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Stereoselective synthesis of (*E*)-4-alkoxy-2-aryl-5-chloro-2-thiazolines

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Abstract—The first synthesis of the title compounds has been achieved starting from chloralamides by a route involving chemical and electrochemical steps. *N*-(1-Alkoxy-2,2,2-trichloroethyl)benzamides were efficiently prepared from chloralbenzamides and were electrochemically converted into *N*-(1-alkoxy-2,2-dichloroethyl)benzamides in high yields by cathodic reduction in a protic medium. Thionation of these compounds with Lawesson's reagent followed by basic treatment gave novel (*E*)-4-alkoxy-2-aryl-5-chloro-2-thiazolines in fair to quantitative yields.
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1. Introduction

Thiazoline chemistry is receiving considerable attention because of its occurrence in biologically active natural products of interest such as curacin A,[1] thiangazole,[2] mirabazoles,[3] apratoxins,[4] etc. Furthermore, thiazolines are being used as building blocks in pharmaceutical drug discovery.[5,6] Some thiazoline derivates present interesting activity such as anti-HIV,[2a] anti-cancer,[7] antimitotic,[1b,1c] and antibiotic[5c] agents. Therefore, new procedures for preparing these compounds attract substantial research interest.

Over the years, a number of approaches to make these heterocycles have been developed.[8] The most commonly used synthetic approaches to these compounds are based on cyclodehydration of β-hydroxythioamides under the Mitsunobu conditions,[5a,9] the Burgess reagent [methyl *N*-(triethylammonium sulfonyl)carbamate],[5a,9b] [bis(2-methoxyethyl)amino]-sulfur trifluoride,[10] or diethylamidosulfur trifluoride.[11] Condensations of 2-aminothiols with nitriles,[12] carboxylic acids,[13] esters,[14] iminoethers,[15] or iminotriflates[16] is also exploitable reactions. Thiazolines have also been prepared from acylamino and thioacylamino alcohols[11,17,18] or by multistep conversions from oxazolines.[19] More recent methods have been described, like ruthenium-catalyzed oxidation of thiazolidine to thiazoline,[20] reaction of aminothiols with *N*-acylbenzotriazoles under microwave irradiation,[21] or annulation of thioamides with 2-alkynoates.[22]

Chloral is an inexpensive multipurpose starting material for organic synthesis.[23] We have recently developed a new preparative methodology based on using chloral derivates having a molecular arrangement suitable to undergo a direct heterocyclization process that is promoted electrochemically. This method was successfully applied to prepare new types of 2-oxazolines,[23,24] which provided access to novel 2-imidazolidinones,[25] 1,3-oxazolidines, and 1,3-thiazolidines.[26] One of the most advantageous features of this synthetic tactic lies in the synthesis of chlorinated oxazolines, since severe problems of chemical incompatibility with the usual chlorinating reagents can be avoided by using certain prechlorinated synthons derived from chloral. Given the previous success of our methodology on the synthesis of 2-oxazolines, and in order to expand the number of 2-thiazoline derivatives available, we recognized the opportunity to attempt an approach to synthesis 5-chloro-2-thiazolines, since these products pertain to a hitherto unknown family of compounds, of interest by themselves, as well as for their synthetic potential.

With the aim of exploring the possibility of adaptation of our earlier preparative strategy to this new objective, chloralamide **2a** was transformed to trichloromethyl thioamide **8a** (Scheme 1, route A) by treatment with Lawesson's reagent[27,28] (LR). In contrast to what was expected on the basis of our previous experiments on 2-oxazoline electrosynthesis, a direct generation of the targeted (*E*)-5-chloro-4-methoxy-2-thiazoline **7a** by cathodic reduction of **8a** was not feasible. This process was found to be totally unselective, probably due to equality in electroactivity at thiocarbonyl and trichloromethyl centers. Fortunately, this adversity could be overcome by carrying out an electroreduction–thionation

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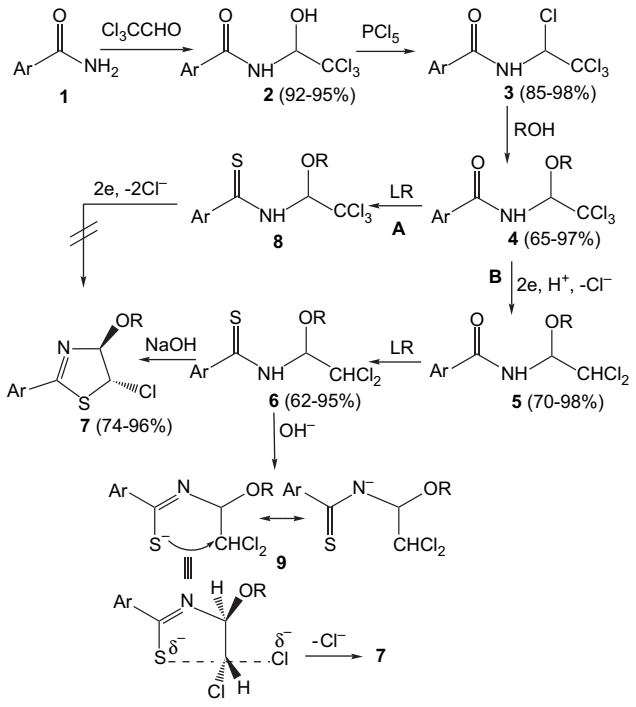
steps run (Scheme 1, route B), instead of the failed thionation–electroreduction reaction sequence.



Entry	Ar	R
a	C_6H_5	CH_3
b	C_6H_5	CH_3CH_2
c	C_6H_5	$C_6H_5CH_2CH_2$
d	4-ClC_6H_4	$C_6H_5CH_2CH_2$
e	4-MeC_6H_4	$C_6H_5CH_2$
f	4-MeC_6H_4	4-$MeOC_6H_5CH_2$
g	2-ClC_6H_4	3,4,5-$(MeO)_3C_6H_2CH_2$
h	2-MeC_6H_4	3,4,5-$(MeO)_3C_6H_2CH_2$

Scheme 1.

2. Results and discussion

Chloralamides **2** were prepared[29] in almost quantitative yields by reaction of chloral hydrate with benzamides **1** (Scheme 1). In order to prepare *N*-(1-alkoxy-2,2,2-trichloroethyl)benzamides **4**, compounds **2** were firstly converted into *N*-(1,2,2,2-tetrachloroethyl)benzamides **3** in high yields by treatment with phosphorus pentachloride, as described previously.[29b,30] Products **3** were selectively monoalkoxylated by simple treatment with a mixture of the corresponding alcohol and triethylamine (ratio 1:1) to give the targeted intermediates **4** in good to quantitative yields.[24]

The viability of a direct transformation of intermediates **4** to products **7** based on previous results concerning the electrosynthesis of 2-oxazolines[23,24] was investigated (route A). Thionation of compound **4a** with LR gave **8a** (72 %), which was electrolyzed in an aprotic medium (−1.6 V vs SCE) leading to a complex mixture of unidentified products instead of the expected thiazoline **7a**, due to an indiscriminate electrode process. In view of this difficulty it was intended that an alternative reaction sequence like route B would be able to provide the required compounds **7**, since the non-sulfurated intermediates **4** would be able to undergo a more selective electrochemical reduction than the sulfurated intermediates **8**. Thus, cathodic reductions of compounds **4** in a protic medium were carried out under constant potential of −1.7 V vs SCE. The electricity consumption was 2 F/mol of **4** in all cases. After electrolyses the reaction products were easily isolated in high yields by simple mixing of the catholyte solution with water and filtration. After crystallization highly pure white compounds were isolated and identified by elemental analysis and IR, MS, and NMR spectroscopy as intermediates **5**.

Complete conversions of amides **5** into thioamides **6** were achieved by treatment with Lawesson's reagent on refluxing toluene for 1 h and isolated by column chromatography, resulting in yellow products in fair to high yields that were identified and characterized by elemental analysis and IR, MS, and NMR spectroscopy.

Alkaline treatment of compounds **6** under mild temperature conditions provided products in good to quantitative yields, which were identified by the usual techniques as (*E*)-4-alkoxy-5-chloro-2-thiazolines **7**. As far as we know, this is the first time that compounds of this type have been synthesized. They seem to have special interest due to a potential capacity to be used as synthetic intermediates to prepare many other heterocyclic derivatives.

^{1}H NMR spectroscopic analyses confirmed that transformation of compounds **6** to products **7** occurs with total stereoselectivity toward the formation of (*E*)-isomers. A transition state between anionic species **9** and final products **7** involving minimal steric interactions between the stationary chlorine atom and a vicinal alkoxyl group explains the stereochemical fate of this internal displacement process. This configurational assignment is firmly supported by categorical studies[31] on stereochemistry of substituted five-membered cyclic compounds, from which it has been established as a general rule that the arrangement of vicinal protons corresponds to a (*E*)-configuration when they show spin coupling constants of $J<5$ Hz, whereas a (*Z*)-configuration always shows coupling constants with $J>5$ Hz, being ~8 Hz the value most frequently found. This method clearly leads to the conclusion that the stereochemistry of compounds **7** corresponds to a (*E*)-configuration, since the coupling constant between H-4 and H-5 protons is remarkably small, with *J* values ranging from 1.0 to 1.2 Hz in all cases.

To conclude, an effective method for the synthesis of previously unattainable (*E*)-4-alkoxy-2-aryl-5-chloro-2-thiazolines is reported. Versatility, good yields, easy availability of starting materials, mildness, and simple experimental procedure are noteworthy advantages of this approach.

3. Experimental

3.1. General

NMR spectra were determined on Bruker AV-200, Bruker AV-300, or Bruker AV-400 with tetramethylsilane as internal reference. Electron-impact mass spectra were obtained on Thermoquest trace MS spectrometer under an ionizing voltage of 70 eV. FAB^+ were obtained on Autospec 5000 VG spectrometer. IR spectra (Nujol emulsions) were recorded on a Nicolet Impact 400 spectrometer. Microanalyses were performed on a Carlo Erba EA-1108 analyzer. Melting points were determined on a Büchi Melting point B-540, and are uncorrected. Electrochemical experiments were performed with an Amel 552 potentiostat coupled to an Amel 721 integrator.

3.2. Electrochemical preparation of *N*-(1-alkoxy-2,2-dichloroethyl)benzamides (5)

Electrolysis of compounds **4** was carried out under constant cathodic potential in a concentric cylindrical cell with two compartments separated by a circular glass frit (medium) diaphragm. A mercury pool (diameter 5 cm) was used as the cathode and a platinum plate as the anode. The catholyte was magnetically stirred. The temperature was kept at approximately 18 °C by external cooling. The reduction was performed in DMF (50 mL)–AcOH (1 mL)–$LiClO_4$ 0.5 M. Anhydrous sodium carbonate (1 g) was placed in the anode compartment to prevent accumulation of electrogenerated acid. Solutions of compounds **4** (5 mmol) were electrolyzed under a cathodic potential of −1.7 V vs SCE. The duration of the electrolyses ranged from 1.8 to 2.0 h. The average current intensity was 10.7 mA/cm^2 at the beginning, and 1.02 mA/cm^2 at the end. The cell voltage values remained below 5 V in all cases. The electricity consumption was 2 F/mol in all cases. Electrolyses carried out using $NaBF_4$, which is a less potentially hazardous electrolyte[32] than $LiClO_4$, gave similar results. These syntheses were found to be reproducible but with moderate current efficiency (around 40%) by working in DMF (50 mL)–AcOH (0.6 mL)–$NaBF_4$ 0.5 M and using graphite (−1.8 V vs SCE) instead of mercury as cathodic material.

All the electrolysis products were isolated by pouring the catholyte solution into ice–water, and the resulting solids were collected by filtration and dried under vacuo. Products **5** were isolated as white solids and were crystallized from the appropriated solvents giving satisfactory IR, ^{1}H NMR, ^{13}C NMR, mass spectra, and elemental analyses.

3.2.1. *N*-(2,2-Dichloro-1-methoxyethyl)benzamide (5a). Crystallization from petroleum ether gave white needles (70%); mp 98–99 °C (Found: C 48.21; H 4.37; N 5.70, $C_{10}H_{11}Cl_2NO_2$ requires: C 48.41; H 4.47; N 5.65); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.53 (s, 3H), 5.70 (dd, 1H, *J*=9.0, 2.2 Hz), 5.90 (d, 1H, *J*=2.2 Hz), 6.82 (d, 1H, *J*=9.0 Hz), 7.46–7.59 (m, 3H), 7.84 (d, 2H, *J*=7.3 Hz); ^{13}C NMR δ ($CDCl_3$, 100.4 MHz) 56.88, 72.26, 82.91, 127.16, 128.78, 132.42, 132.94, 167.69; MS *m*/*z* (%) 215 (3), 182 (12), 176 (23), 164 (52), 105 (100), 77 (82); IR (Nujol) 3222, 1646, 1526, 1460, 1343, 1276, 1191, 1117, 1074, 1026, 784, 694 cm^{-1}.

3.2.2. *N*-(2,2-Dichloro-1-ethoxyethyl)benzamide (5b). Crystallization from petroleum ether gave white needles (80%); mp 98–99 °C (Found: C 50.47; H 4.95; N 5.37, $C_{11}H_{13}Cl_2NO_2$ requires: C 50.40; H 5.00; N 5.34); ^{1}H NMR δ ($CDCl_3$, 200 MHz) 1.26 (t, 3H, *J*=7.0 Hz), 3.71–3.82 (m, 2H), 5.78 (dd, 1H, *J*=9.5, 2.4 Hz), 5.89 (d, 1H, *J*=2.4 Hz), 6.85 (d, 1H, *J*=9.5 Hz), 7.44–7.57 (m, 3H), 7.84 (d, 2H, *J*=6.8 Hz); ^{13}C NMR δ ($CDCl_3$, 50.4 MHz) 14.95, 65.23, 72.67, 81.54, 127.24, 128.83, 132.42, 133.16, 167.59; MS *m*/*z* (%) 224 (4), 218 (14), 216 (22), 178 (11), 105 (100), 77 (58), 51 (18); IR (Nujol) 3211, 1635, 1524, 1466, 1379, 1085, 791, 696 cm^{-1}.

3.2.3. *N*-[2,2-Dichloro-1-(2-phenylethoxy)ethyl]benzamide (5c). Crystallization from petroleum ether gave white needles (75%); mp 88 °C (Found: C 60.45; H 4.99; N 4.16, $C_{17}H_{17}Cl_2NO_2$ requires: C 60.37; H 5.07; N 4.14); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 2.93 (t, 2H, *J*=6.8 Hz), 3.89–3.94 (m, 2H), 5.76 (dd, 1H, *J*=9.5, 2.3 Hz), 5.84 (d, 1H, *J*=2.3 Hz), 6.59 (d, 1H, *J*=9.5 Hz), 7.20–7.26 (m, 5H), 7.45 (t, 2H, *J*=7.7 Hz), 7.58 (t, 1H, *J*=7.7 Hz), 7.71 (d, 2H, *J*=7.2 Hz); ^{13}C NMR δ ($CDCl_3$, 100.4 MHz) 36.00, 70.17, 72.49, 81.59, 126.41, 127.17, 128.39, 128.75, 129.08, 132.39, 132.97, 138.29, 167.53; MS *m*/*z* (%) 216 (3), 182 (4), 105 (77), 104 (100), 91 (22), 77 (68); IR (Nujol) 3250, 1638, 1525, 1467, 1347, 1278, 1122, 1081, 1027 cm^{-1}.

3.2.4. *N*-[2,2-Dichloro-1-(2-phenylethoxy)ethyl]-4-chlorobenzamide (5d). Crystallization from petroleum ether gave white needles (78%); mp 91–93 °C (Found: C 54.77; H 4.28; N 3.80, $C_{17}H_{16}Cl_3NO_2$ requires: C 54.79; H 4.33; N 3.76); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 2.91 (t, 2H, *J*=6.7 Hz), 3.86–3.96 (m, 2H), 5.72 (dd, 1H, *J*=9.4, 2.3 Hz), 5.82 (d, 1H, *J*=2.3 Hz), 6.50 (d, 1H, *J*=9.4 Hz), 7.19–7.26 (m, 5H), 7.41 (d, 2H, *J*=8.5 Hz), 7.62 (d, 2H, *J*=8.5 Hz); ^{13}C NMR δ ($CDCl_3$, 100.4 MHz) 36.03, 70.29, 72.40, 81.73, 126. 44, 128.40, 128.61, 129.01, 129.09, 131.35, 138.33, 138.74, 166.48; MS *m*/*z* (%) 250 (2), 216 (3), 141 (44), 139 (85), 111 (49), 104 (100), 91 (37), 7 (19); IR (Nujol) 3287, 1653, 1526, 1464, 1379, 1344, 1102, 1018, 850, 793, 702 cm^{-1}.

3.2.5. *N*-(2,2-Dichloro-1-benzyloxyethyl)-4-methylbenzamide (5e). Crystallization from petroleum ether gave white needles (98%); mp 120–121 °C (Found: C 60.33; H 5.10; N 4.11, $C_{17}H_{17}Cl_2NO_2$ requires: C 60.37; H 5.07; N 4.14); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 2.42 (s, 3H), 4.71 (d, 1H, *J*=11.9 Hz), 4.77 (d, 1H, *J*=11.9 Hz), 5.86–5.88 (m, 2H), 6.77 (d, 1H, *J*=9.7 Hz), 7.26–7.42 (m, 7H), 7.69 (d, 2H, *J*=8.1 Hz); ^{13}C NMR δ ($CDCl_3$, 100.4 MHz) 21.52, 71.07, 72.62, 80.96, 127.19, 128.01, 128.11, 128.51, 129.43, 130.13, 136.80, 143.08, 167.48; MS *m*/*z* (%) 230 (11), 196 (75), 160 (16), 119 (94), 91 (100), 77 (23), 65 (41); IR (Nujol) 3275, 1645, 1522, 1505, 1462, 1344, 1098, 794, 738, 695 cm^{-1}.

3.2.6. *N*-[2,2-Dichloro-1-(4-methoxybenzyloxy)ethyl)]-4-methylbenzamide (5f). Crystallization from a mixture of petroleum ether and chloroform gave white needles (72%); mp 97–99 °C (Found: C 58.69; H 5.18; N 3.83, $C_{18}H_{19}Cl_2NO_3$ requires: C 58.71; H 5.20; N 3.80); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 2.42 (s, 3H), 3.79 (s, 3H), 4.63 (d, 1H, *J*=11.7 Hz), 4.72 (d, 1H, *J*=11.7 Hz), 5.82–5.85

(m, 2H), 6.77 (d, 1H, J=9.6 Hz), 6.87 (d, 2H, J=8.6 Hz), 7.28 (d, 2H, J=8.1 Hz), 7.32 (d, 2H, J=8.6 Hz), 7.70 (d, 2H, J=8.1 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 21.51, 55.22, 70.76, 72.70, 80.57, 113.90, 127.19, 128.73, 129.41, 129.87, 130.16, 143.04, 159.56, 167.43; FAB$^+$ 368 (M^++1, 30); IR (Nujol) 3289, 1639, 1614, 1535, 1504, 1342, 1299, 1249, 1176, 1089, 1033, 788, 764 cm^{-1}.

3.2.7. *N*-[2,2-Dichloro-1-(3,4,5-trimethoxybenzyloxy)-ethyl]-2-chlorobenzamide (5g). Crystallization from a mixture of petroleum ether and chloroform gave white needles (80%); mp 93–96 °C (Found: C 50.91; H 4.54; N 3.08, $C_{19}H_{20}Cl_3NO_5$ requires: C 50.86; H 4.49; N 3.12); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.83 (s, 3H), 3.86 (s, 6H), 4.67 (d, 1H, J=11.9 Hz), 4.78 (d, 1H, J=11.9 Hz), 5.84–5.87 (m, 2H), 6.66 (s, 2H), 6.97 (d, 1H, J=9.9 Hz), 7.35–7.47 (m, 3H), 7.68 (dd, 1H, J=7.5 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 56.17, 60.87, 71.23, 72.33, 80.63, 105.46, 127.35, 130.33, 130.57, 130.79, 132.06, 132.18, 133.75, 137.90, 153.34, 166.90; MS *m*/*z* (%) 449 (M^++2, 1), 447 (M^++1, 1), 216 (21), 196 (47), 181 (37), 169 (18), 139 (100), 111 (30), 75 (22); IR (Nujol) 3219, 3181, 1659, 1591, 1525, 1506, 1328, 1231, 1128, 1078, 822, 760 cm^{-1}.

3.2.8. *N*-[2,2-Dichloro-1-(3,4,5-trimethoxybenzyloxy-ethyl)]-2-methylbenzamide (5h). Crystallization from a mixture of petroleum ether and chloroform gave white needles (81%); mp 107–109 °C (Found: C 55.92; H 5.46; N 3.30, $C_{20}H_{23}Cl_2NO_5$ requires: C 56.08; H 5.41; N 3.27); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 2.51 (s, 3H), 3.85 (s, 3H), 3.87 (s, 6H), 4.67 (d, 1H, J=12.0 Hz), 4.76 (d, 1H, J=12 Hz), 5.83–5.87 (m, 2H), 6.49 (d, 1H, J=9.5 Hz), 6.66 (s, 2H), 7.23–7.39 (m, 4H); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 20.02, 56.11, 60.81, 71.17, 72.51, 80.42, 105.28, 125.97, 126.66, 130.75, 131.36, 132.18, 134.85, 136.46, 137.86, 153.33, 170.16; MS *m*/*z* (%) 429 (M^++2, 1), 427 (M^+, 1), 198 (41), 196 (72), 181 (36), 169 (16), 160 (8), 148 (8), 138 (7), 119 (100), 91 (48), 65 (16); IR (Nujol) 3292, 3243, 1679, 1592, 1511, 1332, 1236, 1130, 1091, 993, 784, 732 cm^{-1}.

3.3. Preparation of *N*-(1-alkoxy-2,2-dichloroethyl)thiobenzamides (6)

A toluene solution (50 mL) of **5** (3 mmol) and LR (3 mmol) was refluxed for 1 h. After cooling, the suspended solid was filtered off and the solvent was evaporated under reduced pressure. The products were isolated by silica gel column chromatography. Products **6a–e** (ethyl acetate–hexane 1:6); product **6f** (ethyl acetate–hexane 1:3); product **6g** (diethyl ether–hexane 1:1), and product **6h** (dichloromethane–hexane 2:3). Afterward the yellow solids were crystallized from the appropriated solvents. All compounds gave satisfactory IR, ^{1}H NMR, ^{13}C NMR, mass spectra, and elemental analyses.

3.3.1. *N*-(2,2-Dichloro-1-methoxyethyl)thiobenzamide (6a). Crystallization from hexane gave yellow prisms (79%); mp 100–101 °C (Found: C 45.62; H 4.13; N 5.22; S 12.08, $C_{10}H_{11}Cl_2NOS$ requires: C 45.47; H 4.20; N 5.30; S 12.14); ^{1}H NMR δ ($CDCl_3$, 300 MHz) 3.66 (s, 3H), 6.06 (d, 1H, J=2.1 Hz), 6.29 (dd, 1H, J=8.7, 2.1 Hz), 7.43–7.53 (m, 3H), 7.79–7.82 (m, 2H), 7.90 (br s, 1H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz) 58.25, 71.19, 87.45, 126.72, 128.73, 132.01, 140.97, 201.84; MS *m*/*z* (%) 263 (M^+, 2), 227 (8), 192 (33), 164 (13), 121 (100), 104 (26), 77 (34); IR (Nujol) 3273, 1510, 1459, 1365, 1235, 1098, 1011, 959, 794, 697 cm^{-1}.

3.3.2. *N*-(2,2-Dichloro-1-ethoxyethyl)thiobenzamide (6b). Crystallization from hexane gave yellow needles (70%); mp 90–91 °C (Found: C 47.55; H 4.66; N 5.01; S 11.70, $C_{11}H_{13}Cl_2NOS$ requires: C 47.49; H 4.71; N 5.03; S 11.53); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 1.31 (t, 3H, J=7.0 Hz), 3.84–3.96 (m, 2H), 6.06 (d, 1H, J=2.2 Hz), 6.34 (dd, 1H, J=8.4, 2.2 Hz), 7.41–7.45 (m, 2H), 7.52 (tt, 1H, J=7.4, 1.2 Hz), 7.78–7.81 (m, 2H), 7.89 (d, 1H, J=8.4 Hz); ^{13}C NMR δ ($CDCl_3$, 100.4 MHz) 14.99, 66.49, 71.39, 86.01, 126.70, 128.69, 131.96, 140.92, 201.26; FAB$^+$ 278 (M^++1); IR (Nujol) 3287, 1500, 1464, 1378, 1333, 1231, 1087, 947, 798, 694 cm^{-1}.

3.3.3. *N*-[2,2-Dichloro-1-(2-phenylethoxy)ethyl]thiobenzamide (6c). Crystallization from petroleum ether gave yellow needles (76%); mp 86–87 °C (Found: C 57.58; H 4.83; N 4.02; S 9.00, $C_{17}H_{17}Cl_2NOS$ requires: C 57.63; H 4.84; N 3.95; S 9.05); ^{1}H NMR δ ($CDCl_3$, 200 MHz) 2.97 (t, 2H, J=6.2 Hz), 3.94–4.12 (m, 2H), 6.01 (d, 1H, J=2.2 Hz), 6.32 (dd, 1H, J=8.40, 2.2 Hz), 7.22–7.63 (m, 11H); ^{13}C NMR δ ($CDCl_3$, 50.4 MHz): 36.06, 71.28, 71.35, 86.11, 126.53, 126.71, 128.46, 128.61, 129.12, 131.94, 138.18, 140.68, 201.27; FAB$^+$ 354 (M^++1); IR (Nujol) 3288, 1499, 1459, 1367, 1226, 1144, 1088, 1011, 945, 794, 751, 695, 672 cm^{-1}.

3.3.4. *N*-[2,2-Dichloro-1-(2-phenylethoxy)ethyl]-4-chlorothiobenzamide (6d). Crystallization from hexane gave yellow needles (62%); mp 62–65 °C (Found: C 52.62; H 4.22; N 3.55; S 8.23, $C_{17}H_{16}Cl_3NOS$ requires: C 52.52; H 4.15; N 3.60; S 8.25); ^{1}H NMR δ ($CDCl_3$, 200 MHz) 2.92–2.99 (m, 2H), 3.87–3.99 (m, 1H), 4.05–4.16 (m, 1H), 5.98 (d, 1H, J=2.2 Hz), 6.25 (dd, 1H, J=8.2, 2.2 Hz), 7.20–7.27 (m, 5H), 7.32 (d, 2H, J=8.4 Hz), 7.50 (d, 2H, J=8.4 Hz), 7.54 (d, 1H, J=8.2 Hz); ^{13}C NMR δ ($CDCl_3$, 50.4 MHz) 36.04, 71.20, 71.38, 86.17, 126.54, 128.01, 128.46, 128.73, 129.13, 138.27, 138.82, 199.57; MS *m*/*z* (%) 352 (1), 316 (6), 232 (6), 212 (7), 157 (15), 155 (36), 138 (26), 105 (100), 77 (30); IR (Nujol) 3297, 1594, 1507, 1468, 1406, 1371, 1239, 1094, 1013, 948, 841, 793, 762, 701 cm^{-1}.

3.3.5. *N*-(2,2-Dichloro-1-benzyloxyethyl)-4-methylthiobenzamide (6e). Crystallization from petroleum ether gave yellow needles (64%); mp 88 °C (Found: C 57.72; H 4.78; N 3.99; S 9.00, $C_{17}H_{17}Cl_2NOS$ requires: C 57.63; H 4.84; N 3.95; S 9.05); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 2.38 (s, 3H), 4.87 (s, 2H), 6.02 (d, 1H, J=2.2 Hz), 6.43 (dd, 1H, J=8.0, 2.2 Hz), 7.19 (d, 2H, J=7.9 Hz), 7.30–7.43 (m, 5H), 7.58 (d, 2H, J=8.2 Hz), 7.83 (d, 1H, J=8.0 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 21.40, 71.45, 72.50, 85.77, 126.75, 128.10, 128.35, 128.63, 129.26, 136.60, 137.98, 142.81, 200.89; MS *m*/*z* (%) 318 (1), 262 (6), 247 (9), 212 (51), 176 (29), 135 (97), 118 (49), 91 (100), 65 (33); IR (Nujol) 3297, 1492, 1458, 1366, 1325, 1230, 1181, 1139, 1076, 1035, 925, 786, 756, 706, 662 cm^{-1}.

3.3.6. *N*-[2,2-Dichloro-1-(4-methoxybenzyloxy)ethyl]-4-methylthiobenzamide (6f). Crystallization from a mixture

of hexane and dichloromethane gave yellow prisms (95%); mp 92–94 °C (Found: C 56.38; H 5.07; N 3.55; S 8.31, $C_{18}H_{19}Cl_2NO_2S$ requires: C 56.25; H 4.98; N 3.64; S 8.34); ^{1}H NMR. δ ($CDCl_3$, 400 MHz) 2.39 (s, 3H), 3.79 (s, 3H), 4.80 (s, 2H), 6.00 (d, 1H, J=2.2 Hz), 6.38 (dd, 1H, J=8.3, 2.2 Hz), 6.88 (d, 2H, J=8.7 Hz), 7.20 (d, 2H, J=8.1 Hz), 7.35 (d, 2H, J=8.7 Hz), 7.61 (d, 2H, J=8.3 Hz), 7.81 (d, 1H, J=8.1 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 21.42, 55.25, 71.50, 72.25, 85.50, 114.01, 126.76, 128.53, 129.25, 129.97, 137.98, 142.80, 159.76, 200.70; FAB$^+$ 384 (M^++1, 13); IR (Nujol) 3379, 3277, 1610, 1513, 1489, 1342, 1248, 1176, 1076, 935, 821, 789 cm^{-1}.

3.3.7. *N*-[2,2-Dichloro-1-(3,4,5-trimethoxybenzyloxy)ethyl]-2-chlorothiobenzamide (6g). Crystallization from hexane gave pale yellow needles (94%); mp 146–147 °C (Found: C 48.89; H 4.34; N 3.10; S 7.01, $C_{19}H_{20}Cl_3NO_4S$ requires: C 49.10; H 4.34; N 3.01; S 6.90); ^{1}H NMR. δ ($CDCl_3$, 400 MHz) 3.85 (s, 3H), 3.87 (s, 6H), 4.77 (d, 1H, J=11.9 Hz), 4.88 (d, 1H, J=11.9 Hz), 5.99 (d, 1H, J=2.3 Hz), 6.38 (dd, 1H, J=8.4, 2.3 Hz), 6.67 (s, 2H), 7.30–7.42 (m, 3H), 7.51 (dd, 1H, J=7.1, 2.1 Hz), 7.84 (d, 1H, J=8.4 Hz); ^{13}C NMR δ ($CDCl_3$, 100.4 MHz) 56.12, 60.82, 71.08, 72.29, 84.49, 105.64, 127.18, 128.12, 130.09, 130.97, 131.48, 137.99, 141.21, 153.25, 200.05; FAB$^+$ 464 (M^++1, 2); IR (Nujol) 3180, 1597, 1542, 1508, 1332, 1235, 1153, 1128, 1099, 974, 943 cm^{-1}.

3.3.8. *N*-[2,2-Dichloro-1-(3,4,5-trimethoxybenzyloxy)ethyl]-2-methylthiobenzamide (6h). Crystallization from a mixture of petroleum ether and chloroform gave pale yellow prisms (68%); mp 128–130 °C (Found: C 54.14; H 5.28; N 3.20; S 7.20, $C_{20}H_{23}Cl_2NO_4S$ requires: C 54.06; H 5.22; N 3.15; S 7.22); ^{1}H NMR. δ ($CDCl_3$, 400 MHz) 2.43 (s, 3H), 3.86 (s, 3H), 3.87 (s, 6H), 4.77 (d, 1H, J=11.9 Hz), 4.84 (d, 1H, J=11.9 Hz), 5.99 (d, 1H, J=2.2 Hz), 6.44 (dd, 1H, J=8.5 Hz, J=2.2 Hz), 6.67 (s, 2H), 7.21–7.32 (m, 4H), 7.67 (d, 1H, J=8.5 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 19.68, 56.14, 60.84, 71.38, 72.52, 84.34, 105.45, 126.11, 126.38, 129.58, 131.01, 131.69, 132.90, 137.99, 143.21, 153.31, 204.61; FAB$^+$ 444 (M^++1, 5); IR (Nujol) 3189, 1598, 1508, 1332, 1236, 1151, 1130, 1091, 939, 786, 761 cm^{-1}.

3.4. Preparation of (*E*)-4-alkoxy-2-aryl-5-chloro-2-thiazolines (7)

Sodium hydroxide (10 mmol) was added to acetonitrile solutions of compounds **6** (1 mmol), and the reaction mixture was stirred at room temperature for 6 h. After filtration and evaporation of the solvent under reduced pressure, compounds **7** were collected as yellow oils, and were purified by column chromatography. All novel compounds gave satisfactory elemental analyses and IR, ^{1}H NMR, ^{13}C NMR, and mass spectra (FAB$^+$).

3.4.1. 5-Chloro-2-phenyl-4-methoxy-2-thiazoline (7a). Chromatography (silica gel, hexane–ethyl acetate 6:1) gave yellow oil (74%); (Found: C 52.83; H 4.49; N 6.07; S 14.14, $C_{10}H_{10}ClNOS$ requires: C 52.75; H 4.43; N 6.15; S 14.08); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.61 (s, 3H), 5.71 (d, 1H, J=1.2 Hz), 6.00 (d, 1H, J=1.2 Hz), 7.40–7.47 (m, 2H), 7.51–7.60 (m, 1H), 7.87–7.91 (m, 2H); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 56.98, 69.79, 115.33, 128.71, 128.94, 132.10, 132.49, 170.08; FAB$^+$ 228 (M^++1); IR 2931, 2834, 1606, 1527, 1448, 1335, 1308, 1229, 1092, 1035, 944, 909, 814, 767, 733, 690 cm^{-1}.

3.4.2. 5-Chloro-4-ethoxy-2-phenyl-2-thiazoline (7b). Chromatography (silica gel, hexane–ethyl acetate 6:1) gave yellow oil (79%); (Found: C 54.73; H 4.89; N 5.86; S 13.32, $C_{11}H_{12}ClNOS$ requires: C 54.65; H 5.00; N 5.79; S 13.26); ^{1}H NMR δ (CD_3COCD_3, 300 MHz) 1.20 (t, 3H, J=6.0 Hz), 3.79–3.91 (m, 2H), 6.00 (d, 1H, J=0.9 Hz) 6.08 (d, 1H, J=0.9 Hz), 7.53–7.61 (m, 3H), 7.89–7.92 (m, 2H); ^{13}C NMR δ (CD_3COCD_3, 75.4 MHz) 15.59, 65.54, 71.58, 115.04, 129.53, 129.78, 130.81, 133.39, 169.33; MS m/z (%) 241 (M^+, 7), 206 (14), 196 (8), 161 (15), 138 (20), 104 (100), 93 (12), 77 (21), 58 (15); IR 2979, 2900, 1611, 1452, 1326, 1231, 1176, 1090, 1037, 942, 813, 769, 691 cm^{-1}.

3.4.3. 5-Chloro-2-phenyl-4-(2-phenylethoxy)-2-thiazoline (7c). Chromatography (silica gel, hexane–ethyl acetate 6:1) gave yellow oil (80%); (Found: C 64.40; H 5.11; N 4.43; S 10.17, $C_{17}H_{16}ClNOS$ requires: C 64.24; H 5.07; N 4.41; S 10.09); ^{1}H NMR δ ($CDCl_3$, 200 MHz) 2.94 (t, 2H, J=7.2 Hz), 3.87–4.15 (m, 2H), 5.59 (d, 1H, J=1.2 Hz), 6.08 (d, 1H, J=1.2 Hz), 7.23–7.30 (m, 5H), 7.39–7.48 (m, 3H), 7.86 (dd, 2H, J=8.0, 1.4 Hz); ^{13}C NMR δ ($CDCl_3$, 50.4 MHz) 36.28, 70.14, 70.34, 114.31, 126.33, 128.37, 128.67, 128.88, 128.92, 132.11, 132.42, 138.25, 169.80; FAB$^+$ 318 (M^++1); IR 3063, 3023, 2928, 1607, 1525, 1497, 1451, 1327, 1234, 1173, 1090, 908, 816, 733, 695 cm^{-1}.

3.4.4. 5-Chloro-2-(4-chlorophenyl)-4-(2-phenylethoxy)-2-thiazoline (7d). Chromatography (silica gel, hexane–ethyl acetate 6:1) gave yellow oil (94%); (Found: C 58.10; H 4.30; N 4.00; S 9.03, $C_{17}H_{15}Cl_2NOS$ requires: C 57.96; H 4.29; N 3.98; S 9.10); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 2.95 (t, 2H, J=7.2 Hz), 3.94 (dt, 1H, J=9.5, 7.2 Hz), 4.09 (dt, 1H, J=9.5, 7.2 Hz), 5.63 (d, 1H, J=1.2 Hz), 6.05 (d, 1H, J=1.2 Hz), 7.20–7.28 (m, 5H), 7.41 (dd, 2H, J=6.7, 2.0 Hz), 7.80 (dd, 2H, J=6.7, 2.0 Hz); ^{13}C NMR δ ($CDCl_3$, 100.4 MHz) 36.33, 70.28, 70.54, 114.35, 126.41, 128.44, 128.91, 129.02, 130.19, 130.66, 138.27, 138.75, 168.62; FAB$^+$ 352 (M^++1); IR 2919, 1603, 1491, 1401, 1311, 1242, 1176, 1092, 944, 837, 739, 703 cm^{-1}.

3.4.5. 4-Benzyloxy-5-chloro-2-(4-methylphenyl)-2-thiazoline (7e). Chromatography (silica gel, hexane–ethyl acetate 6:1) gave yellow oil (96%); (Found: C 64.12; H 5.11; N 4.31; S 10.16, $C_{17}H_{16}ClNOS$ requires: C 64.24; H 5.07; N 4.41; S 10.09); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 2.41 (s, 3H), 4.80 (d, 1H, J=11.7 Hz), 4.91 (d, 1H, J=11.7 Hz), 5.73 (d, 1H, J=1.2 Hz), 6.15 (d, 1H, J=1.2 Hz), 7.24–7.38 (m, 7H), 7.77 (d, 2H, J=8.2 Hz); ^{13}C NMR δ ($CDCl_3$, 100.4 MHz) 21.62, 70.28, 71.23, 113.47, 128.00, 128.02, 128.50, 128.97, 129.40, 129.52, 137.24, 143.19, 170.07; FAB$^+$ 318 (M^++1); IR 3031, 2925, 1605, 1507, 1455, 1311, 1178, 1073, 940, 818, 734, 699 cm^{-1}.

3.4.6. 5-Chloro-4-(4-methoxybenzyloxy)-2-(4-methylphenyl)-2-thiazoline (7f). Chromatography (silica gel, hexane–ethyl acetate 4:1) gave yellow oil (95%); (Found: C 62.27; H 5.17; N 4.10; S 9.31, $C_{18}H_{18}ClNO_2S$ requires: C 62.15; H 5.22; N 4.03; S 9.22); ^{1}H NMR δ ($CDCl_3$,

400 MHz) 2.41 (s, 3H), 3.81 (s, 3H), 4.74 (d, 1H, J=11.3 Hz), 4.84 (d, 1H, J=11.3 Hz), 5.70 (d, 1H, J= 1.1 Hz), 6.13 (d, 1H, J=1.1 Hz), 6.90 (d, 2H, J=8.4 Hz), 7.25 (d, 2H, J=8.3 Hz), 7.33 (d, 2H, J=8.3 Hz), 7.78 (d, 2H, J=8.4 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 21.62, 55.27, 70.34, 70.98, 113.17, 113.91, 128.97, 129.24, 129.40, 129.53, 129.83, 143.17, 159.49, 169.94; MS m/z (%) 348 (M^++1, 1), 350 (M^++3, 1), 311 (1), 176 (33), 121 (100), 118 (14), 91 (10), 77 (12), 58 (7); IR 2999, 2954, 2931, 2834, 1608, 1514, 1465, 1303, 1248, 1178, 1038 cm^{-1}.

3.4.7. 5-Chloro-2-(2-chlorophenyl)-4-(3,4,5-trimethoxybenzyloxy)-2-thiazoline (7g). Chromatography (silica gel, hexane–ethyl acetate 3:1) gave yellow oil (93%); (Found: C 53.39; H 4.52; N 3.23; S 7.58, $C_{19}H_{19}Cl_2NO_4S$ requires: C 53.28; H 4.47; N 3.27; S 7.49); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.84 (s, 3H), 3.87 (s, 6H), 4.76 (d, 1H, J=11.5 Hz), 4.88 (d, 1H, J=11.5 Hz), 5.75 (d, 1H, J=1.3 Hz), 6.15 (d, 1H, J=1.3 Hz), 6.63 (s 2H), 7.33–7.50 (m, 3H), 7.76 (dd, 1H, J=1.8, 7.6 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 56.12, 60.83, 70.60, 71.61, 105.20, 112.51, 126.92, 130.82, 131.28, 131.43, 132.14, 132.61, 132.86, 137.81, 153.35, 168.07; FAB$^+$ 428 (M^++1, 12); IR 3293, 3056, 2996, 2935, 2838, 1668, 1592, 1506, 1461, 1126, 833, 755 cm^{-1}.

3.4.8. 5-Chloro-2-(2-methylphenyl)-4-(3,4,5-trimethoxybenzyloxy)-2-thiazoline (7h). Chromatography (silica gel, hexane–ethyl acetate 3:1) gave yellow oil (95%); (Found: C 58.94; H 5.33; N 3.38; S 7.82, $C_{20}H_{22}ClNO_4S$ requires: C 58.89, H 5.44; N 3.43; S 7.86); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 2.61 (s, 3H), 3.83 (s, 3H), 3.87 (s, 6H), 4.76 (d, 1H, J=12.0 Hz), 4.87 (d, 1H, J=12.0 Hz), 5.72 (d, 1H, J=1.2 Hz), 6.19 (d, 1H, J=1.2 Hz), 6.63 (s, 2H), 7.24–7.41 (m, 3H), 7.59 (dd, 1H, J=1.3, 7.6 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 21.29, 56.06, 60.82, 70.19, 71.59, 105.01, 113.88, 125.95, 130.23, 131.06, 131.47, 131.52, 132.64, 137.66, 137.82, 153.31, 170.42; MS m/z (%) 407 (M^+, 1), 225 (2), 196 (4), 182 (12), 181 (100), 176 (53), 151 (3), 148 (10), 117 (8), 90 (6), 77 (4); IR 3063, 2997, 2961, 2935, 2876, 1731, 1593, 1507, 1461, 1339, 1235, 1127 cm^{-1}.

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32. Caution must be exercised when handling perchlorates in order to exclude explosion risk. Evaporation of organic solutions containing perchlorates requires to be carried out in vacuo and at moderate temperature. Contact with strong acids must be avoided.