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Enzymatic resolution of *N*-arylaziridine carboxylates ☆

H. M. Sampath Kumar,* M. Shesha Rao, P. Pawan Chakravarthy and J. S. Yadav

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract—*N*-Arylaziridine-2-carboxylates have been enzymatically resolved using the lipase from *Candida rugosa* to afford optically active aziridine carboxylates in moderate to high enantiomeric purity. The absolute configuration of the unknown aziridine carboxylates was assigned as *S* by chemical correlation.

1. Introduction

Aziridine carboxylates are important chiral synthons, which can generate a plethora of useful organic intermediates such as α- and β-amino acids and β-lactams.[1] Furthermore, enantiomerically pure aziridine carboxylates may be used as precursors for the generation of chiral building blocks and enantioselective routes to unusual amino acids can be envisaged through regioselective ring opening reactions involving aziridinoesters.[2] Regio- and stereoselective ring opening with many types of nucleophiles provide access to a great variety of useful synthetic intermediates. In addition to being attractive substrates or building blocks for organic chemists, aziridine carboxylates can also act as chiral auxiliaries, chiral reagents and chiral ligands for asymmetric synthesis.[3] Various chiral aziridines are available in enantiomerically pure form either through asymmetric synthesis[4] or kinetic resolution of racemates.[5]

As the reactivity of three-membered heterocycles can be modified by a suitable choice of substitution on the nitrogen atom, the preparation of enantiomerically pure *N*-substituted aziridine carboxylates is an attractive option. Our literature survey reveals that only a few reports concerning the enzymatic enantiospecific hydrolysis of dimethyl aziridine 2,3-carboxylates and *N*-acylaziridine carboxylates have been reported with moderate to low ee.[5] Furthermore, *N*-arylaziridine-2-carboxylates have been synthesized in low to moderate enantiomeric purity by asymmetric aziridination involving in-built chiral auxiliaries attached to either the olefin or a hydroxamic acid (*S*, 17–49% ee) or even using chiral phase transfer agents derived from cinchona alkaloids (*R*, 45–62% ee). Lipase from *Candida rugosa* (CRL) has been extensively utilized for the kinetic resolution of various racemic substrates.[6]

2. Results and discussion

To our knowledge there have not been any reports on the enzymatic enantioselective hydrolysis of *N*-arylaziridine-2-carboxylates and in this context we herein report the kinetic resolution of racemic *N*-arylaziridine-2-carboxylates via enantioselective hydrolysis by *C. rugosa* lipase (CRL). Racemic aziridines were prepared by the ring contraction of precursor triazoline carboxylates, which were readily obtained through 1,3-dipolar cycloadditions of various aryl azides with methyl acrylates. Hydrolysis was conducted in pH 7.5 phosphate buffer (0.1 M) and due to the low solubility of the substrates in buffer solution, dioxane was used as the co-solvent. The hydrolysis was terminated at around 45–50% conversion by extraction with EtOAc. The crude optically active esters obtained after evaporation of the solvent were flash chromatographed on silica gel (EtOAc/*n*-hexane gradient) to afford pure *N*-arylaziridine carboxylates. The enantiomeric purity was determined by chiral HPLC and ^{1}H NMR-shift reagent methods. Moderate to high enantiomeric purity (70–99%) was observed among the substrates (see Table 1) studied. The absolute

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* Corresponding author. Tel.: +91-40-717-3874; fax: +91-40-2716-0512; e-mail: hmskumar@yahoo.com

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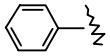
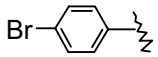
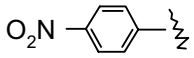
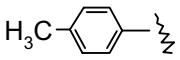
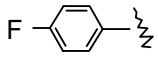
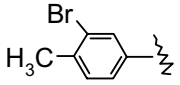
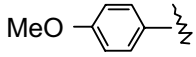
Table 1. Enantioselective hydrolysis of aziridine-2-carboxylates by *C. rugosa*

Entry	Substrate (Ar)	Reaction conditions			Unchanged ester		
		t (h)	E/S[a]	Conversion (%)	$[\alpha]_D^{25}$ $CHCl_3$[b]	Ee (%)[c]	Absolute configuration
1		4	1/2	48	−173.2	84	*S*
2		5	1/2	50	−156.7	99	*S*
3		3	1/2	45	−40.3	12	*S*
4		4.5	1/2	48	−195.5	70	*S*
5		5.5	1/4	44	−18.4	7	*S*
6		5.5	1/4	46	−15.9	15	*S*
7		5	1/2	46	−184.3	79	*S*

[a] E/S refers to enzyme, substrate (wt/wt) ratio.
[b] + or − refers to the sign of the specific rotation.[4]
[c] Determined by chiral HPLC conditions: Chiracel OD™, Daicel, Japan; 5×250 mm, λ 330 nm; 10% isopropanol in hexane; flow rate 0.6 mL/min and by ^1H NMR with $Eu(hfc)_3$ in $CDCl_3$.

configuration of all the unhydrolyzed *N*-arylaziridine carboxylates was determined as *S* by comparing the sign of the specific rotation, based on a literature precedent.[4]

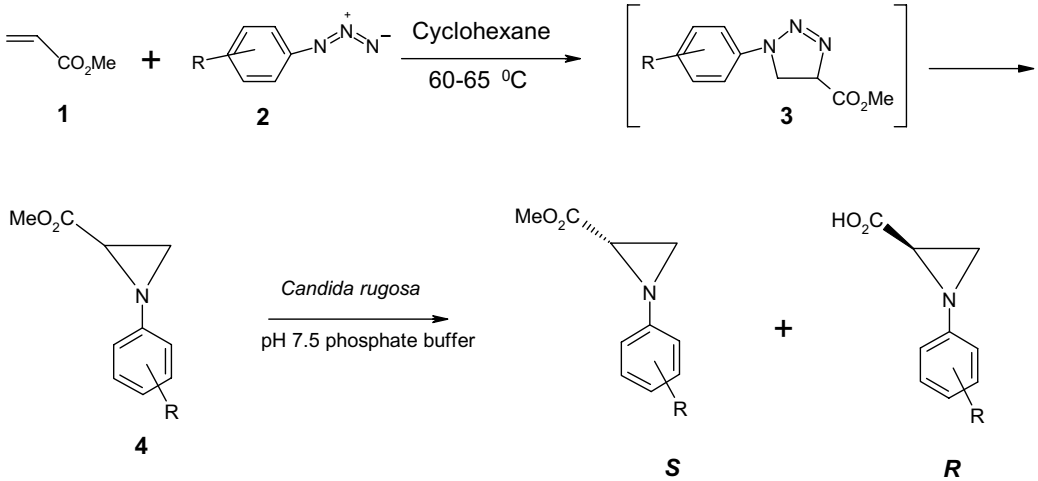
3. Conclusion

We have successfully demonstrated herein, the kinetic resolution of synthetically important *N*-arylaziridine-2-carboxylates in moderate to high enantiomeric purity using *C. rugosa* lipase. All the unhydrolyzed esters were found to be of an (*S*)-configuration.

4. Experimental

4.1. General procedure for the preparation of *N*-arylaziridine-2-carboxylates[7]

Aryl azide (1 mmol) dissolved in 20 mL of dry cyclohexane was heated at 60–65 °C with methyl acrylate (1.1 mmol) for 8–10 h at the end of which the solvent was evaporated under reduced pressure. The residue was chromatographed (silica gel finer than 200 mesh, eluent; EtOAc/*n*-hexane gradient mixture) to afford pure *N*-arylaziridine-2-carboxylate, which was characterized by IR, ^1H NMR, mass spectroscopy and elemental analysis (Scheme 1).



Scheme 1.

4.2. General procedure for *C. rugosa*-catalyzed hydrolysis of the *N*-arylaziridine carboxylates

Racemic *N*-arylaziridine carboxylate (25 mg) was added to a phosphate buffer (pH 7.5, 25 mL, 0.1 M) and treated with *C. rugosa* lipase (Sigma 0.890 units/mg) with vigorous stirring at room temperature (25 °C). The ratio of enzyme/aziridine carboxylate (E/S) employed is reported in Table 1. The pH was adjusted at 7.5 and kept constant by the intermittent addition of 0.1 M NaOH. Dioxane (1–2 mL, 4–8% v/v) was used as the co-solvent to improve the solubility of *N*-arylaziridine carboxylates. The progress of hydrolysis was monitored by TLC and the reaction terminated at 45–50% conversion via simple extraction with ethyl acetate (2×20 mL) after which the organic extract was dried using sodium sulfate and concentrated. The residue was purified by flash chromatography (ethyl acetate/*n*-hexane gradient mixture) to afford the pure *N*-arylaziridine carboxylate.

4.3. Methyl *N*-(phenyl)aziridine-2-carboxylate[4]

$[\alpha]_D^{25}$ −173.2 (*c* 0.25, $CHCl_3$); IR (KBr): 1750 cm^{-1}; ^1H NMR: δ 2.30 (dd, 1H), 2.66 (dd, 1H), 2.81 (dd, 1H), 3.80 (s, 3H), 7.02–7.05 (m, 3H), 7.22–7.26 (m, 2H); MS: *m*/*z* (%) 177 (M^+, 32), 163 (26), 119 (18), 104 (100), 90 (55), 77 (44). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.62; N, 7.90. Found: C, 67.69; H, 6.57; N, 7.97%.

4.4. Methyl *N*-(*p*-bromophenyl)aziridine-2-carboxylate

$[\alpha]_D^{25}$ −156.3 (*c* 0.25, $CHCl_3$); IR (KBr): 1754 cm^{-1}; ^1H NMR: δ 2.26 (d, 1H), 2.63 (s, 1H), 2.75 (dd, 1H), 3.79 (s, 1H), 6.84 (d, 2H), 7.29 (d, 2H); MS: *m*/*z* (%) 255 (M^+, 91), 182 (96), 169 (53), 117 (100), 90 (76), 63 (43). Anal. Calcd for $C_{10}H_{10}BrNO_2$: C, 46.90; H, 3.94; Br, 31.20; N, 5.47. Found: C, 46.98; H, 3.86; Br, 31.32; N, 5.37%.

4.5. Methyl *N*-(*p*-nitrophenyl)aziridine-2-carboxylate[4]

$[\alpha]_D^{25}$ −40.3 (*c* 0.5, $CHCl_3$); IR (KBr): 1758 cm^{-1}; ^1H NMR: δ 2.24 (d, 1H), 2.78 (s, 1H), 2.95 (dd, 1H), 3.82 (s, 3H), 7.06 (d, 2H), 8.18 (d, 2H); MS: *m*/*z* (%) 222 (M^+, 82), 206 (70), 163 (28), 149 (100), 117 (54), 90 (43), 45 (30). Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.06; H, 4.54; N, 12.61; Found: C, 54.15; H, 4.42; N, 12.73%.

4.6. Methyl *N*-(*p*-methylphenyl)aziridine-2-carboxylate[4]

$[\alpha]_D^{25}$ −195.5 (*c* 0.25, $CHCl_3$); IR (KBr): 1756 cm^{-1}; ^1H NMR: δ 2.25–2.28 (m, 4H), 2.59 (dd, 1H), 2.71 (dd, 1H), 3.79 (s, 3H), 6.85 (d, 2H), 7.03 (d, 2H); MS: *m*/*z* (%) 191 (M^+, 66), 177 (30), 133 (35), 119 (100), 106 (65), 92 (60). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.15; H, 6.80; N, 7.4%.

4.7. Methyl *N*-(*p*-fluorophenyl)aziridine-2-carboxylate

$[\alpha]_D^{25}$ −18.4 (*c* 1.5, $CHCl_3$); IR (KBr): 1756 cm^{-1}; ^1H NMR: δ 2.24 (d, 1H), 2.62 (s, 1H), 2.76 (dd, 1H), 3.80 (s, 3H), 6.85 (d, 2H), 6.92 (d, 2H). MS: *m*/*z* (%) 196 (M^++1, 100), 180 (12), 136 (30), 122 (15), 83 (14), 69 (14), 55 (28). Anal. Calcd for $C_{10}H_{10}FNO_2$: C, 61.53; H, 5.16; F, 9.73; N, 7.18. Found: C, 61.60; H, 5.11; F, 9.78; N, 7.26%.

4.8. Methyl *N*-(2-bromo-4-methylphenyl)aziridine-2-carboxylate

$[\alpha]_D^{25}$ −15.9 (*c* 0.025, $CHCl_3$); IR (KBr): 1755 cm^{-1}; ^1H NMR: δ 2.24 (s, 3H), 2.38 (dd, 1H), 3.81 (s, 3H), 6.79 (d, 1H), 6.95 (d, 1H), 7.32 (s, 1H); MS: *m*/*z* (%) 269 (M^+, 30), 198 (36), 107 (100), 79 (62). Anal. Calcd for $C_{11}H_{12}BrNO_2$: C, 48.91; H, 4.48; Br, 29.58; N, 5.19. Found: C, 48.83; H, 4.57; Br, 29.68; N, 5.22%.

4.9. Methyl *N*-(*p*-methoxyphenyl)aziridine-2-carboxylate

$[\alpha]_D^{25}$ −184.3 (*c* 0.5, $CHCl_3$); IR (KBr): 1754 cm^{-1}; ^1H NMR: δ 2.23 (d, 1H), 2.59 (s, 1H), 2.69 (dd, 1H), 3.75 (s, 3H), 3.81 (s, 3H), 6.75 (d, 2H), 6.84 (d, 2H); MS: *m*/*z* (%) 207 (M^+, 95), 192 (26), 134 (100), 121 (62), 77 (24). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.68; H, 6.40; N, 6.89%.

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