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5-Carbonyl-1,3-oxazine-2,4-diones from *N*-Cyanosulfoximines and Meldrum's Acid Derivatives

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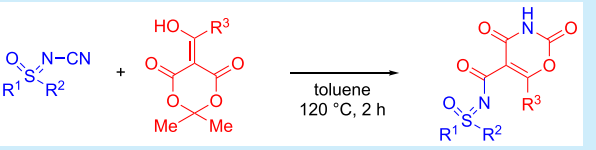
ABSTRACT: At elevated temperatures, *N*-cyanosulfoximines react with Meldrum's acid derivatives to give sulfoximines with *N*-bound 5-carbonyl-1,3-oxazine-2,4-dione groups. A representative product was characterized by single-crystal X-ray structure analysis. The product formation involves an unexpected molecular reorientation requiring several sequential bond-forming and -cleaving processes.

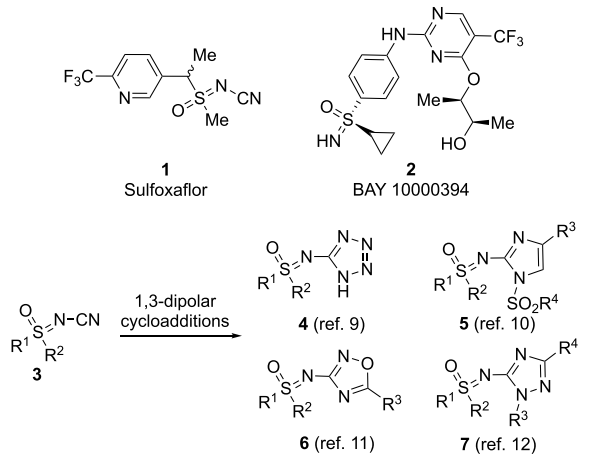


For centuries, organic chemists have discovered unprecedented reaction pathways. Many of those have become the basis for "name reactions".[1] Serendipity, rational design, and computational reaction prediction have all proven fruitful in expanding the preparative boundaries of organic chemistry.[2]

Because of their valuable chemical features and broad bioactivity profiles, sulfoximines have continuously been investigated and developed for applications in both crop protection and medicinal chemistry.[3] For example, the *N*-cyano sulfoximine sulfoxaflor (**1**) is an insecticide developed by Dow AgroSciences, which exhibits a high efficiency against a wide range of sap-feeding insects.[4] In medicinal chemistry, Bayer Pharma introduced Pan-CDK inhibitor BAY 10000394 (**2**), which entered clinical trials (Scheme 1).[5]

The physicochemical properties of sulfoximines can be fine-tuned by functionalizing the S-bound nitrogen. In the series of the respective products, *N*-cyanosulfoximines **3** play a very particular role. They can easily be accessed by well-established synthetic protocols,[6] and their defined stability[7] allows them to be applied as useful intermediates in the preparation of other *N*-functionalized sulfoximine derivatives.[6] Direct applications of *N*-cyanosulfoximines include the aforementioned use of sulfoxaflor (**1**) as insecticide[4] and various attempts to affect enzyme actions in a range of biomedical test systems.[8] To modify the *N*-cyano group of **3**, several 1,3-dipolar cycloadditions have been developed (Scheme 1) providing sulfoximines with various N-bound heterocyclic substituents such as **4**–**7** (Scheme 1).[9−13] We now wondered about reactions of *N*-cyanosulfoximines with another type of cycloaddition partner: Meldrum's acid derivatives **8**.

Scheme 1. Bioactive Sulfoximines and *N*-Cyano Derivatives in 1,3-Dipolar Cycloaddition Reactions



In general, Meldrum's acid derivatives such as **8** have widely been used as acylation agents and precursors for acylketenes **9**.[14] The latter compounds are of interest because they easily undergo [4 + 2] cycloaddition reactions.[15] Accordingly, we expected the formation of 2-sulfoximidoyl-substituted 4*H*-1,3-oxazine-4-one **10aa** when **8a** and *N*-cyanosulfoximine **3a** were heated in toluene (Scheme 2). To our surprise, however, the NMR data of the product were inconsistent with the structure of **10aa**, suggesting that sulfoximine **11aa** was formed. Although unexpected, the generation of **11aa** appeared reasonable taking into account the general reaction behavior of Meldrum's acid derivatives, which also involves the cleavage of ketonic components providing dipolar intermediates **12** (Scheme 2).[14,15]

In order to unequivocally confirm the product structure, an X-ray crystal structure analysis of the sulfoximine obtained

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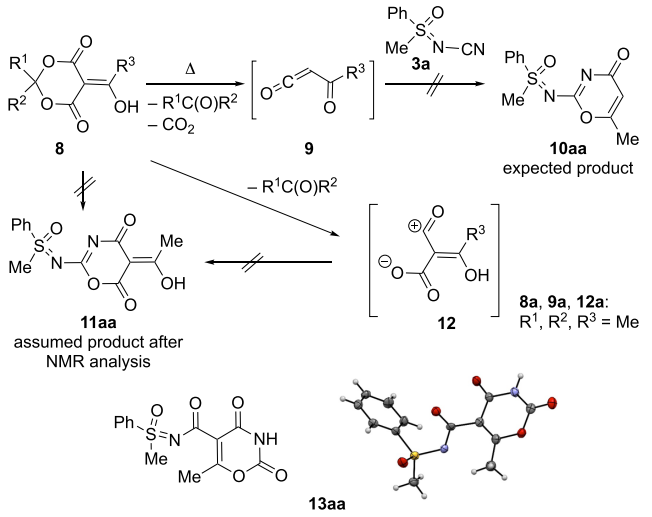
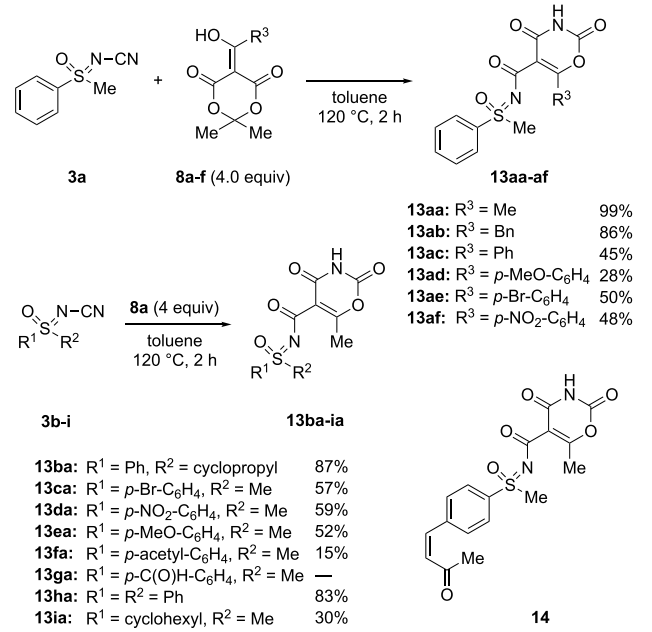
Scheme 2. Reactivity of Meldrum's Acid Derivatives, Assumed Compounds 10aa and 11aa and Obtained Product 13aa[16]



from the reaction of **3a** with **8a** was performed (Scheme 2). Again, we were caught by surprise because none of the so far considered structures were correct. Instead of **10aa** or **11aa**, an isomer of **11aa** (product **13aa**) representing a sulfoximine with an *N*-bound 5-carbonyl-1,3-oxazine-2,4-dione group was found.

Varying the reaction parameters revealed that **13aa** could be obtained in 99% yield when a 1:4 mixture of **3a** and **8a** in toluene was kept for 2 h at 120 °C.[17] Under these conditions, other Meldrum's acid derivatives reacted with **3a** analogously providing the corresponding products **13ab**–**af** in yields ranging from 28% to 86% yield (Scheme 3). In this series, the best results were obtained with substrates **8a** and **8b** having as R^3 a methyl or a benzyl group, respectively. Lower yields were observed with Meldrum's acid derivatives **8c**–**f** having aryl substituents at that position. This was particularly true for

Scheme 3. Substrate Scope

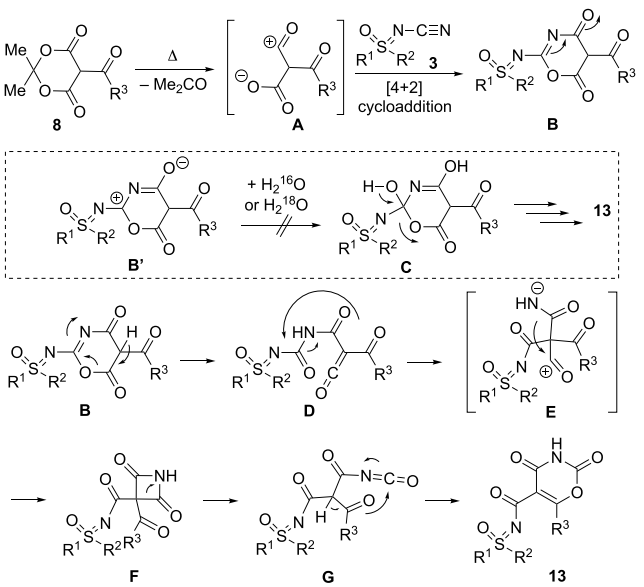


8d bearing an electron-donating ether group on the arene, which gave **13ad** in only 28%. The moderate yield of **13af** (48%) is a result of the water sensitivity of **8f**, which rapidly hydrolyzes. On a 4 mmol scale, **13aa** was obtained in 90% yield.

Next, the sulfur component was varied, and several other *N*-cyanosulfoximines were applied in reactions with Meldrum's acid derivative **8a** (Scheme 3). Again, the yields of the corresponding products **13ba**–**ia** spanned a wide range (from 15% to 87%). Among the *S*-alkyl *S*-aryl derivatives, *S*-cyclopropyl *S*-phenyl sulfoximine **3b** performed best providing **13ba** in 87% yield. For unknown reasons, the presence of a *para* substituent on the arene reduced the product yields (**13ca**–**ga**). Distinct electronic effects were not identified. An interesting observation was made in the reaction of **8a** with *p*-formyl-substituted sulfoximine **3g**. In this case, we expected the formation of **13ga**, but instead compound **14** was obtained (13% yield). Presumably, **14** stemmed from **13ga**, which had undergone a subsequent aldol reaction with in situ formed acetone resulting from the degradation of Meldrum's acid derivative **8a**. NMR spectroscopy suggested an exclusive formation of the *Z* isomer of **14**, which contrasted observations by Bhat and co-workers, who found high *E* selectivities in related organocatalytic reactions providing *α*,*β*-unsaturated ketones.[18] While the use of *S*,*S*-diphenyl sulfoximine **3h** led to **13ha** in 83% yield, *S*,*S*-dialkyl-substituted substrate **3i** afforded **13ia** in only 30% yield.

Scheme 4 shows a tentative multistep reaction sequence converting *N*-cyanosulfoximines **3** and Meldrum's acid

Scheme 4. Proposed Reaction Mechanism



derivatives **8** to the observed products **13**. Because none of the depicted intermediates **A**–**G** could be isolated or detected, the proposed transformation has to be taken with great care. The process is initiated by elimination of acetone from **8** providing zwitterion **A**. (Note that **A** could loose CO_2 leading to acylketene **9**. Then, however, CO_2 would have to re-enter at a later stage because it is part of the product.) Regioselective addition of **A** on *N*-cyanosulfoximine **3** yields intermediate **B**. Initially, we hypothesized that the formation of the *N*-acyl group of **13** involved the addition of water to **B** (or **B′**) to give

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C. Results from reactions under strictly anhydrous conditions and experiments with $H_2{}^{18}O$, however, which did not result in any detectable incorporation of ^{18}O in the product (as determined by MS analysis), made this first assumed reaction pathway unlikely.[19] Taking **B** as starting point, an alternative reaction path was considered beginning with a ring-opening of heterocycle of **B** leading to acylketene **D**. Converting **D** into **13** requires a significant molecular rearrangement with several C−N bond cleavage and formation events. A potential reaction path could involve hypothetic structures such as **E** and **F** leading to acyl isocyanate **G**, which cyclized by attack of the ketonic oxygen of **G** onto the acyl isocyanate group followed by proton shift to give to the observed product **13**.[20]

The irreversibility of the process was shown by a crossover experiment, which also revealed that there was no intermolecular exchange. Thus, neither **13ab** nor **13ha** were detected by ESI MS upon stirring of **3h** and **8b** at 120 °C in the presence **13aa**.

In summary, reactions between *N*-cyanosulfoximines **3** and Meldrum's acid derivatives **8** afforded unexpected products with 5-carbonyl-1,3-oxazine-2,4-dione groups at the sulfoximine nitrogen. X-ray crystal structure analysis revealed the molecular details of a representative product. A multistep reaction sequence starting with a [4 + 2] cycloaddition followed by several scaffold reorientations has been proposed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02504.

Experimental procedures, characterization data, NMR spectra for new compounds, and X-ray crystallography data (PDF)

Accession Codes

CCDC 1993374 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(16) At the lower right of Scheme 2 an ORTEP plot of the molecular structure of **13aa** with the thermal displacement parameters at 50% probability level is shown.

(17) At ambient temperature, the reaction was very slow (ca. 5% conversion of **3a** after 2 h as determined by NMR spectroscopy). At 70 °C, the reaction mixture still contained unreacted **8a**.

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(19) Also the addition of 1.1 equiv of NaCN as potential source for cyanide as nucleophile did not alter the reaction outcome.

(20) We gratefully mention an alternative reaction path for the formation of **13** suggested by a reviewer of the manuscript. If the carbonyl of the Meldrum's acid derivative is attacked by the sp^2-hybridized nitrogen atom of the *N*-cyanosulfoximine, acetone is released. Cleavage of NC^+ and its subsequent migration onto the carboxylate (via a 6-membered ring) forms a neutral species with a C(O)OCN moiety, which rearranges to its more stable isomer **G** by NCO^- cleavage followed by attack of the N atom onto the acylium ion. Finally, **13** is formed from **G** by the last step shown in Scheme 4. Although we initially excluded this mechanism due to the involvement of NC^+, we now see analogies to the formation of *N*-trifluoroacetyl-protected sulfoximines obtained by treatment of *N*-cyanosulfoximines with TFAA (trifluoroacetic anhydride) as described in ref 6b.

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