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Mild Two-Step Conversion of Primary Amides to Alcohols by Reduction of Acylimidodicarbonates with Sodium Borohydride

Ulf Ragnarsson,*^a Leif Grehn,^a Luis S. Monteiro,^b Hernani L. S. Maia^b

^a Department of Biochemistry, University of Uppsala, Biomedical Center, PO Box 576, SE-751 23 Uppsala, Sweden
Fax +46(18)552139; E-mail: urbki@bmc.uu.se

^b Departamento de Quimica, Universidade do Minho, Gualtar, P-4700-320 Braga, Portugal

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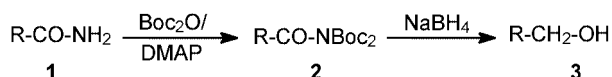
Abstract: Di-*tert*-butyl acylimidodicarbonates, prepared from primary amides with two equivalents of di-*tert*-butyl dicarbonate under catalysis by 4-dimethylaminopyridine, readily undergo selective reductive cleavage of their acyl CO-N bonds by NaBH₄ to provide the corresponding alcohols in high yields.

Key words: alcohols, amides, cleavage, reductions, sodium borohydride

Recently, in connection with studies of model *N*-benzyl acylcarbamates we observed that these substances underwent regiospecific acyl CO-N reductive cleavage under relatively mild conditions.¹ In that context it occurred to us that this reaction might be exploited for synthetic purposes. As a continuation, we now present a simple two-step procedure for conversion of primary amides to alcohols based on similar principles. Rather few transformations of this kind involving hydrogenation, electrochemical and dissolving metal reduction and metal hydride reagents have been reported in the literature.² Some tertiary amides have recently been shown to undergo notably mild reductive cleavage to alcohols by metal hydride reagents.³

As first shown by Grieco et al., secondary amides and lactams undergo facile reaction with di-*tert*-butyl dicarbonate (Boc₂O) in the presence of 4-dimethylaminopyridine⁴ (DMAP) with formation of the corresponding acylcarbamates.⁵ Such compounds react with nucleophiles under cleavage of their acyl-N bonds, as a consequence of which the original amides can be converted to carbamates in two steps. Similarly, primary amides **1** undergo substitution with two equivalents of Boc₂O in the presence of this catalyst to give di-*tert*-butyl acylimidodicarbonates **2**.⁶

Compounds **2** behave as acylating agents,⁷ indicating a significant further electron-withdrawing effect by the second Boc group on nitrogen in comparison with that in



Scheme 1 Two-step conversion of primary amides via di-*tert*-butyl acylimidodicarbonates to alcohols

acylcarbamates. This effect has been measured for **2a** (R = Ph) using cyclic voltammetry (CV).^{1b}

To study the reactivity of di-*tert*-butyl acylimidodicarbonates **2** in more detail with respect to reduction, several compounds **2a–f** listed in Table 1 have been prepared from the corresponding amides **1**.⁶ According to TLC the syntheses of all went to completion within a maximum of 24 hours, which eliminated the need for chromatographic purification of the products. These were all obtained as highly lipophilic solids, some of which like **2e** dissolved easily in light petroleum and therefore occasionally were difficult to recover by recrystallization. The variable yields for individual compounds **2** reflect this fact rather than low reactivity of some amides.

As a prelude to the preparative reduction experiments, attempts were made to characterize the acylimidodicarbonates **2** by CV. These experiments were performed in DMF as described elsewhere.⁸ Although the activation potential could not be determined for all compounds, in two cases (for **2a** and **2d**) we could demonstrate that the introduction of a second Boc group shifted the peaks by over 0.35 V to less negative potential in comparison with the corresponding *N*-benzyl acylcarbamates (Table 1).^{1a,8}

Compounds **2** were reduced to alcohols **3** using an excess of NaBH₄ in EtOH on a 2–3 mmol scale with the simultaneous formation of an equivalent of HNBoc₂.⁹ Although, as demonstrated, the latter compound could generally be efficiently separated from the desired alcohols by chromatography on silica gel, in other cases due to the high lipophilicity of the products this turned out to be more difficult and required rechromatography to provide pure products, all of which have been described before. All reductions with NaBH₄ could be carried out at room temperature except in the case of **2c**. As reflected by its much lower activation potential in comparison with **2a** and **2d** (Table 1), it was less reactive and moderate heating was therefore required. In this experiment also a side-product, formed by the alternative cleavage of a Boc-group from **2c**, could be isolated. Another triacylated ammonia derivative, NBoc₃, known to undergo aminolysis,¹⁰ is also cleaved to HNBoc₂ by NaBH₄ with high selectivity, which exemplifies the dramatic shift in stability of Boc in these compounds in comparison with simple carbamates.¹¹ Attempts to reduce **2c** by cathodic electrolysis⁸ furnished a complex mixture containing HNBoc₂ but only small amounts of **3c**.

Reduction of the proline amide derivative **2f** with both diisobutylaluminium hydride and tri-*tert*-butoxy-aluminium hydride has previously been attempted but only resulted in a meager (<10%) yield of a mixture of the corresponding aldehyde and alcohol.⁷

Concerning the scope of this two-step transformation (Scheme 1), it can be mentioned that several amides **1** have been converted to di-*tert*-butyl acylimidodicarbonates^{7,12} **2** using Boc₂O/DMAP, so a fair amount of information is already available with respect to the first

step. Among these amides are such containing additional ester, carbamate, alcohol and amino functions, some of which undergo additional reaction. As most functional groups other than aldehydes and ketones are stable to NaBH₄,¹³ the corresponding acylimidodicarbonates should therefore normally be compatible with the mild reducing agent used in the second step and provide alcohols accordingly.

Table 1 Synthesis of di-*tert*-Butyl Acylimidodicarbonates **2** and their Reduction to Alcohols **3** by NaBH₄

Amide 1 / Solvent ^c	2		3	
	Yield ^a (%) Mp (°C) -E _p /V	Spectral data of 2 ^b	Yield ^a (%) Mp (°C)	Spectral data of 3 ^b
Benzamide (a)/A	77 ^d 59.5–60.5 1.56 ^f	δ = 1.38 (18 H), 7.47 (p t, <i>J</i> = 7 Hz, 2 H), 7.60 (p t, <i>J</i> = 7 Hz, 1 H), 7.83 (p d, <i>J</i> = 7 Hz, 2 H); 1765, 1740, 1702 cm ⁻¹	n.d. ^e oil	δ = 1.96 (br, 1 H), 4.66 (2 H), 7.26–7.39 (m, 5 H); ca. 3338 (br), 1454, 1021, 735, 697 cm ⁻¹
4-Nitrobenzamide (b)/A	79 ^g 74.5–75.5 0.60, 1.01	δ = 1.43 (18 H), 7.94 (p d, <i>J</i> = 8.4 Hz, 2 H), 8.32 (p d, <i>J</i> = 8.4 Hz, 2 H); 1782, 1745, 1698, 1280 cm ⁻¹	97 93–94	δ = 2.18 (br, 1 H), 4.835 (2 H), 7.53 (d, <i>J</i> = 8.9 Hz, 2 H), 8.21 (d, <i>J</i> = 8.8 Hz, 2 H); 3517, 1603, 1509, 1338, 1057, 736 cm ⁻¹
4-Dimethylaminobenzamide (c)/B	95 ^g 169–170 2.18	δ = 1.38 (18 H), 3.08 (6 H), 6.65 (d, <i>J</i> = 9.1 Hz, 2 H), 7.76 (d, <i>J</i> = 9.1 Hz, 2 H); 1785, 1697, 1595, 1293, 1099 cm ⁻¹	54 oil 12 ^g 180 (dec)	δ = 1.72 (br, 1 H), 2.93 (6 H), 4.54 (2 H), 6.71 (d, <i>J</i> = 8.7 Hz, 2 H), 7.22 (d, <i>J</i> = 8.7 Hz, 2 H) <i>N</i> -Boc-4-dimethylaminobenzamide (side-product): δ = 1.53 (9 H), 3.04 (6 H), 6.65 (d, <i>J</i> = 9.1 Hz, 2 H), 7.72 (d, <i>J</i> = 9.1 Hz, 2 H); E _p /V = -2.26 V
1-Naphthamide (d)/B	90 ^g 67.5–68.5 1.44	δ = 1.26 (18 H), 7.48 (dd, <i>J</i> ₁ = 8.2 Hz, <i>J</i> ₂ = 7.2 Hz, 1 H), 7.54 and 7.60 (2 × p dt, <i>J</i> ₁ = 7 Hz, <i>J</i> ₂ = 1.4 Hz, 1 H + 1 H), 7.79 (dd, <i>J</i> ₁ = 7.1 Hz, <i>J</i> ₂ = 1.2 Hz, 1 H), 7.89 (p d, <i>J</i> = 8 Hz, 1 H), 8.00 (p d, <i>J</i> = 8.2 Hz, 1 H), 8.37 (p d, <i>J</i> = 8 Hz, 1 H); 1792, 1736, 1717, 1102 cm ⁻¹	86/51 61–62	δ = 1.95 (1 H), 5.09 (2 H), 7.41 (dd, <i>J</i> ₁ = 8.1 Hz, <i>J</i> ₂ = 7.1 Hz, 1 H), 7.47 (p d, <i>J</i> = 7 Hz, 1 H), 7.49 and 7.52 (2 × p dt, <i>J</i> ₁ = 7 Hz, <i>J</i> ₂ = 1.6 Hz, 1 H + 1 H), 7.79 (p d, <i>J</i> = 8 Hz, 1 H), 7.85 (p dd, <i>J</i> ₁ = 7.4 Hz, <i>J</i> ₂ = 2 Hz, 1 H), 8.06 (p d, <i>J</i> = 8 Hz, 1 H); 3368–3308 (br), 1003, 800, 792, 774 cm ⁻¹
Cyclohexanecarboxamide (e)/B	74 ^g 67–67.5 –	δ = 1.17–1.36 and 1.41–1.51 (m, ca. 4 H), 1.524 (18 H), 1.62–1.70 (m, ca. 2 H), 1.77 and 1.81 (2 × p t, <i>J</i> = 3 Hz, 1 H + 1 H), 1.90 and 1.93 (2 × m, 1 H + 1 H), 3.16 (tt, <i>J</i> ₁ = 11.3 Hz, <i>J</i> ₂ = 3.4 Hz, 1 H); 1777, 1745, 1702 cm ⁻¹ , estimated purity ≥95%	n.d. ^h oil	δ = 0.88–0.98 (m, 2 H), 1.11–1.32 (m, 3 H), 1.43–1.53 (m, 1 H), 1.63 (1 H), 1.65–1.78 (m, 5 H), 3.44 (d, <i>J</i> = 6.3 Hz, 2 H); ca. 3290 (br), 2924, 2854, 1449, 1036 cm ⁻¹
Boc-L-proline amide (f)/A	85 ^d 109–110 –	δ = 1.42/1.45 (2 × s, 9 H), 1.53/1.56 (2 × s, 18 H), 1.81–2.06 and 2.22–2.35 (m, 4 H), 3.37–3.49 and 3.51–3.64 (m, 2 H), 5.11/5.19 (2 × dd, <i>J</i> ₁ = 8.9 Hz, <i>J</i> ₂ = 3.5/2.7 Hz, 1 H); 1774, 1750, 1708, 1697 cm ⁻¹	84 59.5–60 ⁱ	δ = 1.47 (9 H), 1.56 (m, 1 H), 1.81 (m, 2 H), 1.99 (m, 1 H), 3.28–3.34 and 3.41–3.47 (m, 1 H + 1 H), 3.61 (br, 2 H), 3.95 (br, 1 H); 3438, 1664, 1412, 1049 cm ⁻¹

^a Yields are not optimized.

^b ¹H NMR spectra recorded at 400 MHz in CDCl₃. Proton signals are singlets, when not otherwise stated. Major/minor conformer. FT-IR spectra recorded in KBr pellets (for **3a** and **3e** as films). Only carbonyl and hydroxyl and occasionally strongest bands given. Abbreviation: p = perturbed.

^c Solvents used in the preparation of **2**: acetonitrile (A), dichloromethane (B).

^d Previously described compound (ref.⁷).

^e Twice chromatographed on silica gel with Et₂O/light petroleum 1:4 (traces of HNBoc₂ still visible).

^f See ref.^{1b}

^g Novel compound with satisfactory C,H,N analysis.

^h Chromatographed on silica with Et₂O/CH₂Cl₂ 1:15 but strongly contaminated with Boc-compound(s).

ⁱ [α]_D²⁵ -53.8 and [α]_D²⁵ -56.2 (c 1.0, MeOH), the former value in agreement with literature.

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- (9) **Typical Reduction Procedure:** A solution of **2c** (732 mg, 2 mmol) in abs EtOH (12 mL) was treated with an excess of NaBH₄ (151 mg, 4 mmol) in one batch. After 20 h, when all starting material had been consumed (TLC monitoring), acetone (1 mL) was added, whereupon after 1 h the solvent was evaporated. The obtained foam was dissolved in Et₂O/H₂O, the aqueous phase backwashed once with Et₂O and the combined extracts dried (Na₂SO₄). After evaporation the mixture was purified by chromatography on silica gel (eluent: Et₂O/CH₂Cl₂ 1:15). HNBoc₂ eluted first, followed by pure **3c** (298 mg, 97%); mp 91–92 °C; it was recrystallized from Et₂O/light petroleum.
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