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REGIO-CONTROLLED SYNTHESIS OF 1, 4-BENZOTHIAZINONES

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Abstract – Regio-controlled cyclization of gem-dicyanoepoxides with 2-aminothiophenol and its hydrochloride to form 1,4-benzothiazine-2-one or 3-one is described. The cyclization is highly regioselective and the reaction of the epoxides with 2-aminothiophenol under neutral reaction condition gave 1,4-benzothiazine-2-one as a sole cyclized product, whereas that with hydrochloride of 2-aminothiophenol afforded 1,4-benzothiazine-3-one predominantly. The regioselectivity resulted from the reaction condition is discussed.

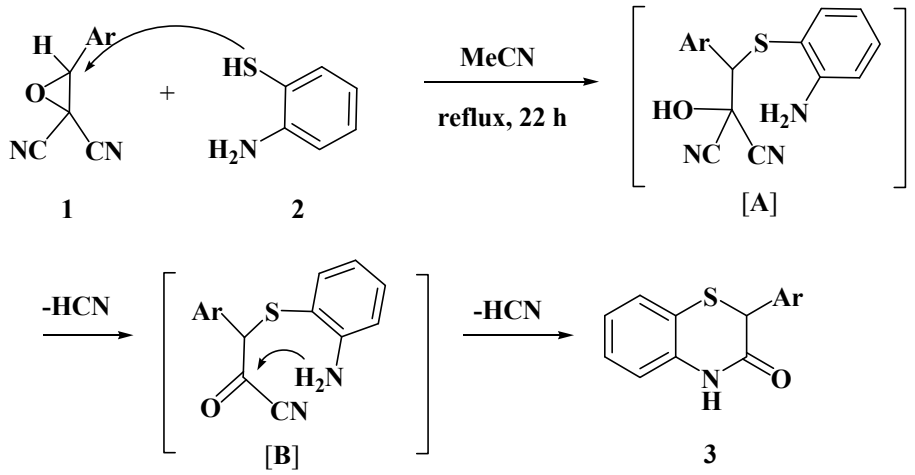
The biological and pharmacological properties of the 1, 4-benzothiazinones were largely studied,[1] particularly, antifungal activity[2-5] as well as a powerful antimicrobial activity.[6,7]

In addition the 1,4-benzothazinones derivatives, which are always of topicality,[8-10] are known for their potential antihypertensive activity,[11] a vasorelaxant activity,[12] inhibiting angiogenesis,[13] anti-Candida,[14] and antimycobacterial agents.[15]

The potential bielectrophile character of two carbons of the epoxide ring,[16a-h] makes it possible to consider the study of their reactivity to reach new heterocycles on the one hand or with heterocycles

already described but obtained by more complex and/or less selective ways of other part.[17-25] Within this framework there, the reaction with the 2-aminothiophénol **2** was studied, under moderated conditions to reach 1,4-benzothiazinones.

Thus, the direct reaction of epoxides **1** with 2-aminothiophenol **2** performed at reflux in acetonitrile, led in one step to the 2-arylbenzothiazin-3-ones **3** with good yields (Scheme 1, Table).



Scheme 1. Synthesis of the 1,4-benzothiazines-3-ones **3**

The reaction is regioselective and the 2-aryl-1,4-benzothiazin-3-ones were obtained with excellent yields. We propose a mechanism (Scheme 1) with passage by a cyanhydrin aminothioether [**A**], resulting from the nucleophilic attack of sulfur on the carbon related to the aryl group of epoxide. This intermediate [**A**] then lead to a second cyanoformyl intermediate [**B**] by losing a molecule of hydrogen cyanide.

The latter can then by a second intramolecular nucleophilic attack of nitrogen of the amine function on carbonyl lead to the cyclization and the formation of the 2-aryl-1,4-benzothiazin-3-ones **3**. Furthermore we do not observe the formation of 3-aryl-1,4-benzothiazin-2-ones which could be obtained by the nucleophilic attack of sulfur on the other carbon of epoxide. The strong nucleophilicity of sulfur compared with nitrogen of the amine function explains the selectivity of the nucleophilic attack on epoxide.

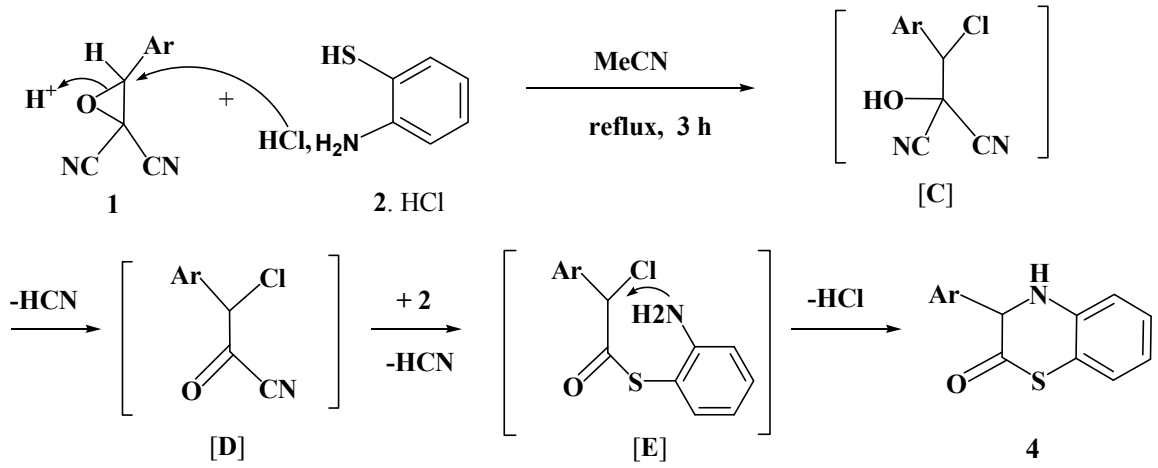
In addition, one also observes selectivity on the level of the electrophilic carbons of epoxide. In effect, carbon related to the grouping aryl is proven to be most electrophilic of the cycle. This selectivity is remarkable because no other competing product is obtained.

All products **3a-3c** were characterized by the conventional physico-chemical methods (IR, NMR and mass spectrometry). Moreover, the compound **3a** in high-resolution mass spectrometry, the MIKE (Mass analyzed Ion Kinetic Energy) spectrum shows the presence of fragment ion of mass m/z = 136 (calcd: 136.0346; found: 136.0340) coming from the molecular ion and corresponding to: $(4\text{-}MeC_6H_4CHS)^+$.

This confirms the exact position of sulfur in the ring.

The regioselectivity of the reaction can be reversed in the presence of acids HX. Indeed, the reaction of the 2-aminothiophenol hydrochloride with epoxides **1** leads to the isomers 3-aryl-1,4-benzothiazin-2-ones **4** resulting from the opposite addition. This is due to the presence of Cl anion in the medium whose nucleophilicity is much larger than that of sulfur.

In this context, the attack of Cl is favoured kinetically, and always takes place on the most electrophilic site, namely the carbon related to the aryl group. This reaction therefore leads selectively to compounds **4** (Scheme 2, Table).



Scheme 2. Synthesis of the 1,4-benzothiazin-2-ones **4**

Table. Synthesis of 2-aryl-1,4-benzothiazin-3-ones **3** and 3-aryl-1,4-benzothiazin-2-ones **4**

Entry	Ar	Mp (°C)	Yields (%)	Compounds
1	4-MeC_6H_4	198-199	80	**3a**
2	4-ClC_6H_4	186-187	90	**3b**
3	4-$NO_2C_6H_4$	202-203	45	**3c**
4	4-MeC_6H_4	180-181	78	**4a**
5	4-ClC_6H_4	143-144	80	**4b**
6	C_6H_5	182-183	76	**4c**

This reaction is interpreted by an electrophilic assistance of the epoxidic cycle by action of HCl, leading to an unstable chlorocyanhydrin [**C**] (Scheme 2). This one easily loses a molecule of hydrogen cyanide to give intermediate cyanoformyl [**D**], which reacts with the 2-aminothiophenol **2** to give α-chloroketone aminothioether [**E**].

The latter evolves through a heterocyclization reaction to give the 1,4-benzothiazin-2-ones **4** (Scheme 2). The proximity of sulfur with the carbonyl group was confirmed by the presence of a fragment ion of mass m/z = 136 coming from the molecular ion **4a-4c** and corresponding to $(C_7H_4OS)^+$.

The structures of heterocycles **4** were established and confirmed by spectroscopic data of ^{1}H NMR, ^{13}C NMR and by mass spectrometry.

In conclusion, the reaction of epoxides **1** with the 2-aminothiophenol and its hydrochloride constitute a simple, and selective method for the synthesis of a new series of 1,4-benzothiazin-2-ones and 3-ones. These compounds are likely to present interesting biological and pharmacological properties.

EXPERIMENTAL

Melting points were taken with a *KOFLER* hot stage apparatus and are uncorrected. The ^{1}H NMR spectra were measured in DMSO-d_6 or ($CDCl_3$ + CF_3CO_2H) solutions on a Bruker 300 MHz spectrometer using TMS as an internal reference (chemical shift in δ ppm), ^{13}C NMR spectra were recorded at 75 MHz. Infrared spectra were determined with a *PERKIN ELMER 1600* Series FT-IR Spectrometer using KBr pellets. Mass spectra were recorded on a *VARIAN MAT 311* and Thermo DSQII-Focus mass Spectrometer.

General procedure for the preparation of 1,4-benzothiazin-3-ones 3a-c

To a solution of epoxide **1** (5 mmol) in MeCN (20 mL), are added the 2-aminothiophenol **2** (5 mmol). The mixture is refluxed for 22 h. The solvent was removed under reduced pressure and the residue obtained is added to a mixture of Et_2O/petroleum ether, the 2-arylbenzothiazin-3-ones **3a-c** (Table) precipitate slowly and are then purified by flash chromatography on alumina column eluted with acetone to give solids which are recrystallized in EtOH.

2-(4-Methylphenyl)-1,4-benzothiazin-3-one (3a): (1.02g, 80%); mp 198-199 °C (mp 200-2002 lit.[26]); IR (KBr): 3200, 1655 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + CF_3CO_2H) δ 2.30 (s, 3H, CH_3), 4.75 (s, 1H, CHS), 7.01-7.32 (m, 8H, Ar), 9.84 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$ + CF_3CO_2H) δ 21.4, 45.8, 118.3, 120.4, 125.9, 127.3, 127.7, 128.1, 130.1, 130.9, 134.7, 139.3, 170.0; HRMS calcd. for ($C_{15}H_{13}NOS$) [M^+] 255.0718; found: 255.0716.

2-(4-Chlorophenyl)-1,4-benzothiazin-3-one (3b): (1.23g, 90%); mp 196-197 °C (mp 198.5-199.5 lit.[26]); IR (KBr): 3220, 1660 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + CF_3CO_2H) δ 4.71 (s, 1H, CHS), 6.93-7.34 (m, 8H, Ar), 10.00 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$ + CF_3CO_2H) δ 45.7, 118.2, 119.8, 122.4, 125.7, 126.1, 127.7, 129.2, 132.4, 133.1, 135.2, 169.8; MS m/z (%): 275 (M^+, 1%), 151 (100), 96 (78), 123 (73).

2-(4-Nitrophenyl)-1,4-benzothiazin-3-one (3c): (0.64g, 45%); mp 202-203 °C; IR (KBr): 3233, 1650

cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CF_3CO_2H) δ 4.77 (s, 1H, CHS), 7.02-7.29 (m, 8H, Ar), 10.11 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$ + CF_3CO_2H) δ 45.1, 118.1, 119.5, 119.9, 125.9, 127.9, 128.0, 129.09, 131.8, 133.9, 134.9, 169.6; HRMS calcd. for ($C_{14}H_{10}N_2O_3S$) [M^+] 286.0381; found: 286.0360.

Preparative procedure for 1,4-benzothiazines-2-ones 4a-c

A suspension of 2-aminothiophenol hydrochloride **2** HCl (1.5 mmol) in MeCN (10 mL), was added epoxide **1** (1 mmol) dissolved in MeCN (5 mL). The reaction mixture is refluxed for 3 h, after evaporation of the solvent the crude oil is dissolved in $CHCl_3$.

The solution is washed with the water, dried over sodium sulfate and evaporated. The residue is dissolved in a mixture of Et_2O and petroleum ether. The 3-aryl-1,4-benzothiazin-2-ones **4a-c** (Table) precipitate after one night in ice and are recrystallized in EtOH.

3-(4-Methylphenyl)-1,4-benzothiazines-2-ones (4a): (0.19g, 78%); mp 180-181 °C; IR (KBr): 3280, 1670 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.4 (s, 3H, CH_3), 4.89 (s, 1H, CHN), 6.95-7.29 (m, 8H, Ar), 10.83 (s, 1H, NH); ^{13}C NMR (75 HMz, DMSO-d_6) δ 21.1, 44.8, 117.4, 118.6, 123.6, 127.6, 127.9, 128.1, 129.5, 133.6, 137.5, 137.6, 166.1; MS m/z (%): 255 (M^+, 31), 105 (100), 136 (58), 226 (19).

3-(4-Chlorophenyl)-1,4-benzothiazines-2-ones (4b): (0.22g, 80%); mp 143-144 °C; IR (KBr): 3211, 1669 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CF_3CO_2H) δ 4.68 (s, 1H, CHN), 6.88-7.56 (m, 8H, Ar), 9.27 (s, 1H, NH); ^{13}C NMR (75 HMz, $CDCl_3$ + CF_3CO_2H) δ 45.6, 117.3, 119.9, 122.2, 125.8, 127.1, 127.8, 129.1, 131.4, 132.2, 135.7, 166.4; MS m/z (%): 275 (M^+, 20), 125 (100), 136 (55), 89 (44).

3-Phenyl-1,4-benzothiazines-2-ones (4c): (0.18g, 76%); mp 182-183 °C; IR (KBr): 3122, 1674 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.95 (s, 1H, CHN), 6.94-7.31 (m, 9H, Ar), 10.86 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 45.1, 117.4, 118.6, 132.6, 127.6, 127.9, 128.2, 128.3, 129.0, 136.6, 137.4, 166.0; MS m/z (%): 242 (M^+, 15), 91 (68), 136 (52), 212 (23), 241 (100).

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