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Novel N→C Acyl Migration Reaction of Acyclic Imides: A Facile Method for α-Aminoketones and β-Aminoalcohols

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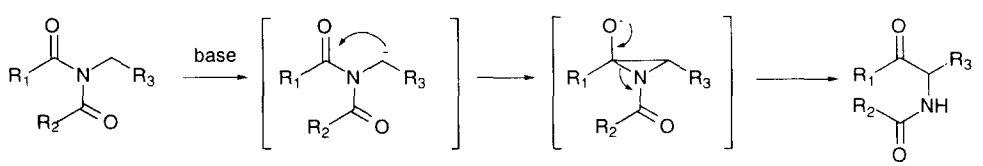
Abstract: The acyclic imides derived from primary benzylic amines and amino acid esters easily undergo the novel N→C acyl migration reaction via a base-generated carbanion, yielding the corresponding α-aminoketones which are expedient precursors for β-aminoalcohols.

Keywords: Amino ketones; Carbanions; Imides; Migration

Imides **1**[1], acyl derivatives of amides and lactams, are used as valuable intermediates and reagents in organic synthesis, such as primary amine synthesis, acylating agents, building blocks for natural product synthesis, and asymmetric synthesis, typically Evans chiral imides.[2] In contrast to the number of cyclic imides[3] used in natural product synthesis and biological research, acyclic imides **1** are a small group in organic synthesis and their uses are limited to some minor transformations such as acylating agents[4-6] and intermediates for hydrolysis of the γ-lactam[7] and interchange of protecting groups.[8] To our knowledge, use of the imides in the carbon-carbon bond formation reaction via intramolecular acyl migration has never been reported in the literature to date. Based on the structure of the imides, we envisioned that the initially formed carbanion neighbor to the imide nitrogen might attack the internal imide carbonyl function and yield the acyl migrated product by leaving the amide anion. The resulting α-aminoketones **2** are expedient precursors for β-aminoalcohols which are useful for the preparation of pharmaceuticals and chiral auxiliaries. We describe that the imides **1** derived from primary benzylic amines and amino acid esters easily undergo the novel N→C acyl migration reaction via a base-generated carbanion producing α-aminoketones **2**. The conventional procedures for the preparation of α-aminoketones[9,10] have mainly employed α-amino acids as precursors. This acyl migration reaction provides an alternative approach to α-aminoketones and β-aminoalcohols.



1 **2**

R_1 = Ar, *tert*-Bu
R_2 = *tert*-BuO
R_3 = Ar, CO_2Et

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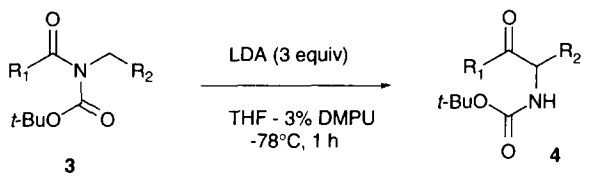
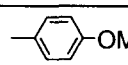
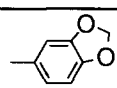
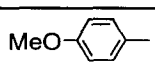
The requisite imides were prepared by reaction of the corresponding amides with di-*tert*-butyl dicarbonate in the presence of *N,N*-dimethylaminopyridine in acetonitrile[11] or condensation of the amide with the acid chlorides in the presence of base in good to excellent yields.[12] In order to examine the acyl migration, we chose the imide **3** (R_1= R_2= Ph) as the model compound and found that the acyl migration took place by treatment with an excess of lithium diisopropylamide (LDA).[13,14] Although one equivalent of LDA is sufficient to form the carbanion of **3**, another equivalent of LDA was essential for completion of the reaction due to the proton abstraction from the α-position of the α-aminoketone **4**. The optimized yield was obtained using LDA (3 equiv.) in the presence of *N,N'*-dimethylpropyleneurea (DMPU, 3 %) as an additive in THF at -78℃.[15] Interestingly, the other strong bases, such as KH, KHMDS, and *s*-BuLi with sparteine, except for LDA did not give any acyl migrated product. Next, we examined the acyl migration reaction of the various imides summarized in Table 1.

Table 1. N→C Acyl Migration Reaction of Imides.

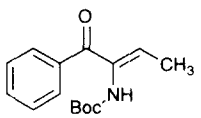


3 **4**

run	R_1	R_2	yield (%)[a]
1	Ph-	-Ph	81
2	Ph-		89
3	Ph-	2-furyl	70
4	Ph-	CO_2Et	91
5	Ph-	CO_2t-Bu	82
6	Ph-		81[b]
7	Ph-		71
8	Ph-		81
9	Ph-		80
10		-Ph	55
11	*t*-Bu-	-Ph	98[c](58)[d]
12	$PhCH_2CH_2$-	CO_2Et	53[c](57)[d]

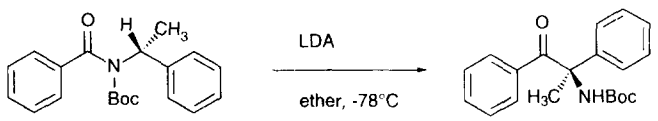
a) Isolated yields. b) Yield of the isomerized α,β-unsaturated ketone **5**. c) Yields based on the consumed starting materials. d) Yields of the recovered starting material.

The reaction of the imides derived from glycine esters afforded the α-protected amino β-ketoesters which are suitable substrates for enantioselective synthesis via dynamic kinetic resolution.[16] In the case of the *N*-allyl imide (run 6), the reaction smoothly took place along with latent isomerization of the double bond to give the (*Z*)-α,β-unsaturated ketone **5** as a single isomer in good yield. Geometry of the double bond was unambiguously determined by NOE difference studies. Migration of the pivaloyl group (run 11) sluggishly proceeded to afford the *tert*-butyl ketone together with considerable recovery of the starting material, though the conversion yield was excellent. The result from the phenylpropionic acid imide (run 12) suggests that the reaction involves the presence of competitive deprotonation causing a low yield and low conversion at the α-position of the carboxylic acid imide. Although we did not investigate the migratory ability of two acyl groups attached to the imide nitrogen, the *N*-*tert*-butoxycarbonyl moiety was found to efficiently serve as the nontransferring group as shown in table.



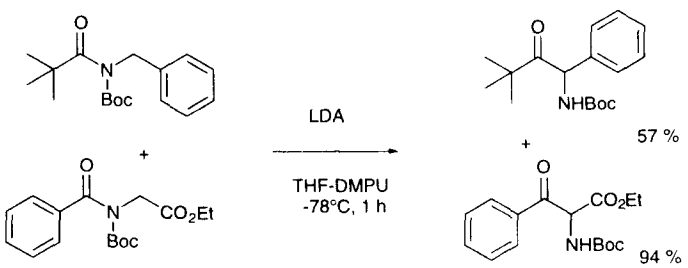
5

A most intriguing example of the acyl migration reaction is the reaction of the imide derived from an optically active amine, which can afford the optically active product with the *tert*-alkylamine function. The imide **6** was easily prepared by the reaction of benzoyl chloride with the lithium anion of *N*-*tert*-butoxycarbonyl-(*R*)-α-methylbenzylamine in 96 % yield. Treatment of **6** under the above standard conditions afforded the expected acyl migrated product **7** in 84 % yield. However, HPLC analysis[17] of the product disclosed severe loss of stereointegrity showing a ratio of 30:70. After reexamination of the solvent, we found that use of ether instead of THF-DMPU furnished the product **7** with 94 % ee in 85 % yield. Beak has recently reported the stereochemistry on lithiation-substitution at the tertiary benzylic carbons of optically active *N*,*N*-aryl-*tert*-butoxycarbonyl-α-methylbenzylamine.[18,19] According to the literature, stereochemistry of the newly formed quaternary carbon center was tentatively assigned as the (*R*)-configuration showing retention during deprotonation-acyl-migration process.



6 **7** 94 % ee

In order to elucidate the mechanism of the acyl migration reaction, we carried out the crossover experiment using the imides in runs 4 and 11. The reaction did not give any cross product as shown below and the results clearly suggest that this acyl migration reaction intramolecularly takes place.



In summary, we have demonstrated a novel N→C acyl migration reaction providing the α-amino ketones. This procedure provides an alternatively expedient access to the α-amino ketones and β-aminoalcohols. Particularly, it is noteworthy that the acyl migration reaction of the (*R*)-α-methylbenzylamine derivative proceeds with retention of stereointegrity to afford the optically active α-amino ketones with a

quaternary carbon center. Further extension of the acyl migration reaction and applications to natural product syntheses are under investigation.

Acknowledgment

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12. Typical procedures for preparation of imides: (a) To a stirred solution of *N*-benzylbenzamide (212 mg, 1 mmol) and DMAP (15 mg, 0.1 mmol) in CH_3CN (3 ml) was added di-*tert*-butyl dicarbonate (286 mg, 1.3 mmol) in CH_3CN (2 ml) at room temperature. After being stirred at room temperature for 18 h, the mixture was diluted with ethyl acetate (15 ml) and washed with water, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate-hexane = 1 : 9) to give the imide (312 mg, 100 %) as a colorless oil. (b) To a stirred solution of (*S*)-*N*-*tert*-butoxycarbonyl-α-methylbenzylamine (500 mg, 2.26 mmol) in THF (10 ml) were added *n*-butyllithium (1.59 M in hexane, 1.57 ml, 2.49 mmol) and triethylamine (0.472 ml, 3.39 mmol) at -78℃ under nitrogen atmosphere. After being stirred at -78℃ for 30 min, benzoyl chloride (0.447 ml, 3.39 mmol) was added dropwise, and the mixture was stirred at -78℃ for 30 min, and then at 0℃ for 15 min. The reaction was quenched with saturated aqueous NH_4Cl and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate-hexane = 1 : 9) to give the imide **6** (702 mg, 96 %) as a colorless oil.
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15. Typical procedure for the acyl migration reaction: LDA was prepared by mixing diisopropylamine (0.145 ml, 0.96 mmol) and DMPU (90 μl) with *n*-BuLi (1.59 M in hexane, 0.6 ml, 0.96 mmol) in THF (1 ml) at -78℃ for 30 min. The imide **3** (R_1= R_2= Ph) (100 mg, 0.32 mmol) in THF (2 ml) was added to the LDA solution at -78℃ and the mixture was stirred at -78℃ for 1 h. The mixture was quenched with aqueous NH_4Cl (3 ml), diluted with ethyl acetate, washed with saturated aqueous NH_4Cl and brine, and dried over Na_2SO_4. Concentration in vacuo followed by column chromatography (silica gel, hexane-ethyl acetate = 4 : 1) gave the product **4** (R_1= R_2= Ph) (81 mg, 81 %) as colorless solids: IR ν_{max}^{KBr} 3386, 2982, 1698, 1497 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.46 (9H,s), 6.02 (1H, br), 6.26-6.28 (1H, d), 7.22-7.52 (8H, m), 7.95-7.96 (2H, d, J = 7.3 Hz).
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