REGIOSELECTIVE SYNTHESIS OF NOVEL SUBSTUTED 1,4-OXAZINES

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(Submitted: 24 April 2015, accepted: 13 May 2015)

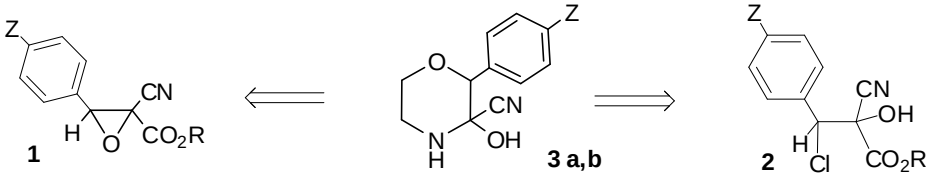
ABSTRACT: A new variety of 1,4-oxazines was prepared by the reaction of cyanoesters epoxides or α-chlorocyanohydrins with 2-aminoethanol. The condensation was carried out under mild conditions at room temperature and at very suitable reaction times with good yields.

RESUME: Une nouvelle variété de 1,4-oxazines a été préparée par réaction des époxydes cyanoesters ou des α-chlorocyanhydrines avec le 2-aminoéthanol. La condensation a été effectuée dans des conditions douces à la température ambiante et à des temps de réaction très convenables avec de bons rendements.

Keywords: Epoxides, cyanhydrins, α-chlorocyanhydrins, 1,4-oxazines.

1. INTRODUCTION

The 1,4-oxazines are highly versatile class of intermediates for the synthesis of compounds exhibiting strong biological activity [1-11] and synthetic utility [12-22]. In connection with our research interest on the synthesis of the heterocyclic compounds [23-25], we describe in this paper a general synthetic method for the synthesis of some substituted 1,4-oxazines through the ring opening of epoxides **1** and addition-elimination reactions carried out by α-cyanohydrins **2,** using 2-aminoethanol as binucleophilic reagent (Scheme 1).



Scheme 1. Retrosynthetic pathways for the preparation of 1,4-oxazines **3**

2. RESULTS AND DISCUSSION

In previous work, we reported that epoxides **1** are easily accessible [26] and serve as potential intermediates in organic synthesis [27-29]. Thus, it is worthy of interest to study their reactivity towards some 1,2-binucleophilic reagents such as 2-aminoethanol, which leads according to an intramolecular heterocyclisation reaction to 2-aryl-3-cyano-3-hydroxy-1,4-oxazines **3** as oily products in fair to good yields. To explain the mechanism of this reaction, we assume that the reaction begins by the attack of the amino group of the 2-aminoethanol on the carbonyl of the ester group. The following step consists on the opening of the epoxide ring due to the attack of the hydroxyl group, which forms an unstable oxazepinone. This latter evolves towards a very reactive cyanoformyl intermediate which reacts with ROH present in the medium through a double addition-elimination reaction to produce 1,4-oxazines **3** as a mixture of two diastereoisomers (Scheme 2, Table 1).

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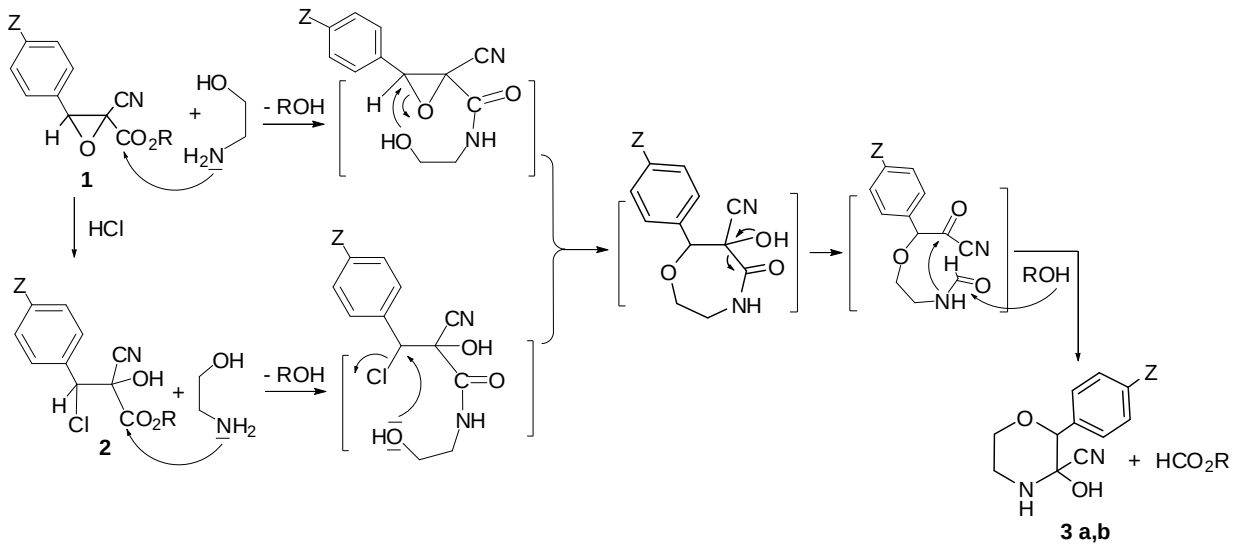
In attempt to assess the α-chlorocyanhydrins **2** easily accessible *via* the ring opening of the epoxides **1** with hydrochloric acid [30], we tested their electrophilic reactivity with 2-aminoethanol under solvent-free conditions to prove that they also may be subject to addition-elimination reactions and those of nucleophilic substitution of the 2-aminoethanol to obtain 1,4-oxazines **3** with very comparable yields to those obtained from epoxides **1** (Scheme 2, Table 2).



Scheme 2 : Synthesis of 1,4-oxazines **3 a,b**

It should be noted that the addition-elimination reactions are faster than the nucleophilic substitutions [31] and the amino group (NH_2) of 2-aminoethanol is more nucleophilic than its oxygenated counterpart (OH). It was thus normal to observe at first the attack of NH_2 on the ester carbonyl (addition-elimination) which is in agreement with the obtained regioisomers **3**.

Table 1:1,4-oxazines **3** from epoxides **1**

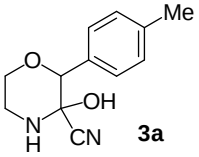
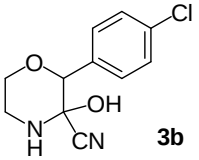
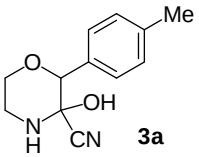
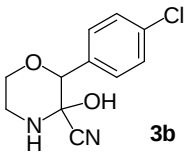
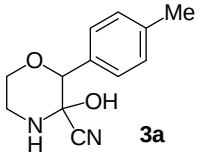
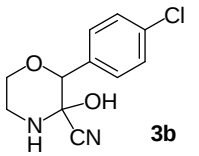
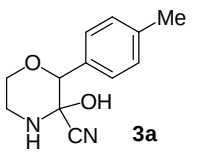
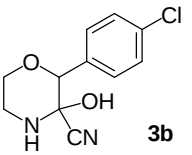
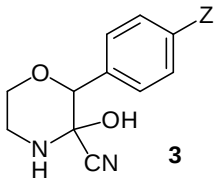
	Z	R	1,4-oxazine	Yield (%)
1	Me	Me	 **3a**	60
2	Cl	Me	 **3b**	65
3	Me	Et	 **3a**	66
4	Cl	Et	 **3b**	60

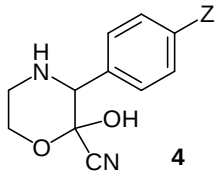
Table 2: **3** from α-chlorcyanohydrins **2**

	Z	R	1,4-oxazine	Yield (%)
5	Me	Me	 **3a**	65
6	Cl	Me	 **3b**	60
7	Me	Et	 **3a**	63
8	Cl	Et	 **3b**	60

It was also possible to envisage that the coupling reaction of 2-aminoethanol and α-chlorohydrins **2** begins by a nucleophilic substitution of the chloride ion by the amino moiety to yield the 1,4-oxazines regioisomers **4**, wherein the nitrogen atom is replaced by the oxygen atom in the 1,4-oxazine ring. This possibility has been ruled out since the examination of the ^{13}C NMR chemical shifts of the quaternary carbon bearing OH and CN groups showing signals at almost 68.0 ppm, which is in agreement with the structures **3** detailed in Scheme 1.



3



4

The two reactions described in Scheme 1 gave rise to a mixture of two 1,4-oxazines diastereoisomers **3** inseparable by column chromatography but readily identifiable through their ^{1}H and ^{13}C NMR spectra. The high resolution mass spectra shows two fragments m/z = 164.0761 corresponding to the sequence $[M_1^{+\bullet}\text{-}C_2ON]^+$ for the product **3a** and the fragment m/z = 184.0208 corresponding to the sequence $[M_2^{+\bullet}\text{-}C_2ON]^+$ for the product **3b** and resulting from both decyanation and decarbonylation reactions.

3. CONCLUSION

In conclusion, we have reported in this work two one-pot and regioselective reactions from *gem*-cyanoester epoxides **1** and α-chlorocyanhydrins **2** available in our laboratory and 2-aminoethanol to produce new families of 1,4-oxazines **3**. The low cost and easy methodology constituted an additional contribution to others reported in the literature. Further studies on the properties and potential synthetic utility of the synthesized 1,4-oxazines **3** are under investigation.

4. EXPERIMENTAL

All reactions were monitored by TLC on silica gel plates (Fluka Kieselgel 60 F_{254}). Crude products were purified using column chromatography on silica gel (Fluka Kieselgel 70-230 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 300 spectrometer at 300 and 75 MHz for ^{1}H and ^{13}C, respectively in DMSO-d6 as solvent and TMS as the internal standard. All NMR spectra were acquired at room temperature. IR spectra were recorded on Brucker Tensor 27. Mass spectra were recorded on a SYNAPT G2 HDMS (Waters) spectrometer in Electrospray Ionization (ESI). Multiplicity of peaks is indicated by: s: singlet; d: doublet; t: triplet; q: quartet; qt: quintuplet; sept: septuplet; m: multiplet.

4.1 General procedure for the synthesis of 2-Aryl-3-cyano-3-hydroxy 1,4-oxazines 3: To a solution of 5 mmol of epoxide **1** or (α-cyanhydrin **2**) was added an excess of 2-ethanolamine (25 mmol). The reaction mixture was stirred for 10 mn, extracted with CH_2Cl_2 (3x20 mL). The organic layer was washed with washed water, dried over Na_2SO_4. After evaporation the solvent, the crude product was purified by flash chromatography on silica gel column (chloroform as eluent). The spectroscopic data of the two families of 1.4-oxazines **3** are as follows.

4.1.1. 2-pTolyl-3-cyano-3-hydroxy-1,4-oxazine 3a. Yield: 60%; IR (KBr): 2250, 3310, 2910 cm^{-1}. The signals of one of both diastereomers: ^{1}H NMR (DMSO-d6, δ ppm, *J* Hz): 2.3 (s, 3H, CH_3), 2.66 (t, 2H, CH_2N, *J* = 9.4), 3.5 (t, 2H, CH_2O, *J* = 9.4), 5.03 (s, 1H, CHN), 7.02-7.38 (m, Ar). ^{13}C NMR (DMSO-d6, δ ppm): 21.0, 49.3, 53.5, 60.8, 67.7, 120.4. 127.6, 129.7, 133.4, 138,3. The signals of the second diastereomer: ^{1}H NMR (DMSO-d6) δ (ppm): 2.4 (s, 3H, CH_3), 2.66 (t, 2H, CH_2N, *J* = 9.4), 3.5 (t, 2H, CH_2O, *J* = 9.4), 5.03 (s, 1H, CHN), 7.02-7.38 (m, Ar). ^{13}C NMR (DMSO-d6, δ ppm): 21.3, 49.3, 53.5, 60.8, 67.7, 120.4. 127.5, 129.7, 133.4, 138.4. HRMS calcd for $[M^{+\cdot}\text{-}C_2ON]^+$: 164.0997 ; found : 164.0761.

4.1.2. 2-(pChlorophenyl)-3-cyano-3-hydroxy-1,4-oxazine 3b. Yield: 65 %; IR (KBr): 2250, 3300, 2920 cm^{-1}. The signals of one of both diastereomers: ^{1}H NMR (DMSO-d6, δ ppm, *J* Hz): 2.65 (t, 2H, CH_2N, *J* = 9.6), 3.5 (t, 2H, CH_2O, *J* = 9.6), 5.14 (s, 1H, CHN), 7.4-7.88 (m, Ar). ^{13}C NMR (DMSO-d6, δ ppm): 49.2, 53.0, 60.7, 68.0, 120.0, 128.6, 129.3, 133.7, 136.4. The signals of the second diastereomer: ^{1}H NMR (DMSO-d6, δ ppm, *J* Hz): 2.65 (t, 2H, CH_2N, *J* = 9.6), 3.5 (t, 2H, CH_2O, *J* = 9.6), 5.13 (s, 1H, CHN), 7.4-7.88 (m, Ar). ^{13}C NMR (DMSO-d6, δ ppm): 49.3, 53.0, 60.7, 68.0, 120.0, 128.6, 129.3, 133.7, 136.4. HRMS calcd for $[M^{+\cdot} - C_2ON]^+$: 184.0450 ; found : 184.0208.

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