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Synthesis of 2-Oxiranyl and Aziridinyl Thiazoles

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Abstract: 2-Oxiranyl and 2-aziridinyl thiazoles **3** and **7** have been prepared by lithiation of thiazoles **1a** and **1b** and reaction with α-halogenocarbonyl compounds [1a, 1c–d] and α-halogenoimines [1b], respectively.

Keywords: lithiation; oxiranyl thiazoles; aziridinyl thiazoles; formyl epoxides

2-Oxiranyl and 2-aziridinyl thiazoles are extremely useful intermediates in synthetic organic chemistry due to the presence in their framework of the thiazole, which is a masked acyl group [2a–c], and the oxiranyl and the aziridinyl moieties which are amenable to numerous elaborations [3a–d,4a–l]. For instance, the elaboration of such oxiranyl and aziridinyl thiazoles may lead to α-hydroxy-β-amino- and α-amino-β-hydroxy-aldehydes [5]. Notwithstanding such synthetic potential, to our knowledge, only a few papers have reported on the preparation of oxiranes and aziridines bearing the thiazolyl group as a substituent in their framework. Benzothiazolyl epoxides have been prepared by the dehydrobromination of the appropriate bromohydrins [6], a stereoselective Darzens-type reaction [7a,8a–b], and the alkylation of parent oxiranyl anions [7b]. Aziridinyl benzothiazoles have been synthesized from lithiated chloroalkylbenzothiazoles and Schiff's bases [9]. A stereoselective synthesis of thiazolyl oxiranes had been mentioned in Modern Synthetic Methods [2a].

In the present paper we wish to report on a very simple and convenient synthesis of 2-oxiranyl and 2-aziridinyl thiazoles based on the reaction of 2-lithiothiazoles with α-halogenocarbonyl compounds and α-halogenoimines.

Lithiation of thiazoles and reactions with α-halogenocarbonyl compounds

2-Lithiothiazole is usually made by lithium-bromine exchange of 2-bromothiazole with *n*-BuLi [10]. We have found that 2-lithio-4-methylthiazole **1c** can be conveniently prepared almost quantitatively by deprotonation of 4-methyl-thiazole **1a** with lithium diisopropylamide (LDA) in THF at -78 °C. Addition of α-chloroacetone to the THF solution of **1c** afforded chlorohydrin **2a** (95% yield). There was no trace of nucleophilic substitution in the α-chloroacetone. Treatment of **2a** with NaOH in isopropanol under mild conditions (room temperature, 1h) furnished oxiranyl thiazole **3a** (98% yield).

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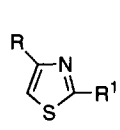
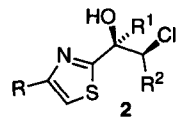
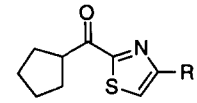


1a R = Me; R_1 = H
1b R = R_1 = H
1c R = Me; R_1 = Li
1d R = H; R_1 = Li
1e R = H; R_1 = $SiMe_3$

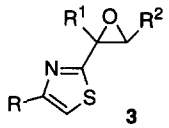


2

2a R = R_1 = Me; R_2 = H
2b R = Me; R_1 = Ph; R_2 = H
2c R = R_1 = R_2 = Me
2d R = Me; R_1 , R_2 = -$(CH_2)_4$-
2e R = H; R_1 , R_2 = -$(CH_2)_4$-

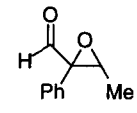


4a R = Me
4b R = H



3

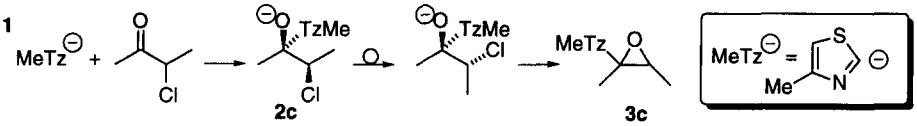
3a R = R_1 = Me; R_2 = H
3b R = Me; R_1 = Ph; R_2 = H
3c R = R_1 = R_2 = Me
3d R = R_2 = Me; R_1 = Ph
3e R = Me; R_1 , R_2 = -$(CH_2)_4$-
3f R = H; R_1 , R_2 = -$(CH_2)_4$-
3g R = R_2 = H; R_1 = Me



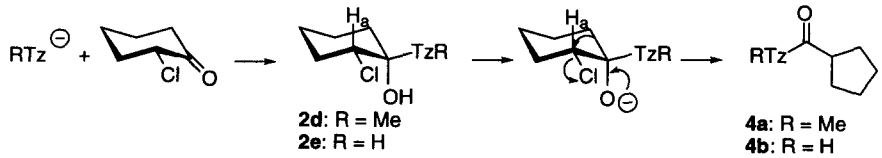
5

The addition of α-chloroacetophenone to lithiated 4-methyl-thiazolyllithium **1c** led straightforwardly to oxiranyl thiazole **3b** (75% yield). The intermediate chlorohydrin **2b**, in this case, could not be isolated. The reaction of **1c** with 3-chloro-2-butanone proceeded with complete diastereoselectivity yielding epoxide **3c** (80% yield) which had the *E* configuration as ascertained by NMR [11]. Such diastereoselectivity could be explained by assuming that lithiothiazole **1c**, in adding to one of the diastereotopic faces of the carbonyl function of 3-chloro-2-butanone, attacks the face that pushes the chloro atom away to give the *syn* chlorohydrin **2c** (not isolated), which then cyclizes, after adopting the suitable antiperiplanar conformation, to the *E* epoxide **3c** (Scheme 1). The idea that nucleophiles attack the carbonyl group of α-haloketones from the less hindered side has precedent [12a–d]. Similarly, the addition of **1c** to the α-bromopropiophenone produced straightforwardly the *E* epoxide **3d** (65% yield) [11]. Accordingly, the addition of **1c** to 2-chlorocyclohexanone gave the expected *syn* chlorohydrin **2d** (95% yield) [11]. However, treatment with NaOH in isopropanol under mild conditions (room temperature for 3 hours) did not furnish the corresponding epoxide **3e**, since the required antiperiplanarity [12a–d] of the OH and Cl groups cannot be achieved. Prolonged reflux gave cyclopentyl thiazolyl ketone **4a** (65% yield). Its formation could be explained by assuming that **2d**, under the basic reaction conditions, undergoes a ring contraction as illustrated in Scheme 2.

Scheme 1



Scheme 2



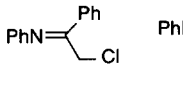
Lithiation of thiazole **1b** with LDA gave a quantitative yield of 2-lithiothiazole **1d**, as proved by its trapping with Me_3SiCl to furnish 2-trimethylsilylthiazole **1e** (95% yield).

Treatment of **1d** with 2-chlorocyclohexanone furnished chlorohydrin **2e** (90% yield) [11] which, as expected, did not cyclize to the corresponding epoxide **3f** but led to ketone **4b** (70% yield) upon treatment with NaOH in isopropanol at 50–70 °C for 48 hours. Epoxide **3g** was straightforwardly obtained in the reaction of **1d** with α-chloroacetone (80% yield).

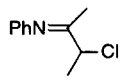
It was interesting to observe that 2-thiazolyl oxiranes **3** could be deblocked to formyl epoxides. Indeed, thiazolyl epoxide **3d** could be elaborated to formyl epoxide **5** (95% yield) by following a known protocol which involves a one-pot, three step sequence (*N*-methylation, reduction and hydrolysis) [2a–c].

Lithiation of thiazoles and reactions with α-halogenoimines

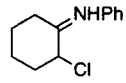
α-Halogenoimines can be easily synthesized from α-halogenoketones and primary amines [13a,b]. In view of this, we planned to synthesize 2-aziridinyl thiazoles from lithiothiazoles and α-halogenoimines. Indeed, we found that 2-lithiothiazole **1d** reacts with α-chloroimine **6a** to give aziridine **7a** (75% yield) and stereoselectively with **6b** to give **7b** (84%). Similarly, the reaction of 2-lithio-4-methyl-thiazole **1c** with α-chloroimine **6b** gave stereoselectively the thiazolyl aziridine **7c** (80% yield), which was proved, by NMR, to have the *E* configuration [11]. Here again the observed stereoselection can be explained by assuming that the thiazolyl anion **1c** (or **1d**) attacks the imine function of **6b** from the less hindered side to give the *syn* chloroamine **8a** (or **8b**) which cyclizes to the aziridine **7b** (or **7c**) after adopting the proper conformation (the Cl and the amino groups in an antiperiplanar arrangement). The reaction of **1c** with α-chloroimine **6c** gave a very good yield of chloroamine **9a** (93%) [11] that could not be cyclized to the aziridine **7d** upon treatment with NaOH even under more severe conditions (reflux for 10 hours). This is to be ascribed to the fact that Cl and the amino groups cannot attain the antiperiplanar arrangement. Similarly, **1d** reacted with **6c** to give **9b** (85%) [11].



6a

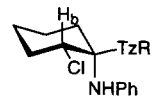


6b

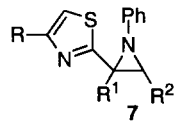


6c

8a : R = Me
8b: R = H



9a: R = Me
9b: R = H



7

7a R = R_2 = H; R_1 = Ph
7b R = H; R_1 = R_2 = Me
7c R = R_1 = R_2 = Me
7d R = Me; R_1 , R_2 = -$(CH_2)_4$-

In conclusion, 2-oxiranyl and 2-aziridinyl thiazoles **3** and **7** can be easily prepared by the reaction of readily available 2-lithiothiazoles **1c** and **1d** with α-halogenocarbonyl compounds [14] and α-halogenoimines, respectively. More work is in progress with the aim of exploiting the above oxiranyl and aziridinyl thiazoles for the preparation of stereodefined α-amino-β-hydroxy- and β-amino-α-hydroxy-aldehydes which are useful intermediates for the synthesis of biologically active compounds.

Preparation of Thiazolyl Oxiranes 3: Typical Procedure. A solution of 396 mg (4 mmol) of **1a** in 4 ml of dry THF was treated with 4.8 mmol of LDA, prepared from *n*-BuLi (4.8 mmol) and diisopropylamine (4.8 mmol) at –78 °C under N_2 atmosphere.

α–Chloroacetone (4.0 mmol) in 2.5 ml of THF was added dropwise after 30 min. The reaction mixture was kept at –78 °C for 3 h and then warmed to RT, quenched with aq. NH_4Cl, extracted with Et_2O, dried over Na_2SO_4 and evaporated under reduced pressure to give almost pure chlorohydrin **2a** (95% yield). A solution of 298 mg of **2a** in 5 ml of isopropanol was treated with 4 ml of 1 N NaOH at RT. After 2 h aq. NH_4Cl was added and the mixture extracted with Et_2O, dried over Na_2SO_4 and evaporated under reduced pressure to give **3a** as an oil (98% yield). All new thiazolyl oxiranes showed consistent IR, MS, ^1H NMR, ^{13}C NMR spectra and satisfactory microanalytical data.

Preparation of Thiazolyl Aziridines 7: Typical Procedure. A solution of 3 mmol of **1b** in 2 ml of dry THF was treated with 3.2 mmol of LDA at –78 °C under N_2 atmosphere. Chloroimine **6b** [13a] (3.0 mmol) in 2.5 ml of THF was added dropwise after 30 min. The reaction mixture was kept at –78 °C for 3 h and then warmed at RT, quenched with aq. NH_4Cl, extracted with Et_2O, dried over Na_2SO_4 and evaporated under reduced pressure to give a residue which was column chromatographed (silica gel, petroleum ether/diethyl ether 1:1) to give **7a** as an oil (75% yield). All new thiazolyl aziridines showed consistent IR, MS, ^1H NMR, ^{13}C NMR spectra and satisfactory microanalytical data.

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