

ASYMMETRIC SYNTHESIS OF CYCLIC IMINO ACIDS VIA CHIRAL SCHIFF BASES

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Abstract - A new method of synthesis of cyclic imino acids is reported. Diastereoselective alkylation of Schiff bases (derived from α -amino esters and (+) or (-) 2-hydroxypinan-3-one) with dihalogeno compounds, followed by hydrolytic cleavage and cyclisation affords the imino esters. Reactions are highly enantioselective, with one exception corresponding to steric crowding.

Various cyclic α -imino acids such as proline and pipecolic acid are not only important constituents of peptides¹, but are also interesting as chiral educts^{2,3}. Although several methods have been published for the synthesis of such chiral products^{2,4-7}, to our knowledge, no general one has been described.

We here wish to report a new convenient method for the synthesis of optically pure α -imino acids and α -substituted α -imino acids by the reaction sequence outlined in scheme I, the key-step is the diastereoselective alkylation by a dihalogeno compound, of chiral Schiff bases prepared from α -amino esters and (2R,3R,5R) HP(+) or (2S,3S,5S) HP (-) 2-hydroxypinan-3-one^{8,9,10}.

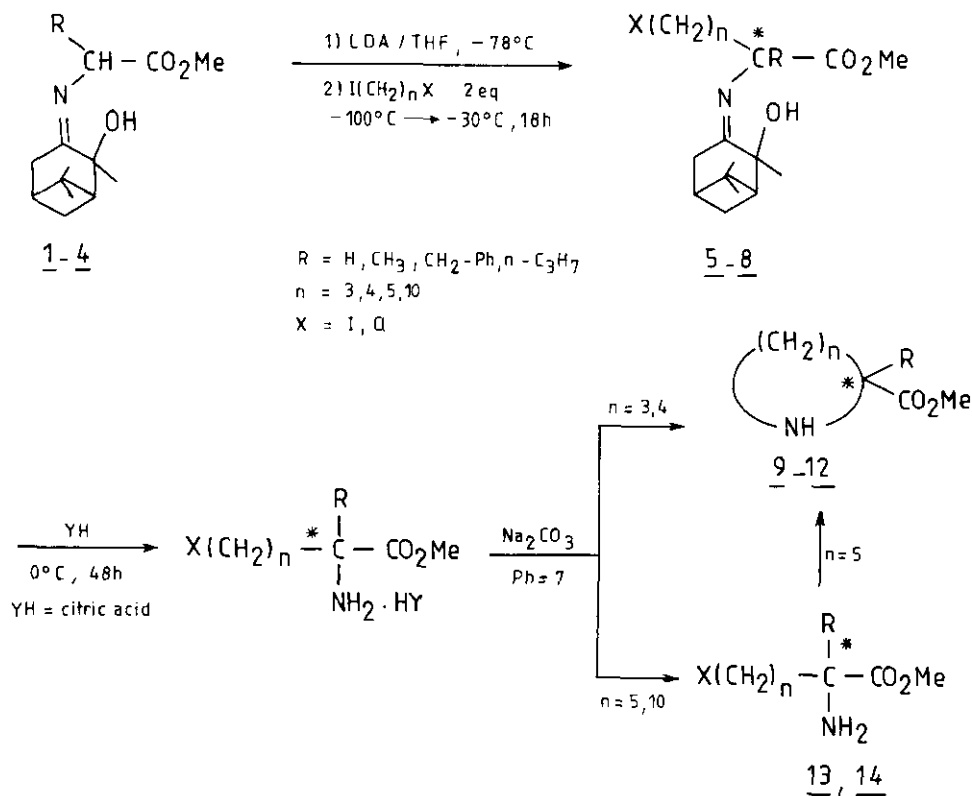


Table I. Synthesis of cyclic imino esters

Schiff base	Alkylating agent		Products			Cyclic imino esters				
	n	X	Prod.	Yield%	$(\alpha)_D^{20} (c)^*$	Prod.	Yield%	$(\alpha)_D^{20} (c)^*$	ee	Conf.
<u>1</u> R=H HP(-)	3	Cl	<u>5a</u>	41	+60.1°(3.4)	<u>9a</u>	55	+38.0°(0.9)	>95	R
	4	I	<u>5b</u>	46	+51.5°(3.5)	<u>9b</u>	79	+13.1°(1.3)	>95	R ⁵
	5	I	<u>5c</u>	51	+45.5°(2.2)					
	10	I	<u>5d</u>	49	+39.4°(1.7)					
<u>2</u> R=CH ₃ HP(+)	3	Cl	<u>6a</u>	56		<u>10a</u>	57	-8.5°(2.6)	>95	S ¹²
	4	I	<u>6b</u>	65	-5.0°(3.4)	<u>10b</u>	78	+8.0°(5.0)	>95	S ⁷
	10	I	<u>6d</u>	75	-5.0°(2.3)					
<u>2'</u> R=CH ₃ HP(-)	5	I	<u>6c</u>	64	+4.1°(2.4)	<u>10c</u>	54	+1.5°(0.8)	>95	R ^x
<u>3</u> R=CH ₂ Ph HP(+)	4	I	<u>7b</u>	51	-4.5°(3.1)	<u>11b</u>	47	+3.0°(4.9)	71	S ^x
<u>4</u> R=C ₃ H ₇ HP(+)	4	I	<u>8b</u>	74	-8.0°(2.2)	<u>12b</u>	80	-0.6°(1.9)	5	S ^x

*Specific rotations were measured in chloroform.

^xPredicted absolute configurations

In general, under nitrogen, to a stirred solution of LDA (2.3mM) in dry THF (20 ml) at -100°C was added the Schiff base (1mM), the mixture was stirred for 30 min. After the addition of the dihalogeno compound the mixture was stirred at -80°C during 5 h and allowed to warm to -30°C. The mixture was poured into a solution of NH₄Cl, the aqueous phase extracted with benzene ; the benzene layer was dried (Na₂SO₄), evaporated and the residue chromatographed over silica gel (ether-hexane 1/4). The purified Schiff base (1mM) was dissolved in THF (7ml) and hydrolysed at 0°C with aqueous citric acid (4 ml) during 48 h. The solvent was evaporated and the aqueous layer extracted with benzene ; the benzene layer containing the ketol was extracted with 15% aqueous citric acid. The combined aqueous layer was basified with sodium carbonate and extracted with diethyl ether. The ethereal extracts were dried (Na₂SO₄) concentrated and the residue purified by column chromatography over silica gel (ether-hexane 4/1). All compounds described here gave ms and ¹H nmr spectra consistent with their structures. The microanalyses were in satisfactory agreement with the calculated values. Optical purities were established by ¹H nmr spectroscopy (0.15-0.2M CCl₄/TMS solution in the presence of 0.2 → 0.6 molar equivalent of d-Eu(hfc)₃).

The results summarized in Table I show that the alkylation occurs with good yields and a very high asymmetric induction for the imines 1 (R=H) and 2 (R=CH₃) ; only a single diastereoisomer is detected by T.L.C or ¹H nmr (200 MHz, solvents : CCl₄, C₆D₆). In contrast with 3 (R=CH₂Ph) and 4 (R=C₃H₇) two diastereoisomers are obtained. The degree of asymmetric induction seems to depend on the size of the substituent R ; the more crowded one gives the lower induction. In order to avoid any racemisation for the glycine derivatives, hydrolysis of Schiff bases was carried out under mild acidic conditions (15% aqueous citric acid at 0°C, pH = 2). Five or six membered cyclic imino esters were easily obtained by neutralisation with sodium carbonate. In contrast, products 5c, 6c, 5d, 6d, after hydrolysis and neutralisation were converted to halogenated amino esters 13c, 14c, 13d, 14d. Cyclisation of 6c required more drastic conditions and was performed in the presence of NaH in THF 12 h at room temperature. Cyclisation failed with long-chain amino esters 13d, 14d which seemed to be very good tensioactives. To determine the absolute configurations, the imino esters were converted to imino acids, some of them were described and configurations assigned^{5,7,12}. As expected in each case alkyl groups entered from the gem-dimethyl side. Thus for the unknown products 10c, 11b, 12b, the configurations can be predicted with a good degree of confidence, they would be respectively R,S,S.

In conclusion the present method has advantages in providing a variety of cyclic α-imino acids in quite high enantiomeric purity.

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11. 13c : Yield = 89%, (α)_D^{20°} = - 13.0° (c = 3.8) ; 13d : Yield = 82% ; 14c : Yield = 81%, (α)_D^{20°} = 9.1° (c = 2.2) ; 14d : Yield = 82%, (α)_D^{20°} = + 4.7° (c = 4.0).
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