Tetrahedron Letters,Vol.26,No.26,pp 3107-3110,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

A CONVENIENT PREPARATION OF β-AMINO ALCOHOLS FROM EPOXIDES AND HALOMAGNESIUM ALKYLAMIDES

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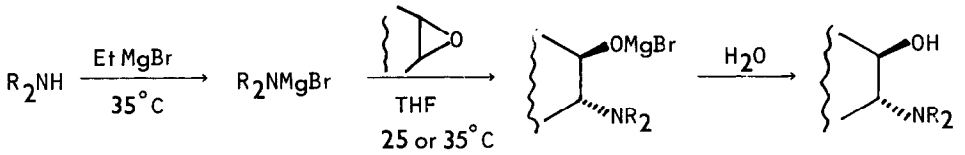
Summary : *Treatment of epoxides with halomagnesium alkylamides in THF affords the corresponding β-amino alcohols in good yields.*

The β-amino alcohol sequence plays a very important part in organic as well as in Medicinal Chemistry.[1] The simplest classical method for preparing β-amino alcohols consists in heating an epoxide with an amine.[2] This preparation is somewhat limited with poorly nucleophilic amines.[2,3] Moreover, drastic conditions being often involved,[2,4] further limitations are encountered with sensitive epoxides. Current studies in our laboratory require the preparation of polycyclic β-amino alcohols of which some examples will be given further on. In numerous cases, we found the classical epoxide aminolysis completely useless. Among the other methods developed in order to promote the reaction of amines with epoxides[5] we were particularly attracted by the results obtained by Overman and Flippin who efficiently used diethylaluminium amides.[6] The only drawback, especially when large scale preparations are needed, lies in using Et_3Al. It might be thought that amino-magnesium derivatives, easily prepared from the corresponding amine and ethyl magnesium bromide, could be advantageously used in place of aluminium amides. Indeed amino-magnesium derivatives are generally considered as strong bases. However it might be expected that the somewhat covalent character of the nitrogen-magnesium bond could be sufficient to confer to magnesium amides efficient nucleophilic reactivity towards epoxides.

This hypothesis was completely verified and we report in the present letter that halomagnesium alkylamides react with epoxides under mild conditions to give, after hydrolysis β-amino alcohols in good yields.



The results obtained from the reaction of representative magnesium amides and epoxides are gathered in the Table.

It is apparent, from the given data, that this simple method is very satisfying. The advantage of these condensations over classical procedures is illustrated by the preparation of 5 and 6 which cannot be obtained by simple condensation of the corresponding amines on the polycyclic epoxides.

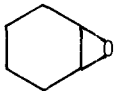
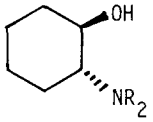
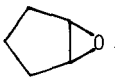
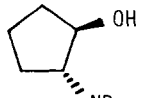
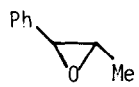
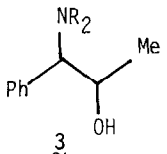
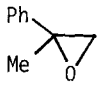
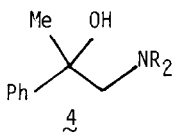
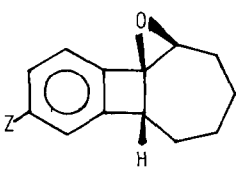
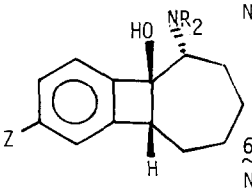
If a too large amount of $MgBr_2$ is present in the reaction medium, large quantities of bromohydrins are formed. Under usual conditions, this by-product is formed in yields varying from 8 to 20 %.

General procedure and identification

The reactions were conducted on a 20 mmol scale. A solution of amine (1.2 equiv.) in 5 ml of THF was added dropwise to a stirred 1.1-1.2 M solution of ethylmagnesium bromide (1.2 equiv.) previously prepared in THF and the reaction mixture maintained at 35°C for 1 h. The epoxide (1 equiv.) in 5 ml of THF was then added to the stirred solution of magnesium amide at room temperature. The reaction mixture was stirred at the temperature and for the time indicated in the Table (disappearance of epoxide was monitored by G.L.C. or T.L.C.). The cooled mixture was poured into a saturated NH_4Cl solution. The aqueous solution was then acidified with cold 2N HCl solution and extracted twice with ether. The aqueous layer was then made alkaline by addition of cold 10 % NaOH solution and extracted with ether. The organic phase was dried over $MgSO_4$ and the solvent removed under vacuum. The crude amino alcohol was purified by recrystallisation on chromatography.

Amino alcohols 1b, 1c, 2b were identified by comparison of their melting points and ^1H NMR spectra with literature data.[6,7] ^1H NMR spectra of 1d, 3a-c and 4 are identical to the ones given in the literature.[5a,7a,8] Melting points of 1e and 2c are identical to the ones given in the literature.[6,9] Moreover their ^1H NMR spectra as well as the spectra of 1a and 2a are in agreement with the spectra of the amino alcohols described above. Finally, 5 and 6 were identified by their combustion analysis and UV, ^1H, ^{13}C NMR spectra.

TABLE : Amino alcohols from epoxides and halomagnesium alkylamides in THF

Epoxide	Amino alcohol	(Reaction temperature °C ; time, h)			mp, °C	Yield[b], %
	 1	NR_2 = $NHPr^i$	a	(25 ; 1.50)	50	82
		$NHBu^t$	b	(25 ; 1)	48-50	73
		NHPh	c	(25 ; 1.50)	60-62	70
		NEt_2	d	(25 ; 0.75)	-	81
			e	(25 ; 1)	48	87
	 2	NR_2 = $NHPr^i$	a	(35^a ; 5)	39-41	70
		NHPh	b	(35^a ; 5)	57-58	73
		NEt_2	c	(35^a ; 2)	29-31	67
	 3	NR_2 = $NHPr^i$	a	(35^a ; 2)		82
		$NHBu^t$	b	(35^a ; 2)		85
		NEt_2	c	(35^a ; 1)		73
	 4	NR_2 = $NHBu^t$		(35^a ; 3.75)		65
		5 Z = H				
		NR_2 = NEt_2	a	(35^a ; 1.50)	65	68
			b	(35^a ; 2)	127	65
		6 Z = F				
		NR_2 = $NHPr^i$	a	(35^a ; 6)		72
		$NHBu^t$	b	(35^a ; 4)		65

a) *Epoxide was added at 25°C.*

b) *Yield of isolated material, purity controlled by c.c.m. analysis.*

Acknowledgement

M.C.C. gratefully acknowledges INSERM for financial support. The authors acknowledge INSERM (CONTRACT).

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(Received in France 4 April 1985)