Asymmetric Synthesis of β-Lactams

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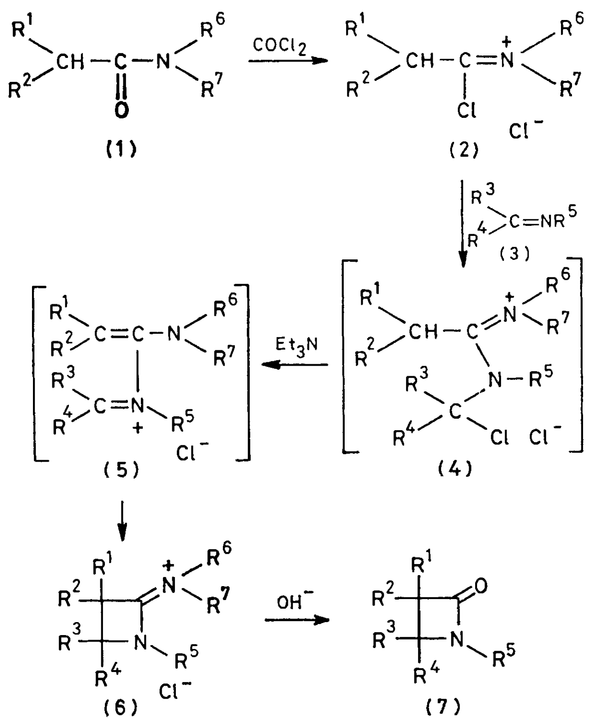
Summary The reaction of α-chloroiminium chlorides with imines in which one of reagents contains a chiral substituent leads diastereoselectively to substituted β-lactams.

From the variety of synthetic methods leading to β-lactam systems only a few have been adopted for asymmetric syntheses.[1–3] The reaction of α-chloroiminium chlorides with imines reported by Ghosez *et al.*[4,5] seemed as if it would be very useful for the diastereoselective synthesis of substituted β-lactams.

The inducing chiral centre may be present in either or both substrates. Thus R^6 in the amide (**1**) can be chiral as well as R^5 in the imine (**3**) (Scheme), and we have examined both possibilities. The reaction of achiral amides (**1**, $R^1 = R^2$) with chiral imines (**3**, R^5 chiral) yielded nonequimolar mixtures of two epimeric β-lactams (**7**) with a new chiral centre at C-4. A similar reaction with the racemic amide (**1**, $R^1 \neq R^2$), which becomes sp^2-prochiral in the intermediate (**5**), however, gave a mixture of the four possible diastereoisomers with new chiral centres at C-3 and C-4.

The second approach, *i.e.* the reaction of chiral amides (**1**, R^6 chiral) with prochiral imines, seemed to be more interesting. The inducing centre can be removed and regenerated easily by hydrolysis of the salt (**6**) yielding a mixture of epimeric ($R^1 \neq R^2$) or enantiomeric ($R^1 = R^2$) β-lactams (**7**). The β-lactams (**7**) were prepared by the procedure in refs. 4 and 5. The appropriate amide (**1**) was treated with an excess of $COCl_2$ giving the salt (**2**), which was treated without separation with 1 mol. equiv. of the imine (**3**) and then Et_3N. Evaporation led to the iminium salt (**6**) which was hydrolysed with 1 M aqueous NaOH and, after extraction, purified by chromatography (SiO_2).



Scheme

The mixtures of diastereoisomers (**7a**—**d**, Table) were separated by h.p.l.c. using three ¾ in × 1 ft columns filled with 10 μ Lichosorb using hexane containing 15—40% of ethyl acetate as eluant, and a refractive index detector.

TABLE. Yields and diastereoisomeric (enantiomeric) ratios for the β-lactams (**7**).

	β-Lactam (**7**)						Diastereoisomeric (enantiomeric) ratio and $[\alpha]_D^{20}$				Total
	R^1	R^2	R^3	R^4	R^5	NR^6R^7	A	B	C	D	% yield
a	H	H	H	Ph	(*S*)-(−)-NCHMePh	NMe_2	1 −28·1°	2·7[a] +28·5°			87
b	Me	Me	H	Ph	,, ,,	NMe_2	2 −95·6°	1[a] +90·6°			85
c	H	Ph	H	Ph	,, ,,	NMe_2	3 +113·0°	1[a] −216·7°	5 —	11 —	64
d	Me	Ph	H	Ph	,, ,,	NMe_2	5 −27·6°	1[a] —	1 —	3 —	92
e	Me	Me	H	Ph	Me	$(+)\text{-}\overline{\mathrm{N[CH_2]_4C}}\mathrm{HEt}$	1 +118·0°	9[b]			60
f	Me	Me	H	Ph	Me	$(+)\text{-NMeCHMeCH}_2\text{Ph}$	1 −67·3°	6[b]			30

[a] A—D are in the order of the R_f value sequence; h.p.l.c. separation and ^1H n.m.r. analysis. [b] Mixtures of enantiomers, the ratio being determined by ^1H n.m.r. spectroscopy with addition of $Eu(tfc)_3$ shift reagent. [α] values are for the mixture of enantiomers.

The ratio of diastereoisomers was also determined by ^1H n.m.r. integration; compound (**7a**) (Table), δ (CCl_4) (isomer A): 1·82 (CH*Me*Ph, d, *J* 7·5 Hz) and 4·17 (C*H*MePh, q, *J* 7·5 Hz); δ (isomer B): 1·35 (CH*Me*Ph, d, *J* 7·5 Hz) and 4·98 (C*H*MePh, q, *J* 7·5 Hz); A : B ratio, 1 : 2·7; compound (**7b**) (Table), δ (CCl_4) (isomer A): 3·97 (4-H, s), 1·9 (CH*Me*Ph, d, *J* 7 Hz), 4·2 (C*H*MePh, q, *J* 7 Hz), and 0·72 and 1·27 (3-Me_2, 2s); δ (isomer B): 3·92 (4-H, s), 1·52 (CH*Me*Ph, d), 4·87 (C*H*MePh, q, *J* 7 Hz) and 0·75 and 1·20 (3-Me_2, 2s); A : B ratio 2 : 1; compound (**7e**) (mixture of enantiomers) δ (CCl_4) 4·33 (4-H, s), 2·90 (NMe, s) and 0·82 and 0·98 (3-Me_2, 2s); the enantiomeric ratio of 1 : 9 was determined from the ^1H n.m.r. spectrum following the addition of $Eu(tfc)_3$ {tris-[3-(2,2,2-trifluoro-1-hydroxyethylidene)-(+)-camphorato]europium}.

For pure compounds the specific optical rotations are given in the Table; for compounds (**7e**) and (**7f**) the rotation is that for the mixture of enantiomers. For compound (**7c**) the *cis* and *trans* configurations for the A,B and C,D diastereoisomers, respectively, was determined on the basis of the coupling constants (2·5 and 0·0 Hz) for 3- and 4-H.

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