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Expeditious formation of 1,2,4-triazine derivatives via a thioisomünchnone cycloaddition reaction

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Abstract

A novel type of heterocyclization reaction involving the [3+2] cycloaddition of *N,N*-dialkylamino-substituted thioisomünchnones with azodicarboxylates gives rise to 1,2,4-triazine derivatives after a selective fragmentation pathway of the transient cycloadducts. The X-ray analysis of **7** accounts for the fate of this particular transformation. An asymmetric version using chiral carbohydrate-based thioisomünchnones has also been disclosed. © 1999 Elsevier Science Ltd. All rights reserved.

The past decade has witnessed the consolidation of mesoionic heterocycles as raw materials in organic synthesis, including the preparation of numerous natural products and their analogs.[1] These heteroaromatics which behave as masked dipoles are willing partners in dipolar cycloaddition reactions.[2] In a series of recent contributions we have demonstrated the enormous versatility of these systems, especially anhydro-4-hydroxy-1,3-thiazolium hydroxides (thioisomünchnones), to afford densely functionalized and often chiral three-,[3] four-,[4] five-[5] and six-membered rings,[6] by an appropriate choice of reactants and reaction conditions.

In pursuing further studies, herein we describe a novel type of cycloadduct fragmentation yielding triazine derivatives, which are still widely used as antiphotosynthetic herbicides to combat weeds in crops and pesticides.[7] Thus, the reactions of thioisomünchnones **1** and **2** with diethyl azodicarboxylate (DEAD) in CH_2Cl_2 at room temperature result in the formation of **7** and **8** in 71% and 50% yield, respectively (Scheme 1). The structure of the crystalline triazinone **7** was established using X-ray techniques (Fig. 1),[8] thereby showing the atom connectivity. This would implicate an unprecedented formation of triazines by reaction of thioisomünchnones with azodicarboxylates. Remarkably, the intermediate cycloadducts (**3** and **4**) could not be isolated. Previous studies dealing with the condensation of thioisomünchnones with nitrogen-containing dipolarophiles gave rise to stable cycloadducts, which upon heating generated acyclic structures, while reaction in ethanol or methanol resulted in addition of the alcohol to the

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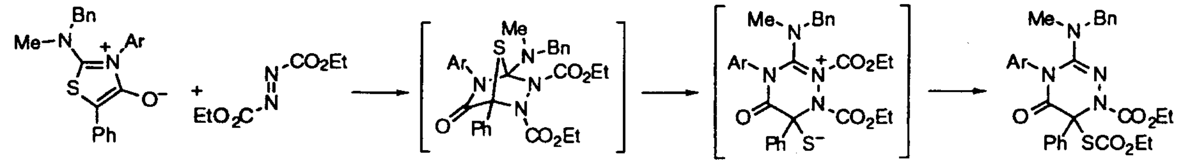
cycloadduct.[9] Likewise, when treated with Raney nickel, such cycloadducts were transformed into imidazolidine-2,4-diones by sulfur extrusion.[10] We believe the pathway shown in Scheme 1 reasonably accounts for the formation of these products. Thus, 1,2,4-triazine derivatives are generated by a selective carbon–sulfur cleavage of the transient cycloadducts, followed by intramolecular attack of the thiolate ion at N-2. Such a rearrangement, which should be favored by the presence of the exocyclic *N,N*-dialkylamino group, alleviates the strain of the polycyclic system.



1 Ar = Ph
2 Ar = 4-MeOC$_6$H$_4$

3-4

5 Ar = Ph
6 Ar = 4-MeOC$_6$H$_4$

7 Ar = Ph
8 Ar = 4-MeOC$_6$H$_4$

Scheme 1.

Next, we have examined the asymmetric version of the above-mentioned protocol in order to explore its scope (Scheme 2). Starting from a commercially available carbohydrate precursor, D-glucamine (1-amino-1-deoxy-D-sorbitol), thioisomünchnones **9** and **10** were formed by a three-step sequence involving: (a) condensation with an aryl isothiocyanate, (b) conventional acetylation with Ac$_2$O/pyridine, and (c) treatment of the resulting thiourea with 2-chloro-2-phenylacetyl chloride. The thioisomünchnones thus obtained were not stable enough to be isolated, but they could be trapped in situ with DEAD in CH$_2$Cl$_2$ solution. Again no cycloadducts were observed and the two triazinones **13** and **14** were obtained as ca. 1:1 diastereomeric mixtures. The absence of facial diastereoselectivity can be attributed to the conformational flexibility of the acyclic sugar template and the remote situation of the chiral moiety. However, each of these compounds was submitted to prolonged heating in toluene affording the heterocyclic derivatives **15** and **16**. The isolation and characterization of structures **7** and **8**, closely related to **13** and **14** which are intermediates en route to triazinone derivatives such as **15** and **16**, also suggest that the spontaneous elimination of H$_2$S observed in certain cycloadditions of thioisomünchones with olefins,[1a,2] might occur by an analogous pathway.

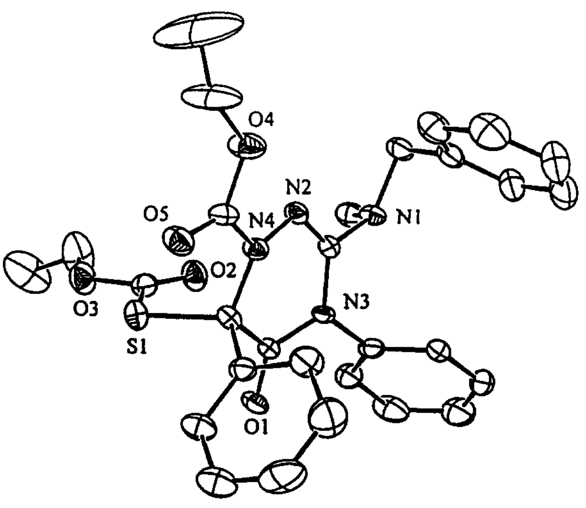
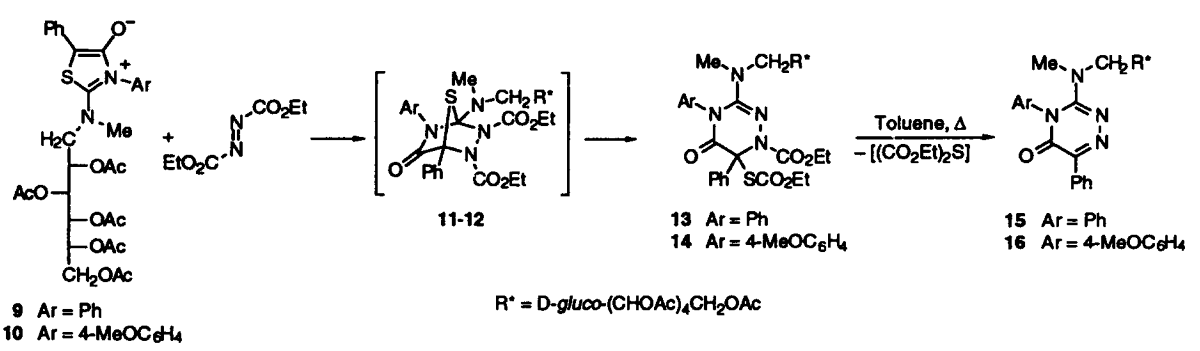
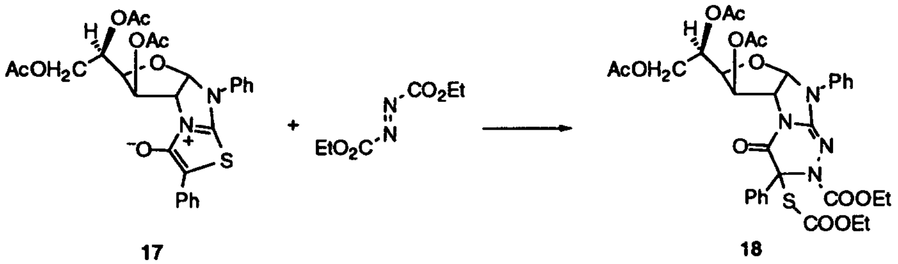


Figure 1.



Scheme 2.

Then, we turned our attention towards a relatively rigid carbohydrate-appended thioisomünchnone (**17**),[6a] which was reacted with DEAD under the same reaction conditions to afford **18** in 78% yield as a single diastereomer, whose configuration at the newly created stereocenter has not yet been elucidated (Scheme 3). This crystalline material was thoroughly characterized by NMR spectroscopy and exhibited similar patterns, at the heterocyclic backbone, to those of **7** and **8**.



Scheme 3.

In summary, we have shown that 1,2,4-triazines which have potential applications in crop protection, can be obtained by novel heterocyclization processes under mild conditions involving the [3+2] cycloaddition of thioisomünchnones with diethyl azodicarboxylate followed by fragmentation of cycloadducts. Further studies to understand the parameters that control the fragmentation and other mechanistic insights are under way.

Acknowledgements

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8. Crystal data of **7**: $C_{29}H_{30}N_4O_5S$, FW=546.63, monoclinic, $P2_1/n$; a=10.663(2) Å, b=26.202(5) Å, c=12.375(2) Å, β=94.25(3)°, V=3448.0(11) Å^3, Z=4, D_{calcd}=1.053 Mg m^{-3}, μ=0.131 mm^{-1}, F(000)=1152. Of 57537 reflections collected, 4915 [R_{int}=0.1987] were independent, GOF=2.122. Final R indices [$F^2>2\sigma(F^2)$]: R_1=0.1457, wR_2=0.3775. Refinement: full-matrix least-squares on F^2. Crystallographic data for the reported structure have been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number CCDC 132765.
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