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N-Phthaloyl-(*S*)-alanyl chloride as a chiral resolving agent for the kinetic resolution of heterocyclic amines

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Abstract—Acylation of heterocyclic amines with *N*-phthaloyl-(*S*)-alanyl chloride under kinetic resolution conditions resulted in the predominant formation of (*S*,*S*)-amides. The diastereoselectivity of resolution depended heavily on the structure of the resolved amine.

1. Introduction

Recently we have developed efficient preparative synthetic methods for individual enantiomers of heterocyclic amines **1**–**3** (Fig. 1) based on the kinetic resolution of racemic amines by optically active acyl chlorides (Fig. 2), namely (*S*)-naproxen chloride **4** and *N*-tosyl-(*S*)-prolyl chloride **5**.[1–3] (*S*)-Enantiomers of amines **1**–**3** have been found to react with acyl chloride **4** under kinetic resolution conditions faster than (*R*)-amines, resulting in the predominant formation of (*S*,*S*)-amides,[1,2] while kinetic resolution using acyl chloride **5** gave (*R*,*S*)-amides as major products.[3] Herein we report the results of the kinetic resolutions of amines **1**–**3** using another readily available chiral resolving agent, *N*-phthaloyl-(*S*)-alanyl chloride **6**.

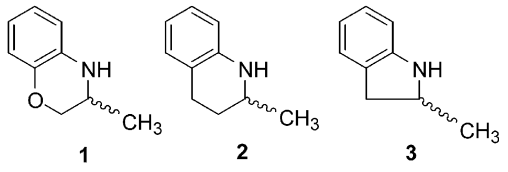

Figure 1. Heterocyclic amines.

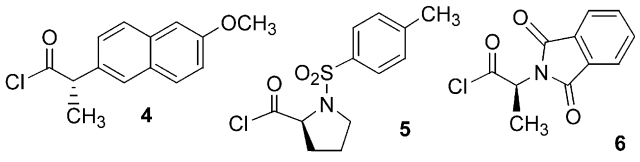

Figure 2. Chiral resolving agents.

We proposed that the above chiral agent **6**, having a bulky substituent (*N*-phthaloyl) at the stereogenic centre, would also promote high stereoselectivity for kinetic resolution.

Acyl chloride **6** was obtained from *N*-phthaloyl-(*S*)-alanine and oxalyl chloride in benzene in the presence of DMF as a catalyst. Freshly prepared acyl chloride **6**, containing less than 3% of impurities (according to ^{1}H NMR spectra), was used for further acylation without additional purification.

2. Results and discussion

Acylation of heterocyclic amines **1**–**3** with acyl chloride **6** was carried out in benzene at room temperature; the ratio of reagents being 2:1 (Scheme 1). Previously it was shown that these conditions were the best ones for the preparative process.[1–3]

The mixtures of the diastereoisomeric amides were enriched with either (*S*,*S*)-diastereomer **7a** (de 40%), **8a** (de 53%) or **9a** (de 19%). Individual (*S*,*S*)-diastereoisomers **7a** and **8a** of high diastereomeric excess (de >99.5% according to HPLC and ^{1}H NMR) were obtained

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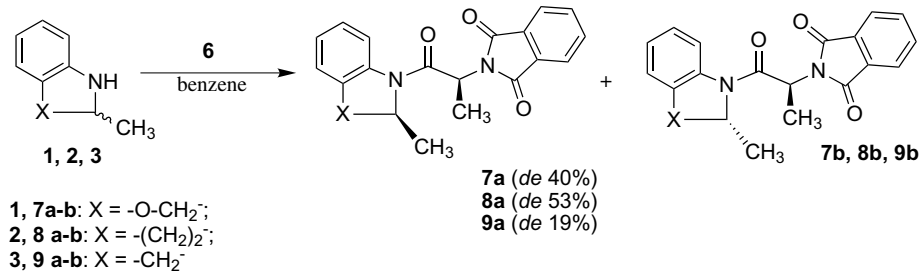
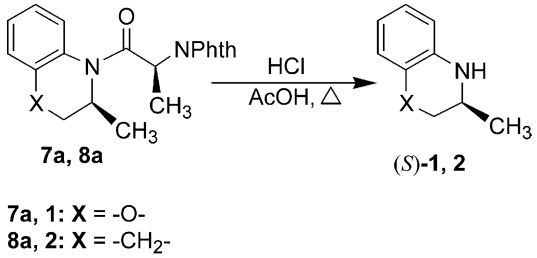


Scheme 1.

by recrystallisation from hexane–EtOAc. It should be noted that although the diastereoselectivity in this case was lower than that with (*S*)-naproxen chloride **4** (de of (*S*,*S*)-amides of amines **1** and **2** was about 80%),[1,2] one recrystallisation of amides **7** and **8** afforded (*S*,*S*)-amides **7a** and **8a** in high de. However, recrystallisation of amide **9** from various solvents did not result in obtaining (*S*,*S*)-amide **9a**. The product proved to be a mixture of (*S*,*S*)- and (*R*,*S*)-amides in a 1:1 ratio.

(*S*,*S*)-Amides **7a** and **8a** were hydrolysed at reflux in a mixture of concentrated HCl and glacial acetic acid (Scheme 2) to give individual (*S*)-isomers of amines **1** and **2** in 95% yield. Enantiomeric excesses of (*S*)-**1** and (*S*)-**2** were determined by HPLC with pre-column derivatisation using (*S*)-naproxen chloride **4**[3], (ee >99%). There is some literature data that indicates that acylation by (*S*)-naproxen[4] or (*S*)-naproxen chloride **4**[5] can result in racemisation of the naproxen fragment. Hence, the results of HPLC determination of the enantiomeric excess with the pre-column derivatisation should be carefully approached. However, if racemisation of the naproxen fragment during derivatisation did occur, the result of ee determination using HPLC would be lower than 99%. Thus we can firmly state that the enantiomeric excess (ee) of (*S*)-amines **1** and **2** is not less than 99%.



Scheme 2.

Thus, it was found that acidic hydrolysis of (*S*,*S*)-amides of *N*-phthaloyl-(*S*)-alanine proceeds without racemisation and makes it possible to obtain (*S*)-enantiomers of the heterocyclic amines **1** and **2** in high enantiomeric excess and with high yields.

Acyl chlorides **4** and **6** can be considered to be close structural analogues having similar types of substituents at the asymmetric carbon, that is one large (naphthyl in the case of acyl chloride **4** or *N*-phthaloyl in the case of acyl chloride **6**), one medium (carbonyl) and one small (methyl). But, if we compare acyl chlorides **4** and **6** having an (*S*)-configuration at the asymmetric centre, according to the commonly accepted Cahn–Ingold–Prelog system[6] (Fig. 3), it is clear that the arrangement of substituents at the stereogenic centres is different. It comes as a surprise that the kinetic resolution of racemic amines **1**–**3** by the two acyl chlorides results in predominant formation of (*S*,*S*)-amides.

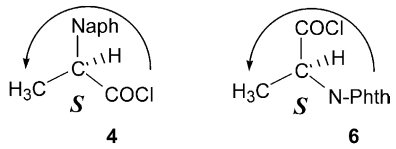


Figure 3.

These data show that both steric and electronic effects of discrete fragments of reagents are responsible for the stereochemical results of the kinetic resolution.

N-Phthaloyl-(*S*)-alanyl chloride is a readily available compound that enables the target amines of high enantiomeric excess to be obtained. In some cases, the use of this resolving agent can be more convenient than that of (*S*)-naproxen chloride.

3. Conclusion

Thus, *N*-phthaloyl-(*S*)-alanyl chloride has been found to be a new chiral agent for kinetic resolution of racemic amines.

4. Experimental

4.1. General

Solvents were purified according to standard procedures. Routine monitoring of reaction mixtures was carried out using Silufol UV 254 (Kavalier) TLC aluminium plated silica gel. Melting points were determined on a Boetius melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured on a Bruker DRX 400 (400 MHz) spectrometer, spectra of amides **7a**,**b**, **8a**,**b** and **9a**,**b**—in DMSO-d_6 at 100 °C, spectra of amines **1**–**3**—in DMSO-d_6 or $CDCl_3$ at ambient tem-

perature. All signals are expressed in ppm (δ) with tetramethylsilane as an internal standard. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. The de values of amides **6a**, **7a** and **8a** were measured by HPLC on a Merck–Hitachi chromatograph with L-4000A Intelligent Pump, L-4000A UV Detector and D-2500A Chromato-Integrator [Hibar Pre-packed Column RT250-4, Lichrosorb Si-60]; mobile phase: hexane–*i*-PrOH = 80:1, flow rate 1 mL/min; UV detection 230 nm; retention times τ_{7a} 16.3, τ_{7b} 14.0, τ_{8a} 16.0, τ_{8b} 17.3, τ_{9a} 17.6, τ_{9b} 17.1 min. Microanalyses were carried out on a CHNS-O model EA-1102 elemental analyser and were in good agreement with the calculated values.

4.2. *N*-Phthaloyl-(*S*)-alanyl chloride 6

Oxalyl chloride (1.75 mL, 20 mmol) and DMF (0.01 mL) were added to a stirred solution of *N*-phthaloyl-(*S*)-alanine (2.25 g, 10 mmol) in a hexane–benzene (1:1) mixture (40 mL). The mixture was stirred at room temperature for 20 h, then evaporated in vacuum to dryness. The residue was treated with dry hexane to give compound **6** as colourless crystals (2.22 g, 93%). ^{1}H NMR ($CDCl_3$): 1.79 (d, $J = 7.1$ Hz, 3H, CH_3); 5.17 (q, $J = 7.1$ Hz, 1H, CH); 7.78 and 7.92 m (4H, C_6H_4).

4.3. *N*-[*N*′-Phthaloyl-(2*S*)-alanyl]-(3*S*)-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine 7a

A solution of *N*-phthaloyl-(*S*)-alanyl chloride **6** (0.38 g, 1.6 mmol) in benzene (15 mL) was added dropwise to a stirred solution of racemic **1** (0.48 g, 3.2 mmol) in benzene (15 mL). The mixture was stirred at room temperature for 20 h, then washed consequently with 1 M HCl, water, 5% $NaHCO_3$, water and dried over $MgSO_4$. The solution was evaporated in vacuum to dryness to give a yellow oily residue, which was recrystallised from hexane–ethyl acetate yielding amide **7a** as colourless crystals (0.25 g, 44%, de 99.8%). Mp: 204–206 °C; $[\alpha]_D^{20} = +331$ (*c* 1.3, benzene). Anal. Calcd for $C_{20}H_{18}N_2O_4$: C 68.56, H 5.18, N 8.00. Found: C 68.43, H 5.13, N 8.09. ^{1}H NMR (DMSO-d_6): 1.15 (d, $J = 6.8$ Hz, 3H, CH_3-benzoxazine); 1.65 (d, $J = 7.4$ Hz, 3H, CH_3-alanine); 4.08 (dd, $J = 11.0$, 3.2 Hz, 1H, C^2H-benzoxazine); 4.21 (dd, $J = 11.0$, 1.7 Hz, 1H, C^2H-benzoxazine); 4.71 (qdd, $J = 6.8$, 3.2, 1.7 Hz, 1H, C^3H-benzoxazine); 5.51 (q, $J = 7.4$ Hz, 1H, CH-alanine); 6.91 (m, 2H, C^6H- and C^8H-benzoxazine); 7.08 (ddd, $J = 8.1$, 7.4, 1.6 Hz, 1H, C^7H-benzoxazine); 7.64 (dd, $J = 8.1$, 1.6 Hz, 1H, C^5 H-benzoxazine); 7.85 (m, 4H, phthaloyl).

4.4. *N*-[*N*′-Phthaloyl-(2*S*)-alanyl]-(2*S*)-2-methyl-1,2,3,4-tetrahydroquinoline 8a

Following the above procedure, and starting with racemic **2** (0.47 g, 3.2 mmol) and *N*-phthaloyl-(*S*)-alanyl chloride **6** (0.38 g, 1.6 mmol), the title compound was obtained as colourless crystals (0.30 g, 54%, de 99.7%). Mp: 230–231 °C; $[\alpha]_D^{20} = +461$ (*c* 1.45, benzene). Anal. Calcd for $C_{21}H_{20}N_2O_3$: C 72.40, H 5.79, N 8.04. Found: C 72.38, H 5.84, N 8.05. ^{1}H NMR (DMSO-d_6): 1.02 (d, $J = 6.5$ Hz, 3H, CH_3-quinoline); 1.31 (dddd, $J = 13.2$, 10.2, 6.7, 5.3 Hz, 1H, C^3H-quinoline); 1.36 (d, $J = 7.5$ Hz, 3H, CH_3-alanine); 2.33 (dddd, $J = 13.2$, 7.6, 5.4, 5.2 Hz, 1H, C^3H-quinoline); 2.49 (ddd, $J = 15.2$, 10.2, 5.4 Hz, 1H, C^4H-quinoline); 2.68 (ddd, $J = 15.2$, 5.3, 5.2 Hz, 1H, C^4H-quinoline); 4.60 (ddq, $J = 7.6$, 6.7, 6.5 Hz, 1H, C^2H-quinoline); 5.48 (q, $J = 7.5$ Hz, 1H, CH-alanine); 7.21 (ddd, $J = 7.8$, 6.8, 1.2 Hz, 1H, C^6H-quinoline); 7.29 (m, 2H, C^5H- and C^7H-quinoline); 7.46 (d, $J = 7.8$ Hz, 1H, C^8H-quinoline); 7.84 (m, 4H, phthaloyl).

4.5. *N*-[*N*′-Phthaloyl-(2*S*)-alanyl]-(2*RS*)-2-methylindoline 9a,b

Following the above procedure, and starting with racemic **3** (0.49 g, 3.6 mmol) and *N*-phthaloyl-(*S*)-alanyl chloride **6** (0.43 g, 1.8 mmol), the title compound was obtained as colourless crystals (0.31 g, 51%). Anal. Calcd for $C_{20}H_{18}N_2O_3$: C 71.84, H 5.43, N 8.38. Found: C 71.98, H 5.52, N 8.45. ^{1}H NMR (DMSO-d_6): 1.26 d and 1.27 d ($J = 6.4$ Hz, 3H, CH_3-indoline); 1.69 d, $J = 7.1$ Hz and 1.81 d, $J = 7.3$ Hz (3H, CH_3-alanine); 2.61 d, $J = 15.9$ Hz and 2.64 d, $J = 15.8$ Hz (1H, C^3H-indoline); 3.26 dd, $J = 15.9$, 8.6 Hz and 3.38 dd, $J = 15.8$, 8.3 Hz (1H, C^3H-indoline); 4.66 (m, 1H, C^2H-indoline); 5.23 q, $J = 7.1$ Hz and 5.25 q, $J = 7.3$ Hz (1H, CH-alanine); 6.95–7.88 (m, 8H, arom.).

4.6. (*S*)-2,3-Dihydro-3-methyl-4H-1,4-benzoxazine (*S*)-1

Amide **7a** (0.20 g, 0.58 mmol) was heated under reflux in a mixture of glacial acetic acid (3 mL) and concd HCl (3 mL) for 10 h. The reaction mixture was evaporated to dryness. Water (5 mL) was added to the residue, the precipitate filtered off and washed with water. The combined aqueous filtrates were made alkaline with 10 M NaOH to pH 9–10 at +5 °C and extracted with $CHCl_3$ (3 × 5 mL). The organic layer was washed with brine, and dried over $MgSO_4$. The solution was evaporated to dryness to give amine (*S*)-**1** as a yellowish oil (0.08 g, 93%), ee 99.0% by HPLC (pre-column derivatisation using (*S*)-naproxen chloride **4**[1]). $[\alpha]_D^{20} = +19.8$ (*c* 1.3, $CHCl_3$). {Lit.[1]: (*S*)-**1**: $[\alpha]_D^{20} = +19.8$ (*c* 1.0, $CHCl_3$)}. Anal. Calcd for $C_9H_{11}NO$: C 72.46, H 7.43, N 9.39. Found: C 72.42, H 7.35, N 9.37. ^{1}H NMR (DMSO-d_6): 1.11 (d, $J = 6.3$ Hz, 3H, Me), 3.39 (dqd, $J = 7.9$, 6.3, 2.8 Hz, 1H, C^3H), 3.61 (dd, $J = 10.2$, 7.9 Hz, 1H, C^2H); 4.08 (dd, $J = 10.2$, 2.8 Hz, 1H, C^2H); 5.46 (br s, 1H, NH), 6.41 (ddd, $J = 7.8$, 7.1, 1.7 Hz, 1H, C^6H), 6.50 (dd, $J = 7.8$, 1.6 Hz, 1H, C^5H), 6.56 (dd, $J = 7.6$, 1.7 Hz, 1H, C^8H); 6.59 (ddd, $J = 7.6$, 7.1, 1.6 Hz, 1H, C^7H).

4.7. (*S*)-2-Methyl-1,2,3,4-tetrahydroquinoline (*S*)-2

Following the above procedure, and starting with amide **8a** (0.21 g, 0.6 mmol), the title compound was obtained as a yellowish oil (0.085 g, 95%). Ee 99.0% by HPLC (pre-column derivatisation using (*S*)-naproxen acyl

chloride **4**[2]). $[\alpha]_D^{20} = -85$ (*c* 1.5, benzene). {Lit.[7]: (*R*)-**2**: $[\alpha]_D^{20} = +85$ (*c* 2.0, benzene)}. Anal. Calcd for $C_{10}H_{13}N$: C 81.59, H 8.89, N 9.52. Found: C 81.45, H 8.84, N 9.58. ^{1}HNMR ($CDCl_3$): 1.19 (d, $J = 6.3$ Hz, 3H, Me), 1.57 (dddd, $J = 12.8$, 11.4, 9.9, 5.4 Hz, 1H, C^3H), 1.91 (dddd, $J = 12.8$, 5.6, 3.5, 2.9 Hz, 1H, C^3H), 2.71 (ddd, $J = 16.4$, 5.4, 3.7 Hz, 1H, C^4H); 2.82 (ddd, $J = 16.4$, 11.4, 5.6 Hz, 1H, C^4H), 3.38 (dqd, $J = 9.8$, 6.3, 2.8 Hz, 1H, C^2H), 3.63 (br s, 1H, NH), 6.44 (dd, $J = 8.3$, 1.2 Hz, 1H, C^8H), 6.58 (td, $J = 7.4$, 1.2 Hz, 1H, C^5H), 6.92–6.96 (m, 2H, C^5H and C^7H).

Acknowledgements

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References and notes

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