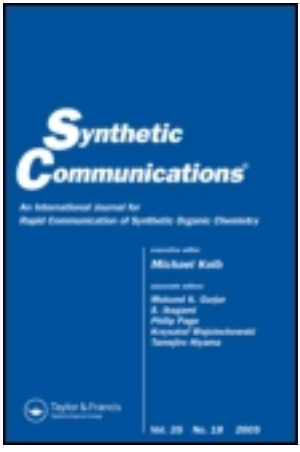


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# One-Pot Reduction of Carboxylic Acids via O-Acylisoureas

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# ONE-POT REDUCTION OF CARBOXYLIC ACIDS *VIA* *O*-ACYLISOUREAS

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**Abstract:** A simple one-pot reduction of aliphatic carboxylic acids to primary alcohols, by treatment with dicyclohexylcarbodiimide followed by lithium borohydride, is reported. The same methodology applied to aromatic carboxylic acids is shown to give a mixture of the alcohols with N-cyclohexylcarboxamides.

The reduction of carboxylic acids to primary alcohols using borohydride reagents in the presence of iodine[1] or trifluoroacetic acid[2] is known. It has also been reported that the formation of an ester with *N*-hydroxysuccinimide[3] or 1-hydroxy-6-nitrobenzotriazole[4] and its reduction *in situ* with sodium borohydride provides a one-pot conversion of an acid to the primary alcohol. Similar processes have been reported using activated species prepared from acids with carbonyldiimidazole,[5] *N,N*-dimethylchloro-methyleniminium chloride,[6] and via acyl fluorides.[7] A significant advantage of carrying out the reduction on an activated intermediate, when compared to using more vigorous reagent systems is that other functional groups (particularly esters) remain unaffected.

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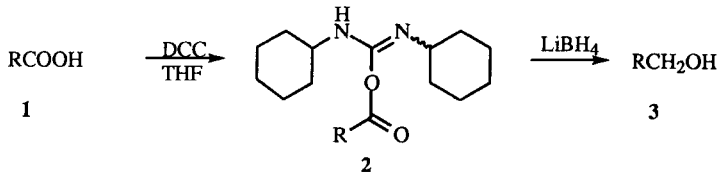



Scheme 1. Formation of *O*-acylisoureas and *in-situ* reduction.



We have found that the formation of *O*-acylisoureas[8] **2**, using dicyclohexylcarbodiimide (DCC), and their subsequent reduction with lithium borohydride, is a simple one-pot conversion of carboxylic acids to primary alcohols (Scheme 1). Use of lithium borohydride is dictated by the unreactivity of the intermediates towards sodium borohydride, but presents no significant disadvantage: reduction of esters, in particular, by lithium borohydride is slow unless a solvent such as methanol is added,[9] and the rate of reduction of an isourea is very much greater.

In principle, reaction of a carboxylic acid with DCC can result in formation of an anhydride, in which case reduction would provide no more than 50% of the corresponding alcohol. Anhydride formation is favoured in solvents where the carboxylic acid is poorly soluble;[10] therefore, reactions were carried out in tetrahydrofuran. Typically, a slight precipitate of dicyclohexylurea (DCU) separated after an extended period, possibly indicating some anhydride formation. In contrast, the reaction of *m*-toluic acid with 0.5 molar equivalents of DCC gave a voluminous precipitate of DCU in a relatively short time, and the anhydride was the major component observed. It is therefore possible to limit the degree of anhydride formation, enabling synthetically useful yields of alcohol to be obtained, by adding a small excess of DCC. Since the *O*-acylisourea may isomerise to the *N*-acyl isomer after an extended period (see below), it is desirable to add the reducing agent soon after formation of the isourea is complete.

Table 1. **3a-3h** from Aliphatic Carboxylic Acids.

| Acid **1** | R | Time for *O*-acyl-isourea formation. | Work-up[a] | Alcohol **3** Yield (%) |
|---|---|---|---|---|
| **1a** | (*E*)-CH=CHPh | 4 h | A | 76 |
| **1b** | $CH_2NHCOPh$ | 2 h | A | 71 |
| **1c** | $CH_2CH_2$-*p*-$C_6H_4OH$ | 6 h | A | 43 |
| **1d** | $CH_2Ph$ | 5 h | B | 52 |
| **1e** | $CH_2$-*p*-$C_6H_4Br$ | 3 h | B | 58.5 |
| **1f** | (S)-CH($CH_2Ph$)NHBoc | 3 h | B | 63 |
| **1g** | (S)-CH($CH_2COO$-*t*-Bu)NHCbz | 30 min | B | 53 |
| **1h** | $CH_2CH_2CH=CH_2$ | 1h | C | 56 |

a. A: quenched with 1M hydrochloric acid; subsequent washing of the organic fraction with aqueous sodium hydrogencarbonate removed any remaining carboxylic acid. B: quenched with saturated aqueous sodium hydrogencarbonate. C: quenched with 1M hydrochloric acid. Yield (as a percentage conversion only) estimated by GC.

Reduction normally required between one and two molar equivalents of lithium borohydride, although the excess was unnecessary in most cases. Reduction was normally mildly exothermic and complete within one hour at room temperature. The bulk of the DCU was removed by filtration during work-up; the little which remained in the crude sample could be removed in most cases by redissolution of the crude sample in ether or hexane and refiltration, and in the remaining cases by chromatography.

Table 2. Alcohols **3i-3l** and Amides **4i-4l** from Aromatic Carboxylic Acids

| Acid **1** | R | Time for *O*-acyl-isourea formation. | Work-up[a] | Alcohol **3** Yield (%) | Amide **4** yield (%) |
|---|---|---|---|---|---|
| **1i** | *p*-$C_6H_4NO_2$ | 3 h | A | 64 | 5 |
| **1j** | α-$C_{10}H_8$ | 4 h | A | 68 | 8 |
| **1k** | *m*- $C_6H_4Me$ | 3 h | A | 48 | 48 |
| **1l** | 2,4-$C_6H_3Me_2$ | 20 min | B | 18 | 0 |
| | | 1 h | B | 78 | 0 |
| | | 2.5 h | B | 11 | 89 |

a. A: quenched with 1M hydrochloric acid; subsequent washing with aqueous sodium hydrogencarbonate removed any remaining carboxylic acid. B: quenched with saturated aqueous sodium hydrogencarbonate.

Examples of the formation and *in-situ* reduction of *O*-acylisoureas **2** are presented in Tables 1 and 2. Functional groups tolerated include double bonds, nitro, amides and carbamates. The difference in reactivity between the *O*-acylisoureas and "normal" esters was demonstrated by a competition experiment: under the conditions for reduction of the *O*-acylisourea derived from *p*-bromophenylacetic acid and DCC (one of the lower-yielding cases), less than 5% of methyl phenylacetate was reduced, even using an excess of lithium borohydride.

Comparisons between the reduction of isourea **2l** and those of the activated esters formed from the same acid with *N*-hydroxysuccinimide, *N*-hydroxyphthalimide, and 1-hydroxybenzotriazole are summarised in Table 3. In all cases but where *N*-hydroxysuccinimide was used, the yields isolated after reduction with lithium

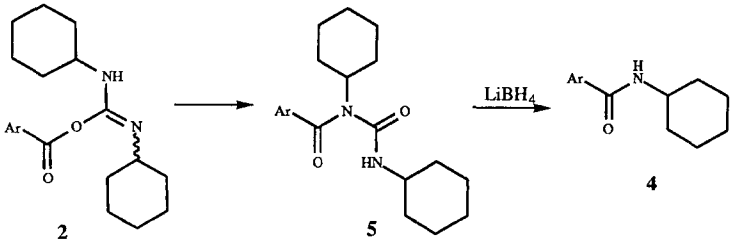
Table 3. Comparisons in the Reduction of 2,4-Dimethylbenzoic Acid

| Activating agent (added after DCC) | Yield, %, using $NaBH_4$ | Yield, %, using $LiBH_4$ |
|---|---|---|
| *N*-Hydroxysuccinimide | 38 | 34 |
| *N*-Hydroxyphthalimide | 36 | 91 |
| 1-Hydroxybenzotriazole | 79 | 85 |
| None | 0 | 78 |



borohydride were roughly comparable and were better than those obtained after reduction with sodium borohydride. However, it was only with the *O*-acylisourea that sodium borohydride completely failed to reduce the intermediate, underlining the comment made earlier concerning the relative reactivity of these species when compared to other activated esters. Interestingly, the yield of alcohol **3f** was comparable to that reported[11] by reduction of **1f** with borane-tetrahydrofuran. By contrast, a respectable yield of aspartate derivative **3g** was obtained using the present method, whereas this was formed only in trace amounts by treatment of **1g** with borane-tetrahydrofuran.

Using aromatic carboxylic acids (Table 2), side-products formed which were identified as *N*-cyclohexylamides **4**, being identical to the products of DCC-mediated coupling of the corresponding acid with cyclohexylamine. It appears that *O*- to *N*- migration of the acyl group occurs (Scheme 2) followed by reductive cleavage of the resulting *N*-acylurea. As would be expected, the yield of amide increased when the time allowed for formation of the DCC adduct **2l** was extended. When the reaction between *m*-toluic acid (**1k**) and DCC was




Scheme 2. Formation of *N*-cyclohexylamides.



monitored by solution IR, initial formation of **2k** was indicated by a single carbonyl stretch (1720 $cm^{-1}$) characteristic of an ester, whereas after 24 h, additional bands arose which were consistent with the *N*-acylurea (1703, 1651, and 1532 $cm^{-1}$) accompanied by a small amount of the anhydride (1791 $cm^{-1}$). In a separate experiment, the *N*-acylurea **5i** formed from *p*-nitrobenzoic acid was isolated and characterised; lithium borohydride reduction of **5i** gave amide **4i** without any trace of the corresponding alcohol. This is consistent with the earlier observation that amides are not reduced by lithium borohydride, and provides evidence for the intermediacy of an *N*-acylurea. This side-reaction, which arose only with aromatic carboxylic acids, can be controlled (other than in the case of *m*-toluic acid, **1k**) by limiting the time allowed for formation of **2**. Reducing the reaction temperature merely inhibited the formation of **2** and variations in concentration appeared to have no effect.

## Experimental

$^1H$ nmr spectra were recorded using a Jeol GSX-270 instrument. Gas chromatography was performed using a Hewlett-Packard chromatograph (HP 5890) fitted with a mass-selective detector (HP 5970MSD) on a capillary column

(HP-1, 23m x 0.2mm x 0.33μm); the oven temperature was increased from an initial 70°C to 240°C at 10°C per minute. Additional low-resolution mass spectra were recorded using a Finnigan MAT TSQ700 triple quadrupole instrument.

*N-Boc-phenylalaninol* (**3f**): A solution of Boc-phenylalanine (**1f**; 123 mg, 0.46 mmol) in anhydrous THF (2 ml) was added dropwise to a stirred solution of DCC (120 mg, 0.58 mmol) in anhydrous THF (5 ml) at room temperature and the mixture was stirred for 3 h. Lithium borohydride (30 mg, 1.4 mmol) was added and, once the initial effervescence had subsided, the mixture was stirred for 16 h, then quenched with aqueous sodium hydrogencarbonate. The mixture was filtered, and the filter cake was washed through with ethyl acetate (10 ml). The organic phase was separated, and the aqueous phase was extracted with additional ethyl acetate (10 ml). The combined organic phases were dried ($MgSO_4$), concentrated under reduced pressure, and the residue purified by chromatography on silica gel in ethyl acetate-hexane (1:4) to give **3f** (72 mg, 63%). $[\alpha]_D^{21}$ -0.74, c 0.4 in chloroform (lit.[11] -0.80, c 1.1 in chloroform); $\delta_H(CDCl_3)$ 1.35 (9H, s), 2.75 (1H, dd), 2.91 (1H, dd), 3.51 (2H, d), 3.78 (1H, m), 3.9 (1H, br s), 5.75 (1H, br d), 7.15-7.3 (5H, m).

*Similarly prepared were:*

Cinnamyl alcohol (**3a**; 1.9 mmol scale; 76%).

*N*-(2-Hydroxyethyl)benzamide (**3b**; 1.5 mmol scale; 71%).

3-(*p*-Hydroxyphenyl)-1-propanol (**3c**; 1.1 mmol scale; 43%).

2-Phenylethanol (**3d**; 1.1 mmol scale; 52%).

2-(*p*-Bromophenyl)ethanol (**3e**; 0.45 mmol scale; 58.5%).

*tert*-Butyl 3(S)-benzyloxycarbonylamino-4-hydroxybutyrate (**3g**; 3.3 mmol scale; 53%). $[\alpha]_D^{21}$ -8.7 (c = 1.1, ethanol). $\nu_{max}$ 3400 (br), 2975, 2957, 1734-1686cm$^{-}$

[1]; $\delta_H(CDCl_3)$ 1.42 (9H, s), 2.44 (1H, br s), 2.53 (2H, d), 3.71 (2H, dd), 4.02 (1H, m), 5.10 (2H, s), 5.48 (1H, d), 7.15-7.4 (5H, m). *m/z* (CI-$NH_3$) 310.165869 ($[MH]^+$; calc. for $C_{16}H_{24}NO_5$ 310.165448), 254, 236, 210, 178, 91 (100%).

4-Penten-1-ol (**3h**; 1.6 mmol scale; 56%).

*p*-Nitrobenzyl alcohol (**3i**; 1.1 mmol scale; 64%), accompanied by *N*-cyclohexyl-*p*-nitrobenzamide (**4i**; 5%). m.p. 202.5-203°C (lit.[12] m.p. 203-204°C). $\delta_H(CDCl_3)$ 0.8-1.9 (10H, m), 3.6 (1H, m), 7.35 (2H, d), 7.9 (1H, d), 8.3 (2H, d). *m/z* (EI) 248 ($M^{+\cdot}$), 206, 167 (100%), 150, 120.

1-Naphthalenemethanol (**3j**; 1.4 mmol scale; 68%), accompanied by *N*-cyclohexyl-1-naphthalenecarboxamide[13] (**4j**; 8%). m.p. 159-160°C. $\delta_H(CDCl_3)$ 0.9-1.95 (8H, m), 2.0-2.2 (2H, m), 4.08 (1H, m), 5.84 (1H, d), 7.4-7.6 (4H, m), 7.8-7.95 (2H, m), 8.26 (1H, d). *m/z* (EI) 253 ($M^{+\cdot}$), 171, 155 (100%), 127.

*m*-Methylbenzyl alcohol (**3k**; 2.2 mmol scale; 48%), accompanied by *N*-cyclohexyl-3-methylbenzamide (**4k**; 48%). m.p. 125.5-126°C (lit.[14] m.p. 121°C). $\delta_H(CDCl_3)$ 1.1-1.8 (10H, m), 2.20 (3H, s), 3.96 (1H, m), 5.94 (1H, br d), 7.15-7.3 (2H, m), 7.50 (1H, d), 7.56 (1H, s); *m/z* (EI) 217 ($M^{+\cdot}$), 136 (*m*-$MeC_6H_4CONH_3^+$), 119 (100%, *m*-$MeC_6H_4CO^+$), 91.

2,4-Dimethylbenzyl alcohol (**3l**; 0.5-0.7 mmol scale; 11-78%), accompanied by *N*-cyclohexyl-2,4-dimethylbenzamide[15] (**4l**; 0-89%). m.p. 163-164°C. $\delta_H(CDCl_3)$ 1.05-2.1 (10H, m), 2.31 (3H, s), 2.40 (3H, s), 3.94 (1H, m), 5.59 (1H, m), 6.95-7.05 (2H, m), 7.22 (1H, d). *m/z* (EI) 231 ($M^{+\cdot}$), 150, 133 (100%), 105.

*N,N-Dicyclohexyl-N-(*p*-nitrobenzoyl)urea* (**5i**): To a stirred solution of DCC (41.2 mg, 0.2 mmol) in THF (2 ml) was added *p*-nitrobenzoic acid (32.6 mg, 0.2 mmol) in THF (1 ml). The mixture was stirred overnight, hexane (2 ml) was added, and after a further 24h, filtration gave **5i** (58.5 mg, 57%). m.p. 199-200°C. Found: C,

62.2; H, 7.1; N, 10.75; $C_{20}H_{27}N_3O_4.2/3H_2O$ requires C, 62.3; H, 7.1; N, 10.9%. $\nu_{max}$ 3300 (br), 2931, 1699, 1650, 1545, 1528 $cm^{-1}$. $\delta_H(CDCl_3)$ 0.8-2.1 (20H, m), 3.52 (1H, m), 4.06 (1H, m), 6.15 (1H, d), 7.73 (2H, d), 8.28 (2H, d); *m/z* (EI)355 ($[M-H_2O]^{+\cdot}$), 281, 248, 207, 150 (100%), 120, 104.

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