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Regioselective $AlPO_4$-Al_2O_3 Promoted Ring-Opening of 2,3-Epoxy Esters

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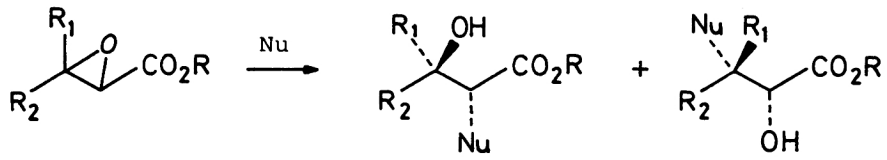
Synthetic $AlPO_4$-Al_2O_3 promotes regioselective ring-opening of 2,3-epoxy esters by some oxygen and sulphur nucleophiles. Ritter type ring-opening with acetonitrile allowed the regioselective introduction of the acetamido group.

1,2,3-Trifunctional acyclic compounds having two adjacent chiral centers, such as 2, 3, and derivatives thereof, are useful building blocks for the synthesis of complex natural products.[1] As depicted in Scheme 1 they can be prepared from easily available substrates such as 2,3-epoxy acids and derivatives 1, by nucleophilic ring-opening of the epoxide.

Obviously the success of a synthetic plan based on such a strategy depends heavily on the ability to control the C-2(α) or C-3(β) attack by the nucleophile.



1 2 3

Scheme 1.

This becomes an important target particulary when both oxiranic carbons are secondary.

Previous work on the subject has shown that amines[2] and carbanions[3] lead to products arising from preferential attack at C-2. However a changeover in regioselectivity is observed when electrophilic activation[4] is employed, thus favouring attack at C-3. Interestingly, activation by transition metal alkoxides has proven to be impressively effective in directing nucleophiles to attack at the C-3 carbon of 2,3-epoxy acids, amides and alcohols.[5]

This[5] as well as other papers published very recently[6] on the subject has prompted us to report our own results regarding the $AlPO_4$-Al_2O_3 promoted regioselective ring-opening of 2,3-epoxy esters by nucleophiles. Earlier work[7] from our laboratories regarding the catalytic activity of synthetic $AlPO_4$-Al_2O_3 systems suggested that these solid acids[8] of Kearby type,[9] which possess both Lewis and Brönsted sites,[10] might be suitable candidates to achieve regiocontrol in the nucleophilic ring-opening of 2,3-epoxy esters. An additional problem present at the outset of our work was to select conditions to avoid nucleophilic attack on the es-

ter group.

Table 1. $AlPO_4$-Al_2O_3 promoted ring-opening of 2,3-epoxy esters 1 to 3

Entry	R	R_1	R_2	Nucleophile[a]	Time/h	Yield of 3/%[b,c]
1	Et	H	Me	PhCOOH	48	80(15)[d]
2	Et	H	Me	PhOH	24	75(21)[d]
3	Et	H	Me	$PhCH_2OH$	36	75(20)[d]
4	Et	H	Me	PhSH	24	70(24)[d]
5	Et	H	Me	EtOH	48	40(50)[d]
6	Et	H	Me	MeOH	12	10[e]
7	Me	H	Me	EtOH	48	[f]
8	Et	H	Me	H_2O	72	<5
9	Et	H	Me	n-$BuNH_2$	72	——
10	Et	H	Me	Me_2NH	72	——
11	Me	CO_2Me	H	PhCOOH	12[h]	71(20)[d]
12	Et	H	Me	MeCN	48[i]	40[g]
13	Et	Me	Me	MeCN	12[i]	85[g]
14	Et	Me	Me	MeCN	12[i]	84[g]
15	Et	$-(CH_2)_4-$		MeCN	12[i]	63[g]
16	Me	CO_2Me	H	MeCN	72[h,i]	——

a) In a typical run, 20 ml of a dichloromethane solution containing 10 mmol (2 equiv.) of the desired nucleophile was added to 7.5 g of $AlPO_4$-Al_2O_3. The resulting slurry was stirred for 30 min and then 5 mmol of 1 in 50 ml of dichloromethane were added. This mixture was stirred for the specified period of time.

b) ^{1}H-NMR analysis of crude mixtures showed the absence of regioisomer 2.

c) Isolated yield.

d) Yield of unreacted 1 recovered.

e) trans-Methyl-2,3-epoxy butanoate was the major product (75% isolated yield).

f) See the text.

g) Yield of 3-acetamido-2-hydroxy butanoates isolated after hydrolisis of the mixtures.

h) In refluxing chloroform.

i) In 30 ml of acetonitrile (solvent and reagent).

The results summarized in Table 1 show that when sulphur and oxygen centered nucleophiles are used (entries 1 to 6), the $AlPO_4$-Al_2O_3 catalyzed ring-opening of 2,3-epoxy esters 1 takes place smoothly under very mild conditions and, most interesting, with high regioselectivity (C-3 attack only). These remarkable results are in sharp contrast with those of Posner et al.[11] which reported complete failure on the attempted ring-opening of 1 (R= Et, R_1= H, R_2= Me) on commercial Al_2O_3.

On the other hand, as expected, basic nucleophiles (entries 9 and 10) caused deactivation of strong Lewis sites of the catalyst. Furthermore, methanol and water (entries 6 and 8) were found to be almost totally inefficient for ring-opening.

Instead, the transesterification product was the major component when methanol was used. Moreover treatment of trans methyl 2,3-epoxy butanoate with ethanol (entry 7) leads to a complex mixture. Column chromatography allowed us to isolate compounds 4 to 8[12] in an 8:15:60:7:10 ratio. In our view this is due to a rapid adsorption of these molecules on the catalyst thus converting strong Lewis acids into weak and inactive Brönsted sites.[13]

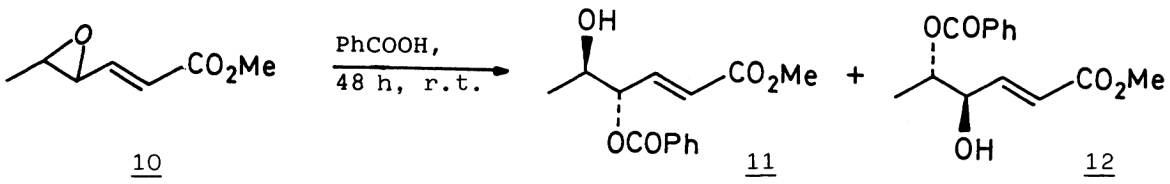
In an effort to achieve regioselective ring-opening with nitrogen nucleophiles we turn our attention to the well-known Ritter-type reaction of epoxides[14-16] with non-basic nitriles.

To our delight a smooth reaction took place on treatment of 1 with acetonitrile yielding mainly ring expanded 2-methyl oxazolines together with minor amounts of 3-acetamido-2-hydroxy butanoates 3 (Nu= MeCONH-). For practical purposes we found it better to hydrolize (wet THF, 24-48 h, r.t.) the crude mixture to the acyclic products 3, (entries 12-16).

Althoug it is premature to draw a mechanistic interpretation accounting for these $AlPO_4$-Al_2O_3 mediated regioselective ring-opening, it is worth noting that our results closely parallel with those recently reported by Sharpless et al.[15,17] As suggested by these authors we feel that regioselectivity is best explained by assuming some kind of simultaneous coordination to the $AlPO_4$-Al_2O_3 catalyst by both the oxiranic oxygen and the carbomethoxy group. Subsequent attack by nucleophile takes place more rapidly at the harder center[18] (C-3). Accordingly, ring-opening of cis dimethyl epoxy succinate (entry 11) with benzoic acid required more drastic conditions, providing the corresponding monoprotected dimethyl tartrate. Furthermore in an additional enlightening experiment, the $AlPO_4$-Al_2O_3 promoted ring-opening of the vinylogous ester 10, by benzoic acid, led only to a 45:55 mixture (85 % yield) of the two regioisomers 11 and 12.

In summary, the synthetic $AlPO_4$-Al_2O_3 systems appear to offer a practical and valuable alternative for the regioselective ring-opening of 2,3-epoxy esters.

Further work is in progress to determine the full scope of the reaction.



10 11 12

Scheme 2.

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