Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 2797–2799

Enzymatic resolution of (*RS*)-2-(1-aminoethyl)-3-chloro-5-(substituted)pyridines

Amy E. Sigmund and Robert DiCosimo*

DuPont Central Research and Development, Experimental Station, PO Box 80328, Wilmington, DE 19880-0328, USA

Received 1 June 2004; accepted 6 July 2004
Available online 11 September 2004

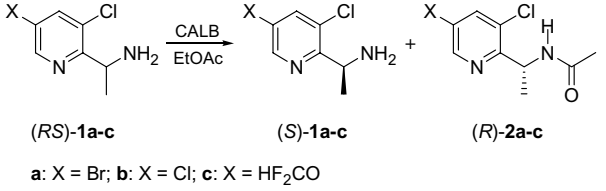
Abstract—The enantioselectivity of the lipase-catalyzed acetylation of several (*RS*)-2-(1-aminoethyl)-3-chloro-5-(substituted)pyridines has been examined. An enantiomeric excess (substrate) of 94% at 55% conversion was obtained for acetylation of the (*R*)-isomer of (*RS*)-2-(1-aminoethyl)-3-chloro-5-bromopyridine by *Candida antartica* lipase B in ethyl acetate, whereas the (*R*)-isomer of (*RS*)-2-(1-aminoethyl)-3,5-dichloropyridine and (*RS*)-2-(1-aminoethyl)-3-chloro-5-(difluoromethoxy)pyridine were each acetylated with significantly lower enantioselectivity. Substitution of methyl propionate, methyl isobutyrate or methyl methoxyacetate for ethyl acetate resulted in decreased enantioselectivity.

1. Introduction

Numerous examples of the enzyme-catalyzed resolution of racemic amines by the enantioselective aminolysis of esters have been reported.[1–4] The resolution of (±)-1-(2-pyridyl)ethylamine was performed using *Candida antartica* lipase B (CALB) to catalyze the enantioselective aminolysis of ethyl acetate by the (*R*)-enantiomer of the racemic amine.[5,6] The resolution of bicyclic heteroarylamines using CALB in ethyl acetate has also been reported to result in high enantioselectivity for the production of the (*S*)-amine.[6] This method has now been examined for the resolution of several 2-(1-aminoethyl)-3-chloro-5-(substituted)pyridines to determine if this particular functional-group substitution of the pyridyl ring affected the enantioselectivity of the reaction.

2. Results and discussion

Seventeen lipases[7] were screened as catalysts for the aminolysis of ethyl acetate by (*RS*)-2-(1-aminoethyl)-3-chloro-5-bromopyridine[8,9] (*RS*)-**1a** (Scheme 1). Triethylamine (TEA, 1 equiv) was added to all the reactions,[10] as the halide-substituted pyridylamines **1a**–**c**[8,9] were not stable as the free amine for long periods of time (as either pure compound, or in solution), and were added to the reactions as the hydrochloride salt. Enzyme-catalyzed reaction rates were significantly slower in the absence of TEA, and only low conversions (<20%) to amide were obtained. There was no aminolysis of ethyl acetate by **1a** hydrochloride or **1a**/TEA in the absence of added enzyme.



(*RS*)-**1a-c** (*S*)-**1a-c** (*R*)-**2a-c**

a: X = Br; **b**: X = Cl; **c**: X = HF_2CO

Scheme 1.

Only CALB catalyzed the production of (*S*)-**1a**[11] with high enantioselectivity (Fig. 1, $E = 27$); a 94% ee at 55% conversion of 0.10 M (*RS*)-**1a** was obtained at 30 °C. Increasing the concentration of (*RS*)-**1a** from 0.10 to 0.30 M resulted in only a slight decrease in ee of (*S*)-**1a** at 55% conversion (Table 1). In all the reactions, ee (*R*)-**2a**[13] was 75–76% at ca. 55% conversion, indicating that (*R*)-**2a** may partially racemize as it is produced. A similar result was previously reported for the resolution of 2-(1-aminoethyl)pyridine by CALB in neat ethyl acetate at 60 °C (99% ee (*S*)-**1**, 75% ee (*R*)-**2** at 56% conversion).[6] Optimal reaction temperature was between 22 and 30 °C, where a slightly lower (*S*)-**1a** ee was observed at 40 °C.

* Corresponding author. Tel.: +1 302 695 9416; fax: +1 302 695 8114; e-mail: robert.dicosimo@usa.dupont.com

0957-4166/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2004.07.043

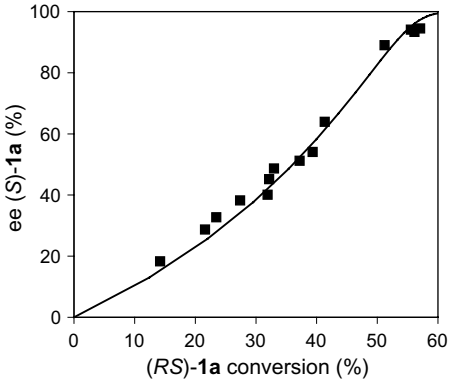


Figure 1. Dependence of enantiomeric excess of (*S*)-**1a** on conversion of (*RS*)-**1a** (0.10–0.30 M) to (*R*)-**2a** using CALB (50 mg/mL) in ethyl acetate (■), and calculated $E = 27$ (fitted curve).

The CALB-catalyzed aminolysis of ethyl acetate by (*RS*)-2-(1-aminoethyl)-3,5-dichloropyridine (*RS*)-**1b** or (*RS*)-2-(1-aminoethyl)-3-chloro-5-(difluoromethoxy) pyridine (*RS*)-**1c** was each less enantioselective than when using (*RS*)-**1a** (Table 1). At conversions of less than 50%, reaction rates for aminolysis of ethyl acetate by (*RS*)-**1b** were ca. 2-fold greater than for (*RS*)-**1a**, whereas reaction rates were ca. 2-fold less for (*RS*)-**1c** than for (*RS*)-**1a**; these relative reaction rates may be related to the effect of changes in the steric bulk of the pyridyl 5-substituent on the reaction rate. Increasing the steric bulk of the acylating agent employed in the CALB-catalyzed resolution of (*RS*)-**1a** (Table 1, entries 4 and 5) also resulted in a significant decrease in enantioselectivity, and only moderately affected the already-low enantioselectivity for the resolution of (*RS*)-**1b** (Table 1, entries 4 and 5).

Although the use of CALB as catalyst for the resolution of (*RS*)-**1a**–**c** was only successful for (*RS*)-**1a**, this reaction can be used to prepare (*S*)-**1a** in high ee. The use of an inexpensive acylating agent (ethyl acetate) as neat solvent eliminates the need to run the reaction under scrupulously dry conditions (such as in the presence of molecular sieves[14]), as any water present in the reaction mixture will simply hydrolyze a small percentage of the acylating agent, and does not result in a yield loss of the desired chiral amine. The low ee for (*R*)-**2a** obtained in these reactions does not allow for the simultaneous production of (*R*)-**1a** in high ee [hydrolysis of (*R*)-**2a** using 6N HCl produces no decrease in ee of the resulting (*R*)-**1a**], but it may be possible to thermally racemize (*R*)-**2a** to (*RS*)-**2a** (as was demonstrated for the *N*-acetyl derivative of 2-(1-aminoethyl)pyridine[6]), and make possible the complete utilization of the racemate for the production of (*S*)-**1a.**

Acknowledgements

The authors thank John Daub and Earl Reed (DuPont Crop Protection Products) for the preparation of **1a**–**c** and **2a**, and Michael Walker, Raphael Shapiro, Albert Casalnuovo, Peter Bloxham, Kingmo Sun and William Moberg (DuPont CPP) for helpful discussions, and confirmation of the chirality of the reaction products.

References

1. Alfonso, I.; Gotor, V. *Chem. Soc. Rev.* **2004**, *33*, 201–209.
2. van Rantwijk, F.; Sheldon, R. A. *Tetrahedron* **2004**, *60*, 501–519.
3. Breen, G. *Tetrahedron: Asymmetry* **2004**, *15*, 1427–1430.
4. Pámies, O.; Éll, A. H.; Samec, J. S. M.; Hermanns, N.; Bäckvall, J.-E. *Tetrahedron Lett.* **2002**, *43*, 4699–4702.
5. Iglesias, L. E.; Sánchez, V. M.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymmetry* **1997**, *8*, 2675–2677.
6. Skupinska, K. A.; McEachern, E. J.; Baird, I. R.; Skerlj, R. T.; Bridger, G. J. *J. Org. Chem.* **2003**, *68*, 3546–3551.
7. Lipases (ICR nos 101–117; ICR 110 = CALB lyo.) were obtained from BioCatalytics, Inc., Pasadena, CA.
8. Foor, S. R. PCT Int. Appl. WO2003080576 A2, 2003; *Chem. Abstr*. **2003**, *139*, 276823.
9. Neubert, T. D.; Piotrowski, D. W.; Walker, M. P. U.S. Patent Appl. 2004044040 A1, 2004; *Chem. Abstr*. **2002**, *136*, 263098.
10. In a typical reaction, 55.2 mg (0.20 mmol) of (*RS*)-**1a** hydrochloride,[8,9] 28 μL (0.20 mmol) of triethylamine, and 100 mg/mL of CALB in 2.0 mL of ethyl acetate were mixed at 30 °C for 24 h. To the reaction mixture was then added 2.0 mL of 20 mM tetradecane (internal standard) in 1:1 acetonitrile/methanol, and the resulting mixture filtered

Table 1. Aminolysis of alkyl esters by (*RS*)-**1a**–**c** catalyzed by *Candida antartica* lipase B[a]

Entry	Compound	Concentration (mM)	Time (h)	Alkyl ester	(*RS*)-**1** (mM)	(*RS*)-**2** (mM)	Conversion (%)	(*S*)-**1** ee (%)	(*R*)-**2** ee (%)	E[b]
1	(*RS*)-**1a**	102	24	Ethyl acetate	45	53	55	94	75	27
2	(*RS*)-**1a**	200	24	Ethyl acetate	92	92	54	91	76	25
3	(*RS*)-**1a**	298	24	Ethyl acetate	133	150	55	89	76	19
4	(*RS*)-**1a**	102	6	Methyl methoxyacetate	49	ND	52	54	ND	5
5	(*RS*)-**1a**	104	6	Methyl isobutyrate	81	ND	23	3.7	ND	1
6	(*RS*)-**1b**	107	6	Ethyl acetate	59	ND	45	47	75	6
7	(*RS*)-**1b**	102	6	Methyl methoxyacetate	47	ND	54	56	ND	5
8	(*RS*)-**1b**	103	6	Methyl isobutyrate	86	ND	17	3.5	ND	1
9	(*RS*)-**1b**	105	6	Methyl propionate	77	ND	27	10	ND	2
10	(*RS*)-**1c**[c]	052	25	Ethyl acetate	26	ND	49	69	68	12

[a] Reactions run at 30 °C in neat alkyl ester as solvent, 50 mg CALB/mL, and 1 equiv TEA per (*RS*)-**1a**–**c** hydrochloride.
[b] Calculated for production of (*S*)-**1a**–**c** according to Ref. 12.
[c] 37.5 mg CALB/mL reaction.

(Gelman 0.2 μm GHP syringe filter) and analyzed by gas chromatography (GC). For HPLC analysis, a 0.100 mL aliqout of the filtrate was mixed with 0.400 mL of 150 mM *N*,*N*-dimethylbenzamide (HPLC internal standard) in 1:1 acetonitrile/methanol. Chiral GC analysis of (*R*)-**2a**–**c** and (*S*)-**2a**–**c** was performed using a GTA-40 column (Advanced Separation Technologies) at 160 °C. No changes in relative amounts of (*R*)- and (*S*)-enantiomers of **2a** were produced by the analysis, verified by analyzing a mixture of 9:1 (*S*)- and (*R*)-**2a**. Chiral HPLC analysis of (*R*)-**2a**–**b** and (*S*)-**2a**–**b** was also performed using UV detection at 280 nm on a (*S*,*S*)-Whelk-01 column (Regis, 25 cm × 4.6 mm id), using 30% isopropanol/70% hexanes (isocratic); ee was consistent with that measured by chiral GC analysis. Quantitation of (*RS*)-**2a** was performed on a DB-1701 GC column (J&W Scientific, 30 m, 0.53 mm OD, 1-μm film thickness). Chiral HPLC analysis of (*R*)-**1a**–**c** and (*S*)-**1a**–**c** was performed using UV detection at 280 nm on a Chiralcel OD-H column (Daicel, 25 cm × 4.6 mm id) at 30 °C and a flow rate of 0.6 mL/min of 0.2% diethylamine in 10% 2-propanol/90% hexanes; *N*,*N*-dimethylbenzamide was used as internal standard.

11. Resolution of (*RS*)-**1a** and (*RS*)-**1b** with (L)-(+)-tartaric acid [yielding (*S*)-**1a** and (*S*)-**1b**, respectively], and (D)-(−)-tartaric acid [yielding (*R*)-**1b**] produced standards used to confirm the enantiospecificity of CALB-catalyzed aminolysis reactions: Smith, H. E.; Schaad, L. J.; Banks, R. B.; Wiant, C. F.; Jordan, C. F. *J. Am. Chem. Soc.* **1973**, *95*, 811–818. The absolute stereochemistry for products **2a**–**c** were inferred from the configuration of the corresponding amines, which were acetylated.
12. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7298.
13. Acetyl chloride (2.31 g, 29.4 mmol) and (*RS*)-**1a** hydrochloride[8,9] (8.00 g, 29.4 mmol) were dissolved in dichloromethane (53 mL) under nitrogen. Triethylamine (6.55 g, 64.7 mmol) was added dropwise with stirring while maintaining temperature <30 °C. The solvent was removed by rotary evaporation, the remaining mixture suspended in dichloromethane (20 mL), and triethylamine hydrochloride removed by filtration. The filtrate was washed with dichloromethane (5 mL), the wash and filtrates combined, and (*RS*)-**2a** recovered as a yellow solid by flash chromatography on silica (300 mL) using 9:1 ethyl ether/dichloromethane (5.33 g, 66% yield): mp 123–125 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.50 (d, J = 2.0 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H), 6.86 (b s, 1H), 5.52 (m, 1H), 2.04 (s, 3H), 1.40 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 156.8, 148.1, 139.6, 130.0, 118.8, 46.5, 23.4, 20.9; HRMS calcd for $C_9H_{10}N_2OBrCl$ (M+1) 276.9743, found 276.9733.
14. Sigmund, A. E.; McNulty, K. C.; Nguyen, D.; Silverman, C. E.; Ma, P.; Pesti, J. A.; DiCosimo, R. *Can. J. Chem.* **2002**, *80*, 608–612.