Removal of Formyl, Acetyl, and Benzoyl Groups from Amides with Conversion into the Corresponding t-Butyl Carbamates

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N-Formyl, -acetyl, and -benzoyl groups can be removed from secondary amides with amines under mild conditions after t-butoxycarbonylation, giving acid-labile t-butyl carbamates.

Formamides, acetamides, and benzamides are quite stable compounds, and often require heating in strongly acidic or basic solutions for cleavage.[1] Therefore, other, more labile protecting groups for amino functions than the classical formyl, acetyl, and benzoyl groups are generally required. We now report the first example of the removal of these three well known protecting groups from model compounds by nucleophiles. The reaction is based on prior exhaustive t-butoxycarbonylation[2,3] and gives rise to acid-labile carbamates. The new procedure should be of interest for deprotection purposes and several variations can be envisaged both with respect to the structure of the functional group to be exhaustively acylated and, particularly, the structure of the new group that will be subsequently attached to the amine.

When the amides (**1a**—**e**) were exhaustively acylated with Boc_2O [Boc = $Bu^tOC(:O)$–], using 4-dimethylaminopyridine (DMAP; 0.1 equiv.) as catalyst, the corresponding Boc-derivatives (**2a**—**e**) could be isolated in excellent yields.† When treated with nucleophiles like 2-diethylaminoethylamine (DEAEA)‡ or hydrazine, (**2a**—**e**) gave the corresponding t-butyl carbamates (**3a**—**e**). The reactions with DEAEA were monitored by ^1H n.m.r. spectroscopy. Quantitative ^1H n.m.r. experiments revealed that the formyl derivative (**2a**) was smoothly converted into (**3a**) in 2 h using a 50% excess of DEAEA in MeCN at room temperature, whereas (**2b**) and (**2c**) required 24 h for complete reaction. The conversion of (**2a**) into (**3a**) could also be accomplished by the much weaker base morpholine. Compound (**3e**) was isolated in 98% yield after treatment with 5 equiv. of hydrazine in MeOH for 1 h (t.l.c.). Similarly, DEAEA (1.5 equiv.) in MeOH after 3 days and in MeCN after 7 days gave (**3e**) in yields of 94 and 91%, respectively. The resulting Boc-derivatives (**3**) are stable to a variety of basic, nucleophilic, reducing, and other reagents, and conditions.[1] The Boc-group can, however, readily be

$$\underset{(1)}{R^1CO\text{–}NHR^2} \xrightarrow{i} \underset{(2)}{R^1CO\text{–}N(Boc)R^2} \xrightarrow{ii} \underset{(3)}{BocNHR^2}$$

a; $R^1 = H, R^2 = Ph$
b; $R^1 = Me, R^2 = Ph$
c; $R^1 = R^2 = Ph$
d; $R^1 = Me, R^2 = CH_2Ph$
e; $R^1 = Me, R^2 = CH_2CH_2Ph$

Reagents: i, Boc_2O, DMAP, MeCN; ii, DEAEA or NH_2NH_2, MeCN or MeOH.

† For experimental procedure, see ref. 3.

‡ Typical experimental procedure: a solution of (**2b**) (1 mmol) in MeCN (5 ml) was treated with DEAEA (2 mmol) for 20 h at room temperature, when t.l.c. indicated that the reaction was complete. Evaporation gave a semi-solid which was partitioned, washed, and dried as described for the precursor (ref. 3). Evaporation gave a 90% yield of pure (**3b**), m.p. 136—137 °C (from heptane) (lit.,[4] 136 °C); ^1H n.m.r. (CD_3CN, 90 MHz) δ 1.48 (s, 9H, Boc).

removed afterwards with a moderately strong acid, at or below room temperature.

All compounds were characterized by ^{1}H n.m.r. spectroscopy. The new compounds (**2a**—**e**) also gave satisfactory C, H, and N analyses. They were also pure by t.l.c.

General methods for exhaustive acylation of amides and urethanes remain to be developed, allowing a wider range of protecting groups to be introduced like Boc above. However, compounds can also be envisaged that, for steric and other reasons, resist such reactions. Reactions of this kind will be explored next.

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References

1 T. W. Greene, 'Protective Groups in Organic Chemistry,' Wiley, New York, 1981.
2 D. L. Flynn, R. E. Zelle, and P. A. Grieco, *J. Org. Chem.*, 1983, **48**, 2424.
3 L. Grehn and U. Ragnarsson, *Angew. Chem.*, 1985, **97**, 519; *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 510.
4 E. Knoevenagel, *Liebigs Ann. Chem.*, 1897, **297**, 148.