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Stereoselective approach to conjugated enone oximes from aliphatic nitro compounds and sulfur ylides

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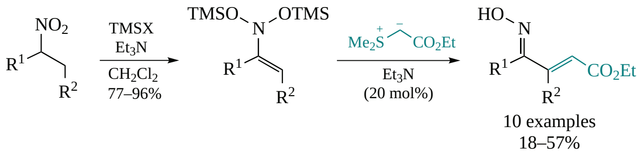
A novel approach to conjugated enone oximes from aliphatic nitro compounds deals with double silylation of *N,N*-bis(silyloxy) enamines followed by a stereoselective reaction with an ester-stabilized sulfur ylide. The proposed mechanism involves the generation of labile nitrosoalkenes as intermediates, which react with the sulfur ylide to give target enone oximes.



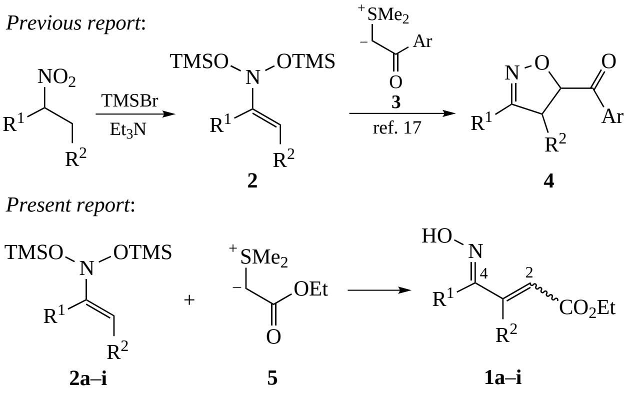
Keywords: ylides, unsaturated oximes, nitro compounds, nitrosoalkenes, Michael addition.

α,β-Unsaturated oximes (conjugated enone oximes) have found recent attention as convenient precursors of six-membered nitrogen heterocycles *via* the transition metal-mediated formal [4+2]-processes driven by the cleavage of labile N–O bond. Thus, a modular synthesis of pyridines by Rh-catalyzed cross-coupling of α,β-unsaturated ketoximes with alkynes[1,2] as well as Rh^{III}-catalyzed formation of pyridine *N*-oxides from enone oximes and α-diazocarbonyl compounds[3] were documented. Acylation of NOH group facilitates the cleavage of the N–O bond and allows using copper catalysts in the aforementioned processes.[4–9]

The synthesis of enone oximes is typically performed by oximation of the corresponding α,β-unsaturated carbonyl compounds.[4,8,10] Another method relies on the silylation of nitro compounds bearing an electron-withdrawing group at the γ-position.[11] In the latter process, the intramolecular reduction of the nitro-group results in the oxidation of the carbon backbone to give enone oximes (for details, see Online Supplementary Materials, Scheme S1). However, carbon–carbon bond forming transformations leading to α,β-unsaturated oximes are rare,[12–14] and to the best of our knowledge no general methods have been described in the literature. Herein, we report on a conceptually novel approach to enone oximes **1** from nitro compounds *via* double silylation of *N,N*-bis(silyloxy) enamines **2** followed by reaction with an ester-stabilized sulfur ylide. The suggested approach exploits unusual umpolung reactivity of *N,N*-bis(silyloxy) enamines **2** as β-C-electrophiles with respect to classical enamines, which are β-C-nucleophiles.[15,16]

In our previous communication,[17] we reported that reaction of *N,N*-bis(silyloxy) enamines **2** with keto-stabilized sulfur ylides of type **3** led to isoxazolines **4** *via* a [4+1]-annulation (Scheme 1). Further studies revealed that the related ester-stabilized sulfur ylide **5** derived from ethyl bromoacetate[18] in reaction with enamines **2** afforded enone oximes **1** instead of expected isoxazolines. Given the aforementioned importance of α,β-unsaturated oximes, this research implies optimization and studying the substrate scope.

Initially, we examined the reaction of model *N,N*-bis(silyloxy) enamine **2a** ($R^1 = Me$, $R^2 = H$) with ylide **5** under various conditions (Table 1). Screening of solvents revealed that in CH_2Cl_2, Et_2O/CH_2Cl_2, THF/CH_2Cl_2 and $CHCl_3$ at 0.5 M concentration of reactants the yields of enone oxime **1a** were higher after 24 h (complete conversion of **2a**) compared to other conventional solvents tested (entries 1–6). Dilution to 0.1 M resulted in a drop of yield (entry 6), as well as caused the decrease in the reaction time to 2 h (entry 7). Raising the temperature and switching to higher boiling 1,2-dichloroethane (1,2-DCE) accelerated the reaction, and full conversion was achieved after 2 h (entry 8). Finally, we observed that the addition of 20 mol% of Et_3N had a positive effect on the yield of target enone oxime **1a** (entry 8). Unfortunately, other changes (the use of excess enamine **2a** or ylide **5**, testing other solvents at elevated temperatures and other Lewis base additives such as DMF, DMPU or TMAO) did not result in any further improvement of



a $R^1 = Me$, $R^2 = H$
b $R^1 = Et$, $R^2 = H$
c $R^1 = Bn$, $R^2 = H$
d $R^1 = CH_2OX$, $R^2 = H$
(**2d** X = TMS, **1d** X = H)
e $R^1 = (CH_2)_2CO_2Me$, $R^2 = H$
f $R^1 = R^2 = H$
g $R^1 = H$, $R^2 = Me$
h $R^1 + R^2 = (CH_2)_3$
i $R^1 = Ph$, $R^2 = H$

Scheme 1

Table 1 Reaction of *N*,*N*-bis(silyloxy) enamine **2a** with ylide **5**: an optimization study.

Entry	Solvent	*t*/h	*T*/°C	Yield[a] of **1a** (%)
1	CH_2Cl_2	24	~20	40[b]
2	$CHCl_3$	24	~20	38[b]
3	$MeCN/CH_2Cl_2$	24	~20	30[b]
4	toluene/CH_2Cl_2	24	~20	33[b]
5	THF/CH_2Cl_2	24	~20	42[b]
6	Et_2O/CH_2Cl_2	24	~20	49[b] (16[c])
7	CH_2Cl_2	2	~20	34[b]
8	1,2-DCE	2	80	46[b] (60[d])

[a] Yields were determined by ^1H NMR with internal standard (trichloroethylene). [b] Ratio **2a**/**5** was 1 : 1, concentration of reagents 0.5 M. [c] Ratio **2a**/**5** was 1 : 1, concentration of reagents 0.1 M. [d] Ratio **2a**/**5** was 1 : 1, concentration of reagents 0.5 M, 20 mol% of Et_3N.

the yield of product **1a** (for more experiments on optimization of conditions, see Online Supplementary Materials, Table S1). Apart from enone oxime **1a**, side products resulting from decomposition of the initial *N*,*N*-bis(silyloxy) enamine **2a** and ylide **5** were detected in reaction mixtures.

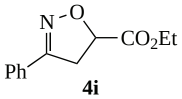
With these optimized conditions in hand, the substrate scope was examined (Table 2) employing a series of *N*,*N*-bis(silyloxy) enamines **2a–i** prepared by silylation of the corresponding nitroalkanes and functionalized nitro compounds with an excess of $TMSBr/Et_3N$ according to previously described protocols[19] (see Scheme 1). NMR analysis of crude mixtures showed that mixtures of enone oximes **1** and their *O*-silyl ethers were formed. For this reason, crude products were treated with NH_4F/MeOH to perform desilylation, and the resulting free oximes **1** were isolated by column chromatography. Reaction of ylide **5** with terminal *N*,*N*-bis(silyloxy) enamines **2a–e** in refluxing 1,2-dichloroethane (procedure i[†]) produced the corresponding enone oximes **1a–e** in moderate yields (see Table 2, entries 1–5). However, with unsubstituted *N*,*N*-bis(silyloxy) enamine **2f** under the same conditions very low yield (<10%) of oxime **1f** was observed (entry 6). This was attributed to a highly reactive character of labile enamine **2f** and its fast decomposition upon heating. Indeed, when reaction was performed at room temperature in Et_2O/DCM mixture (procedure ii[‡]), the desired enone oxime **1f** was obtained in a slightly improved yield (18%). *N*,*N*-Bis(silyloxy) enamines **2g**,**h** with internal double bond are also thermally unstable, and for this reason reactions with ylide **5** were performed at ambient temperature according to procedure ii. Under these conditions, the desired products **1g**,**h** with trisubstituted alkene motif were obtained in acceptable yields (entries 7, 8).

Table 2 Reaction of *N*,*N*-bis(silyloxy) enamines **2a–i** with ylide **5**: substrate scope study.

Entry	**1**, **2**	R^1	R^2	Yield[a] (%) (procedure)
1	**a**	Me	H	57 (i[b])
2	**b**	Et	H	51 (i[b])
3	**c**	Bn	H	28 (i[b])
4	**d**	CH_2OH[c]	H	49 (i[b])
5	**e**	$CH_2CH_2CO_2Me$	H	37 (i[b])
6	**f**	H	H	9 (i[b]), 18 (ii[d,e])
7	**g**	H	Me	55 (ii[d])[f]
8	**h**	$–(CH_2)_3–$		43 (ii[d])
9	**i**	Ph	H	32 (i[b])[g,h]

[a] Yield of isolated material. [b] Procedure i: 1,2-DCE, Et_3N (20 mol%), Δ, 2 h; then NH_4F, MeOH. [c] $R^1 = CH_2OTMS$ in starting *N*,*N*-bis(siloxy) enamine **2d**. [d] Procedure ii: Et_2O/CH_2Cl_2, Et_3N (20 mol%), room temperature, 24 h; then NH_4F, MeOH. [e] Ratio (2*E*,4*E*)-**1f**/(2*Z*,4*E*)-**1f** is 8 : 1. [f] Ratio (2*E*,4*E*)-**1g**/(2*Z*,4*E*)-**1g** is 2 : 1. [g] Ratio (2*E*,4*Z*)-**1i**/(2*E*,4*E*)-**1i** is 13 : 1. [h] In addition to enone oxime **1i**, 42% of ethyl 3-phenyl-4,5-dihydroisoxazole-5-carboxylate **4i** is formed.

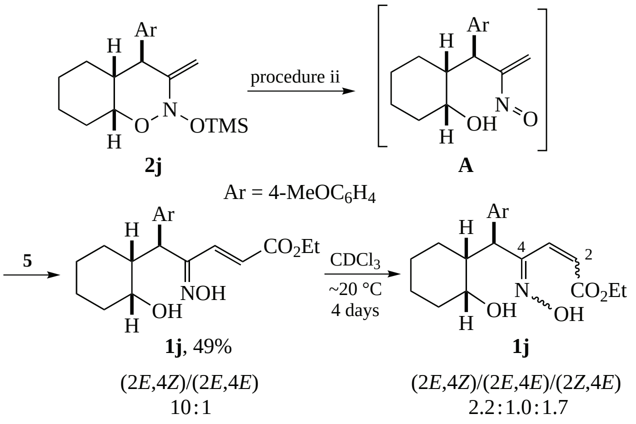
Note that isoxazolines of type **4** (see Scheme 1) were not generally formed in these experiments. However, the case of phenyl-substituted *N*,*N*-bis(silyloxy) enamine **2i** was an exception which brought about a mixture of enone oxime **1i** and isoxazoline **4i** (see Table 2, entry 9). Attempts to separate these two products by column chromatography or crystallization were not successful. To isolate individual compounds, the mixture was subjected to silylation with $TBSCl/Et_3N$. The resulting less polar TBS-ether of **1i** was separated from isoxazoline **4i** by column chromatography, and subsequent desilylation with NH_4F gave free oxime **1i** (see Online Supplementary Materials for a detailed procedure).



4i

Reaction of cyclic *N*-alkoxy,*N*-silyloxy enamine **2j** with sulfur ylide **5** gave an open-chain enone oxime **1j** (Scheme 2). The opening of the 1,2-oxazine ring in the course of the reaction may be an indication of the intermediacy of nitrosoalkene **A** (*vide infra*).

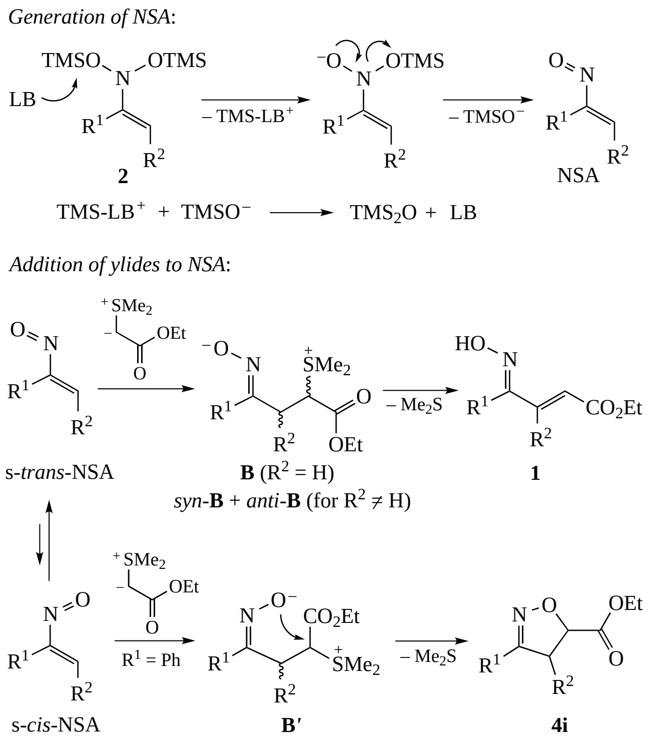
Most of the prepared enone oximes **1** are new. Their structure and stereochemistry were established on the basis of 1D and 2D NMR and elemental analysis. Importantly, the formation of enone oximes **1a–f**,**h–j** was stereoselective, and in most cases only *E*-isomers with respect to the alkene moiety were obtained. The only exception was enone oxime **1g** with trisubstituted C,C-double bond, which was formed as 2 : 1 mixture of *E*/*Z*-isomers. As for the oxime group, in all products the NOH-group was *trans* with respect to the alkene motif. Interestingly, enone oxime **1j** underwent slow isomerization at the C,N- and C,C-double



Scheme 2 *Reagents and conditions*: ylide **5** (1 equiv.), Et_2O/CH_2Cl_2, Et_3N (10 mol%), room temperature, 24 h; then NH_4F, MeOH.

[†] *Procedure i*. To a stirred 1 M solution of ylide **5** (2 ml, 2.0 mmol) in 1,2-dichloroethane were consequently added triethylamine (0.056 ml, 0.4 mmol) and 1 M solution of *N*,*N*-bis(siloxy) enamine **2** (2 ml, 2.0 mmol) in 1,2-dichloroethane. The mixture was heated to gentle reflux with stirring for 2 h. The volatiles were then removed under reduced pressure, and methanol (10 ml) and NH_4F (0.074 g, 2.0 mmol) were added to the residue. After stirring for 15 min at room temperature, the mixture was concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (eluent hexane/ethyl acetate mixtures) to give the desired enone oxime **1**.

[‡] *Procedure ii*. To a stirred 1 M solution of ylide **5** (2 ml, 2.0 mmol) in dichloromethane were consequently added triethylamine (0.056 ml, 0.4 mmol) and 1 M solution of *N*,*N*-bis(siloxy) enamine **2** (2 ml, 2.0 mmol) in diethyl ether. The mixture was stirred at room temperature for 24 h. The further treatment was carried out as in the procedure i.



Scheme 3

bonds upon storage in CDCl$_3$ solution for several days (see Scheme 2).[20,21]

The proposed mechanism for the reaction of *N*,*N*-bis(silyloxy) enamines **2** with sulfur ylides is shown in Scheme 3. We suppose that the process involves unstable nitrosoalkenes NSA as key intermediates.[22,23] Fragmentation of nitroso acetal motif in *N*,*N*-bis(silyloxy) enamine **2** is initially induced by a Lewis base LB, which can be triethylamine, ylide or trimethylsiloxide anion.[24,25] On the next stage, Michael addition of sulfur ylide to NSA produces intermediate **B**, which would eliminate dimethyl sulfide *via* E2-like mechanism producing enone oximes **1**.[14] The observed stereochemistry of the oxime C=N bond (*trans* with respect to the C,C-double bond) originates from the Michael addition to s-*trans*-NSA, which is a dominant conformer for simple nitrosoalkenes.[26] The formation of isoxazoline product **4i** in the case of emanine **2i** with R^1 = Ph can be explained by the cyclization of an isomeric oximate **B′**, which is formed from s-*cis* conformation of the corresponding NSA, namely, (1-nitrosovinyl)benzene. Apparently, for this nitrosoalkene the s-*cis* form is present in a substantial amount as the s-*trans* conformation is somewhat destabilized by a steric repulsion of the N=O group with the phenyl ring.[27]

The observed stereochemistry of enone oximes **1a–f,i** can be rationalized through conformational analysis of transition states for the elimination of dimethyl sulfide from intermediate oximates **B**. As can be seen in Figure 1, the transition state TS2 leading to *Z*-configuration of the C=C bond is destabilized by a steric repulsion between oximate and ethoxycarbonyl groups. When R^2 ≠ H, the stereochemical outcome of the reaction is determined by the ratio of diastereomeric intermediates *anti*-**B** and *syn*-**B** (see Scheme 3). As shown in Figure 1, isomer *E*-**1** is formed from *syn*-**B** *via* TS3, while *Z*-isomer is produced from *anti*-**B** *via* TS4. Thus, a considerable amount of isomer *Z*-**1** can be produced if the formation of intermediate **B** *via* Michael addition to NSA is not diastereoselective (as observed in the case of product **1g** with R^2 = Me).

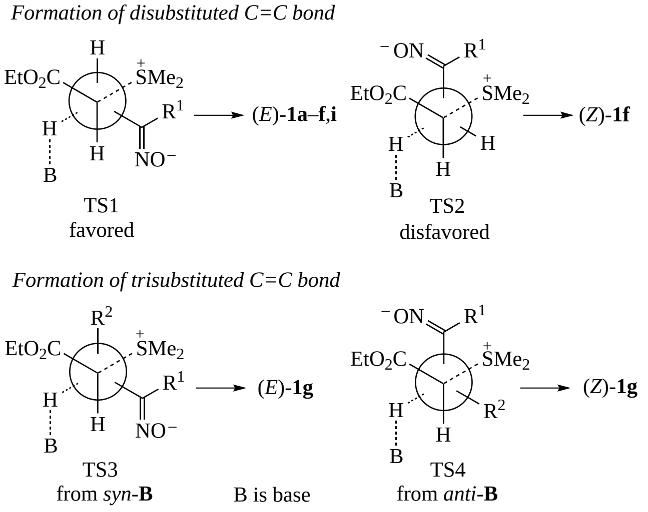


Figure 1 Stereochemical model for the formation of enone oximes **1**.

In conclusion, we have developed a novel approach to α,β-unsaturated oximes starting from aliphatic nitro compounds. The suggested sequence involves double silylation of nitro compounds to afford *N*,*N*-bis(silyloxy) enamines and their subsequent reaction with a sulfur ylide derived from ethyl bromoacetate. The method is general and provides target ene oximes usually as single stereoisomers in moderate yields. The proposed mechanism involves the formation of conjugated nitrosoalkenes as intermediates, which react with the sulfur ylide to give enone oximes.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.09.031.

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