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# Reaction of carbon disulfide with 2-bromoimidazolium salts. Novel bicyclic mesoionic thiazolo[3,2-*a*]imidazoles

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ABSTRACT

A new class of thiazolo[3,2-*a*]imidazole derivatives is obtained in good yields, by reacting 1-methyl-2-bromoimidazolium salts bearing $N^+$-$CH_2COAr$, $N^+$-$CH_2COMe$, $N^+$-$CH_2COOMe$, or $N^+$-$CH_2CN$ fragments, with carbon disulfide in the presence of $Et_3N$ at room temperature. The mesoionic structures of these compounds are established by NMR spectroscopy and by single-crystal X-ray analysis.



*N*-Phenacyl-2-halogenopyridinium salts **I** are useful intermediates for the synthesis of bicyclic heterocycles with a bridgehead nitrogen atom,[1] in particular imidazo[1,2-*a*]pyridinium salts **II**,[2] oxazolo[3,2-*a*]pyridinium salts **III**,[3] and thiazolo[3,2-*a*]pyridines **IV** (Fig. 1).[4]

The use of heteroanalogs of salts **I**, with a different heterocyclic ring (thiazolium or isoquinolinium) and/or heteroatoms instead of halogen was successful.[5] However, the reactivity of *N*-phenacyl-2-halogenoimidazolium salts **1** has not been studied.

In continuation of our ongoing program related to the synthesis of imidazolium salts,[6] we report herein the reaction of *N*-phenacyl-2-bromoimidazolium bromide (**1**) with carbon disulfide in the presence of triethylamine. In addition, this work was extended to analogs with $N^+$-$CH_2COMe$, $N^+$-$CH_2COOMe$, and $N^+$-$CH_2CN$ fragments.

Following the standard methodology,[6a] compounds **1a**–**d** were obtained in good yields by reacting 1-methyl-2-bromoimidazole with 1.5 equiv of different 2-bromoacetophenones at reflux in acetonitrile (Scheme 1). In a similar manner, when 1.2 equiv of bromoacetone, methyl bromoacetate, or bromoacetonitrile was used as quaternization agents, the imidazolium compounds **1e**–**g** were obtained.

Note that no purification was needed and compounds **1a**–**g** were isolated in moderate to good yields (47–95%) by simple filtration after reducing the solvent volume.

Next, inspired by the work of Babaev et al.,[7] the action of carbon disulfide, in the presence of triethylamine, was evaluated on *N*-phenacyl-2-bromoimidazolium bromide (**1a**) (EWG = $COC_6H_5$) as a model reaction.[8] The results showed that the starting material had been consumed (TLC) (Table 1, entry 1) after 30 min.

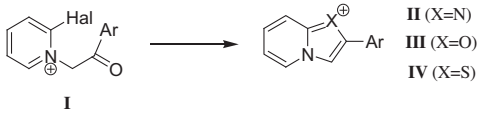
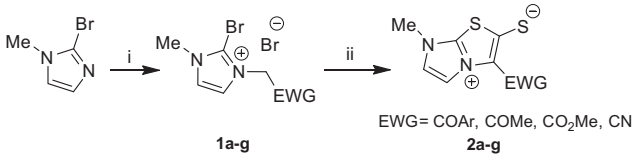



**Figure 1.** Bicyclic heterocycles with a bridgehead nitrogen atom.




**Scheme 1.** Reagents and conditions: (i) $BrCH_2EWG$ (1.2–1.5 equiv), MeCN, reflux, 12 h; (ii) $CS_2$, $Et_3N$, MeCN, 3 h (Ar is defined in Table 1).

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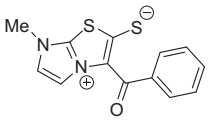
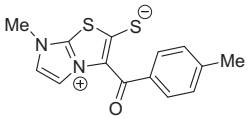
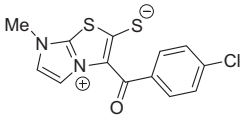
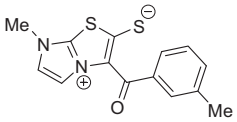
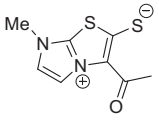
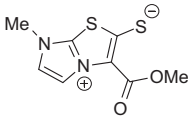
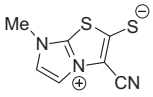
**Table 1**
The mesoionic thiazolo[3,2-*a*]imidazoles prepared

| Product | Structure | Yield[a] (%) |
|---|---|---|
| **2a** |  | 64 |
| **2b** |  | 79 |
| **2c** |  | 55 |
| **2d** |  | 81 |
| **2e** |  | 55 |
| **2f** |  | 46 |
| **2g** |  | 82 |

[a] Yields of isolated pure products.

7-Methyl-3-benzoylthiazolo[3,2-*a*]imidazolium-2-thiolate (**2a**) was obtained in 64% yield.

To demonstrate the efficiency and the scope of the present method, we performed the cyclocondensation reaction using substrates with different electron-withdrawing groups. As shown in Table 1, substrates containing a substituted benzoyl (**1a–d**), acetyl (**1e**), ester (**1f**), or nitrile (**1g**), gave the corresponding products **2a–g** in moderate to high yields under the same reaction conditions.

By analogy to the previously reported mechanism,[7] the $CH_2$ group bearing the electron-withdrawing group in imidazolium salts **1** reacts as a nucleophile with carbon disulfide to give an enethiol betaine that, via intermolecular heterocyclization, replaces the halogen atom at position 2 in the imidazole ring, affording this new class of thiazolo[3,2-*a*]imidazolium-2-thiolates.

The structure of compound **2a**, as a representative example, was elucidated by detailed NMR studies.[8] Unlike the $^1$H NMR spectrum of starting imidazolium salt **1a**,[9] no signal for the methylene group protons (–$CH_2$COAr) was detected for **2a**. At the same time, no significant differences were observed in the chemical shifts of the aromatic protons. However, comparison of the $^{13}$C NMR spectra of compounds **1a** and **2a** showed a significant difference at C6. Thus for the imidazolium salt **1a**, the signal for C6 was detected at 56.6 ppm, while for compound **2a**, it appeared in the region of 139.3 ppm.

The structures of products **2b–g** were established by analogy and by comparison of their $^1$H NMR and $^{13}$C spectra with those of compound **2a**.

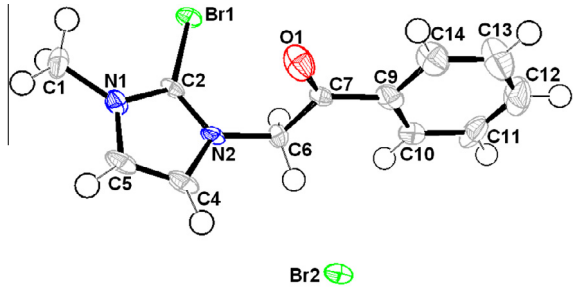



**Figure 2.** ORTEP plot of the X-ray crystal structure of **1a** and the atomic numbering scheme (thermal ellipsoids are drawn at the 50% probability level).[10]

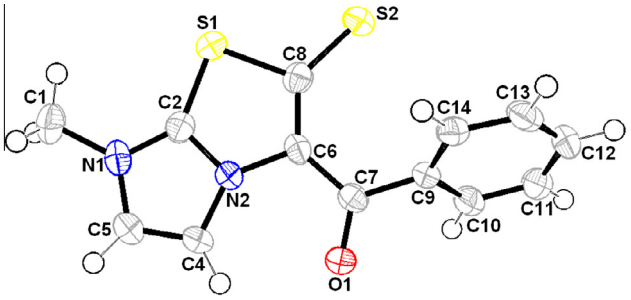



**Figure 3.** ORTEP plot of the X-ray crystal structure of **2a** and the atomic numbering scheme (thermal ellipsoids are drawn at the 50% probability level).[10]

**Table 2**
Selected bond lengths for characterized compounds **1a** and **2a**

| Bonds length (Å) | **1a** | **2a** |
|---|---|---|
| C1–N1 | 1.460(5) | 1.467(3) |
| N1–C2 | 1.330(5) | 1.346(3) |
| C2–N2 | 1.332(5) | 1.342(3) |
| N2–C4 | 1.376(5) | 1.391(3) |
| C4–C5 | 1.344(6) | 1.349(3) |
| C5–N1 | 1.383(5) | 1.378(3) |
| N2–C6 | 1.457(5) | 1.434(3) |
| C6–C7 | 1.511(5) | 1.440(3) |
| C7–O1 | 1.217(4) | 1.243(3) |
| C7–C9 | 1.477(5) | 1.494(3) |
| C2–Br1 | 1.851(4) | – |
| C6–C8 | – | 1.405(3) |
| C8–S1 | – | 1.804(2) |
| C2–S1 | – | 1.710(3) |
| C8–S2 | – | 1.673(3) |

The molecular structures of **1a** and the bicyclic heterocycle with a bridgehead nitrogen atom **2a**, were established by single crystal X-ray diffraction analyses.

Suitable crystals of **1a** and **2a** for X-ray experiments were obtained by slow evaporation from, respectively, methanol/$CHCl_3$ and ethanol/$CH_2Cl_2$ solutions at room temperature. The structures of compounds **1a** and **2a** are shown in Figures 2 and 3, and selected bond lengths for **1a** and **2a** are presented in Table 2.

The crystal structure of mesoionic compound **2a** was compared with the precursor **1a**. Examination showed that the bond lengths of C1–N1, N1–C2, C2–N2, and N2–C4 in **2a** were longer than in compound **1a**. However, the two C–N bond lengths, N2–C6 (1.434(3) Å) and C5–N1 (1.378(3) Å) in **2a** were shorter than the corresponding bonds in **1a** (N2–C6 (1.457(5) Å) and C5–N1 (1.383(5) Å). It is interesting to note that the C6–C7 bond length in compound **2a** (1.440(3) Å) was shorter than the corresponding

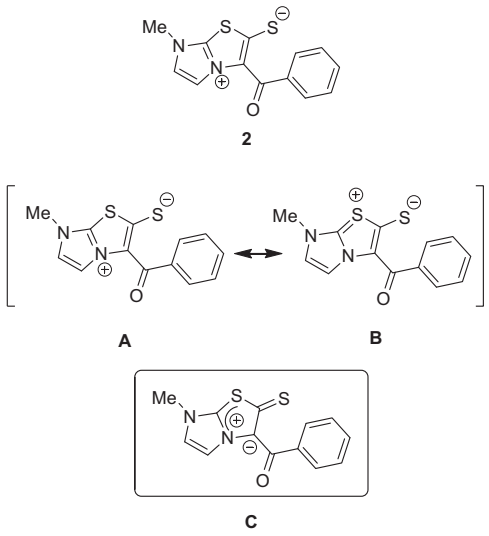



**Figure 4.** Resonance structures **A** and **B**, and ylide character **C** of compound **2**.

bond in compound **1a** (1.511(5) Å). The bond lengths of the phenyl ring and C4–C5 in the imidazole ring were almost unchanged.

The distribution of single and double bonds in the bicyclic compound, 7-methyl-3-(benzoyl)thiazolo[3,2-*a*]imidazolium-2-thiolate (**2a**) was established by analogy with other similar structures.[7,11]

The crystallographic structure of compound **2a** shows that the new heterocyclic compound possesses a bicyclic skeleton with fused thiazole-imidazolium rings. The bicyclic thiazolo[3,2-*a*]imidazole fragment is approximately planar and forms a dihedral angle of a 59.16(5)° with the phenyl ring. The carbonyl group is twisted by 53.11(9)° with respect to the benzene ring. Consequently, the carbonyl group is not conjugated with the phenyl fragment.

In the thiazole fragment, the C2–S1 bond (1.710(3) Å) is shorter than the C8–S1 bond (1.804(2) Å), which indicates the electron delocalization in the thiazole ring. The C2–S1 bond is conjugated with the lone electron pair of the bridging nitrogen atom N2, whereas the C8–S1 bond is not affected by any conjugation.

Therefore, it is more correct to view the structure of **2** as a combination of the two resonance contributors **A** and **B** with alternating single and double bonds. Thus, the delocalization takes place between $N2^{+}$=C2–S1 and N2–C2=$S1^{+}$fragments of the five-membered ring (Fig. 4).

The exocyclic C8–S2 bond has the shortest length (1.673(3) Å) and has, in fact, pronounced double bond character (Table 2). Thus, it is incorrect to represent the mesoionic system as a structure with a single C8–S2 bond and the negative charge on the S2 atom.

Consequently, the ylide character **C** of compound **2** (Fig. 4) and the localization of the negative charge on the C6 atom is a more adequate representation (Fig. 4).

In conclusion, we have found that 1-methyl-2-bromoimidazolium salts bearing a $–CH_2COAr$, $–CH_2COMe$, $–CH_2COOMe$, or $–CH_2CN$ fragment at the quaternary nitrogen, react with carbon disulfide in the presence of $Et_3N$ at room temperature to form a previously unknown class of thiazolo[3,2-*a*]imidazoles. $^1H$ and $^{13}C$ NMR spectroscopy and X-ray crystallographic analysis confirmed the structures. A key feature of the reactivity of **1** is the ability to easily replace the halogen atom at C2 via nucleophilic substitution. The simplicity of the present procedure makes it an interesting alternative to other approaches.

## Acknowledgments

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8. *General procedure for the synthesis of thiazolo[3,2-a]imidazoles* ***2****:* $Et_3N$ (2 mL) was added, under vigorous stirring to a suspension of imidazolium salt **1** (1.0 mmol) and $CS_2$ (1 mL) in $CH_3CN$ (5 mL). The mixture was kept at room temperature for 30 min (monitored by TLC). The product formed was isolated as a yellow solid by simple filtration using a Büchner funnel and was washed with 5 mL THF/$H_2O$ (1:1) mixture. The filtrate was concentrated under reduced pressure, $H_2O$ (5 mL) was added and the residue was extracted with $CHCl_3$ (3 × 10 mL). The extracts were collected, washed with $H_2O$ (15 mL) and brine (15 mL), dried over anhydrous $Na_2SO_4$, and the solvent evaporated under vacuum. Purification by silica gel flash column chromatography (EtOAc), afforded an additional 5–10% of the product. (yield: 64% for **2a**), mp = 192 °C. Selected data for **2a**: $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 8.20 (d, $J$ = 2.1 Hz, 1H), 7.89 (d, $J$ = 2.1 Hz, 1H), 7.73–7.69 (m, 2H, Ar), 7.51–7.34 (m, 3H, Ar), (3.96, 3H, *N*–$CH_3$); $^{13}C$ NMR (62.9 MHz, DMSO-$d_6$) $\delta$ 184.6 (C=O), 173.4 (C), 139.3 (C), 138.9 (C), 131.5 (CH), 129.3 (2 × CH), 128.0 (2 × CH), 126.2 (CH) 119.6 (C), 116.8 (CH), 35.7 (*N*–$CH_3$).
9. *Selected data for* ***1a****:* $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 8.12–8.07 (m, 3H, Ar), 7.96 (s, 1H, Ar), 7.79 (t, $J$ = 7.2 Hz, 1H, Ar), 7.65 (t, $J$ = 7.3 Hz, 2H, Ar), 6.18 (s, 2H, *N*–$CH_2$), 3.92 (s, 3H, *N*–$CH_3$); $^{13}C$ NMR (62.9 MHz, DMSO-$d_6$) $\delta$ 190.8 (C=O), 135.3 (C), 133.7 (CH), 129.6 (2 × CH), 128.0 (2 × CH), 125.5 (CH), 125.4 (CH), 125.2 (C), 56.6 (*N*–$CH_2$), 37.6 (*N*–$CH_3$).
10. *Crystal structure analysis for* ***1a****:* $C_{12}H_{12}Br_2N_2O$, Mr = 360.06 g mol$^{-1}$, monoclinic, space group $P$ 21/$a$, $a$ = 10.1113(7) Å, $b$ = 13.8160(11) Å, $c$ = 10.4189(8) Å, $\beta$ = 114.006(4)°, $V$ = 1329.60(17) Å$^3$, $Z$ = 4, $\rho_c$ = 1.799 g cm$^{-3}$, F(000) = 704, crystal size: 0.54 × 0.42 × 0.36 mm. Crystal structure analysis for **2a**: $C_{13}H_{10}N_2OS_2$, Mr = 274.35 g mol$^{-1}$, monoclinic, space group $P$ 21/$a$, $a$ = 7.8709(8) Å, $b$ = 13.3757(12) Å, $c$ = 12.0879(13) Å, $\beta$ = 106.270(4)°, $V$ = 1221.6(2) Å$^3$, $Z$ = 4, $\rho_c$ = 1.492 g cm$^{-3}$, F(000) = 568, crystal size: 0.24 × 0.07 × 0.06 mm. Crystallographic data (excluding structure factors) for these compounds have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 923502 for **1a** and CCDC 923503 for **2a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif./cif.
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