Double Isomerization of Oxetane Amides to Azetidine Esters with Ring Expansion and Contraction

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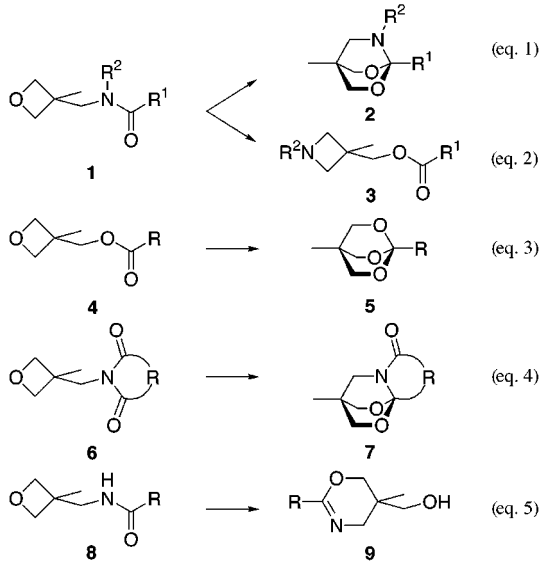
Introduction

Oxetane has been long known as a cyclic ether possessing ring-opening polymerizability,[1] and the cationic polymerization has been developed as a broadly applicable method for synthesizing functionalized polyethers.[2,3] An interesting exception to this generally accepted concept was found by Corey et al. in ortho ester (**5**) synthesis by the Lewis acid catalyzed isomerization of oxetane esters (**4**) (eq 3 in Scheme 1).[4] Thereafter, we have reported a series of similar acid-catalyzed isomerizations of oxetanes having a carbonyl functional group at the 3-position.[5,6] These reactions can be viewed as chemoselective transformation of the oxetane series into other heterocyclic compounds, as shown in Scheme 1: oxetane *tert*-amides (**1**) and oxetane imides (**6**) to bicyclic acetals (**2** and **7**, respectively) (eqs 1 and 4)[5,6] and oxetane *sec*-amides (**8**) to substituted 5,6-dihydro-4*H*-1,3-oxazines (**9**) (eq 5).[5] It is notable that the oxetanyl group does not react intermolecularly even in the presence of Lewis acid. The intramolecular nucleophilic reaction is probably facilitated by the accessibility of the carbonyl oxygen to the α-carbon (relatively 1,6-positioned) in the oxonium species generated by the Lewis acid.

Scheme 1. Chemoselective Isomerization of Oxetanes Having a Carbonyl Functional Group



This paper reports a novel mode of the Lewis acid catalyzed isomerization of oxetane *tert*-amides (**1**: *N*-alkyl-*N*-(3-methyl-3-oxetanyl)methylacylamides, acyl = R^1CO, alkyl = R^2). The isomerization of **1** gives two heterocyclic compounds quite different from each other. One is a bicyclic acetal (**2**) produced by the single isomerization as previously reported,[5] and the other is an azetidine derivative (**3**) having an ester group at the 3-position (eq 2). The latter reaction is an unusual, counterintuitive transformation consisting of two key steps: a four-membered oxetane ring in **1** enlarges first to a [2.2.2]-dioxazabicycle, which is in turn rearranged to a different four-membered azetidine ring. Hereafter, the overall reaction sequence is expressed by the term of "double isomerization" to distinguish it from the known single isomerizations of carbonyl-functionalized oxetanes, as in eqs 1 and 3−5.

Results and Discussion

Preliminary results were gathered from the reaction of **1j**[7] (R^1 = Ph, R^2 = Et) under different reaction conditions such as catalyst, solvent, and temperature (Table 1). When the reaction of **1j** in the presence of a catalytic amount of boron trifluoride etherate (BF_3·OEt_2) was carried out in chlorobenzene at 130 °C, the single isomerization of the type in eq 1 took place. As a result,

(1) Rose, J. B. *J. Chem. Soc.* **1956**, 542−546.

(2) Reviews on the cationic ring-opening polymerization of oxetane: (a) Dreyfuss, M. P.; Dreyfuss, P. In *Encyclopedia of Polymer Science and Engineering*, 2nd ed.; Mark, H. F., Bikales, N. M., Overberger, C. G., Menges, G., Eds.; John Wiley and Sons: New York, 1987; Vol. 10, pp 653−670. (b) Penczek, S.; Kubisa, P. In *Comprehensive Polymer Science*; Allen, G., Ed.; Pergamon Press: Oxford, 1989; Vol. 3, pp 751−786. (c) Desai, H. In *Polymeric Materials Encyclopedia*; Salamone, J. C., Ed.; CRC Press: New York, 1996; Vol. 11, pp 8268−8279.

(3) Our previous works on the cationic ring-opening polymerization of substituted oxetanes: (a) Ogawa, H.; Kodera, Y.; Kanoh, S.; Ueyama, A.; Motoi, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 433−442. (b) Hiruma, T.; Kanoh, K.; Yamamoto, T.; Kanoh, S.; Motoi, M. *Polym. J.* **1995**, *27*, 78−89. (c) Motoi, M.; Saito, E.; Kyoda, S.; Takahata, N.; Nagai, S.; Arano, A. *Polym. J.* **1991**, *23*, 1225−1241. (d) Motoi, M.; Nagahara, S.; Akiyama, H.; Horiuchi, M.; Kanoh, S. *Polym. J.* **1989**, *21*, 987−1001.

(4) (a) Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571−5574. (b) Ducray, P.; Lamotte, H.; Rousseau, B. *Synthesis* **1997**, 404−406.

(5) Nishimura, T.; Kanoh, S.; Senda, H.; Tanaka, T.; Ando, K.; Ogawa, H.; Motoi, M. *J. Chem. Soc., Chem. Commun.* **1998**, 43−44.

(6) Kanoh, S.; Hashiba, T.; Ando, K.; Ogawa, H.; Motoi, M. *Synthesis* **1997**, 1077−1080.

(7) *N*-Ethyl-*N*-(3-methyl-3-oxetanyl)methyl benzamide (**1j**): colorless liquid; bp 140 °C (1 mmHg); ^{1}H NMR ($CDCl_3$, 70 °C) δ 7.35−7.38 (m, H_{Ph}), 4.61 (d, *trans*-OCH_2 to 3-CH_3), 4.30 (d, *cis*-OCH_2 to 3-CH_3), 3.66 (s, 3-CH_2N), 3.29 (q, NCH_2CH_3), 1.39 (s, 3-CH_3), 1.10 ppm (t, NCH_2CH_3); ^{13}C NMR ($CDCl_3$, 25 °C) δ 172.5 (C═O), 136.6 (*ipso*-C_{Ph}), 129.2, 128.4, 126.2 (other-C_{Ph}), 81.7 (C2 and C4), 50.3 (3-CH_2N), 44.8 (NCH_2CH_3), 40.5 (C3), 21.8 (3-CH_3), 13.6 ppm (NCH_2CH_3); IR (neat) 1630 ($\nu_{C=O}$), 975, 820 cm^{-1} ($\nu_{cyclic\ ether}$); HRMS found, *m/e* 233.1427 (calcd for $C_{14}H_{19}NO_2$, *m/e* 233.1417).

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Table 1. Double Isomerization of 1j[a]

					yield (%) [b]	
entry	catalyst (mol %)	solvent	temp (°C)	time (h)	**2j**	**3j**
1	BF_3·OEt_2 (5)	PhCl	130	1.5	56[c]	0
2	BF_3·OEt_2 (5)	PhCl	130	24	0	0
3	$CF_3SO_3CH_3$ (5)	PhCl	130	72	14	53
4	$CF_3SO_3CH_3$ (2)	$PhNO_2$	150	96	0	73
5	CF_3SO_3H (2)	$PhNO_2$	150	68	0	48
6	BnTA[d] (5)	$PhNO_2$	150	96	0	20
7[e]	BnTA[d] (5)	$PhNO_2$	150	96	0	34

[a] Reaction conditions: **1j** (224 mg, 0.92 mmol), anhydrous solvent (1.0 mL). [b] Determined by ^{1}H NMR. The remainder was a polymeric product. [c] Isolated yield. [d] Benzylthiolanium hexafluoroantimonate. [e] The reaction was started from **2j**.

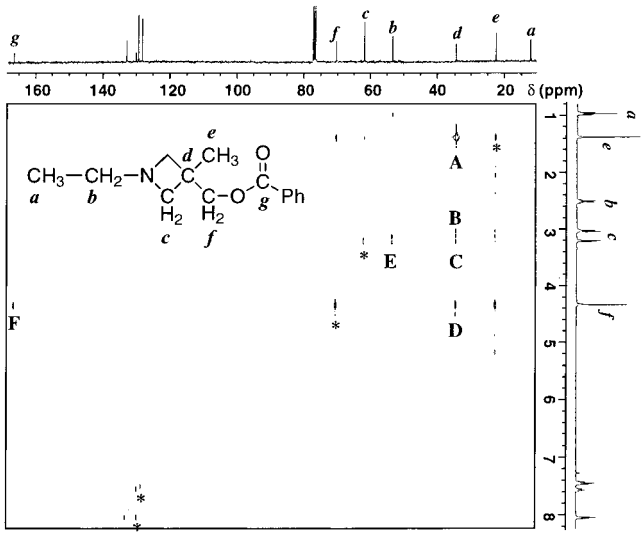


Figure 1. COLOC spectrum of **3j** in $CDCl_3$ (400 MHz, $^{lr}J_{CH}$ = 8 Hz). Selected C−H long-range correlations: **A** = C_d−H_e, **B** and **C** = C_d−H_c, **D** = C_d−H_f, **E** = C_b−*trans*-H_c to 3-CH_3, **F** = C_g−H_f. Asterisks refer to residual $^1J_{CH}$ correlations.

bicyclic acetal **2j**[8] was produced in the early stage of the reaction (entry 1). After 24 h, however, it was completely converted into a polyether having benzamide pendants (entry 2), probably owing to the cationic double ring-opening polymerization.[9] The use of aluminum Lewis acid catalysts such as trimethylaluminum, aluminum triphenoxide, and methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)[10] led to fundamentally similar results.

In sharp contrast, the reaction using MeOTf as a catalyst gave together with **2j** another product (**3j**) having the same molecular weight as those of **1j** and **2j** (entry 3). The ^{1}H NMR spectrum of **3j** showed two sets of doublets at δ 3.03 and 3.21 ppm (Figure 1), suggesting isolated methylene protons characteristic of a four-membered ring. However, a similar type of double doublets due to the oxetanyl *O*-methylene protons of **1j** appeared much more downfield at δ 4.30 and 4.61 ppm.[7] The IR spectrum of **3j** showed a strong stretching band at 1720 cm^{-1}, indicating an ester but not an amide. The C−H connectivity based on the COLOC correlation (correlation spectroscopy via long-range coupling, $^{lr}J_{CH}$ = 8 Hz) revealed clear evidence that **3j** is (1-ethyl-3-methyl-3-azetidinyl)methyl benzoate (Figure 1). Each of the isomerization products, **2j** and **3j**, was produced with complete selection by controlling reaction conditions, especially catalyst and temperature. When the reaction of **1j** with MeOTf was run at 150 °C using anhydrous nitrobenzene as a solvent, **3j** was obtained as the major isomerization product (entry 4). Under these reaction conditions, TfOH and benzylthiolanium hexafluoroanitimonate (BnTA)[11] also acted as catalysts for yielding **3j** (entries 5 and 6). However, the isomerization by any catalyst was more or less accompanied by polymerization, and hence the yield of **3j** began to decrease after reaching maximum. On the other hand, a control reaction starting from **2j** also gave **3j** (entry 7). This evidently reveals that the reaction process from **1j** to **3j** is a double isomerization via **2j**.

Table 2. Yields (%, ^{1}H NMR) of 3 Obtained in the Double Isomerization of 1a−t[a]

	R^1								
					-C_6H_4-*p*-X				
R^2	Me	Et	Pr	Bn	NO_2	Cl	H	OMe	*t*-Bu
Me		**a**, 0		**b**, 0			**c**, 6		**d**, 54
Et	**e**, 0	**f**, 2	**g**, 10		**h**, 58	**i**, 56	**j**, 73	**k**, 64	**l**, 42
Pr	**m**, 0	**n**, 6	**o**, 12				**p**, 70		
Bn	**q**, 0	**r**, 47	**s**, 62				**t**, 75		

[a] The reaction of **1** (0.9 mmol) in anhydrous nitrobenzene (1.0 mL) was carried out using MeOTf (2 mol %) at 150 °C for 48−96 h.

The double isomerization of **1a**−**t** with various combinations of R^1 and R^2 groups was carried out using MeOTf in nitrobenzene at 150 °C. The yields of **3** are summarized in Table 2, where the R^1 and R^2 groups are arranged in the order of increasing bulkiness. From the variation in the yield of **3**, an apparent tendency can be seen that the smaller the R^1 and/or R^2 groups are, the more the yield of **3** decreases. Less bulky acetamides (R^1 = Me) brought about no double isomerization regardless of the R^2 groups. These acetamides, of course, brought about the single isomerization, though the resulting intermediates **2** were consumed by cationic polymerization. Similarly, *N*-methyl-substituted amides (R^2 = Me), except for the exceedingly bulky pivalamide (**1d**), hardly yielded **3**. The combination of the R^1 and R^2 groups leading to more than moderate yields of **3** strongly suggests that the steric repulsion between both groups plays an important role in the ring contraction process of the intermediate **2**.

A plausible mechanism for the double isomerization of **1** can be explained as shown in Scheme 2. The reaction begins with the coordination of an acid catalyst E to the oxetanyl oxygen of **1**,[6] and the resulting oxonium **A** undergoes the intramolecular nucleophilic attack of the amide carbonyl oxygen. As has been recognized by NMR analysis,[12] most **1** also exist as mixtures of two conformers as a result of the restricted rotation around the amide

(8) 7-Ethyl-4-methyl-1-phenyl-2,6,7-dioxazabicyclo[2.2.2]octane (**2j**): isolated yield, 54%; colorless liquid; bp 100−120 °C (1 mmHg); ^{1}H NMR (anhydrous $CDCl_3$) δ 7.60 (dd, *o*-H_{Ph}), 7.29−7.38 (m, *m*- and *p*-H_{Ph}), 3.98 (s, *endo*-OCH_2), 2.99 (s, *endo*-NCH_2), 2.36 (q, NCH_2CH_3), 0.94 (t, NCH_2CH_3), 0.88 ppm (s, C_q-CH_3); HRMS found, *m/e* 233.1439 (calcd for $C_{14}H_{19}NO_2$, *m/e* 233.1417).

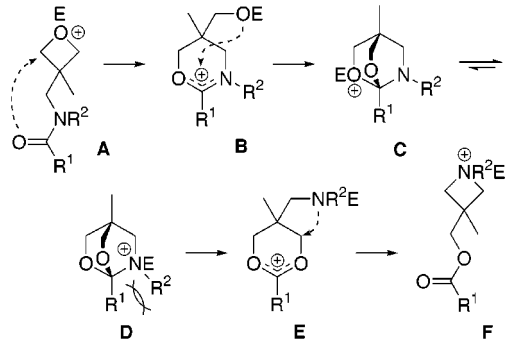
(9) Kanoh, S.; Nishimura, T.; Senda, H.; Ogawa, H.; Motoi, M.; Tanaka, T.; Kano, K. *Macromolecules* **1999**, *32*, 2438−2448.

(10) MAD was prepared according to Aida's method and recrystallized from toluene−hexane under nitrogen: Takeuchi, D.; Aida, T. *Macromolecules* **1996**, *29*, 8096−8100.

(11) BnTA was prepared by Endo's method and recrystallized from 2-propanol: 60% yield, mp 112−113 °C (lit. mp 121.5−122 °C): Endo, T.; Uno, H. *J. Polym. Sci., Polym. Lett. Ed.* **1985**, *23*, 359−363.

(12) Challis, B. C.; Challis, J. A. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, D., Sutherland, I. O., Eds.; Pergamon Press: Oxford, 1979; Vol. 2, pp 957−1065.

Scheme 2. Plausible Mechanism for the Double Isomerization of 1 to 3



C−N bonds. The *s*-cis conformation with respect to the R^1 and R^2 groups should be required for the neighboring group participation. The ratios of *s*-cis and -trans isomers were estimated at nearly 8:2 in $CDCl_3$ at 25 °C, while NMR temperature-dependent line shape analysis showed that the isomer-separated signals of **1** began to broaden or coalesced up to 70 °C. The C−N bonds might become considerably free at the reaction temperature as high as 150 °C. On the other hand, the pivalamides, such as **1d** and **1l**, stay in the favorable *s*-cis conformation independent of temperature. The resulting 1,3-oxazin-2-ylium cation **B** brings about subsequent ring closure to give the oxonium species **C** of **2**. Since **2** is not only a cyclic ether but also a cyclic amine, **C** would change into the more stable ammonium cation **D**, which suffers steric repulsion between the adjacent R^1 and R^2 groups. This makes the $C-N^+$ bond scission feasible, and the resulting 1,3-dioxan-2-ylium cation **E** closes in another way to form an azetidine ring. The stabilization of the cation **E** might be a less crucial factor, because the double isomerization of *N*-ethylbenzamides (**1h**−**k**) resulted in the roughly comparable yields of **3** regardless of the great difference in the electronic effect of the *p*-X-substituent.

In our examination, MeOTf is the preferred catalyst. The very reactive methylating reagent is likely to be extremely short-lived and simply to be serving to generate in situ the true catalytic species, presumably TfOH, following methylation or by hydrolysis with water impurity. The higher yield of **3** for entry 4 over entry 5, in other words, the higher polymer yield for entry 5, may be a specious consequence resulting from the polymerization of **3**. The intermediates **A**−**F** are regarded as potential initiating species for cationic ring-opening polymerization, and protonated species and methylated species (E = H, Me) could possess different polymerizability. Catalysis of thermal latent Lewis acid BnTA, which generates benzyl cation above its decomposition temperature of 80 °C,[11] would be analogously interpreted, though the inevitable polymerization of **3** was accelerated to a greater extent by this catalyst.

The double isomerization of oxetane *tert*-amides **1** serves as a quite different entry into azetidines than the general synthetic methods,[13] which concern the cyclization of α,γ-difunctionalized alkanes or the reduction of β-lactams and malonimides. However, the scope of the reaction for 1,3-substituted azetidine ring formation may be limited by the vigorous reaction conditions and requirement of bulkiness of at least either R^1 or R^2 group in the starting **1**. The double isomerization should be rather deemed to be of primary interest on the basis of the curious mechanistic aspect.

(13) (a) Cromwell, N. H.; Philips, B. *Chem. Rev.* **1979**, *79*, 331−358. (b) Moore, J. A.; Ayers, R. S. In *Chemistry of Heterocyclic Compounds*; Hassner, A., Ed.; Wiley: New York, 1983; Part 2, pp 1−217. (c) Davies, D. E.; Starr, R. C. In *Comprehensive Heterocyclic Chemistry*; Lwowski, W., Ed.; Pergamon Press: Oxford, 1984; Vol. 7, pp 237−284.

Conclusion

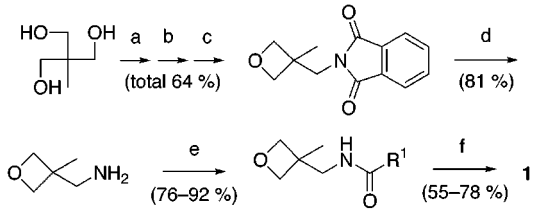
In summary, the reaction of *tert*-amide-substituted oxetanes (**1**), preferably benzamide and pivalamide derivatives, with MeOTf in anhydrous nitrobenzene at 150 °C has been found to give ester-substituted azetidines (**3**) via bicyclic acetals (**2**). This transformation seems unusual and counterintuitive, in that the overall reaction sequence is a double isomerization involving both ring expansion and contraction. Under acid catalysis, **1** undergoes ring expansion by the neighboring group participation of the amide carbonyl group, and then steric repulsion between the adjacent R^1 and R^2 groups in the intermediate **2** likely prompts C−N bond scission followed by ring contraction.

Experimental Section

General Methods. ^1H, ^{13}C, and COLOC NMR spectra were measured in commercial or anhydrous $CDCl_3$ at 400 MHz for ^1H nuclei. IR spectra were recorded in the FT mode. Trimethylaluminum in hexane and TfOH were used as received. Boron trifluoride etherate and MeOTf were purified by fractional distillation under reduced pressure in a nitrogen atmosphere. Anhydrous reagents, such as triethylamine, chlorobenzene, and nitrobenzene, were purified by the conventional methods and distilled under dry nitrogen before use.

The oxetane amides **1** were synthesized from the known oxetane phthalimide (Scheme 3), which was prepared from

Scheme 3[a]



[a] (a) $(EtO)_2CO$, KOH. (b) TsCl, aq. NaOH, (c) Potassium phthalimide (d) i. $N_2H_4 \cdot H_2O$; ii. Raney Ni (*W*-2). (e) $(R^1CO)_2O$, or R^1COCl, TEA, or R^1COOH, DCC, DMAP. (f) R^2Br, K_2CO_3, NaOH, Bu_4NHSO_4.

trimethylolethane according to the procedure described in our previous paper.[6] The phthalimide was converted into oxetanylmethylamine,[5] which was acylated and then *N*-alkylated[14] to give **1** as a mixture of two rotational isomers, except for **1d** and **1l** with the *s*-cis conformer predominating.

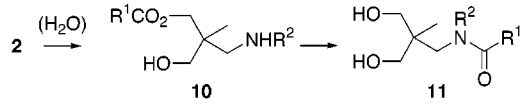
General Procedure for the Double Isomerization of 1. A representative procedure of the double isomerization of **1** is described as follows. To a tube containing **1j** (224 mg, 0.92 mmol) and anhydrous nitrobenzene (1.0 mL) was charged MeOTf in anhydrous nitrobenzene (0.43 mol L^{-1}, 0.05 mL, 0.02 mmol) under a nitrogen atmosphere. The resulting solution was allowed to stand at 150 °C for 96 h. The reaction was quenched with anhydrous triethylamine (0.1 mL), and then the mixture was evaporated. The residue was purified by column chromatography on alumina (EM Aluminumoxid 90; 70−230 mesh ASTM) with ethyl acetate−hexane (2/3 v/v) followed by distillation in vacuo to give **3j** in 63% isolated yield (141 mg). If the boiling point of **3** was assumed lower than or close to that of nitrobenzene, the product was gained by chromatographic workup without evaporation of the solvent. The isolation of **3c** and **3f** failed because

(14) Gajda, T.; Zwierzak, A. *Synthesis* **1981**, 1005−1008.

of poor yields. As example, (1-ethyl-3-methyl-3-azetidinyl)methyl benzoate (**3j**): pale yellow liquid; bp 130−140 °C (1 mmHg); ^{1}H NMR ($CDCl_3$) δ 8.05 (d, J = 7.81 Hz, 2H, *o*-H_{PhCO}), 7.57 (t, J = 7.32 Hz, 1H, *p*-H_{PhCO}), 7.45 (t, J = 7.57 Hz, 2H, *m*-H_{PhCO}), 4.33 (s, 2H, 3-CH_2O), 3.21 (d, J = 7.32 Hz, 2H, *trans*-NCH_2 to 3-CH_3), 3.03 (d, J = 7.33 Hz, 2H, *cis*-NCH_2 to 3-CH_3), 2.51 (q, J = 7.16 Hz, 2H, NCH_2CH_3), 1.38 (s, 3H, 3-CH_3), 0.97 ppm (t, J = 7.33 Hz, 3H, NCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 166.5 (C=O), 132.9 (*p*-C_{PhCO}), 130.2 (*ipso*-C_{PhCO}), 129.5 (*o*-C_{PhCO}), 128.3 (*m*-C_{PhCO}), 70.4 (3-CH_2O), 62.0 (C2 and C4), 53.4 (NCH_2CH_3), 34.5 (C3), 22.7 (3-CH_3), 12.2 ppm (NCH_2CH_3); IR (neat) 1720, 1270, 1110 cm^{-1}; HRMS found, *m*/*e* 233.1427 (calcd for $C_{14}H_{19}NO_2$, *m*/*e* 233.1417).

Isolation of Intermediate 2. Similarly, the single isomerization of **1** using BF_3·OEt_2 as a catalyst was carried out in anhydrous chlorobenzene at 130 °C for 1−1.5 h. The reaction was quenched first with anhydrous triethylamine, and then a small amount of calcium hydride was added. Distillation in vacuo directly from the mixture gave **2**, which was stored in a nitrogen atmosphere because of high sensitivity to moisture; yield was 43−73%. In air, compounds **2** were readily hydrolyzed to amino esters (**10**). In the cases of **2a**−**c**, **e**, **f**, **m**, and **q** having relatively less bulky R^1 and/or R^2 groups, acyl transfer following hydrolysis eventually gave amide alcohols (**11**) as final products (Scheme 4).

Scheme 4



Supporting Information Available: Characterization data and copies of ^{1}H NMR spectra for compounds **1**−**3** (33 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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