Organic LETTERS

Letter

pubs.acs.org/OrgLett

N-Heterocyclic Carbene Catalyzed Sulfenylation of α,β-Unsaturated Aldehydes

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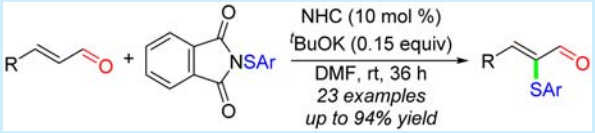
Supporting Information

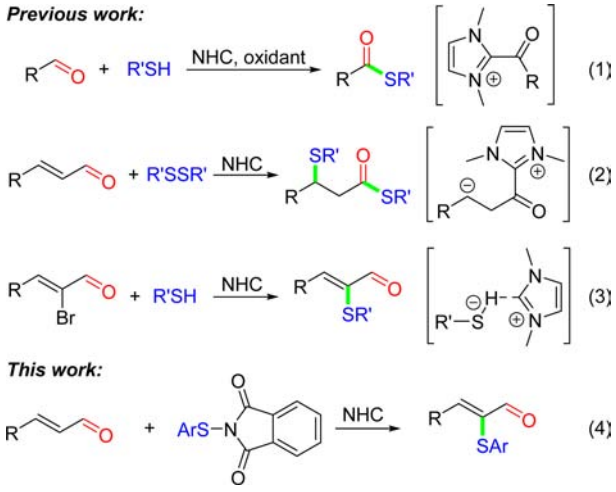
ABSTRACT: An efficient *N*-heterocyclic carbene (NHC) catalyzed sulfenylation reaction of α,β-unsaturated aldehydes with *N*-(arylthio)phthalimide has been developed. A wide variety of α-thioenals can be obtained with good to excellent yields and excellent *Z*-configuration.



Aryl sulfides are privileged motifs found in medicinal chemistry and material science.[1] Among them, vinyl sulfides are also useful synthetic intermediates in synthetic transformations.[2] Due to the many pharmaceutical applications as well as the material values of organosulfur compounds, many remarkable endeavors have been made to develop the construction of carbon−sulfur (C−S) bonds.[3] Over the past decades, significant strategies have been successfully developed for the formation of C−S bonds, mainly including metal-catalyzed cross-coupling reactions, direct substitution reactions, and sulfenylation reactions.[3] Given that organocatalytic sulfenylation reactions using electrophilic sulfur reagents is a powerful approach, several stereoselective C−S bond formation methods have been documented.[4] However, the construction of vinyl sulfides by an organocatalytic strategy is still lacking.[5] As such, the development of an efficient and environmentally friendly sulfenylation method avoiding transition metal catalysts or organometallic reagents is highly desirable.

Recently, the *N*-heterocyclic carbene (NHC) catalyzed reaction has emerged as a powerful strategy in organic chemistry.[6] Traditionally, it can efficiently catalyze the umpolung reactions of aldehydes via the "Breslow intermediate", which is formed through the nucleophilic addition of NHC to aldehyde.[7] This reactive intermediate can be trapped by various electrophilic species.[6] Important advances in NHC catalyzed reactions have been achieved, such as the benzoin condensation,[6,8] the Stetter reaction,[6,9] and reaction of aldehydes with some unconventional reaction partners.[6k,10] Meanwhile, NHC-catalyzed formation of C−S bonds has also been developed.[11] In 2012, Takemoto and co-workers developed an NHC-catalyzed thioesterification of aldehydes with thiols in the presence of a stoichiometric amount of phenazine as the oxidant (Scheme 1, eq 1).[11a] Yadav and co-workers developed NHC-catalyzed dithiolation of α,β-unsaturated aldehydes with disulfides (Scheme 1, eq 2).[11b] In 2014, He, Dai and co-workers developed an NHC-catalyzed formal cross-coupling reaction of α-haloenals with thiols (Scheme 1, eq 3).[11c] Besides these three activation models described above (Scheme 1), another NHC-catalyzed reaction model for the construction of C−S bonds remains undeveloped. In 2006, Fu and co-workers developed an NHC catalyzed intramolecular Heck reaction,[12] in which the carbene was added to the electrophilic β carbon of the α,β-unsaturated ester to generate an enolate intermediate (vide infra). Later, other groups reported similar results by using this strategy.[13] However, to the best of our knowledge, there are no reports of NHC-catalyzed formation of C−S bonds by this strategy. Herein, we report the NHC-catalyzed sulfenylation of α,β-unsaturated aldehydes, which leads to the formation of α-thioenals (Scheme 1, eq 4).

Scheme 1. NHC-Catalyzed C−S Bond Formation

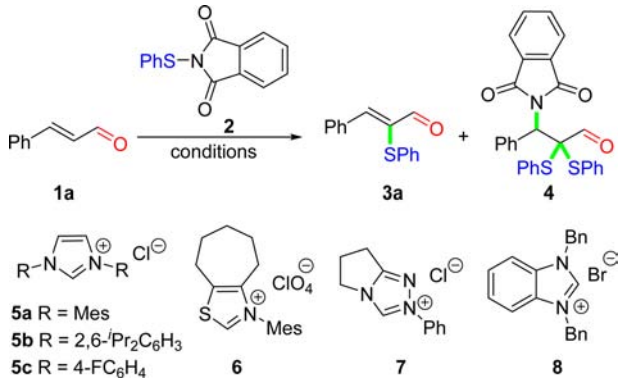


Our initial studies were carried out with readily available cinnamaldehyde **1a** as the test substrate (Table 1). Treatment of **1a** with *N*-(phenylthio) phthalimide **2** in the presence of 0.1 equiv of imidazolium **5a** and 0.15 equiv of potassium carbonate in THF at room temperature for 36 h afforded the desired α-thioenal **3a** in 27% yield with excellent *Z*-selectivity (Table 1, entry 1).[14] When control experiments in the absence of **5a**, base, or both **5a** and base were conducted, no desired product

Received: September 29, 2016
Published: October 27, 2016

DOI: 10.1021/acs.orglett.6b02939
Org. Lett. 2016, 18, 5708−5711

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	base	solvent	3a yield (%)[b]
1	**5a**	K_2CO_3	THF	27
2	–	–	THF	NR
3	–	K_2CO_3	THF	NR
4	**5a**	–	THF	NR
5	**5b**	K_2CO_3	THF	12
6	**5c**	K_2CO_3	THF	trace
7	**6** or **7** or **8**	K_2CO_3	THF	NR
8	DABCO	–	THF	NR
9	PPh_3	–	THF	NR
10	**5a**	K_2CO_3	toluene	33
11	**5a**	K_2CO_3	CH_3CN	35
12	**5a**	K_2CO_3	CH_2Cl_2	24
13	**5a**	K_2CO_3	DMF	42
14	**5a**	K_2CO_3	DMSO	29
15[c]	**5a**	K_2CO_3	DMF	45 + **4** (10%)
16[d]	**5a**	K_2CO_3	DMF	48 + **4** (20%)
17[c]	**5a**	Cs_2CO_3	DMF	72
18[c]	**5a**	^{t}BuOK	DMF	86

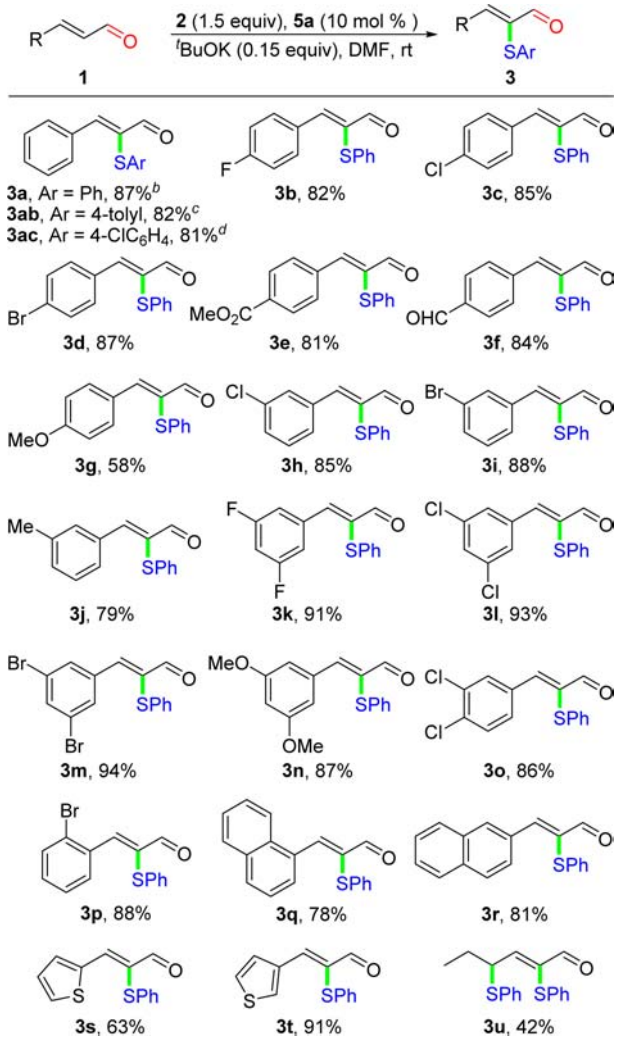
[a]Reactions were carried out with compound **1a** (0.20 mmol), **2** (0.24 mmol), catalyst (10 mol %), base (0.15 equiv) in solvent (1.0 mL) at room temperature under N_2 for 36 h. [b]Isolated yield. [c]1.5 equiv of **2** was used. [d]2.0 equiv of **2** was used.

was detected in these cases (Table 1, entries 2–4). Next we tried to optimize the reaction by varying different parameters systematically. Imidazolium **5b** bearing bulky substituents resulted in only a 12% yield; the reason may be ascribed to the bulkiness of the *ortho*-substitution decreasing the NHC's nucleophilicity (Table 1, entry 5). Surprisingly, a catalyst analogue of **5a** with a 4-F phenyl group (**5c**) afforded only a trace amount of the product, suggesting that the electronic character of the aromatic substituent in the phenyl moiety plays an important role in this reaction (Table 1, entry 6). A decrease in the electron density of the phenyl group has a decreasing effect on the yield. Other NHC precatalysts thiazolium **6**, triazolium **7**, or benzimidazole **8** were all investigated, but the desired product **3a** was not observed (Table 1, entry 7). Other nucleophilic catalysts such as 1,4-diazabicyclo[2.2.2]octane (DABCO) or PPh_3 both were ineffective for this sulfenylation reaction (Table 1, entries 8, 9).[15] Then various solvents were screened; DMF gave the best results (Table 1, entries 10–14).

During the optimization studies, the reaction yields ranged from moderate to low, as much of the starting material remained. In order to improve the conversion of cinnamaldehyde, an excess of **2** was used. However, only slightly increased yields were observed together with a side product **4** (Table 1, entries 15, 16). The structure of **4** was confirmed by X-ray analysis,[16] which may be formed from **3a**. To our delight, higher yields were obtained when stronger bases were employed (Table 1, entries 17, 18). The desired product **3a** was obtained in 86% yield when ^{t}BuOK was used as the base (Table 1, entry 18).

Having identified the optimized conditions, we tested this new method in a series of substrates with different substitution patterns of the aromatic ring. In general, a variety of *α,β*-unsaturated aldehydes with different substituents on the aromatic ring were found to be tolerable in this process. And the reaction was readily scalable without losing any efficiency (Scheme 2, **3a**). Other arylthiol phthalimides were also suitable for this reaction (Scheme 2, **3ab**, **3ac**). Substrates with electron-deficient substituents at the 3 or 4 position of the phenyl ring resulted in the desired *α*-thioenals with high yields (Scheme 2, **3b–f**, **3h**, **3i**). Notably, substrate with two aldehyde groups offered the desired product in high yield with both aldehyde groups retained (Scheme 2, **3f**). Electron-donating substituents

Scheme 2. NHC-Catalyzed Sulfenylation of *α,β*-Unsaturated Aldehydes[a]



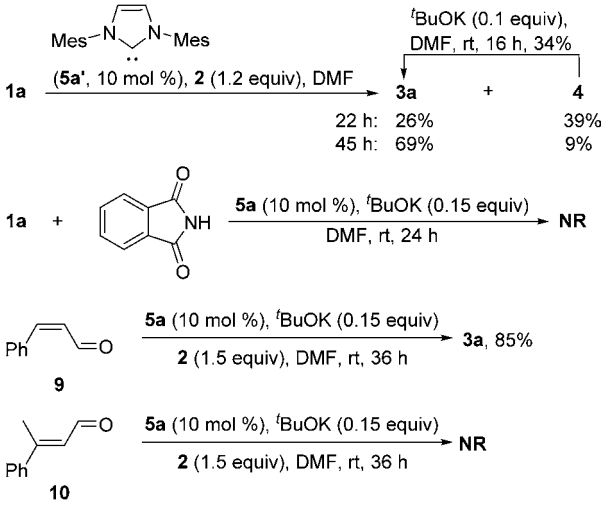
[a]Reactions were carried out with compound **1** (0.20 mmol), **2** (0.30 mmol), **5a** (0.02 mmol), ^{t}BuOK (0.03 mmol) in DMF (1.0 mL) at room temperature under N_2 for 36 h. Yields shown are for the isolated products. [b]1.0 g scale. [c]*N*-(4-Tolylthio) phthalimide was used. [d]*N*-(4-Chlorophenylthio) phthalimide was used.

DOI: 10.1021/acs.orglett.6b02939
Org. Lett. 2016, 18, 5708–5711

at the para positions resulted in a decrease in yield. The negative effect of the electron-rich substrate on the yield may be attributed to the low reactivity of the C−C double bond with the NHC catalyst. Disubstituted substrates with halogen or methoxyl substituents also worked very well (Scheme 2, **3k**−**o**). Interestingly, the existence of a substituent on the ortho position did not hamper the reaction (Scheme 2, **3p**, **3q**). Satisfactorily, substrates with a thiophene ring at the 2 or 3 position offered the desired thioenals with good to excellent yields (Scheme 2, **3s**, **3t**). Unfortunately, an aliphatic α,β-aldehyde substrate resulted in the formation of two C−S bonds, and the desired product was not observed, which was probably due to the deprotonation occurring at the allylic position under the basic conditions (Scheme 2, **3u**).[17]

In order to shed light on the origin of the catalytic activity in the sulfenylation reaction, some experiments were performed (Scheme 3). Treatment of **1a** with commercial available free

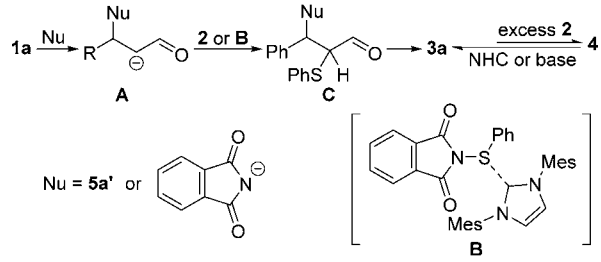
Scheme 3. Mechanistic Studies



carbene **5a′** in the absence of any other bases for 22 h resulted in **3a** and **4** in 26% and 39% yield, respectively. By prolonging the reaction to 45 h, 69% of **3a** and 9% of **4** were obtained. Additionally, treatment of **4** with ^{t}BuOK for 16 h returned **3a** in 34% yield. These results indicated that **4** can be transformed to **3a** through an elimination reaction with the aid of a carbene or a base. Reaction of **1a** with phthalimide under the optimal conditions in the absence of **2** gave no conjugate addition product. However, using 0.1 equiv of potassium phthalimide or ^{t}BuOK both resulted in **3a** with measurable yields (14% or 12%) after 22 h.[16] These results demonstrated that the phthalimide ion can catalyze this reaction in the presence of **2**; a similar phenomenon was observed in an amine catalyzed aminosulfenylation of enals.[18] Thus, such thiol reagents also play a role in the addition step. *Z*-Cinnamaldehyde **9** also returned the thioenal **3a** with *Z* configuration in 85% yield under the optimal conditions (Scheme 3), suggesting that the sulfenylation reaction did not follow a direct substitution mechanism, but the double bond should be added to yield a single bond intermediate. Additionally, control experiments in the presence of radical scavengers (BHT or TEMPO) were conducted, and the desired product was obtained with comparable yields, indicating the reaction may not follow a radical mechanism.[16] Furthermore, β-methyl substituted cinnamaldehyde **10** resulted in no desired product, presumably because of steric hindrance.

Taking into account the previous observations, a plausible mechanism is illustrated in Scheme 4. First, addition of a

Scheme 4. Proposed Mechanism



nucleophile to the electrophilic β-carbon of the α,β-unsaturated aldehyde generates an enolate **A**. The nucleophile may be NHC **5a′** or a phthalimide ion; unfortunately, an attempt to capture the addition intermediate by ^{1}H NMR failed.[19] Next intermolecular nucleophilic attack of the electrophilic sulfur reagent **2** or an active species **B** gives intermediate **C**.[4] Further deprotonation of the α-proton of **C** and liberation of Nu completed the catalytic cycle resulting in the formation of compound **3a**.

In summary, we have developed the first NHC-catalyzed sulfenylation reaction of α,β-unsaturated aldehydes with *N*-(arylthio)phthalimide, providing a new method for the construction of sp^2 C−S bonds with the aldehyde group retained. A variety of thioenals were obtained with high to excellent yields. Further investigations on the mechanism and other NHC-catalyzed construction of C−S bonds are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02939.

Experimental procedures, characterization data for all new compounds; and copies of ^{1}H, ^{13}C NMR spectra (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (NSFC-21302151, 21672170), Natural Science Basic Research Plan in Shaanxi Province of China (2016JM2004), Education Department of Shaanxi Province (13JS115), NFFTBS (No. J1210057), and the Northwest University for financial support.

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DOI: 10.1021/acs.orglett.6b02939
Org. Lett. 2016, 18, 5708−5711