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Synthesis of α-Thiooximes by Addition of Thiols to *N*,*N*-Bis(oxy)-enamines: A Comparative Study of S-, N-, and O-Nucleophiles in Michael Reaction with Nitrosoalkene Species

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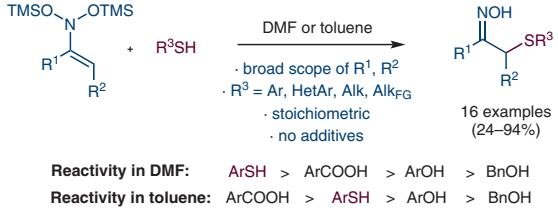

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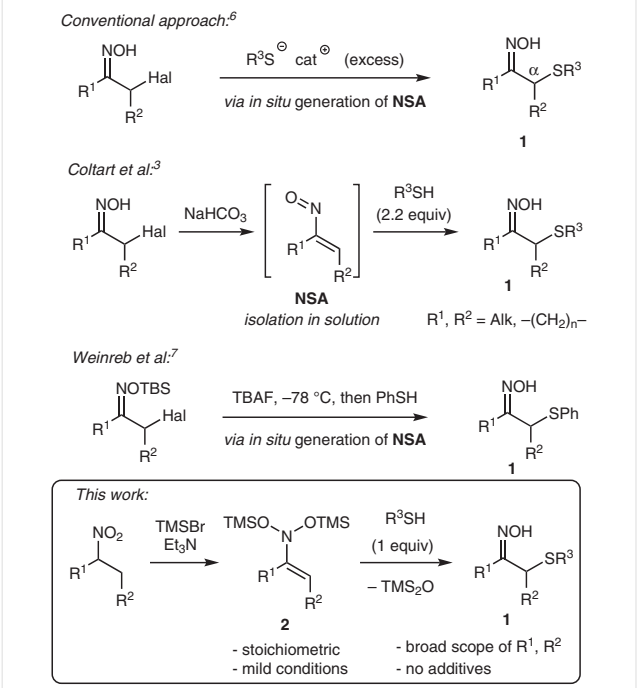
Abstract Nucleophilic addition of thiols to *N*,*N*-bis(oxy)enamines (nitrosoalkene acetals) produce valuable α-thiooximes in a highly efficient manner. The reaction was found to be solvent-dependent, likely because of distinct mechanisms operating in nonpolar and basic solvents (involving either Brønsted acid or Lewis base catalysis). By performing a series of competition experiments, the relative reactivity of S-, N-, and O-nucleophiles in reaction with *N*,*N*-bis(oxy)enamines was determined for the first time. Interestingly, the relative nucleophilicity was found to be highly dependent on the solvent, which allows regioselective control of these reactions by using an appropriate medium.

Key words thiols, nitrosoalkenes, oximes, Michael addition, solvent effects

Michael addition of S-nucleophiles to conjugated nitrosoalkenes (NSA) is a promising strategy for the synthesis of α-thiooximes **1** (Scheme 1), which are important bioactive compounds,[1] ligands,[2] and precursors of synthetically valuable α-thioketones,[3] 1,2-mercaptoamines,[4] and 1,2-mercaptohydroxylamines.[1b] However, because of the unstable and reactive character of most NSA dervatives,[5] achieving successful Michael addition is challenging and depends on many factors including temperature, concentration, and, especially, the nature of the NSA precursor.[5d–f]

Conventional precursors of NSA are α-halooximes, which eliminate HHal upon the action of a base.[5c] Since the 1960s numerous examples of the reaction of S-nucleophiles with α-halooximes have been reported.[6] Although good yields were generally observed, the reaction required an excess of thiolate, which also acted as a base to generate the nitrosoalkene intermediate. In a recent procedure developed by Coltart et al., NSA were generated in a dilute solution prior the reaction with a nucleophile.[3] However, this procedure is applicable only to sterically demanding trisubstituted nitrosoalkenes,[5a] for which polymerization proceeds slowly under dilute conditions. Furthermore, 2.2 equivalents of S-nucleophile (thiol) are used on the second stage. Weinreb and co-authors[7] successfully utilized TBS-ethers of α-halooximes as NSA sources in reaction with thiophenol. This method employs an almost stoichiometric amount of thiol, however, equimolar amount of tetrabutylammonium fluoride (TBAF) is needed to generate NSA.

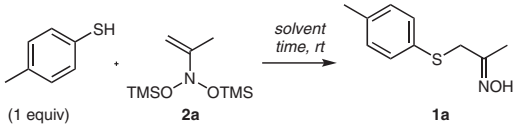


Scheme 1 Previous and suggested approaches to α-thiooximes **1**

Recently, we reported that *N*,*N*-bis(siloxy)enamines **2**, accessible by double silylation of nitroalkanes,[8] serve as highly efficient equivalents of NSA in reactions with N- and O-nucleophiles.[9] In these reactions, a stoichiometric amount of nucleophile is used in H-form, and no special additives such as bases or fluoride sources are needed. In this paper, we report studies on the reaction of enamines **2** with aromatic and aliphatic thiols, which led to the development of a highly efficient and general protocol for the synthesis of α-thiooximes **1**. Furthermore, here we report a first comparative study on the Michael addition of S-, N-, and O-nucleophiles to nitrosoalkene species.

Initially, interaction of model *N*,*N*-bis(siloxy)enamine **2a** with *p*-thiocresol was explored in different solvents (Table 1). In all tested solvents, except *N*,*N*-dimethylformamide (DMF), formation of the desired α-thiooxime **1a** was slow and a considerable amount of starting material remained after 2 h (entries 1–3). Prolonged exposure resulted in increased conversion and yield in hexane and toluene (entries 6 and 7). However, in reactions conducted in DMF and CH_2Cl_2 no substantial increase of yield was observed after 2 h (entries 5 and 8).

Table 1 Reaction of *p*-Thiocresol with Enamine **2a**: An Optimization Study



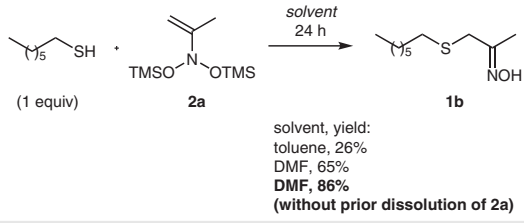
(1 equiv) **2a** **1a**

Entry	Solvent	Time (h)	Yield of **1a** (%)[a]
1	CH_2Cl_2	2	13[b]
2	hexane	2	37[c]
3	toluene	2	27
4	DMF	2	43[d]
5	CH_2Cl_2	24	31
6	hexane	24	77
7	**toluene**	**24**	**78**
8	DMF	24	48
9	no solvent	24	43
10	water	24	52
11	urea/ChCl (2:1)[d]	24	37

[a] Determined by ^{1}H NMR analysis with internal standard.
[b] Conversion of **2a**: 56%.
[c] Conversion of **2a**: 55%.
[d] Conversion of **2a**: >99%.
[d] ChCl: choline chloride.

We also attempted the synthesis of product **1a** under green conditions. Thus, solvent-free coupling of *p*-thiocresol with enamine **2a** delivered oxime **1a** in 43% yield (Table 1, entry 9). A slightly better result (52% yield) was obtained in the reaction carried out 'on water' (entry 10). Recently, deep eutectic solvents (DES) were demonstrated to be highly efficient for reactions involving nitrosoalkenes.[6f] In our reaction, however, the use of urea-choline chloride DES resulted in rather poor yield of α-thiooxime **1a** (entry 11).

Surprisingly, the reaction of enamine **2a** with less acidic *n*-heptanethiol in toluene produced the desired adduct **1b** only in 26% yield (Scheme 2). Switching to DMF, however, gave product **1b** in much higher yield (65%). Further increase in the yield of **1b** (up to 86%) was achieved by adding a solution of *n*-heptanethiol in DMF to *N*,*N*-bis(siloxy)enamine **2a** without prior dissolution of the latter. This can be attributed to the previously observed limited stability of enamines of type **2** in DMF.[9c]

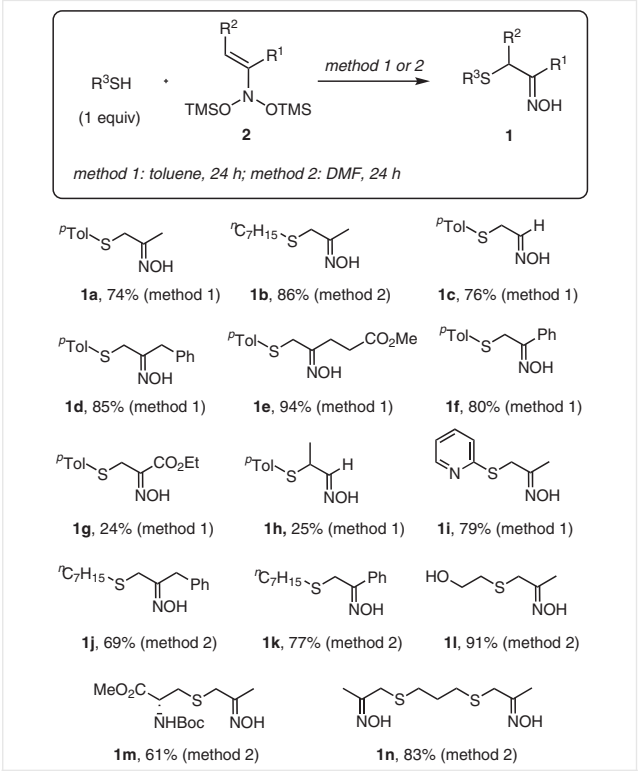


Scheme 2 Reaction of *n*-heptanethiol with enamine **2a**

These model experiments demonstrate that different media are needed for reactions with aromatic and aliphatic thiols.[10] With the optimized conditions in hand, the substrate scope was studied. As can be seen from Scheme 3, various bis(oxy)enamines **2** successfully reacted with an equimolar amount of *p*-thiocresol in toluene (method 1) to afford the corresponding α-thiooximes **1** in good yields. Importantly, reactions involve surrogates of highly unstable mono-substituted nitrosoalkenes or even nitrosoethylene as intermediates.[5a] Addition of *p*-thiocresol to bis(oxy)enamines **2** bearing an electron-withdrawing group ($R^1 = CO_2Et$) or internal double bond ($R^1 = H$, $R^2 = CH_3$) produced the corresponding products **1g** and **1h** in only moderate yields.

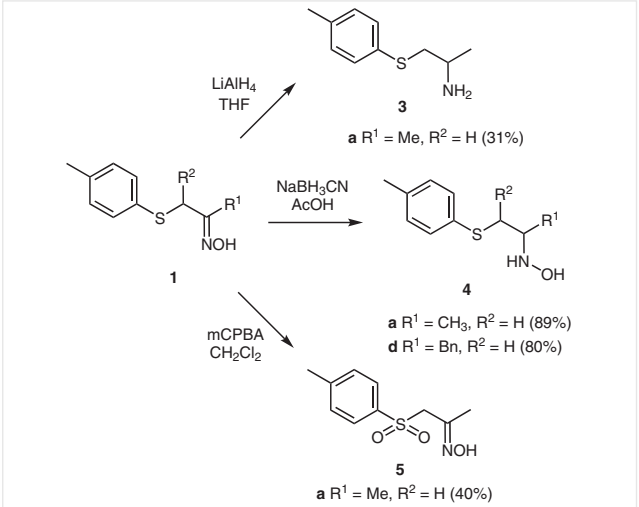
Different thiols reacted with enamines **2** to give the corresponding α-thiooximes **1** in good yields (Scheme 3). Reactions with aromatic thiols were conducted in toluene (method 1), whereas more nucleophilic aliphatic thiols reacted smoothly with enamines **2** in DMF solution (method 2). The reaction is well-tolerated by nucleophilic pyridine and alcohol moieties, as demonstrated by the synthesis of products **1i** and **1l**. Protected L-cysteine was also successfully oximinoalkylated at the free SH-group (see adduct **1m**). Dioxime **1n**, prepared from 1,3-propanedithiol, is a known chelating ligand for Cu(II).[2d]

Most of the oximes were isolated as dynamic mixtures of *E*- and *Z*-isomers (for details see the Supporting information).



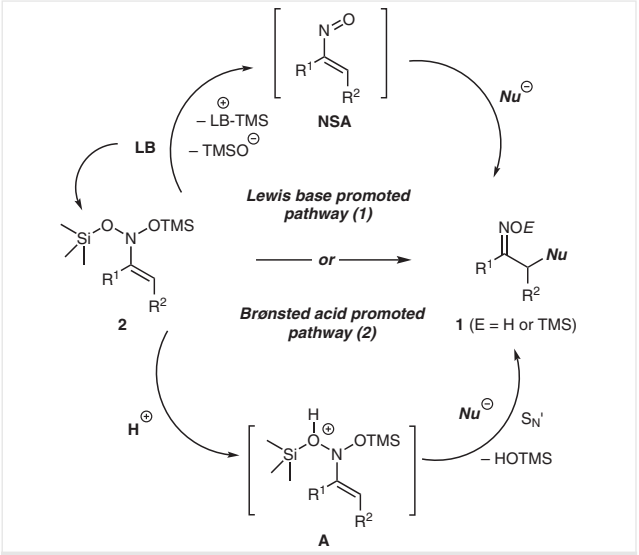
Scheme 3 Reaction of thiols with enamines **2**: a substrate scope study

α-Thiooximes **1** are useful precursors of vicinal N,S-containing organic compounds, as shown in Scheme 4. Thus, model α-thiooximes **1a** and **1d** were transformed into the corresponding amines **3** and hydroxylamines **4** by selective reduction of the oxime group or into sulfones **5** by oxidation of the sulfide moiety. 1-(*p*-Tolylthio)propan-2-amine (**3a**) exhibits antidepressant activity in mice, as described previously.[11]



Scheme 4 Representative transformations of α-thiooximes **1**

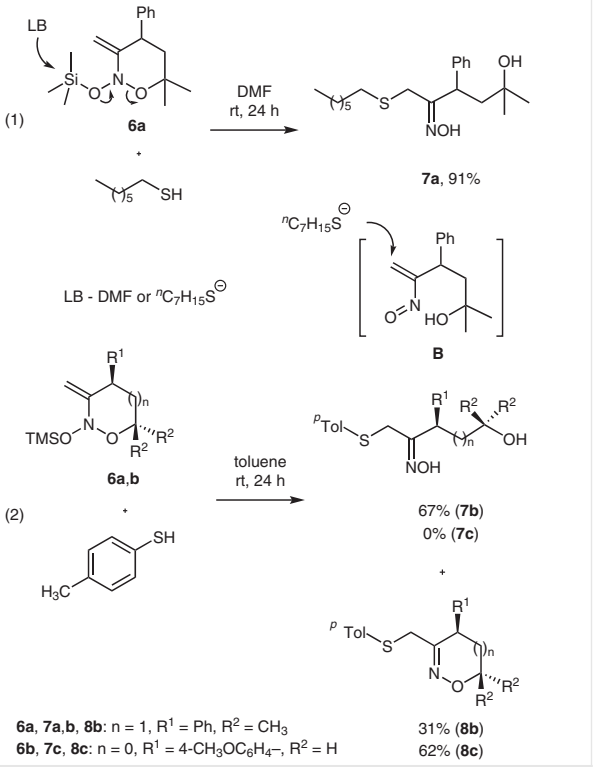
The mechanism of thiol addition to bis(oxy)enamines **2** is of particular concern (Scheme 5). Two reaction pathways can be suggested based on our previous studies with HO-acids:[9c] (1) the generation of NSA from enamine **2** upon the action of Lewis base (LB – solvent or thiolate anion) followed by Michael addition of S-nucleophile (elimination-addition mechanism) or (2) the Brønsted acid promoted S_N' substitution of the OTMS-group with a thiolate-anion in cation **A**. Given that thiols are both nucleophiles and Brønsted acids, both pathways can in principle operate. Furthermore, the realization of these pathways may depend on the solvent. In most reactions carried out in DMF, the appearance of a light-blue color was observed, indicating the generation of transient NSA.



Scheme 5 Lewis base and Brønsted acid promoted mechanisms leading to α-thiooximes **1**

To reveal the exact mechanism involved, experiments with a non-symmetrical en-nitrosoacetals **6**[12] were performed (Scheme 6).

In the reaction of **6a** with 1-heptanethiol in DMF (Scheme 6, reaction 1), only the open-chain product **7a** was formed, suggesting the participation of nitrosoalkene **B** as intermediate. In the experiment with *p*-thiocresol in toluene (Scheme 6, reaction 2), in addition to open-chain product **7b**, the cyclic oxime ether **8b** was also isolated. The latter cannot arise from nitrosoalkene **B**, and is likely to form through the Brønsted acid promoted S_N' substitution of the OTMS-group (Scheme 5, pathway (2)). In the case of five-membered cyclic bis(oxy)enamine **6b**, only the isoxazoline product **8c** was isolated. Thus, it can be suggested that, in DMF, reactions proceed only through the nitrosoalkene pathway (1), whereas in toluene both pathways (1) and (2) are realized.



Scheme 6 Addition of thiols to non-symmetrical en-nitrosoacetals **6**

Low performance of aliphatic thiols in toluene (Scheme 2) can be explained by their lesser acidity compared with thiophenols and thus an inability to promote pathway (2).

Although many nucleophiles have been involved in reaction with nitrosoalkenes[5b,c] and nitrosoacetals **2**,[9] their relative reactivity has not been studied before. Therefore, we conducted a series of competition experiments employing *p*-thiocresol, *n*-heptanethiol, *p*-ethylphenol, benzoic acid, diethylamine, and benzyl alcohol as reference nucleophiles. In these competition experiments, a pair of nucleophiles was reacted with one equivalent of model enamine **2a** in either DMF or toluene. The distribution of products (average of two experiments each) is shown in Figure 1.

The overall trend in reactivity of nucleophiles deduced from these experiments is shown below (Figure 2, lines (1) and (2)). Benzyl alcohol proved to be the least reactive both in DMF and toluene. As for other nucleophiles, different selectivities were observed in DMF and toluene. For example, *p*-thiocresol was found to the most reactive in DMF, whereas in toluene, benzoic acid reacted with **2a** most readily.

Reactivity in toluene:

(1) PhCOOH > *p*-$CH_3C_6H_4SH$ > Et_2NH > *p*-EtC_6H_4OH > BnOH

Reactivity in DMF:

(2) *p*-$CH_3C_6H_4SH$ > Et_2NH > PhCOOH > *p*-EtC_6H_4OH > BnOH

Figure 2 Relative reactivity of S-, N-, and O-nucleophiles

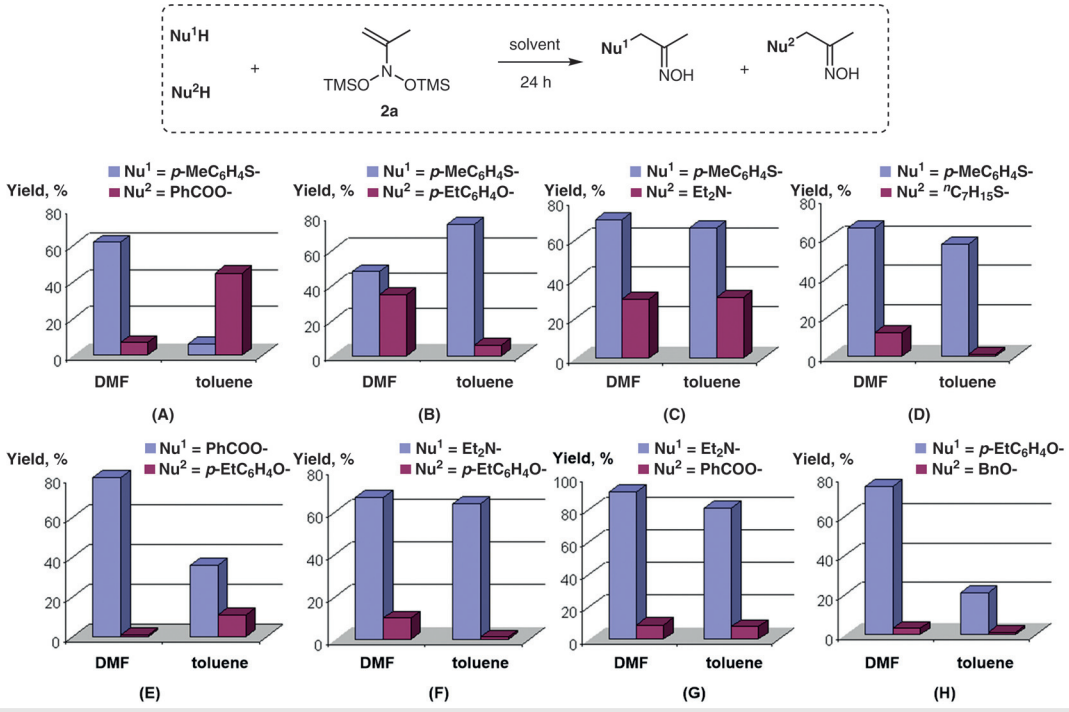


Figure 1 Competition experiments on the addition of various S-, N-, and O-nucleophiles to *N*,*N*-bis(oxy)enamine **2a**

The observed trends are in line with the hypothesis that different mechanisms are operating in DMF and toluene. In toluene, the reactivity generally correlates with the acidity of the H-form of nucleophile, as can be expected assuming the protic acid promoted pathway (2). Diethylamine is an exception, since being a strong nucleophile it initiates the nitrosoalkene pathway (1) independently of the solvent used. Interestingly, in the competition experiment with benzoic acid and diethylamine in toluene (Figure 1 (G), toluene), the addition of diethylamine dominated, in contradiction to the trend shown in Figure 2. This is likely because of the deprotonation of benzoic acid under these conditions that blocks Brønsted acid promoted pathway (2).

In DMF, the reactivity trend is more complicated. In the competition experiments conducted in DMF, the addition of *p*-thiocresol dominated over the addition of benzoic acid and diethylamine (cf. data in Figures 1 (A) and (C)). Presumably, the transient nitrosoalkene NSA reacts not with *p*-thiocresol itself, but with its highly nucleophilic anion, which is reversibly generated upon dissociation of thiol in DMF. For this reason, *p*-thiocresol is more reactive than the more nucleophilic diethylamine (Figure 1 (C), DMF). Therefore, for reactions in DMF both nucleophilicity and acidity of HNu are important.

In conclusion, a general protocol for the synthesis of α-thiooximes **1** from nitroalkanes has been developed. The suggested method is based on the addition of thiols to readily available *N*,*N*-bis(oxy)enamines **2** without the need for additives such as bases or the fluoride anion. The reactivity of aliphatic and aromatic thiols toward enamines **2** was found to be somewhat different and solvent dependent, which was attributed to two distinct mechanisms taking place. In DMF, thiols were found to be more reactive as compared to alcohols, phenols, amines, and carboxylic acids. These results may be helpful in controlling regioselectivity in reactions of nitrosoalkene species with substrates bearing several nucleophilic sites.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591973. Supporting Information contains experimental procedures, characterization data, copies of NMR and FT-IR spectra and primary data for Figure 1.

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(10) **General procedure for the addition of thiophenols to *N*,*N*-bis(oxy)enamines 2 (method 1):** To a stirred solution of *N*,*N*-bis(oxy) enamine **2** (1 mmol) in toluene (6 mL) was added *p*-thiocresol (124 mg, 1 mmol) or pyridine-2-thiol (111 mg, 1 mmol). After keeping for 24 h at room temperature, methanol (5 mL) was added and the mixture was stirred for 1 h and concentrated in vacuum (ca. 45 °C). The residue was subjected to column chromatography on silica gel to give the corresponding α-thiooxime **1**. Yields are given in Scheme 3 and in the Supporting information.

1-(*p*-Tolylthio)propan-2-one oxime (1a): White crystals; mp 81–83°C (pentane–Et_2O); R_f = 0.29 (EtOAc–hexane, 1:1); dynamic mixture of *E*/*Z*-isomers, ratio 3:1. ^{1}H NMR (300 MHz, $CDCl_3$, *E*-isomer): δ = 8.35–8.23 (br, 1 H, NOH), 7.31–7.24 (d,

J = 8.1 Hz, 2 H, 2 × =CH), 7.09 (d, J = 8.1 Hz, 2 H, 2 × =CH), 3.56 (s, 2 H, CH_2), 2.32 (s, 3 H, H_3C-Ar), 1.99 (s, 3 H, H_3C-C=N). ^{13}C NMR (50 MHz, DEPT135, $CDCl_3$, *E*-isomer): δ = 155.09 (C=N), 137.19 (C=*C*-CH_3), 131.39 and 129.84 (4 × =CH), 131.00 (=C-*S*), 39.93 (CH_2), 21.16 (H_3C-Ar), 12.89 (H_3C-C=N). ^1H NMR (300 MHz, $CDCl_3$, *Z*-isomer): δ = 8.53–8.38 (br, 1 H, NOH), 7.31 (d, J = 8.1 Hz, 2 H, 2 × =CH), 7.09 (d, J = 8.1 Hz, 2 H, 2 × =CH), 3.79 (s, 2 H, CH_2), 2.32 (s, 3 H, H_3C-Ar), 1.92 (s, 3 H, H_3C-C=N). ^{13}C NMR (50 MHz, DEPT135, $CDCl_3$, *Z*-isomer): δ = 154.94 (C=N), 136.84 (C=*C*-CH_3), 131.78 (=C-*S*), 130.33 and 129.84 (4 × =CH), 30.68 (CH_2), 21.19 (H_3C-Ar), 19.22 (H_3C-C=N). FTIR (KBr): 3239 (s, br), 3104 (s, sh), 3022 (s, sh), 2920 (s), 2870 (s), 1660 (m), 1493 (s), 1448 (s), 1411 (s), 1368 (s), 1270 (m), 1230 (w), 1159 (m), 1091 (m), 1018 (s), 963 (s), 867 (m), 805 (s), 721 (m), 629 (m), 500 (s) cm^{-1}. HRMS: m/z $[M+H]^+$ calcd. for $[C_{10}H_{14}NOS]^+$: 196.0793; found: 196.0791.

General procedure for the addition of aliphatic thiols to *N*,*N*-bis(oxy)enamines 2 (method 2): A solution of thiol (1 mmol) in dimethylformamide (1.5 mL) was added to the corresponding *N*,*N*-bis(oxy)enamine **2** (1 mmol; 2 mmol for product **1n**) with vigorous stirring. After keeping for 24 h at room temperature, methanol (5 mL) was added and the mixture was stirred for 1 h and concentrated in vacuum (ca. 45 °C). The residue was dried in vacuum (1 Torr, ca. 50 °C) to remove DMF and then subjected to column chromatography on silica gel to give the corresponding α-thiooxime **1**. Yields are given in Scheme 3 and in the Supporting information.

1-(Heptylthio)propan-2-one oxime (1b): Oil; R_f = 0.89 (EtOAc–hexane, 1:1); single isomer. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.25 (s, 1 H, NOH), 3.19 (s, 2 H, CH_2C=N), 2.44 (t, J = 7.4 Hz, 2 H, CH_2S), 2.00 (s, 3 H, CH_3), 1.61–1.51 and 1.41–1.24 (2 m, 2 H and 8 H, 5 × CH_2), 0.89 (t, J = 6.8 Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.72 (C=N), 36.47 (*C*H_2C=N), 31.80, 31.30, 29.27, 28.94, 28.86 and 22.67 (6 × CH_2), 14.13 and 12.64 (2 × CH_3). HRMS: m/z $[M+Na]^+$ calcd. for $[C_{10}H_{21}NOSNa]^+$: 226.1239; found: 226.1236.

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