Pergamon

Tetrahedron Letters, Vol. 38, No. 47, pp. 8283-8286, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10168-X

Factors Affecting the [3,2]-Sigmatropic Rearrangements of Didehydropiperidinium Ylids

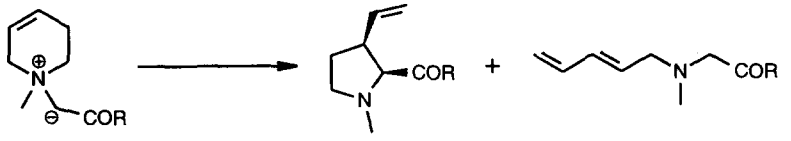
David J. Hyett, J.B. Sweeney,* Ali Tavassoli
Department of Chemistry, University of Reading, Whiteknights, Reading, RG6 6AD, UK.

and

Jerome F. Hayes
SmithKline Beecham Pharmaceuticals, Old Powder Mills, Leigh, Tonbridge, TN11 9AN, UK.

Abstract : The [3,2] sigmatropic rearrangements of cyclic ammonium ylides have been studied with a view to optimizing rearrangement at the expense of elimination

The [3,2]-sigmatropic rearrangements of unsaturated ammonium ylids are known to be valuable synthetic transformations.[1] For instance, it is known that such rearrangement of *N*-acylmethyl-*N*-methyl-1,2,3,6-tetrahydropyridine ylids (**1**) proceeds with high stereoselectivity to furnish *cis* disubstituted pyrrolidines (**3**),[2] whilst the reaction under the same conditions of analogous *N*-(ethoxycarbonyl)methyl-*N*-methyl ylids (**2**) furnishes only the product (**4**) of elimination (scheme 1).[3]



(**1**, R=Ph)
(**2**, R=OEt)

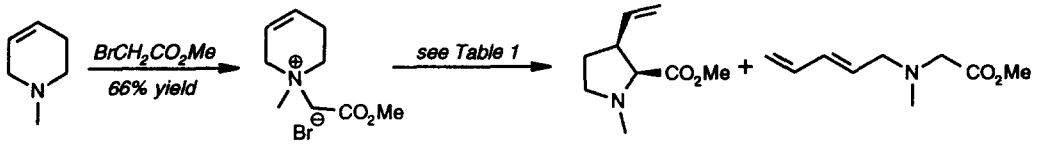
(**3**)
only product
(R=Ph)

(**4**)
only product
(R=OEt)

Scheme 1

Given our interest in the synthesis of kainic acid analogues, an area of much interest of late,[4] we were keen to reinvestigate the latter reaction, which would be a powerful synthetic tool if it could be biased towards formation of rearranged product rather than elimination product. We report here the preliminary results of our studies into the factors responsible for this retardation of sigmatropic rearrangement of these alkoxycarbonyl ylids and confirm that, under appropriate conditions, [3,2]-rearrangement of ylids such as (**2**) is a viable synthetic process.

Methyl ester (**5**) was easily prepared formed by the reaction of *N*-methyl-3,4-didehydropiperidine and methyl bromoacetate. Reaction of this ylid at room temperature with a variety of bases in different solvents was unproductive, in that only starting materials were isolated. Only when the reaction was performed using methanolic sodium methoxide did a reaction occur: under these conditions, no rearranged product (**6**) was isolated but diene (**7**) was obtained in 63% yield, confirming previous observations[3] (scheme 2 and table 1).



(**5**) (**6**) (**7**)

Scheme 2

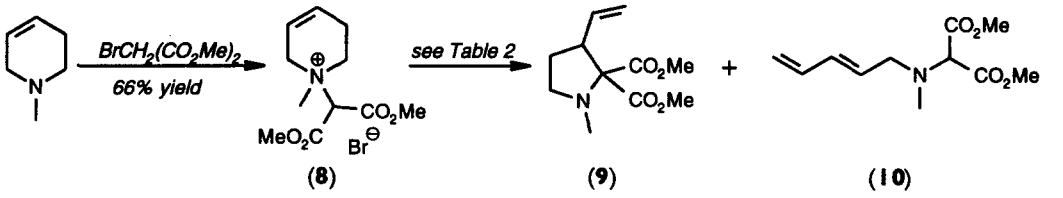
When the reaction was performed in THF, using LDA as base, however, a small amount of rearranged product (**6**) *was* isolated. This pyrrolidine was obtained as a single diastereoisomer whose relative stereochemistry was assigned as *cis*- on the basis of the ^{3}J coupling constant seen for the C2 and C3 protons (^{3}J=8.79Hz) which compares well with that observed for other *cis*-2,3-disubstituted pyrrolidines.[5] Similar yields of pyrrolidine (**6**) and diene (**7**) were obtained using a stronger base, ^{n}BuLi, but use of sodium hydride as base significantly improved the yield of rearrangement and replacement of THF by DME afforded the best yield (58%) so far obtained in our labs. for the rearrangement reaction (table 1).

Solvent	Base	Reaction Temperature	Yield (**6**)/%	Yield (**7**)/%
THF	NaH	ambient	No Reaction	
THF	DBU	ambient	No Reaction	
MeOH	DBU	ambient	No Reaction	
THF	NaOMe	ambient	No Reaction	
MeOH	NaOMe	ambient	0	63
THF	LDA	Reflux	20	8*
THF	^{n}BuLi	Reflux	21	7*
THF	NaH	Reflux	50	8
DME	NaH	Reflux	58	5

*remainder unreacted starting material

Table 1

Having demonstrated the viability of the [3,2]-rearrangement reaction, we turned our attention next to studying the influence of anion stability upon the transformation. To this end, we prepared *N*-methyl-*N*-di(methoxycarbonyl)methyl-3,4-didehydropiperidinium bromide (**8**), reasoning that the greater stability of its negative charge would stabilze the ylid, thereby compensating for the slowness of rearrangement reaction, encouraging formation of rearrangement product (**9**) and leading to lesser amounts of elimination product (**10**).



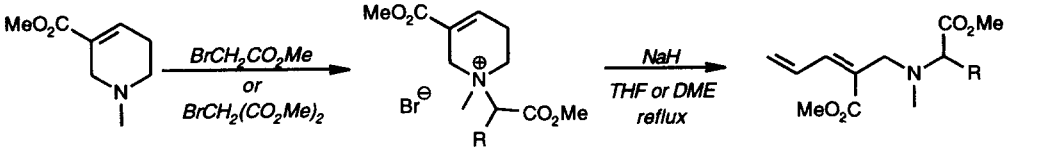
Scheme 3

This prediction was realized in practice using a variety of bases (scheme 3 and table 2). In this rearrangement, best yields were obtained using DBU as base and comparable results were obtained using DME or THF as solvent.

Solvent	Base	Reaction Temperature	Yield (**9**)/%	Yield (**10**)/%
THF	NaH	Reflux	30	0
THF	NaH	Reflux	20	0
THF	BuLi	Reflux	46	0
THF	DBU	Reflux	58	0
THF	DBU	Reflux	56	0
THF	NaH	Reflux	27	7
THF	DBU	Reflux	73	0
DME	NaH	Reflux	57	0
DME	DBU	Reflux	79	0

Table 2

When the reactivity of the alkenic portion of the rearrangement substrate was altered from electron-neutral to electron-deficient in an attempt to enhance the rate of nucleophilic attack upon the alkene in the rearrangement, elimination was instead enhanced (scheme 4). Thus, when the *N*-methyl-*N*-(carboxymethyl)methyl ammonium salt (**11**) (derived from commercially-available arecoline) was treated with sodium hydride in DME or THF, only diene (**12**) was isolated from the reaction (scheme 4). When the corresponding malonyl analogue (**13**) was reacted, a similar yield of diene (**14**) was obtained, indicating that the presence of an electron-withdrawing substituent on the double bond had increased the acidity of the C4 protons to the extent that even the enhanced stability of the ylid derived from (**13**) could not compensate for the rapidity of elimination.

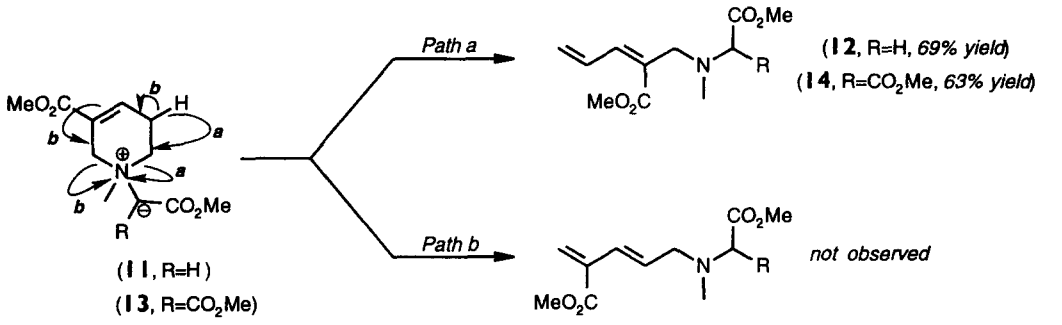


(**11**, R=H)
(**13**, R=CO_2Me)

(**12**, R=H, *69% yield*)
(**14**, R=CO_2Me, *63% yield*)

Scheme 4

These reactions show that E_2-like elimination is in operation, rather than an E_2'-like process (path a in scheme 5).



Scheme 5

Thus, our studies have revealed certain factors affecting the balance between rearrangement and elimination processes during the reaction of didehydropiperidinium salts with a variety of bases. Further delineation of the controlling features of these transformations is currently underway in our laboratories.

Acknowledgements

We thank the EPSRC and SmithKline Beecham Pharmaceuticals (Industrial CASE award to A.T.), the Nuffield Foundation and ZENECA (award from Strategic Research Fund to J.B.S.) for support. We also thank Mr. R. Paisley for his past achievements.

References

1. Baldwin, J.E.; Hackler, R.E.; Kelly, D.P.; *J. Amer. Chem. Soc.*, **1968**, *90*, 4758; *idem*, *J. Chem. Soc., Chem. Commun.*, **1968**, 537, 538.
2. Mageswaran, S.; Ollis, W.D.; Sutherland, I.O.; *J. Chem. Soc. Perkin. Trans. 1*, **1981**, 1953; Mageswaran, S.; Ollis , W.D; Sutherland, I.O.; *J. Chem. Soc. Chem. Comm.*, **1973**, 656.
3. Burns, B.; Coates, B.; Neeson, S.; Stevenson, P.J.; *Tetrahedron Lett.*, **1990**, *31*, 4351; Neeson, S.J.; Stevenson, P.J.; *Tetrahedron Lett.*, **1988**, *29*, 3993.
4. See, for instance, Sasaki, N.A.; Dockner, M.; Chiaroni, A.; Riche, C.; Potier, P.; *J. Org. Chem.*, **1997**, *62*, 765; Maeda, H.; Kraus, G.A.; *J. Org. Chem.*, **1997**, *62*, 2314, and references therein.
5. Carpes, M.J; Miranda, P.C.; Correia, C.R.; *Tetrahedron Lett.*, **1997**, *38*, 1869.

(*Received in UK* 3 *September* 1997; *revised* 15 *September* 1997; *accepted* 19 *September* 1997)