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SYNTHETIC CONTROL BASED ON CHIRAL 2-HALOPYRIDINIUM SALTS II. THE KINETIC RESOLUTION OF RACEMIC AMINES

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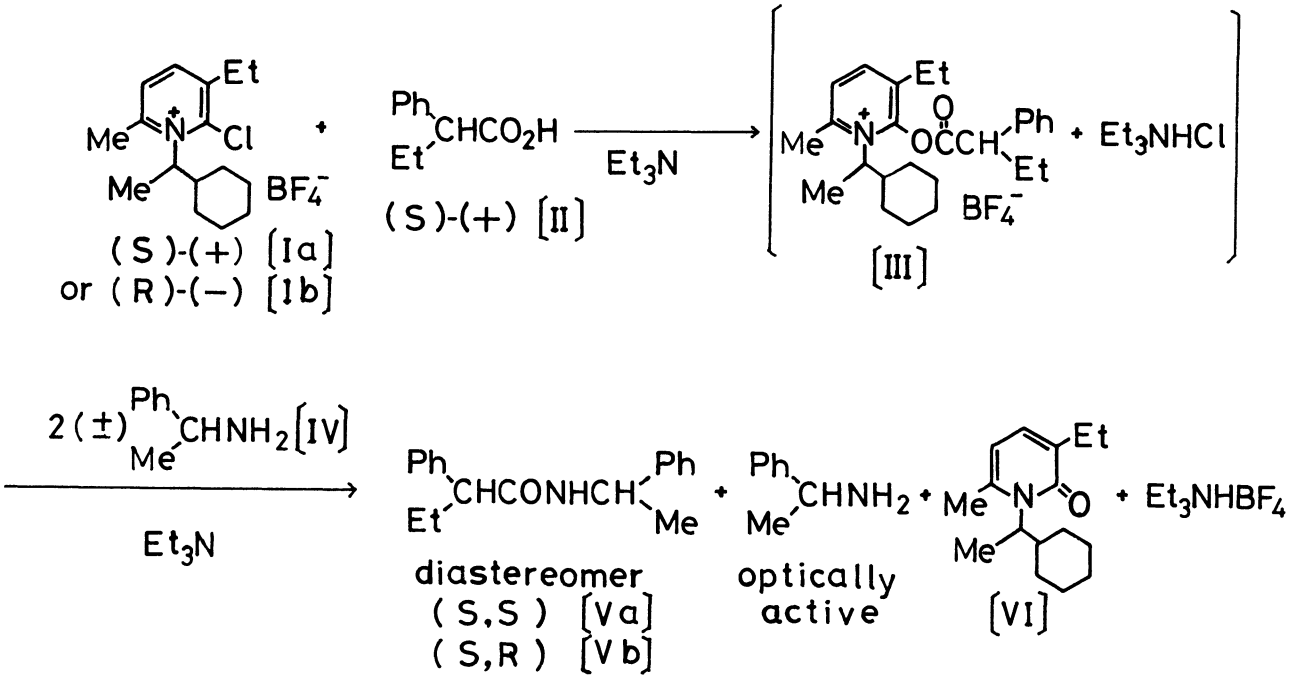
Various racemic amines are kinetically resolved by use of (S)-(+)-2-chloro-1-(1-cyclohexylethyl)-3-ethyl-6-methylpyridinium tetrafluoroborate (I) and (S)-(+)-2-phenylbutanoic acid (II).

In the previous paper,[1] we described a new method for the preparation of chiral 2-halopyridinium salts. In the present communication, we wish to report the kinetic resolution of racemic amines using a chiral 2-chloropyridinium salt and a chiral carboxylic acid.

There have so far been reported several methods for the kinetic resolution of racemic amines, which include the reaction of ethyl hydrogencarbonic chiral carboxylic anhydrides with racemic amines,[2] the reaction of chiral carboxylic anhydrides with racemic amines,[3] and the reaction of chiral carboxylic acids with racemic amines using dicyclohexylcarbodiimide as a coupling reagent.[4] In these reactions, the chiral recognition with respect to racemic amines is only due to the asymmetry of the carboxylic acid derivatives, so that the enantiomeric purity of the resolved amine is considerably low. In order to resolve racemic amines kinetically in better enantiomeric purity, the kinetic resolution using a chiral coupling reagent as well as a chiral carboxylic acid was tried. The present method is represented by the following procedure for the kinetic resolution of racemic 1-phenylethylamine. To a stirred mixture of (±)-1-phenylethylamine [IV] (1 mmol) and triethylamine (1 mmol) in CH_2Cl_2 (1.5 ml), was added a mixture of (S)-(+)-2-chloro-1-(1-cyclohexylethyl)-3-ethyl-6-methylpyridinium tetrafluoroborate [Ia] (0.5 mmol) and (S)-(+)-2-phenylbutanoic acid [II] (0.5 mmol) in CH_2Cl_2 (2 ml) over 10 min at room temperature under an argon atmosphere, and the reaction mixture was

stirred for 15 h. After the reaction was quenched with 5% hydrochloric acid, the excess 1-phenylethylamine was recovered from the aqueous layer and found to be in 17% enantiomeric excess and enriched in the R configuration. N-1-Phenylethylbutanamide [V] was isolated from the organic layer, purified by thin layer chromatography on silica gel and found to possess $[\alpha]_{546}^{24}$ + 18.0° (c=1.04, MeOH). This value corresponded to 23% diastereomeric excess enriched in the (S,S) configuration.[5] On the other hand, the use of (R)-(-)-2-chloropyridinium salt [1b] gave the amide in 14% diastereomeric exess enriched in the (S,R) configuration[5] under the same reaction conditions. It should be pointed that both the (S,S) amide and the (S,R) amide were obtained in nearly equal amounts when an achiral pyridinium salt, i.e., 2-chloro-1-ethyl-3-methylpyridinium tetrafluoroborate was employed as a coupling reagent.

The results of these experiments showed that two enantiomeric amines were distinguished by the chiral intermediate, 2-acyloxypyridinium salt [III], formed by the reaction of a chiral pyridinium salt [I] with a chiral carboxylic acid [II], and that the chiral recognition was mainly dependent on the asymmetry of the pyridinium salt rather than that of the carboxylic acid.



Further, it was found that the present kinetic resolution was almost independent of the solvents as shown in Table 1. However, the racemization of the chiral carboxylic acid occurred when CH_3CN, DMF, or 3-ethyl-3-pentanol was used as a solvent.

In the case where the kinetic resolutions were run using a ten or fiftyfold excess of the amine, the diastereomeric excess of the amide was expectedly higher than those observed when a twofold excess of the amine was employed. This is simply because the concentration of (S)- and (R)-1-phenylethylamines remains essentially constant throughout the course of the reaction when the amines are present in large excess.

Table I. The Formation of Diastereomeric N-1-Phenylethylbutanamide

Pyridinium Salt	Solvent	Temp.	Amide Synthetic Yield (%)	Diastereomeric Excess (%)
(S)-(+)	CH_2Cl_2	r.t.	84	(S,S) 23
(S)-(+)	CH_2Cl_2	r.t.	76*	(S,S) 45
(S)-(+)	CH_2Cl_2	r.t.	79**	(S,S) 47
(R)-(-)	CH_2Cl_2	r.t.	82	(S,R) 14
(R)-(-)	CH_2Cl_2	r.t.	81*	(S,R) 28
(S)-(+)	CH_2Cl_2	0°C	60	(S,S) 31
(S)-(+)	$CHCl_3$	r.t.	85	(S,S) 24
(S)-(+)	$CHCl_3$	0°C	74	(S,S) 35
(S)-(+)	C_6H_6	r.t.	82	(S,S) 19
(S)-(+)	$C_6H_5NO_2$	r.t.	76	(S,S) 19
(S)-(+)	$C_6H_5OCH_3$	r.t.	82	(S,S) 22
(S)-(+)	C_5H_5N	r.t.	89	(S,S) 15

* A tenfold excess of 1-phenylethylamine was employed.
**A fiftyfold excess of 1-phenylethylamine was employed.

Various racemic amines were resolved by the chiral pyridinium salt [Ia] and (S)-(+)-2-phenylbutanoic acid [II] in CH_2Cl_2 at room temperature as shown in Table II.

Table II. The Kinetic Resolution of Racemic Amines

Racemic Amine	Yield (%) of Amide	Enantiomeric Excess (%) of Recovered Amine
1-phenylethylamine	84	17[a]
1-(1-naphthyl)ethylamine	73	37[b]
1-(2-naphthyl)ethylamine	71	30[c]
ethyl 2-amino-2-phenylacetate	86	6[d]

a) Based on $[\alpha]_D^{26}$ + 26.6° (c=0.79, MeOH). b) Based on $[\alpha]_D^{19}$ + 61.6° (c=2.22, EtOH), E. Samuelsson, Chem. Abstr., 18, 1833 (1924). c) Based on $[\alpha]_D^{19}$ + 19.4° (c=1.86, EtOH), E. Samuelsson, Chem. Abstr., 18, 1833 (1924). d) Based on $[\alpha]_D^{20}$ - 21.40° (c=5.652, MeOH), H. Helinger, H. Kleimann, and I. Ugi, Justus Liebigs Ann. Chem., 706, 37 (1967).

It is noted that the chiral substituent of the pyridinium salt plays an important role in the present kinetic resolution of racemic amines.

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References and Note

1) M. Shiono, T. Shibanuma, and T. Mukaiyama, Chem. Lett., 1041 (1976).

2) H. Helinger, H. Kleimann, and I. Ugi, Justus Liebigs Ann. Chem., 706, 37 (1967).

3) R. Weidmann and A. Horeau, Bull. Soc. Chim. Fr., 1976, 117.

4) O. Červinka, E. Kroupova, and O. Belousky, Collect. Czech. Chem. Commun., 33, 3551 (1968); O. Červinka and J. Fusek, ibid., 38, 441 (1973).

5) (S,S) amide and (S,R) amide were prepared according to the method given in the above literature 2).

(S,S) amide : $[\alpha]_{546}^{24}$ - 54.5° (c=1.05, MeOH)

(S,R) amide : $[\alpha]_{546}^{24}$ + 134.2° (c=1.07, MeOH)

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