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Efficient synthetic procedure to new 2-imino-1,3-thiazolines and thiazolidin-4-ones promoted by acetonitrile electrogenerated base†‡

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A novel and convenient strategy is described for the regioselective conversion of *N,N′*-disubstituted thioureas and 1,2-dielectrophiles into the highly biologically valuable 2-imino-thiazoline and 2-imino thiazolidine-4-one derivatives. The synthesis proceeds through a process with good yield promoted by an electrogenerated base (EGB) obtained with high current efficiency.

1. Introduction

Despite the broad synthetic organic procedures already described, there is still a need to develop new organic reactions, to allow better connection of reactive functions and reagents. Electrochemistry is probably the key to introduce new reaction discoveries, based on uncommon but promising organic intermediates to evolve such unexplored chemical transformations.

Electrogenerated radical anions and anions are basic reagents, called EGBs, which can be used to deprotonate and to initiate many base catalyzed reactions.[1] The use of EGBs in organic synthesis is well documented.[2] Radical anions as EGBs have great potential in synthesis, as demonstrated in the stereoselective cyclopropanation to homoquinones from phenacyl carbenes, that we have recently highlighted.[3] Moreover carbanions, that can be easily obtained at the cathode, are typical strong bases that can provide useful nucleophiles from acidic components of the reaction mixture. The preparative scaled reaction to 3,4-disubstituted quinazoline-2-ones has been successfully promoted by cyanomethyl anions as the EGB, starting from anilines.[4]

This electrochemical strategy relies on the choice of the particular type of designed acidic substrates, difficult to be deprotonated, which may leave many unexplored chemical reactivities. However our approach is mainly focused on yielding and developing new electrosynthetic routes to highly demanded compounds.

4-Thiazolidinones and related heterocycles are intensively explored for the design of new drug-like molecules.[5,6] Despite the variety of 4-thiazolidinone bearing compounds, the search for new antibacterial, antiviral, anti-inflammatory,[7] and antidiabetic agents[8] is the main direction associated with the thiazolidinone framework. Nowadays this research area is mainly focused on the design of new anticancer agents.[9] A positive perspective of 4-thiazolidinones is linked to a polypharmacological approach where the affinity towards various targets is regarded as an advantage in the treatment of inflammation and cancer.[10] Apoptosis induced by 4-thiazolidinones has been demonstrated in various cancer cells.[11,12] The 2-amino(imino)-4-thiazolidinones are effective growth inhibitors of HT29 adenocarcinoma cells,[13] and human lung cancer cell lines H460,[14] or fused as imidazo-[2,1-*b*]thiazole S100-inhibitors for cancer and autoimmune disease treatment.[15]

Currently, the search for compounds possessing combined types of activities is of special interest, especially with simultaneous antiproliferative or cytostatic effects, such as the combination of anticancer, antioxidant and anti-inflammatory activities. In this field, the search for new 4-thiazolidinone compounds, and fused 2-imino-1,3-thiazolidine frameworks, with DNA binding activity[16] or demonstrated Alzheimer's disease neurodegenerative inhibition activity,[17] is a promising direction to design, develop and scale alternative electrochemical synthetic methodologies.

The first reports on the synthesis of 2-imino-1,3-thiazolines were published more than a century ago and comprise condensation reactions of unsubstituted thioureas and α-haloketones that, under acidic conditions and due to emerged isomerism problems, gave rise to variable amounts of side-products.[18] A general approach toward 2-imino-1,3-thiazolidines involves the intramolecular cyclization of *N*-(2-hydroxyethyl)thiourea derivatives in an acetic

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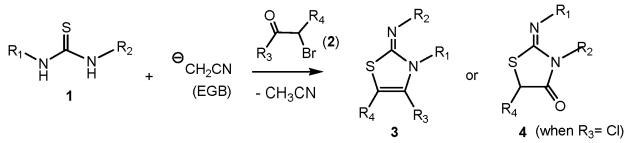
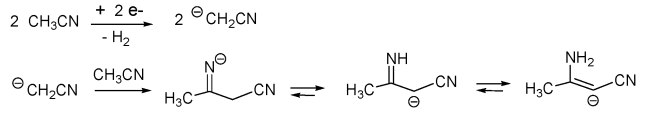
† Dedicated to Professor Fructuoso Barba on the occasion of his 75th birthday.

‡ Electronic supplementary information (ESI) available: Copies of the ^{1}H and ^{13}C NMR spectra, IR and MS of the new compounds **3** and **4** are provided. See DOI: 10.1039/c8nj01992d



Scheme 1 Outline of the synthetic procedure described in this paper.



Scheme 2 Cathodic formation of 3-amino-crotonitrile anion.

medium or, alternatively, in the presence of triphenylphosphine and diethyl azodicarboxylate.[19] Recent multicomponent reactions of aromatic α-haloketones, primary amines and phenyl isothiocyanate afforded 4-aryl-2-(*N*-phenylimine)thiazoles in a moderate yield,[20] which is only increased when the porcine trypsin enzyme is used as a catalyst,[21] or when 1,3-disubstituted thioureas are exposed to 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT).[22]

However, these moieties have also been prepared in a less general approach starting from aziridines upon treatment with thiocyanuric acid,[23] from 2-vinylaziridines in the reaction with phenyl-isothiocyanate,[24] or from 1-(phenylthiocarbamoyl) aziridines under acid catalysis.[25] One effective literature entry to 2-imino-1,3-thiazolines and thiazolidin-4-ones uses 1-arylmethyl-2-(bromomethyl)aziridines *via* ring transformation,[26] which proceeds in a straightforward manner giving a good yield.

At present, imino-thiazolidines have been regioselectively synthesized *via* the base promoted cyclization of epoxy-sulfonamides and heterocumulenes,[27] and at the same time imino-thiazolidin-4-ones have just been obtained through a three component tandem annulation promoted by visible light.[28]

One of the most striking advantages of the electrochemical processes to generate bases is the excellent control of the base strength, depending on the choice of the solvent. Furthermore, the amount of electrogenerated base (EGB) is a function of the imposed current density and the duration of the electrolysis, which can also be adjusted.[29]

With the aim of investigating the scope and limitations of acetonitrile anions, as a strong EGB, in the synthesis of new biologically active heterocyclic molecules, we focused now our attention on using electrochemistry as a tool to prepare 2-(*N*-substituted)imino-1,3-thiazoline moieties (**3**) and 2-(*N*-substituted)-imino-1,3-thiazolidine-4-ones (**4**), as outlined in Scheme 1. The result is herein reported as a novel and safe strategy for the conversion of readily available substrates into these highly valuable 2-imino-thiazolidine derivatives that proceeds through a process with good yield and is promoted by a high current efficiency EGB.

2. Results and discussion

It is well established that the electrochemical reduction of acetonitrile, in the presence of a quaternary ammonium salt as a supporting electrolyte, yields the corresponding cyanomethyl anion, a strong basic entity, with a pK_a value in DMSO of *ca.* 32,[30] capable of removing a weak acidic proton. When this reduction is performed at a platinum, graphite or stainless-steel cathode, under an argon atmosphere, the anion of 3-aminocrotonitrile[31] is also formed at room temperature, by the nucleophilic attack of the cyanomethyl anion to a new solvent molecule, as indicated in Scheme 2.

However, the use of low temperatures and sacrificial anodes, such as magnesium or aluminium, in an undivided cell, avoids to a large extent this undesired dimerization reaction. It occurs because the subsequently formed magnesium cations, present in solution, stabilize the cyanomethyl anions by ion-pair association.[32] This fact allows, under these experimental conditions, the cyanomethyl anion to act as an EGB, not as a nucleophile, and therefore to be used as a promoter in the abstraction of protons from substrates as amines, amides or similar weak acidic molecules.

The optimal quantity (equivalents) of EGB to get a complete consumption of the starting substrate will depend on the designed process, bearing in mind that, in the absence of a proton donor, one equivalent of the cyanomethyl carbanion is produced in a 1 F mol^{-1} process. Subsequently, the amount of EGB in the catholyte will be controlled by the total circulated charge through the electrochemical cell (solution).

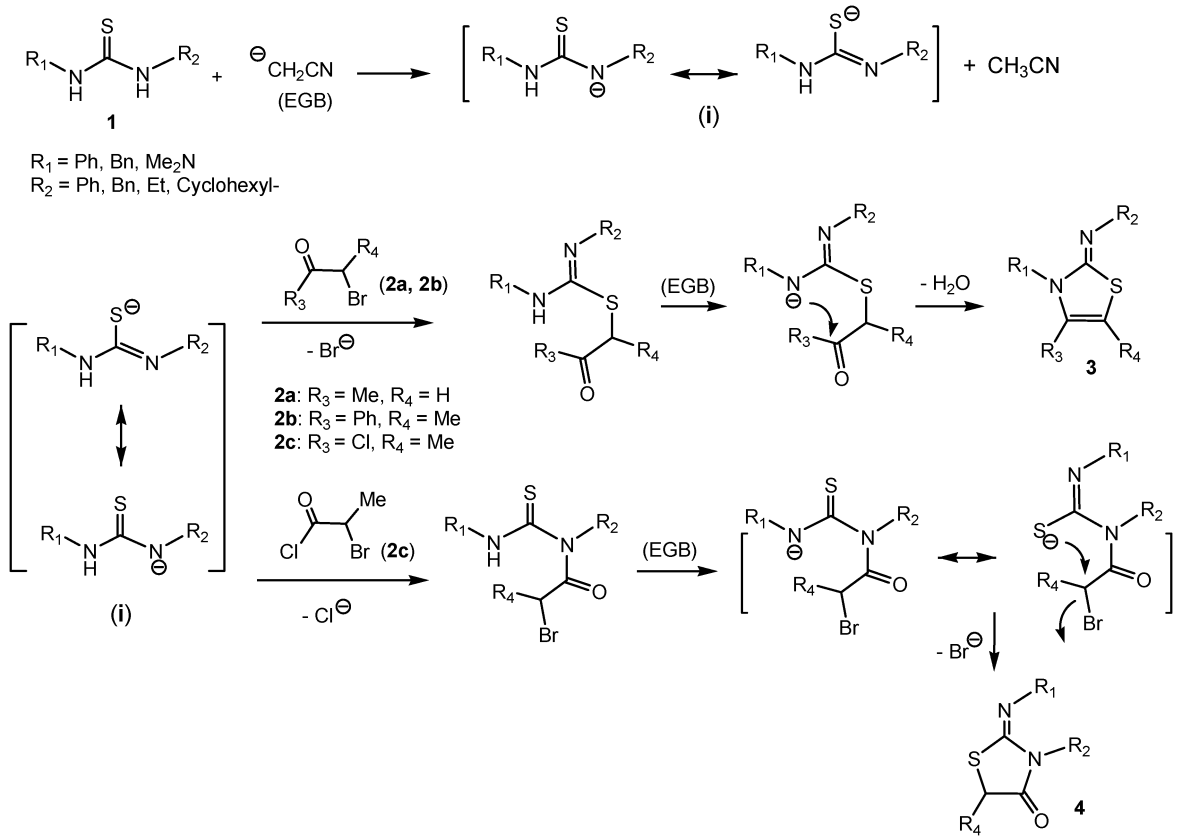
Thioureas are versatile reagents that can be deprotonated by cyanomethyl anions in a high extent, leading to a first stabilized nitride (thiolate) (**i**), as indicated in Scheme 3. The needed quantity of EGB to react with disubstituted thioureas (**1**) should be twice the amount of **1**, because both N–H bonds on **1** are desirable to be activated by deprotonation, although not at the same step. The experimental procedure involves, once the current supplier is switched off, the provision of the corresponding *N*,*N*′-disubstituted thiourea (**1**) to the reaction medium.

The freshly generated nitride (**i**), stabilized through an imino-thiolate resonance form, attacks further an organic 1,2-dielectrophile molecule (**2**), later introduced into the catholyte.

α-Halocarbonyl compounds are well known electro-reducible substrates, both under protic and aprotic solvents. For this reason, the presence of compounds **2** is avoided in the electrolytic solution under the applied galvanostatic conditions, needed to produce the EGB.

The formation of **3** starts with a nucleophilic thiolation reaction to the C–Br bond on **2**, followed by a new proton abstraction by EGB that leads to a new nitride intermediate. After ring closure, the latter provides the desired heterocycle. In the synthesis of compound **4**, the freshly prepared nitride (**i**) is acylated by the propionyl chloride (**2c**), to afford an amide that is further deprotonated by a new EGB molecule. Depending on the nature of **2**, the final cyclization evolves *via* an addition reaction to the ketone carbonyl group, or *via* a nucleophilic substitution to the C–Br bond, leading respectively to 2-(*N*-substituted)imino-1,3-thiazoline moieties (**3**) or 2-(*N*-substituted)imino-1,3-thiazolidine-4-ones (**4**).

An interesting feature of this procedure is its regioselectivity. In all cases only one regioisomer was formed during the reaction,



Scheme 3 Mechanism proposal to 2-(*N*-substituted)imino-1,3-thiazolines (**3**) and 2-(*N*-substituted)imino-1,3-thiazolidin-4-ones (**4**).

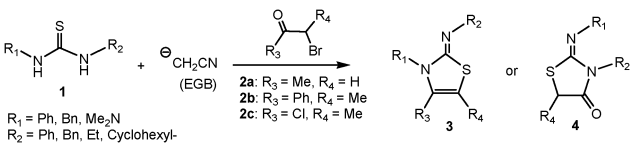
as the result of a first deprotonation of **1** (the more acidic NH group when unsymmetrical thiourea is used). The electronic effects of the substituents, that should stabilize (or not) the nitride, will determine the easier proton abstraction from **1**. Furthermore, depending on the nature of the 1,2-dielectrophile (**2**), the latter will be attacked by nitrogen or by a sulfur atom. No other heterocycles were isolated, such as the plausible 1,3-disubstituted imidazole-2-thione; the only by-product was 3-aminocrotonitrile.

Whereas a detailed mechanism proposal is above indicated, the reaction was successfully extended to a variety of symmetrical and unsymmetrical alkyl and aryl thioureas (**1a–g**).

The isolated yields on the 1,3-thiazoline products **3(a–h)** and **4(a, f, and g)**, formed from disubstituted thioureas **1(a–g)** (with alkyl: benzyl, ethyl and cyclohexyl, aryl: phenyl, and other groups such as dimethylamino) and the three different 1,2-dielectrophiles **2(a–c)**, are summarized in Table 1. The complete characterization of these new compounds was performed according to their spectroscopic and spectrometric properties.

The heterocyclization reaction that evolves to the thiazoline ring is supported by the heteronuclear multiple bond correlation (gradient HMBC), a two-dimensional spectrum (^{13}C and ^{1}H-NMR data) of **3g**, that is shown in Fig. 1. The two methylene hydrogen atoms of a benzyl group, directly joined to the nitrogen of the imino function at the 2-position of the ring (that appear at δ = 4.40 ppm) correlate, according to a two-bond distance, with quaternary sp^2 carbon (at the *ipso* position) of the benzene ring (δ = 147.1 ppm) rather than with the quaternary carbon at 141.7 ppm. Contrary to this correlation, the ethyl group at the 3-position of the ring (–CH_2– at 3.67 ppm) correlates properly, according to a three-bond distance, with the quaternary sp^2 carbon at 141.7 ppm, as well as the protons in the methyl group at the 5-position of the ring (δ = 1.94 ppm) which is also observed in the figure.

Table 1 Obtained yields on heterocycles **3** and **4**, in the reaction of disubstituted thioureas (**1**) (1.0 mmol) with EGB (2.2 eq.) and dielectrophiles **2** (1 mmol). Electrolytic conditions: stainless steel cathode, magnesium anode, (CH_3CN/0,1 M $TBABF_4$)



Entry	R_1	R_2	R_3	R_4	%Yield **3**	%Yield **4**
1a	Ph	Ph	Me	H	68 (**3a**)	—
1b	Et	Bn	Me	H	71 (**3b**)	—
1c	Cyclohexyl	Me_2N	Me	H	70 (**3c**)	—
1d	Ph	Me_2N	Me	H	67 (**3d**)	—
1e	Bn	Ph	Me	H	76 (**3e**)	—
1f	Et	Ph	Me	H	80 (**3f**)	—
1b	Et	Bn	Ph	Me	83 (**3g**)	—
1f	Et	Ph	Ph	Me	79 (**3h**)	—
1a	Ph	Ph	Cl	Me	—	67 (**4a**)
1f	Et	Ph	Cl	Me	—	74 (**4f**)
1g	Bn	Me_2N	Cl	Me	—	82 (**4g**)

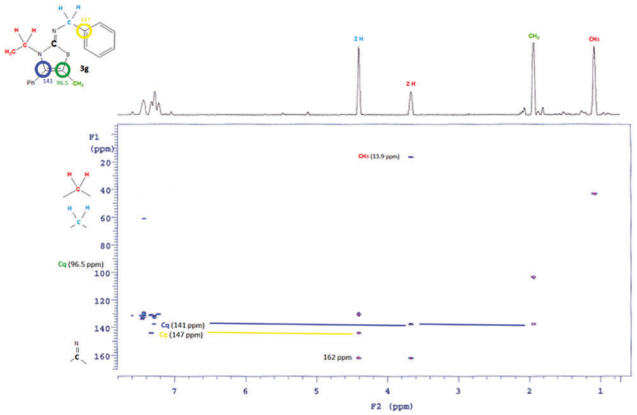


Fig. 1 Two-dimensional HMBC correlation spectrum of **3g** in $CDCl_3$.

This EGB promoted procedure has many advantages to be considered: (1) this is a regioselective synthesis whose steps occur all into the one-pot electrochemical cell: once the cyanomethyl anion is formed at the cathode surface, and the current supplier is switched off, the consecutive addition of the corresponding disubstituted thiourea and 1,2-dielectrophile proceeds in the same beaker. (2) The use of toxic or dangerous reactants, such as a transition-metal catalyst, needed in other 1,3-thiazoline conventional processes, is suppressed because now the base is electrogenerated "*in situ*". (3) The described procedure is quite versatile and can be generalized to alkyl and aryl thioureas. Depending on the starting 1,2-dielectrophile one can produce a high variety of 1,3-thiazolines (**3**) or 1,3-thiazolidin-4-ones (**4**) in good yield.

3. Experimental section

The electrolyses were carried out using a Tacussel type PJT 35-2 potentiotat and a DC-Power Promax Model FA-672 as a constant current supply. The temperature was maintained constant at 0 °C by a cryostat Grant Model LTD 6G. IR spectra were recorded as dispersions in KBr or NaCl films using a Brucker Alpha ATR spectrophotometer. The mass spectra (EI, ionizing voltage 70 eV) were obtained on a THERMOFISHER ITQ-900 spectrometer, with a DIP/GC-MS_n mass-selective detector. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker Advance 300 MHz spectrometer or a Varian Unity 500 MHz spectrometer in $CDCl_3$ solutions with tetramethylsilane (TMS) as the internal standard. The chemical shifts are given in ppm. Two-dimensional HMBC correlation NMR experiments were performed in the Varian Unity 500 MHz spectrometer. Melting points were measured on a Reichert Thermovar microhot stage apparatus and are uncorrected. Elemental analyses were performed on a Leco CHNS Model 932 analyzer.

The *N*,*N*′-disubstituted thioureas (**1**) were synthesized according to the experimental protocol reported by Perveen *et al.*[33]

3.1 Electrochemical formation of a cyanomethyl anion

Electrolysis of a solution of dry acetonitrile (100 mL) and tetrabutylammonium tetrafluoroborate ($TBABF_4$) (0.1 M) as the supporting electrolyte was carried out under galvanostatic conditions (I = 80 mA), maintained under an inert argon atmosphere and cooled at 0 °C. The solution was placed in an undivided electrochemical cell, with a stainless steel grid cathode (apparent area about 20 cm^2) and a magnesium rod as a sacrificial anode (9 cm^2) (Fig. 2).

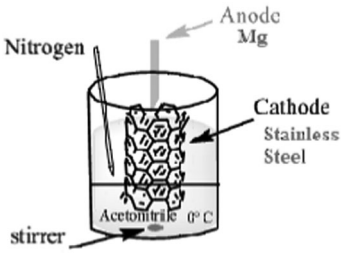


Fig. 2 Electrolytic cell for acetonitrile reduction.

The imposed current was switched-off after a charge of 520 coulombs was circulated through the cell (in a consumption process of 1.0 faraday per mole of the desired acetonitrile anion formed). Subsequently 5.4×10^{-3} mol of cyanomethyl anion were obtained, and immediately 2.5×10^{-3} mol of *N*,*N*′-disubstituted thiourea were added to the reaction medium.

3.2 Preparation of 2-imino 1,3-thiazolines (3) and 2-imino 1,3-thiazolidin-4-ones (4)

After 1 h of stirring the EGB with thiourea (**1**), always under an argon atmosphere at 0 °C, 2.7×10^{-3} mol of a 1,2-dielectrophile (**2**) were introduced into the solution and it was further kept under stirring for 2 h up to room temperature. Once the reaction was finished, the solvent was removed under reduced pressure.

The residue was extracted with ether and the organic phase was dried over anhydrous $MgSO_4$ and concentrated by evaporation. The resulting residue was purified by chromatography on a silica gel 60 (20 × 3 cm) column using petroleum ether/ethyl acetate (7/3 v/v) as the eluent. Elemental analyses and spectroscopic descriptions of the new compounds **3** and **4** are given below.

4-Methyl-3-phenyl-2-(*N*-phenylimino)-1,3-thiazoline[34] (3a). Solid. m.p: 134–136 °C. IR (KBr) ν = 3119, 2977, 1602, 1569, 1474, 1114, 1020, 693, 636 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.85 (s, 3H), 5.60 (s, 1H), 7.05 (d, 2H, J = 7.8 Hz), 7.25 (t, 3H, J = 7.8 Hz), 7.38 (t, 3H, J = 7.8 Hz), 7.50 (d, 2H, J = 7.8Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.3, 94.2, 121.5, 122.5, 128.7, 129.6, 129.8, 135.1, 137.5, 152.2, 160.7. EI-MS: m/z (relative intensity): 266(M^+, 92), 265(M^+ −1, 100), 251(4), 234(3), 226(2), 189(2), 163(1), 119(17), 104(1), 77(15).

2-(*N*-Benzylimino)-3-ethyl-4-methyl-1,3-thiazoline (3b). Solid. m.p: 103–106 °C; IR (KBr) ν = 3020, 2985, 1602, 1579, 1490, 1440, 1350, 1240, 1010, 750, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (t, 3H, J = 6.8 Hz), 2.04 (s, 3H), 2.57(s, 2H), 4.10 (q, 2H, J = 6.8 Hz), 6.05 (s, 1H), 7.06 (d, 2H, J = 7.9 Hz), 7.15–7.35 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.8, 17.1, 47.5, 64.2, 91.7, 121.5, 125.1, 125.4, 131.5, 138.7, 160.4. EI-MS: m/z (relative intensity): 232(M^+, 35), 119(100), 112(42), 77(47). Anal. calcd for $C_{13}H_{16}N_2S$: C, 67.24; H, 6.90; N, 12.07; S, 13.79. Found: C, 67.20; H, 6.94; N, 12.06; S, 13.80.

3-Cyclohexyl-4-methyl-2-(*N*,*N*-dimethylhydrazono)-1,3-thiazoline (3c). Oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.18–1.38 (m, 4H), 1.64 (t, 4H, J = 10.3 Hz), 1.81(d, 2H, J = 14.7 Hz), 2.05 (s, 3H), 2.47 (s, 6H), 3.84 (bs, 1H), 5.40 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 16.3, 25.2, 26.3, 28.8, 47.2, 57.0 (N–CH(–CH_2)–CH_2), 94.6 (–CH═), 135.7 (═C–N–), 165.0 (–C═N–). EI-MS: m/z (relative intensity): 239(M^+, 100), 224(4), 195(1), 182(4), 157(12), 142(5), 114(37), 100(11). Anal. calcd for $C_{12}H_{21}N_3S$: C, 60.30; H, 8.80; N, 17.60; S, 13.40. Found: C, 60.21; H, 8.84; N, 17.55; S, 13.39.

4-Methyl-2-(*N*,*N*-dimethylhydrazono)-3-phenyl-1,3-thiazoline (3d). Solid. m.p: 72–74 °C. IR (KBr) ν = 3030, 2926, 1633, 1606, 1592, 1487, 1449, 1357, 1027, 750, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.04 (s, 3H) 3.09 (s, 6H), 5.30 (s, 1H), 7.02 (t, 1H, J = 7.3 Hz), 7.06 (d, 2H, J = 7.3 Hz), 7.32 (tt, 2H, J_1= 7.9 Hz, J_2 = 2.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.6, 42.6, 88.4, 121.3, 122.7, 129.3, 136.6, 151.2, 155.3. EI-MS: m/z (relative intensity): 233(M^+, 30), 190(100), 189(85), 156(4), 149(10), 145(5), 115(5), 97(5), 77(9). Anal. calcd for $C_{12}H_{15}N_3S$: C, 61.80; H, 6.44; N, 18.03; S, 13.37. Found: C, 61.77; H, 6.48; N, 18.01; S, 13.74.

3-Benzyl-4-methyl-2-(*N*-phenylimino)-1,3-thiazoline (3e). White needles. m.p: 109–111 °C [Lit.[22] 111–113 °C].

3-Ethyl-4-methyl-2-(*N*-phenylimino)-1,3-thiazoline (3f). Solid. m.p: 99–102 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.33 (t, 3H, J = 6.9 Hz), 2.13 (d, 3H, J = 1.0 Hz), 3.99 (q, 2H, J = 6.9 Hz), 5.54 (d, 1H, J = 1.0 Hz), 7.05 (t, 1H, J = 7.3 Hz), 7.11 (d, 2H, J = 7.3 Hz), 7.33 (t, 2H, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.6, 14.4, 39.6, 93.3, 121.9, 121.9, 123.3, 129.3, 135.0, 150.2, 160.7. EI-MS: m/z (relative intensity): 218(M^+, 100), 189(56), 150(7), 114(77), 105(33), 79(9), 77(17). Anal. calcd for $C_{12}H_{14}N_2S$: C, 66.05; H, 6.42; N, 12.84; S, 14.68. Found: C, 66.06; H, 6.49; N, 12.71; S, 14.62.

3-Ethyl-2-(*N*-benzylimino)-5-methyl-4-phenyl-1,3-thiazoline (3g). Solid. m.p: 155–157 °C. IR (KBr) ν = 3042, 2926, 1641, 1606, 1450, 1359, 1027, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.09 (t, 3H, J = 6.9 Hz), 1.94 (s, 3H), 3.67 (q, 2H, J = 6.9 Hz), 4.40 (s, 2H), 7.20–7.47 (m, 10H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 13.1, 13.9, 40.6, 58.5, 106.5, 126.5, 127.7, 128.3, 128.8, 128.9, 130.3, 131.4, 135.1, 141.7, 147.1, 162.0. EI-MS: m/z (relative intensity): 308(M^+, 100), 280(M^+ −28, 55), 253(8), 204(25), 176(30), 147(14), 116(12), 105(10), 91(16), 77(6), 65(6). Anal. calcd for $C_{19}H_{20}N_2S$: C, 74.03; H, 6.49; N, 9.09; S, 10.39. Found: C, 73.92; H, 6.49; N, 9.01; S, 10.42.

3-Ethyl-5-methyl-4-phenyl-2-(*N*-phenylimino)-1,3-thiazoline (3h). Solid. m.p: 109–111 °C. IR (KBr) ν = 3057, 3024, 2971, 2926, 1601, 1563, 1487, 1443, 1322, 1253, 1077, 760, 699. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.16 (t, 3H, J = 6.9 Hz), 1.92 (s, 3H), 3.76 (q, 1H, J = 6.9 Hz), 7.04 (t, 1H, J = 7.4 Hz), 7.10 (d, 2H, J = 7.1 Hz), 7.30–7.40 (m, 4H), 7.42–7.50 (m, 3H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 12.9, 13.9, 40.9, 106.7, 121.9, 123.0, 128.9, 129.1, 129.6, 130.4, 134.5, 145.5, 152.3, 158.8. EI-MS: m/z (relative intensity): 294(M^+, 100), 265(12), 251(14), 190(52), 147(10), 104(5), 77(4). Anal. calcd for $C_{18}H_{18}N_2S$: C, 73.47; H, 6.12; N, 9.52; S, 10.88. Found: C, 73.48; H, 6.49; N, 9.79; S, 10.82.

5-Methyl-3-phenyl-2-(*N*-phenylimino)-1,3-thiazolidin-4-one (4a). Solid. m.p: 94–96 °C [Lit.[35] 98–99 °C]; IR (KBr) ν = 2974, 1714, 1638, 1374, 1329, 1225, 1067, 769 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.74 (d, 3H, J = 6.9 Hz), 4.23 (q, 1H, J = 7.2 Hz), 6.97 (d, 2H, J = 7.4 Hz), 7.15 (t, 1H, J = 7.2 Hz), 7.35 (t, 2H, J = 7.7 Hz), 7.38–7.52 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 20.0, 42.8, 121.2, 124.8, 128.2, 129.1, 129.3, 129.5, 135.1, 148.5, 154.2, 175.1. EI-MS: m/z (relative intensity): 282(M^+, 100), 281(M^+ −1, 73), 253(10), 194(26), 163(38), 118(6), 104(76), 91(14), 77(40), 51(29).

2-(*N*-Ethylimino)-5-methyl-3-phenyl-1,3-thiazolidin-4-one (4f). Solid. m.p: 94–97 °C. IR (KBr) ν = 3054, 2970, 1706, 1634, 1379, 1245, 765, 731, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.15 (t, 3H, J = 7.2 Hz), 1.72 (d, 3H, J = 7.2 Hz), 3.31 (q, 2H, J = 7.2 Hz), 4.20 (q, 1H, J = 7.2 Hz), 7.25 (d, 2H, J = 7.2 Hz), 7.35-7.48 (m, 3H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 15.2, 19.9, 42.1, 47.2, 128.0, 128.6, 129.1, 135.3, 151.0, 174.9. EI-MS: m/z (relative intensity): 234(M^+, 19), 233(M^+ −1, 100), 219(4), 205(9), 191(4), 177(3), 151(12), 118(18), 104(7), 91(7), 77(11). Anal. calcd for $C_{12}H_{14}N_2OS$: C, 61.54; H, 5.98; N, 11.97; S, 13.68. Found: C, 61.48; H, 6.01; N, 11.83; S, 13.62.

2-(*N*-Benzylimino)-3-(dimethylamino)-5-methyl-1,3-thiazolidin-4-one (4g). Solid. m.p: 87–89 °C. IR (KBr) ν = 3047, 2968, 1727, 1637, 1238, 761, 682 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.62 (d, 3H, J = 6.8 Hz), 2.97 (s, 6H), 3.95 (q, 1H, J = 6.8 Hz), 4.5 (d, 2H, J = 4.9 Hz), 7.22–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 19.5, 39.6, 43.1, 55.9, 126.7, 127.3, 128.3, 139.1, 149.0, 172.8. EI-MS: m/z (relative intensity): 263(M^+, 100), 219(8), 191(5), 172(14), 151(4), 132(18), 118(17), 117(12), 91(68), 65(21). Anal. calcd for $C_{13}H_{17}N_3OS$: C, 59.29; H, 6.51; N, 15.96; S, 12.17. Found: C, 59.26; H, 6.46; N, 15.89; S, 12.14.

4. Conclusions

Although numerous organic reactions (commonly acid-catalyzed) have already been described to get 2-imino-1,3-thiazolines (**3**) and 1,3-thiazolidin-4-ones (**4**), the importance of such heterocycles as biologically active compounds, particularly as promising drugs that induce apoptosis in cancer cells, deserves further synthetic procedures to be developed. Herein a new, efficient and promising scale-up alternative process is described by means of electrochemical methodology. The cathodic generation "*in situ*" of active bases (EGB promoters), with adequate control of the amount and strength of the base, is often highly desirable in the development of new synthetic reactions, such as the preparation here described. Hence new derivatives of these valuable five membered ring frameworks are now fully characterized.

Conflicts of interest

The authors declare no conflict of interest.

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