

Synthesis and Alkylation of 5-(3-Chlorobenzo[*b*]thien-2-yl)-*4H*-1,2,4-triazole-3-thiol Under Classical and Microwave Conditions.
AM1 Semiempirical Calculations for
Investigating the Regioselectivity of Alkylation

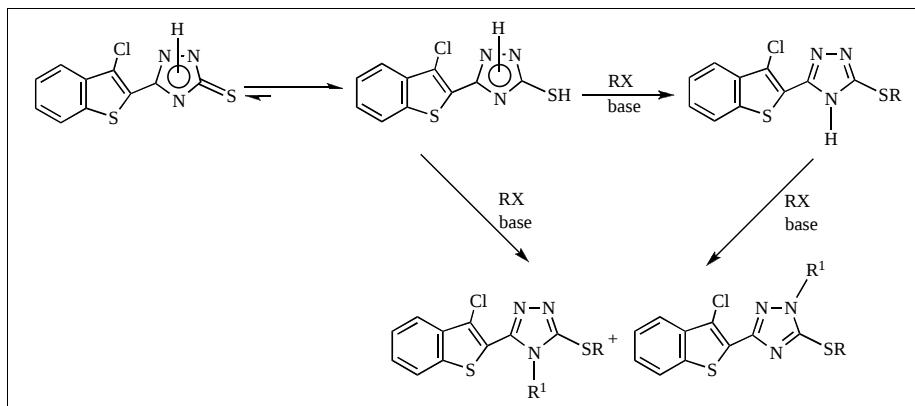
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Under microwave irradiation (MWI), 5-(3-chlorobenzo[*b*]thien-2-yl)-*4H*-1,2,4-triazole-3-thiol (**3**) was synthesized in a good yield by intramolecular cyclization of the carbonyl thiosemicarbazide **2**. A regioselective S-alkylation of **3** with benzyl chloride or allyl bromide has been achieved by using triethylamine as a base, while other different basic conditions led to a mixture of bis(alkylated) derivatives N⁴, S- and S, N²-, under both of classical and MWI conditions. The relative stabilities, charge densities, dipole moments and electronic energies of reactants, transition states and intermediates were calculated by the AM1 method and used for investigating the regioselectivity.

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Introduction.

Literature is enriched with progressive advances for the synthesis and pharmacological action of fused heterocycles. Those containing the benzo[*b*]thiophene nucleus are associated with diverse biological activities against inflammatory, analgesic [1,2], microbial [3], and herbicidal [4] effects. Substituted-1,2,4-triazoles also have pharmacological properties including sedative, nicotine antagonistic, anticonvulsant [5-7] and antitumor [8] activities; the 3-thio analogs act as angiotensin II antagonists [9], anticonvulsant [10] and dopamine D3 antagonists [11,12].

The recent role of microwave (MW) irradiation in performing organic reactions [13-16], attracted our attention to develop its use in our laboratory [17-22] and in the present work both of the conventional and MW irradiation conditions were performed to explore the optimum conditions for the synthesis of new benzo[*b*]thienyl-1,2,4-triazoles and investigating the selectivity encountered on their alkylation. The AM1 calculations [23] were performed, using MOPAC7

program package [24], to explain the regioselectivity of the alkylation reactions.

Results and Discussion.

3-Chloro-2-chlorocarbonylbenzo[*b*]thiophene (**1**) was obtained in 82% yield by MW irradiation for 2 min of cinnamic acid with SOCl₂ in presence of catalytic amount of pyridine in a closed Teflon vessel; conventional heating required 1 h to give 69% yield [25]. When compound **1** was reacted with thiosemicarbazide in dry acetone under MWI for 2 min, it gave the corresponding acyl thiosemicarbazide **2** in high yield (90%), compared to the 78 % yield resulted from conventional heating for 2 h [26]. Under basic conditions, the thiosemicarbazide **2** was converted to 5-(3-chlorobenzo[*b*]thien-2-yl)-*4H*-1,2,4-triazole-3-thiol (**3**) in 54% yield upon reflux for 4 h [26], while under MWI the reaction time was dramatically reduced to 3 min with an improvement in the isolated yield (85%) (Scheme 1).

Alkylation of the 1,2,4-triazole-3-thione may afford four possible mono alkylated derivatives depending on the alkylating agent and the applied conditions. However,

alkylation of **3** with one or two equivalents of benzyl chloride in presence of triethylamine gave only the S-alkylated product **4** in 89 and 94% yield, after 1 h heating under reflux and after 1.5 min irradiation under MW, respectively (Table 1).

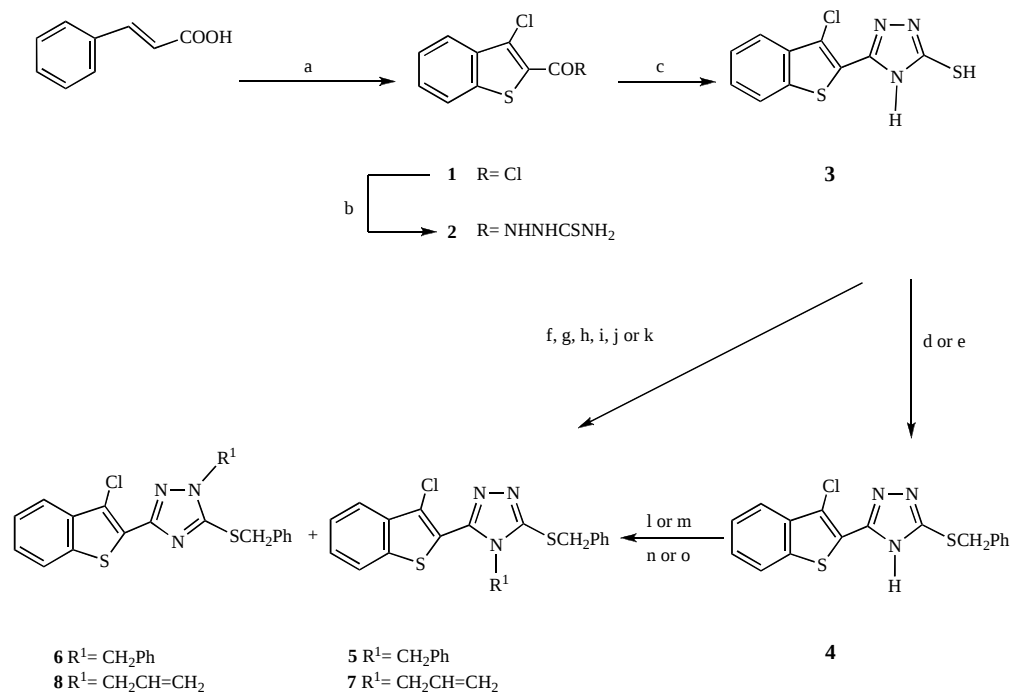
On the other hand, benzylation of **3** with one equivalent of benzyl chloride using different bases, powdered KOH, NaH or K_2CO_3 in DMF as a solvent, afforded a mixture of the bis(benzylated) products N⁴, S- **5** and S, N²- **6** in addition to the recovery of the starting material **3**. When two equivalents of benzyl chloride were used under the last various reaction conditions, the products **5** and **6** were obtained in comparable total yields (84-89%) within 3-5 h (Scheme 1). Improvement of the isolated total yields to 90-94% and significant reductions in reaction times have been achieved under the irradiation with MW (Table 1).

The reactions were monitored on TLC, where the bis(benzylated) products could always be identified by their R_f values ($R_f^{N-4} > R_f^{N-2}$). The structures of products were assigned based on ir and 1H nmr spectra as well as elemental analyses. The 1H nmr spectrum of **4** showed two singlets at $\delta = 14.49$ and 4.45 ppm due to the NH proton of the triazole ring and SCH_2 protons,

respectively. Compound **5** showed instead of the NH signal, a singlet for the NCH_2 -benzyl protons at $\delta = 5.30$ ppm which appeared at a higher field than that at $\delta = 5.43$ ppm of its isomeric structure **6**. The differentiation between the two isomers with N-4 and N-2 substituents could be concluded from their 1H nmr spectra based on literature [27-30] for chemical shift data of the N-methyl derivatives of substituted 1,2,4-triazoles; the benzyl $-CH_2-$ protons on N-2 should be deshielded than that on the N-4 atom. Accordingly, the isomeric ratio in the crude mixture could be estimated before the purification, whereby the ratio of the N-4-benzyl isomer was much higher than that of N-2-benzyl one (96: 4). This regioselective alkylation may presumably be due to the steric effects of the benzo[*b*]thiophene ring on position 1 of the triazole ring which prohibited the substitution on N-1.

Allylation of compound **4** by allyl bromide in presence of K_2CO_3 in DMF gave also a mixture of the bis(alkylated) products **7** and **8** in 88 and 92% total yield with ratio 86:14, respectively, after 4 h stirring and 2 min of MW irradiation. The 1H nmr spectrum of compound **7** showed the NCH_2 -allyl protons as a doublet of doublet of doublet at $\delta = 4.67$ ppm with

Scheme 1



- a) $SOCl_2$, Pyridine, DMF, MWI 2 min; b) $NH_2NHCSNH_2$, Acetone, MWI 3 min; c) NaOH (4%), MWI 3 min; d) $ClCH_2Ph$, NEt_3 , EtOH, reflux 1 h; e) $ClCH_2Ph$, NEt_3 , EtOH, MWI 1.5 min; f) $ClCH_2Ph$, KOH, DMF, reflux 4 h; g) $ClCH_2Ph$, KOH, DMF, MWI 3 min; h) $ClCH_2Ph$, NaH, DMF, st. 4 h; i) $ClCH_2Ph$, NaH, DMF, MWI 3 min; j) $ClCH_2Ph$, K_2CO_3 , DMF, st. 5 h; k) $ClCH_2Ph$, K_2CO_3 , DMF, MWI 3.5 min; l) $ClCH_2Ph$, KOH, DMF, reflux 3 h; m) $ClCH_2Ph$, KOH, DMF, MWI 2.5 min; n) $CH_2=CHCH_2Br$, K_2CO_3 , DMF, st. 4 h; o) $CH_2=CHCH_2Br$, K_2CO_3 , DMF, MWI 2 min

coupling constants $J = 1.60, 3.00$ and 5.40 Hz. Conversely, compound **8** showed these protons as a doublet at a lower field at $\delta = 4.78$ ppm with coupling constant $J = 5.30$ Hz. Accordingly, it can be deduced that compound **7** has a suitable geometry for the coupling between NCH_2 and $=\text{CH}_2$ protons, which is not present in compound **8**.

Formation of the bis(alkylated) products **5** and **6** may be due to the tautomerism exhibited in triazole ring in **3**, resulting from the mobility of the NH proton [31], where the thione [32,33] and the thiol tautomers [34] may exist. Similarly, compounds **7** and **8** were formed due to the mobility of NH proton in compound **4**.

Allylation of compound **3** with allyl bromide was also studied by using the same previous procedures under both conventional and MWI conditions. Thus, compound **3** was reacted with one equivalent of allyl bromide in the presence of triethylamine to give the S-alkylated product 3-allylthio-5-(3-chlorobenzo[*b*]thien-2-yl)-4*H*-1,2,4-triazole (**9**) in 91% yield after reflux for 0.5 h (Scheme 2), while under MWI the yield was 98% and the time was reduced to 1 min

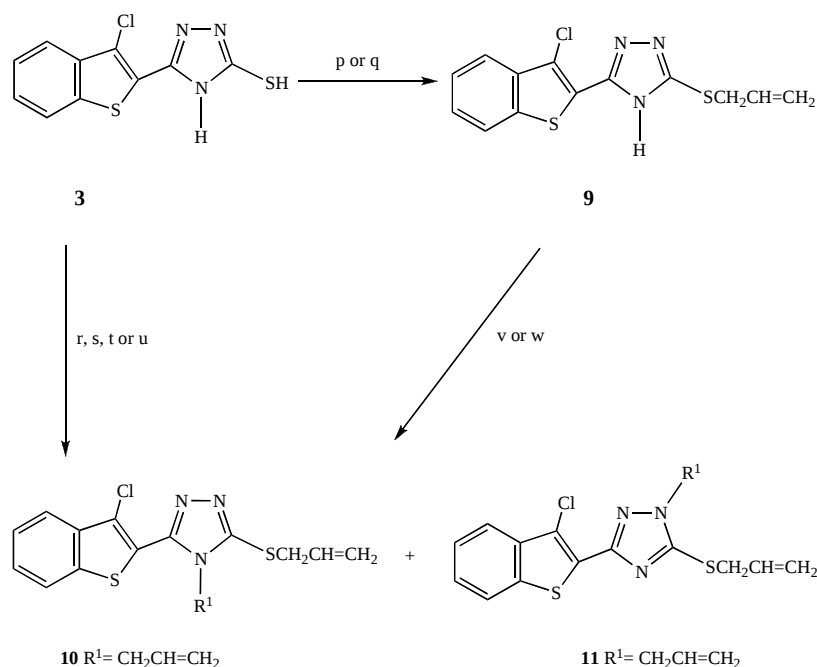
(Table 1). The ir spectrum of **9** showed bands at 1644 and 3193 cm^{-1} for the $\text{C}=\text{N}$ and NH groups, respectively. Its ^1H nmr spectrum showed two doublets at $\delta = 5.09$ and 5.28 ppm due to $=\text{CH}_2$, a doublet at $\delta = 3.85$ ppm due to SCH_2 , a multiplet at $\delta = 5.88\text{--}5.96$ ppm due to $=\text{CH}$ and a singlet at $\delta = 14.50$ ppm for the NH group.

In a similar manner to that used for the benzylation of **3**, the allylation of **3** and **9** by two and one equivalents of allyl bromide, respectively, in presence of K_2CO_3 or NaH in DMF, produced also a mixture of the bis(allylated) compounds **10** and **11**, under both classical and MW conditions in 89-90% yield after 3-4 h and 94-96% yield after 1.5-2.0 min, respectively (Table 1).

^1H nmr analysis of the crude mixture showed that compounds **10** and **11** exist as 97:3 mixture of isomers, respectively. Compound **10** showed NCH_2 -allyl protons at $\delta = 4.80$ ppm which appeared at a higher field than that at $\delta = 4.94$ ppm of its isomeric structure **11**.

The apparent regioselectivity in the alkylation of **3** has been investigated by studying the possible equilibrium of the tautomers of **3** founded by the mobility of two protons

Scheme 2



- p) $\text{CH}_2=\text{CHCH}_2\text{Br}$, NEt_3 , EtOH, reflux 0.5 h; q) $\text{CH}_2=\text{CHCH}_2\text{Br}$, NEt_3 , EtOH, MWI 1 min;
 r) $\text{CH}_2=\text{CHCH}_2\text{Br}$, K_2CO_3 , DMF, st. 4 h; s) $\text{CH}_2=\text{CHCH}_2\text{Br}$, K_2CO_3 , DMF, MWI 2 min;
 t) $\text{CH}_2=\text{CHCH}_2\text{Br}$, NaH , DMF, st. 3 h; u) $\text{CH}_2=\text{CHCH}_2\text{Br}$, NaH , DMF, MWI 2 min;
 v) $\text{CH}_2=\text{CHCH}_2\text{Br}$, K_2CO_3 , DMF, st. 4 h; w) $\text{CH}_2=\text{CHCH}_2\text{Br}$, K_2CO_3 , DMF, MWI 2 min

Table 1

Comparison between reaction times and yields obtained from conventional and MWI conditions.

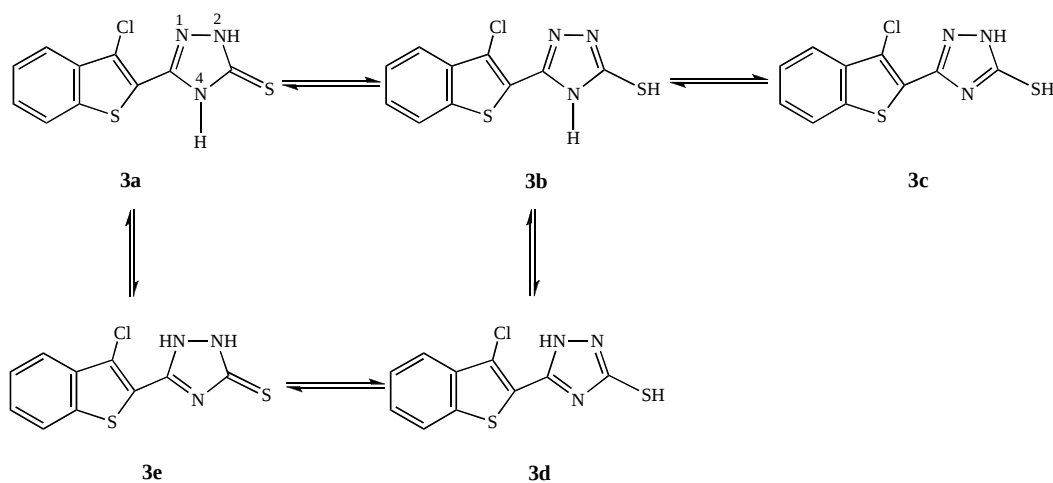
Compound No	Reagent*	Conditions Base	Solvent	Conventional method		Microwave method	
				Time (hour)	Yield (%) ⁺	Time (min)	Yield (%)
1	a	C ₃ H ₅ N	DMF	1.0	69 [25]	2.0	82
2	b	-	(Me) ₂ CO	2.0	78 [26]	2.0	90
3	c	NaOH	H ₂ O	4.0	54 [26]	3.0	85
4	d, e	NEt ₃	EtOH	1.0	89	1.5	94
5, 6	f, g	KOH	DMF	4.0	87	3.0	93
5, 6	h, i	NaH	DMF	3.0	84	3.0	90
5, 6	j, k	K ₂ CO ₃	DMF	5.0	86	3.5	91
5, 6	l, m	KOH	DMF	3.0	89	2.0	94
7, 8	n, o	K ₂ CO ₃	DMF	4.0	88	2.0	92
9	p, q	NEt ₃	EtOH	0.5	91	1.0	98
10, 11	r, s	K ₂ CO ₃	DMF	4.0	90	2.0	96
10, 11	t, u	NaH	DMF	3.0	89	2.0	96
10, 11	v, w	K ₂ CO ₃	DMF	3.0	89	1.5	94

* See schemes; ⁺ % yield of the crude mixture.

which led to five possible tautomeric forms **3a-e** (Scheme 3). Existence of the thione-thiol equilibrium in 5-substituted-3-thione-4H-1,2,4-triazole has been reported [31,35]. Compound **3** readily dissolves in alkaline solution to generate the anions of the tautomeric forms **3b-d** due to the acidity of the triazole ring protons resulting from its aromatic character [36].

method in the MOPAC 7.0 program [24]. All the structures were optimized to a gradient norm of 0.1 in the gas phase. The results of the calculations of heat of formation, relative stability, dipole moments, the highest occupied molecular orbital energies and the lowest unoccupied molecular orbital energies as well as the charge density on triazole heteroatoms are given in Table's 2, 3 and 4.

Scheme 3



To interpret the regioselectivity of alkylation of the triazole, semiempirical gas phase AM1 calculations [23] for reactants, transition states and intermediates have been used. Theoretical calculations were carried out at the Hartree-Fock level (RHF) using AM1 semiempirical SCF-MO

The atomic charge density localized on the sulfur atom in each tautomer **3b-d** (Table 2) was found to be greater than that on nitrogen atoms in the triazole ring, which explained the higher reactivity of the sulfur than nitrogen atoms in the triazole ring, which explained the higher

reactivity of the sulfur than nitrogen atoms towards the electrophilic attack presumably due to the higher nucleophilic properties and the lower electronegativity of the sulfur atom [37].

Comparison of the calculated relative stability (RS) of the possible thione-thiol tautomers led to the conclusion that the equilibrated tautomers have favored the thiol form **3b** to be the more predominant one. The relative stability of thiols **3b**, **3c** and **3d** compared to **3a** were -6.061, -1.692 and -3.754 kcal, respectively. Moreover, **3a** has been found to have more relative stability than **3e** (RS -12.867 kcal). Consequently, the stability of thiols can be stated in the order **3b** > **3d** > **3c** > **3a** > **3e**. Furthermore, charge density measurements for the anionic forms of compounds **3a-e**, generated by proton-abstraction from thiol groups, showed that the negative charge density was more localized on the sulfur atom than that on the nitrogen atoms. The above relative stability energy calculations and electron density measurements could explain the preference formation of the mono S-alkylated products **4b**, and **9b**.

in equilibrated tautomeric forms that upon reaction with alkyl halides gave the corresponding bis(alkylated) derivatives (Scheme 4).

Charge density measurements localized on triazole nitrogen atoms of tautomers of both S-alkylated derivatives **4b-d** and **9b-d** as intermediates and their anionic transition states showed that the N-4 atom has the highest negative charge density followed by N-2 and then N-1. This explains the isomeric ratio obtained experimentally, where N-4 substituted products were obtained in much higher yield than the N-2 substituted products, whereas no products from substitution on N-1 were isolated. Moreover, the relative stability energy calculations for possible substitution on N-4, N-2 and N-1 also coincide with the experimental results (Table 3 and 4). Furthermore, a steric hindrance factor may also contribute to prohibiting substitution on N-1.

Conclusion.

A regioselective alkylation of 5-benzothiophene-1,2,4-triazole-3-thiol has been achieved to give the

Table 2

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

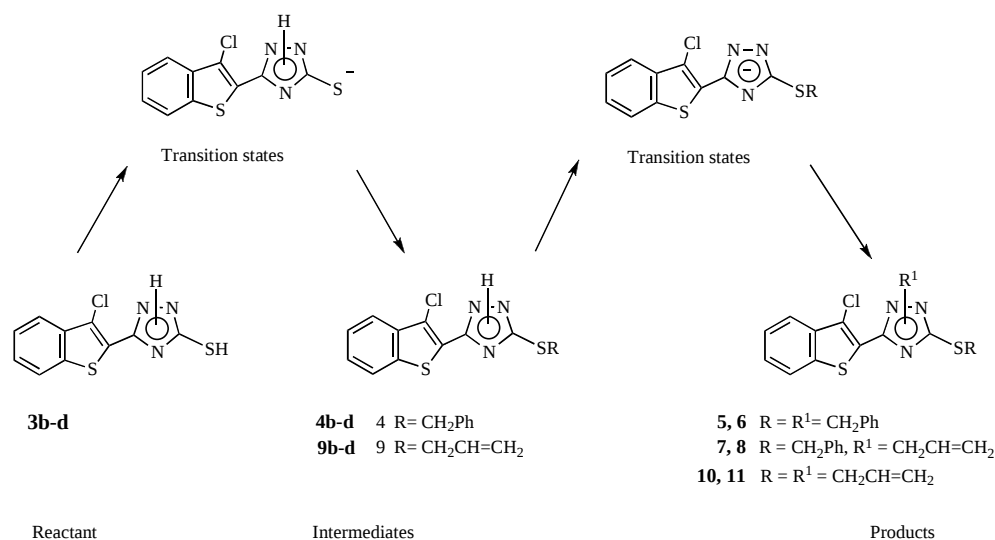
Tautomer	Heat of Formation (ΔH_f)	μ	E_{HOMO}	E_{LUMO}	Charge Density	Relative stability (RS)
No	Kcal	Debye	eV	eV	on triazole heteroatoms	Kcal
3a	121.577	5.547	-8.570	-1.277	-0.200 (S) -0.277 (N-4) -0.238 (N-2) -0.028 (N-1)	-6.061 (3b – 3a) -1.692 (3c – 3a) -3.754 (3d – 3a)
3b	115.516	4.436	-8.507	-0.994	0.210 (S) -0.193 (N-4) -0.093 (N-2)	-4.369 (3b – 3c) -2.307 (3b – 3d)
3c	119.885	1.545	-8.358	0.6654	-0.039 (N-1) 0.209 (S) -0.166 (N-4) -0.166 (N-2) -0.049 (N-1)	
3d	117.823	3.870	-8.567	-1.163	0.239 (S) -0.170 (N-4) -0.063 (N-2) -0.157 (N-1)	
3e	134.144	5.962	-8.754	-1.174	-0.006 (S) -0.171 (N-4) -0.220 (N-2) -0.193 (N-1)	-12.867 (3a – 3e) -16.221 (3d – 3e)

[†]RS = The difference in the heat of formation between each two possible tautomers.

In the present work, formation of the bis(alkylated) products **5-8** and **10, 11** can be presumed to pass through the S-alkylated derivatives **4** and **9** which could generate one or more of the anionic transition states that may exist

mono S-alkylated derivatives which upon further alkylation gave the N⁴, S- bis(alkylated) products selectively; the S, N²- bis(alkylated) products were obtained as minor ones.

Scheme 4



The AM1 calculations data are in agreement with the resulting isomeric ratio distribution in experimental data where the electrophilic attack occurs predominately at the N-4 atom and to less extent at N-2 atom. MW irradiation has accelerated the reaction rates.

EXPERIMENTAL

Chemistry.

Melting points were determined with a Melt-temp apparatus and are uncorrected. TLC performed on Baker-

Flex silica gel 1B-F plates using ethyl-acetate-hexane as developing solvent and the spots were detected by UV light absorption. Irradiation was done in a domestic microwave oven EM-230M (800 Watt output power under defrost temperature). The ir spectra were recorded with Perkin-Elmer 1430 spectrometer. ¹H 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. Isomer ratios were obtained on the basis of ¹H nmr analysis of the product mixture. Elemental analyses were performed in the unit of Microanalyses at Faculty of Science, Cairo University.

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 triazole heteroatoms for the intermediate tautomers.

Tautomer	Heat of Formation (ΔH _f)	μ	E _{HOMO}	E _{LUMO}	Charge Density	Relative stability (RS)
No	Kcal	Debye	eV	eV	on triazole heteroatoms	Kcal
4b	138.077	6.536	-8.568	-1.059	-0.180 (N-4) -0.029 (N-2) -0.059 (N-1)	-3.097 (4b – 4c) -4.610 (4b – 4d)
4c	141.174	2.332	-8.294	-0.590	-0.166 (N-4) -0.172 (N-2) -0.051 (N-1)	-1.513 (4c – 4d)
4d	142.687	3.435	-8.469	-1.097	-0.131 (N-4) -0.046 (N-2) -0.157 (N-1)	
9b	127.801	3.935	-8.228	-0.967	-0.197 (N-4) -0.102 (N-2) -0.039 (N-1)	-4.027 (9b – 9c) -3.132 (9b – 9d)
9c	131.828	2.602	-8.298	-0.619	-0.173 (N-4) -0.170 (N-2) -0.052 (N-1)	1.095 (9c – 9d)
9d	130.933	3.591	-8.266	-1.098	-0.164 (N-4) -0.070 (N-2) -0.156 (N-1)	

¹RS = The difference in the heat of formation between each two possible tautomers.

Table 4

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

Tautomer No	Heat of Formation (ΔH_f) Kcal	μ Debye	E_{HOMO} eV	E_{LUMO} eV	Charge Density on triazole heteroatoms	Relative stability (RS) Kcal
4b	90.083	6.790	-4.499	2.439	-0.132 (N-4) -0.116 (N-2) -0.096 (N-1)	-0.521 (4b – 4c) -4.408 (4b – 4d)
4c	90.604	5.903	-4.347	2.439	-0.144 (N-4) -0.119 (N-2) -0.094 (N-1)	-3.887 (4c – 4d)
4d	94.491	8.318	-4.211	2.499	-0.167 (N-4) -0.109 (N-2) -0.121 (N-1)	
9b	82.466	6.294	-4.262	2.505	-0.117 (N-4) -0.089 (N-2) -0.083 (N-1)	-0.090 (9b – 9c) -0.232 (9b – 9d)
9c	82.562	6.986	-4.260	2.608	-0.141 (N-4) -0.110 (N-2) -0.095 (N-1)	-0.136 (9c – 9d)
9d	82.698	3.580	-3.889	-1.098	-0.155 (N-4) -0.170 (N-2) -0.081 (N-1)	

ⁱRS = The difference in the heat of formation between each two possible tautomers.

3-Chloro-2-chlorocarbonylbenzo[*b*]thiophene (**1**).

A mixture of cinnamic acid (0.304 g, 2.3 mmol), pyridine (0.05 ml), dry DMF (0.1 ml) and (0.6 ml) thionyl chloride was irradiated by MW for 2 min in a closed Teflon vessel. The mixture was taken up in 10 ml of dry hexane, heated and decanted from the gummy residue. The yellow decanted solution solidified to give yellow crystals, mp 111-113 °C, Lit. mp 110-112 °C [25].

3-Chlorobenzo[*b*]thiophene-2-carbonyl thiosemicarbazide (**2**).

A mixture of compound **1** (0.230 g, 1 mmol), dry acetone (5 ml) and thiosemicarbazide (0.091 g, 1 mmol) was irradiated by MW for 2 min in a closed Teflon vessel. The product was recrystallized from ethanol as yellow crystals, mp 201-202 °C, Lit. mp 200-202 °C [26].

5-(3-Chlorobenzo[*b*]thien-2-yl)-4*H*-1,2,4-triazole-3-thiol (**3**).

A mixture of compound **2** (0.285 g, 1 mmol) and aqueous sodium hydroxide (4%, 10 ml) was irradiated by MW for 3 min. The mixture was cooled, filtered and acidified with dilute hydrochloric acid. The precipitate was collected by filtration, washed with water and recrystallized from ethanol to give yellow crystals, mp 283-284 °C, Lit. mp 281-282 °C [26]; ir (potassium bromide): 3232-3355 (NH), 1638 (C=N), 1591 (C=C) cm^{-1} ; ^1H nmr (dimethyl sulfoxide- d_6): δ 7.52-7.56 (m, 2H, 5-H, 6-H benzothiophene), 7.82-7.85 (m, 1H, 4-H benzothiophene), 8.07-8.10 (m, 1H, 7-H benzothiophene), 14.00 (s, 2H, deuterium oxide-exchangeable, NH, SH).

Anal. Calcd. for $\text{C}_{10}\text{H}_6\text{ClN}_3\text{S}_2$: C, 44.86; H, 2.26; N, 15.69. Found: C, 44.91; H, 2.69; N, 15.64.

General Method for the Alkylation.

Conventional Method (CM).

To a solution of compound (10 mmol) in a solvent (50 ml) and base (10 or 20 mmol), the appropriate alkyl halide (10 or 20

mmol) was added with stirring. The conditions of the reaction are shown in Table 1. The solvents were removed by evaporation under reduced pressure in case of ethanol, when DMF was used as solvent; the reaction mixture was poured on crushed ice. The obtained products were washed with water, dried and recrystallized from ethanol and in case of mixtures; the products were separated by column chromatography.

Microwave method (MW)

A mixture of compound (1 mmol), base (1 or 2 mmol) and appropriate alkyl halide (1 or 2 mmol) in solvent (5 ml) was irradiated by MW in a closed Teflon vessel. The obtained reaction mixture was treated as described above (Table 1).

3-Benzylthio-5-(3-Chlorobenzo[*b*]thien-2-yl)-4*H*-1,2,4-triazole (**4**).

This compound was obtained as yellow crystals, mp 175-177 °C; ir (potassium bromide): 3286 (NH), 1652 (C=N), 1597 (C=C), 2956 (C-H al.) cm^{-1} ; ^1H nmr (dimethyl sulfoxide- d_6): δ 4.45 (s, 2H, SCH_2), 7.21-7.43 (m, 5H, Ar-H), 7.51-7.55 (m, 2H, 5-H and 6-H benzothiophene), 7.85 (d, 1H, 4-H benzothiophene, $J = 7.70$ Hz), 8.07 (d, 1H, 7-H benzothiophene, $J = 6.90$ Hz), 14.49 (s, 1H, deuterium oxide-exchangeable, NH).

Anal. Calcd. for $\text{C}_{17}\text{H}_{12}\text{ClN}_3\text{S}_2$: C, 57.05; H, 3.38; N, 11.74. Found: C, 57.17; H, 3.63; N, 11.41.

4-Benzyl-3-benzylthio-5-(3-chlorobenzo[*b*]thien-2-yl)-1,2,4-triazole (**5**).

This compound was separated by column chromatography (eluent EtOAc: Hexane, 1:35) as white plates, (78%, CM) yield, mp 131-132 °C; ir (potassium bromide): 1629 (C=N), 1570 (C=C), 2920 (C-H al.) cm^{-1} ; ^1H nmr (dimethyl sulfoxide- d_6): δ 4.49 (s, 2H, SCH_2), 5.30 (s, 2H, NCH_2), 7.11-7.42 (m, 10H, phenyl protons), 7.50-7.55 (m, 2H, 5-H and 6-H benzothiophene), 7.85 (dd, 1H, 4-H benzothiophene, $J = 1.50, 7.70$ Hz), 8.06 (dd, 1H, 7-H benzothiophene, $J = 1.50, 7.70$ Hz).

Anal. Calcd. for $C_{24}H_{18}ClN_3S_2$: C, 64.34; H, 4.05; N, 9.38. Found: C, 64.72; H, 4.41; N, 8.97.

2-Benzyl-3-benzylthio-5-(3-chlorobenzo[*b*]thien-2-yl)-1,2,4-triazole (**6**).

This compound was separated by column chromatography (eluent EtOAc: Hexane, 1:35) as white plates, (3%, CM) yield, mp 139-140 °C; ir (potassium bromide): 1600 (C=N), 1570 (C=C), 2967 (C-H al.) cm^{-1} ; 1H nmr (dimethyl sulfoxide- d_6): δ 4.73 (s, 2H, SCH_2), 5.43 (s, 2H, NCH_2), 7.23-7.48 (m, 12H, phenyl protons, 5-H and 6-H benzothiophene), 7.82 (d, 1H, 4-H benzothiophene, $J = 7.70$ Hz), 7.92 (d, 1H, 7-H benzothiophene, $J = 7.70$ Hz).

Anal. Calcd. for $C_{24}H_{18}ClN_3S_2$: C, 64.34; H, 4.05; N, 9.38. Found: C, 64.51; H, 3.71; N, 8.94.

4-Allyl-3-benzylthio-5-(3-chlorobenzo[*b*]thien-2-yl)-1,2,4-triazole (**7**).

This compound was separated by column chromatography (eluent EtOAc: Hexane, 1:27) as yellow crystals, (80%, CM) yield, mp 118-119 °C; ir (potassium bromide): 1637 (C=N), 1572 (C=C), 2921 (C-H al.) cm^{-1} ; 1H nmr (dimethyl sulfoxide- d_6): δ 4.50 (s, 2H, SCH_2), 4.67 (ddd, 2H, NCH_2 , $J = 1.60, 3.00, 5.40$ Hz), 5.17, 5.25 (2dd, 2H, $=CH_2$, $J = 0.80, 16.80, 1.50, 11.50$ Hz), 5.91 (ddd, 1H, $=CH$, $J = 4.60, 11.50, 16.80$), 7.25-7.32 (m, 3H, phenyl protons), 7.40-7.47 (m, 4H, phenyl protons, 5-H and 6-H benzothiophene), 7.83 (dd, 1H, 4-H benzothiophene, $J = 1.50, 7.70$ Hz), 7.92 (dd, 1H, 7-H benzothiophene, $J = 1.50, 7.70$ Hz).

Anal. Calcd. for $C_{20}H_{16}ClN_3S_2$: C, 60.36; H, 4.05; N, 10.56. Found: C, 60.60; H, 4.34; N, 10.35.

2-Allyl-3-benzylthio-5-(3-chlorobenzo[*b*]thien-2-yl)-1,2,4-triazole (**8**).

This compound was separated by column chromatography (eluent EtOAc: Hexane, 1:27) as yellow crystals, (9%, CM) yield, mp 111-113 °C; ir (potassium bromide): 1626 (C=N), 1561 (C=C), 2952 (C-H al.) cm^{-1} ; 1H nmr (dimethyl sulfoxide- d_6): δ 4.41 (s, 2H, SCH_2), 4.78 (d, 2H, NCH_2 , $J = 5.30$ Hz), 5.13, 5.22 (2d, 2H, $=CH_2$, $J = 10.70, 17.50$ Hz), 5.97 (ddd, 1H, $=CH$, $J = 5.30, 10.70, 16.80$ Hz), 7.23-7.32 (m, 3H, phenyl protons), 7.43-7.54 (m, 4H, phenyl protons, 5-H and 6-H benzothiophene), 7.87 (dd, 1H, 4-H benzothiophene, $J = 1.50, 6.10$ Hz), 7.93 (dd, 1H, 7-H benzothiophene, $J = 1.50, 6.10$ Hz).

Anal. Calcd. for $C_{20}H_{16}ClN_3S_2$: C, 60.39; H, 4.05; N, 10.56. Found: C, 60.62; H, 4.29; N, 10.34.

3-Allylthio-5-(3-chlorobenzo[*b*]thien-2-yl)-4H-1,2,4-triazole (**9**).

This compound was obtained as Pale yellow crystals, mp 156-157 °C; ir (potassium bromide): 3193 (NH), 1644 (C=N), 1580 (C=C), 2979 (C-H al.) cm^{-1} ; 1H nmr (dimethyl sulfoxide- d_6): δ 3.85 (d, 2H, SCH_2 , $J = 5.30$ Hz), 5.09, 5.28 (2d, 2H, $=CH_2$, $J = 9.90, 16.80$ Hz), 5.88-5.96 (m, 1H, $=CH$), 7.45-7.55 (m, 2H, 5-H and 6-H benzothiophene), 7.83 (d, 1H, 4-H benzothiophene, $J = 7.70$ Hz), 8.04 (d, 1H, 7-H benzothiophene, $J = 7.70$ Hz), 14.50 (s, 1H, deuterium oxide-exchangeable, NH).

Anal. Calcd. for $C_{13}H_{10}ClN_3S_2$: C, 50.72; H, 3.27; N, 13.65. Found: C, 50.93; H, 3.49; N, 13.33.

4-Allyl-3-allylthio-5-(3-chlorobenzo[*b*]thien-2-yl)-1,2,4-triazole (**10**).

This compound was separated by column chromatography (eluent EtOAc: Hexane, 1:25) as white crystals (84%, CM) yield,

mp 56-57 °C; ir (potassium bromide): 1639 (C=N), 1566 (C=C), 2985 (C-H al.) cm^{-1} ; 1H nmr (dimethylsulfoxide- d_6): δ 3.90 (d, 2H, SCH_2 , $J = 6.90$ Hz), 4.80 (d, 2H, NCH_2 , $J = 5.30$ Hz), 5.10 (2d, 2H, $=CH_2$, $J = 10.70, 16.80$ Hz), 5.30 (2d, 2H, $=CH_2$, $J = 10.70, 16.80$ Hz), 5.90-5.96 (m, 2H, $=CH$), 7.48-7.53 (m, 2H, 5-H and 6-H benzothiophene), 7.83 (d, 1H, 4-H benzothiophene, $J = 7.70$ Hz), 8.04 (d, 1H, 7-H benzothiophene, $J = 7.70$ Hz).

Anal. Calcd. for $C_{16}H_{14}ClN_3S_2$: C, 55.24; H, 4.06; N, 12.08. Found: C, 54.94; H, 4.24; N, 11.95.

2-Allyl-3-allylthio-5-(3-chlorobenzo[*b*]thien-2-yl)-1,2,4-triazole (**11**).

This compound was separated by column chromatography (eluent EtOAc: Hexane, 1:25) as white crystals (2%, CM), mp 63-65 °C; ir (potassium bromide): 1639 (C=N), 1565 (C=C), 2932 (C-H al.) cm^{-1} ; 1H nmr (dimethyl sulfoxide- d_6): δ 3.76 (d, 2H, SCH_2 , $J = 6.70$ Hz), 4.94 (d, 2H, NCH_2 , $J = 5.30$ Hz), 5.02, 5.08, 5.16, 5.26 (4dd, 4H, $=CH_2$, $J = 1.50, 16.80, 1.50, 11.40$ Hz), 5.88-5.97 (m, 2H, $=CH$), 7.57-7.62 (m, 2H, 5-H and 6-H benzothiophene), 7.88-7.92 (m, 1H, 4-H benzothiophene), 8.13-8.16 (m, 1H, 7-H benzothiophene).

Anal. Calcd. for $C_{16}H_{14}ClN_3S_2$: C, 55.24; H, 4.06; N, 12.08. Found: C, 54.89; H, 4.10; N, 12.01.

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