Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

Reactivity of *N*-thioamido amidines with halogenated alkyl derivatives: synthesis of 4,5-disubstituted 2-alkylaminothiazoles

Akila Khilifi[a]; Noureddine Raouafi[a]; Issa Tapsoba[b]; Khaled Boujlel[a]; Mohamed Lamine Benkhoud[a]
[a] Laboratoire de Chimie Analytique et Electrochimie, Faculté des Sciences de Tunis, Tunis, Tunisia [b] Laboratoire de Chimie Organique: Structure et Réactivité, Université de Ouagadougou, UFR-SEA, Ouagadougou, Burkina Faso

To cite this Article Khilifi, Akila , Raouafi, Noureddine , Tapsoba, Issa , Boujlel, Khaled and Lamine Benkhoud, Mohamed(2008) 'Reactivity of *N*-thioamido amidines with halogenated alkyl derivatives: synthesis of 4,5-disubstituted 2-alkylaminothiazoles', Journal of Sulfur Chemistry, 29: 6, 593 — 605
To link to this Article: DOI: 10.1080/17415990802346002
URL: http://dx.doi.org/10.1080/17415990802346002

Journal of Sulfur Chemistry
Vol. 29, No. 6, December 2008, 593–605

Taylor & Francis
Taylor & Francis Group

Reactivity of *N*-thioamido amidines with halogenated alkyl derivatives: synthesis of 4,5-disubstituted 2-alkylaminothiazoles

Akila Khilifi[a], Noureddine Raouafi[a]*, Issa Tapsoba[b], Khaled Boujlel[a] and Mohamed Lamine Benkhoud[a]

[a]*Laboratoire de Chimie Analytique et Electrochimie, Faculté des Sciences de Tunis, Campus Universitaire Tunis El-Manar 2092, Tunis, Tunisia;* [b]*Laboratoire de Chimie Organique: Structure et Réactivité; Université de Ouagadougou, UFR-SEA, Ouagadougou, Burkina Faso*

(*Received 2 November 2007; final version received 27 June 2008*)

2-Bromoacetate ethyl ester **4**, 2-chloroacetonitrile **5**, 2-bromo-1-(4-nitrophenyl)ethanone **6**, and 2-chloroacetone **7** react with *N*-thioamido amidines **3** to yield the corresponding 4,5-disubstituted 2-alkylamino thiazoles **8**, **9**, **10**, and **11** after the release of an amine molecule. The reaction of the amidines **3** with benzyl bromide **12**, 4-chlorobutyronitrile **13**, 3-bromopropionate ethyl ester **14**, 3-chloropropionate ethyl ester **15**, and 4-nitrobenzyl chloride **16** does not lead to the cyclic derivatives but gives opened-ring intermediates **17**, **18**, **19**, **20**, and **21**. The cyclization mechanism is discussed on the basis of the study of the opened-ring intermediates which have been isolated in some cases and the AM1 and PM3 semi-empirical energetic calculations.

Keywords: *N*-thioamido amidines; 4,5-disubstituted 2-alkylamino thiazoles; opened-ring intermediates; cyclization; AM1 and PM3 semi-empirical calculations

1. Introduction

The thiazole ring is present in many isolated natural products such as Didmolamide A and B, Dendroamide A, Bistratamides E–J, and Tenuecyclamides A–D (*1–6*). Molecules containing the thiazole ring display a large spectrum of utilizations in many fields of medicine as anticancer agents: thia-netropsin and Bleomycin (*7–11*). The 2-aminothiazole is a subclass family that forms a useful structural compound for the synthesis of polymers (*12*). It has also found application in drug target molecules for ailments ranging from allergies to HIV infections, dyes, and pigments (*13–17*). Also it can serve as starting reactants for the synthesis of many interesting heterocyclic fused-ring compounds such as imidazolothiazole and pyrimidothiazole, which have pharmacological activity (*18–22*). In this work, we report the synthesis of a family of amidines bearing a thioamido group and their condensation with functionalized halogenoalkyl derivatives in basic medium with the aim to prepare the corresponding substituted 2-alkylaminothiazolines. The

*Corresponding author. Email: noureddine.raouafi@gmail.com

ISSN 1741-5993 print/ISSN 1741-6000 online

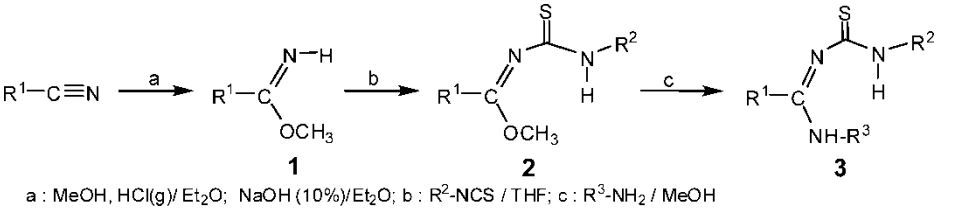
DOI: 10.1080/17415990802346002
http://www.informaworld.com

mechanism of the reaction is discussed by considering the intermediates isolated during the course of the reaction and the energetic calculations using semi-empirical methods.

2. Results and discussion

2.1. *Synthesis of imidates, N-thioamido imidates and N-thioamidio amidines*

Imidates **1** were synthesized by alcoholysis of aromatic and benzylic nitrile compounds according to the well-known Pinner reaction by bubbling anhydrous HCl gas into an equimolar mixture of aromatic or benzylic nitrile derivatives and methanol (*23*). The basic neutralization of the resulting imidate hydrochloric salt with a 10% aqueous sodium hydroxide solution leads to the corresponding imidates in satisfactory yields. The condensation of various isothiocyanates to the imidates **1** in anhydrous tetrahydrofuran resulted in *N*-thioamido imidates **2** formation (*24*). Then, *N*-thioamido imidates **2** were left to react with primary amines in anhydrous methanol, allowing *N*-thioamido amidines **3** formation after the substitution of methoxy group by amino group (*13*) (Scheme 1).



Scheme 1.

The above described reaction leads to a large variety of *N*-thioamidoimidates **2** and trisubstituted amidines **3** (Table 1).

2.2. *Synthesis of 4,5-disubstituted 2-alkylaminothiazoles*

Synthesis process of the new 2-aminothiazole family is outlined in Scheme **2**. The preparation of products **8**, **9**, **10**, and **11** (Table 2) consists of the cyclocondensation of *N*-thioamidoamidines

Table 1. Synthesized *N*-thioamido imidates **2** and amidines **3**.

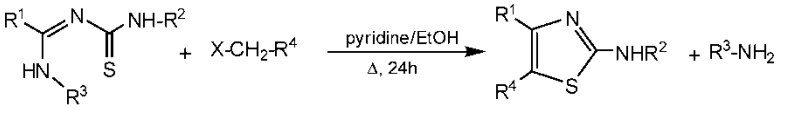
Entry	R^1	R^2	R^3
2a	Ph	Ph	–
2b	Ph	CH_2-Ph	–
2c	Ph	CH_2-CH_3	–
2d	CH_2-Ph	Ph	–
2e	CH_2-Ph	CH_2-Ph	–
3a	Ph	Ph	CH_2-Ph
3b	Ph	CH_2-Ph	CH_2-Ph
3c	Ph	Et	CH_2-Ph
3d	CH_2-Ph	Ph	CH_2-Ph
3e	CH_2-Ph	CH_2-Ph	CH_2-Ph
3f	Ph	Ph	CH_2-pyr[a]

[a]pyr: pyridinyl.

Table 2. Synthesized thiazolines derivatives **8**, **9**, **10**, and **11**.

Entry	X	R^1	R^2	R^4
8a	Br	Ph	Ph	CO_2Et
8b	Br	Ph	Bn	CO_2Et
8c	Br	Ph	CH_3CH_2	CO_2Et
8d	Br	CH_2-Ph	Ph	CO_2Et
9a	Br	Ph	Ph	$C(O)-Ph-p-NO_2$
9b	Br	CH_2-Ph	CH_2-Ph	$C(O)-Ph-p-NO_2$
10a	Cl	Ph	Ph	CN
10b	Cl	CH_2-Ph	CH_2-Ph	CN
11a	Cl	Ph	Ph	$C(O)-CH_3$
11b	Cl	CH_2-Ph	CH_2-Ph	$C(O)-CH_3$

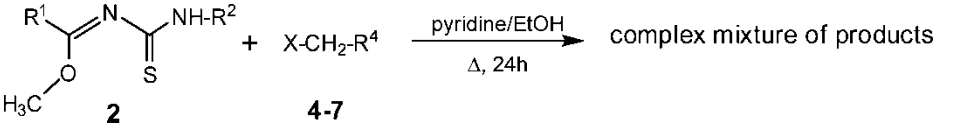
3 with 2-halo alkyl derivatives **4**, **5, 6**, and **7** bearing a strong electron withdrawing group in refluxing ethanol in the presence of one equivalent of pyridine (Scheme 2).



3 **4-7** **8-11**

Scheme 2.

During the course of reaction an amine molecule R^3-NH_2 was released. The use of *N*-thioamido imidates **2** instead of *N*-thioamido amidines **3** did not yield the products **8**, **9**, **10**, and **11** but give a complex mixture of products (Scheme 3).



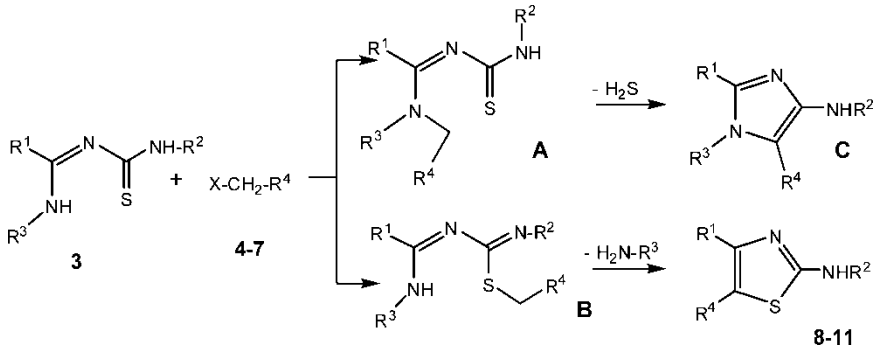
2 **4-7**

Scheme 3.

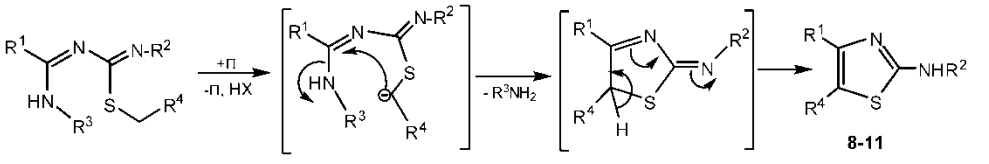
Two possible intermediates **A** and **B** may be formed. The first one **A** could be obtained from the *N*-alkylation of the $NH-R^3$ moiety, whereas the second one **B** results from an *S*-alkylation of thioamide group (Scheme 4).

As described above (Scheme 5) only the intermediate **B** could give an anionic form which leads by cyclization to the corresponding 2-alkylimino-5-thiazole, which can tautomerize to 2-alkylamino thiazoles **8–11**. The intermediate **A** could evolve to the substituted imidazoles **C** via an intramolecular cyclization favored by H_2S molecule elimination. But no trace of compound **C** was isolated or detected during the course of the reaction. The relative position of the methylene group to the electron withdrawing group influences the ring closure reaction.

No cyclic derivatives have been obtained when reacting amidines **3** with benzyl bromide **12**, 4-chlorobutyronitrile **13**, 3-bromopropionate ethyl ester **14**, 3-chloropropionate ethyl ester **15**, nor with *p*-nitrobenzyl chloride **16**; however, opened-ring intermediates **17**, **18**, **19**, **20**, and **21** were isolated. These intermediates did not show any characteristic band at about 1200 cm^{-1} related to the stretching vibration of the C=S bond; but they do reveal the presence of a bands at 1640 cm^{-1} assigned to C=N function. This result is in favor of the formation of intermediate **B** (Scheme 4). For compounds **17–21**, when the isolated intermediates **B** were heated in presence of pyridine in



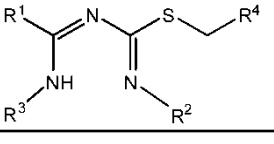
Scheme 4.



Scheme 5.

ethanol for 24 h or more, only the reactants products were recovered. This may be due to the low acidity of protons of the methylene group directly linked to the sulfur atom. The presence of an electron withdrawing groups is essential to have acidic protons which are easy to remove. The location of the EWG in β (entry **18** and **19**) or γ (entry **20**) positions with respect to the sulfur has shown a dramatical decrease in the acidity of the methylene group proton and turned them to be inert. In the case of benzyl bromide, the introduction of a strong withdrawing group in para position to the methylene chloride (entry **21**) did not give cyclization products, that is probably too far to affect enough the methylene group to increase its acidity (Table 3).

Table 3. Isolated intermediates **17**, **18**, **19**, **20**, and **21**.



	X	R^1	R^2	R^3	R^4
17a	Br	Ph	Ph	CH_2-Ph	Ph
17b	Br	CH_2-Ph	CH_2-CH_3	CH_2-Ph	Ph
18a	Br	Ph	Ph	CH_2-Ph	CH_2CO_2Et
18b	Br	CH_2-Ph	Ph	CH_2-Ph	CH_2CO_2Et
19a	Cl	Ph	Ph	CH_2-Ph	$(CH_2)_2CO_2Et$
20a	Cl	Ph	Ph	CH_2-Ph	$(CH_2)_2-CN$
20b	Cl	Ph	Ph	$CH_2-C_5H_4N$	$(CH_2)_2$-CN
21a	Cl	CH_2-Ph	CH_2-Ph	CH_2-Ph	Ph-*p*-NO_2
21b	Cl	CH_2-Ph	Ph	Ph	Ph-*p*-NO_2

2.3. *Spectroscopic study*

2.3.1. *IR spectroscopy*

IR spectra of the thiazoline derivatives show the absence of the characteristic stretching vibration band of the C=S function at 1200 cm^{-1}. Cyclization has slightly affected the stretching vibration band of C=N function. The wave number is initially at about 1620–1660 cm^{-1} in amidines **3** and becomes at about 1600 cm^{-1} after cyclization.

2.3.2. *NMR spectroscopy*

The analysis of the ^{1}H-NMR spectra of thiazolines points out the presence of a new quartet and triplet assigned to the ethyl group of ester function introduced by bromoacetate ethyl ester for compounds **8** and singlet assigned to the methyl group of acetyl function for compounds **11**. For the thiazoles **9** and **10**, the presence of some new aromatic protons is visible. For all compounds **8**, **9**, **10**, and **11**, the total absence of the R^3 protons is noticeable due to the elimination of an amine molecule R^3-NH_2 during the ring closure.

In ^{13}C-NMR spectrum for compounds **8**, the presence of new signals related to the ethylcarboxyl function was noted. Also, the spectral data show some characteristic peaks for compounds **9** and **10** such as the presence of a new quaternary carbon located to the higher field related to the C=O carbon for compounds **9** and **11** or a signal at about 110 ppm which is characteristic of nitrile group introduced by chloroacetonitrile for the substrates **10**. The absence of the carbon signals related to the amine group R^3-NH_2 is common for all the compounds.

2.3.3. *Mass spectrometry*

All CI-MS show the M^+; $(M + H)^+$ and $(M + 2H)^+$ peaks for compounds **8**, **9**, **10**, and **17**. They also reveal the existence of some common fragments like $(M-OEt)^+$ or $(M-CO_2Et)^+$ for the compounds **8** and **17**.

2.4. *Semi-empirical calculations*

2.4.1. *Charge calculations of nitrogens of amidines **3***

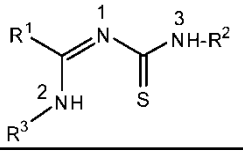
In order to gain best insight into the reactivity of amidines **3**, quantum calculations in the semi-empirical level, using the AM1 (*25*) and PM3 methods (*26*), have been performed to determine the different nucleophilic charges of centers (Table 4). Also, the geometry was optimized and the atoms charges have been calculated for the intermediates **A** and **B** which leads to some representative aminothiazoles (**8c**, **9a**, **10a**).

From the previous table we could deduce that the nitrogen N2 is, in all cases, more basic than the nitrogen N3, which are less basic than the sulfur atom. According to the electron density it seems plausible that alkylation on nitrogen 2 or 3 may occur when the amidine **3** is treated with the 2-halogenated alkyl derivatives as illustrated in Scheme 4.

2.4.2. *Geometry optimization of intermediates and energy calculations*

The energetic quantum calculations show that the intermediates formed by the *S*-alkylation of the starting amidines **3** with halo alkyl derivatives are more easily obtained during the course

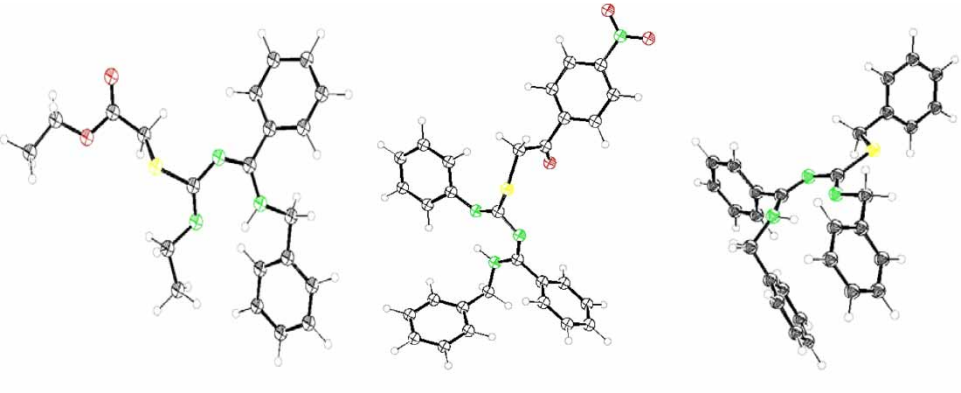
Table 4. Charges of nitrogen and sulfur atoms in the amidines **3**.



Entry	N1		N2		N3		S	
Calculation method	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3
3a	−0.293	−0.355	−0.461	−0.078	−0.414	0.226	−0.028	−0.437
3b	−0.291	−0.342	−0.462	−0.085	−0.446	0.115	−0.060	−0.457
3c	−0.293	−0.345	−0.443	−0.086	−0.447	0.114	−0.077	−0.453
3d	−0.324	−0.372	−0.483	−0.074	−0.414	0.223	−0.059	−0.439
3e	−0.324	−0.354	−0.493	−0.093	−0.445	0.110	−0.087	−0.458
3f	−0.290	−0.356	−0.447	−0.074	−0.411	0.226	−0.046	−0.458

Table 5. Optimized geometries of compounds **8c**, **9a**, and **10b**.

Parameters	**8c**	**9a**	**10b**
ΔG (**B**), KJ/mol	1060.8	1646.2	1531.5
ΔG, (**A**), KJ/mol	1305.6	1728.6	1633.2
ΔG, (**A**–**B**), KJ/mol	244.8	82.4	101.7
Charge on C (**A**)	−0.11	−0.17	−0.04
Charge on H (**A**)	0.206	0.193	0.202
Charge on H (**A**)	0.203	0.192	0.199
Charge on C (**B**)	−0.43	−0.47	−0.30
Charge on H (**B**)	0.194	0.202	0.211
Charge on H (**B**)	0.211	0.196	0.201



of the reaction than that produced by the *N*-alkylation (**A**) ($\Delta G \sim 82 - 245$ kJ/mol). Also the results confirm that the hydrogen of the methylenic group linked to the sulfur atom is more basic (intermediate **B**) than those bearing the nitrogen atom (intermediate **A**), so it could be easily deprotonated in basic medium.

3. Experimental

3.1. *Synthesis of N-thioamido imidates 2*

To a solution of 10.0 mmole of imidates **1** in 15 ml of anhydrous diethyl ether, 11.0 mmole of an isothiocyante derivative were added; the solution was left for stirring at room temperature for 24 h. The solvent was evaporated under reduced pressure. The resulting oil was washed twice with 5 mL of petroleum ether and allowed to stay at room temperature for 3–4 days to crystallize giving the amidines **2**. The solid was purified by recrystallization in absolute ethanol (*27–30*).

3.1.1. *2a: (Z)-methyl N-phenylcarbamothioylbenzimidate*

Yield 2.51 g (93%). Solid m.p.: 144 °C; IR ($CHCl_3$) ν (cm^{-1}): 3384, 1655, 1202; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 3.71$ (s, 3H, CH_3), 7.12–8.21 (m, 11H, NH, Ar); ^{13}C-NMR ($CDCl_3$): $\delta = 54.0$, 121.5, 122.6, 125.4, 126.3, 128.1, 128.4, 129.8, 130.5, 162.0, 191.0.

3.1.2. *2b: (Z)-methyl N-benzylcarbamothioylbenzimidate*

Yield 2.58 g (91%). Solid m.p.: 120 °C; IR ($CHCl_3$) ν (cm^{-1}): 3396, 1657, 1212; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 3.89$ (s, 3H, CH_3), 4.91 (d, 2H, $^3J_{H-H} = 6.8$ Hz, CH_2), 7.04–8.05 (m, 11H, NH, Ar); ^{13}C-NMR ($CDCl_3$): $\delta = 49.7$, 55.0, 127.7, 128.2, 128.9, 129.5, 129.8, 132.0, 136.1, 136.7, 158.8, 191.2.

3.1.3. *2c: (Z)-methyl N-ethylcarbamothioylbenzimidate*

Yield 1.84 g (83%). Solid m.p.: 113 °C; IR ($CHCl_3$) ν (cm^{-1}): 3386, 1663, 1222; ^{1}H- NMR (300 MHz, $CDCl_3$): $\delta = 1.22$ (t, 3H, $^3J_{H-H} = 7.2$ Hz, CH_3), 3.67 (q, 2H, $^3J_{H-H} = 7.0$ Hz, CH_2), 3.91 (s, 3H, CH_3), 6.92–7.88 (m, 11H, NH, Ar); ^{13}C-NMR ($CDCl_3$): $\delta = 13.5$, 40.4 , 55.1, 128.3, 128.9, 129.8, 136.2, 158.4, 190.8.

3.1.4. *2d: (Z)-methyl 2-phenyl-N-(phenylcarbamothioyl)acetimidate*

Yield 2.44 g (86%). Solid m.p.: 118 °C; IR ($CHCl_3$) ν (cm^{-1}): 3384, 1665, 1217; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 3.68$ (s, 3H, CH_3), 4.03 (d, 2H, $^3J_{H-H} = 6.6$ Hz, CH_2), 6.98–8.04 (m, 11H, NH, Ar); ^{13}C-NMR ($CDCl_3$): $\delta = 36.0$, 54.0, 127.0, 128.8, 129.4, 130.1, 132.5, 134.9, 136.0,137.6, 163.2, 190.0.

3.1.5. *2e: (Z)-methyl N-benzylcarbamothioyl-2-phenylacetimidate*

Yield 2.41 g (81%). Solid m.p.: 81 °C; IR ($CHCl_3$) ν (cm^{-1}): 3394, 1662, 1229; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 3.82$ (s, 3H, CH_3), 4.08 (d, 2H, $^3J_{H-H} = 7.3$ Hz, CH_2), 4.61 (d, 2H, $^3J_{H-H} = 6.5$ Hz, CH_2), 6.89–8.13 (m, 11H, NH, Ar); ^{13}C-NMR ($CDCl_3$): $\delta = 54.9$, 40.0, 48.9, 127.7, 127.9, 128.4, 128.6, 129.3, 129.9, 135.8, 136.7, 161.41, 191.02.

3.2. *Synthesis of N-thioamido amidines 3*

A mixture of the imidate **2** (10.0 mmole) and primary amine (11.0 mmole) in methanol (10 mL) was stirred at room temperature for 2–3 days. The crude product was filtered off and recrystallized from the ethanol to yield the amidines **3** as white solid (*30*).

3.2.1. *3a: (Z)-N-phenyl-N′-(phenylcarbamothioyl)benzimidamide*

Yield 3.13 g (91%). Solid m.p.: 155 °C; IR ($CHCl_3$): ν (cm^{-1}): 3424, 1651, 1221; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 4.57$ (d, 2H, $^3J_{H-H} = 6.5$ Hz, CH_2), 7.02–8.95 (m, 17H, NH, Ar); ^{13}C-NMR ($CDCl_3$): $\delta = 46.4$, 120.6, 122.9, 126.9, 127.3, 128.1, 128.2, 128.3, 130.5, 133.6, 134.2, 138.6, 139.2, 160.6, 175.2.

3.2.2. *3b: (Z)-N-benzyl-N′-(benzylcarbamothioyl)benzimidamide*

Yield 2.78 g (80%). M.p.: 96 °C; IR ($CHCl_3$): ν (cm^{-1}): 3414, 1649, 1227; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 4.82$ (d, 2H, $^3J_{H-H} = 6.4$ Hz, CH_2), 4.89 (d, 2H, $^3J_{H-H} = 6.7$ Hz, CH_2), 6.96–8.04 (m, 17H, NH, Ar); ^{13}C-NMR ($CDCl_3$): $\delta = 49.4$, 54.3, 125.7, 126.2, 127.5, 127.9, 128.5, 128.7, 130.2, 136.1, 158.7, 176.2.

3.2.3. *3c: (Z)-N-benzyl-N′-(ethylcarbamothioyl)benzimidamide*

Yield 2.46 g (83%). Solid m.p.: 95 °C; IR ($CHCl_3$): ν (cm^{-1}): 3380, 1636, 1232; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.22$ (t, 3H, $^3J_{H-H} = 8.0$ Hz, CH_3), 3.83 (q, 2H, $^3J_{H-H} = 7.7$ Hz, CH_2), 4.52 (d, 2H, $^3J_{H-H} = 6.5$ Hz, CH_2), 7.07–8.84 (m, 12H, NH, Ar); ^{13}C-NMR ($CDCl_3$): $\delta = 13.7$, 40.3, 54.3, 126.6, 127.0, 128.6, 128.9, 129.1, 130.5, 136.2, 140.0, 157.7, 179.9.

3.2.4. *3d: (Z)-N-benzyl-2-phenyl-N′-(phenylcarbamothioyl)acetimidamide*

Yield 2.90 g (81%). Solid m.p.: 106 °C; IR ($CHCl_3$): ν (cm^{-1}): 3380, 1661, 1227; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 4.08$ (d, 2H, $^3J_{H-H} = 6.4$ Hz, CH_2), 4.62 (d, 2H, $^3J_{H-H} = 6.7$ Hz, CH_2), 7.22–8.08 (m, 17H, NH, Ar); ^{13}C-NMR ($CDCl_3$): $\delta = 36.6$, 48.5, 126.4, 126.8, 127.9, 128.2, 129.1, 129.2, 134.8, 137.0, 137.4, 158.2, 174.3.

3.2.5. *3e: (Z)-N-benzyl-N′-(benzylcarbamothioyl)-2-benzylacetimidamide*

Yield 3.24 g (87%). Solid m.p.: 154 °C; IR ($CHCl_3$): ν (cm^{-1}): 3391, 1619, 1239; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 3.22$ (d, 2H, $^3J_{H-H} = 7.7$ Hz, CH_2), 4.37 (d, 2H, $^3J_{H-H} = 6.5$ Hz, CH_2), 4.51 (d, 2H, $^3J_{H-H} = 6.5$ Hz, CH_2), 7.17–7.78 (m, 17H, NH, Ar); ^{13}C-NMR ($CDCl_3$): $\delta = 48.2$, 49.6, 54.3, 126.5, 127.6, 127.9, 128.4,128.6, 129.1, 134.5, 137.5, 156.5, 183.2.

3.2.6. *3f: (Z)-N′-(phenylcarbamothioyl)-N-(pyridin-2-ylmethyl)benzimidamide*

Yield 3.36 g (90%). Solid m.p.: 132 °C; IR ($CHCl_3$): ν (cm^{-1}): 3409, 1617, 1229; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 4.83$ (d, 2H, $^3J_{H-H} = 6.6$ Hz, CH_2), 7.21–8.34 (m, 16H, NH, Ar), 8.89 (d, 1H, $^3J_{H-H} = 8.8$ Hz, CHAr); ^{13}C-NMR ($CDCl_3$): $\delta = 53.4$, 122.1, 122.5, 128.0, 128.6, 129.2, 129.8, 131.0, 131.8, 132.5, 132.9, 135.2, 136.9, 158.1, 162.8, 178.1.

3.3. *Synthesis of thiazolines*

A mixture of amidine **3** (2.0 mmole), 2-halogenated alkyl derivatives (2.1 mmole) in 10 mL ethanol, and 2.1 mmole of pyridine was heated under reflux for 24 h. Water (20 mL) was added to the reaction mixture and the product was extracted twice with 15 mL of chloroform. The chloroform evaporated and the resulting oil was washed with 10 mL petroleum ether and allowed to

stay at room temperature for 2–3 days to crystallize yielding the thiazolines (or the *S*-alkylated amidines).

3.3.1. *8a: Ethyl-4-phenyl-2-(phenylamino)thiazole-5-carboxylate*

Yield 5.70 g (88%). Solid m.p.: 190 °C; IR (CH_3Cl): ν (cm^{-1}) 3395, 1699; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.21$ (t, 3H, $^3J_{H-H} = 7.8$ Hz, CH_3), 4.18 (q, 2H, $^3J_{H-H} = 7.4$ Hz, CH_2), 7.11–7.67 (m, 11H, NH, Ar); ^{13}C-NMR ($CDCl_3$): $\delta = 14.2$, 60.8, 109.9, 120.1, 124.5, 127.6, 129.1, 129.4, 129.7, 134.0, 139.2, 158.4, 161.6, 168.1; MS (CI, NH_3): m/z (M^+): 324, ($M^+ + H$): 325, ($M^+ - OEt$): 279, ($M^+ - CO_2Et$): 253. Elemental analysis (found/calculated): C: 66.52/66.64; H: 5.02/4.97; N: 8.59/8.64.

3.3.2. *8b: Ethyl-2-(benzylamino)-4-phenylthiazole-5-carboxylate*

Yield 5.04 g (80%). Solid m.p.: 140 °C; IR (CH_3Cl): ν (cm^{-1}): 3393, 1697; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.24$ (t, 3H, $^3J_{H-H} = 7.2$ Hz, CH_3), 4.23 (q, 2H, $^3J_{H-H} = 7.7$ Hz, CH_2), 4.35 (q, 2H, $^3J_{H-H} = 6.5$ Hz, CH_2), 7.07–7.69 (m, 11H, NH, Ar); ^{13}C-NMR ($CDCl_3$): $\delta = 14.2$, 60.6, 49.4, 109.6, 126.2, 126.9, 127.9, 128.7, 129.4, 130.0, 135.7, 136.5, 159.1, 161.7, 171.8. Elemental analysis (found/calculated): C: 67.21/67.43; H: 5.42/5.36; N: 8.39/8.28.

3.3.3. *8c: Ethyl-2-(ethylamino)-4-phenylthiazole-5-carboxylate*

Yield 4.69 g (85%). Solid m.p.: 96 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.12$ (t, 3H, $^3J_{H-H} = 7.3$ Hz, CH_3), 1.22 (t, 3H, $^3J_{H-H} = 7.6$ Hz, CH_3), 3.13 (q, 2H, $^3J_{H-H} = 7.6$ Hz, CH_2), 4.25 (q, 2H, $^3J_{H-H} = 7.4$ Hz, CH_2), 7.31–8.33 (m, 11H, NH, Ar); ^{13}C-NMR ($CDCl_3$): $\delta = 13.5$, 14.2, 41.5, 60.9, 108.3, 121.1, 124.2, 125.3, 138.0, 158.1, 161.6, 167.0; MS (CI, NH_3): m/z (M^+): 276, ($M^+ + H$): 277, ($M^+ - OEt$): 231, ($M^+ - (CO_2Et + S)$): 171. Elemental analysis (found/calculated): C: 60.59/60.85; H: 5.72/5.84; N: 10.29/10.14.

3.3.4. *8d: Ethyl-4-benzyl-2-(phenylamino)thiazole-5-carboxylate*

Yield 5.67 g (84%). Solid m.p.: 125 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.32$ (t, 3H, $^3J_{H-H} = 7.5$ Hz, CH_3), 3.78 (q, 2H, $^3J_{H-H} = 7.8$ Hz, CH_2), 4.22 (q, 2H, $^3J_{H-H} = 6.6$ Hz, CH_2), 7.03–7.67 (m, 11H, NH, Ar); ^{13}C-NMR ($CDCl_3$): $\delta = 14.4$, 36.2, 60.7, 110.5, 120.2, 124.7, 126.2, 128.3, 128.8, 129.6, 130.0, 139.3, 160.4, 162.3, 168.0; MS (CI, NH_3): m/z (M^+): 338, ($M^+ + H$): 339, ($M^+ - OEt$): 277.

3.3.5. *9a: (4-nitrophenyl)(4-phenyl-2-(phenylamino)thiazol-5-yl)methanone*

Yield 5.2 g (65%). Solid m.p.: 170 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.13$–7.62 (m, 11H, NH, Ar); 7.88 (d, 2H, $^4J_{H-H} = 8.1$ Hz, Char), 8.08 (d, 2H, $^4J_{H-H} = 8.0$ Hz, CHar); ^{13}C-NMR ($CDCl_3$): $\delta = 120.2$, 122.9, 123.1, 125.7, 128.2, 129.8, 129.9, 138.2, 142.9, 158.1, 161.2, 175.4; MS (CI, NH_3): m/z (M^+): 401, ($M^+ + H$): 402, ($M^+ - (p\text{-}O_2N{-}Ph{-}CH{=}O)$): 243, ($M^+ - (p\text{-}O_2N{-}Ph{-}CO){-}S$): 182.

3.3.6. *9b: (4-benzyl-2-(benzylamino)thiazol-5-yl)(4-nitrophenyl)methanone*

Yield 5.73 g (67%). Solid m.p.: 146 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 4.52$ (d, 2H, $^3J_{H-H} = 6.5$ Hz, CH_2), 5.62 (d, 2H, $^3J_{H-H} = 6.6$ Hz, CH_2), 6.71–7.73 (m, 11H, NH, Ar), 8.07 (d, 2H, $^4J_{H-H} = 8.1$ Hz, Char), 8.28 (d, 2H, $^4J_{H-H} = 8.2$ Hz, CHar); ^{13}C-NMR ($CDCl_3$): $\delta = 50.5$, 51.8, 119.3, 124.4, 127.1, 128.2, 128.5, 128.7, 128.9, 129.1, 130.5, 132.6, 133.1, 134.2, 141.2, 149.0, 159.3, 170.4. Elemental Analysis (found/calculated): C: 67.25/67.12; H: 4.52/4.46; N: 9.91/9.78.

3.3.7. *10a: 4-phenyl-2-(phenylamino)thiazole-5-carbonitrile*

Yield 4.15 g (75%). Solid m.p.: 220 °C; IR (CH3Cl): ν (cm^{-1}): 3495, 2115; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 6.92$–7.81 (m, 10H, CHar), 8.01 (br, 1H, NH); ^{13}C-NMR ($CDCl_3$): $\delta = 114.5$, 119.9, 125.3, 127.9, 128.8, 129.8, 130.3, 132.2, 138.6, 151.1, 161.9, 167.1; MS (CI, NH_3): m/z (M^+): 305, ($M^+ + H$): 306, ($M^+ - (Ph\text{-}CH_2 + PhCH_2NH)$): 223, ($M^+ - NC\text{-}NHCH_2Ph$): 173. Elemental analysis (found/calculated): C: 69.25/69.29; H: 4.25/4.00; N: 15.12/15.15.

3.3.8. *10b: 4-benzyl-2-(benzylamino)thiazole-5-carbonitrile*

Yield 4.2 g (69%). Solid m.p.: 155 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 4.58$ (d, 2H, CH_2), 5.73 (d, 2H, $^3J_{H-H} = 6.7$ Hz, CH_2), 7.07–7.33 (m, 11H, CHar), 7.54 (br, 1H, NH); ^{13}C-NMR ($CDCl_3$): $\delta = 42.5$, 51.0, 114.4, 122.2, 125.6, 126.8, 127.4, 129.9, 138.2, 152.9, 160.9, 165.2.

3.3.9. *11a: 1-(4-Phenyl-2-(phenylamino)thiazol-5-yl)ethanone*

Yield 3.5 g (60%). Solid m.p.: 139.1 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 2.12$ (s, 3H, CH_3), 7.02–7.57 (m, 10H, CHar), 9.05 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): $\delta = 28.8$, 120.5, 125.0, 125.6, 128.6, 129.4, 129.7, 135.2, 139.2, 157.8, 168.9, 190.8. Elemental analysis (found/calculated): C: 69.29/69.36; H: 4.49/4.79; N: 9.63/9.52.

3.3.10. *11b: 1-(4-Benzyl-2-(benzylamino)thiazol-5-yl)ethanone*

Yield 4.4 g (65%). Solid m.p.: 83.6 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 2.11$ (s, 3H, CH_3), 3.63 (s, 2H, CH_2); 4.4 (d, 2H, $^3J_{H-H} = 6.5$ Hz, CH_2), 7.07–7.28 (m, 10H, Ar), 9.32 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): $\delta = 27.1$, 43.6, 65.8, 118.5, 123.0, 125.5, 127.4, 128.3, 129.8, 130.0, 136.7, 140.5, 165.3, 170.9, 190.5.

3.3.11. *17a: (NZ,N′E)-phenyl-N-(benzylamino)(phenyl)methylene-N′-phenylcarbamimidothioate*

Yield 7.15 g (85%). Solid m.p.: 154 °C; IR (CH_3Cl) ν (cm^{-1}): 3495; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 4.11$ (s, 2H, CH_2), 4.62 (s, 2H, CH_2), 6.95–8.03 (m, 21H, NH, Ar); ^{13}C-NMR ($CDCl_3$): $\delta = 36.4$, 47.1, 122.9, 123.4, 127.6, 127.8, 128.6, 128.7, 129.0, 130.3, 132.2, 135.6, 136.7, 137.9, 142.9, 157.2, 164.1; MS, m/z (M^+): 459, ($M^+ + H$): 460, ($MH^+ - C_2H_4$): 432, ($M^+ - CH_2S$): 413.

3.3.12. *17b: (NZ,N′Z)-phenyl-N-1-(benzylamino)-2-phenylethylidene-N′-ethylcarbamimidothioate*

Yield 6.73 g (87%). Orange oil. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.23$ (t, 3H, $^3J_{H-H} = 7.7$ Hz, CH_3), 3.27 (q, 2H, $^3J_{H-H} = 7.9$ Hz, CH_2), 4.14 (s, 2H, CH_2), 4.59 (s, 2H, CH_2), 6.88–8.77 (m, 15H, Char), 8.89 (br, 1H, NH); ^{13}C-NMR ($CDCl_3$): $\delta = 13.9, 36.9, 39.8, 46.7, 127.6, 127.8, 128.4, 128.5, 128.6, 128.9, 129.0, 129.1, 130.6, 132.5, 132.9, 134.1, 136.2, 136.6, 143.6 164.6, 168.4$. Elemental analysis (found/calculated): C: 74.23/74.38; H: 6.62/6.50; N: 10.62/10.84.

3.3.13. *18a: Ethyl-2-((NZ,N′Z)-N-((benzylamino)(phenyl)methylene)-N′-phenylcarbamimidoylthio) acetate*

Yield 5.94 g (69%). Orange oil. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.27$ (t, 3H, $^3J_{H-H} = 7.6$ Hz, CH_3), 2.23 (t, 2H, $^3J_{H-H} = 7.7$ Hz, CH_2), 3.25 (t, 2H, $^3J_{H-H} = 7.4$ Hz, CH_2), 4.18 (q, 2H, $^3J_{H-H} = 6.6$ Hz, CH_2), 4.78 (d, 2H, $^3J_{H-H} = 6.5$ Hz, CH_2), 6.78–7.92 (m, 16H, NH, Ar); ^{13}C-NMR ($CDCl_3$): $\delta = 14.2, 44.0, 49.1, 60.7, 65.8, 121.5, 124.7, 125.1, 125.3, 126.9, 127.0, 127.5, 128.5, 128.9, 129.3, 129.8, 130.0, 131.5, 134.2, 137.2, 138.2, 162.5, 167.5, 170.1$. Elemental analysis (found/calculated): C: 69.81/69.59; H: 5.99/5.84; N: 10.01/9.74.

3.3.14. *18b: Ethyl-2-((NZ,N′Z)-N-(1-(benzylamino)-2-phenylethylidene)-N′-phenylcarbamimidoylthio)acetate*

Yield 5.43 g (63%). Solid m.p.: 72 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.41$ (t, 3H, $^3J_{H-H} = 7.0$ Hz, CH_3), 2.14 (t, 2H, $^3J_{H-H} = 7.5$ Hz, CH_2), 3.67 (t, 2H, $^3J_{H-H} = 7.6$ Hz, CH_2), 4.53 (q, 2H, $^3J_{H-H} = 7.8$ Hz, CH_2), 4.65 (d, 2H, $^3J_{H-H} = 6.7$ Hz, CH_2), 7.21–7.37 (m, 16H, NH, Ar); ^{13}C-NMR ($CDCl_3$): $\delta = 14.1, 30.9, 43.6, 43.8, 55.0, 65.1, 125.3, 127.4, 127.4, 127.5, 128.6, 128.9, 129.1, 129.5, 134.7, 138.1, 156.5, 161.5, 170.9$. Elemental analysis (found/calculated): C: 70.23/70.09; H: 6.32/6.11; N: 7.42/7.17.

3.3.15. *19a: Ethyl-3-((NZ,N′Z)-N-((benzylamino)(phenyl)methylene)-N′-phenylcarbamimidoylthio) propanoate*

Yield 5.34 g (60%). Orange oil. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.27$ (t, 3H, $^3J_{H-H} = 8.1$ Hz, CH_3), 2.02 (t, 2H, $^3J_{H-H} = 7.8$ Hz, CH_2), 2.44 (dd, 2H, $^3J_{H-H} = 7.9$ Hz, CH_2), 3.51 (t, 2H, $^3J_{H-H} = 7.4$ Hz, CH_2), 4.15 (q, 2H, $^3J_{H-H} = 7.7$ Hz, CH_2), 4.48 (d, 2H, $^3J_{H-H} = 6.8$ Hz, CH_2), 6.78–7.33 (m, 16H, NH, Ar), ^{13}C-NMR ($CDCl_3$): $\delta = 14.4, 24.6, 27.6, 31.2, 60.4, 60.5, 121.9, 123.2, 124.5, 126.3, 126.6, 126.9, 127.5, 127.7, 128.0, 128.4, 128.7, 129.5, 130.5, 132.2, 135.3, 137.6, 156.0, 161.6, 173.1$. Elemental analysis (found/calculated): C: 70.17/70.09; H: 6.04/6.11; N: 7.33/7.17.

3.3.16. *20a: (NZ,N′Z)-2-cyanoethyl-N-(benzylamino)(phenyl)methylene-N′-phenylcarbamimidothioate*

Yield 5.17 g (65%). Orange oil. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 2.14$ (m, 2H, CH_2), 2.52 (t, 2H, $^3J_{H-H} = 7.9$ Hz, CH_2), 3.57 (t, 2H, $^3J_{H-H} = 7.7$ Hz, CH_2), 4.68 (d, 2H, $^3J_{H-H} = 6.9$ Hz, CH_2), 6.99–8.07 (m, 15H, Ar), 8.56 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): $\delta = 14.6, 28.1, 33.9, 60.9, 118.6, 121.6, 122.5, 125.3, 127.1, 127.8, 128.3, 128.7, 128.8, 129.0, 129.2, 129.5, 129.7, 130.4, 132.8, 136.1, 161.7, 166.6$.

3.3.17. *20b: (NZ,N′Z)-2-cyanoethyl-N′-phenyl-N-(phenyl(pyridin-2-ylmethylamino)methylene)carbamimidothioate*

Yield 4.7 g (59%). Orange oil. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 2.13$ (m, 2H, CH_2), 2.6 (q, 2H, $^3J_{H-H} = 7.8$ Hz, CH_2), 3.66 (q, 2H, $^3J_{H-H} = 7.5$ Hz, CH_2); 4.63 (d, 2H, $^3J_{H-H} = 6.7$ Hz, CH_2), 7.11–8.14 (m, 14H, Ar), 8.92 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): $\delta = 14.3$, 28.2, 29.7, 60.9, 118.6, 120.3, 122.2, 122.9, 125.6, 127.4, 128.4, 128.6, 129.4, 130.0, 135.4, 137.2, 156.0, 166.7. Elemental analysis (found/calculated): C: 69.28/69.15; H: 5.23/5.30; N: 17.68/17.53.

3.3.18. *21a: (NE,NZ)-4-nitrobenzyl-N-1-(benzylamino)-2-phenylethylidene-N′-phenylcarbamimidothioate*

Yield 6.7 g (68%). Solid m.p.: 91.3 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 3.56$ (s, 2H, CH_2); 4.44 (d, 2H, $^3J_{H-H} = 6.9$ Hz, CH_2), 4.70 (s, 2H, CH_2), 5.89 (s, 1H, NH), 7.13–8.26 (m, 14H, Ar); ^{13}C-NMR ($CDCl_3$): $\delta = 43.9$, 44.8, 60.9, 123.9, 124.3, 127.6, 128.7, 128.9, 129.3, 129.5, 129.6, 130.3, 134.3, 135.0, 138.3, 144.5, 167.3, 171.0. Elemental analysis (found/calculated): C: 71.04/70.84; H: 5.73/5.55; N: 11.12/11.02.

3.3.19. *21b: (NZ,N′Z)-4-nitrobenzyl-N′-phenyl-N-(2-phenyl-1-(phenylamino)ethylidene) carbamimidothioate*

Yield 4.9 g (62%). Solid m.p.:58.5 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 3.69$ (s, 2H, CH_2); 4.73 (d, 2H, $^3J_{H-H} = 7.0$ Hz, CH_2), 7.22–7.87 (m, 16H, Ar); 8.04 (d, 2H, $^3J_{H-H} = 7.9$ Hz CHar); 8.28 (d, 2H, $^3J_{H-H} = 8.2$ Hz CHar); ^{13}C-NMR ($CDCl_3$): $\delta = 44.5$, 44.8, 116.3, 122.5, 123.6, 124.0, 124.3, 126.8, 127.9, 128.0, 128.2, 129.3, 129.5, 129.6, 130.1, 134.6, 138.2, 140.7, 168.1, 170.9. Elemental analysis (found/calculated): C: 70.04/69.98; H: 5.14/5.03; N: 11.81/11.66.

4. Conclusion

In this work, we have synthesized 2-aminothiazoles by reaction between *N*-thioamido amidines and 2-halogenated alkyl derivatives bearing an electron withdrawing group in the α position with regard to the halogen atom. The structure of the final product suggests the formation of intermediates by an *S*-alkylation of the starting *N*-thioamido amidines **3** with halogenated alkyl derivatives, which leads by cyclization to the corresponding 2-aminothiazoles. When the EWG is in β or γ positions, the protons of the methylenic group directly linked to the sulfur atom of the intermediates are not acidic enough to be removed easily and the opened ring intermediates can be isolated.

Acknowledgements

The authors thank MESRST (Ministère de l'Enseignement Supérieur, la Recherche Scientifique et la Technologie) (Lab CH–02) for the financial support.

References

(1) Rudi, A.; Chill, L.; Aknin, M.; Kashman, Y. *J. Nat. Prod*. **2003,** *66,* 575–577.
(2) You, S.-L.; Razavi, H.; Kelly, J.W. *Angew. Chem. Int. Ed*. **2003,** *42,* 83–85.
(3) You, S.-L.; Kelly, J.W. *J. Org. Chem*. **2003,** *68,* 9506–9509.
(4) You, S.-L.; Kelly, J.W. *Chem. Eur. J.* **2004,** *10,* 71–75.

(5) You, S.-L.; Kelly, J.W. *Tetrahedron* **2005,** *61,* 241–249.
(6) You, S.-L.; Deechongkit, S.; Kelly, J.W. *Org. Lett.* **2004,** *6,* 2627–2630.
(7) Poulvier, B.; Houssin, R.; Baily, C.; Henichart, J.P. *J. Heterocycl. Chem.* **1989,** *26,* 1643–1647.
(8) Silvermann, R.B. *The Organic Chemistry of Drug Design and Drug Action*; Academic Press: London, 1992, p. 263.
(9) Umezawa, H.; Suhara, Y.; Taketa, T.; Maeda, K. *J. Antibiot*. **1966,** *19,* 210–215.
(10) Umezawa, H.; Takeuchi, S.; Hori, T.; Sawa, T.; Ishizuka, T.; Komai, T. *J. Antibiot*. **1972,** *25,* 409–420.
(11) Das, J.; Chen, P.; Norris, D.; Padmanabha, R.; Lin, J.; Moquin, R.V.; Shen, Z.; Cook, L.S.; Doweyko, A.M.; Pitt, S. et al. *J. Med. Chem*. **2006,** *49,* 6819–6832.
(12) Mulvaney, J.E.; Marvel, C.S. *J. org. Chem*. **1961,** *26,* 95–97.
(13) Gottlieb, M.S.; Schroff, R.; Schanker, H.M.; Weisman, J.D.; Fan, P.T.; Wolf, R.A.; Saxon, A. *N. Engl. J. Med*. **1981,** *305,* 1425–1431.
(14) Barre-Sinoussi, F.; Chermann, J.C.; Rey, F.; Nugeyre, M.T.; Chamaret, S.; Gruest, J.; Dauguet, C.; Axler-Blin, C.; Vezinet-Brun, F.; Rouzioux, C. et al. *Science* **1983,** *220,* 868–871.
(15) Masuda, N.; Yamamoto, O.; Fuji, M.; Oghami, T.; Fujiyasu, J.; Kontani, T.; Moritomo, A.; Orita, M.; Kurihara, H.; Koga, H. et al. *Bioorg. Med. Chem*. **2004,** *12,* 6171–6182.
(16) Schinazi, R.F.; Mead, J.R.; Feorino, P.M. *AIDS Res. Hum. Retroviruses* **1992,** *8,* 963–990.
(17) Esnouf, R.; Ran, J.; Ross, C.; Jones, Y.; Stammers, D.; Stuart, D. *Nat. Struct. Biol*. **1995,** *2,* 303–308.
(18) Abignent, E.; Arena, F.; De Capraris, P.; Ferreri, C.; Marmo, E.; Ottavo, R.; Rossi, F.; Giasi, M. *Farmaco Ed. Sci*. **1981,** *36,* 893–904.
(19) Abignent, E.; Arena, F.; De Capararis, P. *Farmaco Ed. Sci*. **1977,** *32,* 735–746.
(20) Dashkevich, L.B.; Korbelainen, E.S. *Chem. Heterocycl. Comp*. **1967,** *2,* 457–459.
(21) Budriesi, R.; Ioan, P.; Locatelli, A.; Cosconati, S.; Leoni, A.; Ugenti, M.P.; Andreani, A.; Di Toro, R.; Bedini, A.; Spampinato, S. et al. *J. Med.Chem*. **2008,** *51,* 1592–1600.
(22) Van Telman, E.E.; Murphy, W.J. *J. Am. Chem. Soc*. **1970,** *92,* 7204–7206.
(23) Baccar, B.; Mathis, F. *C. R. Acad. Sci. Paris* **1965,** *261,* 174–177.
(24) Etienne, A.M.; Le Berre, A.; Lonchambon, G.; Roques, J.; Lemmens, B. *C. R. Acad. Sci. Paris Série C* **1976,** 537–540.
(25) Carpenter, J.E.; Weinhold, F. *J. Mol. Struct*. (*Theochem*) **1988,** *169,* 41–62.
(26) PM3, Stewart, J.J.P. *J. Comput. Chem*. **1989,** *10,* 221–264.
(27) Hajjem, B.; Benkhoud, M.L.; Baccar, B. *Bull. Soc. Chim. Belg.* **1992,** *101,* 445–448.
(28) Harizi, A.; Hajjem, B.; Baccar, B. *Rev. Roum. Chim.* **1998,** *43,* 35–40.
(29) Tapsoba, I.; Adhoum, N.; Ben Khoud, M.L.; Kossai, R.; Boujlel, K. *Synth. Commun.* **2003,** *33,* 1675–1682.
(30) Chmekh, R.; Tapsoba, I.; Medini, H.; Maisonhaute, E.; Benkhoud, M.L.; Boujlel, K. *J. Electroanal. Chem*. **2007,** *599,* 85–90.