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Thermolysis-Induced Two- or Multicomponent Tandem Reactions Involving Isocyanides and Sulfenic-Acid-Generating Sulfoxides: Access to Diverse Sulfur-Containing Functional Scaffolds

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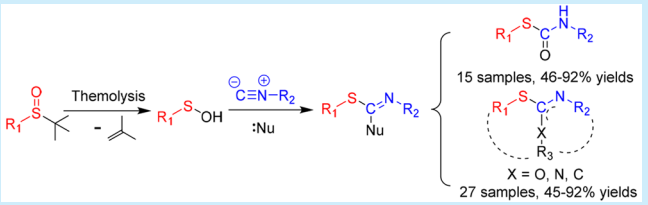
Supporting Information

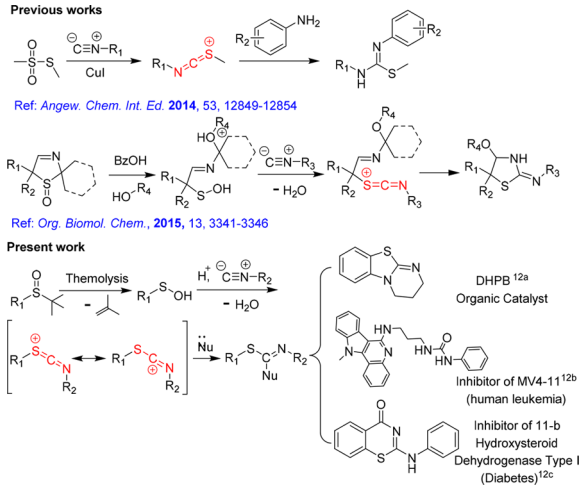
ABSTRACT: Direct reaction of isocyanides with some sulfenic-acid-generating sulfoxides led to the effective formation of the corresponding thiocarbamic acid *S*-esters in good to high yields. A multicomponent reaction involving isocyanide, sulfoxide, and a suitable nucleophile has also been developed, providing ready access to a diverse range of sulfur-containing compounds, including isothioureas, carbonimidothioic acid esters, and carboximidothioic acid esters.



One of the driving forces behind the development of modern synthetic methodology is the demand for ever-increasing molecular diversity in chemical, biological, and medical research. In this regard, multicomponent reactions[1] represent a set of unique synthetic tools to meet the diversity demand because of their efficient transformation of several functional groups into a new one. Traditional multicomponent reactions without transition-metal catalysis mostly involve the use of at least one carbonyl group (aldehyde or ketone) as a reacting component.[2] Multicomponent reactions can move beyond carbonyl group with transition-metal catalysis.[3] Among all multicomponent reactions reported, reactions that involve isocyanides probably attracted the most attention because of the dual nucleophilic and electrophilic properties of the reactive carbon center. However, from the early studies of the Passerini reaction[4] or Ugi reaction[5] to the more recent developments,[6] most of the isocyanide-involved multicomponent reactions still use a carbon-based electrophilic center. Therefore, expanding the general scope of multicomponent reactions to incorporate isocyanides and noncarbon electrophiles would represent a significant advance in the field.

We recently demonstrated the application of *tert*-butyl sulfoxides as stable surrogates to sulfinyl halides for the synthesis of sulfinic acid derivatives and other sulfoxides,[7] and for the synthesis of aryl[4,5]isothiazoles through an all-heteroatom Wittig process.[8] As an effort to further explore *tert*-butyl sulfoxide chemistry, we have recently examined the reaction of benzyl isocyanide with phenyl *tert*-butyl sulfoxide in toluene. Intriguingly, after 2 h of reaction, *N*-benzyl *S*-phenyl thiocarbamate was isolated as the major product (89% yield). Because it is well-known that sulfenic acid can be generated in situ via thermolysis of a *tert*-butyl sulfoxide or other alkyl sulfoxides with *β*-hydrogen,[9] we surveyed the literature for documented examples of multicomponent reactions between an electrophilic sulfur center and isocyanide. To the best of our knowledge, to date there were very limited reports on such reactions (Scheme 1).

Scheme 1. Multicomponent Reactions Involving Isocyanides and Electrophilic Sulfur Centers



Maes et al. reported a three-component reaction using isocyanides, aryl amines, and thiosulfonates under Cu(I) catalysis, which was thought to proceed through an imino-methylene sulfonium intermediate.[10] Martens et al. reported that when certain 2,2- and 5,5,-tetraalkylated 2,5-dihydro-1,3-thiazole S-monoxides were treated with isocyanides in alcoholic solvents in the presence of benzoic acid, isothiourea derivatives were

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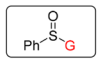
generated, and the reaction was supposed to proceed through a sulfenic acid related reaction pathway.[11] These reports are supportive of our hypothesis that the reaction between benzyl isocyanide and phenyl *tert*-butyl sulfoxide may also go through sulfenic acid and form an iminomethylene sulfornium intermediate (Scheme 1). Water molecules released in the formation of the sulfonium ion can act as a nucleophile to trap the iminomethylene sulfonium, hence leading to the formation of thiocabamate. If one can utilize this reaction pathway in a general way, then many important classes of molecules such as those shown in Scheme 1 could be conveniently accessed.[12]

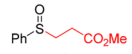
On the basis of this proposed mechanism, the formation of the iminomethylene sulfornium intermediate also requires a proton source. This can be furnished from another sulfenic acid molecule. Alternatively, an externally provided proton source should facilitate the reaction, as observed when 0.1 equiv of acetic acid was used (see the Supporting Information). To gather evidence that supports the sulfenic acid pathway, we tested some other sulfoxides, known to generate the corresponding sulfenic acids upon treatment under thermolytic conditions, for their reactions with benzyl isocyanide in toluene under heating conditions. The results are listed in Table 1. These five phenyl

Table 1. Reactions of Benzyl Isocyanide with Alkyl Phenyl Sulfoxides That Can Generate Sulfenic Acids

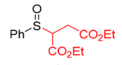


1a
100 °C, 2 h; 89%

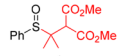
1b
100 °C, 4 h; 45%



1c
80 °C, 16 h; 88%



1d
40 °C, 2 h; 25%



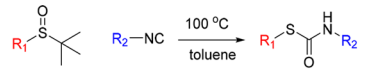
1e
40 °C, 2 h; 28%

alkyl sulfoxides were heated in toluene at temperatures reported to efficiently generate sulfenic acid.[13] Among these sulfoxides, *tert*-butyl- and methoxycarbonylethyl sulfoxides gave the targeted product **3a** in very good yields (88−89%), while others gave much inferior results (25−45% isolated yield of **1b**, **1d**, **1e**). Furthermore, LC-HRMS spectra of the reaction mixture of **1a**, **2a** and 4 or 8 equiv of $H_2{}^{18}O$ indicated 15% or 48% of ^{18}O-labeled **3a**, respectively, well above the natural abundance of that for **3a** (see the Supporting Information). The ^{18}O-labeling experiment supports water's nucleophilic attack to the proposed intermediate, rather than a direct oxygen migration from sulfur to the carbon center. Taken together, these results are consistent with the mechanism outlined in Scheme 1.

Given that *tert*-butyl sulfoxides produced high yield and that their synthesis in general would be easier to handle than the methoxycarbonylehtyl sulfoxides, all subsequent investigations were focused on the use of *tert*-butyl sulfoxides. Commonly used solvents were screened for the reaction of benzyl isocyanide with phenyl *tert*-butyl sulfoxide. Toluene was still found to be the best, as compared to other aprotic high-boiling polar solvents (dioxane, DMF, or DMSO) that gave 65−28% isolated yields for **3a**. Using THF, methanol, acetonitrile, or dichloromethane as solvent, no desired product **3a** was detectable under refluxing conditions, presumably as a result of inadequate reaction temperature (lower than the threshold value for thermolysis of **1a**).

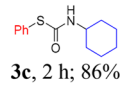
Further examples of reactions of isocyanides with *tert*-butyl sulfoxides are listed in Table 2. The first eight examples are

Table 2. Substrate Scope for Reactions of Isocyanides with *tert*-Butyl Sulfoxides

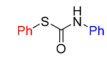


3a, 2 h; 89%

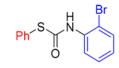
3b, 2 h; 78%



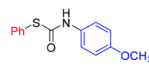
3c, 2 h; 86%



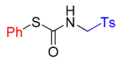
3d, 2 h; 84%



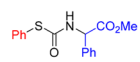
3e, 2 h; 78%



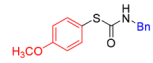
3f, 2 h; 85%



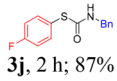
3g, 2 h; 81%



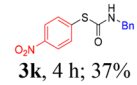
3h, 2 h; 76%



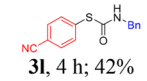
3i, 2 h; 92%



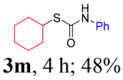
3j, 2 h; 87%



3k, 4 h; 37%



3l, 4 h; 42%



3m, 4 h; 48%

3n, 4 h; 56%

3o, 4 h; 46%

reactions using phenyl *tert*-butyl sulfoxides; various alkyl and aryl isocyanides gave satisfactory isolated yields (76−89%) of the expected products. For reactions with benzyl isocyanide, substituted phenyl sulfoxides were tested. *Para*-methoxy- or fluoro-substitution gave excellent results (products **3i** and **3j**). But nitro- and cyano-substitutions lowered the isolated yield to ∼40% (**3k** and **3l**). For alkyl *tert*-butyl sulfoxides, the yields were generally low and were in the 40−50% range (**3m**, **3n**, and **3o**).

Subsequently, we proceeded to examine the multicomponent reactions of benzyl isocyanide with a *tert*-butyl sulfoxide and an amine or alcohol as the extra nucleophile. Among the various alcohols and amines tested, only aryl amines gave satisfactory results. For reactions with added alcohols, small amounts of the corresponding products, usually less than ca. 10%, were detected by LC-HRMS, with the major products being identical to the thiocarbamates from the two-component reactions. For reactions with added alkyl amines, no desired multicomponent nor two-component reaction products were isolated, and the *tert*-butyl sulfoxide as starting material was consumed. This can probably be explained by the requirement of acidic conditions for the desired reaction to proceed. Addition of conventional alkylamine with high pK_a will produce ammonium ion and deplete sulfenic acid. A similar outcome was observed in the multicomponent reaction using isocyanides, thiosulfonates, and amines.[10] Successful examples of reactions involving aryl amines are listed in Table 3.

Mechanistically, the intermolecular multicomponent reactions potentially face the issue of competing addition to the sulfenic acid by an amine nucleophile instead of the intended isocyanide. We performed control experiments in the absence of isocyanide. Heating a toluene solution of phenyl *tert*-butyl sulfoxide in the presence of either aniline or benzyl amine did not lead to isolatable amine adducts. Instead, a sulfonyl *S*-ester was obtained (see the Supporting Information). When a less than stoichiometric amount of isocyanide was used in the reaction with aniline, both the isothiourea (three-component) and the sulfonyl *S*-ester products were isolated. These results indicated that under

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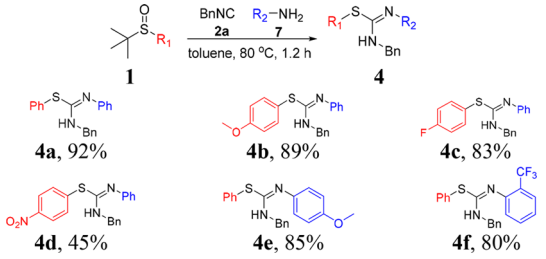
Table 3. Successful Examples of Intermolecular Multicomponent Reactions

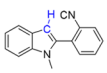
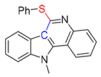
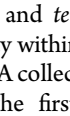
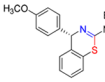
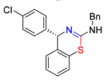
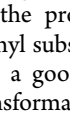


those reaction conditions amines could not effectively attack sulfenic acid but isocyanides could.

To overcome the above limitations in intermolecular multicomponent reactions, we sought to investigate intramolecular versions of the reaction by incorporating the extra nucleophilic functional group within the molecular skeleton of either the sulfoxide or the isocyanide. While the intramolecular cases may be classified more properly as tandem reactions, success in such an approach will result in many different heterocyclic scaffolds.

To our satisfaction, intramolecular tandem reactions of isocyanides and *tert*-butyl sulfoxides, bearing an extra nucleophilic moiety within either reactant, are generally successful with high yields. A collection of examples are listed in Table 4. In those examples, the first two are with alcohols as intramolecular nucleophiles that produced carbonimidothioic acid esters. When a hydroxyl group is present at the γ-position relative to the isocyanide, the produced carbonimidothioate moiety is a sulfanyl-5,6-dihydro-4*H*-[1,3]oxazine derivative (product **5a**, entry 1, Table 4). When a hydroxyl group is at the β-position to the sulfoxide, the carbonimidothioate moiety is formed as [1,3]oxathiolan-2-ylideneamine (product **5b**, entry 2, Table 4). Entry 3 in Table 4 is an example of carbon nucleophile. Phenyl *tert*-butyl sulfoxide was reacted with isocyanide **2c** that contained an indol-2-yl group. The formed carboximidothioate moiety is present in the product **5c** as a fused quinoline ring with a phenylsulfanyl substitution. Note that the sulfanyl group can be turned into a good leaving group (sulfone) after oxidization. Further transformation to displace the sulfone with propylenediamine led to a key intermediate for a class of MV4-11 inhibitors[12b] for cancer drug development (Scheme 1 and the Supporting Information). In entry 4, the sulfoxide contained an *ortho*- primary amide group, which led to efficient formation of the acyl isothiourea moiety present in a class of inhibitors against type-I 11ß-hydroxysteroid dehydrogenase for potential diabetes treatment (Scheme 1).[12c] Note that intramolecular trapping of sulfenic acid by an amide group was reported before.[14] In our case of entry 4 reaction, only 5% of amide-trapped product was obtained, indicating that addition of isocyanide to sulfenic acid is faster than intramolecular amide trapping (see the Supporting Information). Entry 5 is an example of aryl amine at the β-position to the sulfoxide. The formed isothioureas is represented as 2-amino-benzothiozole (product **5e**). Entries 6–12 in Table 4 are examples with starting materials that contain an alkyl amine three carbon atoms away from the sulfoxide group. These produced benzene-fused 2-amino-[1,3]thiazines with respectable yields (68–91%). Because many examples in Table 4 involve chiral centers in addition to the sulfoxide group, an evaluation of the preservation of nonsulfur chiral center was performed using the reaction of entry 6. Both the racemic and the optically enriched (97.1% de) starting **1i** were used. Little racemization could be observed under this thermolytic procedure, as the optically enriched material produced **5f** with 96.6% ee (see the Supporting Information).

Table 4. Successful Examples of Tandem Reactions with a Third Intramolecular Nucleophile

entry	sulfoxide	isocyanide	product	yield (%)
1	**1a**	 **2b**	 **5a**	72
2	**1f**	BnNC **2a**	 **5b**	78
3	 **1a**	 **2c**	 **5c**	58
4	 **1g**	PhNC **2a**	 **5d**	79
5	 **1h**	BnNC **2a**	 **5e**	88
6	 **1i**	BnNC **2a**	 **5f**	87
7	 **1j**	BnNC **2a**	 **5g**	91
8	 **1k**	BnNC **2a**	 **5h**	83
9	 **1l**	BnNC **2a**	 **5i**	68
10	 **1m**	BnNC **2a**	 **5j**	84
11	 **1n**	BnNC **2a**	 **5k**	86
12	 **1o**	BnNC **2a**	 **5l**	90

Finally, we sought to further expand the scope of the isocyanide-sulfoxide tandem reaction by using starting materials that contained a fourth functional group, which could potentially lead to more complex heterocycles. As shown in Table 5, interesting results were obtained with these trials. Entry 1 in Table 5 used an intermolecular three-component reaction where the aryl amine contained an *ortho*-methoxycarbonyl group. The formed isothiourea then reacted further with the methyl ester to form a heterocyclic product **6a**. From entries 2–5 in Table 5, sulfoxides with an amino group were reacted with isocyanides containing an aliphatic carboxylic acid methyl ester, which could be conveniently prepared from the corresponding amino acids. These methyl aliphatic carboxylates did not go through tandem transformation as expected, and the final products retained the ester group for further manipulation. In contrast, entries 6 and 7 are examples with benzyl aliphatic carboxylates. In these cases,

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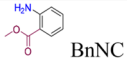
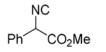
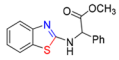
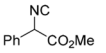
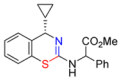
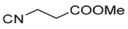
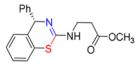
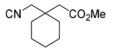
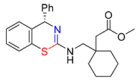
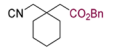
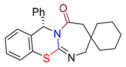
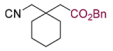
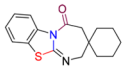
Table 5. Examples of Tandem Reactions with Additional Functional Group

entry	sulfoxide	isocyanide	product	yield (%)
1	 **1a**	 **7a** **2a**	 **6a**	90
2	 **1h**	 **2d**	 **6b**	78
3	 **1o**	 **2d**	 **6c**	84
4	 **1i**	 **2e**	 **6d**	86
5	 **1i**	 **2f**	 **6e**	80
6	 **1i**	 **2g**	 **6f**	75
7	 **1h**	 **2g**	 **6g**	85
8	 **1i**	**2f**	 **6h**	88
9	 **1h**	**2f**	 **6i**	86

additional tandem reaction occurred with the benzyl ester group to form new rings in the final products (**6f** and **6g**). Therefore, methyl or benzyl esters of aliphatic carboxylates appear to offer controllable subsequent reactions, which would be desirable as synthetic options. Entries 8 and 9 are examples with a tosyl group in the isocyanide starting materials. Again, additional rings were formed in the final products with excellent yields (**6h** and **6i**, 86–88%). Note that product **6i** belongs to an important class of organocatalysts (Scheme 1), which are usually synthesized using multistep procedures with moderate yields.[12a]

In summary, we presented general examples of reactions between isocyanides and sulfenic-acid-generating sulfoxides in two- or multicomponent fashions and in tandem fashions. These reactions with electrophilic sulfur centers can produce diverse sulfur-containing chemical scaffolds in good to excellent yields. We believe those are valuable additions to the chemists' synthetic tool set for achieving molecular diversity in many research fields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03593.

Procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

In memory of Professor Changqi Hu (1940–2017).

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