Deacylation of Esters, Thioesters and Amides by a Naphthalene-Catalysed Lithiation

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Abstract: The reaction of different esters, thioesters and amides derived from pivalic, benzoic and 4-tert-butylenzoic acids with an excess of lithium and a catalytic amount of naphthalene (8 mol%) led, after methanolation, to the corresponding alcohols, thiols and amines, respectively, through a reductive non-hydrolytic procedure. This methodology represents a reasonable alternative to other non-reductive protocols.

Key words: esters, thioesters, amides, deacylation, lithium

Acyl derivatives of alcohols, thiols and amines (esters, thioesters and amides, respectively) are very often used to protect those functional groups, because they fit the general requirements for that purpose: (a) easy preparation by standard acylation methods, and (b) relative easy deprotection under different conditions to liberate again the corresponding deacylated compound.1 Concerning hydrolysis under basic conditions (nucleophilic cleavage) the reactivity follows the series: thioesters > esters > amides, the latter being rather resistant to this process. Other methodologies for acyl removal involve acidic hydrolysis,2 β-elimination processes (for instance, for fluorenylethoxycarbonyl derivatives),3 reduction with dissolving metals,4 hydride sources5 and electrolysis,6 and enzymatic methods.7

On the other hand, in the last few years we have been using an arene-catalysed lithiation to perform metallations under very mild reaction conditions.8–10 Among other uses,11 this methodology has been shown to be applicable to the cleavage of trityl ethers12 and amines,13 for the deprotection of allyloxy- or benzylxycarbonyl-protected alcohols, amines and thiols.15 In this paper we wish to report on the use of a naphthalene-catalysed lithiation to perform the deacylation of representative esters, thioesters and amides under very mild non-hydrolytic conditions.

The reaction of different alkyl or aryl pivalates 1a–e with an excess of lithium (1:9 molar ratio) and a catalytic amount of naphthalene (1:0.16 molar ratio) in THF at 0 °C for two to four hours led, after quenching with methanol, to the corresponding alcohols 2a–d and phenol 2e (Equation 1 and Table 1, entries 1–5). The same process can also be applied to a dipivalate like compound 1f, which under the same reaction conditions afforded after one hour the expected diol 2f in almost quantitative yield (Table 1, entry 6). Very good results were obtained for aromatic esters, such as benzoates 1g and 1h and the corresponding 4-tert-butyld derivative 1i, which gave alcohols 2a or 2d in almost quantitative yield (Table 1, entries 7–9).

When pivalic or benzoic acid derived thioesters 1j–l were treated using the same protocol, the expected thiols 2j and 2k were obtained in variable yields (Equation 1 and Table 1, entries 10–12). Finally, both pivalamides 1m–p and the benzamide 1q under the aforementioned reductive deprotection conditions furnished deacylated amines 2m–p, generally in good yields (Equation 1 and Table 1, entries 13–17). The reductive removal of the pivaloyl group of N-octylpivalamide was also attempted following the same procedure previously used by us in the deprotection of tritylated primary amines,13 (deprotonation with n-butyllithium and treatment with trimethylsilyl chloride before performing the lithiation step) however, the reaction failed in this case, the starting amide being quantitatively recovered.

In general, the deprotection of pivaloyl bearing substrates gave the expected products in good yields, except those in which the R substituent was cyclohexyl (Table 1, entries 4 and 11) or a sterically hindered group, like a tertiary alky (Table 1, entry 3) or an aryl group substituted at both ortho positions (Table 1, entry 5). The application of the methodology to the functionalised amide 1o gave only a moderate yield (Table 1, entry 15), probably due to the participation of the generated lithium amide as a base in β-elimination processes.

All substrates bearing a benzoyl (1g, 1h, 1l and 1q) or a 4-tert-butylenzo group (1i) gave excellent yields of the debenzoylated products, being in some cases higher than the obtained with the corresponding pivaloyl derivatives (compare entry 4 with 8 and entry 10 with 12).
<table>
<thead>
<tr>
<th>Entry</th>
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<tr>
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<td>2 h</td>
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The deacylation of starting materials having an allylic or benzylic R group was also attempted. Benzyl and geranyl pivalates, N,N-diallylpivalamide and N-benzyl-N-methylpivalamide were submitted to the lithiation process, but the desired deacylated alcohols or amines were not formed. In this case, the reductive cleavage of the allylic or benzylic carbon–heteroatom bond was the preferred reaction pathway, leading to the formation of the corresponding lithium pivalates or pivalamides and the allylic or benzylic organolithium reagents RLi. In the latter would give the corresponding hydrocarbons upon reaction with methanol. Toluene was detected (GC-MS) in the crude of the reactions with benzylic substrates, which would confirm the cleavage of the benzyl–heteroatom bond.

Concerning a possible reaction mechanism, in the case of the benzoic and 4-tert-butylbenzoic acid derived substrates, we were not able to identify any of the corresponding by-products. Starting materials 1 were easily prepared by acylation of the corresponding alcohols, thiols or amines (after their transformation into the corresponding salts with n-butyl-lithium) with the corresponding acyl chlorides under standard conditions.

The general experimental information is given elsewhere. All reagents used for the synthesis of substrates 1 and naphthalene were commercially available (Acros, Aldrich) and were used without further purification. Lithium powder was prepared according to the procedure described in the literature. Commercially available n-BuLi was titrated with a 1 M solution of s-BuOH in xylene using 1,10-phenanthroline as indicator. Commercially available anhyd THF (99.9%, water content ≤ 0.006%, Acros) was used as a solvent in all the reactions. All glassware was dried in an oven at 100 °C and cooled to r.t. under argon before use.

### Esters, Thioesters and Amides 1: General Procedure

n-BuLi (1.6 M solution in hexane; 6.3 mL, 10.0 mmol) was added dropwise to a stirred solution of the corresponding alcohol 2a–f, thiol 2j–k or amine 2m–p in anhyd THF (10 mL) under Ar at 0 °C. After 10 min, pivaloyl, benzoyl or 4-tert-butylbenzoyl

<table>
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<th>Entry</th>
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<th>Product</th>
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<tr>
<td>17</td>
<td>1q</td>
<td>15 min</td>
<td>2m</td>
<td>94</td>
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</table>

*Yields were determined by quantitative GC using commercially available compounds 2 and n-dodecane (internal standard) or n-hexadecane (internal standard for 2e) in the determination of response factors.*

The deacylation of starting materials having an allylic or benzylic R group was also attempted. Benzyl and geranyl pivalates, N,N-diallylpivalamide and N-benzyl-N-methylpivalamide were submitted to the lithiation process, but the desired deacylated alcohols or amines were not formed. In this case, the reductive cleavage of the allylic or benzylic carbon–heteroatom bond was the preferred reaction pathway, leading to the formation of the corresponding lithium pivalates or pivalamides and the allylic or benzylic organolithium reagents RLi. The latter would give the corresponding hydrocarbons upon reaction with methanol. Toluene was detected (GC-MS) in the crude of the reactions with benzylic substrates, which would confirm the cleavage of the benzyl–heteroatom bond.
chloride (10.0 mmol) was added over ca. 5 min. After stirring for 1 h at the same temperature, the crude reaction mixture was adsorbed onto basic alumina, transferred to a short column of basic alumina and eluted with hexane. Evaporation of the solvent (15 Torr) afforded the expected pure esters, thiosteres and amides I.

1-Decyl Pivatate (1a)\(^{20}\)
Colourless oil; yield: 66%; \(R_f\) 0.90 (hexane–EtOAc, 9:1).

1H NMR: \(\delta = 0.88\) (t, 3 H, \(J = 6.6\) Hz, \(CH_2CH_3\)), 1.20 (s, 9 H, \(\text{C}(CH_3)_3\)), 1.22–1.41 (m, 14 H, \(CH_2\)), 1.55–1.68 (m, 2 H, \(CH_2CO\)), 4.04 (t, 2 H, \(J = 6.6\) Hz, \(CH_2O\)).

13C NMR: \(\delta = 14.1\) (CH), 22.6 [3 C, \(\text{C}(CH_3)_3\)], 25.7 (CH), 28.6 (CH), 29.25 (CH), 29.3 (CH), 29.4 (CH), 29.6 (CH), 31.9 (CH), 32.8 (CH\(_2\)), 41.5 [\(\text{C}(CH_3)_3\)] 63.0 (CO), 171.3 (C=O).

MS: \(m/z\) (%): 185 (M\(^{+}\) – 57, 2), 140 (18), 111 (11), 103 (89), 97 (15), 85 (27), 84 (10), 83 (13), 71 (11), 70 (15), 69 (12), 57 (100), 56 (19), 55 (15).

2-Octyl Pivatate (1b)\(^{21}\)
Colourless oil; yield: 88%; \(R_f\) 0.87 (hexane–EtOAc, 9:1).

1H NMR: \(\delta = 1727\) (C=O), 1166 (CO) cm\(^{-1}\).

1H NMR: \(\delta = 0.88\) (t, 3 H, \(J = 6.8\) Hz, \(CH_2CH_3\)), 1.02–1.71 (m, 13 H, \(CH_2CH_3\), 5 \(\times\) CH), 1.18 [s, 9 H, \(\text{C}(CH_3)_3\)], 4.78–4.94 (m, 1 H, CH).

13C NMR: \(\delta = 14.0\) (CH\(_2\)), 19.8 (CH\(_2\CO\)), 22.5 (CH), 25.3 (CH\(_3\)), 27.1 [3 C, \(\text{C}(CH_3)_3\)], 29.1 (CH), 31.7 (CH), 35.9 (CH\(_3\)), 38.7 [\(\text{C}(CH_3)_3\)], 70.5 (CO), 178.1 (C=O).

MS: \(m/z\) (%): 157 (M\(^{+}\) – 57, <1), 129 (10), 112 (15), 103 (14), 85 (35), 71 (33), 57 (100), 56 (11).

3,7-Dimethyl-3-octyl Pivatate (1c)
Colourless oil; yield: 75%; \(R_f\) 0.69 (hexane–EtOAc, 9:1).

1H NMR: \(\delta = 1725\) (C=O), 1175 (CO) cm\(^{-1}\).

1H NMR: \(\delta = 0.90–0.94\) (m, 2 H, \(CH_2\)), 1.17 [s, 9 H, \(\text{C}(CH_3)_3\)], 1.42 (s, 3 H, \(CH_2CO\)), 1.46–1.99 (m, 7 H, 3 \(\times\) CH\(_3\)).

13C NMR: \(\delta = 7.8\) (CH\(_3\)), 21.2 (CH\(_3\)), 22.5 (CH), 23.1 (CH\(_3\)), 27.2 [4 C, \(\text{C}(CH_3)_3\)], 27.7 (CH), 30.9 (CH), 38.0 (CH), 39.2 (CH\(_3\)), 39.3 [\(\text{C}(CH_3)_3\)], 84.2 (CO), 177.5 (C=O).

MS: \(m/z\) (%): 185 (M\(^{+}\) – 57, <1), 157 (11), 141 (57), 99 (10), 85 (87), 73 (11), 71 (37), 70 (20), 69 (18), 57 (100), 55 (24).

HRMS: \(m/z\) calc'd for \(C_{13}H_{25}O_3\) (M\(^{+}\), 242.2246; found, 242.2241.

Cyclohexyl Pivatate (1d)\(^{22}\)
Colourless oil; yield: 56%; \(R_f\) 0.43 (hexane–EtOAc, 9:1).

IR (neat): \(1728\) (C=O), 1167 (CO) cm\(^{-1}\).

1H NMR: \(\delta = 1.08–1.87\) (m, 10 H, \(CH_2\)), 1.19 [s, 9 H, \(\text{C}(CH_3)_3\)], 4.68–4.80 (m, 1 H, CH).

13C NMR: \(\delta = 23.4\) (2 C, \(CH_2\)), 25.4 (CH\(_3\)), 27.1 [3 C, \(\text{C}(CH_3)_3\)], 31.3 (2 C, \(CH_3\)), 38.7 [\(\text{C}(CH_3)_3\)], 71.7 (CO), 177.9 (C=O).

MS: \(m/z\) (%): 184 (M\(^{+}\) – 1), 143 (45), 125 (11), 99 (12), 85 (54), 83 (26), 69 (27), 57 (100), 55 (16).

Mesityl Pivatate (1e)\(^{23}\)
Colourless oil; yield: 91%; \(R_f\) 0.84 (hexane–EtOAc, 9:1).

IR (neat): \(1751\) (C=O), 1602 (HC=CH), 1139 (CO) cm\(^{-1}\).

1H NMR: \(\delta = 1.39\) [s, 9 H, \(\text{C}(CH_3)_3\)], 2.08 (s, 6 H, \(CH_2Ph\)), 2.25 (s, 3 H, \(CH_3Ph\)).

13C NMR: \(\delta = 16.1\) (2 C, \(CH_2Ph\)), 20.7 (\(CH_2Ph\)), 27.3 [3 C, \(\text{C}(CH_3)_3\)], 39.2 [\(\text{C}(CH_3)_3\)], 129.1 (2 C, \(Ph\)), 129.6 (2 C, \(Ph\)), 134.9 (Ph), 145.9 (Ph), 176.1 (C=O).

MS: \(m/z\) (%): 318 (M\(^{+}\) – 1), 304 (11), 303 (50), 180 (10), 179 (83), 178 (29), 164 (12), 163 (100), 161 (34), 118 (12).

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**Naphthalene-Catalysed Litigation of Compounds 1; General Procedure**

A solution of the ester, thioster or amide 1 (1.0 mmol) in THF (2 mL) was dropwise added to a green suspension of Li powder (63 mg, 9.0 mmol) and naphthalene (20 mg, 0.16 mmol) in THF (5 mL), under Ar at 0 °C. After stirring at the same temperature for the time indicated in Table 1, MeOH (5 mL) was carefully added, the cooling bath was removed and the reaction was stirred until it had warmed to r.t. The yields of the decyated products were determined by quantitative GC. Commercially available alcohols 2a-f, thiols 2j,k, amines 2m-p, n-dodecane (internal standard) and n-hexadecane (internal standard for 2e) were used in the determination of response factors. Compounds 2 (commercially available) were characterised by comparison of their physical and spectroscopic data with authentic samples.

**Acknowledgment**

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