Chemoselective Alcoholysis of Acylureas

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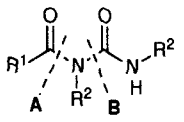
Two methods for the chemoselective alcoholysis of acylureas were developed to generate esters and amides, respectively. In alcoholysis using sodium methoxide in methanol, methoxide attacked the acyl carbonyl to give the corresponding methyl ester. While in alcoholysis using lithium benzyloxide in diethyl ether, benzyloxide attacked the urea carbonyl to give the amide. The chemoselectivity originates in the different chelating abilities of the metals and the polarity of the solvents.

In recent papers, acylurea has been utilized for stereoselective synthesis.[1-4] However the solvolysis (removal of the auxiliary) has been problematic, because acylureas (Scheme 1) have three continuous amide bonds in the molecule. In this study, two methods for the chemoselective alcoholysis were developed to generate esters and amides, respectively. We now describe the first study on chemoselective alcoholysis of acylureas.

Acylureas **1a–f** (Scheme 2, 3) were prepared from carboxylic acids and carbodiimides[2] (Table 1). Alcoholysis of oleoylurea **1a** with sodium alkoxide or lithium alkoxide, in methanol or diethyl ether, were investigated. The reaction with sodium methoxide in methanol at 0 °C gave methyl oleate **2a** (68%, Table 2) and the urea **3a** (90%) with cleavage of the amide bond at position A (Scheme 1). However, the reaction with lithium methoxide in methanol gave amide **4a** in 65% yield with cleavage of the amide bond at B. The best yield of **4a** (98%) was obtained from the reaction of **1a** with LiOBn in diethyl ether at room temperature.



Scheme 1

In a similar manner, alcoholysis using NaOMe/MeOH was investigated at 0 °C. The reaction of **1b** and **1d** which have a conjugated acyl carbonyl group gave methyl benzoate **2b** and methyl cinnamate **2d** in poor yields (trace). Amide **4c** (35%) was obtained in the reaction of **1c**. In contrast to the previous reaction[2] of tricyclic acylurea **1e**, bicyclic acylurea **1g**, and 3-hydroxyacylureas **1h** and **1i**, which gave the corresponding esters **2e** (86%),[3] **2g** (94%),[2] **2h** (96%)[1], and **2i** (96%)[1] with no epimerization, the reaction of the hindered acyl carbonyl of bicyclic acylurea **1f** produced the tricyclic imide **6f** (45%). The nitrogen of the generated amide **4f** might attack the neighboring ester carbonyl group to give **6f**.

In order to investigate the B-cleavage of acylurea, the alcoholysis with LiOBn in diethyl ether was carried out (Table 2). The reaction of **1a–d** gave **4a–d** in moderate to excellent yields, respectively. Carbamates **5** were not obtained. They might be hydrolyzed in the basic conditions during quenching by addition of water. To avoid exchange of lithium and iodine, sodium benzyloxide was used as the reagent for the reaction of **1e**. The corresponding amide **4e** (16%) was obtained with retention of the configuration. The reaction of **1f** produced **6f** (29%).

We postulate the following explanation for the chemoselectivity. In the reaction of acylurea with NaOMe in methanol, the sodium cation and methoxide anion are separated by methanol, a polar solvent.[5] The free methoxide attacks the less hindered acyl carbonyl to give the methyl ester and urea (cleavage A). The reactivity of methoxide is low for the conjugated acyl carbonyl **(1b, 1d)**. In the reaction of the hindered acyl carbonyl **(1c, 1f)**, the methoxide attacks the less hindered urea carbonyl

Table 1. *Spectral Data of* **1a–f**

Product	Yield (%)	mp (°C)	IR (KBr, cm^{-1})	^1H NMR ($CDCl_3$, TMS) δ, J (Hz)
1a[b]	38	oil	3290, 2930, 2860, 1710, 1645, 1530, 1460, 1230	0.88 (t, J = 7.2, 3 H), 1.00–2.18 (m, 46 H), 2.40 (t, J = 7.0, 2 H), 3.57–4.12 (m, 2 H), 5.35 (t, J = 4.3, 2 H), 7.18 (d, J = 7.5, 1 H)
1b[a]	76	175–175.5	3270, 3050, 2930, 1710, 1625, 1580, 1540, 1385	0.70–2.30 (m, 20 H), 3.25–3.70 (m, 1 H), 3.85–4.28 (m, 1 H), 6.15 (br d, J = 7.9, 1 H), 7.20–7.50 (m, 5 H)
1c[a]	84	151–151.5	3340, 2930, 1710, 1665, 1510, 1280	0.76–2.12 (m, 20 H), 1.62 (d, J = 6.5, 3 H), 3.36–3.88 (m, 1 H), 3.88–4.35 (m, 1 H), 4.98 (q, J = 6.5, 1 H), 6.13 (d, J = 7.0, 1 H), 6.72–7.10 (m, 3 H), 7.10–7.42 (m, 2 H)
1d[b]	72	164.5–165	3300, 3000, 2930, 1710, 1655, 1605, 1545	0.75–2.25 (m, 20 H), 3.55–4.33 (m, 2 H), 6.71 (d, J = 15.5, 1 H), 7.05 (br d, J = 8.0, 1 H), 7.30–7.58 (m, 5 H), 7.69 (d, J = 15.5, 1 H)
1f[a]	73	134–135	3310, 2930, 1750, 1700, 1665, 1535, 1405, 1260	0.75–2.11 (m, 22 H), 2.93–3.10 (m, 1 H), 3.10–3.21 (m, 1 H), 3.21–3.37 (m, 2 H), 3.45–3.87 (m, 1 H), 3.64 (s, 3 H), 3.87–4.28 (m, 1 H), 6.20 (dd, J = 5.0, 2.9, 1 H), 6.39 (dd, J = 5.0, 2.9, 1 H), 7.13 (d, J = 7.6, 1 H)

[a] Satisfactory microanalyses obtained: C ± 0.46, H ± 0.10, N ± 0.16; exception **1f**, C − 0.59.
[b] HRMS (FAB): (MH^+) ± 0.0004.

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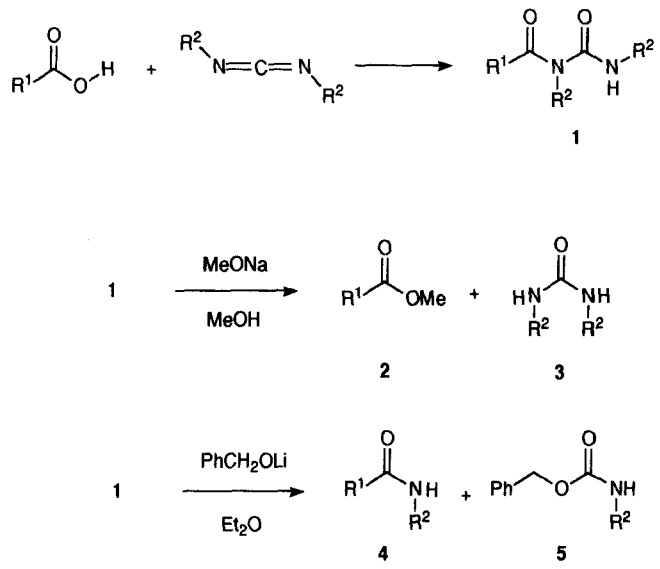
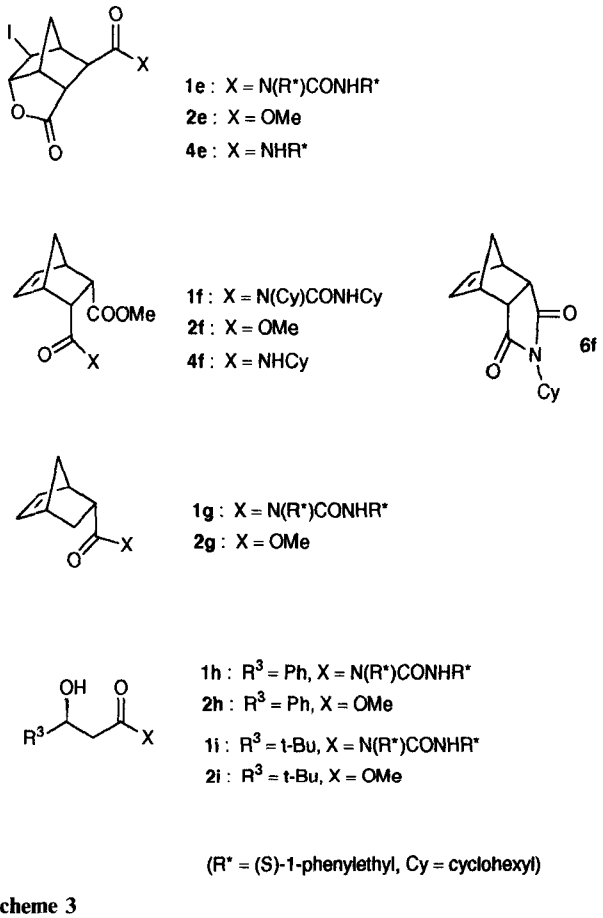


1, 4	R^1	R^2	2	R^1
a	$(CH_2)_7CH=CH(CH_2)_7CH_3$	Cy	a	$(CH_2)_7CH=CH(CH_2)_7CH_3$
b	Ph	Cy	b	Ph
c	$CH(OPh)CH_3$	Cy	c	$CH(OPh)CH_3$
d	CH=CHPh	Cy	d	CH=CHPh

Cy: cyclohexyl

Scheme 2



Scheme 3

Table 2. Yields of Alcoholysis of **1**

Starting Material	NaOMe in MeOH		LiOBn in Et_2O	
	Product	Yield (%)[a]	Product	Yield (%)[a]
1a	**2a**[b]	68	**4a**[b]	98
1b	**2b**	trace	**4b**[c]	66
1c	**4c**	35	**4c**[c]	76
1d	**2d**	trace	**4d**[c]	93
1e	**2e**	86[d]	**4e**[b]	16
1f	**6f**	45	**6f**[c]	29

[a] Isolated Yields.
[b] HRMS (FAB): (MH^+) **2a**, **4e** ± 0.0004; 4a + 0.0014.
[c] Satisfactory microanalyses obtained: C ± 0.42, H ± 0.18, N ± 0.23.
[d] Ref. 3.

resulting in cleavage B. In the reaction with LiOBn in diethyl ether, lithium strongly chelates with the most electron rich oxygen, namely that of the carbonyl in the urea moiety, in a non-polar solvent.[6] Accordingly, benzyl oxide attacks the urea carbonyl to cause the cleavage B.

The following alternative explanation is also plausible.[7] In the reaction with NaOMe in MeOH, deprotonation from NH by methoxide results in the enolization of the urea carbonyl. On the other hand, in diethyl ether, a non-polar solvent, hydrogen bonding between the NH and the oxygen of the acyl carbonyl easily causes the enolization of the acyl carbonyl. The un-enolized carbonyl is more reactive to the alkoxide. Accordingly the reaction in NaOMe/MeOH and that in LiOBn/Et_2O gave esters **2** and amides **4**, respectively.

Melting points were uncorrected. ^1H NMR spectra were observed with a JEOL EX-90 spectrometer. IR spectra were obtained on a Hitachi I-2000 spectrophotometer. Acylureas **1** were prepared by the method in our previous paper.[2] The yields and spectral data are shown in Table 1.

Solvolysis with Sodium Methoxide in Methanol:
A solution of MeONa (3 mmol) in MeOH (5 mL) was added to the solution of acyclurea **1** (1 mmol) in MeOH (10 mL) at 0 °C, and stirred for 3 h at 0 °C. The solution was concentrated and EtOAc (5 mL) was added. The suspended solution was filtered with suction and the filtrate was concentrated. The products were separated by column chromatography on silica gel, eluting with hexane–EtOAc (4:1), to give the ester **2**.

Solvolysis of Acylurea with Lithium Benzyloxide in Diethyl Ether:[8]
A solution of butyllithium (3 mmol) in hexane (1.62 mol/L) was added dropwise to a solution of benzyl alcohol (3 mmol) in Et_2O (10 mL) at 0 °C under an N_2 atmosphere. A solution of acylurea **1** (1 mmol) in THF (2 mL) was slowly added to the solution at 0 °C. The temperature was raised to r.t. and the solution was stirred for 3 h. The reaction was quenched by addition of water (10 mL). The organic layer was separated, dried ($MgSO_4$) and concentrated in vacuo. The products were separated by column chromatography on silica gel, eluting with hexane–EtOAc Diethyl Ether (4:1) to give the amide **2**. The yields are shown in Table 2 and the spectral data are given in Table 3.

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Table 3. Spectral Data of **4a–e** and **6f**

Product[a]	mp (°C)	IR (KBr, cm^{-1})	^1H NMR ($CDCl_3$, TMS) δ, J (Hz)
4a	oil	3300, 2920, 1640, 1550, 1430	0.50–2.38 (m, 38 H), 0.88 (t, J = 5.8, 3 H), 3.55–4.00 (m, 1 H), 5.10–5.56 (m, 1 H), 5.34 (t, J = 5.0, 2 H)
4b	152–153	3330, 3240, 2930, 1650, 1540, 1500, 1335	0.85–2.19 (m, 10 H), 3.76–4.21 (m, 1 H), 5.75–6.16 (m, 1 H), 7.29–7.60 (m, 3 H), 7.60–7.93 (m, 2 H)
4c	87–88	3310, 3080, 2930, 1650, 1540, 1500, 1235	0.72–2.05 (m, 10 H), 1.56 (d, J = 7.2, 3 H), 3.47–4.07 (m, 1 H), 4.65 (q, J = 7.2, 1 H), 6.29 (br d, J = 7.2, 1 H), 6.71–7.16 (m, 3 H), 7.16–7.49 (m, 2 H)
4d	152–153	3280, 3070, 2930, 1660, 1625, 1560, 1350, 1220	0.82–2.27 (m, 10 H), 3.68–4.15 (m, 1 H), 5.30–5.70 (m, 1 H), 6.35 (d, J = 15.1, 1 H), 7.14–7.50 (m, 5 H), 7.61 (d, J = 15.1, 1 H)
4e	186–187.5	3320, 2970, 1775, 1660, 1535, 1260, 1175, 1005	1.50 (d, J = 6.8, 3 H), 2.30 (s, 2 H), 2.58 (d, J = 1.5, 1 H), 2.88 (s, 1 H), 3.02–3.07 (m, 1 H), 3.15–3.23 (m, 1 H), 4.83 (s, 1 H), 5.05 (dq, J = 6.8, 6.8, 1 H), 5.13 (d, J = 5.2, 1 H), 5.70–5.85 (m, 1 H), 7.29–7.50 (m, 5 H)
6f	158–159	3330, 2930, 2860, 1700, 1630, 1580, 1375	0.87–2.40 (m, 12 H), 3.16 (dd, J = 3.1, 1.7, 2 H), 3.22–3.47 (m, 2 H), 3.80 (tt, J = 12.2, 3.6, 2 H), 6.08 (t, J = 2.0, 2 H)

[a] Satisfactory microanalyses obtained: C ± 0.42, H ± 0.17, N ± 0.23; exception **4b**, C + 0.46, and HRMS (FAB): (MH^+) ± 0.0014.
[b] Yield of alcoholysis using NaOMe in MeOH.

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