Asymmetric Synthesis of Amines from Chiral Nitriles and Racemic Alcohols

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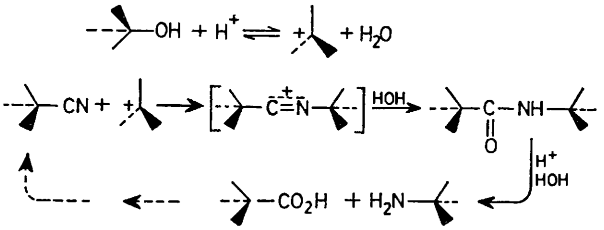
Summary Under the conditions of the Ritter reaction chiral nitriles react with racemic alcohols and give mixtures of diastereoisomeric non-racemic monosubstituted amides; these mixtures were hydrolysed to amines enriched in one of the enantiomers.

The Ritter reaction is a well known indirect method of preparation of amines. During this reaction carbocations generated in a strongly acidic medium react with nitriles and give substituted amides *via* the corresponding nitrilium salts.[1]

Attempts to obtain chiral amines from chiral alcohols and achiral nitriles in the presence of $(Ph_2CCl)SbCl_6$ were successful in the case of octan-2-ol only. The mechanism of this reaction is, however, different from the usually accepted one for the Ritter reaction.[2]

A small degree of retention of configuration has been observed in 1,2 H-shift reactions involving carbocations from chiral substrates.[3] The reaction of a prochiral carbocation with a chiral carbon atom is also known to occur in intramolecular 1,5 H-shift reactions,[4] and the generation of relatively stable chiral carbocations has been observed in the ferrocenyl system.[5]



Scheme

We assumed that the use of chiral nitriles and racemic alcohols in the Ritter reaction could lead to the diastereoselective formation of substituted amides, since the reaction of a prochiral carbocation with a chiral nitrile should result in diastereoisomeric nitrilium salts as intermediates and thus the mixture of amines obtained after hydrolysis should contain an excess of one of the enantiomers (Scheme).

The reactions of the (*S*) nitriles (I)—(III) with the racemic alcohols (IV)—(IX) were investigated as a source of amines enriched in one enantiomer. The $[\alpha]_D$ values for the starting nitriles agreed well with literature values[6–8]

	R^1R^2CHCN				R^3R^4CHOH	
	R^1	R^2	$[\alpha]^{20}_{D}$ (neat)		R^3	R^4
(I)	Ph	MeO	−51·8°	(IV)	Me	Ph
(II)	Ph	Et	−19·8°	(V)	Et	Ph
(III)	Me	MeO	−85·9°	(VI)	Pr^i	Ph
				(VII)	Me	α-Naphthyl
				(VIII)	$PhCH_2$	Ph
				(IX)	Me	Mesityl

The syntheses were carried out by the addition of conc. H_2SO_4 (0·5 ml) to a mixture of the nitrile (5 mmol) and alcohol (5 mmol) in 5 ml of solvent. After the reaction was completed (30 min) the mixture was poured into ice and the crude amide isolated. The latter was hydrolysed completely with 20% HCl (16 h) to give the amine R^3R^4-$CHNH_2$. After distillation, the optical rotation was measured and compared with the literature value, providing the enantiomeric excess (e.e.) % for a given synthesis. In all cases the amine obtained contained an excess of one enantiomer, confirming our foregoing assumption.

The chemical yields of the reaction (including the hydrolysis of the amides) were between 60 and 75%. The enantiomeric excess varied from 1 to 8%. In all cases examined (with one exception, see Table) the use of the (*S*) nitrile led to the formation of an excess of the (*R*)-enantiomer of the amine.

The Table shows the results from the reaction of (*S*)-α-methoxyphenylacetonitrile (I) with the alcohols (IV)—(IX) (C_6H_6, 0 °C, 30 min).

The reaction of an excess of the (*S*)-alcohol (IV) with the racemic nitrile (I) (Et_2O, 20 °C, 30 min) gives a racemic mixture of amides Ph(MeO)CHCONHCH(Me)Ph. This result confirmed the generation of a prochiral carbocation. The possibility of thermodynamic control of the process, in this case equilibration of the diastereomeric amides under the reaction conditions, was also investigated, by studying the reaction of the chiral amide Ph-CH(MeO)$CONHCH_2$Ph, prepared from chiral (*S*)-α-methoxyphenylacetyl chloride and optically pure (*S*)-(−)-α-methylbenzylamine, with the racemic alcohol (IV) under standard conditions. The product was the starting amide with unchanged optical purity.

TABLE. Reactions of the racemic alcohols (IV)—(VIII) with the (*S*) nitrile (I) giving the amines $R^3R^4CHNH_2$

Starting alcohol	$[\alpha]^{20}_{D}$ (found)	Configuration of amine	% e.e.
(IV)	+0·69[a]	*R*	1·7
(V)	+0·15[b]	*R*	0·7
(VI	+0·06[c]	*R*	0·5
(VII)	+3·63[d]	*R*	4·5
(VIII)	+0·16[e]	*S*	0·4
(IX)	+3·37[f]	*R*	7·0

Literature values: [a] $[\alpha]^{23}_{D}$ +40·7° (neat) (W. Leithe, *Monatsh.*, 1929, **51**, 381). [b] $[\alpha]^{24}_{D}$ 21·2° (neat) (H. E. Smith, S. L. Cook, and M. E. Waren, *J. Org. Chem.*, 1964, **29**, 2265). [c] $[\alpha]^{20}_{D}$ +0·5° (neat) (O. Cervinka and V. Dedek, *Coll. Czech. Chem. Comm.*, 1920, **35**, 724). [d] $[\alpha]^{25}_{D}$ +80·8° (neat) (E. Samuelsson, Thesis, University of Lund, 1923: *Chem. Abs.*, 1924, **18**, 1833). [e] $[\alpha]^{15}_{D}$ −35·6° (D. Leithe, *Ber.*, 1932, **65**, 660). [f] α^{20}_{D} +47·5° (neat, 1 dm) (H. Pracejus and H. Ripperger, *Z. Chem.*, 1968, **8**, 268).

An increase in the reaction time (up to 24 h) caused a decrease in the chemical yield and a change in the composition of the diastereomeric amides. This effect could be due to preferential decomposition of one of the diastereomers, since it was found experimentally that, under certain conditions, the diastereomer which is formed in lowest yield is preferentially decomposed.

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