

Stepwise Cycloadditions of Mesoionic Systems: Thionation of Thioisomünchnones by Isothiocyanates

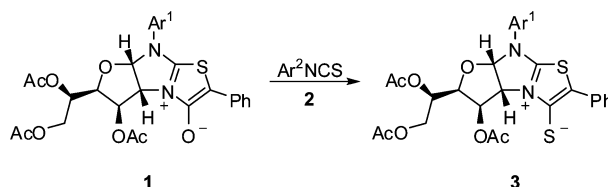
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ABSTRACT



An unusual thionation strategy of mesoionic compounds with aryl isothiocyanates enables a facile synthesis of 1,3-thiazolium-4-thiolate systems. The mechanistic pathway of such a transformation most likely involves a stepwise 1,3-dipolar cycloaddition, which is supported by theoretical calculations performed with a two-layer hybrid method (B3LYP/6-31G(d):PM3).

Mesoionic heterocycles, which may exhibit large dipole moments and optical susceptibilities, are attracting considerable interest as second- and third-order nonlinear systems and near-infrared dyes, thus finding a potential niche in optoelectronics.¹ The synthetic manipulation of these heteroaromatics is invariably associated to their dipole character in cycloaddition reactions, a fact successfully exploited in natural products chemistry and in the construction of other five- and six-membered rings.² Recent developments with a usual family of mesoionic dipoles, 1,3-thiazolium-4-olates (generally referred to as thioisomünchnones), have unveiled further reactivity patterns that give rise to three- and four-membered rings, hitherto unknown in 1,3-dipolar cycloadditions.³

This Letter also discloses an unexpected thionation of thioisomünchnones by reaction with aryl isothiocyanates leading to the corresponding 1,3-thiazolium-4-thiolates. Although the reaction of some mesoionic rings with both isocyanates and isothiocyanates has been known for many years,⁴ detailed studies by Potts and associates suggested the formation of stable 1:1 cycloadducts with such heterocumulenes.⁵ In the 1980s, however, Hamaguchi and Nagai were able to demonstrate the mesoionic nature of these adducts and proposed a pathway to explain their formation.⁶

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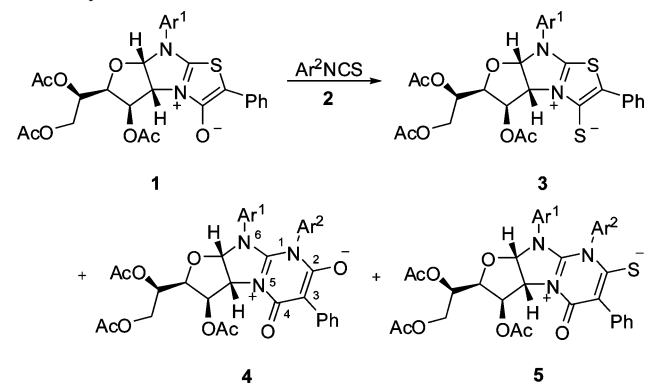
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Table 1. Reaction of Thioisomünchnones **1** with Aryl Isothiocyanates



entry	Ar ¹	Ar ²	compound (% yield)		
1	Ph	Ph	3a (23)	4a (16)	
2	Ph	4-MeOC ₆ H ₄	3a (16)	4b (4)	5b (12)
3	Ph	4-NO ₂ C ₆ H ₄	3a (64)	4c (20)	
4	4-MeOC ₆ H ₄	Ph	3b (32)	4d (4)	
5	4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	3b (26)		5e (12)
6	4-MeOC ₆ H ₄	4-NO ₂ C ₆ H ₄	3b (60)	4f (2)	
7	4-NO ₂ C ₆ H ₄	Ph	3c (7)	4g (5)	5g (37)
8	4-NO ₂ C ₆ H ₄	4-MeOC ₆ H ₄	3c (5)		5h (22)
9	4-NO ₂ C ₆ H ₄	4-NO ₂ C ₆ H ₄	3c (40)	4i (7)	5i (31)

Like other cases of chemical serendipity, the present yet conceptually simple O/S exchange also provides new structural and mechanistic insights into the unique character of thioisomünchnones as masked dipoles, which should elicit additional synthetic pursuits.

Compound **1a** (Ar¹ = Ph) was chosen as the parent thioisomünchnone; this is a stable, inherently chiral mesoionic structure that can be easily generated from a carbohydrate precursor.⁷ Moreover, previous studies have proven the versatility of this substance toward diverse dipolarophiles en route to other polycyclic systems derived from α -pyridones,⁸ chiral thiiranes,⁹ 1,2,4-triazines,¹⁰ and 4-oxopyrimidinium-6-olates (e.g., **4**).¹¹

With the aim of harnessing the cycloadditive methodology in the synthesis of new mesomeric betaines containing exocyclic sulfur atoms, we carried out the reaction of thioisomünchnones **1a–c** with aryl isothiocyanates (**2**) in

dichloromethane at room temperature. Reaction times were established by monitoring the disappearance of the reagents by thin-layer chromatography (benzene–acetonitrile, 3:1). In all cases, the corresponding 1,3-thiazolium-4-thiolate systems **3a–c** could be isolated along with minor amounts of the mesomeric betaines **4** (Table 1). Remarkably, compounds **5** were equally isolated from the reaction mixtures, in low to moderated yields, when 4-methoxyphenyl isothiocyanate was employed as dipolarophile (entries 2, 5, and 8) or when an electron-withdrawing group (4-nitrophenyl) was linked to the imidazolinic nitrogen of **1** (entries 7–9).

It is noteworthy that conversion of **1** into **3** could not be achieved by usual thionation reagents (e.g., Lawesson's reagent).¹²

Suitable crystals for X-ray diffraction could be obtained for compound **3a**, thereby revealing the mesoionic nature of this tricycle (Figure 1).

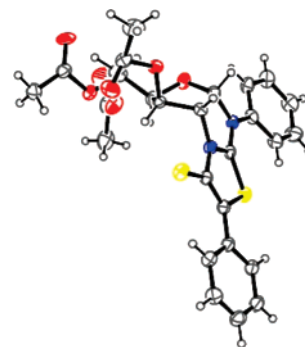


Figure 1. X-ray structure of **3a**.

As mentioned above, betaines **4** had also been obtained by direct reaction of **1** with the corresponding aryl isothiocyanates and their structures unambiguously inferred from spectroscopic data.¹¹ In the present study, the solid-state structure of **4a** could also be solved by X-ray crystallography, although crystal data revealed a reasonable static molecular disorder, which presumably arises from the unsteady configuration of the imidazolinic nitrogen. Individual molecular structures of both invertomers, which are found in 4:1 ratio at the crystal, could be computationally disentangled (Figure 2).

The aryl groups attached to the nitrogen atoms of the heterocycle adopt an offset stacked arrangement in both invertomers, thus behaving as a potential class of dynamic molecular tweezers at room temperature.¹³

¹H NMR spectra of compounds **4**, recorded at room temperature, evidenced the magnetic nonequivalence of the *ortho* and *meta* *N*-aryl protons in both CDCl₃ and DMSO-*d*₆. These facts point to the existence of a slow nitrogen

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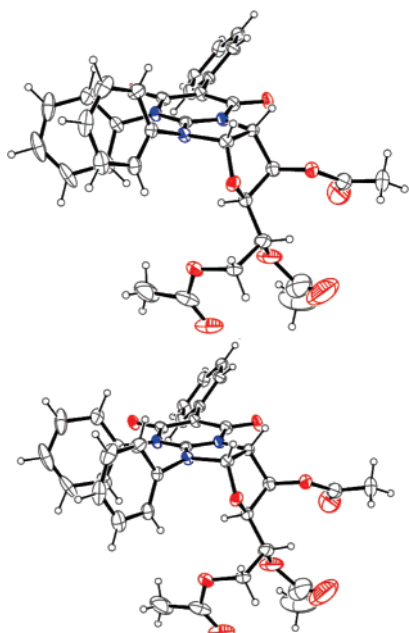


Figure 2. ORTEP for the major (up) and minor (down) invertomers of **4a**.

inversion and/or a slow rotation of *N*-aryl bonds on the NMR time-scale. Variable temperature experiments allowed us to calculate, for instance, a rotational barrier of 18.7 kcal.mol⁻¹ for the *N*-aryl bond of **4d** in DMSO-*d*₆.

However, ¹H and ¹³C NMR spectra of betaines **4** showed only one signal set for the sugar framework at temperatures ranging from 295 to 235 K, thus evidencing the fast interconversion of both invertomers in CDCl₃ solution. On the other hand, chemical shifts of the H-1', H-2', and H-3' sugar protons are strongly dependent on concentration (see Supporting Information). At first glance and as concentration increases, one could envisage the existence of intermolecular interactions that would be analogous to those encountered in the crystalline state, where aryl groups at C-3 and N-1 of the imidazopyridinium system of vicinal molecules are in edge to face close contact (see Supporting Information).¹⁴ Accordingly, such an interaction between adjacent molecules can be viewed as a dimerization process, for which the corresponding equilibrium can be formulated.

Equation 1 gives the observed chemical shift as a function of the monomer (δ_m) and dimer (δ_d) chemical shifts and the equilibrium constant (*K*), where *c* is the concentration.¹⁵

$$\delta_{\text{obs}} = \delta_m + (\delta_d - \delta_m)[1 + 4cK - (1 + 8cK)^{1/2}]/4cK \quad (1)$$

A further iterative analysis of the dilution plot of the H-1' proton versus δ_m , δ_d , and *K* variations gave optimal solutions

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for δ_m and δ_d of 5.97 and 5.41 ppm, respectively, with an rms error of 0.003 and having *K* = 23.6 M⁻¹. Figure 3 shows

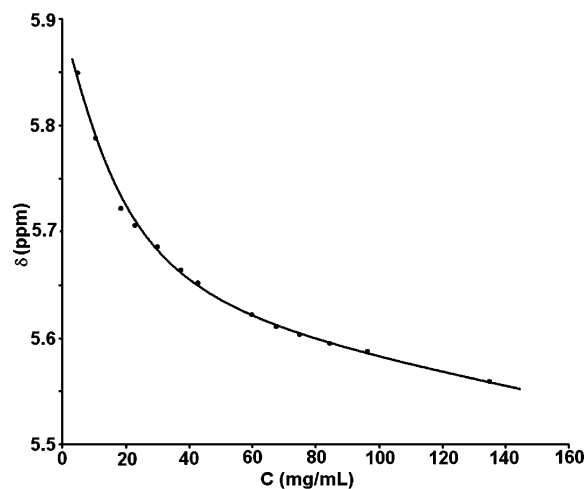


Figure 3. Plot of δ (ppm) versus *c* (mg/mL) for the H-1' signals of **4b**.

the calculated curve and the observed proton shifts for the H-1' signals of **4b**.

The structure of compounds **5** was deduced from their NMR spectra, which are analogous to those of **4**, although the pseudothiocarbonyl group, which resonates at ~178 ppm, shifts downfield (~25 ppm) the signal of the adjacent C-Ph. Elemental analyses and mass spectra agree with the thionation of the pyrimidium ring, and the sulfur position was established by proving that **3** does not react with aryl isocyanates under the same conditions that produce the betaine derivatives **5**.

Although a conventional 1,3-dipolar cycloaddition of **1** with the aryl isothiocyanate, followed by the removal of sulfur from the initial cycloadduct **6**, could explain the formation of **5**, the isolation of **4** equally uncovers the transient existence of the corresponding aryl isocyanate, which must be formed during the conversion of **1** into **3**. Scheme 1 shows a putative reaction mechanism that involves

Scheme 1. Possible Reaction Mechanism

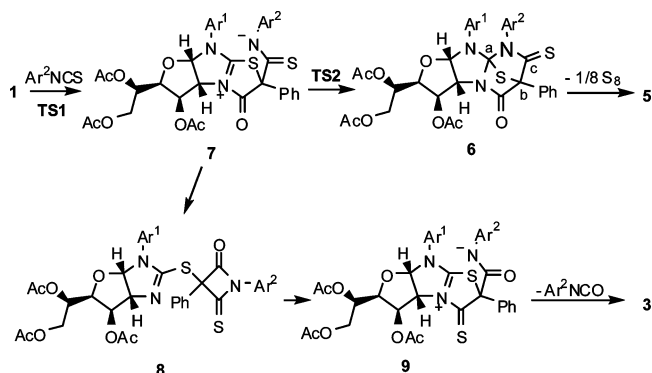
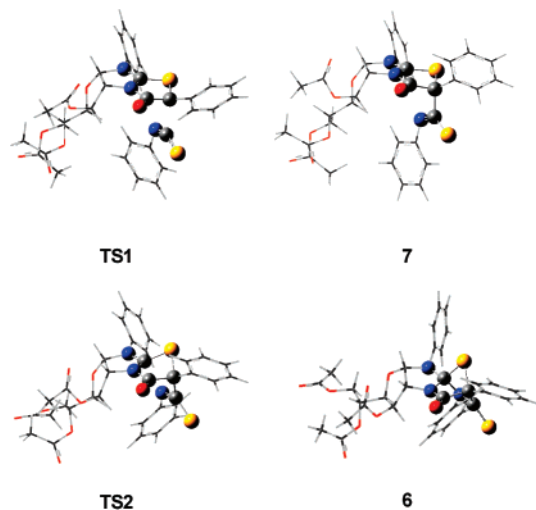


Table 2. 1,3-Dipolar Cycloaddition of the Thioisomünchnone **1a** with Phenyl Isothiocyanate^a



structure ^b	energy ^c	C _a -N	C _a -S	C _b -C _c	C _b -S
TS1	18.03	3.107	1.705	2.226	1.842
7	9.32	2.985	1.701	1.615	1.962
TS2	15.50	2.186	1.766	1.600	1.925
6	-1.04	1.488	1.897	1.565	1.903

^a Ball and stick and wireframe formats correspond to the layers treated at the B3LYP/6-31G(d) and PM3 levels, respectively. ^b Atoms C_a, C_b, and C_c are identified in the structure **6** of Scheme 1. ^c Relative to electronic energy of the reagents, in kcal mol⁻¹.

the stepwise 1,3-dipolar cycloaddition of **1** and the aryl isothiocyanate. The zwitterionic intermediate **7** could lead to the cycloadduct **6**, and then to betaine **5** or the azetidine **8** by nucleophilic attack of the nitrogen onto the next carbonyl group. The opposite process, starting from **8**, would justify the formation of both **3** and the corresponding aryl isocyanate, which is required for the synthesis of betaines **4**.

The mechanistic insight outlined in Scheme 1 appears to be consistent with the above experimental results (Table 1). Thus, an electron-withdrawing group on Ar¹ increases the

electrophilicity of the C(a) atom (entries 7–9), while an electron-releasing substituent on Ar² increases the nucleophilicity of its contiguous N atom (entries 2, 5, 8). Overall, the synergy of both effects results in a higher yield of compound **5**.

In stark contrast, more electron-donating groups on Ar¹ (entries 1–6) favor a preferential attack of the N atom to the carbonyl group of **7**, thus accounting for the formation of **8** and subsequently of **3**.

The presence of electron-withdrawing substituents on Ar² increases the global reaction yield, presumably due to the enhanced electrophilicity of the thiocarbonyl group.

Further experimental support of this pathway comes from the fact that **5** could not be obtained by reaction of **4** with aryl isothiocyanates.

In order to clarify the concertedness degree of the 1,3-dipolar cycloaddition, we have investigated the geometries and energies associated with the reactants, products and transition structures that take place along the reaction of **1a** and PhNCS using an ONIOM(B3LYP/6-31G(d):PM3) method.¹⁶ Table 2 shows the transition structures **TS1** and **TS2**, the high-energy zwitterionic intermediate **7**, and the cycloadduct **6** located for the *endo* 1,3-dipolar cycloaddition of **1** and **2**. Comparable structures were also found for the *exo* approach of the reagents.¹⁷

In conclusion, this contribution highlights a facile and unexpected transformation of 4-olate- into 4-thiolate-based mesoionic rings, together with betaine derivatives, which overall reveal the existence of a cascade cycloaddition. Further structural investigations and synthetic applications are under way.

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Supporting Information Available: Synthetic procedures, ¹H and ¹³C NMR spectra for all new compounds, crystal data for compounds **3a** and **4a** in CIF format, and computational data for both intermediates (**6** and **7**) and transition structures (**TS1** and **TS2**). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(17) Since **3** could also be generated by a [2 + 2] cycloaddition of **1** with ArNCS, we have computed this process at the same level of theory, finding instead higher (~2-fold) activation energy barriers.