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Azodicarboxamides vs. Azodicarboxylates in Reactions against Thioisomünchnones: 1,3-Dipolar Cycloaddition or Nucleophilic Addition?

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This communication presents the first study on the use of azodicarboxamides against mesoionic heterocycles as 1,3-dipoles. The reactions yield thioureido compounds. Their formation could be explained, on the basis of experimental results and preliminary theoretical calculations, by a nucleophilic addition followed by rearrangement; however, a formal 1,3-dipolar cycloaddition and subsequent fragmentation and rearrangement of the transient cycloadducts could not be ruled out. Reactions are carried out in refluxing toluene and are complete in 90–240 min. Structural elucidation of the products is based on single-crystal X-ray analysis, as well as other spectroscopic data and 2D-NMR correlations.

Introduction

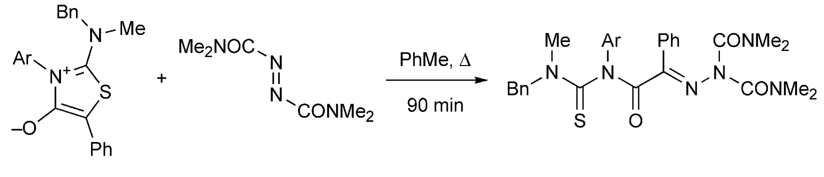
1,3-Dipolar cycloaddition is a powerful and versatile methodology to gain ready access to heterocycles in a stereochemically controlled fashion.[1,2] Whether these reactions proceed by a concerted mechanism, synchronous or not, as first proposed by Huisgen et al.[3] or rather evolve stepwise by means of diradicals or zwitterionic species is still a matter of controversy. Only in the last decade have several sound computational studies been reported to help understanding the way this reaction occurs.[4–11]

Thioisomünchnones (1,3-thiazolium-4-olates or anhydro-4-hydroxy-1,3-thiazolium hydroxides) constitute a group of mesoionic heterocycles that behave as masked dipoles in 1,3-dipolar cycloadditions due to their thiocarbonyl ylide structure.[12–15] This ability makes them very valuable starting materials in the synthesis of a vast array of heterocycles by reaction with homo- and heterodipolarophiles.[2]

In our laboratory we have been studying the reactivity of 2-alkylthioisomünchnones and 2-aminothioisomünchnones. The occurrence of a tautomeric equilibrium and a non-dipolar behaviour of the former have been reported.[16–18] On the other hand, 2-(dilakylamino) derivatives yield highly functionalised, and often chiral, three-,[19–21] four-,[20–22] five-,[23–27] and six-membered rings,[28,29] by appropriate choice of the reactants.[30]

Regarding the use of azo compounds as dipolarophiles, pioneering work by Sheradsky and Itzhak described the formation of cycloadducts, hydrazinothiazols, and open-chain thioxohydrazides by reaction of 2-phenylthioisomünchnones with azodicarboxylates.[31,32] In addition, we have reported the formation of 1,2,4-triazines,[28] and 1,3,4-thiadiazoles,[27] by reaction of 2-(dialkylamino)thioisomünchnones with dialkyl azodicarboxylates.

No examples on the use of azodicarboxamides as dipolarophiles in reactions with any type of mesoionic heterocycles were found.



1 Ar = $4\text{-}O_2NC_6H_4$
2 Ar = Ph
3 Ar = $4\text{-}MeOC_6H_4$

4

5 Ar = $4\text{-}O_2NC_6H_4$
6 Ar = Ph
7 Ar = $4\text{-}MeOC_6H_4$

Scheme 1.

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We present herein our preliminary findings on the reaction between mesoionic compounds and azodicarboxamides. Interestingly, we came across an unprecedented result, since these reactions produced open-chain thioureas, instead of any kind of heterocyclic compound. These processes take place with complete atom economy, giving rise to highly functionalised molecular structures (Scheme 1).

Results and Discussion

Reactions of thioisomünchnones **1**–**3** in refluxing toluene with *N*,*N*,*N′*,*N′*-tetramethylazodicarboxamide (**4**) resulted in the formation of the crystalline solids **5**–**7** in 37–61% yields. Reactions were completed, as determined by tlc, in 90 min.

IR and ^{13}C NMR spectroscopic data reveal the existence of one C=S group and several C=O functions in the three compounds. Suitable crystals for X-ray diffractometry could be obtained for compound **6** (Figure 1), thus proving unequivocally the acyclic structure formed.

In order to corroborate these unexpected results, thioisomünchnones **1**–**3** were also allowed to react with 1,1′-azobis(dimorpholide) (**8**) in refluxing toluene to afford compounds **9**–**11** as crystalline solids in moderate to good yields (40–75%) (Scheme 2).

To further extend the initial exploration on the scope of this process, three asymmetric, carbohydrate-based thioisomünchnones were studied. The tricyclic mesoionic compounds **12**–**14**, synthesised according to a previously published protocol,[33] feature a rigid carbohydrate backbone and a 2-[(alkyl)(aryl)amino] group on the 1,3-thiazolium-4-olate moiety. When **12**–**14** were allowed to react with 1,1′-azobisdimorpholide (**8**) in refluxing toluene, the thioureido compounds **15**–**17** were isolated in modest yields (15–35%) as the sole reaction products. Again, no intermediate cycloadducts were detected (Scheme 3).

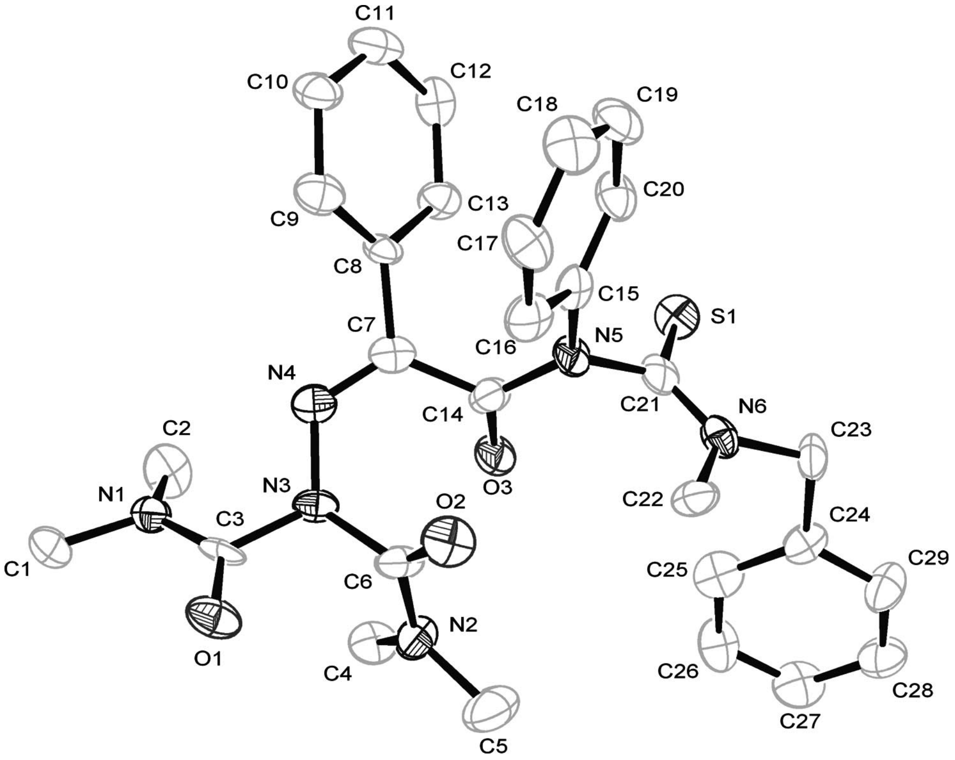
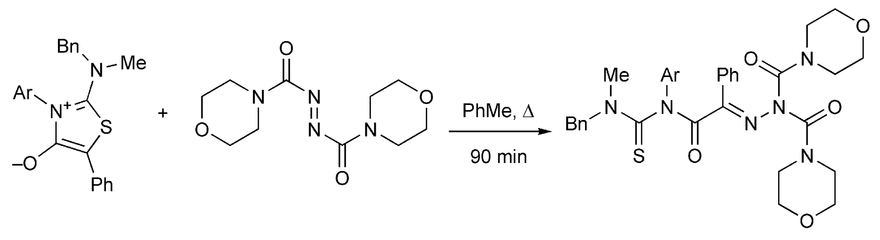


Figure 1. Crystal structure of **6**.

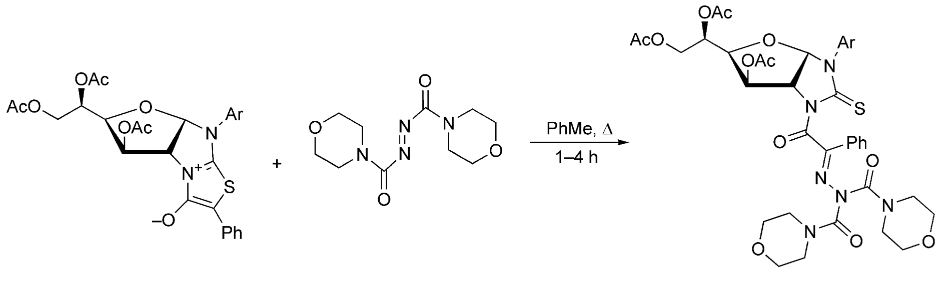


1 Ar = 4-$O_2NC_6H_4$
2 Ar = Ph
3 Ar = 4-$MeOC_6H_4$

8

9 Ar = 4-$O_2NC_6H_4$
10 Ar = Ph
11 Ar = 4-$MeOC_6H_4$

Scheme 2.



12 Ar = 4-$O_2NC_6H_4$
13 Ar = Ph
14 Ar = 4-$MeOC_6H_4$

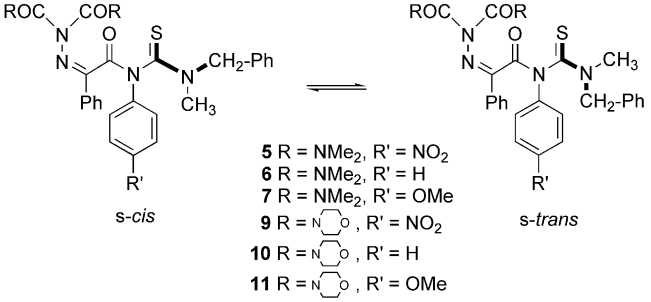
8

15 Ar = 4-$O_2NC_6H_4$
16 Ar = Ph
17 Ar = 4-$MeOC_6H_4$

Scheme 3.

Table 1. Selected ^{13}C NMR chemical shifts (δ [ppm]) for **5**–**7**, **9**–**11** and **15**–**17**.

	5	**6**	**7**	**9**	**10**	**11**	**15**	**16**	**17**
C=S	182.8	184.3	184.4	182.9	184.7	184.0	174.7, 176.4	175.5, 176.9	175.8, 176.8
NC=O	156.6	156.7	156.6	155.4	154.9	154.8	155.1, 155.0	155.1, 155.2	155.1, 155.2
PhC=N	145.5	145.4	145.7	145.8	150.2	150.2	144.0, 147.1	144.8, 147.4	144.9, 147.5
NCH_2	58.7, 57.7	58.6, 57.7	58.5, 57.6	58.7, 57.5	58.8, 58.2	58.8, 58.2			
NCH_3	37.3, 37.2	37.4, 37.2	37.3, 37.2	42.3, 38.7	41.1, 39.4	41.1, 39.4			



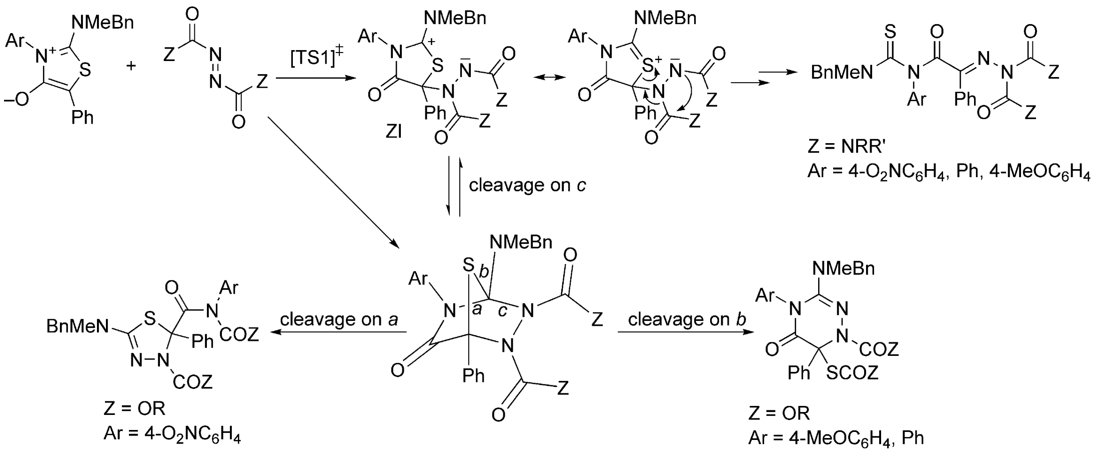
5 R = NMe_2, R' = NO_2
6 R = NMe_2, R' = H
7 R = NMe_2, R' = OMe
9 R = N◯O, R' = NO_2
10 R = N◯O, R' = H
11 R = N◯O, R' = OMe

Figure 2. s-*cis*/s-*trans* isomerism in **5**–**7** and **9**–**11**.

Once the structure of **6** was unequivocally determined by X-ray analysis, the molecular structures of **5**, **7**, **9**–**11**, and **15**–**17** were assigned to open-chain thioureas on the basis of analogous IR and, essentially, ^{1}H and ^{13}C NMR spectroscopic data, including 2D NOE experiments and heteronuclear multiple-bond correlation techniques (HMBC). Characteristic ^{13}C chemical shifts are gathered in Table 1.

Duplicate signals, both in the ^{13}C and ^{1}H NMR spectra, have been attributed to conformational s-*cis*/s-*trans* isomers at the thiourea unit of **5**–**7**, and **9**–**11**, as shown in Figure 2. In contrast, peak splitting for **15**–**17** corresponds to hindered rotation around the N–C=O group.

The unexpected formation of thioureido compounds **5**–**7**, **9**–**11**, and **15**–**17**, can be explained by a 1,3-dipolar cycloaddition followed by cleavage and rearrangement of the transient cycloadducts, in agreement to previous reports.[27,28] In the present study, however, the endocyclic *N*-aryl group (4-nitrophenyl, phenyl or 4-methoxyphenyl) exerts no influence on the way that cycloadducts cleave. This fact opens the prospect for a noncycloadditive mechanism, in which the first step would be a nucleophilic ad-



Scheme 4.

dition. Both possibilities are shown in Scheme 4, along with those reported for azodicarboxylates for the sake of comparison.

In order to clarify the mechanism, initial DFT calculations were carried out with the Gaussian03 program package.[34] Two reactions were studied, those of **1** and **2** with **4**. Optimisation of reactants and location of the first transition structure (TS1) of the process and the corresponding zwitterionic intermediates (ZI) were computed at the B3LYP/6-31G* level.[35,36] Transition structures and stationary points were characterised by frequency calculations. These calculations rendered a stepwise mechanistic pathway.

Figure 3 shows the structures for TS1, and ZI. Relevant data for these structures are gathered in Table 2.

TS1 ZI

TS1(**1**+**4**): Ar = 4-$O_2NC_6H_4$, R = $CONMe_2$ ZI(**1**+**4**): Ar = 4-$O_2NC_6H_4$, R = $CONMe_2$

TS1(**2**+**4**): Ar = Ph, R = $CONMe_2$ ZI(**2**+**4**): Ar = Ph, R = $CONMe_2$

Figure 3. Structures for TS1 and ZI.

Table 2. Addition of **1** and **2** with **4a**. Energy and distances for TS1 and ZI.

	ΔE[a]	d_1[b]	d_2[b]
TS1(**1** + **4**)	14.67	1.783	2.989
TS1(**2** + **4**)	14.80	1.777	3.065
ZI(**1** + **4**)	7.90	1.494	2.916
ZI(**2** + **4**)	7.17	1.493	2.970

[a] Relative to energy [kcal/mol] of the reagents. [b] Distances [Å].

According to these preliminary computational studies, a mechanism can be proposed. In this mechanism the formation of the cycloadducts is not necessary, yet a cycloadditive pathway is not irrefutably ruled out. These results, therefore, add on a better understanding on the concerted vs. stepwise question.

Conclusion

We have shown that highly functionalised thioureido compounds can be readily obtained by reaction of 2-aminothioisomünchnones with azodicarboxamides. Although the reaction can be envisaged as a nucleophilic addition/rearrangement process, a formal 1,3-cycloaddition followed by fragmentation of the cycloadducts cannot be ruled out. Preliminary DFT calculations support a stepwise process. In order to establish the scope and limitations of this protocol, and to gain further insight into its mechanism, new experimental and theoretical studies are currently under way.

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