Exploiting Synthetic Chemistry with Mesoionic Rings: Improvements Achieved with Thioisomünchnones†

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Received December 2, 2004

ABSTRACT

The chemistry of mesoionic rings, especially their use as masked dipoles, has been a fruitful area of research since the late 1950s. With recent advances in the control of regio- and stereochemistry, the dipolar cycloaddition led to widespread application. In this Account, we illustrate our contribution employing thioisomünchnones, a class of mesoionics that has found use in creating a series of heterocyclic systems hitherto inaccessible by conventional 1,3-dipolar cycloaddition. We also provide some rationalizations from computations and comment on future directions

A Bit of Background

Mesoionics are five-membered heterocycles that cannot be satisfactorily represented by Lewis structures not involving charge separation. This implies a certain degree of aromatic character (in terms of $[4n + 2]\pi$ electrons) in the positively charged ring, which is counterbalanced by a negatively charged exocyclic atom. It should also be pointed out that this definition of mesoionics does not exclude five-membered rings fused to other heterocycles. Although these ring systems can now be found in some advanced textbooks of organic chemistry,[1] mesoionic compounds are still viewed as exotic structures, even within the heterocyclic community. It took a long time before mesoionics were judiciously ranked among five-membered heteroaromatics, thereby excluding other dipolar species and especially the otherwise isoelectronic six-membered mesomeric betaines. The obvious need for clarification grew out of the work of Ollis and his associates since the late 1940s, who divided mesoionics into two classes of heterocycles (Figure 1).[2] Here, A, B, C, D, E, and F represent substituted carbon atoms or heteroatoms, and the superscripts denote the number of electrons contributing to the delocalized π-system. In structures **1**, A and C should be either divalent or trivalent heteroatoms, while in **2** such a requirement is fulfilled by the B and C atoms. This restriction is essential to retain a structural usefulness. Thus, inspection of structures **1** tells us that they contain a masked allyl-type dipole that can be unfettered by a 1,3-dipolar cycloaddition with a wide range of dipolarophiles to give complex heterocyclic systems. A key enabling aspect of this freedom is the effectiveness of such a synthetic methodology to solve problems of regio- and stereocontrol, which represent the linchpin of this Account. In stark contrast, structures represented by **2** are simply dipolar species susceptible to ring opening to produce acyclic valence tautomers, which can then undergo further transformations.[2] Consider, for instance, a couple of mesoionics (**1a** and **2a**) containing two sulfur atoms in the ring and an exocyclic oxygen atom, each showing quite distinct chemical properties.

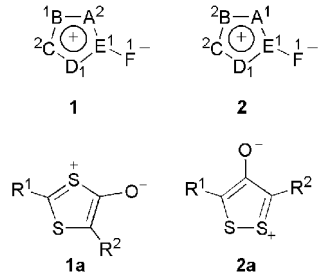

FIGURE 1. The two general types of mesoionic heterocycles.

Compound **1a** (1,3-dithiolium-4-olate) may be represented by charged forms corresponding to the sextet and octet canonical structures of a thiocarbonyl ylide dipole. Such a representation cannot be applied to **2a**, which undergoes protonation on the exocyclic oxygen, a characteristic of heteroaromatic betaines nevertheless.

† In Memoriam Dr. Juan Carlos del Amo.

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10.1021/ar040212r CCC: $30.25
Published on Web 04/12/2005

It is now clear that the term mesoionic has resulted in new vistas of structural representations, as well as in extending the concept of heteroaromaticity. Assuming the structural constraints imposed on mesoionic heterocycles, there is a large number (nearly 230 different structures) of five-membered rings that may be considered mesoionics. In practice, however, the electronegativity of the atoms also imposes further constraints, and as a result, about 50 ring systems can be synthetically accessible. It is especially appealing to detect whether they contain a masked dipole that could be exploited in a synthetic scheme. Common 1,3-dipoles present in the parent heterocyclic system include the azomethine ylide, the azomethine imine, the carbonyl or thiocarbonyl ylides, and the thiocarbonyl imine. Numerous mesoionics contain nitrogen and sulfur as dominant nuclear atoms capable of stabilizing a positive charge. The almost omnipresent exocyclic atom in mesoionics is oxygen. If the system has no betainic character, the oxygen atom will not undergo protonation or alkylation with the exception of strong reagents. Exocyclic imino or carbanoid groups have received less attention, although such mesoionics should no doubt provide attractive results.

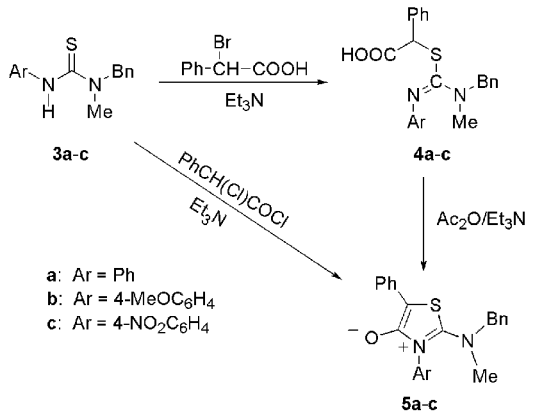
Unravelling of the origins and evolution of mesoionic rings is both delightful and amusing and illustrates how the language has often enriched chemistry. Although the first mesoionics, like other organic milestones, were prepared by the end of the 19th century, chemists realized the significance of their unusual structures only several decades later and proudly dubbed them after geographical places.[3] *Sydnones* (1,2,3-oxadiazolium-5-olates) and *münchnones* (1,3-oxazolium-5-olates) after Sydney and München/Munich, respectively, have become common petnames and shorter surrogates of the corresponding IUPAC terms.

The 1,3-dipolar cycloaddition chemistry of mesoionics has largely been explored and has proven to be a valuable tool in natural product synthesis and for the construction of other heterocycles, especially five- and six-membered systems.[2b,4−6] Some recent improvements include the use of transition metals to prepare mesoionics such as münchnones and isomünchnones,[7] which can further be transformed into biologically interesting molecules.[5,8]

N,N-Dialkylamino Thioisomünchnones

Early in our synthetic program, we were attracted by the variety of 1,3-dipoles that may be obtained from mesoionic systems. Pre-eminent among these are münchnones, which contain an azomethine ylide and their thio analogues: thiomünchnones (1,3-thiazolium-5-olates) and thioisomünchnones (1,3-thiazolium-4-olates). The latter contain a thiocarbonyl ylide within their backbone and, to a large extent, have been the subject of our interest. It is not by chance that, with a few exceptions, the majority of mesoionics contain a nitrogen atom owing to its ability to accept a positive charge, thereby imparting a degree of stability to the ring. It is often necessary to enhance the delocalization still further and surrounding aryl substituents play well such a role.[4,5]

Scheme 1. Ring-Closure Mesoionization from Trisubstituted Thioureas

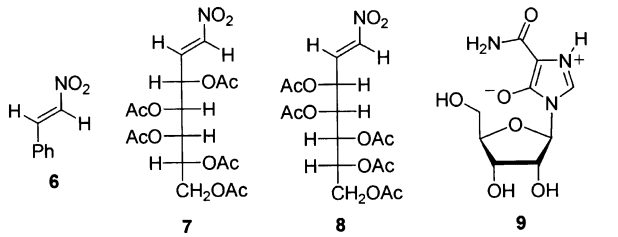


We envisioned that an additional exocyclic nitrogen atom could also lead to stable mesoionics, and as we shall see later, this surmise proved to be true, and moreover, a dialkylamino group also exerted unexpected stereodirecting effects. The scheme was put easily into practice by employing *N,N,N*′-trisubstituted thioureas as starting materials, which reacted with α-bromophenylacetic acid in the presence of Et_3N. This leads to thioglycolic acid intermediates that undergo further cyclodehydration to *N,N*-dialkylamino thioisomünchnones with acetic anhydride/triethylamine. A more straightforward conversion of thioureas **3a**−**c** into the corresponding mesoionics **5a**−**c** can be accomplished with α-chlorophenylacetic acid chloride plus triethylamine (Scheme 1).[9]

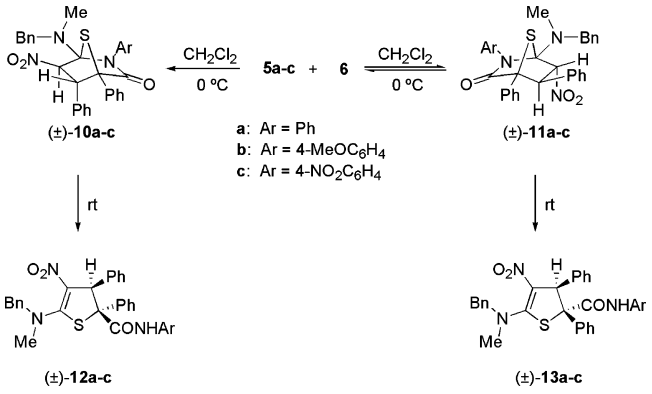
This preparation of mesoionics is actually a variation of an improved method developed by Potts and associates, which utilizes 1,2-bielectrophiles (α-haloacyl halides) and 1,3-binucleophiles such as N-monosubstituted thioamides.[10] The Ac_2O/Et_3N mixture is essential for this reaction to occur smoothly because it is thought that mesoionic formation involves an initial S-alkylation step that requires removal of a proton. It is likely that Et_3N causes the formation of a mixed acetic anhydride with acids **4a**−**c** and these intermediates are involved in the cyclization. With Ac_2O alone, the overall transformation requires high temperatures, while weak bases such as pyridine (pK_a = 5.2) are ineffective. Instead, Et_3N (pK_a = 11.4) promotes "mesoionization" under mild conditions.

Construction of Five- and Six-Membered Rings

Among electron-deficient olefins, nitroalkenes were especially addressed in view of the versatility of a nitro group in organic synthesis. Along with trans-β-nitrostyrene (**6**), the *O*-protected chiral nitroalkenes **7** and **8** derived from



Scheme 2. Formation of Dihydrothiophenes from Thioisomünchnones and *trans*-β-Nitrostyrene



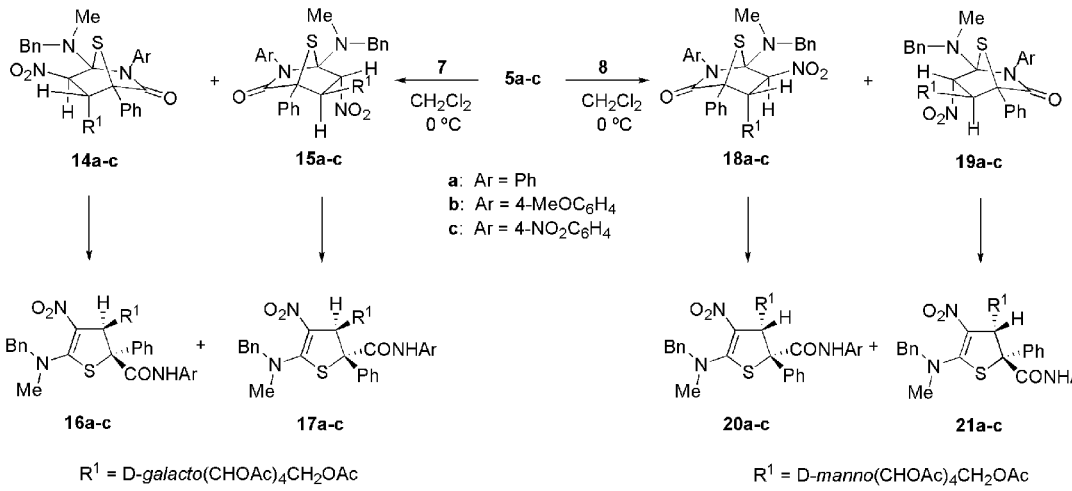
D-galactose and D-mannose, respectively, were explored.[9a] These carbohydrate-templated dipolarophiles would eventually permit facial diastereoselection, also taking advantage of the fact that sugar nitroalkenes could lead directly to C-nucleosides. We were equally motivated by the scarce examples of mesoionic nucleosides; Bredinin (**9**), isolated three decades ago, shows immunosuppressive properties, and its aglycon, itself derived from imidazolium-5-olate, is effective against carcinomas.[11] Likewise, carbohydrate-derived münchnones have been employed in the synthesis of fused systems such as indolizines and imidazopyridines, which serve as glycosidase inhibitors.[12]

Mesoionics **5a**−**c** react smoothly with trans-β-nitrostyrene (**6**) in CH_2Cl_2 at room temperature to give, after 48 h, a diastereomeric mixture of racemic dihydrothiophenes, which can be separated by flash chromatography (Scheme 2). NMR experiments in $CDCl_3$ at 0 °C give evidence for the formation of the transient cycloadducts, and in fact, the endo cycloadduct **11b** could be isolated from the reaction mixture by precipitation with cold ether under such conditions. Asymmetric versions of this methodology were achieved by reacting mesoionics **5** with nitroalkene **7** leading exclusively to diastereomers **16** and **17** (Scheme 3). We succeeded in obtaining suitable crystals of **16a** and **17a** for X-ray diffractometry, thereby elucidating their structures in an unambiguous fashion.

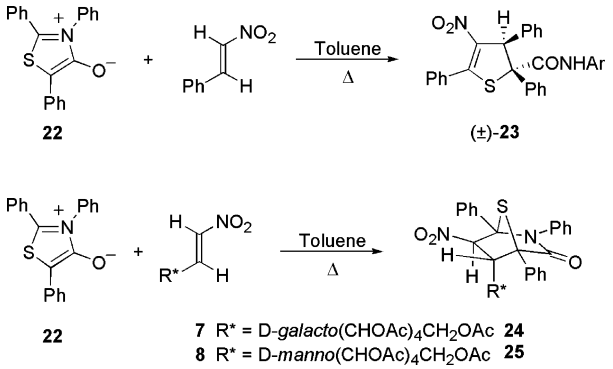
As before, working in $CDCl_3$ at 0 °C allowed us to identify the intermediates **14** and **15** by NMR techniques, the stability of which follows the sequence **b** > **a** > **c**. The transformation of **14** into **16** was faster than that of **15** into **17**, and **15b** could likewise be isolated and its structure elucidated. A $CDCl_3$ solution of **15b** was monitored by ^{1}H NMR at room temperature, showing after 30 days a mixture of **16b** and **17b** in 1:1.4 ratio. Thus, a stable cycloadduct may undergo a retro-dipolar cycloaddition to produce starting materials that, after recombination, yield the two observed cycloadducts. On the other hand, **15b** could be transformed into **17b** in quantitative yield by silica gel catalysis in CH_2Cl_2. NMR experiments at 0 °C also evidenced the formation of cycloadducts **14a** and **15a** (1:1.7 ratio). A similar stereochemical control could be secured by the use of the chiral nitroalkene **8** leading to the dihydrothiophene series **20** and **21** (structures of **20a** and **21a** were determined by X-ray diffraction). A solution of **5b** and **8** in $CDCl_3$ at 0 °C produces the corresponding cycloadducts **18b** and **19b** in 1:1.3 ratio. After warming to room temperature, the former converted into **20b** while **19b** slowly transformed into **21b**. The newly created stereocenters on compounds **20** and **21** have the opposite configuration of those of **16** and **17**, respectively. This result highlights the facial selectivity provided by two complementary carbohydrate auxiliaries (epimers at C2 and C4) and the discriminating effect exerted by the first stereogenic carbon.

Formation of dihydrothiophenes was unprecedented because common thioisomünchnones react with olefinic dipolarophiles to give stable cycloadducts, which eventually fragment into α-pyridones.[4,5] At first glance, we suspected that the nitroalkene, rather than the mesoionic nucleus, could be responsible for the difference of reactivity. Control experiments (Scheme 4) with thioisomünchnone **22** and β-nitrostyrene (**6**) slowly afforded (refluxing toluene, 6 days) the dihydrothiophene **23** in 43% yield. Only cycloadducts **24** and **25** could be isolated under similar conditions starting from the chiral nitroalkenes **7** and **8**, and such reactions did not go further.

Scheme 3. Stereocontrolled Syntheses of Chiral Dihydrothiophenes

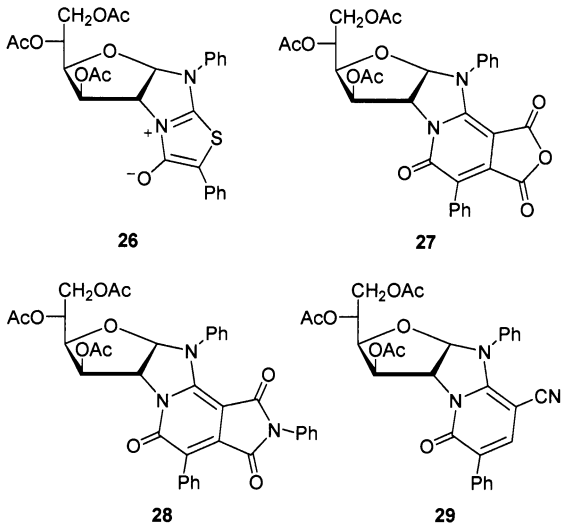


Scheme 4. Steric Courses for the Reactions of Mesoionic 22 with Nitroalkenes



The enhanced reactivity of 2-aminothioisomünchnones **5**, as well as their regio- and stereochemical outcome, can be rationalized by theoretical arguments.[9a] Replacement of a phenyl group at C2 of the mesoionic ring with an amino functionality leads to an increase of the HOMO energy. MO calculations, even at discrete semiempirical levels due to the great number of heavy atoms involved, nicely reflected the steric origin of the facial diastereoselectivity and ruled out the influence of secondary orbital or Coulombic interactions. Chiral nitroalkenes reacted with complete facial stereoselection in favorable approaches that move away the bulkier sugar substituent from the heterocyclic ring.

The reactivity of 2-(*N*,*N*-dialkylamino)thioisomünchnones toward other electron-deficient alkenes (acrylonitrile, dimethyl maleate, or methyl vinyl ketone) follows a similar fate giving rise to dihydrothiophenes.[13] Saddle points calculated at both semiempirical and DFT levels predicted the observed regioisomer, as well as the energetically favored exo approach of dipolarophiles. A more complex 2-aminothioisomünchnone (**26**), however, afforded highly functionalized and polycyclic α-pyridone derivatives such as **27**−**29**, upon reaction with symmetrical and unsymmetrical alkene dipolarophiles.



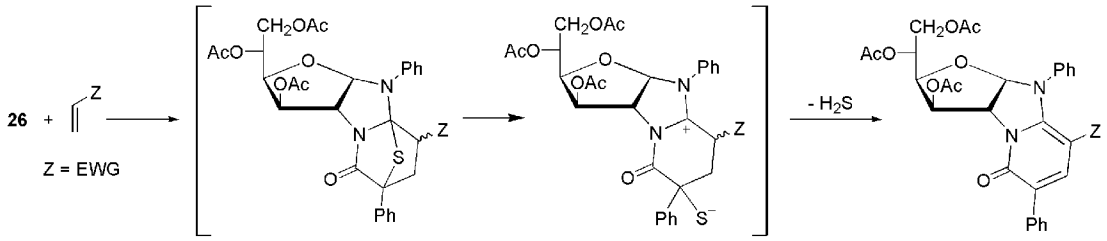
One realizes that the electronic effect supplied by the lone pair of an exocyclic nitrogen atom should stabilize the cation-like intermediate generated by C−N bond breaking. This consideration equally illustrates the accelerating effect of an amino group at C2 on the reactivity of the parent thioisomünchnone. In the case of **26**, however, the competing C−S scission emerges (in fact, the rapid extrusion of hydrogen sulfide bubbles is evident at the onset) yielding an energetically favored ortho-fused heterocycle devoid of strain (Scheme 5).

The nature of the aryl substituent at the endocyclic nitrogen atom (i.e., the aryl group located at C3 of the mesoionic ring) should also be a key factor in controlling the stability of the transition state. Reactions with triple bonds illustrate this point as mesoionics **5a** (Ar = Ph) or **5b** (Ar = 4-$MeOC_6H_4$) reacted with methyl propiolate or dimethyl acetylenedicarboxylate to give preferentially α-pyridones after sulfur extrusion, whereas **5c** (Ar = 4-$NO_2C_6H_4$) led to thiophene derivatives with elimination of 4-nitrophenyl isocyanate, which could be isolated as byproduct.[14] Assuming either concerted or stepwise mechanisms, after C−N scission an electron-withdrawing substituent will stabilize a transition state or dipolar intermediate, in which elimination of Ar−NCO competes favorably with the alternative C−S cleavage. Likewise, the lone pair of the exocyclic *N*,*N*-dialkylamino group will spread the charge at the bridgehead carbon (Scheme 6).

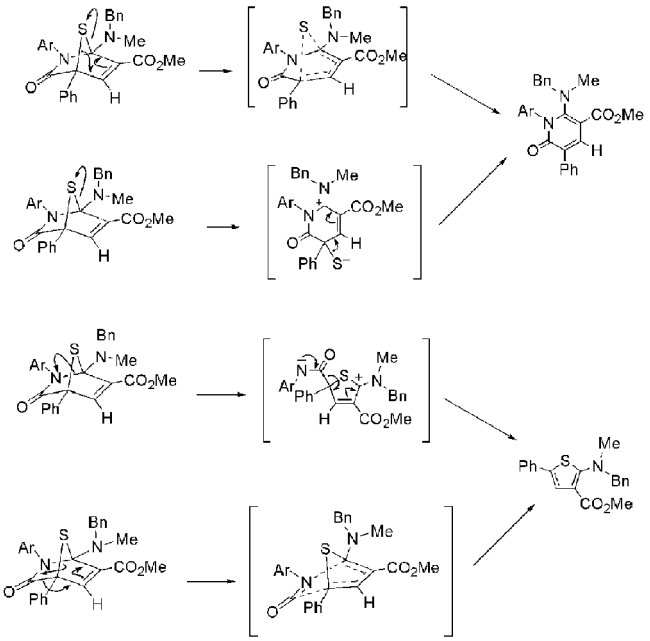
The favorable C−S cleavage, as long as thioisomünchnones **5a** or **5b** are involved, could also be detected in a novel synthesis of 1,2,4-triazines using diethyl azodicarboxylate as dipolarophile.[15] Remarkably, 1,2-diaza-1,3-butadienes react with 2-aminothioisomünchnones in a chemoselective fashion on the olefinic bond leaving intact the azo group. This fact could unequivocally be established by single-crystal X-ray analyses and corroborated by theoretical calculations.[16] Employing simplified models for both the mesoionic dipole and the azadiene, calculations predict that cycloadditions involving the C−C double bond are both kinetically (Scheme 7, reactions a and b with lower $\Delta E^{\ddagger}$ values) and thermodynamically favored (Scheme 7, reactions a−d with lower ΔE_R values) with respect to attacks on the azo group. The simulated processes a and b can be considered concerted but asynchronous. Thus, the dipolar cycloaddition appears to be consistent with a Michael-type addition, which also agrees with the strong nucleophilic character of the mesoionic dipole at C5 with an electrostatic charge of −0.79.

Asymmetric explorations using homochiral carbohydrate-based 1,2-diaza-1,3-butadienes of D-arabino configuration also revealed a complete facial selectivity with respect to the azoalkene.[16−18] In this case, dihydrothiophenes exclusively arose from the attack of the mesoionic dipole to the *Re*,*Re* face of the unsaturated sugar (Scheme 8). In a further study aimed at elucidating the stereodifferentiating effects exerted by the acyclic sugar azadiene, we computed the transition structures arising from **5a** and **30** (having a chiral moiety with D-arabino configuration),[16] as well as those derived from **5a** and a chiral dipolarophile of D-lyxo configuration (identical to **30** except the opposite configuration of the second ste-

Scheme 5. Hypothetical Fragmentations of Cycloadducts Derived from [3 + 2] Cycloadditions to a Tricyclic Thioisomünchnone (26)



Scheme 6. Fragmentation of Cycloadducts Derived from *N,N*-Dialkylaminothioisomünchnones and Alkynes: Pericyclic versus Stepwise Processes



reogenic center of the sugar chain).[17] That opposite configuration at C-2′ in a D-lyxo framework causes a major steric hindrance between the acetate group at C-2′ with the dipole phenyl group at C-5. Overall, the steric effect of the second stereocenter increases the *Re*,*Si*-face attack with respect to the dipole, while decreasing the face selectivity of the dipolarophile as some *Si*,*Si*-face attack takes place too.

β-Lactams versus Thiiranes

If there is a distinctive feature of 2-aminothioisomünchnone cycloadditions, it should surely be their behavior toward aldehydes. We were gratifyingly rewarded after seeing that the X-ray-solved structure of compound **37** surprisingly revealed itself as a *β*-lactam derivative, generated by condensation of **5a** with *p*-anisaldehyde.[19] This synthetic result was obtained starting from thioisomünchnones **5a** or **5c**, regardless of the electronic character of the aldehydic partner, and in every case, *β*-lactams were formed as mixtures of cis and trans diastereomers with respect to the relative orientation of the two aryl groups at C3 and C4 (Scheme 9). Separation of these cis and trans *β*-lactams could further be achieved by crystallization or chromatography, thereby facilitating their structural elucidation.[20]

A rationale for the conversion of thioisomünchnones and aromatic aldehydes into *β*-lactams is depicted in Scheme 10 and comprises a triple cascade reaction of an initial [3 + 2] dipolar cycloaddition, spontaneous cleavage of the endocyclic C−N bond, and rearrangement of the resulting zwitterionic intermediate. The overall transformation is triggered by a series of stereoelectronic events. Opening of the thia-oxazabicycles alleviates their ring strain, and the positive charge created by this intramolecular elimination is stabilized by the lone pair of the *N*,*N*-dialkylamino nitrogen. In a complementary fashion, an electron-withdrawing substituent on the aromatic group will stabilize the negative charge. The subsequent rearrangement to the four-membered ring is basically a nucleophilic attack of the amide nitrogen on the endocyclic carbon atom with the heterocyclic oxygen as the leaving group. This displacement induces the configurational inversion at C5 of the five-membered intermediate. It is therefore clear that exo and endo approaches of the aromatic aldehyde in the cycloaddition step control the stereochemical outcome leading to *cis*- and *trans*-*β*-lactams, respectively.

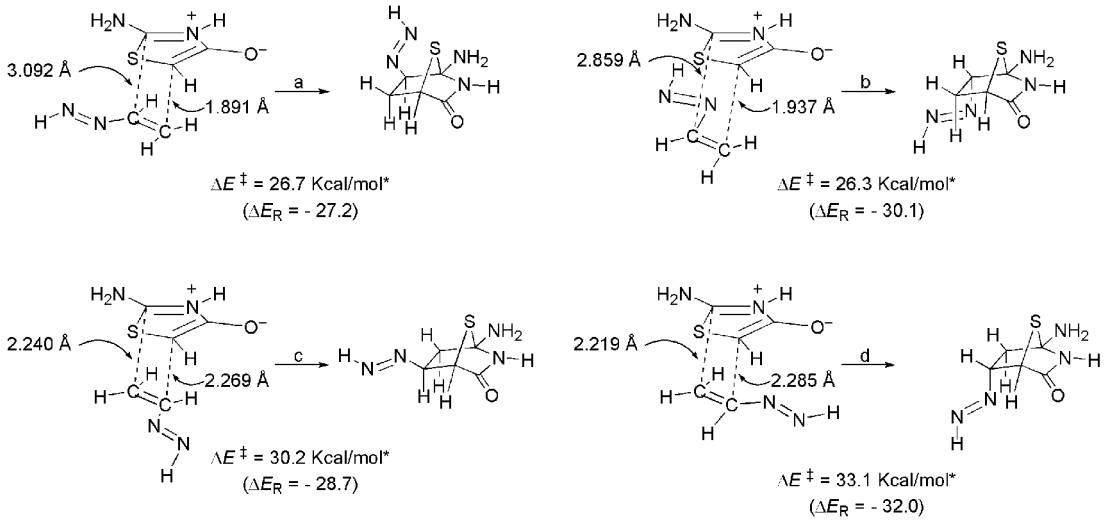
It is noteworthy that semiempirical calculations (at the PM3 level) do not satisfactorily account for the experimental results, as they predict a slight imbalance (in terms of stabilized transition structures) favoring the endo approach, which would lead to *trans*-*β*-lactams. Introduction of electronic correlation (via B3LYP/6-31G* calculations), however, gives a lower activation energy for the exo approach, which after cycloadduct cleavage, leads to *β*-lactams with a relative cis stereochemistry.

In light of these mechanistic insights, formation of *β*-lactams from other mesoionics can actually be interpreted as sequential processes initiated by [3 + 2] cycloadditions,[19,20] rather than [2 + 2] additions involving ketene tautomers, which have been claimed to be the real intermediates.[21,22]

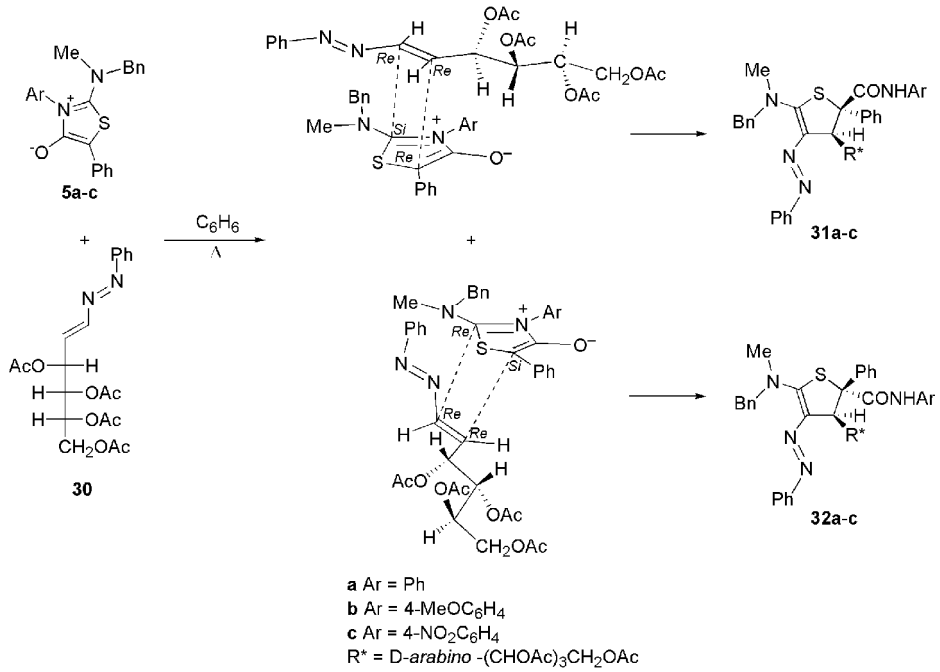
We did expect that an electron-donating aryl group on the thioisomünchnone partner would disfavor C−N bond breaking of the initial cycloadducts. This surmise proved to be true after testing the condensation of aryl aldehydes with **5b** (Ar = 4-MeOC$_6$H$_4$), which produced solely a thiirane derivative.[20] In this case, the reversible cleavage of the initial cycloadduct is shifted to an alternative dipolar intermediate generated by the now favored C−S bond breaking (Scheme 11).

As mentioned earlier, mesoionics **5a** or **5c** react with aromatic aldehydes, irrespective of their electron-withdrawing or electron-releasing substituents (**33**−**35**), yield-

Scheme 7. Asynchronous Cycloadditions of 1,2-Diaza-1,3-butadiene and 2-Amino-1,3-thiazolium-4-olate



Scheme 8. Diastereofacial Cycloadditions of *N,N*-Dialkylaminothioisomünchnones to Chiral Diazabutadienes

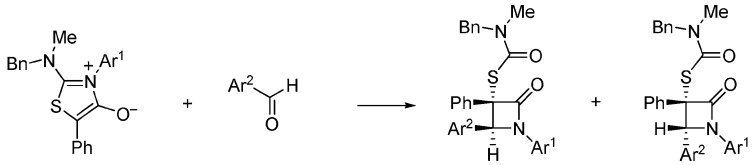


ing β-lactams. Further studies with aliphatic aldehydes, however, revealed that mixtures of thiiranes and β-lactams are often obtained. Remarkably, O-protected sugar aldehydes led exclusively to thiiranes, which introduces a new family of glycoanalogues.[23,24] As outlined above, after C−N or C−S bond scissions, a good nucleophile (either ArN^- or S^-) displaces a better yet leaving group (an oxonium ion) to afford β-lactams or thiiranes. However, in the case of sugar aldehydes, the absence of β-lactams can be ascribed to severe crowding in the zwitterionic intermediate caused by the polyacetylated side chain. This chiral version also proceeded with little facial selectivity. Computation equally suggests that this is likely to be due to the high degree of pyramidalization of the carbonyl group in all the transition structures. Because that group is near-sp^3 hybridized, the steric factor responsible for facial discrimination is alleviated once the saddle point is reached.

Non-Cycloadditive Strategies: 2-Alkylthioisomünchnones

A suitable epilogue of this synthetic journey is the exploration of new vistas other than [3 + 2] cycloadditions. Unlike the 2-aryl-substituted derivatives, 2-alkylated mesoionics may bridge the gap. While the search for valence tautomers has been a recurrent theme in mesoionic chemistry without conclusive evidence,[2] spectroscopic techniques pointed to a tautomeric equilibrium between 2-methylthioisomünchnone and 2-methylenethiazolidin-4-one.[25] This substance behaved as a masked dipole nevertheless, affording cycloadducts or heterocycles derived thereof. In a recent study, we were able to intercept the 2-alkylidenethiazol-4(5*H*)-one tautomer of 3,5-diphenyl-2-methylthioisomünchnone by reaction with strong electrophiles (Scheme 12).[26] Aliphatic acid chlorides yielded

Scheme 9. Synthesis of Functionalized Monobactams from *N,N*-Dialkylaminothioisomünchnones and Aldehydes



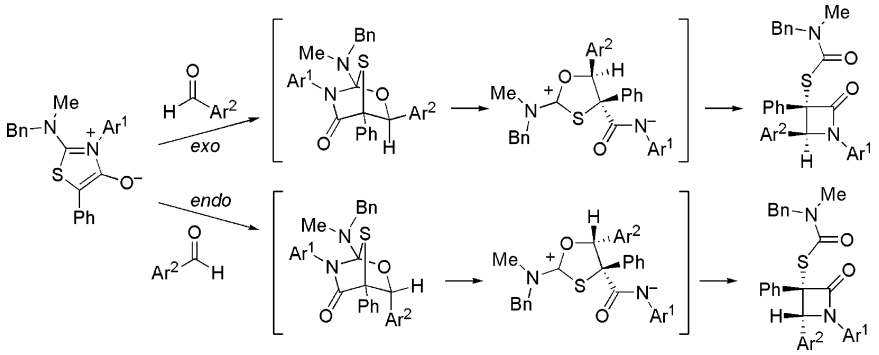
5a Ar^1 = Ph
5b Ar^1 = 4-$NO_2C_6H_4$

33 Ar^2 = Ph
34 Ar^2 = 4-$MeOC_6H_4$
35 Ar^2 = 4-$NO_2C_6H_4$

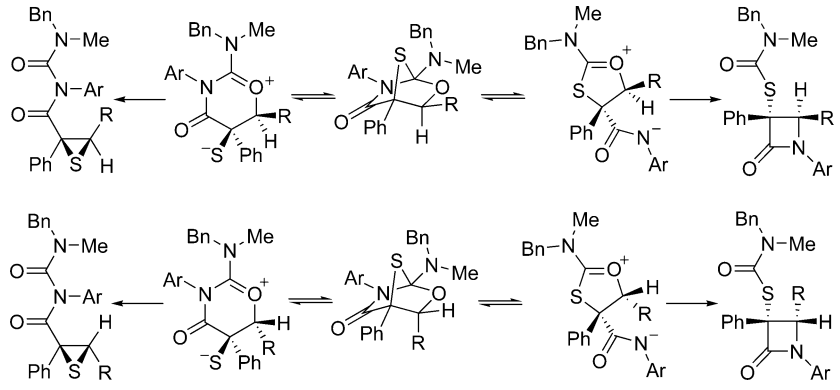
36-41 **42-47**

Ar^1	Ar^2	Isolated yields (%)		Cis/Trans Ratio
Ph	Ph	**36** (41)	**42**(34)	65:35
Ph	4-$MeOC_6H_4$	**37** (54)	**43** (20)	70:30
Ph	4-$NO_2C_6H_4$	**38** (−)	**44** (30)	59:41
4-$NO_2C_6H_4$	Ph	**39** (35)	**45** (25)	57:43
4-$NO_2C_6H_4$	4-$MeOC_6H_4$	**40** (30)	**46** (20)	60:40
4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	**41** (42)	**47** (25)	58:42

Scheme 10. Domino Sequence for the Thioisomünchnone-Carbonyl Cycloaddition Leading to *cis*- and *trans*-Monobactams



Scheme 11. Divergent Mechanistic Proposals Accounting for β-Lactams and Thiiranes

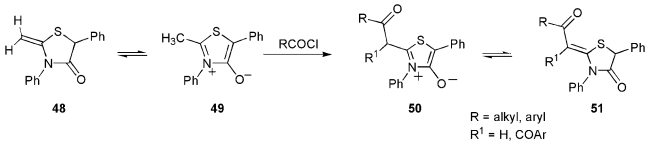


α-aryl-substituted ketones, whereas their aromatic counterparts led to α-aryl-substituted β-diketones.

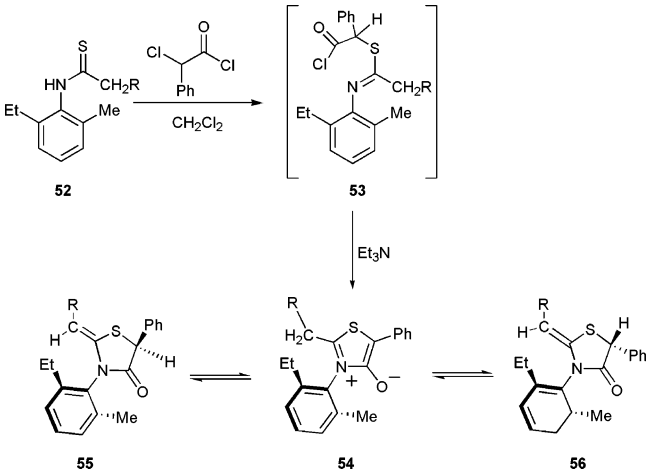
It is relevant to note that B3LYP/6-31G* calculations predict a tiny energy difference (ΔE < 0.02 kcal/mol) between the tautomeric forms **48** and **49**. At the same level, Mulliken charge analysis also reveal the nucleophilic character of the exocyclic carbon at C2 of the mesoionic ring. The cis disposition between the sulfur atom and the acyl substituent in **51** (R = CH_3, R^1 = H) could be determined by X-ray diffraction, and such an arrangement should presumably be attributed to an intramolecular nonbonded S···O interaction (1,5-intra mode), having its origin in $n_{C=O}-\sigma^*_{C-S}$ orbital overlap effect.[27] The solid-state structure also shows the orthogonal disposition of phenyl groups located at N3 and C5, with respect to the heterocyclic ring.

In a further study, the tautomeric equilibrium has been evaluated in other 2-alkylthioisomünchnones (Scheme

Scheme 12. Reaction of 2-Methylthioisomünchnone with Acid Chlorides



Scheme 13. Synthesis and Tautomeric Equilibria of 2-Alkylthioisomünchnones



13).[28] In compounds **54**−**56**, the presence of o,o′-disubstituted phenyls at N3 slows free rotation around the N−Ar bond. Furthermore, tautomers **55** and **56** exhibit an element of axial chirality owing to chemically different ortho substituents. The tautomeric equilibrium is especially complex, and at the outset it contains a 3:1 cis/trans mixture (with respect to the relative disposition of the ethyl group and the phenyl substituent at C5) of **55** and **56**. At equilibrium, the approximate composition of **54**/**55**/**56**, determined by NMR monitoring, is 1:2.2:2.2. The cis/trans equilibration proceeds slowly (several days) and only occurs when the concentration of the mesoionic structure (**54**) approaches its equilibrium value. Accordingly, protonation of **54** at C5, either on its upper or on its lower face, takes place faster than rotation around the N−Ar bond of the thiazolidinone tautomer, which could be exploited en route to nonbiaryl atropisomers.

Conclusions and Outlook

Mesoionic structures, still rare species within the vast field of heterocyclic chemistry, are excellent dipoles with widespread application in synthesis. Our contribution, outlined above, illustrates the application of 2-aminothioisomünchnones in the preparation of unusual rings employing [3 + 2] cycloadditions. Stereoselectivity can also be fine-tuned with the assistance of sugars as chiral controllers. Mechanistic considerations, validated by computation, make also possible a unified approach to predict both the fragmentation and evolution of cycloadducts. Research in this area seems far from being exhausted. The tautomeric equilibria of certain 2-alkylthioisomünchnones can now be exploited for synthetic purposes.

But mesoionics could do much more. These systems may display large hyperpolarizabilities and hence they could be substitutes for the polyene bridges present in molecules with second- and third-order nonlinear optical properties.[29] In addition, mesoionics have also found application as near-infrared dyes for the development of NIR semiconductor lasers.[30]

We hope that our explorations and the attractiveness of these zwitterionic structures will stimulate further methodologies in synthesis, as well as imaginative and varied applications.

The authors gratefully acknowledge a group of talented collaborators whose names appear in the references. Special thanks go to Mark E. Light (University of Southampton) for diligently solving numerous crystal structures, which were instrumental in identifying the stereochemical outcome. We also thank the Ministry of Science and Technology (Grants BQU2002-00015 and BQU2003-05946) and the Autonomous Government of Extremadura (Grant 2PR02-A016) for generous support of this work.

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AR040212R