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DIASTEREOSELECTIVE SYNTHESIS OF CHIRAL THIIRANES BY 1,3-DIPOLAR CYCLOADDITION OF IMIDAZO[2,1-*b*]THIAZOLIUM-4-OLATE SYSTEMS WITH AROMATIC ALDEHYDES

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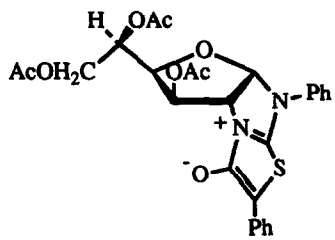
Summary: The regiospecific and diastereoselective 1,3-dipolar cycloaddition of imidazo[2,1-*b*]thiazolium-4-olate systems with aromatic aldehydes gives thiiranes, which undergo thermal decomposition to olefins.

Mesoionic compounds have proven to be valuable intermediates in organic chemistry from both physical and synthetic perspectives.[1] These substances contain a masked 1,3-dipole within their framework and are therefore willing participants in 1,3-dipolar cycloadditions.

We recently reported the synthesis and reactivity of a chiral imidazo[2,1-*b*]thiazolium-4-olate system (**1**) toward acetylenes[2] and aryl isocyanates[3]. In both cases, elimination of sulfur took place under the reaction conditions to afford imidazo[1,2-*a*]pyridin-4-one and imidazo[1,2-*a*]pyrimidin-5-ylium-2-olate systems, respectively.

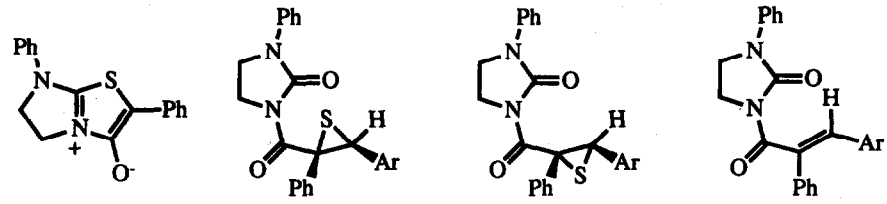


1

The reaction of mesoionic heterocycles with carbonyl compounds has been scarcely studied and, to our knowledge, only two reports have appeared in the literature. Thus *N*-acylenamines were obtained from 1,3-oxazolium-5-olate systems by ring-opening of the initial 1:1-cycloadducts.[4] Nevertheless, in a further study some cycloadducts were isolated in the reaction of 1,3-oxazolium-4-olates with carbonyl compounds.[5]

As a continuation of our studies dealing with the generation and utilization of mesoionic systems *via* the tandem cyclization-cycloaddition process, we have explored the reaction of the imidazo[2,1-*b*]thiazolium-4-olate **2** with aromatic aldehydes.

Compound **2** (30%) was obtained by reaction of *N*-phenylimidazolidine-2-thione with α-bromophenylacetic acid and triethylamine in benzene and subsequent ring-closure of the thioglycolic acid with acetic anhydride-triethylamine. Reaction of **2** with benzaldehyde and 4-methoxybenzaldehyde, in toluene at reflux, gave enantiomeric mixtures of **3a,4a** (65%) and **3b,4b** (32%), respectively.

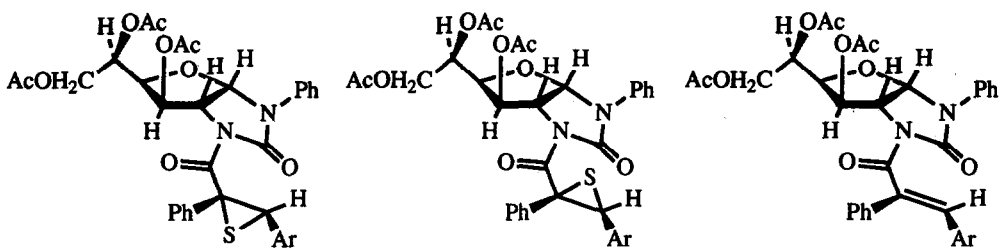


2 **3** **4** **5**

a; Ar = C_6H_5 **b**; Ar = 4-$MeOC_6H_4$ **c**; Ar = 4-$Me_2NC_6H_4$

This process constitutes a novel ring-opening pathway of the initial 1:1-cycloadduct yielding thiiranes. Furthermore, the cycloaddition of **2** with 4-(*N*,*N*-dimethylamino)benzaldehyde gave the olefin **5c** (35%) by spontaneous desulfurization subsequent to the cycloadduct-opening.

In order to evaluate the scope of this reaction, particularly with regard to its regio- and stereoselectivity, we have examined the cycloaddition reaction of a chiral mesoionic heterocycle with aromatic aldehydes. The reaction of **1** with 4-(*N*,*N*-dimethylamino)benzaldehyde gave similar amounts of two diastereomeric products (**6a** and **7a**)[6]. The structure of **6a** was fully resolved[7] by single-crystal X-ray analysis and a perspective view of its molecular structure is depicted in Figure 1. The structure of **7a** was unequivocally established when a mixture of **6a** and **7a** was desulfurizated by heating at reflux in toluene for 48 h. This process yielded exclusively the olefin **8a**[8], whose structure retains the relative configuration of **6a** and **7a** in accordance with the stereospecific thermal decomposition of episulfides[9].



6 **7** **8**

a; Ar = 4-$Me_2NC_6H_4$ **b**; Ar = C_6H_5 **c**; Ar = 4-$MeOC_6H_4$
d; Ar = 3-$MeOC_6H_4$ **e**; Ar = 4-$NO_2C_6H_4$

Similarly, the reaction of **1** with benzaldehyde, 4-methoxybenzaldehyde, and 3-methoxybenzaldehyde gave **6b-d**[10], respectively. In these cases, however, diastereomers **7b-d** were not isolated. Structures of compounds **6b-d** were assigned on the basis of their ^1H- and ^{13}C-NMR data, which were markedly analogous to those of **6a**. When 4-nitrobenzaldehyde was used as dipolarophile, the corresponding thiirane could not be obtained, but instead the olefin **8e**[10] was isolated as evidenced by its spectroscopic data.[11]

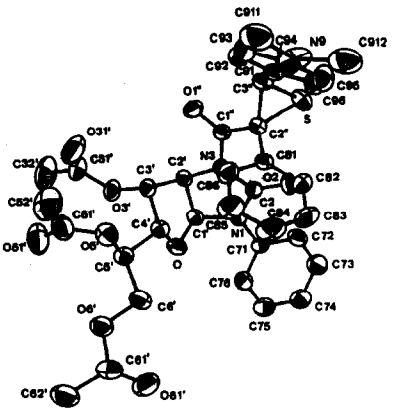
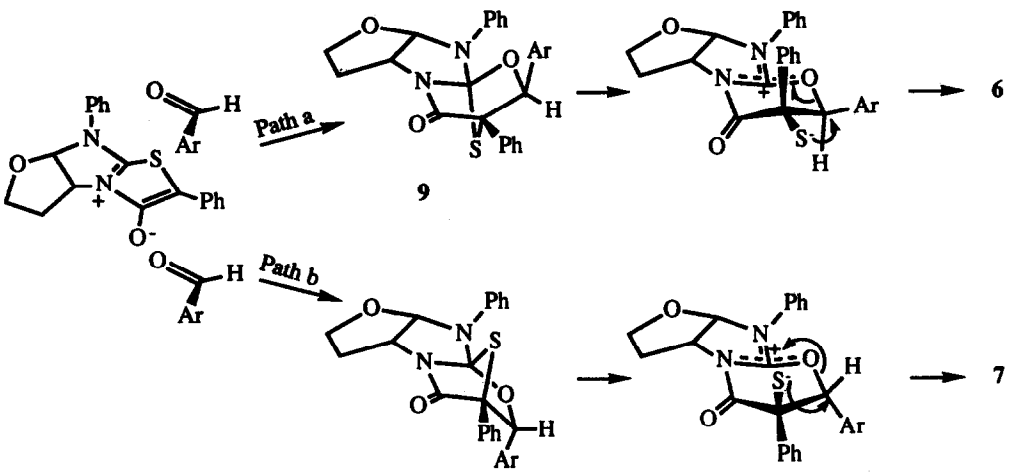


Figure 1. Molecular structure of **6a**

The preferential formation of diastereomers **6** and **7** indicates the regiospecific and selective *endo*-approach of both reagents, as well as the highly stereocontrolled cycloadduct-opening. A possible mechanism for this process is depicted below. The *endo*-approaches of the aldehyde to the mesoionic heterocycle involve the strained cycloadducts **9** and **10**. Both, the thermal breaking of the weak C–S bond and the resulting conformational change allow the episulfidation by an intramolecular nucleophilic displacement.



10

The regio and stereochemical course of these reactions can be rationalised in terms of the second-order PMO theory.

Further explorations on asymmetric synthesis of thiiranes and full details of this communication are currently under way in our laboratory.

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References and notes

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6. Selected data for **6a**: 15%, mp 192-193°, $[\alpha]_D$ +106° (*c* 0.5, $CHCl_3$); IR (KBr) 1760 (C=O ester) and 1683 cm^{-1} (C=O amide); UV (CH_2Cl_2) 267 nm (ε_{mM} 18.5); ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.91 (s, 1H, thiirane ring); ^{13}C-NMR (50.33 MHz, $CDCl_3$): δ 149.68 (s, C=O urea), 53.99 (s, thiirane ring), and 46.93 (d, thiirane ring). **7a**: 11%, mp 201-202°, $[\alpha]_D$ -71° (*c* 0.5, $CHCl_3$); IR (KBr) 1753 (C=O ester) and 1680 cm^{-1} (C=O amide); UV (CH_2Cl_2) 272 nm (ε_{mM} 26.8); ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.86 (s, 1H, thiirane ring); ^{13}C-NMR (50.33 MHz, $CDCl_3$): δ 149.63 (s, C=O urea), 54.23 (s, thiirane ring), and 47.11 (d, thiirane ring).
7. Diánez, M. J., Estrada, M. D., Pérez-Garrido, S., and López-Castro, A., *Acta Crystallograph.*, in press.
8. Selected data for **8a**: Mp 184-185°, $[\alpha]_D$ +184° (*c* 0.5, $CHCl_3$); IR (KBr) 1753 (C=O ester) and 1668 cm^{-1} (C=O amide); UV (CH_2Cl_2) 356 and 242 nm (ε_{mM} 15.2 and 18.6); ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.05 (s, 1H, alkene); ^{13}C-NMR (50.33 MHz, $CDCl_3$): δ 150.84 (s, C=O urea), 137.98 (d, alkene), and 130.60 (s, alkene).
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10. Yields and physical data for **6b**: 24%, mp 188-189°, $[\alpha]_D$ +152° (*c* 0.5, $CHCl_3$). **6c**: 16%, mp 157-158°, $[\alpha]_D$ +122° (*c* 0.5, $CHCl_3$). **6d**: 31%, mp 141-142°, $[\alpha]_D$ +125° (*c* 0.5, $CHCl_3$). **8e**: 50%, mp 137-138°, $[\alpha]_D$ +100° (*c* 0.5, $CHCl_3$).
11. Satisfactory elemental analyses were obtained for all new compounds.

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