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Polarity reversal induced by electrochemically generated thiazol-2-ylidenes: The Stetter reaction

Monica Orsini [a,*], Isabella Chiarotto [b], Giovanni Sotgiu [a], Achille Inesi [b,**]

[a] Dip. Elettronica Applicata, Università Roma Tre, via Vasca Navale, 84, Roma 00146, Italy
[b] Dip. Ingegneria Chimica Materiali Ambiente, Università "La Sapienza", via Castro Laurenziano, 7, Roma 00161, Italy

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ABSTRACT

The inversion of the normal reactivity (umpolung) of aldehydes has been induced via *N*-heterocyclic carbenes (NHCs) thiazol-2-ylidenes **2a** or **3a**, generated by simple electrolyses of solutions containing thiazolium salt **2** or **3**. Accordingly, 1,4-dicarbonyl compounds have been obtained, in mild conditions and in moderate to very high yields, via 1,4-addition of the Breslow intermediates to the suitable Michael acceptor. The procedure has been performed in classical organic solvents (VOCs) as well as in room temperature ionic liquids (RTILs). The different reactivity of aliphatic aldehydes *vs* the one of aromatic and heteroaromatic aldehydes has been emphasized.

1. Introduction

N-Heterocyclic carbenes (NHCs) are cyclic carbenes bearing at least one α-amino substituent [1–4]. Stable *N*-heterocyclic carbenes **I** (imidazol-2-ylidenes or thiazol-2-ylidenes; X = N–R^1 or X = S respectively) [5] are prepared by deprotonation at C^2 carbon atom of imidazolium salts (**II**; X = N–R^1) or thiazolium salts [**II**; X = S] [6] or by reduction of imidazolin-2-thiones [**III**] [7] (Scheme 1).

The deprotonation is carried out in THF or in a mixture liquid ammonia/aprotic polar solvent [6,8] in the presence of a base such as NaH, KH, KOtBu or deprotonated DMSO. Potassium hexamethyldisilazide has been suggested as possible selective base. The reduction of **III** has been achieved by potassium in boiling THF [8]. Some problems related to these procedures (thermal sensitivity of free imidazol-2-ylidenes, solubility of KH and NaH, selectivity, etc.) have been emphasized [9].

Recently, an alternative electrochemical procedure has been reported [10,11]. 1-Butyl-3-methylimidazol-2-ylidene **1a** has been obtained by cathodic reduction of 1-butyl-3-methyl-imidazolium cation **1b** (Scheme 2).

The procedure was carried out via electrolysis of 1-butyl-3-methyl-1H-imidazolium tetrafluoroborate **1** (i.e. a room temperature ionic liquid, RTIL) without any use of bases or reducing agents and in total absence of classic organic solvents (VOCs) and was extended to other 1,3-dialkylimidazolium salts [12–14].

During the last decade, *N*-heterocyclic carbenes have been extensively proposed as excellent ligands for transition-metal catalysis [9,15,16] and as versatile organocatalysts in a wide range of organic reactions (benzoin condensation, Stetter reaction, transesterification reaction [1,2,17], etc.). In organic synthesis, the Stetter reaction has received considerable attention as possible catalytic carbon–carbon bond forming reaction through unconventional mode of reactivity. In fact, the Stetter reaction is the 1,4-addition of an activated aldehyde (catalyzed by cyanide ions or *N*-heterocyclic carbenes) to a suitable Michael acceptor, yielding 1,4-dicarbonyl compounds.

In the classical procedures, the Stetter reaction is performed using thiazolium salts as precatalysts, in the presence of bases. VOCs or RTILs [18], were used as solvents and Et_3N or K_2CO_3 as bases, i.e. as deprotonating agents towards thiazolium salts, according to the formation of *N*-heterocyclic carbenes (thiazolium-2-ylidenes). The plausible mechanism of reaction is reported in Scheme 3. Reaction of the carbene **IV** with the aldehyde gives the zwitterionic structure **V**. Proton transfer affords acylanion equivalent, commonly known as the Breslow intermetiate **VI**. Carbon–carbon bond formation results from nucleophilic attack of the acylanion equivalent into a Michael acceptor generating **VII**. Proton transfer gives **VIII**, which leads to the 1,4-dicarbonyl compound and the regeneration of the catalyst.

As part of a program directed at the utilization of electrochemically generated *N*-heterocyclic carbenes in new and simpler organic synthetic procedures [17,19–21], we have explored the reactiv-

* Corresponding author. Tel.: +39 06 57337075; fax: +39 06 57337026.
** Corresponding author. Tel.: +39 06 49766782; fax: +39 06 49766749.
E-mail addresses: morsini@uniroma3.it (M. Orsini), achille.inesi@uniroma1.it (A. Inesi).

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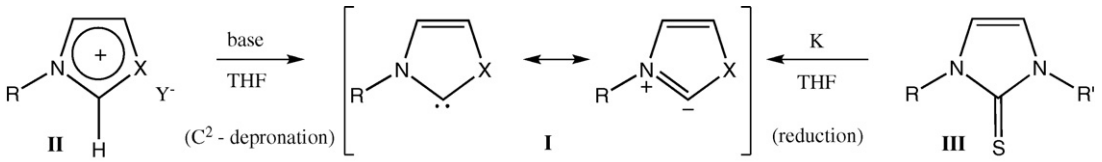
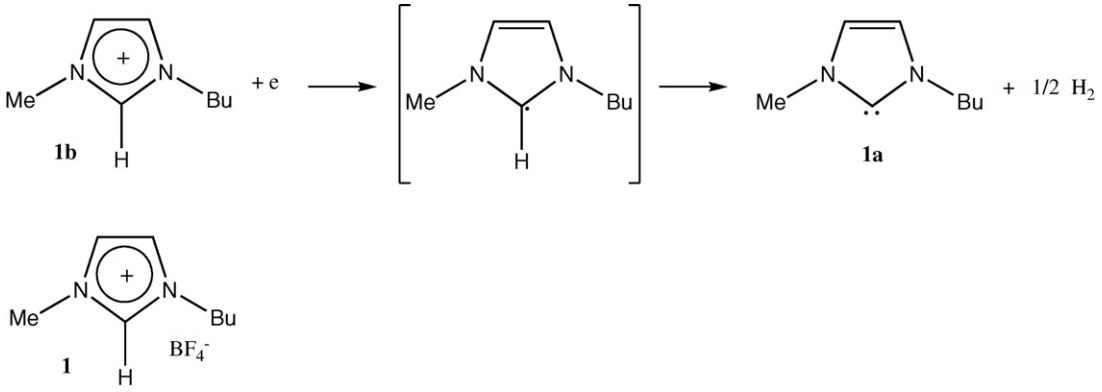


Scheme 1.



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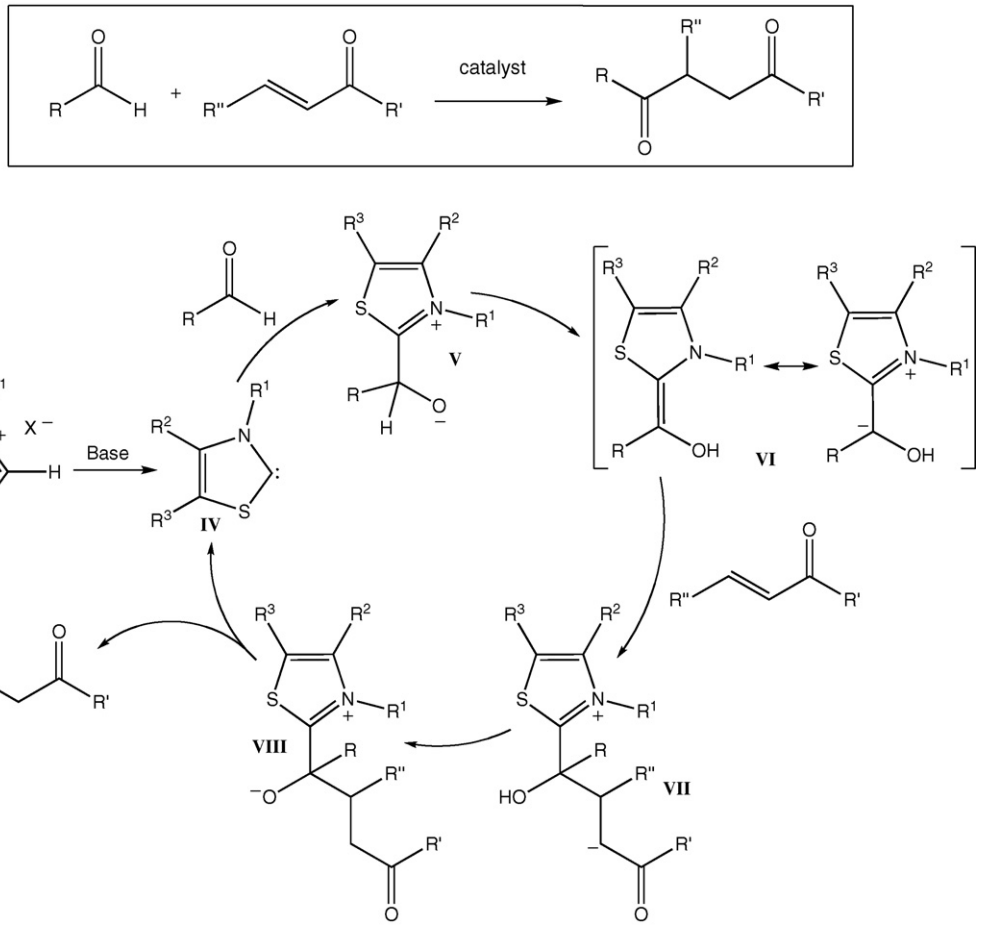
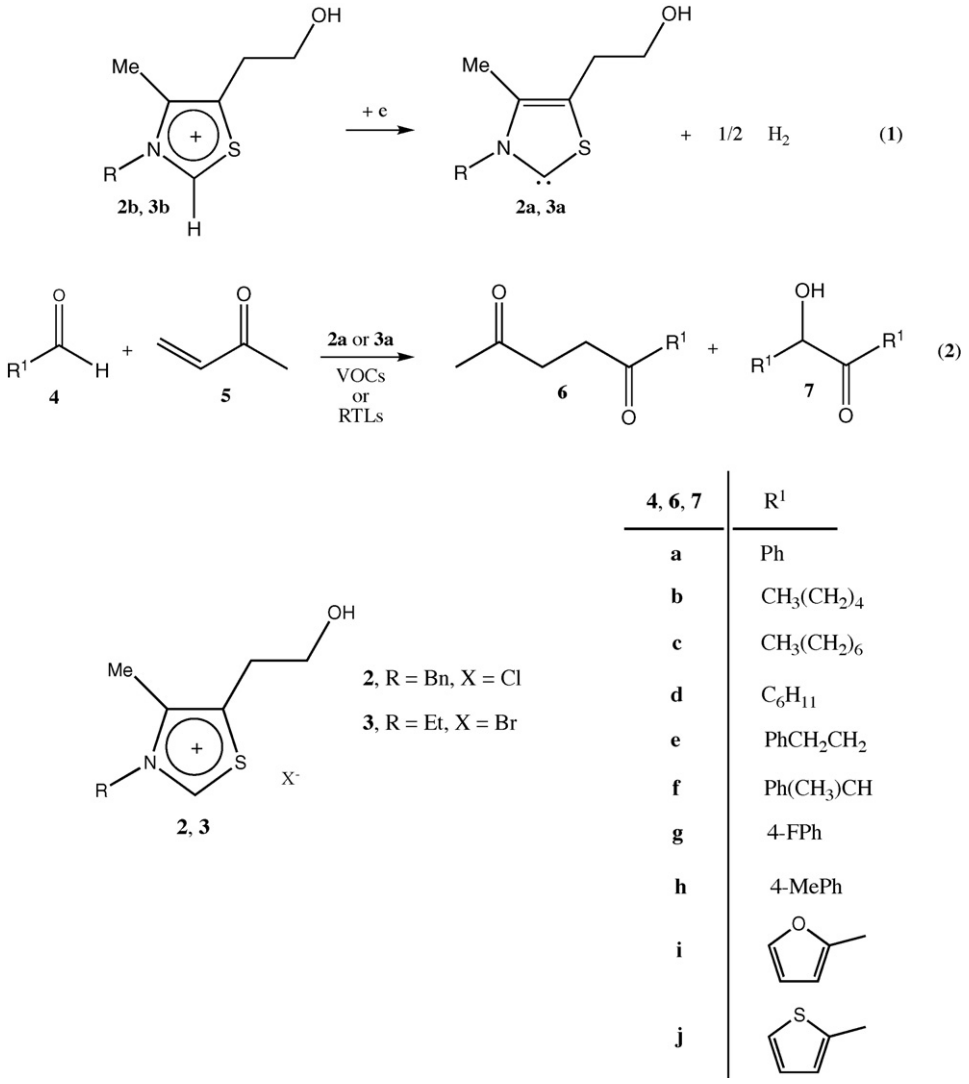


Scheme 3.



Scheme 4.

ity of aliphatic, aromatic and heteroaromatic aldehydes **4a**–**j** *vs* an appropriate Michael acceptor (α,β-unsaturated carbonyl, **5**) in the presence of electrochemically reduced thiazolium salt **2** or **3** (i.e. in the presence of thiazol-2-ylidenes **2a** or **3a**) (Scheme 4).

The aim of this investigation was the setting-up an alternative electrochemical methodology of synthesis, *via* Stetter reaction, of 1,4-dicarbonyl compounds **6a**–**j**, useful synthons for natural and pharmaceutical products [2]. The procedure has been performed in VOCs (DMF, DMSO, CH_3CN) as well as in RTIL **1** (1-butyl-3-methyl-1H-imidazolium tetrafluoroborate).

2. Experimental

2.1. Starting material

CH_3CN was distilled twice from P_2O_5 and CaH_2; *N*,*N*-dimethylformamide (DMF) was distilled from activated alumina under reduced pressure; dimethylsulphoxide (DMSO) was used without any purification; 1-butyl-3-methyl-imidazolium tetrafluoborate (BMIM-BF_4) was heated under vacuum at 45 °C for 2 h. Tetraethylammonium hexafluorophosphate (TEAHFP) was dried under high vacuum at 45 °C for 24 h. 3-Benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride **2** (Aldrich), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide **3** (Aldrich), aldehydes **4a**–**j** (Aldrich) and 1-buten-3-one **5** (Aldrich) were used as received without any purification.

2.2. Instrumentation

GC–MS measurements were carried out on a SE 54 capillary column using a Fisons 8000 gas chromatograph coupled with a Fisons MD 800 quadrupole mass selective detector. ^1H and ^{13}C NMR spectra were recorded using a Bruker AC 200 spectrometer using $CDCl_3$ as internal standard. Voltammetric measurements in BMIM-BF_4 were performed with an Amel System 5000 in a three-electrode cell; acquisition software was a CorrWare for windows version 2.8d1 Scribner. 492/GC/3 and 492/Pt/1 Amel micro-electrodes were employed, using a platinum counter electrode and a 373/SSG/6 Ag/AgCl reference electrode. Voltammetric measurements in organic solvents (DMSO, DMF, CH_3CN) were performed with an Amel 552 potentiostat equipped with an Amel 566 function generator and an Amel 563 multipurpose unit in three-electrode cell; the curves were displayed on an Amel 863 recorder. 492/GC/3 and 492/Pt/1 Amel micro-electrodes were employed, using a platinum counter electrode and the reference electrode was a modified saturated calomel electrode. Electrolyses under galvanostatic control were carried out with an Amel 552 potentiostat equipped with an Amel 721 integrator. A two-compartment

cell was used; the cathode was a disc of reticulated vitreous carbon (9 mm diameter) or a Pt spiral (apparent area 1.0 cm^2) and the counter electrode was a Pt spiral (apparent area 0.8 cm^2).

2.3. Typical experiment

2.3.1. Electrolysis of thiazolium salt **2** in BMIM-BF_4 followed by the addition of benzaldehyde **4a** and 1-buten-3-one **5**

The electrolysis of 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride **2** (2 mmol) in BMIM-BF_4 (2.0 cm^3) was carried out under galvanostatic conditions (I = 47 mA cm^{-2}) with continuous nitrogen bubbling, at 65 °C. The anolyte (1.5 cm^3 of BMIM-BF_4) was separated from the cathodic compartment through a G-3 glass septum. At the end of the electrolysis, benzaldehyde **4a** (4 mmol) and 1-buten-3-one **5** in large excess (1.0 cm^3) were added to the catholyte, the solution was stirred at 65 °C for 2 h and then at r.t. for 12 h. The reaction mixture was extracted with diethyl ether (3× 10 cm^3, allowing to stand under stirring with diethyl ether 15 min each time). After removing the solvent from the combined ethereal layers under reduced pressure, the crude reaction mixture was analyzed by ^{1}H NMR.

2.3.2. Electrolysis of thiazolium salts **2** or **3** in organic solvent VOCs followed by the addition of aldehydes **4a**–**j** and 1-buten-3-one **5**

The electrolysis of solvent–0.4 mol dm^{-3} thiazolium salt **2** or **3** solution (5.0 cm^3) was carried out under galvanostatic conditions (I = 47 mA cm^{-2}) with continuous nitrogen bubbling, at 65 °C. The anodic solution (DMF–0.1 mol dm^{-3} TEAHFP) was separated from the cathodic compartment through a porous glass plug filled with methylcellulose in DMF–TEAHFP.

At the end of the electrolysis, aldehydes **4a**–**j** (4 mmol) and 1-buten-3-one **5** in large excess (1.0 cm^3) were added to the catholyte, the solution was stirred at 65 °C for 2 h and then at r.t. for 12 h. When DMF and DMSO were used as solvent, the catholyte was poured into water (150 ml) and extracted with diethyl ether (3× 30 cm^3). When CH_3CN was used, the solvent was evaporated under reduced pressure and the residue extracted with diethyl ether (3× 30 cm^3). After removing the solvent from the combined ethereal layers under reduced pressure, the crude reaction mixture was analyzed by ^{1}H NMR.

All products were purified by flash chromatography, using *n*-hexane–ethyl acetate 95:5 as eluent and they were identified by comparison of their spectra data with data reported in literature.

2.3.3. Phenyl-pentane-1,4-dione **6a** [22]

^{1}H NMR ($CDCl_3$), δ: 2.23 (s, 3H), 2.86 (t, 2H, J = 6.0 Hz), 3.25 (t, 2H, J = 6.0 Hz), 7.38–7.53 (m, 3H), 7.95 (d, 2H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$), δ: 30.1, 32.4, 36.9, 128.0, 128.5, 133.1, 136.5, 198.5, 207.5. MS m/e (relative intensity): 176 ($M^{\bullet+}$, 5), 161 (21), 105 (100), 77 (3).

2.3.4. n-Decane-2,5-dione **6b** [23]

^{1}H NMR ($CDCl_3$), δ: 0.76 (t, 3H, J = 6.2 Hz), 1.10–1.17 (m, 4H), 1.38–1.52 (m, 2H), 2.06 (s, 3H), 2.32 (t, 2H, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$), δ: 13.8, 22.3, 23.3, 29.8, 31.2, 35.9, 36.7, 42.6, 207.1, 209.5.

2.3.5. n-Dodecane-2,5-dione **6c** [24]

^{1}H NMR ($CDCl_3$), δ: 0.85 (t, 3H, J = 6.4 Hz), 1.24 (br s, 8H), 1.51–1.59 (m, 2H), 2.16 (s, 3H), 2.42 (t, 2H, J = 7.4 Hz), 2.56–2.70 (m, 4H). ^{13}C NMR ($CDCl_3$), δ: 13.9, 22.5, 23.8, 28.9, 29.1, 29.8, 31.6, 36.0, 36.8, 42.8, 207.1, 209.5. MS m/e (relative intensity): $M^{\bullet+}$ absent, 155 (2), 127 (15), 114 (100), 99 (35), 71 (69), 57 (44), 43 (7).

2.3.6. 1-Cyclohexylpentane-1,4-dione **6d** [25]

^{1}H NMR ($CDCl_3$), δ: 1.13–1.29 (m, 5H), 1.56–1.82 (m, 5H), 2.11 (s, 3H), 2.24–2.35 (m, 1H), 2.63 (br s, 4H). ^{13}C NMR ($CDCl_3$), δ: 25.5, 25.7, 25.8, 28.3, 28.4, 29.9, 34.0, 36.7, 50.6, 207.4, 212.6. MS m/e (relative intensity): $M^{\bullet+}$ absent, 139 (2), 99 (100), 83 (54).

2.3.7. 7-Phenylheptane-2,5-dione **6e** [22]

^{1}H NMR ($CDCl_3$), δ: 2.15 (s, 3H), 2.58–2.92 (m, 8H), 7.13–7.29 (m, 5H). ^{13}C NMR ($CDCl_3$), δ: 29.6, 29.8, 36.1, 36.8, 44.1, 126.0, 128.2, 128.4, 141.0, 207.2, 208.4. MS m/e (relative intensity): 204 ($M^{\bullet+}$, 14), 161 (4), 146 (100), 133 (23), 105 (72), 99 (58), 91 (43), 71 (32).

2.3.8. Mixture of 6-phenylheptane-2,5-dione **6f** and 2-methyl-2-phenyl-1,5-hexanedione **6′f** [24,26]

6f ^{1}H NMR ($CDCl_3$), δ: 1.36 (d, 3H, J = 7.0 Hz), 2.10 (s, 3H), 2.45–2.70 (m, 4H), 3.78 (q, 1H, J = 7.0 Hz), 7.15–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$), δ: 17.4, 29.8, 34.7, 37.1, 52.8, 127.1, 127.8, 128.8, 140.6, 207.2, 209.5. MS m/e (relative intensity): $M^{\bullet+}$ absent, 105 (10), 99 (100), 71 (11), 43 (8).

6′f ^{1}H NMR ($CDCl_3$), δ: 1.41 (s, 3H), 2.03 (s, 3H), 2.16–2.26 (m, 4H), 7.15–7.36 (m, 5H), 9.46 (s, 1H). ^{13}C NMR ($CDCl_3$), δ: 17.3, 29.4, 29.8, 38.4, 53.1, 127.0, 127.5, 129.0, 139.1, 201.8, 207.8. MS m/e (relative intensity): $M^{\bullet+}$ absent, 174 (2), 118 (100), 99 (6), 43 (36).

2.3.9. 1-[4-(Fluoro)-phenyl]pentane-1,4-dione **6g** [27]

^{1}H NMR ($CDCl_3$), δ: 2.23 (s, 3H), 2.86 (t, 2H, J = 6.2 Hz), 3.21 (t, 2H, J = 6.2 Hz), 7.10 (app. t, 2H, J = 8.7 Hz), 7.98 (dd, 2H, J = 8.7 Hz and J = 5.5 Hz). ^{13}C NMR ($CDCl_3$), δ: 30.0, 32.2, 37.0, 115.6 (d, ^2J = 21.9 Hz), 130.6 (d, ^3J = 9.3 Hz), 133.0 (d, ^4J = 3.0 Hz), 165.7 (d, ^1J = 254.7 Hz), 196.9, 207.2. MS m/e (relative intensity): 194 ($M^{\bullet+}$, 7), 179 (54), 151 (30), 123 (100), 71 (10), 43 (13).

2.3.10. 1-[4-(Methyl)-phenyl]pentane-1,4-dione **6h** [28]

^{1}H NMR ($CDCl_3$), δ: 2.22 (s, 3H), 2.37 (s, 3H), 2.84 (t, 2H, J = 6.4 Hz), 3.22 (t, 2H, J = 6.4 Hz), 7.22 (d, 2H, J = 8.0 Hz), 7.85 (d, 2H, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$), δ: 21.6, 30.1, 32.2, 37.0, 128.1, 129.2, 134.1, 143.9, 198.1, 207.5.

2.3.11. 1-(2-Furyl)-pentane-1,4-dione **6i** [29]

^{1}H NMR ($CDCl_3$), δ: 2.18 (s, 3H), 2.82 (d, 2H, J = 6.4 Hz), 3.08 (d, 2H, J = 6.4 Hz), 6.48 (dd, 1H, J = 3.6 Hz and J = 1.4 Hz), 7.16 (d, 1H, J = 3.6 Hz), 7.53 (d, 1H, J = 1.4 Hz). ^{13}C NMR ($CDCl_3$), δ: 29.9, 32.0, 36.6, 112.2, 117.1, 146.3, 152.3, 187.7, 207.1.

2.3.12. 1-(2-Thiophen)-pentane-1,4-dione **6j** [22]

^{1}H NMR ($CDCl_3$), δ: 2.19 (s, 3H), 2.82 (t, 2H, J = 6.4 Hz), 3.17 (t, 2H, J = 6.4 Hz), 7.08 (app. t, 1H, J = 4.9 Hz) 7.58 (dd, 1H, J = 4.9 Hz and J = 1.2 Hz), 7.71 (d, 1H J = 3.6 Hz). ^{13}C NMR ($CDCl_3$), δ: 30.0, 32.9, 37.0, 128.1, 132.0, 133.5, 143.6, 191.4, 207.1.

2.3.13. 2-Hydroxy-1,2-diphenylethanone **7a** [30]

^{1}H NMR ($CDCl_3$), δ: 4.25 (br s, 1H), 5.94 (s, 1H), 7.25–7.41 (m, 8H), 7.90 (d, 2H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$), δ: 76.2, 127.7, 128.5, 128.6, 129.1, 133.6, 133.8, 139.0, 199.0.

2.3.14. 1,2-Bis-[(4-fluoro)-phenyl]-2-hydroxyethanone **7g** [31]

^{1}H NMR ($CDCl_3$), δ: 4.54 (d, 1H, J = 5.6 Hz), 5.88 (d, 1H, J = 5.6 Hz), 6.94-7.09 (m, 4H), 7.24–7.31 (m, 2H), 7.87–7.94 (m, 2H). ^{13}C NMR ($CDCl_3$), δ: 75.3, 116.0 (d, ^2J = 22.1 Hz), 116.2 (d, ^2J = 21.8 Hz), 129.5 (d, ^3J = 8.3 Hz), 131.8 (d, ^3J = 9.6 Hz), 134.7, 134.8, 161.8 (d, ^1J = 162.3 Hz), 166.9 (d, ^1J = 171.5 Hz), 197.1.

2.3.15. 1,2-Bis-[(4-methyl)-phenyl]-2-hydroxyethanone **7h** [30]

^{1}H NMR ($CDCl_3$), δ: 2.26 (s, 3H), 2.33 (s, 3H), 4.51 (1br s), 5.90 (s, 1H), 7.12–7.27 (m, 6H), 7.81 (d, 2H, J = 8.2 Hz). ^{13}C NMR ($CDCl_3$),

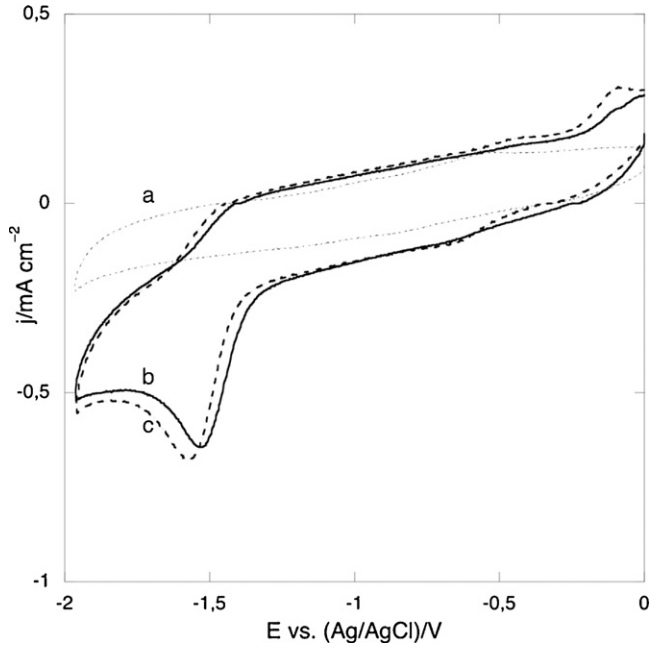


Fig. 1. Cyclic voltammetric curves for RTIL **1** (curve a), for RTIL **1** containing **2** ($c = 1.0 \times 10^{-2}$ mol dm^{-3}, curve b) and for RTIL **1** containing **3** ($c = 1.0 \times 10^{-2}$ mol dm^{-3}, curve c). Vitreous carbon cathode, $\nu = 200$ mV s^{-1}, reference Ag/AgCl, $T = 50.0$ °C.

δ: 21.6, 21.7, 75.7, 127.6, 129.2, 129.3, 129.8, 130.2, 136.3, 138.3, 144.6, 198.5.

3. Results and discussion

3.1. Preliminary voltammetric investigation

The voltammetric curves of the solutions containing **1**, **2** or **3** (DMF, DMSO, CH_3CN as solvent, Et_4NPF_6 as supporting electrolyte, $\nu = 0.2$ V s^{-1}, r.t.) show a single irreversible and diffusion controlled wave related to the monoelectronic reduction of cations **1b**, **2b** and **3b** to carbenes **1a**, **2a** and **3a** respectively and dihydrogen (Schemes 2 and 4, react. 1).

The values of the peak potentials of **2** and **3** are strongly more positive with respect to the one of **1** ($Ep_2 = -1.63$ V, $Ep_3 = -1.66$ V, $Ep_1 = -2.55$ V, *vs* SCE, $c = 5.0 \times 10^{-3}$ mol dm^{-3}, DMSO as solvent, vitreous carbon cathode, $\nu = 200$ mV s^{-1}, $T = 25.0$ °C). These values are moderately affected by the nature of the solvent and of the cathodic material (C, Pt).

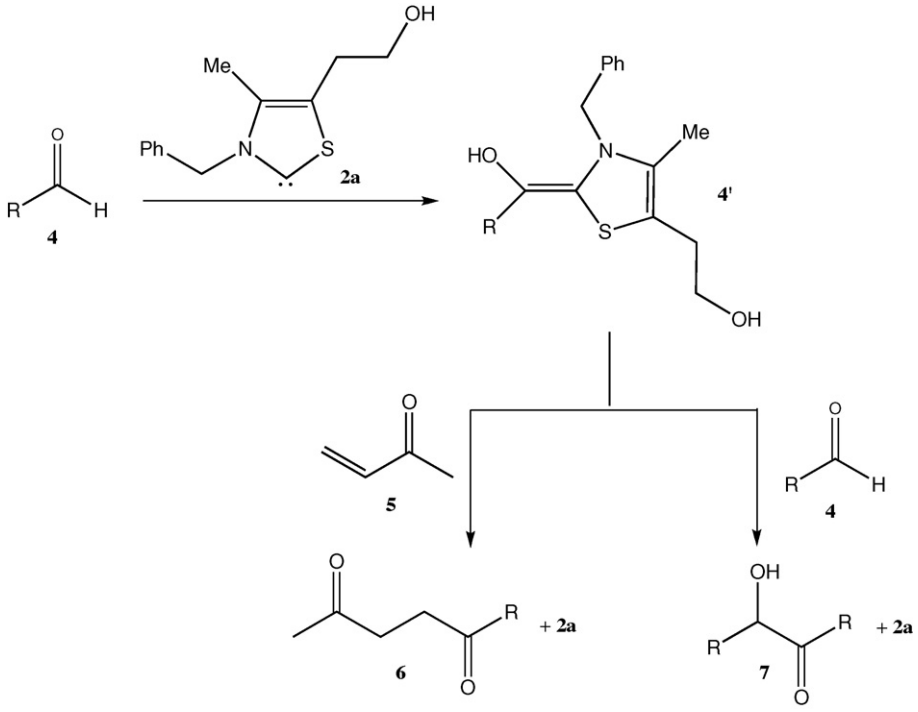
Likewise, the voltammetric curves of **2** and **3**, recorded for the solutions of RTIL **1** as solvent, show a single irreversible monoelectronic wave ($Ep_2^* = -1.50$ V and $Ep_3^* = -1.60$ V *vs* reference Ag/AgCl, $\nu = 200$ mV s^{-1}, $T = 50.0$ °C, Fig. 1). Therefore, the selective cathodic reduction of **2** and **3** to thiazol-2-ylidenes **2a** and **3a**, can be performed in organic solvent as well as in ionic liquid **1**.

These remarks suggested to study the Stetter reaction with the following procedure: the solutions of **2** or **3** (in organic solvents or in RTIL **1**), previously electrolyzed under galvanostatic conditions, were added of aldehydes **4** and 1-buten-3-one **5** and stirred, at controlled temperature, for a prefixed interval of time. The workup of the resulting solutions afforded 1,4-dicarbonyl compounds **6**. In addition, as byproducts, α-hydroxyketones **7** might be obtained.

N-Heterocyclic carbenes **2a** and **3a** are catalysts able to induce the inversion of the normal reactivity (reverse polarity or umpolung) of an aldehyde **4** via formation of an acylanion equivalent **4′** (Breslow intermediate). The acylanion equivalent performs a nucleophilic attack to the Michael acceptor **5**, added to the reaction mixture (Stetter reaction), or to another aldehyde molecule (benzoin condensation).

Therefore, in any setting-up of new procedures of synthesis of 1,4-dicarbonyl compounds **6** via Stetter reaction, the possible presence of α-hydroxyketones **7** as byproducts (benzoin condensation) must be controlled (Scheme 5).

To optimize the procedure, as concerns both yield and selectivity, i.e. **6** *vs* **7**, several experiments were performed using different: (a) reaction time and temperature, (b) number of Faradays, consumed at the electrodes, per mol of aldehyde **4** added to the



Scheme 5.

Table 1
Reactivity of benzaldehyde **4a** *vs* Michael acceptor **5** in electrolyzed solutions of thiazolium salt **2** (0.4 mol dm^{-3})[a]. Solvent: DMF, CH_3CN, DMSO, and BMIM-BF_4. Effect of solvent, time and temperature reaction and *Q* on the yield and selectivity.

Entry	Solvent	*Q*[b] (F mol^{-1})	Time and temp.[c]	Products (yields %)[d]			**6a** selectivity (%)[e]
				4a	**6a**	**7a**	
1	DMF	0.25	A	74	14	4	78
2	DMF	0.25	B	36	36	7	83
3	DMF	0.10	C	64	14	4	78
4	DMF	0.20	C	30	34	20	63
5	DMF	0.25	C	20	46	23	67
6	DMF	0.40	C	31	38	13	75
7	CH_3CN	0.25	C	48	14	19	44
8	DMSO	0.25	C	14	62	16	79
9[f]	BMIM-BF_4	0.25	C	35	46	13	78

[a] Electrolyses were carried out under galvanostatic control (I = 47 mA cm^{-2}) in a divided cell, reticulated C cathode, Pt anode.
[b] Number of Faradays supplied to the electrodes per mole of **4a**.
[c] Benzaldehyde **4a** and 1-buten-3-one **5** were added to the cathodic compartment at the end of the electrolysis, afterwards the cathodic solution was stirred for 20 h at r.t. (A) or 48 h at r.t. (B) or 2 h at 65 °C and 12 h at r.t. (C).
[d] Yield calculated with respect to benzaldehyde **4a** and determined by ^{1}H NMR spectrum of crude reaction mixture.
[e] Selectivity towards the formation of **6a** evaluated as [**6a**/(**6a** + **7a**)] × 100.
[f] The cathode was a Pt spiral.

electrolyzed solutions, and (c) solvents (VOCS: DMF, DMSO, CH_3CN or RTIL: **1**).

Benzaldehyde **4a** and thiazolium salt **2** were taken as model substrate and model precatalyst respectively. The results, reported in Table 1, can be summarized as follows.

3.2. Reaction time and temperature

Both the yields of **6a** and **7a** increase on increasing reaction time and temperature; on the contrary the selectivity of the Stetter reaction decreases on increasing the temperature (Table 1, entries 1 and 2 *vs* 5).

3.3. Number of Faradays per mole of aldehydes, Q

Assuming the reduction of thiazolium salt **2** to thiazol-2-ylidenes **2a** as a monoelectronic process (Scheme 3, react. 1), the number of Faradays per mole of aldehydes consumed during the electrolysis affects the molar ratio (ρ) carbene/aldehyde present in the solution at the end of the electrolyses. The yield of **6a**, as well as the one of **7a**, increases on increasing of *Q* (and consequently of ρ) from 0.10 to 0.25 (Table 1, entries 3–5). Further increases of *Q* (*Q* = 0.4 Faraday mole^{-1}) and ρ do not affect the yields of **6a** and **7a** according to the catalytic role of the electrogenerated carbene **2a** (Table 1, entry 6).

3.4. Effect of the nature of the solvent

As regards the optimization of the solvent, among VOCs and RTILs, DMSO turned to be the best solvent with respect to yield and selectivity (Table 1, entries 5, 7, 8, and 9).

In order to evaluate the generality and the synthetic potential of the procedure, the reactivity of a wide range of aldehydes (aromatic **4a**, **g**, **h** aliphatic **4b**–**f** and heteroaromatic aldehydes **4i**, **j**) *vs* Michael acceptor **5** was investigated, in DMSO solutions, in the presence of electrogenerated thiazol-2-ylidenes. To compare the reactivity of different aldehydes, the investigation was carried out according to the optimized conditions reported in Table 1, entry 8. The results (yields of 1,4-dicarbonyl compounds **6a**–**j**, α-hydroxyketones **7** as well as the ones of unconverted aldehydes), reported in Table 2, show that:

Table 2
Electrochemical synthesis of 1,4-dicarbonyl compounds **6a**–**j** by electrolyses of DMSO-0.4 mol dm^{-3} thiazolium salt **2** followed by addition of aldehydes **4a**–**j** and Michael acceptor **5**[a].

Entry	Aldehyde	Products (yields %)[b]			**6** Selectivity (%)[c]
		6	**7**	**4**	
1	**4a**	62 (**6a**)	16 (**7a**)	14 (**4a**)	79
2	**4b**	73 (**6b**)	–	18 (**4b**)	100
3[d]	**4b**	67 (**6b**)	–	13 (**4b**)	100
4	**4c**	79 (**6c**)	–	20 (**4c**)	100
5	**4d**	78 (**6d**)	–	21 (**4d**)	100
6	**4e**	93 (**6e**)	–	6 (**4e**)	100
7[e]	**4f**	79 (**6f**)	–	7 (**4f**)	100
8	**4g**	51 (**6g**)	32 (**7g**)	17 (**4g**)	62
9[f]	**4g**	61 (**6g**)	33 (**7g**)	5 (**4g**)	65
10[d]	**4g**	71 (**6g**)	24 (**7g**)	4 (**4g**)	75
11	**4h**	37 (**6h**)	13 (**7h**)	45 (**4h**)	74
12	**4i**	49 (**6i**)	–	42 (**4i**)	100
13	**4j**	34 (**6j**)	–	65 (**4j**)	100

[a] Electrolyses were carried out under the optimized conditions reported in Table 1, entry 8.
[b] Yield calculated with respect to aldehyde **4** and determined by ^{1}H NMR spectrum on crude reaction mixture.
[c] Selectivity towards the formation of **6** evaluated as [**6**/(**6** + **7**)] × 100.
[d] Thiazolium salt **3** instead of **2** was used in the DMSO solutions.
[e] The formation of the byproduct 2-methyl-2-phenyl-1,5-hexanedione **6′f** was observed (13% of yield with respect to aldehyde **4f** and determined by ^{1}H NMR on crude reaction mixture).
[f] Temperature and reaction time 65 °C and 18 h.

(1) aliphatic aldehydes **4b**–**f** furnished 1,4-dicarbonyl compounds **6b**–**f** in high yields (93–73%) with complete selectivity (100%) (Table 2, entries 2–7);
(2) heteroaromatic aldehydes **4i**, **j** furnished 1,4-dicarbonyl compounds **6i**, **j** in moderate yields (49–34%) and complete selectivity (100%) (Table 2, entries 12 and 13);
(3) moderate yields (62–37%) and selectivity (79–62%) mark aromatic aldehydes **4a**, **g**, **h** (Table 2, entries 1, 8–11).

The key step of the Stetter reaction as well as of the benzoin condensation is the formation of the acylanion equivalent (Breslow intermediate). Therefore the reactivity of the Breslow intermediate **4′** is affected by the nature of the aldehydes:

(i) in the case of aliphatic **4b**–**f** and heteroaromatic **4i**, **j** aldehydes, the 1,2-addition (Breslow intermediate–parent aldehyde) is not competitive with the 1,4-addition (Breslow intermediate–Michael acceptor);
(ii) in the case of aromatic aldehydes **4a**, **g**, **h** the 1,2-addition (Breslow intermediate–parent aldehyde) is competitive with the 1,4-addition (Breslow intermediate–Michael acceptor).

Besides, with aromatic aldehydes, a remarkable increase in the yields of 1,4-dicarbonyl compounds may be achieved on varying the nature of the precatalyst and/or time and temperature of the reaction. It must be considered that, in the classical procedures, the thiazolium salts **2** and **3** (owing to the peculiar substituents present in the structure of the thiazolium cation) have been indicated as the best precatalysts, in the presence of bases, *vs* aliphatic and aromatic aldehydes respectively [1].

Accordingly to this suggestion, the use in the present procedure of the thiazolium salt **3**, instead of **2**, allows a significant increase in yield of the Stetter reaction with aromatic aldehydes, e.g. **6h** was obtained in 71% yield (**3** as precatalyst) *vs* 51% yield (**2** as precatalyst) (Table 2 entry 8 *vs* 10). Moreover, the use of the thiazolium salt **3** as precatalyst in the case of aliphatic aldehydes, e.g. **4b**, leads to decrease of the yield of **6b**: 67% (**3a** as catalyst) *vs* 73% (**2a** as catalyst, Table 2, entry 3 *vs* 2).

Finally, further increases on the yield of the Stetter reaction, with aromatic aldehydes, may be achieved on increasing temperature and reaction time; in fact, **6f** was obtained in 61% yield (18 h, 65 °C) instead of 51% (2 h, 65 °C and 12 h, r.t., Table 2, entry 9 *vs* 8).

4. Conclusions

An alternative procedure of synthesis of 1,4-dicarbonyl compounds **6a**–**j** (useful synthons for the synthesis of natural and pharmaceutical products) has been set up via 1,4-addition of aldehydes **4a**–**j** to a suitable Michael acceptor **5** (Stetter reaction) in the presence of *N*-heterocyclic carbenes **2a** and **3a** as catalysts. The 1,4-dicarbonyl compounds **6a**–**j** have been obtained in moderate to very high yields.

The procedure involves the inversion of the normal reactivity (umpolung) of aldehydes, induced by heterocyclic carbenes **2a** and **3a**, generated by electrolysis of solutions of thiazolium salts **2** and **3** (VOCs or RTILs as solvents).

The nature of the aldehydes and of the solvents, the molar ratio catalyst/substrate, the temperature and reaction time affect the yields of the 1,4-dicarbonyl compounds and the selectivity of the procedure, i.e. the reactivity of the Breslow intermediate *vs* the Michael acceptor (Stetter reaction) or the parent aldehyde (benzoin condensation).

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