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Iodide-Catalyzed Synthesis of Secondary Thiocarbamates from Isocyanides and Thiosulfonates

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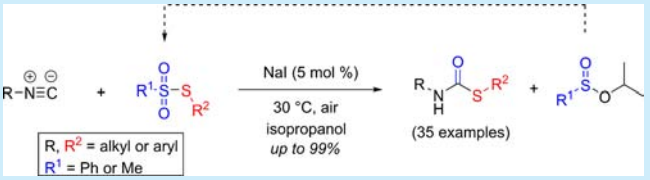
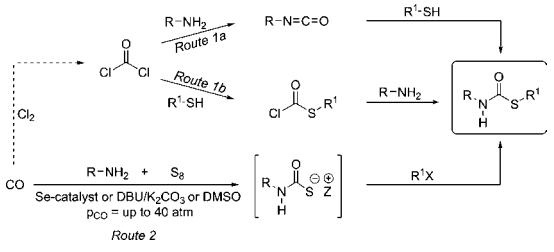
Supporting Information

ABSTRACT: A new method for the synthesis of secondary thiocarbamates from readily available isocyanides and thiosulfonates with broad functional group tolerance is reported. The reaction proceeds under mild reaction conditions in isopropanol and is catalyzed by inexpensive sodium iodide.



Thiocarbamates constitute an important class of biologically active compounds with various applications, including their use as herbicides (Thiobencarb, Orbencarb, and Molinate), pesticides, antifertility agents, and antivirals.[1] Secondary thiocarbamates are hitherto far less explored than the tertiary ones. Among the classical approaches toward secondary thiocarbamates, the two-step reaction of phosgene with a primary amine and a thiol (or the reverse) (Scheme 1, route 1)

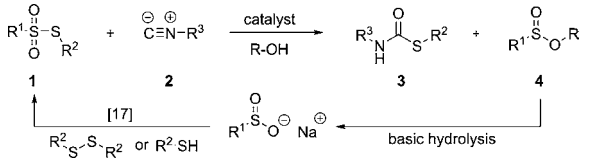
Scheme 1. Classical Approaches toward Secondary Thiocarbamates



is the most commonly applied synthetic route.[2,3] Other phosgene derived C_1-reagents such as di-*tert*-butyl dicarbonate[4] and carbonyldiimidazole[5] have also been used. Carbon monoxide (CO) can be considered a promising replacement of phosgene, as it allows the direct introduction of the C_1-fragment.[6] Thiocarboxylation via the reaction of primary amine, CO, and S_8 via a Se-catalyzed,[7] base- or solvent-mediated[8] reaction yields a thiocarbamate salt which upon *S*-alkylation gives the target compounds (route 2).[9]

In general, the reported routes toward secondary thiocarbamates share disadvantages such as the use of hazardous reagents (CO, phosgene, isocyanate).[10] Consequently, there is considerable interest for efficient and mild methods to synthesize secondary thiocarbamates with a broad scope.[11] In continuation of our interest in isocyanide chemistry,[12] and based on our previously reported method for isothiourea synthesis,[12d] we envisioned that thiocarbamates could be synthesized by reaction of isocyanides with thiosulfonates,[13] two compound classes which generally show low to moderate toxicity (Scheme 2).[14]

Scheme 2. New Approach toward Secondary Thiocarbamates



Isocyanides have emerged as very useful C_1 building blocks in modern organic chemistry[15] and are readily obtained commercially or through synthesis, from the corresponding amine by formylation and subsequent dehydration or via the Hofmann isocyanide synthesis.[16] Thiosulfonates can generally be synthesized from the corresponding sodium sulfinates by sulfenylation or from disulfides by selective oxidation.[17] *S*-Methyl methanethiosulfonate and *S*-phenyl benzenethiosulfonate are commercial reagents.

We started our optimization with the reaction of *S*-phenyl benzenethiosulfonate (**1a**) and *tert*-butyl isocyanide (**2a**) to give *S*-phenyl *tert*-butylthiocarbamate (**3a**) (section 3 Supporting Information, SI). When we applied the reaction conditions of our previously developed isothiourea synthesis (CuI catalyst, 75 °C, 2-MeTHF, 20 h, 4 Å MS) on the model system, only 28% of **3a**

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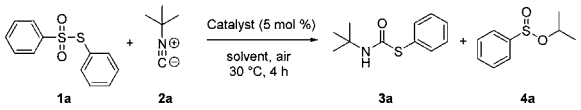
was obtained.[12d] Clearly, completely different reaction conditions and a different reaction mechanism are required for efficient thiocarbamate synthesis. The use of an alcohol as solvent proved to be essential for efficient thiocarbamate formation (Table 1, entries 2−5), with the corresponding alkyl benzenesulfinate as the byproduct (Scheme 2). As alkyl sulfinates (**4**) can be transformed into sodium sulfinates by basic hydrolysis (section 4 SI), the byproduct can be recycled into **1**. Interestingly, sodium iodide, an inexpensive inorganic salt used as a nutrition additive, efficiently catalyzes the coupling between **1a** and **2a** while other sodium halide salts and I_2 perform poorly (Table 1, entries 1−2, 6−8). The transformation does not require a transition metal catalyst and can be executed under air. Moreover, a reaction temperature of 30 °C is sufficient to achieve full conversion in 4 h affording **3a** in 97% isolated yield. The reaction was readily scaled to 10 mmol.

Table 1. Summary of Reaction Optimization[a]



1a 2a 3a 4a

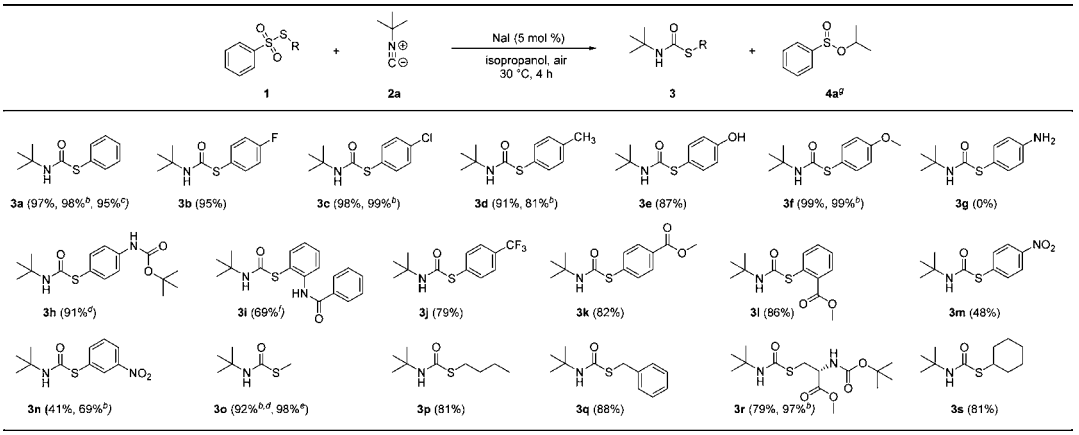
entry	solvent	catalyst	yield **3a** (%)[b]	yield **4a** (%)[b]
1	isopropanol	–	19	20
2	isopropanol	NaI	93 (97)[c]	93 (95)[c]
3	2-MeTHF	NaI	12	0
4	toluene	NaI	0	0
5	1,4-dioxane	NaI	18	0
6	isopropanol	NaBr	34	33
7	isopropanol	NaCl	25	27
8[d]	isopropanol	I_2	46	46

[a]Reaction conditions: *S*-Phenyl benzenethiosulfonate (**1a**, 0.5 mmol), *tert*-butyl isocyanide (**2a**, 0.6 mmol), catalyst (5 mol %), solvent (0.5 mL), 30 °C, 4 h, air. [b]^{1}H NMR yield using 1,3,5-trimethoxybenzene as internal standard. [c]Isolated yield. [d]I_2 (2.5 mol %) was added to the reaction.

With the optimized conditions in hand [**1a** (1.0 mmol), **2a** (1.2 mmol), NaI (5 mol %), isopropanol (0.5 mL), 30 °C, 4 h, air] we evaluated the scope of the reaction (Scheme 3). First, *tert*-butylisocyanide (**2a**) was coupled with a variety of *S*-aryl benzenethiosulfonate reagents (**1**). Weakly electron-withdrawing (**1b−c**) and electron-donating (**1d−i**) substituents were tolerated well, and the corresponding *S*-aryl *tert*-butylthiocarbamates were obtained in high yield (**3a−3i**). While a hydroxyl group is tolerated (**3e**), an amino group proved to be incompatible (**3g**). However, carbamate or amide protection delivered the corresponding thiocarbamates **3h** and **3i** in good to excellent yields. Especially **3i** is interesting, as it shows that *ortho*-substitution is tolerated. Good yields were also observed with *S*-aryl benzenethiosulfonates bearing strong electron-withdrawing substituents such as a trifluoromethyl and alkoxycarbonyl group (**3j−l**). Also in this case *ortho*-substitution in the thiosulfonate reagent does not hamper the reaction. Only with extreme functionalities as exemplified by a nitro group a lower yield was obtained (**3m−n**). *S*-Alkyl benzenethiosulfonates (**1o−s**), including challenging ones such as the cysteine derived **1r**, were well tolerated and gave the corresponding *S*-alkyl *tert*-butylthiocarbamates in high yield (**3o−s**). *S*-Aryl/alkyl methanethiosulfonates could also be used as coupling partners to give the same thiocarbamates (**3a**, **3c−d**, **3f**, **3n**, **3o**, **3r**). In this case, the volatile byproduct isopropyl methanesulfinate (**4b**) is readily removed *in vacuo*, greatly simplifying the workup. Simple filtration over a silica plug is then sufficient to purify the thiocarbamate. For certain thiocarbamates a higher yield was obtained when the sodium methanethiosulfinate derived reagent was used (**3n** and **3r**). This offers one the choice between an easy workup or the recovery of the isopropyl sulfinate byproduct and its recycling by selecting respectively the methane- or the benzenethiosulfonate reagent.

Next, the scope of the reaction with respect to the isocyanide reagent was investigated with **1a** as thiosulfonate (Scheme 4). Besides **2a**, other tertiary isocyanides were well tolerated, even the bulky adamantyl isocyanide (**5a−c**). We were pleased to find that our new protocol is also compatible with secondary and primary isocyanides (**5d−k**). In addition, different functional groups were tolerated in the isocyanide, such as ether (**5k**, **5n**) or ester (**5b**, **5i**, **5j**) groups. Notably, the reaction of methyl isocyanoacetate (**2i**), featuring an acidic methylene functionality, delivers the desired thiocarbamate in good yield (**5i**). Unfortunately, when TosMIC (**2l**) was used, **5l** was not formed. Gratifyingly, our method tolerates aromatic isocyanides, which is

Scheme 3. *S*-Aryl/Alkyl Benzenethiosulfonate (1) Scope[a]



[a]Reaction conditions: *S*-Aryl/alkyl benzenethiosulfonate (1.0 mmol), *tert*-butyl isocyanide (**2a**, 1.2 mmol), NaI (5 mol %), isopropanol (0.5 mL), 30 °C, 4 h, air. [b]*S*-Aryl/alkyl methanethiosulfonate (1.0 mmol), 40 °C, 6 h. [c]10 mmol scale. [d]50 °C, 15 h. [e]5 mmol scale. [f]27% of bis(2-benzamidophenyl)disulfide was isolated. [g]Up to 99% **4a**.

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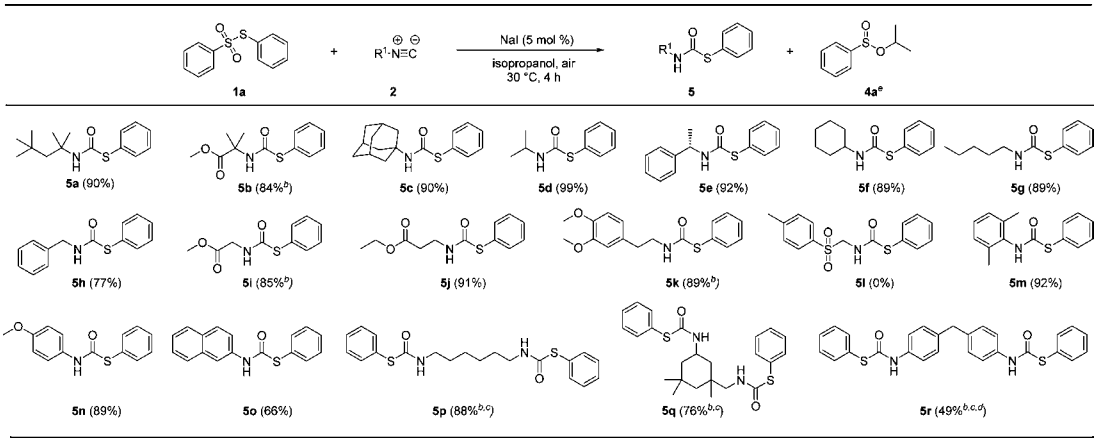
Scheme 4. Isocyanide Scope[a]

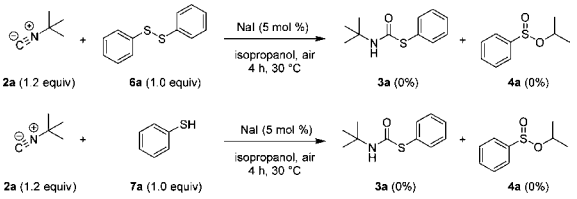


[a]Reaction conditions: *S*-Phenyl benzenethiosulfonate (**1a**, 1.0 mmol), isocyanide (**2**, 1.2 mmol), NaI (5 mol %), isopropanol (0.5 mL), 30 °C, 4 h, air. [b]15 h. [c]*S*-Phenyl benzenethiosulfonate (**1a**, 1.0 mmol), diisocyanide (**2**, 0.5 mmol), NaI (10 mol %). [d]50 °C. [e]Up to 90% **4a**.

not self-evident because these compounds readily polymerize (**5m**–**o**).[15] Diisocyanides (**2o**–**r**) derived from industrially important diamines (hexamethylenediamine, isophorone-diamine, and 4,4′-diaminophenylmethane)[18] used for polyurethane synthesis were subsequently evaluated, and the desired thiocarbamates were obtained in moderate to good yields (**5p**–**r**). To illustrate the synthetic potential of our newly developed transformation, *S*,*S*′-diphenyl hexane-1,6-diylbisthiocarbamate (**5p**) was transformed in high yield into dialkyl hexane-1,6-diylbiscarbamates (**8a**–**b**), which can be used for polyurethane synthesis, by reaction with an alcohol using NEt_3 as a base (section 6, SI).[18]

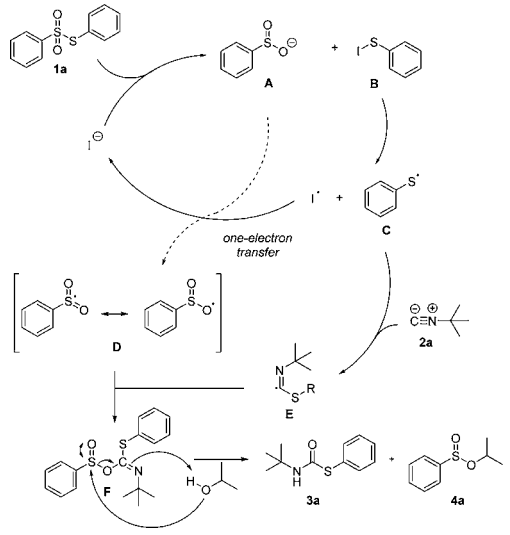
Control reactions demonstrate that the choice of the appropriate sulfenylating agent is essential for the thiocarbamate synthesis as diphenyl disulfide **6a** or thiophenol **7a** does not lead to the formation of **3a** (Scheme 5). Performing the reaction in

Scheme 5. Control Experiments: Sulfenylating Agent



dry isopropanol or under argon does not influence the yield, so water and air could be excluded as the carbonyl oxygen source of **3a** (Table S6). When NaI was replaced by PhSI (**B**),[19] **3a** and **4a** were also obtained (Scheme S6) which suggests the involvement of **B** in the reaction. In the presence of radical inhibitors (TEMPO, Galvinoxyl, and BHT) low yields of **3a** and **4a** were obtained pointing to a radical pathway (Table S6). Subsequently, EPR experiments (section 5.3, SI) were executed on reactions with DMPO added in order to trap short living radicals formed during the reaction. This revealed the presence of a thiophenol radical (**C**) and benzenesulfinate radical (**D**). Even when NaI was omitted, **D** was still detected meaning that the background reaction (Table 1, entry 1) is also radical in nature and does not seem to involve a direct insertion reaction of isocyanide.[13] Based on these experiments, we propose a radical reaction mechanism as outlined in Scheme 6. First, **1a** reacts with sodium iodide yielding benzenesulfinate (**A**) and PhSI (**B**). Then **B** undergoes

Scheme 6. Proposed Mechanism for the Synthesis of 3a



homolytic cleavage to yield the thiophenol radical **C**.[20] Subsequently, **C** adds to isocyanide **2a** furnishing radical **E**. Reaction of **E** with benzenesulfinate radical **D** forms intermediate **F**. Finally, alcoholysis of intermediate **F** with isopropanol generates **3a** and **4a**. Intermediate **D** is formed via electron transfer from benzene sulfinate **A** to the iodine radical, which is plausible based on its low oxidation potential.[21] Regeneration of iodide justifies its role as a catalyst.

In conclusion, we have developed a novel, facile, and direct approach toward secondary *S*-alkyl and *S*-aryl thiocarbamates based on readily available isocyanides and thiosulfonates. The reaction proceeds under very mild reaction conditions and uses inexpensive NaI as a catalyst. Isopropanol is used both as a reaction partner and as a green solvent.[22] Our transition-metal-free protocol shows a broad scope with respect to both isocyanide and thiosulfonate reaction partners and is therefore suitable for the synthesis of a broad range of secondary thiocarbamates. Around 90% of the reaction products reported in this study are hitherto unknown compounds, based on Scifinder and Reaxys. In addition, the straightforward transformation into industrially relevant carbamates illustrates the synthetic potential of this new methodology.

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■ ASSOCIATED CONTENT

Supporting Information

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Optimization data, experimental procedures, characterization of new compounds and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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(10) Health (H) rating of CO (H = 3), $COCl_2$ (H = 4), and isocyanates (e.g., tBuNCO (H = 3)) shows high toxicity. Scale from 0 (low) to 4 (high).

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(14) Health (H) rating of isocyanides (e.g., **2a**: H = 2, **2h**: H = 2, **2m**: H = 1) and thiosulfonates (e.g., **1a**: H = 0, **1o**: H = 1) shows low to moderate toxicity; Scale from 0 (low) to 4 (high).

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