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Regioselective synthesis of new variety of 1,4-benzothiazines

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Abstract: A facile and regioselective synthesis of 1, 4-benzothiazines was achieved with a variety of α-cyano α-alkoxy carbonyl epoxides and 2-aminothiophenol in the presence or no of HCl in the reaction medium. The structures of the newly synthesized compounds were confirmed by spectral studies.

Keywords: α-cyano α-alkoxy carbonyl, 2-aminothiophenol, regioselective, 1,4-benzothiazines.

1. Introduction

We have recently described a new procedure for regio-controlled synthesis[1] of 1,4-benzothiazin-2-ones or 1,4-benzothiazin-3-ones from gem-dicyanoepoxides. These epoxides react essentially as a synthetic equivalent of ketene dication[2] and allow in particular the introduction of a carbonyl function.In this paper, we will describe the general preparation of 1,4-benzothiazines types: alkyl 3-hydroxy-2-aryl-2,4-dihydro-2H-benzo[b][1,4]thiazine-3-carboxylate **3** and their isomers alkyl 2-hydroxy-3-aryl-3,4-dihydro-2H-benzo[b][1,4]thiazine-2-carboxylate **6** from functionalized epoxides bearing other withdrawing substituents: α-cyano and α-alkoxy carbonyl epoxides that are easily accessible[3] and are important synthetic intermediates in organic chemistry.[4-8] For that, we have reviewed the relevant literature since 2000 and we have found that the interest in 1.4-benzothiazines is increasingly growing. In fact, the 1,4-benzothiazines are the best known to possess biologically diverse activities[9-11] such as antimicrobial,[12-21] antifungal,[15,17,22-24] antioxidant agents,[25] anticancer,[16,17,26,27] inhibitors of beta-ribosidases,[28] antiproliferative activity,[29] potential vasodilators,[30] antitumor,[31] Antimalarial,[32] immunostimulating, [33] analgesic, [34] and as potent lipoxygenase inhibitors.[35] 1,4- benzothiazines display other properties like novel dyes based on skeleton of 1,4-benzothiazines[36] and behave as semiconductors.[37]

2. Results and discussion

With hind sight, these interesting properties of the 1.4-benzothiazines, have led many chemists to explore new pathways for the synthesis of these compounds.[22, 25, 26, 27] Also, we consider that the synthesis of 1,4-benzothiazines from α-cyano α-alcoxy carbonyl epoxides is another alternative to

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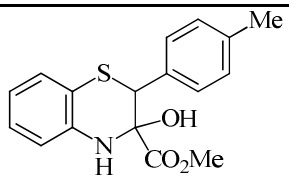
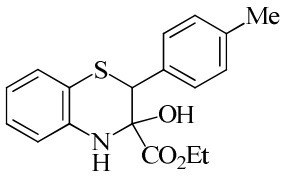
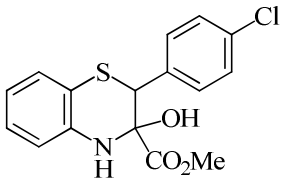
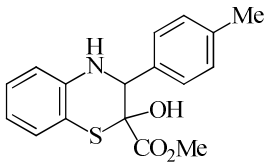
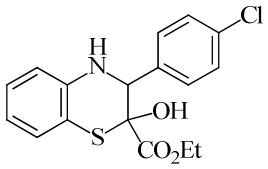
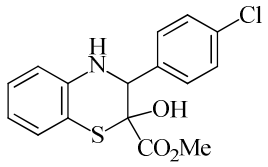
those known in the literature.[11,19, 20,21,38-62] We have opted for the following simple procedure: the reactants are mixed and heated under reflux of acetonitrile. These conditions have allowed us to perform the reaction with good yields (Table 1).

Table1: Synthesis of 1,4-benzothiazines **3** and their diastereoisomers **6**

Entry	Structures	mp	Yield[b] (%)	Compounds
1		188-190	60	**3a**
2		oil	60	**3b**
3		138-139	50	**3c**
4		196-198	40	**6a**
5		oil	60	**6b**
6		oil	40	**6c**

Several types of reactivity of these α-cyano α-alcoxycarbonyl epoxides are SN_2 type reactions between nucleophiles and the two epoxides carbon atoms. However, when there is a steric hindrance at the level of the nucleophile, the reaction takes place in this case on the carbonyl of ester group. In our present work, the two carbon atoms of α-cyano-α-alcoxycarbonyl epoxides act as potential electrophilic centers.

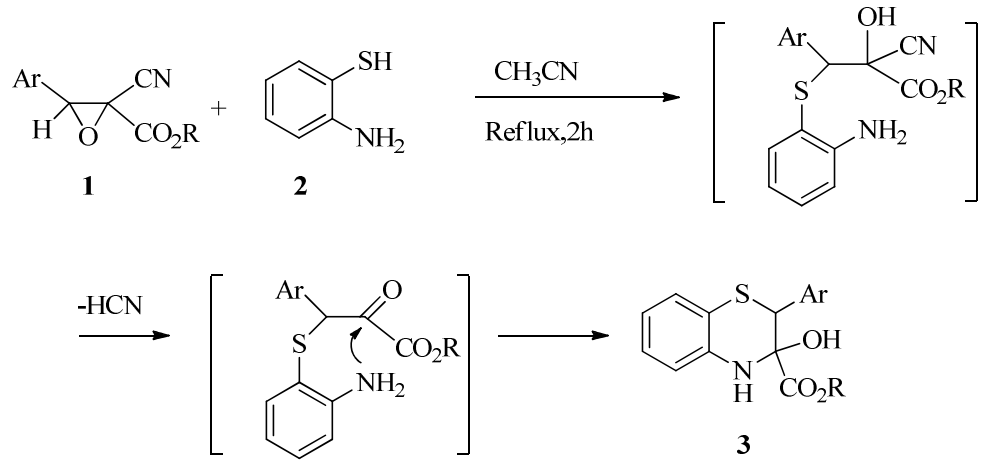


Figure 1. Synthesis of 1,4-benzothiazines derivatives **(3a-c)**

The reaction is regioselective. This is shown by the fact that in all the compounds obtained the sulfur atom is next to the aromatic group (mass spectrometry) which shows that the sulfur atom exclusively attacks the carbon related to the aryl group of epoxide. The strong nucleophilicity of sulfur compared to nitrogen of the amine function explains the selectivity of the nucleophilic attack on the epoxide. Scheme 1 shows that the mechanism of the reaction proceeds with the regioselective opening of the epoxides, by the attack from the sulfur atom leading, followed by that of nitrogen atom. This reaction leads to alkyl 3-hydroxy-2-aryl-2,4-dihydro-2H-benzo[b][1,4]thiazine-3-carboxylate **3** through cyahydrins and α-ketoesters as intermediates. Then, we have carried out again these same reactions using of 2-aminothiophenol hydrochloride instead of 2-aminothiophenol. In these conditions the medium contains three nucleophiles: the sulfur atom, the nitrogen of amine function and the chloride anion. The presence of protons in the medium will weaken the nucleophilicity of the sulfur and the nitrogen and attack of the chloride anion is kinetically favored, and will always take place on the most electrophilic site, namely the carbon bonded to the aryl.

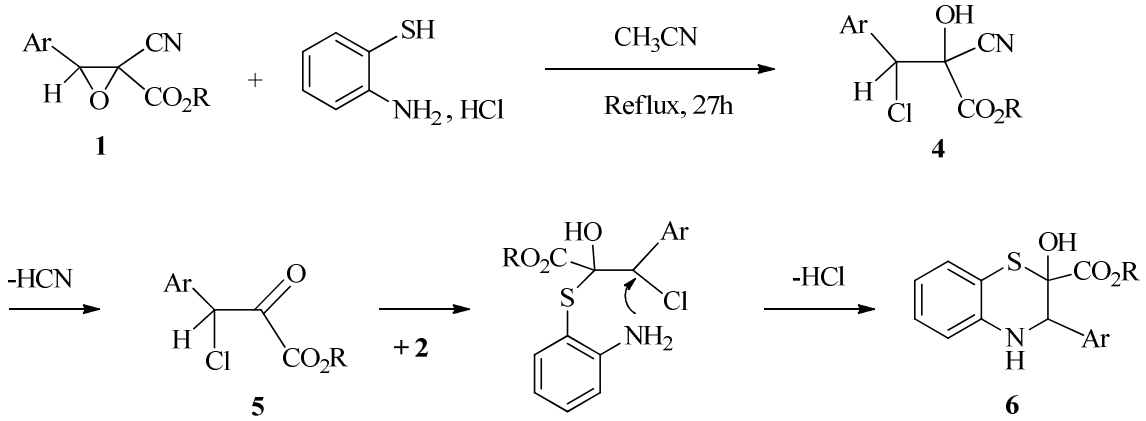


Figure 2. Synthesis of 1,4-benzothiazines **(6a-c)**

The mechanism (Figure 2) of this reaction is established[63], we have shown that the catalytic effect of HCl can be accounted by its attack on the oxygen allowing the ring opening of the epoxide to give the corresponding halohydrins 4 which lead by reaction with 2-aminothiophenol to the alkyl 2-hydroxy-3-aryl-3,4-dihydro-2H-benzo[b][1,4] thiazine-2-carboxylate **6**. Given that the halohydrins **4** are isolables, we have checked that the direct reaction between the 2-aminophenol and the halohydrins gives the same products 6 which confirm again the mechanism of Figure 2.

These two reactions presented in both schemes **1** and **2** always give a mixture of two diastereoisomers which we did not manage to separate by column chromatography.The determination of the configuration of major product was confirmed in agreement with 1H NMR, 13C NMR and mass spectrometry. All products **3** and **6** were characterized by the conventional physico-chemical methods (IR, NMR and mass spectrometry). These compounds in mass spectrometry, spectrum shows the presence of fragment ion of mass m/z coming from the molecular ion and corresponding to the sequence AR-CH_2-S or to the sequence AR-CH_2NH. This confirms the exact position of sulfur or nitrogen in each one of obtained products.

3. Experimental Section:

3.1. General procedure for the preparation of 1,4-benzothiazines 3a-c: To a solution of epoxide **1** (1 mmol) in acetonitrile (20 mL), are added the 2-aminothiophenol (1 mmol). The mixture is refluxed for 25 h. The hydrogen cyanide is trapped by a solution 0.1N KOH in a bubbler. Then, the solvent is removed under reduced pressure and the residue obtained is purified by flash chromatography on silica column eluted with chloroform / petroleum ether 2:1.

3.1.1. Methyl 3-hydroxy-2-(p-tolyl)-3,4-dihydro-2H-benzo[b][1,4]thiazine-3-carboxylate (3a): 0.18 g (60%); M.p. 188-190 °C; IR (KBr) cm^{-1}: 3483 (NH), 2983 (OH), 1742 (CO). The signals of diastereomer 1 : 1H NMR (300 MHz, DMSO-d6): δ 2.31 (s, 3H, CH_3), 4.74 (s, 1H, CHS), 3.82 (s, 3H, CO_2Me), 5.41 (s, 1H, OH); 6.38-7.35 (m, Ar); 13C NMR (75 MHz, DMSO-d_6): δ 21.34, 54.55, 64.31, 83.0, 114.33, 115.27, 116.92, 127.18, 127.96, 129.58, 131.62, 135.86, 140.19, 150,15, 163.31. The signals of diastereomer 2 : 1H NMR (300 MHz, DMSO-d6): δ 2.48 (s, 3H, CH_3), 4.74 (s, 1H, CHS), 3.82 (s, 3H, CO_2Me), 5.41 (s, 1H, OH); 6.38-7.35 (m, Ar); 13C NMR (75 MHz, DMSO-d_6): δ 21.34, 54.0, 64.31, 83.0, 114.33, 115.27, 116.92, 127.18, 127.96, 129.58, 131.62, 135.86, 140.19, 150,15, 166.0.; EIMS: m/z ($C_{17}H_{17}NO_3S$) 315 ($M^{+\cdot}$, 46.6%), 297($M^{+\cdot}$-H2O, 52.7%), 225 (100 %),135 (31.5 %), 119 (28.4%).

3.1.2. Ethyl 3-hydroxy-2-(p-tolyl)-3,4-dihydro-2H-benzo[b][1,4]thiazine-3-carboxylate (3b): 0,19 g (60%); IR (KBr) cm^{-1}: 3378 (NH), 2982 (OH), 1746 (CO). The signals of diastereomer 1: 1H NMR (300 MHz, DMSO-d6): δ 2.40 (s, 3H, CH3), 4.7 (s, 1H, CHS), 1.28 (t, 3H, $CO_2CH_2CH_3$), 4.7 (q, 2H, $CO_2CH_2CH_3$), 6.4-7.5 (m, Ar); 13C NMR (75 MHz, DMSO-d6): δ 14.21, 21.49, 57.0, 63.92, 83.92, 115.28, 116.56, 122.69, 125.80, 127.22, 128.01, 130.36, 134.81, 140.14, 150.21, 162.77. The signals of diastereomer 2: 1H NMR (300 MHz, DMSO-d6): δ 2.30 (s, 3H, CH_3), 4.7 (s, 1H, CHS), 1.21 (t, 3H, $CO_2CH_2CH_3$), 4.29 (q, 2H, $CO_2CH_2CH_3$), 6.4-7.5 (m, Ar); 13C NMR (75 MHz, DMSO-d6): δ 14.31, 21.34, 57.0, 62.37, 83.92, 114.29, 117.01, 123.17, 127.01, 127.59, 129.55, 130.75, 135.90, 141.92, 154.08, 167.0.; EIMS: m/z ($C_{18}H_{19}NO_3S$) 225 (100%), 116 (7.14%), 91 (7.14%), 108 (17.14%).

3.1.3.Methyl2-(4-chlorophenyl)-3-hydroxy-3,4-dihydro-2H-benzo[b][1,4]thiazine-3-carboxylate (3c): 0,17 g (50 %); M.p. 138-139 °C; IR (KBr) cm^{-1}: 3337 (NH), 2999 (OH), 1745 (CO). The signals of diastereomer 1: 1H NMR (300 MHz, DMSO-d6): δ 5.59 (s, 1H, CHS), 1.26 (t, 3H, $CO_2CH_2CH_3$), 4.28 (q, 2H, $CO_2CH_2CH_3$),6.6-7.9 (m, Ar); 13C NMR (75 MHz, DMSO-d6): δ 14.43, 52.07, 62.76, 84.43, 116.45; 122.23; 127.61; 129.08; 129.24; 130.38; 133.23; 135.20; 141.24; 149.67; 163.74. The signals of diastereomer 2: 1H NMR (300 MHz, DMSO-d6): δ 5.59 (s, 1H, CHS), 0.95 (t, 3H, $CO_2CH_2CH_3$), 4.06 (q, 2H, $CO_2CH_2CH_3$), 6.6-7.9(m, Ar); 13C NMR (75 MHz, DMSO-d6): δ 13.09, 52.07, 62.76, 84.43, 118.62, 127.42, 128.33, 129.16, 129.61, 130.61, 134.86, 136.72, 141.24, 149.67, 163.0.; EIMS: m/z ($C_{17}H_{16}NO_3SCl$) 245 (100%), 210 (20%), 122 (10%), 108 (40%).

3.2.Preparative procedure for 1,4-benzothiazines 6a-c: A suspension of 2-aminothiophenol hydrochloride (1.5 mmol) in acétonitrile (10 mL), was added epoxide **1** (1 mmol) dissolved in acétonitrile (5 mL). The reaction mixture is refluxed for 27 hours. The hydrogen cyanide is trapped by a solution of 0.1N KOH in a bubbler. Then, the solvent is removed under reduced pressure and the crude oil obtained is dissolved in chloroform.

The chloroform solution is washed with the water, dried over sodium sulfate and evaporated. The residue is purified by flash chromatography on silica column eluted with chloroform / petroleum ether 2:1.

3.2.1. Methyl 2-hydroxy-3-(p-tolyl)-3,4-dihydro-2H-benzo[b][1,4]thiazine-2-carboxylate (6a): 0,12 g (40%); M.p. 196-198 °C; IR (KBr) cm-1: 3375 (NH), 2999 (OH), 1752 (CO). The signals of diastereomer 1: 1H NMR (300 MHz, DMSO-d6): δ 2.5 (s, 3H, CH3), 6.09 (s, 1H, CHN), 3.54 (s, 3H, CO_2Me), 7.1-7.5 (m, Ar); 13C NMR (75 MHz, DMSO-d6): δ 21.24, 53.73, 66.58, 82.74,122.87, 125.35, 126.81, 128.30, 129.58, 129.79, 133.95, 135.61, 138.80, 153.57, 168.87. The signals of diastereomer 2: 1H NMR (300 MHz, DMSO-d6): δ 2.31 (s, 3H, CH_3), 6.09 (s, 1H, CHN), 3.54 (s, 3H, CO_2Me), 7.1-7.5 (m, Ar); 13C NMR (75 MHz, DMSO-d_6): δ 21.24, 53.99, 66.58, 82.47, 122.87, 125.91, 127.89, 129.09, 129.58, 129.79, 133.95, 135.61, 138.80, 153.57, 173.42; EIMS: m/z ($C_{17}H_{17}NO_3S$) 314 ($M^{+\cdot}$-1, 1,1%), 286(6%), 108 (3%), 134 (18 %), 162 (98.5%).

3.2.2.Ethyl3-(4-chlorophenyl)-2-hydroxy-3,4-dihydro-2H-benzo[b][1,4]thiazine-2-carboxylate (6b): 0.2 g (60%); IR (KBr) cm^{-1}: 3378 (NH), 2980 (OH), 1740 (CO). The signals of diastereomer 1: 1H NMR (300 MHz, DMSO-d6): δ 6.16 (s, 1H, CHN), 1.29 (t, 3H, $CO_2CH_2CH_3$), 4.21 (q, 2H, $CO_2CH_2CH_3$), 7.4-7.7 (m, Ar); 13C NMR (75 MHz, DMSO-d6): δ 14.07, 63.03, 65.51, 82.38, 115.27, 122.39, 123.52, 125.94, 126.83, 128.52, 134.14, 135.62, 136.02, 153.51, 168.27. The signals of diastereomer 2: 1H NMR (300 MHz, DMSO-d6) δ 6.16 (s, 1H, CHN), 1.23 (t, 3H, $CO_2CH_2CH_3$), 4.53 (q, 2H, $CO_2CH_2CH_3$), 7.4-7.7 (m, Ar); 13C NMR (75 MHz, DMSO-d6): δ 20.0, 63.51, 65.02, 82.38, 116.55, 122.88, 125.16, 126.42, 127.25, 128.52, 131.83, 135.62, 136.02, 153.51, 173.27; EIMS: m/z ($C_{17}H_{16}NO_3SCl$) 245 (100%), 210 (14%), 108 (25%), 137 (7%).

3.2.3.Methyl3-(4-chlorophenyl)-2-hydroxy-3,4-dihydro-2H-benzo[b][1,4]thiazine-2-carboxylate (6c): 0.134 g (40 %); IR (KBr) cm^{-1}: 3381 (NH), 3053 (OH), 1752 (CO). The signals of diastereomer 1: 1H NMR (300 MHz, DMSO-d6): δ 6.01 (s, 1H, CHN), 3.92 (s, 3H, CO_2Me), 5.4 (s, 1H, OH); 6.39-7.38 (m, Ar); 13C NMR (75 MHz, DMSO-d6): δ 59.0 , 66.55, 84.41, 114.43, 115.37, 116.93, 127.19, 128.96, 129.68, 131.72, 135.87, 140.20, 151.15, 164.31. The signals of diastereomer 2: 1H NMR (300 MHz, DMSO-d6): δ 6.01 (s, 1H, CHN), 3.92 (s, 3H, CO2Me), 5.4 (s, 1H, OH); 6.39-7.38 (m, Ar); 13C NMR (75 MHz, DMSO-d6): δ 59.0 , 64, 55; 84.41, 114.43, 115.37, 116.93, 127.19, 128.96, 129.68, 131.72, 135.87, 140.20, 151,15; 162.31; EIMS: m/z ($C_{16}H_{14}NO_3SCl$) 245 (100%), 108 (46%), 137 (3.5 %), 210 (7.14%).

4. Conclusion

We developed an efficient and simple alternative for the preparation of 1,4-benzothiazines from their corresponding epoxides. Prominent among the advantages of this new method are operational simplicity, good yields and an easy workup procedure.The observed regioselectivity stems from the different forces of nucleophilicity of the nucleophile atoms present in the medium.Further work is currently in progress in our laboratory to extend the application of these new regioselective synthetic methods.

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