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Synthesis and Characterization of Stable 2-Cyano-2-Carboximidic Acid Alkyl Ester-Oxiranes and 2, 2-Dicarboximidic Acid Dialkyl Ester-Oxiranes

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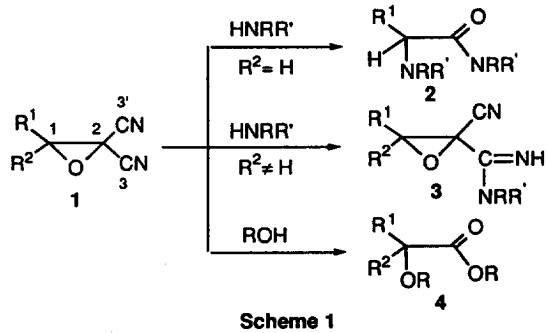
Abstract: Bases catalyse the addition of primary alcohols on dicyano oxiranes to afford stable imidates. Depending on the catalyst it is possible to obtain either a mixture of Z and E monoimidates **5** in 3 to 1 ratio (NEt_3) or the E imidate in 95% ($BrNBu_4$), or the bisimidates **6** (NaOMe). © 1999 Elsevier Science Ltd. All rights reserved.

Alpha-beta unsaturated epoxides are polyfunctional compounds whose changeable behaviour towards nucleophiles depends on both sterical and chemical factors. Although some approaches have been attempted to rationalize parts of the huge among of datas available, for exemple by MNDO calculations and HSAB theory,[1] it still remains hazardous to make dogmatic predictions in this field.

During our work on dicyano-oxiranes **1**, we had frequently the opportunity of checking this statement as illustrated on scheme 1. For compounds **1** C_1 and C_3 are the preferential sites of nucleophilic attack. Whereas primary or secondary amines give α-aminoamides **2** by initial ring opening if R^2=H and new functionalized epoxides **3** by reaction on one nitrile if $R^2 \neq H$,[2] water or primary alcohols furnish only ring opened products **4** whatever the nature of R^2.[3]



Scheme 1

In the following article we show that it is possible to direct the addition of primary alcohols onto the C_3 leading to new epoxides **5** and **6**, bearing respectively one and two imidate functions. The starting point of this work was the unexpected formation of compounds **5** (Scheme 2) when oxiranes **1** are reacted with two equivalents of pyridine in ethanol. Mixing the same compounds in ether or THF leads to the exclusive formation

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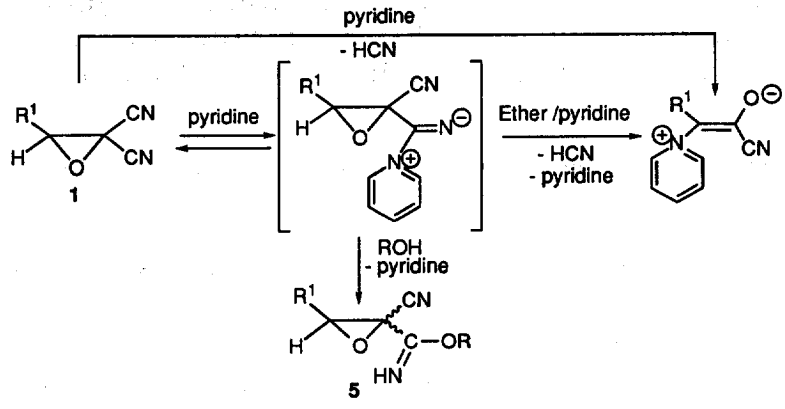
of pyridinium ylids.[4] Looking at the literature let us learn that one similar observation was briefly mentioned without further investigation,[5,6] so that we decided to study this reaction in more details considering the synthetic potential of such highly functional epoxides.



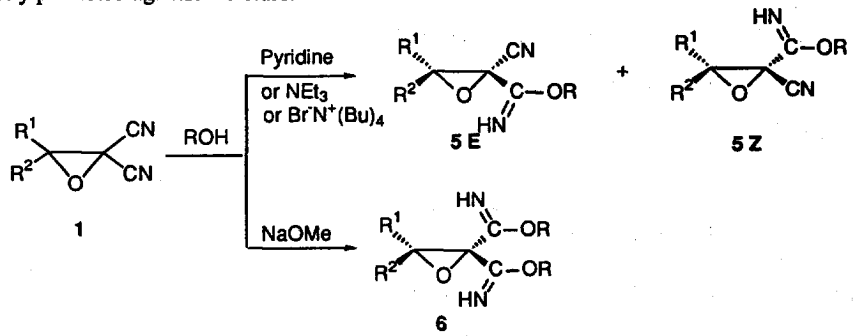
Scheme 2

To rationalize these observations we can imagine that a reversible addition on C_3 could be the kinetic compound in all cases, the reaction pathway depending then on the nature of the solvent. In absence of alcohol the ylid formation could result from the addition of pyridine either on C_1 of the starting oxirane or on C_1 on the intermediate. In the presence of primary alcohols the intermediate could undergo protonation, followed by addition-elimination, leading to the corresponding imidate.

Anyway, it appears that pyridine can efficiently induce chimiospecific addition of alkohol on one of the nitrile of compounds **1**. This effect is still observed for substoechiometric amount of the base confirming its catalytic action. Addition of primary alcohols on a poorly basic nitrile, that is bearing electrononegative substituents is generally catalysed by alcoholates so that the presence of both nitrile and oxygen geminal to each nitrile of **1** could favor a similar mechanism involving the tertiary amine or other nucleophiles as depicted further. The reaction affords a mixture of two diastereoisomers **5 E** and **5 Z** corresponding to the reaction on the trans and cis nitrile according to the substituent on C_1 (scheme 3).[7] The expected preferential formation of the regioisomer **5 E** simply reflects the lower steric hindrance on the corresponding side of **1**. For similar reason, the **5 E / 5 Z** ratio depends on the nature of the alcohol, from 3/1 for MeOH to 6/1 for iBuOH, with a much slowler reaction in this last case. No addition occurs with secondary or tertiary alcohols. Considering the presumed mechanism we attempted to favor even more the formation of **5 E** by using hindered pyridine derivatives such as 2,6-lutidine, quinoline or isoquinoline. With all these catalysts we indeed obtained an excellent regioselectivity (no trace of **5 Z** was detected on ^{1}H NMR spectra) but to the detriment of chimioselectivity as alkoxyesters **4** were formed competitively with **5 E** (ratio 45/55). Replacement of pyridine by triethylamine leads to similar ratio **5 E / 5 Z** but facilitate the purification of the crude products mixture by easy evaporation of the catalyst. Finally, after screening of different catalysts a high regioselective and efficient formation of **5 E** was optimized by using an equimolar amount of tetrabutylammonium bromide (1 hour, room temperature, yields over 90 %, ratio **5 E / 5 Z** > 9/1, large scale).[8] Bromide ion should act similarly as tertiary amines as activating agent by reversible addition on one nitrile. Protonation of the intermediate gives in this case an imidoyl bromide which further reacts with alcohols. Nevertheless, this comparison does not provide satisfying explanation for the higher

explanation for the higher regioselectivity observed with this catalyst. Probably, the tetrabutylammonium counter-ion remains in some way associated with the activated intermediate.

5 E and **5 Z** cannot be fractionated by distillation. Both diastereoisomers could be separated by silica gel chromatography, except for some less favorable cases which were charactarized on the mixture on the basis of ^1H NMR and IR datas.[9] The crude mixture are pure enough for further reactions and can be stored for prolonged time if correctly protected against moisture.



5	R^1	R^2	R	%	ratio[a] E/Z
a	Tol	H	Me	98	3/1
b	Tol	H	Et	98	4/1
c	Tol	H	i-Bu	90	6/1
d	Tol	H	C_2H_4OH	80	b
e	$pClC_6H_4$	H	Me	98	3/1
f	$pClC_6H_4$	H	Et	98	3/1
g	2,5-$Cl_2C_6H_3$	H	Me	95	4/1
h	Ph	H	Me	96	3/1
i	Et	H	Me	91	E
j	Tol	Me	Me	80	-
k	Et	Ph	Et	98	-
l	Bz	Bz	Et	66	-

6	R^1	R^2	R	%
a	Ph	H	Me	98
b	Tol	H	Me	98
c	$pClC_6H_4$	H	Me	90
d	$pNO_2C_6H_4$	H	Me	80
e	2,5-$Cl_2C_6H_3$	H	Me	98

[a] ratio obtained with NEt_3 as catalyst. [b] reaction realized only with NBu_4Br

Scheme 3

To our knowledge, imidate's formation using bromide as catalyst as never been described but is probably limited to strongly electrophilic cyano groups as confirmed by the insensitivity of the residual nitrile. Nevertheless using sodium methanolate as much stronger basic catalyst we were able to prepare bisimidates **6**[10] as white, stable, cristalline solids with good to excellent yields (80 to 98%, Scheme 3).[11]

In conclusion, we found that tetrabutylammonium bromide allows to direct the addition of alcohols towards one nitrile of epoxides **1**, whereas NaOMe leads to the addition of alcohol on both nitriles. This reaction has a major interest because it gives access to epoxyiminoether which cannot be synthesized by the method of Pinner,[12] since this reaction is carried out under conditions which open the cycle of the epoxide. Moreover these compounds have a significant synthetic potential since iminoether function is known to give easily addition-elimination.[12]

References and notes

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(7) Typical experimental procedure for the synthesis of monoimidates **5** Z and E: NEt_3 (10 mmol) was added to a solution of epoxide[13] **1** (10 mmol) in alcohol (50 ml) and the mixture was stirred at room temperature for 8h (R^2= H) to 24h ($R^2 \neq H$, or R=iBu). The solvent was then evaporated to give a mixture of Z and E imidates, pure enough to be used in further reaction, in some cases it is possible to separate them by chromatography on silica gel with ether/petroleum ether as eluent.

(8) Typical experimental procedure for the synthesis of monoimidates **5** E: Tetrabutyl ammonium bromide (10 mmol) was added to a solution of epoxide **1** (10 mmol) in alcohol (40 ml) and the mixture was stirred at room temperature for 1h (R^2= H). The solvent was then evaporated, addition of ether afford a precipitate of $N(Bu)_4Br$ which was eliminated by filtration. Evaporation of ether gives the imidate **5** E in 95% ratio.

(9) **5a** E. Chromatography (Et_2O/petroleum ether: 25/75) afforded **5a E** (Rf: 0.23) as pale yellow oil. ^1H NMR ($CDCl_3$) δ: 2.34 (s, 3H), 3.87 (s, 3H), 4.16 (s, 1H), 7.20-7.33 (m, 4H), 7.81 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 21.3, 52.2, 54.7, 65.1, 115.2, 126.3, 126.4, 129.4, 139.9, 159.8. Anal. calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.82; H, 5.57; N, 13.23. HRMS: calcd: 216.0899, found: 216.0900

5a Z. Chromatography (Et_2O/petroleum ether: 25/75) afforded **5a Z** (Rf: 0.39) as pale yellow oil. ^1H NMR ($CDCl_3$) δ: 2.30 (s, 3H), 3.62 (s, 3H), 4.62 (s, 1H), 7.18-7.12 (m, 4H), 7.52 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 21.3, 53.3, 54.3, 64.7, 113.1, 126.5, 126.6 129.4, 140.5, 163.3. Anal. calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.44; H, 5.58; N, 12.59. HRMS: calcd: 216.0899, found: 216.0900

(E+Z)-5a: (1/3) IR (liquid film) ν: 3300, 2240 and 1660 cm^{-1}.

(10) Typical experimental procedure for the synthesis of bisimidates **6**: To a solution of epoxide **1** (60 mmol) in dry methanol (100 ml) at 0 °C was added slowly 4N NaOMe (3 ml). After 3h at rt, the solvent was evaporated, the crude mixture dissolved in CH_2Cl_2 (100 ml) and the organic layer washed twice with water (50 ml), dried with $Na_2S_2O_4$. Evaporation of the solvent afford the bisimidate **6** which was recrystallized in ether.

(11) **6c** 83 °C. IR (nujol) ν: 3300 and 1650 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.57 (s, 3H), 3.86 (s, 3H), 4.25 (s, 1H), 7.24-7.31 (m, 5H), 7.71 (s, 1H), 7.92 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 53.8, 54.4, 63.5, 63.6, 127.6, 128.6, 130.6, 135.0, 163.7, 165.7. Anal. calcd. for $C_{12}H_{13}N_2O_3Cl$: C, 53.64; H, 4.88; N, 10.43; Cl, 13.19. Found: C, 53.57; H, 4.91; N, 10.31; Cl, 13.21.

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(13) Epoxides **1** were prepared in a two-step procedure : for the first one, a Knoevenagel-Cope condensation, see Gardner, P.D. ; Brandon, R.L. *J. Org. Chem.* **1957** *22*, 1704-1705. Texier-Boullet, F. ; Foucaud, A. *Tetrahedron Lett.* **1982**, *23*, 4927-4928. For the second step, a stereospecific epoxidation of olefin by sodium hypochlorite, see Baudy, M. ; Robert, A. ; Foucaud, A. *J. Org. Chem.* **1978**, *43*, 3732-3736.