Pergamon

Tetrahedron Letters, Vol. 37, No. 8, pp. 1301-1304, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02379-8

A New Dynamic Resolution Strategy for Asymmetric Synthesis

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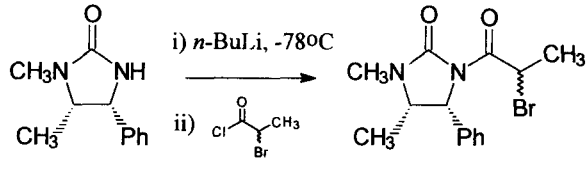
Abstract: Two different and complementary auxiliary based dynamic resolution processes have been developed; the use of crystallisation induced dynamic resolution and/or dynamic kinetic resolution enables the preparation of either enantiomeric product using a single chiral auxiliary as illustrated in the preparation of D or L-alanine derivatives.

In recent years there has been a resurgence in interest in the concept of dynamic kinetic resolution (DKR)[1] in which a chirally labile substrate undergoes asymmetric transformation to form a chirally stable product in optical and chemical yield of greater than 50%. The efficiency of the process is dependent upon the relative rates of equilibration of the substrate and of the transformation of each isomer to give products. There is some aesthetic as well as practical appeal in utilising a strategy which will transform a racemate into an optically enriched product and some impressive examples have been reported.[2]

In this paper we present a new auxiliary based strategy for the preparation of enantiomerically enriched compounds using a single antipodal chiral auxiliary. The success of the approach is a consequence of the use of a novel crystallisation induced dynamic resolution (CIDR) in conjunction with a new but more conventional dynamic kinetic resolution (DKR) process.

(4*R*,5*S*)-1,5-Dimethyl-4-phenylimidazolidin-2-one **1** provided the stable chiral frame for the substrate. This chiral auxiliary is readily synthesised in one step from the thermal fusion of (-)-ephedrine hydrochloride and urea.[3] The α-bromopropionyl imide **2** was furnished as an epimeric mixture by treatment of the N-*lithio* anion of **1** with 2-(*RS*)-bromopropionyl chloride (scheme 1).

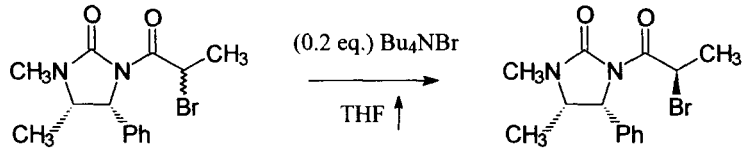


1 2'*RS*-**2**, 76% Yield

Scheme 1

Treatment of the individual diastereomers of **2** with tetra-*n*-butylammonium bromide (0.2 eq.) in d_8-THF resulted in epimerisation to a (44:56) ratio of 2'*S*-**2**/2'*R*-**2** diastereomers.[4] When an equimolar mixture of 2'*S*-**2**/2'*R*-**2** diastereomers was subjected to the equilibrating conditions and the solvent allowed to evaporate over 24 hours, the 2'*R*-**2** diastereomer was isolated as the sole product in excellent yield (scheme 2). The tetra-

n-butylammonium bromide was removed by aqueous extraction and the enantiopure 2'*R*-**2**[5] could be further purified either by column chromatography or by recrystallisation.



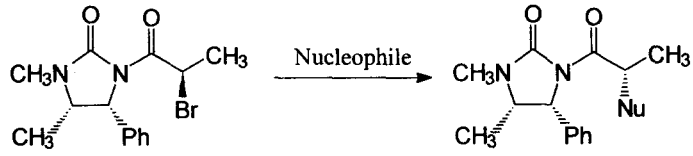
2'*RS*-**2** 2'*R*-**2**

91% Yield, >98% d.e.

Scheme 2

This is an example of a crystallisation-induced asymmetric disequilibration, a relatively uncommon process which constitutes an asymmetric transformation of the second kind. Interestingly the diastereomer which crystallises out of solution first is the one which predominates in solution; this is contrary to the van't Hoff-Dimroth rule.[6]

Epimerisation is not spontaneous at room temperature and both diastereomers of **2** appear to be stable in a range of solvents.[7] The lability at C-2' can be readily induced using a suitable halide source and we assume that this proceeds by simple S_N2 displacement but have not ruled out alternative mechanisms. The preparation of 2'*R*-**2** is only of synthetic value if it can be transformed into other useful enantiomerically enriched materials. Since the C-2' stereocentre is not spontaneously labile it is possible for 2'*R*-**2** to undergo nucleophilic substitution with good to excellent stereoselectivity providing that the reagents used are not too basic and that the generation of solubilised 'bromide' by-products is kept to a minimum. The results of some nucleophilic substitution reactions are summarised in Table 1.



2'*R*-**2** **3-5**

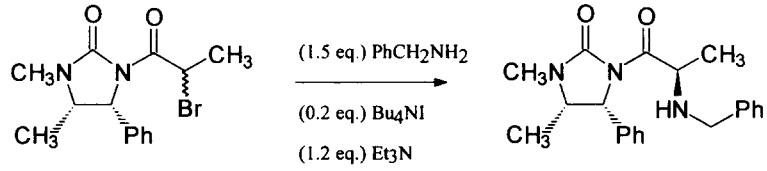
Entry	Nucleophile	Solvent	Product	Nu	Yield %	d.e. %[a]
1[b]	Sodium Azide	THF	**3**	N_3	trace[c]	-
2[d]	Sodium Azide	MeCN	**3**	N_3	90[e]	54
3[f]	Benzylamine	THF	**4**[g]	$PhCH_2NH$	86[e]	83
4[f]	Pyrrolidine	THF	**5**	*c*-$(CH_2)_4N$	96[e]	>98[h]

All reactions carried out at 30°C using 3.0 equiv. nucleophile over 28 hrs (2 & 4) or 5 days (1 & 3). [a] Determined by ^{1}H nmr. [b] 0.15M with respect to SM. [c] Recovered SM with epimerisation (15%) and azide **3** (10-15%). [d] 0.5M with respect to SM. [e] Isolated yield. [f] 0.3M with respect to SM. [g] Stereochemistry of major diastereomer assigned as 2'*S* [8]. [h] Only one diastereomer by ^{1}H nmr.

Table 1

As with most dynamic resolution strategies this approach provides access to only one of the two enantiomeric forms of the desired product. Whilst both enantiomers of the imidazolidinone **1** are available, we thought that the prospect of being able to access either enantiomeric series of the desired product from one enantiomeric form of the chiral auxiliary may be of some value. From our observations[9] we reasoned that 2'*R*-**2** appeared to be thermodynamically more stable (and hence less reactive) than 2'*S*-**2** and therefore a more conventional DKR may enable us to prepare the enantiomeric compounds.

We have been most encouraged by our initial results which support such a proposal. Thus treatment of a (1:1) diastereomeric mixture of **2** with catalytic tetra-*n*-butylammonium iodide[10] (0.2 eq.) and benzylamine (1.5 eq.) in the presence of triethylamine (1.2 eq.) gave the benzyl protected alanine derivative **4** in quantitative yield with a d.r. 87:13 (scheme 3). The sense of chirality at the C-2' stereocentre in the major product is opposite to that of the analogous product derived from the CIDR approach (table 1, entry 3).



2'*RS*-**2**

2'*R*-**4** major product
74% d.e.

Scheme 3

We have shown that by using CIDR in conjunction with DKR we are able to prepare both chiral antipodes of some alanine derivatives using one enantiomeric form of the imidazolidinone chiral auxiliary. The ability of sulfur, oxygen and carbon nucleophiles to undergo nucleophilic displacements under conventional DKR conditions has previously been shown[2a,b,d] and would clearly extend the utility of this methodology. Perhaps more exciting is the prospect of identifying other substrates which may undergo both CIDR and DKR. We are currently exploring a number of these possibilities as we believe that CIDR in its own right and certainly in conjunction with DKR may become a powerful new approach for asymmetric synthesis.

ACKNOWLEDGEMENTS

We thank the University of Sussex for provision of a studentship (K.J.). We also thank Glaxo-Wellcome, Zeneca (Strategic Research Fund), Rhone-Poulenc Rorer for continuing generous financial support of our programme. We gratefully acknowledge the contributions of Dr A.G. Avent, Dr P.B Hitchcock, Dr A.K. Abdul-Sada and C. Dadswell and the EPSRC Mass Spectrometry Service at Swansea.

REFERENCES AND NOTES

All new compounds reported in this communication exhibit satisfactory spectroscopic data.

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4. Epimerisation of **2** was followed using ^{1}H nmr spectroscopy by integration of the methine doublets (δ 5.30, δ 5.35). The 2'*S*-**2** diastereomer epimerised more rapidly than the 2'*R*-**2** diastereomer ($t_{1/2} \approx 1$ hour and 2.5 hours respectively); an equilibrium mixture with 12(±2)% d.e. in favour of 2'*R*-**2** was obtained within 24 hours in d_8-THF at room temperature.
5. The absolute stereochemistry of the 2'*S*-**2** diastereomer was confirmed by X-ray crystallography.
6. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley-Interscience, 1993; pp. 297-464; Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; Wiley-Interscience, 1981; pp. 369-378; Harris. M. M. *Progr. Stereochem.* **1958**, *2*, 157-195 and references therein.
7. TLC analysis of a range of solvents containing the individual diastereomers of **2** indicated that no significant epimerisation occurred after one week in any of the following solvents: petrol, diethyl ether, ethyl acetate, dichloromethane, methanol, acetonitrile.
8. The major diastereomer of **4** was found to have the 2'*S* absolute stereochemistry. Treatment of **4** with NaOMe gave methyl N-benzylalinate with an optical rotation $[\alpha]^{25}_D$ -37.2 (*c* 0.71, MeOH). This is consistent with that for methyl N-benzyl-(*S*)-alinate reported by L. Szilagyi and Z. Gyorgydeak, *J.Am.Chem.Soc.*, **1979**, *101*, 427; $[\alpha]^{21}_D$ -41.0. (See also Ref. 2(c) for the *R* enantiomer.)
9. The slower rate of epimerisation of 2'*R*-**2** and the fact that this diastereomer predominates at equilibrium indicates that it is thermodynamically more stable. We have also made the qualitative observation that 2'*S*-**2** generally reacts faster than 2'*R*-**2** in alkylation reactions using the individual diastereomers of **2**.
10. When *n*-Bu_4NBr was used to induce epimerisation under otherwise identical reaction conditions the resulting stereoselectivity was modest (d.e. 36%). Since the rate of epimerisation of diastereomers **2** with *n*-Bu_4NI and *n*-Bu_4NBr appears to be comparable we suspect that the enhanced selectivity is achieved by the relative reactivities of iodo derivatives of 2'*R*-**2** and 2'*S*-**2** generated *in-situ*; though this is still to be confirmed.

(*Received in UK* 22 *November* 1995; *revised* 13 *December* 1995; *accepted* 15 *December* 1995)