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Enantioselective Benzoylation of α-Amino Esters Using (*S*)-1-Benzoyl-2-(α-acetoxyethyl)benzimidazole, a Chiral Benzimidazolide

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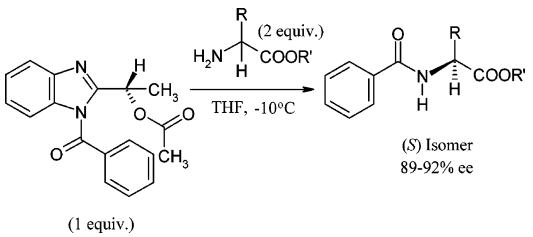

A new chiral benzimidazolide is developed as a nonenzymatic acylating agent for enantioselective benzoylation of racemic α-amino esters. The process is highly efficient, which exhibits uniformly high enantioselectivity for α-amino esters with or without aryl substituents under mild reaction conditions. The chiral benzimidazolide is inexpensive and is easily accessible.

Nonenzymatic enantioselective nucleophilic acylating agents for kinetic resolution have attracted a lot of attention in recent years.[1] Effective kinetic resolution requires the presence of one or more stereocenters with additional binding sites in the chiral acylating agent for rigid diastereomeric transition states. Although kinetic resolution of α-amino esters by enzymatic processes is abundantly documented,[2] some very effective nonenzymatic enantioselective acylating agents for kinetic resolution have been reported and they exhibit excellent stereodiscrimination properties. For example, Atkinson reported the use of *N*-benzoyl-*N*-ethanoylamino-2-[(*S*)-1-*tert*-butyldimethylsilyloxy-2-methylpropyl]quinazolin-4(3*H*)-one for kinetic resolution of racemic valine methyl ester with 94% ee.[3] Similarly, Mioskowski et al. used *N*-acetyl-(1*S*,2*S*)-bis(trifluoromethanesulfonamide) for kinetic resolution of (±)-phenylalanine methyl ester with 80% ee.[4]

Many of these reported methods suffer from the disadvantage of use of expensive starting materials or synthetically inconvenient routes. We describe herein a novel route which employs synthetically easily accessible and inexpensive materials for enantioselective benzoylation of α-amino esters resulting in the kinetic resolution of the same.

Enantiomerically pure α-amino esters are particularly important synthons for the preparation of pharmaceuticals,[5a−e] agrochemicals, and food ingredients and are fundamental building blocks in important bioactive molecules, such as peptides, proteins, and many other natural products.[5f] They are extensively used as a source of chiral materials in stereoselective organic synthesis.[6]

Azolides or *N*-acylazoles are powerful acylation agents.[7] The carbonyl carbon of the acyl group of azolides is electrophilic, and different carbon and heteroatom nucleophiles react easily with the same under mild conditions. Moreover, the azole part offers an effective leaving group in acylation reactions. So far, there seems to be no effort to use these powerful acylating agents for enantioselective acylation/kinetic resolution of α-amino esters. Benzimidazolide, the *N*-acylbenzimidazole, can be obtained very easily, and a chiral center can be incorporated in the benzimidazole part by reaction of *o*-phenylene diamine with requisite chiral carboxylic acid.[8] We report the development of (*S*)-1-benzoyl-2-(α-acetoxyethyl)benzimidazole (BAEB) **3**, a novel chiral benzimidazolide, as an effective chiral acylating agent for kinetic resolution of α-amino esters.

Condensation of *o*-phenylene diamine with (*S*)-lactic acid is reported to afford (*S*)-2-(α-hydroxyethyl)benzimidazole (**1**).[9] This molecule has a chiral substituent on the benzimidazole side

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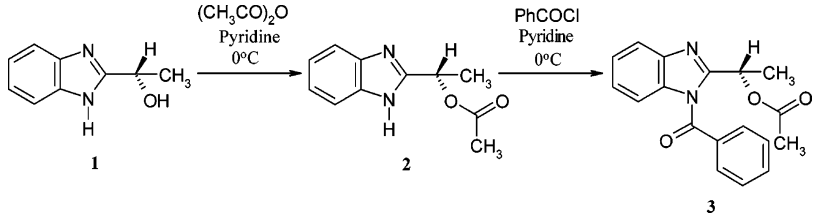
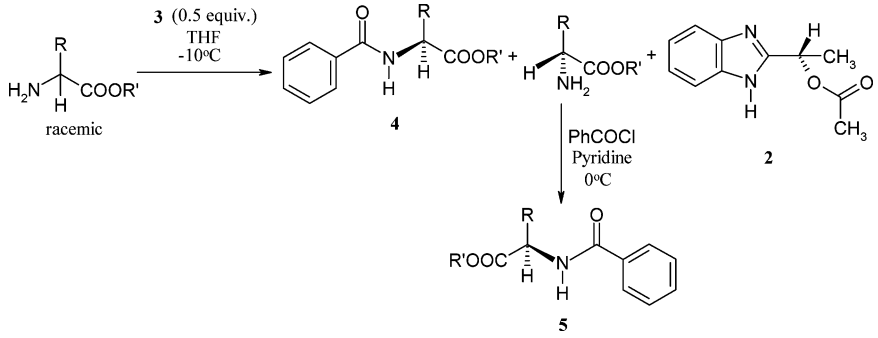
SCHEME 1. Preparation of BAEB 3



SCHEME 2. Enantioselective Benzoylation of α-Amino Esters



arm, which offered the chiral environment required in the azole part. Reaction of **1** with acetic anhydride in pyridine yielded (*S*)-2-(α-acetoxyethyl)benzimidazole (**2**) as the only product. This on benzoylation yielded the chiral benzimidazolide (*S*)-1-benzoyl-2-(α-acetoxyethyl)benzimidazole (BAEB) **3** (Scheme 1). Pyridine was the most suitable reagent as well as solvent for carrying out the benzoylation reaction among the other reaction conditions (THF, DMAP; THF, triethylamine; acetonitrile, K_2CO_3; THF, 2 equiv of **2**). The formation of **2** from **1** offered a dual advantage; it protected the hydroxyl group of **1** to eliminate a competitive reaction site for benzoyl transfer form **3** to the amino group, and it also offered the advantage of the presence of a bulky group with an additional heteroatom close to the reaction site for possible conformationally rigid diastereomeric transition states.

The utility of BAEB in kinetic resolution of α-amino esters was to be next investigated. Reaction of 1 equiv of BAEB was carried out with 2 equiv of various racemic α-amino esters. It was found that BAEB preferentially acylated the *S* isomer of α-amino ester to yield (*S*)-*N*-benzoyl amino esters (**4**). The unreacted α-amino esters were converted to *N*-benzoyl amino esters (**5**) and were found to be of *R* configuration. The only other product isolated was **2** (Scheme 2). The ester group of **3** was found to be unaffected during the benzoyl transfer reaction. Evidently, the acetyl group of the ester part does not enjoy the advantage of the azolide acyl (benzoyl) group, namely, more electrophilic character and better leaving group ability after acyl transfer reaction. This is in agreement with the noted powerful acyl transferring ability of the azolides discussed above. Chiral identities of *N*-benzoyl amino esters were established by comparison with rotation of authentic compounds reported in literature.[10]

The enantiomeric excesses of *N*-benzoyl amino esters were determined by HPLC using a chiral stationary phase (Chiralcel OD, *n*-hexane/2-propanol 98/2, Table 1). The best result in terms of enantioselective acylation was observed for the ester of phenylglycine (91.8%) (Table 1, compound **4e**), and lowest enantioselectivity was observed for the ester of alanine (89.1%) (Table 1, compound **4a**). Thus BAEB seems to be almost equally effective against α-amino esters with the presence of aryl substituents such as esters of phenylalanine and phenylglycine (Table 1, entries 3 and 5) as well as with aliphatic side chains as in esters of alanine, leucine, and valine (Table 1, entries 1, 2, and 4). Some of the previously reported kinetic resolving agents do not exhibit this level of uniform enantioselectivities.

The selectivity factors (s = rate of fast-reacting enantiomer/rate of slow-reacting enantiomer) obtained for enantioselective benzoylation of α-amino esters ranged from $s = 51.4$ at 49.9% conversion to $s = 73.6$ at 49.7% conversion at −10 °C. When the reaction of alanine ethyl ester with BAEB was carried out at rt, it showed a much lower selectivity factor, $s = 1.7$ at 52.6% conversion. The reaction at rt was faster and was completed in 90 min as compared to 12 h required for completion at −10 °C. The % enantioselectivity at rt was a mere 19.1 for benzoylated alanine ethyl ester and 21.2 for unreacted alanine ethyl ester.

In summary, the synthesis of BAEB is quite easy, convenient, and cost-effective. BAEB serves as an effective reagent for kinetic resolution of α-amino esters. The use of benzimidazolide BAEB offers mild neutral reaction conditions. The level of stereoselectivity furnished by BAEB ranges from good to excellent and is comparable or better than most nonenzymatic methods reported so far for this purpose. This is the first ever example of the use of an azolide for enantioselective acylation/kinetic resolution of α-amino esters.

Experimental Section

Preparation of (*S*)-2-(α-Acetoxyethyl)benzimidazole 2. A solution of **1** (4.86 g, 30 mmol) and Ac_2O (3.8 mL, 40 mmol) in 50 mL of dry pyridine was stirred at 0 °C for 5 h. The reaction mixture was poured into cold water to give a white crystalline solid which was filtered and washed with water to give 4.8 g of pure

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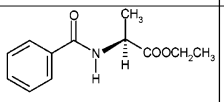
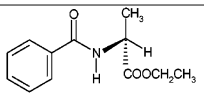
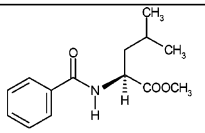
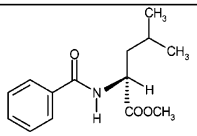
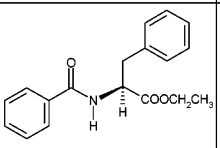
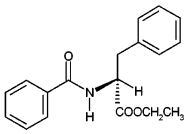
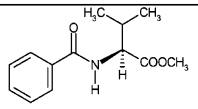
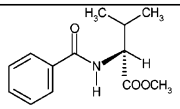
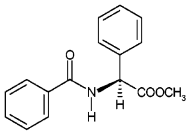
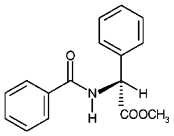
TABLE 1. Enantiomeric Excess % Data of Enantioselective Benzoylation of α-Amino Esters

Entry	(*S*) Isomer	ee (%)	(*R*) Isomer	ee (%)	Conversion[a] (%)	Selectivity Factor[b]
			(Unreacted amino ester converted to *N*-benzoyl amino ester)			
1	 **4a**	89.1	 **5a**	88.8	49.9	51.4
2	 **4b**	90.2	 **5b**	90.4	50.1	60.6
3	 **4c**	91.7	 **5c**	91.0	49.8	73.2
4	 **4d**	89.9	 **5d**	89.9	50.0	57.6
5	 **4e**	91.8	 **5e**	90.6	49.7	73.6

[a] The conversion was calculated by the equation: conversion = (ee of starting material)/[(ee of starting material) + (ee of product)].[11] [b] Equation used to calculate the selectivity factor ($s = k_{fast}/k_{slow}$): $s = \ln[1 - \text{conversion}(1 + \text{ee of product})]/\ln[1 - \text{conversion}(1 - \text{ee of product})]$.[11]

compound **2**: yield 78%; mp 159−161 °C; $[\alpha]^{19}_D = -156.9$ (*c* 1, $CHCl_3$); IR (KBr) 3454, 3053, 2987, 2935, 2831, 2732, 2671, 2631, 1746, 1592, 1541, 1484, 1444 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 9.6 (s, 1H), 7.80−7.78 (m, 1H), 7.44−7.43 (m, 1H), 7.28−7.26 (m, 2H), 6.08 (q, J = 6.7 Hz, 1H), 2.14 (s, 3H), 1.85 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.25, 152.90, 123.08, 66.91, 31.04, 21.11, 18.88. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.71; H, 5.88; N 13.73. Found: C, 64.66; H, 5.91; N, 13.76; *m*/*z*: 205.89 $[M + H]^+$.

Preparation of (*S*)-1-Benzoyl-2-(α-acetoxyethyl)benzimidazole (BAEB) 3. Benzoyl chloride (3.5 mL, 30 mmol) was added dropwise to a stirred solution of **2** (4.08 g, 20 mmol) in 40 mL of dry pyridine at 0 °C. The solution was stirred at the same temperature for further 6 h. The reaction mixture was poured onto ice pieces. The solid obtained was filtered and washed with ice-cold water. The crude compound was crystallized using $CHCl_3$/petroleum ether to give 4.9 g of compound **3** as white crystals: yield 80%; mp 87−89 °C; $[\alpha]^{19}_D = +167.8$ (*c* 1, $CHCl_3$); IR (KBr)

3057, 3040, 2988, 2935, 1731, 1706, 1596, 1531, 1489, 1453 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.81−7.79 (m, 2H), 7.74−7.68 (m, 1H), 7.56−7.51 (m, 2H), 7.31−7.24 (m, 2H), 7.14−7.08 (m, 1H), 6.67 (d, J = 8.0 Hz, 1H), 6.19 (q, J = 6.6 Hz, 1H), 2.01 (s, 3H), 1.86 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.47, 168.61, 155.48, 142.17, 134.44, 133.59, 132.99, 130.36, 129.19, 124.45, 124.13, 120.54, 113.41, 66.24, 20.86, 19.02. Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.13; H, 5.20; N, 9.09. Found: C, 70.19; H, 5.16; N, 9.05; *m*/*z*: 309.78 $[M + H]^+$.

Representative Procedure for Enantioselective Benzoylation of α-Amino Esters. A solution of **3** (2 mmol) and racemic α-amino ester (4 mmol) in 30 mL of THF was stirred at −10 °C for 12 h. The reaction was quenched with aq HCl and extracted with $CHCl_3$. The organic extract was dried over anhyd Na_2SO_4, which on evaporation afforded (*S*)-*N*-benzoyl amino ester (**4**). The unreacted α-amino ester was recovered from aqueous layer and on derivatization with benzoyl chloride in the presence of pyridine yielded (*R*)-*N*-benzoyl amino ester (**5**).

Supporting Information Available: IR, ^1H NMR, ^{13}C NMR, and mass spectra of **3**, spectral characterization of (*S*)-*N*-benzoyl amino esters **4a**−**e**, chiral HPLC analysis of *N*-benzoyl amino esters **4a**−**e** and **5a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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