ONE-POT SYNTHESIS OF 1,4-BENZOXAZIN-2-ONES AND 1,4-BENZOXAZINES FROM EPOXIDES

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Abstract : The 3-aryl-2H-1,4-benzoxazin-2-ones 7a-e, 2-alkoxycarbonyl-3-aryl-3,4-dihydro-2-hydroxy-2H-1,4-benzoxazines 9a-f and 2-alkoxycarbonyl-3-aryl-2H-2-hydroxy-1,4-benzoxazines 10 have been prepared, with good yields, through reacting of gem-difunctionnalized epoxides with α-aminophenol.

The benzoxazines constitute a class of compounds of very important biological interest (1), furthermore they are used as organic inhibitors (2).

Except for 2- or 3-benzoxazines and 3-phenyl-2H-1,4-benzoxazines (3), literature has known only a very reduced number of articles dealing with the synthesis of derivatives of 3-phenyl-1,4-benzoxazines despite the interest that these compounds present. Furthermore, all the methods used previously (2-6) remain very expensive, less selective and necessitating several stages.

As the gem difunctionnalized epoxides are compounds easily accessible (7-9), it has appeared to us that they are worthy of interest to study their reactivity with the α-aminophenol. In fact, the bielectrophile character potential (10-12) of two carbons of the epoxides cycle would allow to postulate that this reaction could have constituted a new way to have access to 1,4-benzoxazines and 1,4-benzoxaninones.

Thus, the action of the α-aminophenol 4 on the epoxides gem-dicyano 1 in the ebb of the acetonitrile during 12 hours behaved in a sole stage to a new serie of derivatives of 3-aryl-2H-1,4-benzoxazin-2-ones 7a-e with excellent yields (table I, scheme I).

This reaction proceeds first by the opening of the epoxide cycle by the most nucleophile site of the α-aminophenol which leads to the unstable cyanhydrine 5 that evolves to a very reactive derivative cyanoformyle 6 (13), capable to react, second, with the other site of the α-aminophenol to lead by a heterocyclisation reaction to 3-aryl-2H-1,4-benzoxazin-2-ones 7a-e (Scheme I). Their structure has been established on the basis of an IR, RMN and mass spectrum.

Scheme I

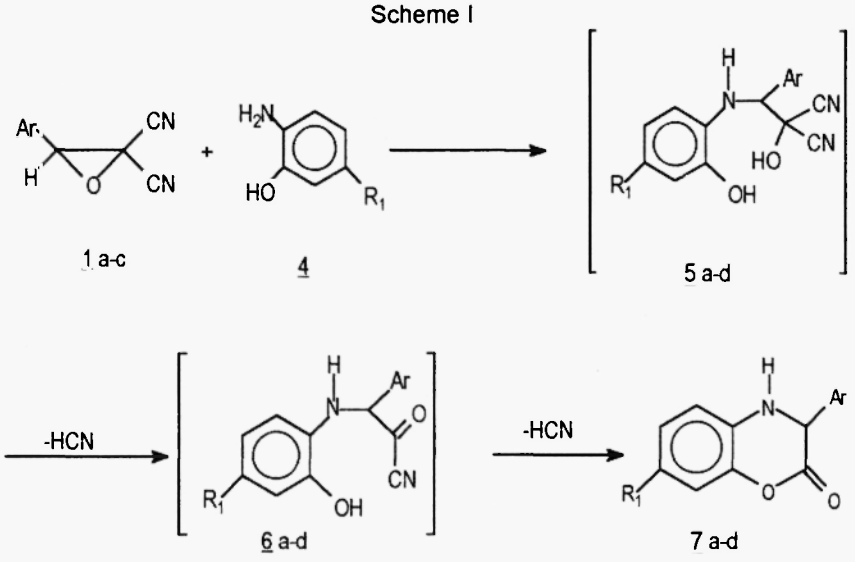


Table 1 : Synthesis of 3-aryl-2H-1,4-benzoxazin-2-ones 7a-e

Entry	R_1	Ar	Products (yields[a], mp °C)
a	H	4-MeC_6H_4	7a (90, 115-6)
b	H	C_6H_5	7b (85, 92-3)
c	H	4-ClC_6H_4	7c (85, 157-8)
d	COOH	4-MeC_6H_4	7d (80, 265-7)
e	COOH	4-ClC_6H_4	7d (75, 260-2)

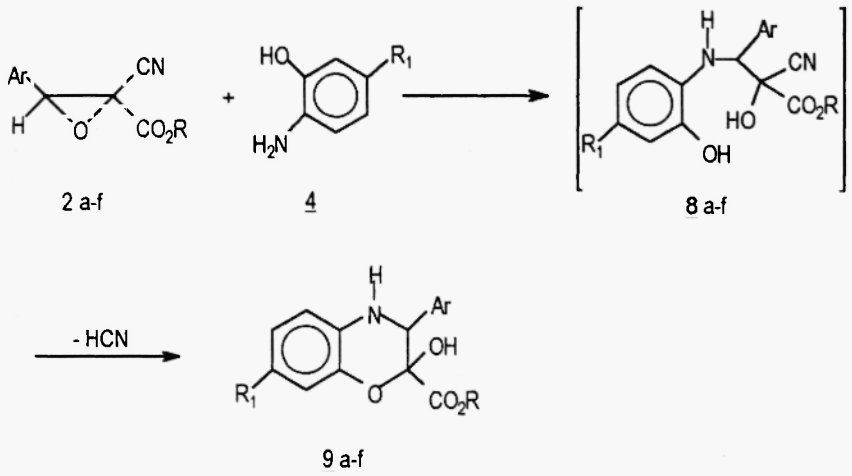
a : Isolated yields after flash chromatography on silica gel petroleum ether/ethyl acetate 4:1 as eluent.

Considering results that we have obtained with the epoxides gem-dicyano 1, we have planned to extend this study by opposing this time some epoxides cyanoesters 2 with the α-aminophenol.

To this effect, we have realised the direct reaction of the epoxides 2 with the α-aminophenol at reflux of the acetonitrile and we have obtained with some good yields the 2-alkoxycarbonyl-3-aryl-3,4-dihydro-2-hydroxy-2H-1,4-benzoxazines 9a-f (table II, Scheme II).

By being based on the mechanism described in the literature on the reactivity of the epoxides cyanoesters, this reaction proceeds by the opening of the epoxide by the grouping amine of the α-aminophenol, driving to an unstable cyanhydrine 8 that evolves through intramolecular reaction to 2-alkoxycarbonyl-3-aryl-3,4-dihydro-2-hydroxy-2H-1,4-benzoxazines with elimination of a molecule of cyanhydric acid (Scheme II).

Scheme II



2 a-f 4 8 a-f

9 a-f

Table 2 : Synthesis of 2-alkoxycarbonyl-3-aryl-3,4-dihydro-2-hydroxy-2H-1,4-benzoxazines 9a-f and 2-alkoxycarbonyl-3-aryl-2-hydroxy-2H-1,4-benzoxazines 10.

Entry	Ar	R_1	R	Products 9 (yields[a], mp °C)	Products 10 (yields, mp °C)
a	4-MeC_6H_4	H	Me	9a (70, 125-6)	10a (60, oil)
b	4-ClC_6H_4	H	Me	9b (82, 186-8)	-
c	C_6H_5	H	Me	9c (75, b)	-
d	4-MeC_6H_4	H	Et	9d (70, 135-6)	10d (75, oil)
e	4-ClC_6H_4	H	Et	9e (80, 92-4)	-
f	C_6H_5	H	Et	9f (84, 134-6)	-
g	4-MeC_6H_4	COOH	Me	-	10g (80, 250-52)
h	4-MeC_6H_4	COOH	Et	-	10h (75, 240-42)

a : Isolated yields after flash chromatography on silica gel petroleum ether/ethyl acetate 4:1 as eluent

b : Hygroscopic compound

When the duration of this reaction is increased to 48 hours, the 2-alkoxycarbonyl-3-aryl-2-hydroxy-2H-1,4-benzoxazines 10g-h are obtained (table 2, scheme III).

We have verified this result by making a direct thermolyse of 9 that effectively lead to the benzoxazines 10a, d (table 2, scheme III). These compounds are also obtained, when methyl or ethyl 3-aryl-3-halo-2-cyano-2-hydroxy propanoates 3 (14) as the substrate are subjected to the same reaction under the same conditions for 16 hours (table 3).

Scheme III

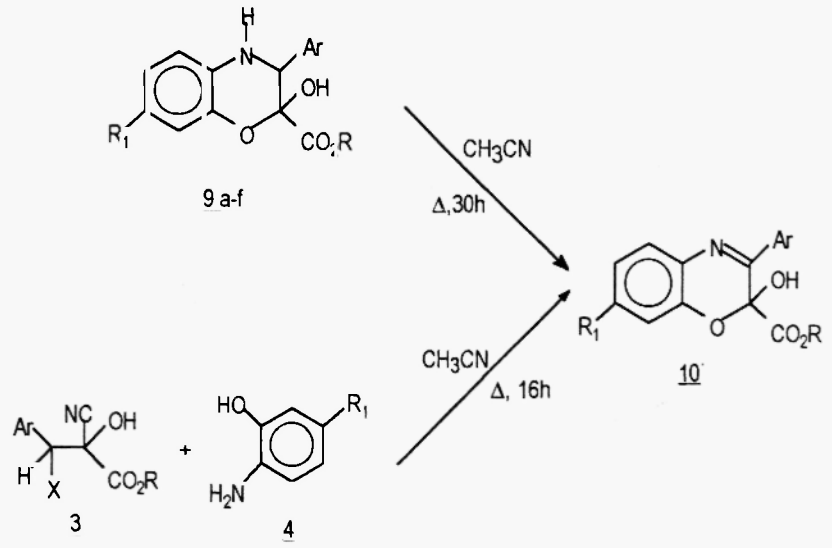


Table 3 : Synthesis of 10 from 3

entry	Ar	R_1	R	Product (Yields [a])
a	4-MeC_6H_4	H	Me	10a (50)
b	4-MeC_6H_4	H	Et	10d (60)

a : Isolated yields after flash chromatography on silica gel petroleum ether/ethyl acetate 4:1 as eluent.

In conclusion, as epoxides 1-2 are easily available starting materials, and as the reaction is highly regioselective and is one-pot procedure, our new route to a novel 1,4-benzoxazin-2-ones and 1,4-benzoxazines seems of interest to us and compares favourably with existing methods. Further studies of the potential biological. properties and of the synthetic utility of the products are under investigation.

EXPERIMENTAL

NMR spectra were at 300 MHz on a AM 300 WB spectrometer. ^1H and ^{13}C chemical shifts (δ) are given in ppm relative to TMS as internal standard. IR spectra were determined with a Perkin Elmer 297 spectrometer. Mass spectra were recorded at Nermag R10-10-C spectrometer. Melting points were taken with a Kofier haut stage apparatus and are uncorrected.

Synthesis of 3-aryl-2H-1,4-benzoxazin-2-ones 7a-e

A solution of epoxides 1a-c (5 mmoles) in acetonitrile (15 mL) was added the α-aminophenol 4 (5 mmoles) in acetonitrile (15 mL). The solution was refluxed for 12 hours. The reaction mixture was concentrated to dryness under reduced pressure, extracted with dichloromethane (3 x 20 mL), washed with water and dried over anhydrous magnesium sulfate. Evaporation of solvent gave a crude products which were purified by flash chromatography on silica gel column (ethyl acetate/ petroleum ether : 4/1). Their spectroscopic data are as follows. For example :

7a: IR: 1734 (CO) and 3360 (NH).

^{1}H NMR ($CDCl_3$) δ ppm: 2.37 (s, 3H, CH_3); 4.29 (s, 1H, NH); 5.02 (s, 1H, CH), 6.78-7.38 (m, 8H, Ar).

^{13}C NMR : 21.57 (CH_3); 59.43 (CH); 115.30-141.33 (Ar-ring C); 165.86 (CO).

Mass spectrum m/e cal. = 240.094 $(M+H)^+$; found = 240 $(M+H)^+$.

7e: IR: 1735 (CO) and 3363 (NH).

^{1}H NMR ($CDCl_3$) δ ppm : 4.10 (s, 1H, NH); 5.85 (s, 1H, CH); 7.21-8.35 (m, 7H, Ar); 9.80 (s, 1H, OH).

^{13}C NMR : 66.34 (CH); 116.11-142.15 (Ar ring C); 167.48 (CO); 192.04 (COOH).

Mass spectrum m/e cal. = 285.092 $(M+H)^+$; found = 285 $(M+H)^+$.

Synthesis of 2-alkoxycarbonyl-3-aryl-3,4-dihydro-2-hydroxy-2H-1,4-benzoxazines 9a-f

A solution of epoxides cyanoesters 2a-f (10 mmoles) in 30 mL of acetonitrile and the α-aminophenol 4 (10 mmoles) was refluxed for 12 h. The reaction mixture was concentrated and extracted with dichloromethane (60 mL). The organic layers were separated and washed with water (2 x 50mL). After usual work-up, products were separated by flash chromatography on silica gel column (ethyl acetate/ petroleum ether : 4/1). Their spectroscopic data are as follows. For example :

9a: IR: 1730 (CO); 3378 (NH) and 3465(OH).

^{1}H NMR ($CDCl_3$) δ ppm: 2.38 (s, 3H, CH_3); 3.79 (s, 3H, OCH_3); 4.43 (s, 1H, NH); 4.66 (s, 1H, NCH); 6.70-6.85 (br s, 1H, OH); 6.70-7.50 (m, 8H, Ar).

^{13}C NMR : 21.58 (CH_3); 53.80 (CHN); 59.65 (OCH_3); 94.31 (OCOH); 115.43-141.42 (Ar-ring C); 168.76 (CO).

Mass spectrum m/e cal. = 300.115 $(M+H)^+$; found = 300 $(M+H)^+$.

9d: IR: 1737 (CO); 3372 (NH) and 3463 (OH).

^{1}H NMR ($CDCl_3$) δ ppm: 1.28 (t, 3H, $OCH_2\underline{CH_3}$); 2.37 (s, 3H, CH_3); 4.02 (q, 2H, $O\underline{CH_2}CH_3$); 4.44 (s,1H, NH); 4.68 (s, 1H, NCH); 6.70-6.85 (br s, 1H, OH); 6.70-7.50 (m, 8H, Ar).

^{13}C NMR : 14.39 ($OCH_2\underline{CH_3}$); 21.87 (CH_3); 53.80 (CHN); 59.11 (OCH_3); 63.34 ($O\underline{CH_2}CH_3$); 94.04 (OCOH); 116.42-141.56 (Ar-ring C); 168.40 (CO).

Mass spectrum m/e cal. = 314.131 $(M+H)^+$; found = 314 $(M+H)^+$.

Synthesis of 2-alkoxycarbonyl-3-aryl-2-hydroxy-2H-1,4-benzoxazines 9a-f

A solution of 5 mmoles of cyanhydrines 3 and 5 mmoles of α-aminophenol in 40 ml of acetonitrile was heated to reflux for 16 hours. Then solvent was evaporated under reduced pressure, the residue was taken up with dichloromethane, the dichloromethane was washed with water and evaporated after drying over anhydrous magnesium sulfate. The products were separated by flash chromatography on silica gel column (ethyl acetate/ petroleum ether : 4/1). Their spectroscopic data are as follows. For example :

10a: IR: 1615 (C=N); 1700 (CO) and 3545 (OH).

^{1}H NMR ($CDCl_3$) δ ppm: 2.42 (s, 3H, CH_3); 3.65 (s, 3H, OCH_3); 4.76 (br s, 1H, OH); 6.84-7.77 (m, 7H, Ar)

^{13}C NMR : 21.87 (CH_3); 53.80 (CHN); 54.55 (OCH_3); 90.06 (OCOH); 116.56-142.42 (Ar-ring C), 144.02 (C=N); 170.19 (CO). Mass spectrum m/e cal. = 298.100 $(M+H)^+$; found = 298 $(M+H)^+$.

10d: IR: 1612 (C=N); 1697 (CO) and 3540 (OH).

^{1}H NMR ($CDCl_3$) δ ppm: 1.29 (t, 3H, OCH_2CH_3); 2.40 (s, 3H, CH_3); 3.72 (q, 2H, OCH_2CH_3); 4.33 (s,1H, OH); 9.80 (br s, 1H, OH); 6.70-8.30 (m, 7H, Ar).

^{13}C NMR : 14.57 (OCH_2CH_3); 21.87 (CH_3); 53.80 (CHN); 59.11 (OCH_3), 62.79 (OCH_2CH_3); 94.04 (OCOH); 113.94-142.02 (Ar-ring C); 144.02 (C=N); 168.43 (COOEt); 207.38 (COOH).

Mass spectrum m/e cal. = 312.11 $(M+H)^+$; found = 312 $(M+H)^+$.

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