Regioselectivity of the Reactions of 4,5-Diphenylimidazole-2-thione with 1-Chloro-2,3-epoxy-propane and 1-Bromo-propene, Efficient Precursors for Imidazo[2,1-*b*]thiazine and Thiazole. Effect of Microwave and Solid Support

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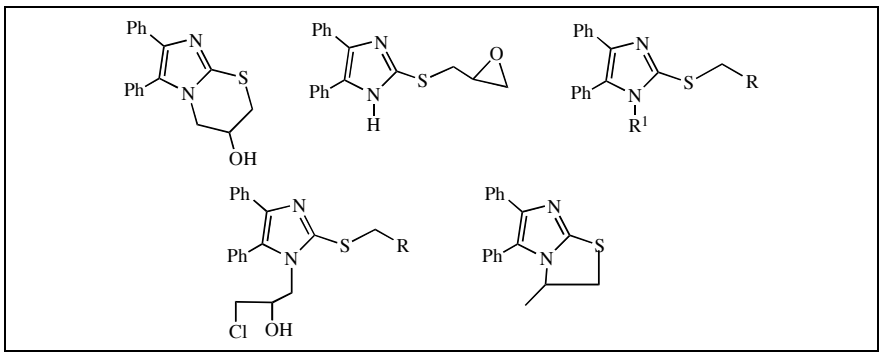

A solid support under microwave (MW) irradiation without solvent allowed the synthesis of the 2,3-epoxy-propyl-thioimidazole **4**, regioselectively, and prohibited its cyclization to give the imidazo[2,1-*b*]thiazine **3** from the reaction of 4,5-diphenylimidazole-2-thione (**1**) with 1-chloro-2,3-epoxy-propane (**2**). The formation of the latter required basic conditions whereby it became the sole product; the change of the basic catalyst changed the ratio of the two products under both conventional and microwave (MW) conditions. A regioselective allylation of **1** with allyl bromide in presence of triethylamine gave the S-allyl **8**, while in presence of potassium carbonate led to the S,N-bis(allylated) derivative **9**. The intramolecular ring closure of **8** in presence of sulfuric acid afforded the imidazothiazole **16**. Protection of the sulfur in **1** and subsequent reaction with allyl bromide gave the N-allylated derivative and with **2** gave N-3-chloro-prop-1-yl derivative that shed light on the preferred route for the formation of **3** and **4**. The reactivity encountered during the alkylation of **1** with **2** has been theoretically investigated by using the AM1 method.

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INTRODUCTION

The imidazole core is a common moiety in a large number of natural products and pharmacologically active compounds [1]. Moreover, valuable biological applications such as antifungal [2], anti-thyroid [3] and antiasthmatic [4] activities have been associated with 2-thiosubstituted imidazoles. Its annulations with a thiazine or thiazole ring provide imidazo-thiazines and thiazoles with a wide spectrum of biological and pharmacological properties including antifungal [5], bactericidal, fungicidal [6], benzodiazepine receptors [7], vasodilators and hypotensives properties [8].

Due to environmental and economical aspects, solvent-free methods are of great interest in order to develop more clean, safe and easy procedures to perform. The use of solvent-free conditions and/or solid supported reagents coupled with microwave (MW) irradiation allowed the preparation of various classes of compounds in an accessible manner [9-12]. As a continuation of our program on the use of microwave (MW) irradiation in the synthesis of heterocyclic compounds [10-23], we report herein the optimum conditions for the regioselective alkylation of 4,5-diphenyl-1,3-dihydroimidazole-2-thione (**1**) with 1-chloro-2,3-epoxy-propane (**2**) and allylation with 1-bromo-prop-2-ene and efficient syntheses of imidazothiazine and thiazole. The presence of a solid support, MW and solvent-free conditions played a great role on the reactivity of the different carbons in 1-chloro-2,3-epoxy-propane (**2**) towards the nucleophilic nature of the alkylating reagents.

RESULTS AND DISCUSSION

The reaction of diphenylimidazole thione with epichlorohydrin was reported [24] to give the imidazothiazine **3** in 48% yield. The reaction was carried out by heating the reactants to 85 °C, in a mixture of butanone and *N*,*N*-dimethylacetamide for two hours to provide the salt of **3** whose basification gave **3**.

In the present work, the alkylation of 4,5-diphenylimidazole-2-thione (**1**) with epichlorohydrin (**2**) has been investigated using different reaction conditions under both conventional and MW irradiation. Thus, the alkylation in presence of 1.1 or 2.2 equivalents of KOH in polar solvents (methanol or water) at room temperature for 24 hours afforded the corresponding imidazothiazine **3** in 70-72% yield; subjection to MW irradiation required 2-3 minutes only to afford 85-86% yield (Table 1). Similar results were also obtained when KOH was replaced by K_2CO_3 either under conventional or MW conditions. The preferential alkylation of the thioimidazole **1** at the sulfur atom has been due to its higher nucleophilicity [22]. Accordingly, it can be concluded that the formation of the imidazothiazine **3** could be through the formation of the thiolate anion intermediate to give **4**, which underwent an intramolecular ring closure *via* a nucleophilic attack of the imidazole nitrogen on the oxirane carbon atom. Otherwise, the attack of the thiolate could occur at the oxirane carbon followed by intramolecular cyclization to give the same product.

On the other hand, compound **3** was prepared directly from the thioimidazole **1** in aqueous media without a deprotonating agent that can be due to the high acidity of the hydrogen atoms. The ^{1}H NMR spectrum of the product **3** showed two doublet of doublets at δ_H 3.11 and 3.26 ppm assigned to SCH_2 with J_{gem} 12.6 Hz and two doublet of doublets at δ_H 3.55 and 3.76 ppm due to NCH_2 with J_{gem} 13.0 Hz; the assignment based on considering the electronegativity of S and N. The spectrum also showed one characteristic exchangeable proton at δ_H 5.61 ppm due to the OH proton and a multiplet at δ_H 4.26-4.30 ppm due to the CH-proton. These data were in agreement with that reported [24] in literature but with a reverse assignment of the two methylene groups. The product **3** was also identical with that obtained in low yield by the cyclization of 2-[(2,3-dihydroxyprop-1-yl)thio]-4,5-diphenyl-1*H*-imidazole [25].

When triethylamine was used as a base for the reaction of **1** with **2**, two products were obtained and identified, based on their spectral and elemental analyses; compound **3** as the major product and the epoxide derivative **4** as minor one. The reaction required reflux in acetone for 30 min or irradiation by MW for 2 min. Prompted by these observations; we have attempted to find the optimum conditions that afford selectively the oxirane **4**. Thus, the coupling under solvent free conditions has been also adopted under MW irradiation. When a mixture of **1** and epichlorohydrin (**2**) were adsorbed on the surface of bentonite, alumina or silica gel and then irradiated by MW for 2 minutes in a closed Teflon vessel, the desired oxirane **4** was obtained in 90-94% yield (Table 1). Further irradiation of **4** by MW in presence of excess of **2** for 10 minutes gave **3** in 90% yield (Scheme 1) and the S,N-bis(epoxide) derivative **5** was not formed.

Scheme 1

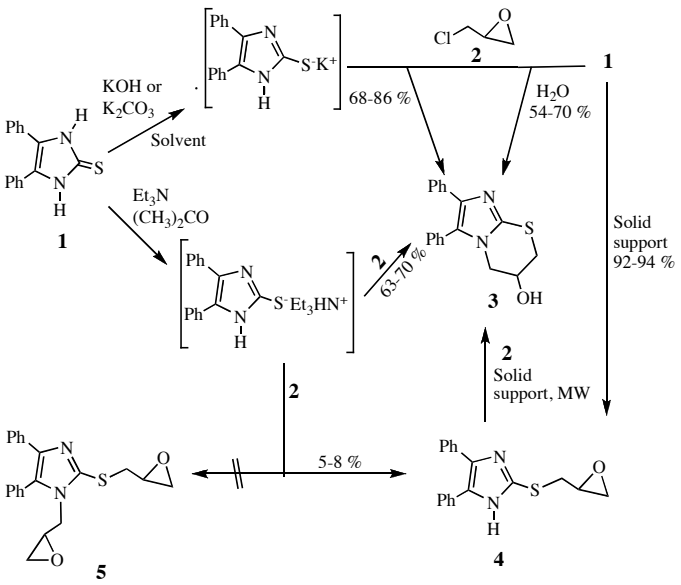


Table 1

Reaction conditions for the alkylation of **1** with epichlorohydrin (**2**).

Entry	Solvent	Base	Solid Support	CM/MW	Time	Product distribution	
						3 (%)	4 (%)
a	MeOH	KOH	-	CM	24.0 h	72	-
b	H_2O	KOH	-	CM	24.0 h	70	-
c	MeOH	KOH	-	MW	2.0 min	86	-
d	H_2O	KOH	-	MW	3.0 min	85	-
e	DMF	K_2CO_3	-	CM	24.0 h	68	-
f	DMF	K_2CO_3	-	MW	2.0 min	80	-
g	H_2O	-	-	CM	8.0 h	54	-
h	H_2O	-	-	MW	6.0 min	70	-
i	Me_2CO	NEt_3	-	CM	30 min	63	5
j	Me_2CO	NEt_3	-	MW	2.0 min	76	8
k	-	-	bentonite	MW	2.0 min	-	94
l	-	-	Al_2O_3	MW	2.0 min	-	92
m		-	Silica gel	MW	2.0 min	-	92
n		-	-	MW	10.0 min	90	-

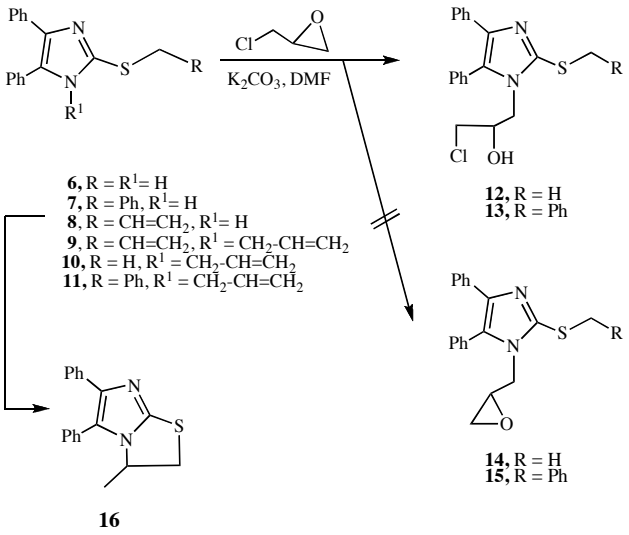
The structure of compound **4** was confirmed from its ^{1}H NMR spectrum which showed the absence of the exchangeable signal assigned for the OH proton of **3** and appearance of two doubled doublets at δ_H 3.32 and 3.41 ppm due to SCH_2, a doublet at δ_H 3.65 due to OCH_2 and a multiplet at δ_H 4.22-4.26 ppm assigned to the C*H*- proton of the epoxy ring. The ^{13}C NMR spectrum confirmed the presence of SCH_2 and OCH_2 at δ_c 37.5 and 48.8, respectively, as well as one tertiary carbon resonance at δ_c 70.2 ppm.

In light of that, we can deduce that the regioselective alkylation **1** with epichlorohydrin in solvent free media gave the epoxide derivative **4** in excellent yield, whereby no by-products were detected.

In order to shed more light on the reaction of epichlorohydrin with the imidazole thione, the S-protected imidazoles became required before the reaction with epichlorohydrin. Although the alkylation of imidazol-ethione was known [26-30], we have reinvestigated the reactions under MW irradiations whereby the S-protected derivatives **6,7** and **8** were prepared in 92-97% yield within few minutes (Table 2), upon allylation [26-30] with 1.1 equivalent of allyl bromide in presence of triethylamine as base. When, the allylation of **1** took place with 1.1 equivalent of allyl bromide in presence of potassium carbonate in DMF as solvent, a mixture of the S-allyl and S,N-bis(allylated) derivatives **8** and **9** were obtained in addition to the recovery of the starting material. In contrast, when 2.2 equivalents of allyl bromide were used in presence of potassium carbonate, the S,N-bis(allylated) derivative **9** was obtained in 84% and 94% yield, after 5 h heating under reflux and after 2 min irradiation under MW, respectively (Table 2). Alternatively, **9** has been prepared under the same reaction conditions in 82% and 91% yield by further allylation of **8** (Scheme 2). The ^{1}H-^{1}H DQFCOSY experiment facilitated the spectral assignment of **9**. Thus, the ^{1}H NMR spectrum of **9** showed NCH_2-allyl protons at δ_H 5.32 and 5.36 ppm as two doublets and SCH_2-allyl protons at δ_H 5.16 and 5.28 ppm as two doublets. The bis-allylation was confirmed by the disappearance of NH protons, which appeared in the precursors at the down field region at δ_H 12.50-12.59 ppm one exchangeable signal due to the NH proton of the imidazole ring.

Further alkylation of **6** and **7** with allyl bromide in DMF using potassium carbonate as base gave the bis(alkylated) derivatives **10** and **11**, respectively (Scheme 2). Heating of **6** or **7** with allyl bromide and/or epichlorohydrin under reflux for 4-6 h gave the bis-alkylated derivatives **10-13** in 78-82% yields; while when the reactions were achieved under microwave (MW) irradiation, the yields were 90-96% and the time was reduced to 2.0-3.5 min (Table 2). However, when the reactions of **6** and **7** with **2** were carried out on a solid support and MW irradiation, **12** and **13** were formed. Their ^{1}H NMR spectra showed the disappearance of the signal of the NH proton. The NMR spectrum of **11** showed a singlet at δ_H 2.70 ppm due to SCH_3 protons instead of a doublet at 4.40 assigned to NCH_2 and two doublets at δ_H 4.93 and 5.18 ppm due to H-1 and H-1'. The H-2 resonated as multiplet at δ_H 5.77-5.80 ppm.

Scheme 2



On the other hand, the S-allyl derivative **8** undergoes an intramolecular cyclization under acidic conditions using concentrated sulfuric acid at 0 ºC to give the imidazo-thiazole **16** in 86% yield. The ^{1}H NMR spectrum of the cyclized derivative **16** showed a doublet at δ_H 1.26 ppm due to the CH_3 protons and a multiplet at the lower field δ_H 4.44-4.50 ppm due to the C*H*CH_3 proton.

Table 2

Comparative data of conventional and MW methods for the synthesis of compounds **6-16**.

Compound No	Starting Material	Conventional method (CM)		Microwave method (MW)	
		Time (h)	Yield%	Time (min)	Yield%
6	**1**	0.5	82	1.0	96
7	**1**	2.0	80	2.0	92
8	**1**	1.0	85	1.0	97
9^{i}	**1**^{i}	5.0	84	2.0	94
9^{ii}	**8**^{ii}	4.0	82	2.0	91
10	**6**	4.0	82	2.0	96
11	**7**	4.0	80	2.5	92
12	**6**	5.0	80	3.0	94
13	**7**	6.0	78	3.5	90
16	**8**	3.0	86	-	-

i. Prepared from **1**; **ii**. Prepared from **8**.

In order to interpret the preferential mode of reaction of **1** with **2** to give the imidazothiazine **3** or epoxide derivative **4**, a theoretical approach by means of semiemperical AM1

method has been carried out using the MOPAC7 program package [31]. Thus, the heat of formation, dipole moment, and the highest occupied molecular orbital energies E_{HOMO}, the lowest unoccupied molecular orbital energies E_{LUMO}, the charge density on heteroatoms as well as relative stability of reactants, transition states and products have been calculated (Table 3).

The predominance of the thione form of **1** over the respective thiol form has been confirmed in a former work [22]. The higher electron density on the sulfur atom than the nitrogen atom could lead to the conclusion that the sulfur atom should have more nucleophilic capability to react regioselectively with 1-chloro-2,3-epoxypropane (**2**) to give **4**. However **2** can be attacked on C-1 or on C-3 *via* opening and subsequent ring closure to form the epoxide ring on the other carbon; examples of both ways of opening are known in literature [32-34]. *Ab initio* molecular orbital calculations indicated that a normal nucleophilic attack of a hydroxide ion at the C-1 position of 1-bromo-2,3-epoxypropane has been concluded whereas an indirect pathway operated *via* the nucleophilic attack on C-3 when **2** was used to give the same product [31,32]. Since the product **3** has a six membered ring, the formation of a five membered ring has been excluded and consequently the attack on C-2 of the epoxide ring has not been considered; the relative stability of the formed ring and not the nucleophilic attack from the least hindered site has been realized [24].

Thus, the regioselective alkylation of **1** [22], to give **4** could take place *via* displacement of the chlorine atom or opening the epoxide ring to give the anionic transition states **TS-1** which could be cyclized to **4**. If a proton transfer has taken place to give **TS-2**, it could be cyclized to **3**, which also formed *via* **TS-3** from **4**. Analyzing the charge density in the reactant, transition states and products revealed that the charge density localized on the oxygen atom is higher than that localized on the imidazole nitrogen atoms of all transition states which promoted the proton transfer in **TS-1** to give **TS-2** followed by intramolecular attacked by the nitrogen atom.

Moreover, comparison of the calculated relative stability (**RS**) of the transition states and products led to the conclusion that the competitive reaction favors formation of the imidazothiazine **3** as the the predominant product. The relative stability of the imidazothiazine **3** compared to the epoxide derivative **4** was -33.918 Kcal. Furthermore, the **TS-2** has greater relative stability than **TS-1** and **TS-3**.

Consequently, the stability of transition states can be stated in the order **TS-2** > **TS-1** > **TS-3** indicating that the formation of **3** could be *via* **TS-2**. This explains the predominant formation of **3** rather than **4**; the latter requires the less stable **TS-1**, which readily rearranges into **TS-2**. Moreover, the formation of the chloropropyl derivatives **12** and **13** from the S-protected analogues **6** and **7** indicated that the formation of **TS-2** *via* **TS-1** is the preferred route. In this manner, the surprising formation of the imidazothiazine **3** as the sole product and the S-epoxide derivative **4** was formed only under MW irradiation on a solid support in dry media became apparent; in a previous work [35], the alkylation on the imidazole nitrogen atom occurred in presence of K_2CO_3 and not Et_3N presumably due to the extent of abstraction of a proton from N-H of the imidazole ring.

In conclusion the intramolecular ring closure towards the nitrogen atom afforded the imidazothiazine **3** which could occur in solution even in the neutral media. A solid support under MW irradiation without solvent allowed the synthesis of the 2,3-epoxy-propyl-thioimidazole **4**, regioselectively, and prohibited its cyclization to give the imidazo[2,1-*b*]thiazine **3** from the reaction of 4,5-diphenylimidazole-2-thione (**1**) with 1-chloro-2,3-epoxy-propane (**2**). The later required basic conditions where it became the sole product; the basic catalyst changed the ratio of the two products under both the conventional and MW, this in addition to the expected improvements in the yields of the alkylated products in less reaction time.

Scheme 3

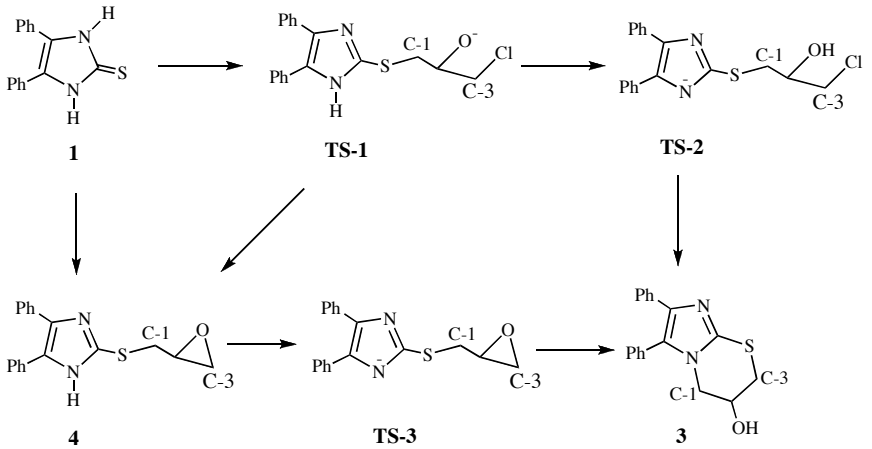


Table 3

Calculated (AM1) Heat of Formation (kcal), Relative Stability (kcal), Dipole Moments, (μ, debye), HOMO Orbital Energies (E_{HOMO}, eV) and Charge Density on heteroatoms for the reactant, transition states and products.

Tautomer No	Heat of Formation (ΔH_f) Kcal	μ Debye	E_{HOMO} eV	E_{LUMO} eV	Charge Density on heteroatoms	Relative stability (RS) Kcal
1	103.617	6.425	-8.003	-0.676	-0.236 (N-1) -0.236 (N-3) -0.266 (S)	
TS1	30.848	19.946	-3.885	1.760	-0.199 (N-1) -0.165 (N-3) 0.268 (S) -0.682 (O) -0.338 (C-1) 0.221 (C-2) -0.138 (C-3)	-35.618 (**TS-2 – TS-1**)
TS2	-4.770	3.047	-4.301	3.162	-0.159 (N-1) -0.135 (N-3) 0.236 (S) -0.352 (O) -0.353 (C-1) 0.040 (C-2) -0.110 (C-3)	-61.760 (**TS-2 – TS-3**)
TS3	56.990	4.311	-4.163	3.214	-0.140 (N-1) -0.148 (N-3) 0.238 (S) -0.306 (O) -0.303 (C-1) -0.022 (C-2) -0.086 (C-3)	
3	62.286	4.027	-8.089	-0.252	-0.149 (N-1) -0.103 (N-3) 0.332 (S) -0.309 (O) -0.065 (C-1) -0.029 (C-2) -0.362 (C-3)	-33.918 (**3 – 4**)
4	96.204	2.194	-8.001	-0.298	-0.177(N-1) -0.148 (N-3) 0.273 (S) -0.252 (O) -0.275 (C-1) -0.048 (C-2) -0.088 (C-3)	

[i]RS = The difference in the heat of formation between each two energetic states

EXPERIMENTAL

Chemistry. Melting points were determined with a Melt-Temp apparatus and are uncorrected. TLC was performed on Baker-Flex silica gel using ethyl acetate-hexane as developing solvents, and the spots were detected by UV light absorption. The irradiation was done, unless otherwise stated, in a closed Teflon cylindrical vessel that was placed at the center of a rotating plate inside the oven EM-230M (1200 watt output power). The vessel was supported by a frame for safety. The vessel has an outside diameter 6.5 cm and a length of 6.0 cm whereas the space inside the vessel was 3.0 cm wide and 2.0 cm length. More 2.0 cm in the length inside the vessel was used for the screw of the cover in order to be tight. The oven was adjusted on the defrost mode with the fixed output power. IR spectra were recorded with Perkin-Elmer 1430 spectrometer. ^{1}H NMR spectra were recorded on Jeol spectrometer (500 MHz). Chemical shifts δ are given in ppm relative to the signal for TMS as internal standard. The elemental analyses were performed by the microanalysis unit at the Faculty of Science, Cairo University.

General procedure of the reaction of 1 with epichlorohydrin.

Conventional method (CM). To a solution of compound **1** (1 mmol) in the appropriate solvent (50 mL) and base (1.1 mmol), epichlorohydrin (**2**) (1.1 mmol) was added. The conditions of the reaction are shown in Table 1. The reaction mixture was poured onto crushed ice in the case of DMF or otherwise the product was removed under reduced pressure. Water was added and the product was collected by filtration and recrystallized from ethanol.

Microwave method (MW). A mixture of compound **1** (0.5 mmol), appropriate solvent (5 mL), base (0.55 mmol), and epichlorohydrin (**2**) (0.55 mmol) in a closed Teflon vessel was irradiated by MW. The obtained reaction mixture was treated with water and the product was crystallized from ethanol (Table 1).

Microwave and solid support method. A mixture of compound **1** (0.5 mmol) and epichlorohydrin (**2**) (0.55 mmol) were adsorbed on the surface of activated bentonite, alumina or silica gel (0.3 g) and mixed uniformly in a closed Teflon vessel and then irradiated by MW for 2 min. After cooling, the product was extracted by boiling ethanol. The ethanol was evaporated and the product was recrystallized from ethanol to give **4**.

6,7-Diphenyl-2*H*,3*H*,4*H*-3-hydroxytetrahydroimidazo[2,1-*b*][1,3]thiazine (3). This compound [24,25] was obtained as colorless crystals, mp 210-212 ºC, lit. mp 219-220 °C, lit. mp 210-212 °C; ir (KBr): 1574 (C=C), 1625 (C=N) and 3215 (NH) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.11 (dd, 1H, J = 6.9, J = 12.6 Hz, SCH_2), 3.26 (dd, 1H, J = 6.3, J_{gem} = 12.6 Hz, SCH_2), 3.55 (dd, 1H, J = 6.3, J_{gem} = 13.0 Hz, NCH_2), 3.76 (dd, 1H, J = 3.4, J_{gem} = 13.0 Hz, NCH_2), 4.26-4.30 (m, 1H, CHO), 5.61 (s, 1H, D_2O exchangeable, OH), 7.18-7.27 (m, 6H, Ar-H), 7.31-7.41 (m, 4H, Ar-H). *Anal*. Calcd. for $C_{18}H_{16}N_2SO$ (308.40): C, 70.10; H, 5.23; N, 9.08. Found: C, 69.92; H, 5.39; N, 9.36.

4,5-Diphenyl-2-thiomethyloxiraneimidazole (4). This compound was obtained as colorless crystals, mp 265-266 ºC; ir (KBr): 1565 (C=C), 1610 (C=N) and 3198 (NH) cm^{-1}. ^1H nmr ($CDCl_3$): δ 3.32 (dd, 1H, J = 6.1, J_{gem} = 15.3 Hz, SCH_2), 3.41 (dd, 1H, J = 2.3, J_{gem} = 15.3 Hz, SCH_2), 3.65 (d, 2H, J = 2.3 Hz, OCH_2), 4.22-4.26 (m, 1H, CHO), 7.26-7.30 (m, 6H, Ar-H), 7.41-7.43 (m, 4H, Ar-H); ^{13}C nmr δ 37.5 (SCH_2), 48.8 (OCH_2), 70.2 (CHO), 126.7, 127.9, 128.8, 129.0, 129.7, 131.2, 140.7 (Ar-C). *Anal*. Calcd. for $C_{18}H_{16}N_2SO$ (308.40): C, 70.10; H, 5.23; N, 9.08. Found: C, 70.21; H, 4.99; N, 9.26.

General procedure for the preparation of the S-alkyalted derivatives (6-8).

Conventional method (CM). To a mixture **1** (1 mmol) and triethylamine (1.1 mol) in ethanol (50 mL), the appropriate alkyl halide (1.1 mmol) was added. The mixture was heated under reflux for 0.5-2 h. The ethanol was removed under reduced pressure and the product was recrystallized from ethanol. (Table 2)

Microwave method (MW). A mixture of **1** (1 mmol), triethylamine (1.1 mol), ethanol (5 mL) and the appropriate alkyl halide (1.1 mmol) in a closed Teflon vessel was irradiated by MW. The obtained mixture was treated as described above (Table 2).

4,5-Diphenyl-2-thiomethylimidazole (6). This compound [28,29] was obtained as colorless crystals, mp 190-191 ºC; ir (KBr): 1575 (C=C), 1660 (C=N), 3210 (NH) cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.53 (s, 3H, CH_3), 7.18-7.30 (m, 5H, Ar-H), 7.34-7.51 (m, 5H, Ar-H), 12.50 (s, 1H, D_2O exchangeable, NH). *Anal*. Calcd. for $C_{16}H_{14}N_2S$ (266.36): C, 72.15; H, 5.30; N, 10.52. Found: C, 72.39; H, 5.41; N, 10.79.

4,5-Diphenyl-2-thiobenzyl-imidazole (7). This compound [26,27] was obtained as colorless crystals, mp 184-185 ºC, lit. mp 185-186 °C, lit. [30] mp 183 °C; ir (KBr): 1540 (C=C), 1690 (C=N), 3218 (NH) cm^{-1}. ^1H nmr ($CDCl_3$): δ 4.35 (s, 2H, CH_2Ph), 7.17-7.29 (m, 8H, Ar-H), 7.34-7.44 (m, 7H, Ar-H), 12.59 (s, 1H, D_2O exchangeable, NH). *Anal*. Calcd. for $C_{22}H_{18}N_2S$ (342.46): C, 77.16; H, 5.30; N, 8.18. Found: C, 76.89; H, 5.42; N, 8.06.

4,5-Diphenyl-2-thioallylimidazole (8). This compound [26,27] was obtained as colorless needles, mp 174 ºC, lit. mp 181-182 °C; ir (KBr): 1580 (C=C), 1642 (C=N), 3194 (NH) cm^{-1}. ^1H nmr ($CDCl_3$): δ 3.73 (d, 2H, $J_{3,2}$ = 6.1 Hz, SCH_2-allyl), 5.05 (d, 1H, $J_{1,2}$ = 9.9 Hz, $=CH_2$), 5.22 (d, 1H, $J_{1,2}$ = 16.9, $=CH_2$), 5.89-5.97 (m, 1H, -CH=), 7.16-7.29 (m, 5H, Ar-H), 7.35-7.50 (m, 5H, Ar-H), 12.57 (s, 1H, D_2O exchangeable, NH). *Anal*. Calcd. for $C_{18}H_{16}N_2S$ (292.40): C, 73.94; H, 5.52; N, 9.58. Found: C, 73.71; H, 5.29; N, 9.42.

General procedure for the alkylation of the S-alkylated thioimidazoles 6-8.

Conventional method (CM). To a solution of S-alkylated **6-8** (1 mmol) in DMF (25 mL), potassium carbonate (2.2 mmol) was added followed by allyl bromide and/or epichlorohydrin (2.2 mmol). The mixture was heated under reflux for 4-6 h, then cooled and poured onto crushed ice. The products were washed with water, dried and recrystallized from ethanol (Table 2).

Microwave method (MW). A mixture of S-alkylated **6-8** (1 mmol), DMF (5 mL), potassium carbonate (2.2 mmol) and allyl bromide and/or epichlorohydrin (2.2 mmol) in a closed Teflon vessel was irradiated by MW for 2-3.5 min. The obtained reaction mixture was treated as described above (Table 2).

1-Allyl-2-thioallyl-4,5-diphenylimidazole (9). This compound was obtained as colorless crystals, mp 122 ºC; ir (KBr): 1535 (C=C), 1685 (C=N) cm^{-1}. ^1H nmr (DMSO-d_6): δ 3.95 (d, 2H, $J_{3,2}$ = 6.9 Hz, SCH_2-allyl), 4.80 (d, 2H, $J_{3,2}$ = 5.3 Hz, NCH_2-allyl), 5.16 (d, 1H, $J_{1,2}$ = 9.9 Hz, $=CH_2$(S)), 5.28 (d, 1H, $J_{1',2}$ = 17.6 Hz, $=CH_2$(S)), 5.32 (d, 1H, $J_{1,2}$ = 10.7 Hz, $=CH_2$(N)), 5.36 (d, 1H, $J_{1',2}$ = 17.6 Hz, $=CH_2$(N)), 5.59-6.01 (m, 2H, -CH= (S), -CH= (N)), 7.17-7.26 (m, 3H, Ar-H), 7.32-7.37 (m, 2H, Ar-H), 7.40-7.50 (m, 5H, Ar-H). *Anal*. Calcd. for $C_{21}H_{20}N_2S$ (332.46): C, 75.87; H, 6.06; N, 8.43. Found: C, 75.58; H, 5.97; N, 8.13.

1-Allyl-2-thiomethyl-4,5-diphenylimidazole (10). This compound was obtained as yellow crystals, mp 205-206 ºC; ir (KBr): 1515 (C=C), 1672 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.70 (s, 3H, CH_3), 4.40 (d, 2H, $J_{3,2}$ = $J_{3',2}$ = 3.1 Hz, NCH_2-allyl), 4.93 (d, 1H, $J_{1,2}$ = 17.3 Hz, $=CH_2$), 5.18 (d, 1H, $J_{1',2}$ = 10.7 Hz, $=CH_2$), 5.77-5.80 (m, 1H, -CH=), 7.11-7.20 (m, 3H, Ar-H), 7.31-7.35 (m, 2H, Ar-H), 7.41-7.49 (m, 5H, Ar-H). *Anal*. Calcd. for $C_{19}H_{18}N_2S$ (306.43): C, 74.47; H, 5.92; N, 9.14. Found: C, 74.29; H, 5.65; N, 9.03.

1-Allyl-2-thiobenzyl-4,5-diphenylimidazole (11). This compound was obtained as colorless crystals, mp 218-219 ºC; ir (KBr): 1529 (C=C), 1682 (C=N) cm^{-1}. ^1H nmr ($CDCl_3$): δ 4.11 (d, 2H, $J_{3,2}$ = $J_{3',2}$ = 7.6 Hz, NCH_2-allyl), 4.34 (s, 2H, CH_2Ph), 4.75 (d, 1H, $J_{1,2}$ = 17.6 Hz, $=CH_2$), 5.04 (d, 1H, $J_{1,2}$ = 10.7 Hz, $=CH_2$'), 5.55-5.62 (m, 1H, -CH=), 7.13-7.27 (m, 10H, Ar-H), 7.40-7.52 (m, 5H, Ar-H). *Anal*. Calcd. for $C_{25}H_{22}N_2S$ (382.15): C, 78.50; H, 5.80; N, 7.32. Found: C, 78.39; H, 5.46; N, 7.54.

1-(3-Chloro-2-hydroxyprop-1-yl)-2-thiomethyl-4,5-diphenylimidazole (12). This compound was obtained as colorless syrup; ir (KBr): 1583 (C=C), 1637 (C=N), 3345 (O-H) cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.65 (s, 3H, CH_3), 3.50 (dd, 1H, J = 4.6, J_{gem}= 13.7 Hz, NCH_2), 3.60 (d, 2H, J= 8.1 Hz, CH_2Cl), 3.73 (dd, 1H, J= 4.6, J_{gem}= 13.7 Hz, NCH_2), 4.08-4.12 (m, 1H, CH), 4.20-4.26 (m, 1H, D_2O exchangeable, OH), 7.20-7.29 (m, 5H, Ar-H), 7.35-7.48 (m, 5H, Ar-H). *Anal*. Calcd. for $C_{19}H_{19}ClN_2OS$ (358.89): C, 63.59; H, 5.34; N, 7.81. Found: C, 63.23; H, 5.45; N, 8.02.

1-(3-Chloro-2-hydroxyprop-1-yl)-2-thiobenzyl-4,5-diphenylimidazole (13). This compound was obtained as colorless syrup; ir (KBr): 1587 (C=C), 1640 (C=N) and 3337 (O-H) cm^{-1}. ^1H nmr ($CDCl_3$): δ 3.46 (dd, 1H, J= 6.1, J_{gem}= 13.0 Hz, NCH_2), 3.54 (d, 2H, J = 8.4 Hz, CH_2Cl), 3.68 (dd, 1H, J= 6.1, J_{gem}= 13.0 Hz, NCH_2), 4.06-4.10 (m, 1H, CH), 4.18-4.25 (m, 1H, D_2O exchangeable, OH), 4.37 (s, 2H, CH_2Ph), 7.22-7.30 (m, 5H, Ar-H), 7.37-7.47 (m, 5H, Ar-H). *Anal*. Calcd. for $C_{25}H_{23}Cl\ N_2OS$

(434.98): C, 69.03; H, 5.33; N, 6.44. Found: C, 69.27; H, 5.12; N, 6.93.

5,6-Diphenyl-2*H*,3*H*-3-methyltetrahydroimidazo[2,1-*b*][1,3]-thiazole (16). To a cooled solution of concentrated sulfuric acid (10 mL) was added 4,5-diphenyl-2-thioallylimidazole (**8**) with stirring during 1 h at 0 ºC, then the stirring was continued for 2 h at room temperature. The reaction mixture was poured onto crushed ice. The product was washed with water, dried and recrystallized from ethanol to give **16** as colorless crystals, mp 242-244 ºC. ^{1}H nmr (DMSO-d_6): δ 1.26 (d, 3H, J = 6.9 Hz, CH_3), 3.36 (dd, 1H, J = 4.6, J_{gem} = 13.7 Hz, SCH_2), 3.39 (dd, 1H, J = 5.3, J_{gem} = 13.7 Hz, SCH_2), 4.44-4.50 (m, 1H, CH), 7.15-7.22 (m, 3H, Ar-H), 7.30-7.35 (m, 2H, Ar-H), 7.38-7.50 (m, 5H, Ar-H). *Anal*. Calc*d*. for $C_{18}H_{16}N_2S$ (292.40): C, 73.94; H, 5.52 N, 9.58. Found: C, 73.72; H, 5.40; N, 9.39.

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