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Enantioselective benzoylation of racemic amines using chiral benzimidazolide as a benzoylating agent

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Abstract—Enantioselective acylation/kinetic resolution of racemic amines has been achieved by using a chiral benzimidazolide, namely, (*S*)-1-benzoyl-2-(α-acetoxyethyl)benzimidazole **2**. This nonenzymatic acylating reagent requires mild reaction conditions and proceeds with good enantioselectivity.

1. Introduction

Chiral amino functionality is found in several important pharmaceutical compounds with varying chemotherapeutic properties.[1] Enantiomerically pure amines are used as resolving agents,[2] chiral auxiliaries[3] and catalysts[4] in stereoselective organic synthesis. The increasing need for nonracemic amines has accelerated the development of various efficient methodologies for resolution and asymmetric synthesis for their production. Despite the advances that have been achieved in the asymmetric synthesis of amines,[5] kinetic resolution remains a valuable alternative for obtaining individual stereoisomers. Kinetic resolution of racemates includes both enzymatic and nonenzymatic processes. Several enzymatic processes have been reported,[6] and the development of nonenzymatic enantioselective nucleophilic acylating agents for kinetic resolution of amines has received significant attention in recent years.[7]

Fu et al. achieved the enantioselective acylation of racemic amines using planar-chiral DMAP derivatives as acylating agents to give products with up to 91% ee at −78 °C.[7c] Atkinson et al. developed enantioselective acylating agents for the kinetic resolution of amines derived from 3-(*N*,*N*-diacylamino)quinazolin-4(3*H*)-ones (DAQs) to give products with excellent levels of enantioselectivity (up to 95% ee).[7d] The kinetic resolution of (±)-1-phenylethylamine was achieved by Mioskowski et al. using *N*-acetyl-(1*S*,2*S*)-bis(trifluoromethanesulfonamide) to give acetamide derivative with up to 84% ee at room temperature and up to 90% ee at −20 °C.[7g]

Several enzymes work with excellent stereoselectivities.[6a] Achieving a comparable level of stereoselection with nonenzymatic enantioselective acylating agents requires some basic structural features in the acylating agent. The enantioselective acylation/kinetic resolution requires facile acyl transfer process involving an electrophilic acyl group and a suitable chiral influence within the acylating agent. This challenge has inspired many groups to develop different enantioselective acylating agents as mentioned above. Azolides have an electrophilic acyl group, and different carbon and heteroatom nucleophiles react easily with this under mild conditions. Moreover, the azole part offers an effective leaving group in acylation reactions. The presence of a stereogenic centre within the azolide can offer a solution to the search for nonenzymatic acylating agent for kinetic resolution. We, accordingly, selected a chiral benzimidazolide for the purpose of enantioselective acylation.

2. Results and discussion

We have recently established that (*S*)-1-benzoyl-2-(α-acetoxyethyl)benzimidazole **2** (Fig. 1) serves as an effective enantioselective benzoylating agent for racemic α-amino esters.[8]

We now extend the use of (*S*)-1-benzoyl-2-(α-acetoxyethyl)benzimidazole as an effective chiral acylating agent for

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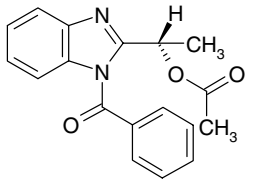

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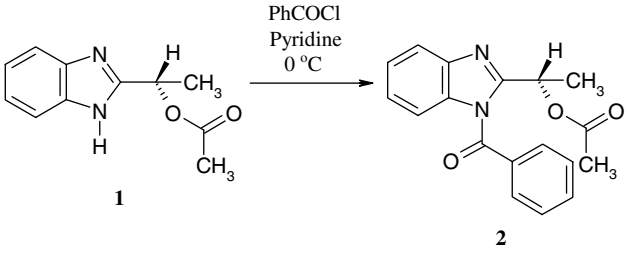
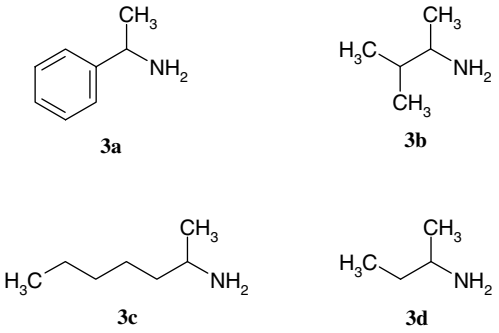
Figure 1. (*S*)-1-Benzoyl-2-(α-acetoxyethyl)benzimidazole.



1 **2**

Scheme 1. Preparation of chiral benzimidazolide.

kinetic resolution of amines. The racemic amines **3a–d** used for the purpose are shown in Figure 2.



3a **3b** **3c** **3d**

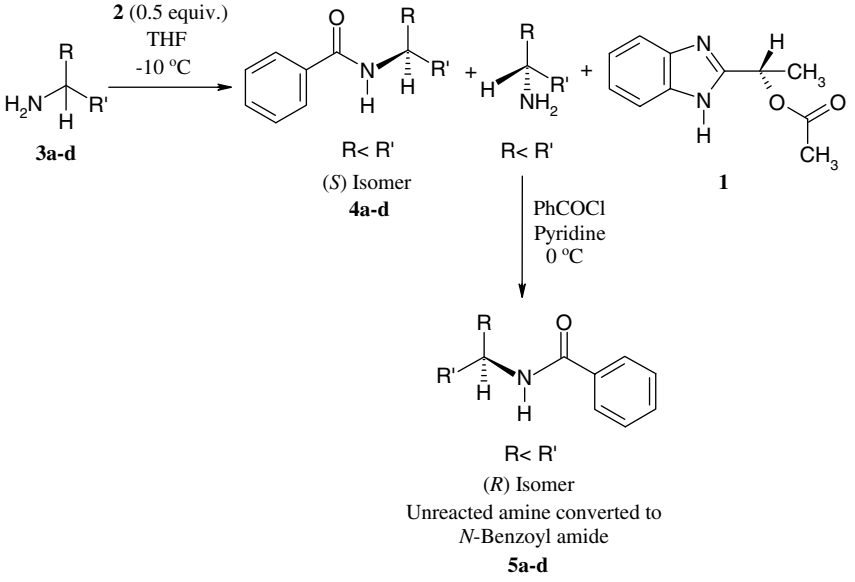
Figure 2. Racemic amines.

The chiral benzimidazolide, (*S*)-1-benzoyl-2-(α-acetoxyethyl)benzimidazole **2** was prepared by benzoylation of (*S*)-2-(α-acetoxyethyl)benzimidazole **1** (Scheme 1).

The reaction of 1 equiv of (*S*)-1-benzoyl-2-(α-acetoxyethyl)benzimidazole was carried out with 2 equiv of racemic amines (Scheme 2). The stereochemical preference of (*S*)-1-benzoyl-2-(α-acetoxyethyl)benzimidazole appeared the same as for α-amino esters,[8] that is, it preferentially acylated the (*S*)-isomer of amines to yield (*S*)-*N*-benzoyl amides **4a–d**. The unreacted amines were converted to *N*-benzoyl amides **5a–d** and were found to be of (*R*)-configuration.

Acylation reactions of racemic amines with (*S*)-1-benzoyl-2-(α-acetoxyethyl)benzimidazole were performed at −10 °C. The enantiomeric excesses of (*S*) and (*R*) isomers of *N*-benzoyl amides obtained by the reaction of (*S*)-1-benzoyl-2-(α-acetoxyethyl)benzimidazole with racemic amines are shown in Table 1.

Considerably high enantioselectivity was observed in case of 1-phenylethylamine (89.9%) (Table 1, compound **4a**) as compared to other amines. The presence of an aryl ring in the substrate usually introduces nonbonded interactions such as π–π interactions and π–H attractive interaction. These usually enhance stereodiscrimination and accordingly the stereoselection was found to be slightly better in the resolution of 1-phenylethylamine compared to the remaining amines, **3b–d**. In the case of aliphatic amines without an aryl substituent, **3b–d**, the level of stereoselection was found to be almost the same for all the aliphatic amines under study. In aliphatic amines, **3b–d**, the nonbonded interactions seem to be absent and the enantiodiscrimination observed seems to be entirely due to steric



Scheme 2. Enantioselective benzoylation of racemic amines.

Table 1. Enantioselective benzoylation of racemic amines

Entry	Substrate	(*S*)-Isomer[a]	ee[b] (%)	(*R*)-Isomer (unreacted amine converted to *N*-benzoyl amide)	ee[b] (%)	Conversion[c] (%)	Selectivity factor[d]
1	**3a**	**4a**	89.9	**5a**	89.2	49.8	56.5
2	**3b**	**4b**	82.8	**5b**	78.7	48.7	25.3
3	**3c**	**4c**	83.2	**5c**	82.9	49.9	27.8
4	**3d**	**4d**	83.3	**5d**	76.7	47.9	25.2

[a] Absolute configurations of *N*-benzoyl amides were established by comparison with the specific rotation of authentic compounds reported in the literature.
[b] Enantiomeric excesses of *N*-benzoyl amides were determined by HPLC using a chiral stationary phase (Chiralcel OD, *n*-hexane/2-propanol 98:2).
[c] Conversion was calculated by the equation: conversion = (ee of starting material)/[(ee of starting material) + (ee of product)].
[d] Equation used to calculate the selectivity factor ($s = k_{fast}/k_{slow}$): $s = \ln[1 - \text{conversion}(1 + \text{ee of product})]/\ln[1 - \text{conversion}(1 - \text{ee of product})]$.

factors. The better enantiodiscrimination observed in the case of α-amino esters observed earlier,[8] can be accounted for the presence of an ester functionality along with an aryl ring in a few cases.

3. Conclusion

The resolving agent employed, namely, (*S*)-1-benzoyl-2-(α-acetoxyethyl)benzimidazole **2** is easily accessible, inexpensive and offers resolution under mild conditions with satisfactory levels of enantioselectivity. Several azolides are excellent acylating agents and the introduction of a stereogenic centre in the same compound is an achievable task. This work offers an opportunity for the development of new chiral azolides for the same purpose.

4. Experimental

4.1. General

Optical rotations were measured on Jasco DIP-1000 digital polarimeter. Enantiomeric excesses were determined on HPLC Thermo Finnigan spectra system using Daicel Chiralcel OD column with UV detector. ^{1}H NMR spectra were scanned in $CDCl_3$ on Bruker 300 MHz spectrometer with TMS as an internal standard. IR spectra were recorded on Shimadzu FTIR-4200. Elemental analyses were carried on Carlo Enra instrument EA-1108 Elemental analyzer. All melting points are uncorrected. Temperatures are recorded in °C. Boiling point of petroleum-ether used was in the range of 60–80 °C. (*S*)-1-Benzoyl-2-(α-acetoxyethyl)benzimidazole **2** was prepared according to our previously reported procedure.[8]

4.2. Representative procedure for the enantioselective benzoylation of racemic amines

A solution of **2** (2 mmol) and racemic amine **3a**–**d** (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 amide **4a**–**d**. The unreacted amine was recovered from aqueous layer and on derivatization with benzoyl chloride in the presence of pyridine yielded (*R*)-*N*-benzoyl amide **5a**–**d**.

4.2.1. (*S*)-*N*-Benzoyl-1-phenylethylamine 4a. Mp: 122–123 °C; $[\alpha]_D^{19} = -17.9$ (*c* 1, $CHCl_3$) {lit.[9] $[\alpha]_D^{26} = -20.1$ (*c* 1.02, $CHCl_3$)}; IR (KBr): 3357, 3082, 3054, 3030, 2974, 2932, 1634, 1602, 1578, 1518, 1488, 1454 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, $J = 7.0$ Hz, 2H; ArH), 7.53–7.27 (m, 8H; ArH), 6.32 (br d, $J = 6.2$ Hz, 1H; NH), 5.40–5.30 (m, 1H; CH), 1.62 (d, $J = 7.0$ Hz, 3H; CH_3); Anal. Calcd for $C_{15}H_{15}NO$: C, 80.00; H, 6.67; N 6.22. Found: C, 79.95; H, 6.65; N, 6.29.

4.2.2. (*S*)-*N*-Benzoyl-3-methyl-2-butylamine 4b. Mp: 73–75 °C; $[\alpha]_D^{19} = +12.4$ (*c* 1, $CHCl_3$); IR (KBr): 3317, 3056, 2965, 2924, 2873, 1629, 1578, 1532, 1491, 1457 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, $J = 7.8$ Hz, 2H; ArH), 7.49–7.38 (m, 3H; ArH), 5.96 (br s, 1H; NH), 4.13–4.04 (m, 1H; CH), 1.87–1.76 (m, 1H; CH), 1.18 (d, $J = 6.3$ Hz, 3H; CH_3), 0.98 (d, $J = 3.9$ Hz, 3H; CH_3), 0.95 (d, $J = 3.3$ Hz, 3H; CH_3); Anal. Calcd for $C_{12}H_{17}NO$: C, 75.39; H, 8.90; N 7.33. Found: C, 75.45; H, 8.94; N, 7.26.

4.2.3. (*S*)-*N*-Benzoyl-2-heptylamine 4c. Mp: 70–71 °C; $[\alpha]_D^{19} = +14.6$ (*c* 1, $CHCl_3$) {lit.[10] $[\alpha]_D^{25} = +9.0$ (*c* 1, $CHCl_3$, 51% ee)}; IR (KBr): 3300, 3067, 2966, 2952, 2923, 2851, 1633, 1603, 1579, 1537, 1489, 1467, 1457 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, $J = 6.6$ Hz, 2H; ArH), 7.52–7.40 (m, 3H; ArH), 5.90 (br d, $J = 7.3$ Hz, 1H; NH), 4.26–4.12 (m, 1H; CH), 1.58–1.50 (m, 2H; CH_2), 1.40–1.28 (m, 6H; $3 \times CH_2$), 1.23 (d, $J = 6.6$ Hz, 3H; CH_3), 0.88 (t, 3H; CH_3); Anal. Calcd for $C_{14}H_{21}NO$: C, 76.71; H, 9.59; N 6.39. Found: C, 76.77; H, 9.63; N, 6.33.

4.2.4. (*S*)-*N*-Benzoyl-2-butylamine 4d. Mp: 86–88 °C; $[\alpha]_D^{19} = +12.5$ (*c* 1, $CHCl_3$); IR (KBr): 3296, 3066, 2969, 2930, 2875, 1629, 1602, 1578, 1539, 1489, 1454 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, $J = 6.9$ Hz, 2H; ArH), 7.49–7.37 (m, 3H; ArH), 5.95 (br s, 1H; NH), 4.16–4.07 (m, 1H; CH), 1.62–1.53 (m, 2H; CH_2), 1.23 (d, $J = 6.9$ Hz, 3H; CH_3), 0.97 (t, 3H; CH_3); Anal. Calcd for $C_{11}H_{15}NO$: C, 74.58; H, 8.47; N 7.91. Found: C, 74.54; H, 8.43; N, 7.99.

References

1. (a) Clifton, J. E.; Collins, I.; Hallet, P.; Hartley, D.; Lunts, L. H. C.; Wicks, P. D. *J. Med. Chem.* **1982**, *25*, 670; (b) Barmore, R. M.; Logan, S. R.; VanWagenen, B. C. *Tetrahedron Lett.* **1998**, *39*, 3451; (c) Berger, M.; Albrecht, B.;

Berces, A.; Ettmayer, P.; Neruda, W.; Woisetschlager, M. *J. Med. Chem.* **2001**, *44*, 3031.
2. Nieuwenhuijzen, J. W.; Grimbergen, R. F. P.; Koopman, C.; Kellogg, R. M.; Vries, T. R.; Pouwer, K.; van Echten, E.; Kaptein, B.; Hulshof, L. A.; Broxterman, Q. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 4281.
3. Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895.
4. Adamo, M. F. A.; Aggarwal, V. K.; Sage, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 8317.
5. (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069; (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407.
6. (a) Irimescu, R.; Kato, K. *J. Mol. Catal. B: Enzym.* **2004**, *30*, 189; (b) Kitaguchi, H.; Fitzpatrick, P. A.; Huber, J. E.; Klibanov, A. M. *J. Am. Chem. Soc.* **1989**, *111*, 3094; (c) Puertas, S.; Brieva, R.; Rebolledo, F.; Gotor, V. *Tetrahedron* **1993**, *49*, 4007; (d) Pozo, M.; Gotor, V. *Tetrahedron* **1993**, *49*, 4321.
7. (a) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264; (b) Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 234; (c) Ie, Y.; Fu, G. C. *Chem. Commun.* **2000**, 119; (d) Al-Sehemi, A. G.; Atkinson, R. S.; Fawcett, J.; Russell, D. R. *Tetrahedron Lett.* **2000**, *41*, 2239; (e) Al-Sehemi, A. G.; Atkinson, R. S.; Fawcett, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 257; (f) Al-Sehemi, A. G.; Atkinson, R. S.; Fawcett, J.; Russell, D. R. *Chem. Commun.* **2000**, 43; (g) Arseniyadis, S.; Valleix, A.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3314; (h) Arseniyadis, S.; Subhash, P. V.; Valleix, A.; Mathew, S. P.; Blackmond, D. G.; Wagner, A.; Mioskowski, C. *J. Am. Chem. Soc.* **2005**, *127*, 6138; (i) Tanaka, T.; Fang, X.; Azuma, T.; Uchida, S.; Ishida, T.; In, Y.; Iwata, C.; Maezaki, N. *J. Chin. Chem. Soc.* **2000**, *47*, 865; (j) Maezaki, N.; Furusawa, A.; Uchida, S.; Tanaka, T. *Tetrahedron* **2001**, *57*, 9309.
8. Karnik, A. V.; Kamath, S. S. *J. Org. Chem.* **2007**, *72*, 7435.
9. Nagao, Y.; Yagi, M.; Ikede, T.; Fujita, E. *Tetrahedron Lett.* **1982**, *23*, 201.
10. Sanchez, V. M.; Rebolledo, F.; Gotor, V. *J. Org. Chem.* **1999**, *64*, 1464.