation of amides* 1a–f *and* h–q, *general procedure.* A solution or slurry of thoroughly dried, finely powdered amide (10.0 mmol) in dry acetonitrile (10–20 ml) was treated with DMAP (122 mg, 1.0 mmol), followed by a solution of Boc_2O (2.40 g, 11.0 mmol) in dry acetonitrile (5 ml) in one portion with rapid stirring. Evolution of carbon dioxide started and, after a few min, all solid generally dissolved completely (gentle heating if necessary). For times indicated in Table 1, the resulting light brown solution was stirred at room temperature with exclusion of atmospheric moisture. When TLC (toluene/acetonitrile 2:1) confirmed that all starting material had been completely consumed, the reaction mixture was evaporated to dryness at ambient temperature. The oily or semisolid residue was partitioned between ether (200 ml) and 1 M aqueous $KHSO_4$ (100 ml), the organic extract washed in turn with 1 M aqueous $KHSO_4$, 1 M aqueous $NaHCO_3$ and saturated aqueous NaCl (3×50 ml each) and dried over $MgSO_4$. After treatment with decolourizing carbon, the colourless or faintly brownish filtrate was taken to complete dryness and the last traces of volatile components removed under high vacuum at 40 °C. The crude, chromatographically pure Boc analogues were obtained as white solids or almost colourless oils which, in most cases, soon solidified in the cold. For purification, yield and properties, see Table 1.

Direct preparation of di-tert-*butyl* N-*benzyliminodicarboxylate* 2g *from benzylamine and* Boc_2O. A solution of benzylamine (1.07 g, 10 mmol) in dry acetonitrile (5 ml) was treated with Boc_2O (7.20 g, 33 mmol) in small portions with vigorous agitation. After a few min, solid DMAP (244 mg, 2.0 mmol) was introduced and the brownish reaction mixture stirred at ambient temperature. This reaction was slightly exothermic and there was a copious evolution of gas which subsided after a few h. The reaction was monitored by TLC

(system above) which indicated that the reaction was not complete after 24 h. A further quantity of Boc_2O (2.40 g, 11 mmol) was added and the stirring continued for an additional 24 h (only one spot on TLC). Most of the solvent was removed by evaporation and the remaining brownish oil worked up in analogy to the above procedure. The yield of crude, essentially pure *2g*, obtained as an almost colourless oil, was quantitative (3.1 g). For purification and physical data, see Table 1.

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