Electrosynthesis of *N*-Substituted Imidazole-2-thiones

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Abstract: The electrochemical eduction of phenacyl azide thiosemicarbazones **2** in aprotic DMF/$LiClO_4$ medium at the mercury cathode in a divided cell and under controlled potential leads to *N*-substituted imidazolethiones **3** in a one-pot reaction with good yields.

Key words*:* cathodic reduction, phenacyl azide thiosemicarbazones, nucleophilic addition, cyclization, imidazole-2-thiones

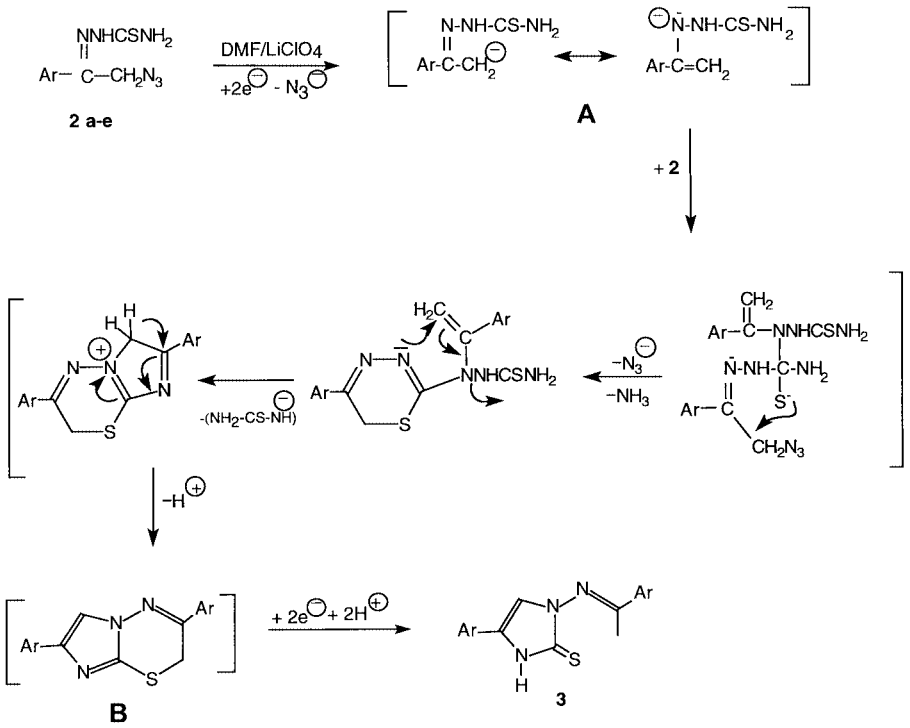
Several years ago, we reported the cathodic reduction of phenacyl bromide semicarbazones in aprotic medium leading to the dimeric semicarbazones, in almost quantitative yield, which were converted into either 1,4-diarylbutane-1,4-diones and 2,5-diarylfurans[1] or 3,6-diarylpyridazines.[2] However, when these reactions were carried out under highly dilution conditions 3,7-diaryl-2*H*-imidazo[2,1-*b*][1,3,4]oxadiazines were obtained.[3] The subsequent reduction in protic medium, EtOH/$LiClO_4$, at a constant potential [between –1.52 V and –1.65 V vs. SCE (saturated calomel electrode) depending on the oxadiazine] using mercury as working electrode, yielded 4-aryl-1-(1-arylethylidenamino)-1,3-dihydro-2-imidazolones.[4]

For the synthesis of the corresponding imidazolethiones in a similar way, we tried to prepare phenacyl bromide thiosemicarbazones from phenacyl bromide and thiosemicarbazide, but this reaction afforded 1,3,4-thiadiazines[5a,b] and 1,3-thiazoles[5c] by the nucleophilic attack of the sulfur atom on the C–Br bond. To avoid this, bromide was replaced by an azide group. The reductive cleavage of the C–N_3 bond was already reported by Lund, [6]describing the transformation of phenacyl azide into acetophenone under protic conditions in a $2e^-/2H^+$ process.

This process is similar to the conversion of phenacyl bromide semicarbazones into *N*-substituted imidazolones, previously reported by us, but in this case two steps were implicated and the first step had to be carried out under conditions of high dilution because competition between a substitution and an addition reaction could take place.

Compounds **2** were electrolyzed under aprotic conditions in order to obtain the expected thiadiazines. However, compounds **3** were obtained in good yields from the one-pot reaction (Scheme).

Voltammetric studies in DMF/$LiClO_4$ as solvent-supporting electrolyte employing mercury cathode as working



Ar = **a**: Ph, **b**: *4-MeO* C_6H_4, **c**: *4-Me* C_6H_4, **d**: *4-Cl* C_6H_4, **e**: *4-Br* C_6H_4.

Scheme

Table 1 Peak Potentials (vs. Ag/AgCl) for **2 a–e** in DMF/$LiClO_4$[a]

2	a	b	c	d	e
Ar	C_6H_5	4-$MeOC_6H_4$	4-MeC_6H_4	4-ClC_6H_4	4-BrC_6H_4
E_{pc} (V)	–1.72	–1.89	–1.84	–1.69[b]	–1.68[c]

[a] ν = 0.5 V/s.
[b] ν = 0.1 V/s.
[c] ν = 0.3 V/s.

electrode, glassy carbon as auxiliary and Ag/AgCl as reference, gave for the thiosemicarbazones **2a–e** the E_{pc} shown in Table 1. Under these conditions the C–N_3 group is easly reduced than the C=S in the thiosemicarbazone as was demonstrated by running the cyclic voltammetry of phenacyl azide (E_{pc} = –0.97 V) and acetophenone thiosemicarbazone (E_{pc} = –1.95 V) in DMF/$LiClO_4$ and a HMDE (hanging mercury drop electrode) at 0.5 V/s.

The electrochemical reduction of **2a–e** using DMF/$LiClO_4$ on a mercury cathode at constant working potential between –1.68 and –1.89 V vs. SCE (depending on the phenacyl azide thiosemicarbazone) gave 4-aryl-1-(1-arylethylidenamino)-1,3-dihydroimidazole-2-thiones **3**.

The assignment of product structure is based on the disappearance of the strong azide band at ν = 2100 cm^{-1} in the IR spectra and is in a good agreement with the expected reduction of the C–N_3 bond instead of the C=S bond. The electrogenerated compounds **3a–e** showed in ^{1}H NMR spectra a singlet for three protons at δ = 2.22 corresponding to a methyl group at an unsaturated carbon. A broad singlet at δ = 8.9 was assigned to the NH of the imidazolethione ring. A singlet corresponding to the proton on C-5 appears at δ = 6.9. The chemical shift in ^{13}C NMR spectra for the signal corresponding to C-5 is δ = 103.9. Other relevant ^{13}C NMR signals are at δ = 12.9 and 169.2 belonging to the methyl group and the C=S respectively.

The first step takes place with the cleavage of the C–N_3 to give the corresponding anion **A** (Scheme). The presence of this anion was confirmed by running the electrolysis in the presence of phenol. In this case, acetophenone thiosemicarbazone was isolated as the only product with a current consumption of two electrons per molecule of substrate.

Subsequent nucleophilic attack of anion **A** to the C=S bond of another substrate molecule followed by ammonia and thiourea elimination led to the formation of the corresponding 3,7-diaryl-2*H*-imidazo[2,1-*b*][1,3,4]thiadiazine **B** as a not isolable intermediate (due to the cleavage of the C–S bond at the applied working potential, in a similar way to the imidazooxadiazine which yielded the corresponding *N*-substituted 2-imidazolone[4] at potentials around –1.6 V vs. SCE). The presence of thiourea in the

Table 2 Physical and Spectroscopic Data of **1**[a]

Product	Ar	mp (°C)[b]	IR (KBr or film		^{1}H NMR ($CDCl_3$), δ, *J*, (Hz)			^{13}C NMR ($CDCl_3$) δ				MS *m*/*z* (%)
			$\nu_{C=O}$	N_3	CH_2	arom	others	CH_2	arom	C=O	others	
1a	C_6H_5	17[c]	1696	2105	4.53 (s, 2 H)	7.4–7.7 (m, 3 H) 7.8–8 (m, 2 H)		54.8	127.8, 128.1, 129, 134.1	193.1		161 (M^+, 0.2), 136 (0.9), 105 (100), 91 (3), 77 (55), 51 (21)
1b	4-$MeOC_6H_4$	74–76	1684	2126	4.48 (s, 2 H)	6.93 (d, 2 H, *J* = 8.8) 7.86 (d, 2 H, *J* = 8.8)	3.86 (s, 3 H	54.5	114.1, 127.5, 130.2, 164.3	191.6	55.5	191 (M^+, 1), 135 (100), 107 (7), 92 (11), 77 (12)
1c	4-MeC_6H_4	63–65	1690	2102	4.52 (s, 2 H)	7.28 (d, 2 H, *J* = 8.1) 7.79 (d, 2 H, *J* = 8.1)	2.42 (s, 3 H)	54.7	127.9, 129.6, 131.9, 145.1	192.7	21.6	175 (M^+, 0.1), 119 (100), 105 (12), 91 (64), 65 (15)
1d	4-ClC_6H_4	58–60	1695	2106	4.5 (s, 2 H)	7.45 (d, 2 H, *J* = 8.7) 7.82 (d, 2 H, *J* = 8.7)		54.8	129.3, 130.9, 132.6, 140.6	192.0		195 (M^+, 0.2), 141 (33), 139 (100), 113 (16), 111 (50), 104 (2), 75 (40), 51 (8)
1e	4-BrC_6H_4	86[c]	1695	2117	4.51 (s, 2 H)	7.62 (d, 2 H, *J* = 9) 7.75 (d, 2 H, *J* = 9)		54.8	129.4, 132.3, 133.1, 138.1	192.3		241 (M^+ + 2, 0.1), 239 (M^+, 0.1), 185 (100), 184 (100), 157 (40), 155 (40), 131 (1.4), 129 (1.5), 104 (3.6), 75 (24)

[a] Satisfactory microanalyses obtained for all new compounds: C ± 0.24; H ± 0.14; N ± 0.17.
[b] Uncorrected.
[c] **1a** Lit[15a] mp 17°C. **1e** Lit[15a] mp 86–87°C.

Table 3 Compound **2a–e** Prepared[a]

Product	mp (°C)[b]	IR (KBr or film ν (cm^{-1})	^{1}H NMR (CDCl2); δ *J* (Hz)			^{13}C NMR ($CDCl_3$), δ				MS *m/z* (%)
			CH_2	arom	others	CH_2	arom	C=S	others	
2a	110–112	3406, 3192, 3157, 2105, 1606, 1511, 1263, 1104	4.15 (s, 2 H)	7.3–7.7 (m, 5 H)	3.86 (s, 3 H) 6.62 (s, 2 H) 8.77 (s, 1 H)	55.1	127, 130.1, 130.9, 135.8	179.4	147.4	235 (M^+ + 1, 1), 234 (M^+, 7), 177 (100), 136 (6), 103 (14), 77 (21), 60 (15)
2b	125–126	3422, 3270, 3160, 2100, 1600, 1498, 1248, 1106	4.12 (s, 2 H)	7.02 (d, 2 H, *J* = 8.8) 7.26 (d, 2 H, *J* = 8.8)	3.84 (s, 3 H) 6.4 (s, 2 H) 8.8 (s, 1 H)	55.2	115.5, 122, 128.7, 147, 161.3	179.3	55.4	264 (M^+, 3), 208 (100), 166 (8), 133 (25), 77 (8), 60 (16).
2c	126–128	3415, 3256, 3167, 2101, 1604, 1500, 1293, 1107	4.13 (s, 2 H)	7.22 (d, 2 H, *J* = 8.9) 7.54 (d, 2 H, *J* = 8.9)	2.39 (s, 3 H) 6.58 (s, 2 H) 8.76 (s, 1 H)	55	126.9, 130.7, 132.5, 140.9, 143.9	179.5	21.3	249 (M^+ + 1, 1), 248 (M^+, 4), 192 (100), 150 (12), 118 (22), 91 (24), 75 (12), 60 (24).
2d	157–159	3426, 3282, 3170, 2112, 1604, 1488, 1268, 1092	4.13 (s, 2 H)	7.26 (d, 2 H, *J* = 8.5) 7.52 (d, 2 H, *J* = 8.5)	6.45 (s, 2 H) 8.65 (s, 1 H)	55.3	128.4, 128.6, 130.6, 137.4, 146.0	179.6		270 (M^+ + 2, 1), 268 (M^+, 5), 214 (34), 212 (100), 170 (5), 139 (7), 137 (18), 111 (12), 102 (13), 75 (12), 60 (17).
2e	159–160	3428, 3282, 3170, 2114, 1603, 1502, 1284, 1114	4.13 (s, 2 H)	7.19 (d, 2 H, *J* = 8.4) 7.69 (d, 2 H, *J* = 8.4)	6.45 (s, 2 H) 8.62 (s, 1 H)	54.6	124, 128.6, 132.3, 129.3, 145	178.9		314 (M^+ + 2, 3), 312 (M^+, 3), 258 (76), 256 (77), 183 (22), 181 (21), 155 (18), 157 (17),102 (66), 75 (74), 60 (100), 104 (3.6), 75 (24)

[a] Satisfactory microanalyses obtained for all new compounds: C ± 0.22, H ± 0.17, N ± 0.21.
[b] Uncorrected.

crude reaction mixture was detected by reaction with monochloroacetic acid and sodium 1,2-naphthoquinone-4-sulfonate.[7] The total consumption of current, determined by coulometry, was 2 F mol^{-1}.

These *N*-substituted imidazole-2-thiones can be obtained in a one-pot reaction. It is not necessary to work at a very low substrate concentration, as in the case of phenacyl bromide semicarbazones because of the higher reactivity of the C=S versus the C=O group towards the electrogenerated nucleophile.

Imidazolethiones have been used as polymerization initiators[8] or as vulcanization accelerators[9] of neoprene rubber. Some 4-aryl-2-imidazolethiones have been employed in medicine as antidepressants,[10] other have shown antimicrobial,[11] antibacterial[12] or analgesic[13] activity. Thus 4-phenylimidazolidine-2-thione is an inhibitor of human alkaline phosphatase and diamine oxidase.[14]

The electrolyses were carried out using an Amel potentiostat Model 552 with an electronic integrator Amel Model 721. Mass spectra (EI, ionizing voltage 70 eV) were determined using a Hewlett-Packard Model 5988A mass-selective detector equipped with a Hewlett-Packard MS Chem Station. IR spectra of the compounds were recorded as dispersions in KBr or as film on NaCl plates, on a Perkin-Elmer Model 583 spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) spectra were recorded on a Varian Unity 300 apparatus with $CDCl_3$ (^{1}H, ^{13}C) as internal standard. Melting points were determined on a Reichert Thermovar microhot stage apparatus, and are uncorrected. Elemental analyses were performed on a Perkin-Elmer Model 240-B analyzer. Cyclic voltammetric potentials were determined on a Metrohm apparatus Model 663 VA Stand and a Scanner VA E612. The potential values are given in volts. Analytical HPLC was performed on a Hewlett-Packard 5033 instrument, using a reverse phase column and 80% MeOH/H_2O as the eluent. All products were purified by silica gel 60 (230–400 mesh) using toluene/MeOH (20:1) or (40:1) as eluent.

Phenacyl bromides and the thiosemicarbazide are commercially available and were used without purification. Phenacyl azides were prepared according to the general method[15] with the following modifications: solutions of phenacyl bromides (25 mmol) in MeOH (40 mL) were poured over an aqueous solution of NaN_3 (1.63 g, 25 mmol, 40 mL) in an ice bath. After 2 h the phenacyl azides **1** were obtained in almost quantitative yields by removing the solvent in vacuum to dryness, extracting the crude mixture with Et_2O (80 mL)

Table 4 Compounds **3a–e** Prepared[a]

Product	Ar	Yield (%) (mg)	mp (ºC)[b]	IR (KBr or film) ν (cm^{-1})	MS *m/z* (%)	^{1}H NMR ($CDCl_3$); *δ*, *J* (Hz)					^{13}C NMR ($CDCl_3$), δ				
						CH_3	arom	CH=	NH	others	CH=	arom	C=S	CH_3	others
3a	C_6H_5	78 (227)	130–132	3059, 2924, 1601, 1555, 1443, 1325, 1271, 1129, 1053, 763, 691, 631	293 (M^+, 53), 278 (10), 193 (53), 178 (100), 149 (19), 134 (66), 133 (26), 118 (50), 103 (42), 91 (50), 77 (98).	2.22 (s, 3 H)	7.27–7.4 (m, 6 H) 7.75–7.8 (m, 4 H)	6.9 (s, 1 H)	8.9 (br s, 1 H)		103.9	125.9, 127.7, 128.2, 128.4, 128.6, 128.9, 134.8, 137.7, 145.9, 151.4	169.2	12.9	
3b	4-Me OC_6H_4	70 (247)	165–167	3109, 2926, 1608, 1568, 1510, 1250, 1175, 1029, 832	353 (M^+, 45), 205 (12), 164 (49), 148 (100), 134 (27), 121 (16), 103 (8), 92 (35), 77 (40).	2.2 (s, 3 H)	6.92 (d, 4 H, *J* = 8.7) 7.73 (d, 4 H, *J* = 8.7)	6.75 (s, 1 H)	8.75 (br s, 1 H)	3.82 (s, 3 H) 3.85 (s, 3 H)	102	113.8, 114, 127.2, 127.3, 128, 130.5, 145.7, 151.2, 159.4, 160.4	169.3	12.8	55.3
3c	4-Me C_6H_4	74 (237)	142–145	3028, 2923, 1611, 1559, 1510, 1449, 1340, 1273, 1127, 1054, 819, 729, 609	321 (M^+, 62), 306 (7), 203 (16), 189 (22), 174 (11), 148 (53), 147 (39), 132 (100), 118 28), 103 (7), 91 (89), 77 (8), 65 (34).	2.16 (s, 3 H)	7.2–7.26 (m, 4 H) 7.6–7.8 (m, 4 H)	6.84 (s, 1 H)	9.25 (br s, 1 H)	2.36 (s, 3 H) 2.38 (s, 3 H)	103	125.8, 129.1, 129.3, 129.4, 132.2, 135, 137.5, 139, 146.1, 151.5	169.4	12.9	21.2
3d	4-Cl C_6H_4	76 (275)	148–150	3068, 2927, 1600, 1556, 1490, 1474, 1340,1263, 1139, 1088, 1010, 841, 726, 693	363 (M^+ + 2,2), 361 (M^+, 2), 291 (6), 289 (8), 229 (35), 227 (91), 214 (34), 212 (100), 169 (16), 167 (46), 152 (48), 113 (16), 111 (45), 76 (57), 75 (64), 60 (46).	2.22 (s, 3 H)	7.3–7.4 (m, 4 H) 7.7–7.8 (m, 4 H)	6.9 (s, 1 H)	8.9 (br s, 1 H)		104.4	127.2, 128.7, 128.8, 132.2, 133.3, 133.5, 135.1, 136.1, 144.8, 150.4	169.1	12.7	

Table 4 (continued)

Product	Ar	Yield (%) (mg)	mp (ºC)[b]	IR (KBr or film) ν (cm^{-1})	MS *m/z* (%)	^{1}H NMR ($CDCl_3$); δ, *J* (Hz)					^{13}C NMR ($CDCl_3$), δ				
						CH_3	arom	CH=	NH	others	CH=	arom	C=S	CH_3	others
3e	4-Br C_6H_4	76 (342)	213–215	3045, 2922, 1600, 1550, 1480, 1392, 1268, 1072, 1004, 824, 728	453 (M^+ +4), 451 (M^+ + 2,12), 449 (M^+, 7), 379 (17), 256 (25), 254 (25), 196 (44), 174 (100), 157 (67), 155 (66), 102 (86), 77 (90), 76 (92), 51 (42).	2.18 (s, 3 H)	7.46–7.6 (m, 4 H) 7.6–7.7 (m, 4 H)	6.9 (s, 1 H)	8.8 (br s, 1 H)		104.5	121.7, 123.3, 127.4, 131.6, 131.7, 132.8, 133.6, 136.5, 145, 150.3	169.3	12.8	

[a] Satisfactory microanalyses obtained for all new compounds: C ± 0.31, H ± 0.16, N ± 0.21.
[b] Uncorrected.

and H_2O (80 mL) and drying the ethereal solution with $MgSO_4$. Physical and spectroscopic properties of **1** are summarized in Table 2.

Phenacyl Azide Thiosemicarbazones 2; General procedure
A solution of **1** (20 mmol) in MeOH (20 mL) was slowly added dropwise in MeOH/H_2O (80 mL, 1:1) and 5% HCl (2 mL) to a solution of thiosemicarbazide (3.64 g, 40 mmol) under rapid stirring below 10 ºC. The stirring was maintained during 24 h to complete the reaction. The quantitatively precipitated solids **2a–e** was isolated by suction and crystallized from EtOH. Physical and spectroscopic properties of **2** are summarized in Tables 3.

Electrosynthesis of Imidazole-2-thiones 3; General Procedure
The electrochemical reductions were carried out using a concentric cell with two compartments separated by a porous (D3) glass tubing diaphragm and equipped with a magnetic stirrer. The solvent supporting electrolyte (SSE) was DMF 0.05M in $LiClO_4$. Anhyd solid K_2CO_3 (2.0 g, 145 mmol) was added to the anodic compartment for "in situ" neutralization of the generated $HClO_4$. Anode: platinum. Anolyte: $LiClO_4$ (0.42 g, 4.0 mmol) in DMF (≤ 0.01% H_2O) (10 mL). Cathode: mercury pool (20 cm^2). Catholyte: $LiClO_4$ (1.5 g, 14 mmol) and the corresponding thiosemicarbazone (2.0 mmol) in anhyd DMF (30 mL). A constant cathodic potential between –1.68 and –1.89 V vs. SCE (depending on the nature of **2**) was applied. The reaction time was about 1 h. At the end of the electrolysis (it was considered finished when the current fell down to zero) the cathodic solution was poured onto ice water (500 mL). After 12 h, the precipitated solid was filtered and dried under reduced pressure and chromatographed on a silica gel (17 × 2.5 cm) column, using toluene/MeOH (20:1) as eluent. Solid compounds were crystallized from EtOH. Compounds **3a–e** are described now for the first time (Table 4).

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