

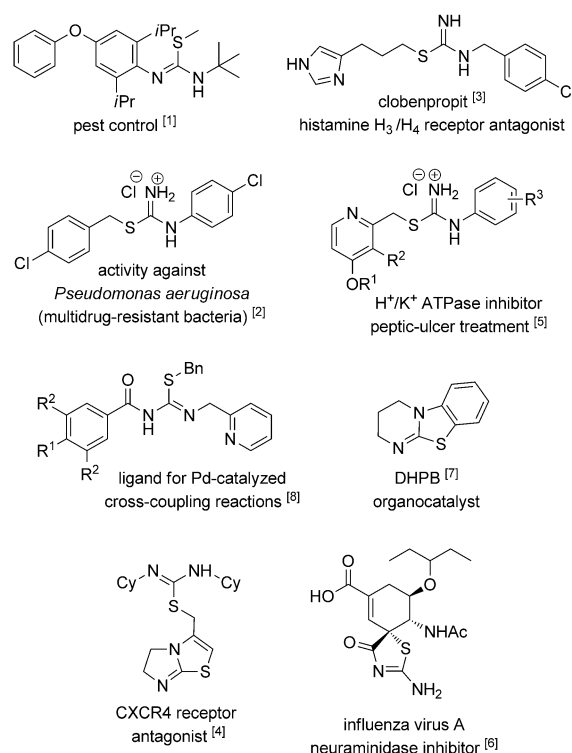
Sustainable Three-Component Synthesis of Isothioureas from Isocyanides, Thiosulfonates, and Amines**

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In memory of Alan Katritzky (1928–2014)

Abstract: Multiple applications of isothioureas as fine chemicals (or their precursors) are known, but a general sustainable method for their synthesis was hitherto unavailable. We report a novel general approach towards *S*-alkyl and *S*-aryl isothioureas through a copper(I)-catalyzed three-component reaction between amines, isocyanides, and thiosulfonates. The formal synthesis of a superpotent sweetener further illustrates the applicability of our method.

Isothioureas have attracted considerable attention owing to their interesting agrochemical and medicinal applications.^[1–6] Furthermore, they have been used as organocatalysts^[7] and ligands in transition-metal catalysis^[8] (Scheme 1). Isothioureas are important synthetic intermediates for the synthesis of guanidines, as illustrated by the many procedures that have been reported for this transformation in the past decade.^[9] Remarkably, in contrast to the various important applications reported, only limited research effort has been devoted to the efficient and sustainable synthesis of isothioureas.^[10] *S*-Alkyl isothioureas are classically prepared from the corresponding thioureas by *S*-alkylation. For example, *S*-methylisothioureas, which are the most common intermediates in the synthesis of



Scheme 1. Applications of isothioureas. Bn = benzyl, Cy = cyclohexyl.

guanidines, are synthesized by the use of carcinogenic and neurotoxic MeI.

The major disadvantages of these classical methods for the synthesis of *S*-alkyl isothioureas are the health risk, flammability, and reactivity of the reagents.^[11] We therefore envisioned a new synthetic strategy based on a three-component coupling of amines, thiosulfonates, and isocyanides that overcomes these disadvantages and delivers the desired isothioureas in a single step (Scheme 2). This approach also enables the synthesis of *S*-aryl-substituted isothioureas, which are difficult to obtain directly from thioureas.^[12]

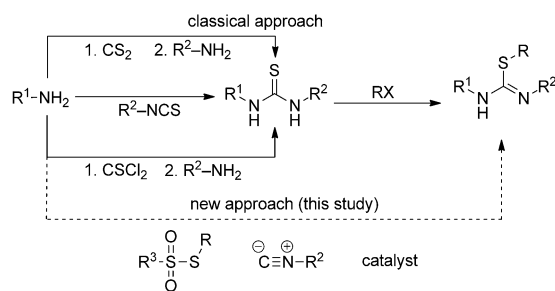
In contrast to the classical methods, the reagents required for our new approach have low toxicity and are readily available. Generally, thiosulfonates are prepared from the corresponding sulfinates by sulfenylation or from disulfides by selective oxidation.^[13,14] *S*-Methyl methanethiosulfonate, which is the main sulfur reagent used in this study, can also be synthesized from dimethyl sulfoxide in high yield in a one-pot

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Scheme 2. Classical and new routes to isothioureas.

process.^[14a] Isocyanides are readily obtained from amines by formylation and dehydration with a variety of dehydrating agents.^[15,16] Isocyanides have been widely studied and have emerged as highly useful C₁ building blocks in modern organic chemistry.^[16,17] Owing to their unique nature, isocyanides can react with electrophiles, nucleophiles, and radicals.^[16] They can also insert into metal–carbon and metal–heteroatom bonds in transition-metal-catalyzed reactions.^[18–20] A reaction between isocyanides and thiosulfonates, however, has not been reported previously.

The synthesis of *N*-*tert*-butyl-*S*-methyl-*N'*-phenylisothiourea (**4a**) from the commercial reactants aniline (**1a**), *S*-methyl methanethiosulfonate (**2a**), and *tert*-butyl isocyanide (**3a**) was chosen as the test system for optimization studies.^[21] A variety of Pd and Cu species were tested (Table 1, entries 1–13). CuI was found to be the best catalyst, and the addition of a base was found to inhibit the reaction (see Table S2 in the Supporting Information). The choice of an appropriate sulfonylating reagent is essential for the desired coupling, as dimethyl disulfide did not give **4a** (see Scheme S1 in the Supporting Information). Pleasingly, the reaction proceeds smoothly under air and does not require an inert atmosphere. A catalyst loading of 1 mol% was sufficient at a reaction temperature of 75 °C (see Table S1). The reaction tolerates a wide range of solvents (see Table S4); renewable 2-methyltetrahydrofuran (2-MeTHF) was chosen with respect to the overall sustainability of the process. Serendipitously, we discovered that the yield of **4a** can be further improved by the addition of 4 Å molecular sieves (MS) to the reaction mixture (Table 2, entry 1).

The scope of the reaction was investigated under the optimal conditions (**1a** (1.7 mmol), **2a** (1.0 mmol), **3a** (2.5 mmol), CuI (1 mol%), 4 Å MS (300 mg), 2-MeTHF (2.5 mL), 75 °C, 20 h, air; Table 2). Anilines bearing electron-donating and weakly electron-withdrawing substituents were tolerated well, and the corresponding isothioureas were obtained in high yields (Table 2, entries 2–6 and 12–15). When MS were omitted, substantially lower yields were observed. The difference is remarkable for the electron-rich substrates 4-methoxy- and 2-methylthioaniline. The corresponding isothioureas **4i** and **4o** were obtained in only 18 and 38 % yield, respectively, without MS (Table 2, entries 12 and 15). Good yields were observed for anilines bearing moderately electron-withdrawing substituents (Table 2, entries 7 and 8). When very strongly electron-withdrawing groups were present (3-NO₂, 4-NO₂, 4-CN), a lower yield was observed,

Table 1: Catalyst screening.^[a]

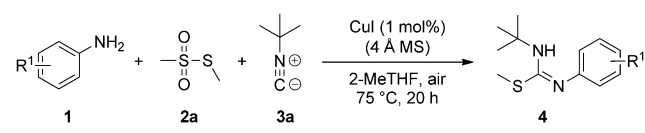
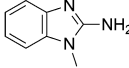
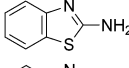
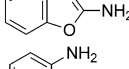
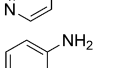
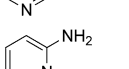
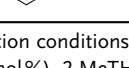
Entry	Catalyst	Yield [%] ^[b]	Remaining 2a [%] ^[b]
1	Pd(OAc) ₂	0	0
2	[Pd(dba) ₃]	0	0
3	Cu ^I I	42/40 ^[c]	45
4	Cu ^I Br	36	30
5	Cu ^I Cl	32	45
6	Cu ^I Br·(CH ₃) ₂ S	37	21
7	Cu ^I OAc	7	9
8	Cu ^I ₂ S	20	21
9	Cu ^I ₂ O	0	21
10	(Cu ^I OTf) ₂ ·toluene	24	60
11	Cu ^{II} Cl ₂	39	36
12	Cu ^{II} Br ₂	37	32
13	Cu ^{II} OTf ₂	21	63
14	Ag(OTf)	0	72
15	ZnCl ₂	18	39
16	Sc(OTf) ₃	28	42
17	In(OTf) ₃	32	51
18	GaCl ₃	20	63
19	AlCl ₃	34	30
20	FeBr ₃ (98 %)	33	48
21	FeCl ₂ (99.999 %)	32	54
22	BF ₃ ·OEt ₂	29	54
23	B(C ₆ F ₅) ₃	27	42
24	–	15	36

[a] Reaction conditions: aniline (**1a**, 1 mmol), *S*-methyl methanethiosulfonate (**2a**, 1 mmol), *tert*-butyl isocyanide (**3a**, 1 mmol), catalyst (5 mol %), 2-MeTHF (5 mL), 75 °C, 20 h, Ar. [b] The yield was determined by ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. [c] Yield of the isolated product.

and in this case the addition of MS did not influence the yield (Table 2, entries 9–11). This result motivated us to further study the reaction conditions for these specific substrates. Pleasingly, the yield of **4i–k** could be improved by using more of the catalyst (2.5 mol %) and more **3a** (3.3 equiv; Table 2, entries 9–11). Secondary anilines can also be used, as exemplified by *N*-methylaniline (**1p**; Table 2, entry 16). The developed reaction can be extended to challenging hetero-aromatic amines of the azole and azine type (Table 2, entries 18–23). Interestingly, cyanamide could also be used as a substrate (Table 2, entry 17).

Next, the scope of the reaction with respect to the isocyanide reagent was investigated with **1a** or **1b** and **2a** as coupling partners (Table 3). After all, reactions of isocyanides under transition-metal/Lewis acid catalysis are often limited to tertiary isocyanides.^[18] Gratifyingly, our method also tolerates primary and secondary isocyanides to yield the desired isothioureas in moderate to high yield. With isopropyl isocyanide (**3g**), a reduced yield of **5k** was observed owing to the low boiling point of **3g**. The yield was improved to 65 % by using a sealed vial (Table 3, entry 11). For pentyl (**3b**), benzyl (**3f**), and isopropyl isocyanide (**3g**), the influence of the electronic nature of the aniline was also investigated. We found that besides tertiary, also primary and secondary

Table 2: Scope of the reaction with respect to the (hetero)aryl amine.^[a]

					
Entry	(Hetero)aryl amine	Product		Yield [%] ^[b]	
				without MS ^[c]	with MS ^[a]
1	R ¹ = H	1a 4a		73 ^[d]	97 ^[e]
2	R ¹ = 4-Cl	1b 4b		73	88
3	R ¹ = 4-F	1c 4c		70	98
4	R ¹ = 4-CH ₃	1d 4d		56	84
5	R ¹ = 3-CH ₃	1e 4e		64	83
6	R ¹ = 2-CH ₃	1f 4f		60	95
7	R ¹ = 4-CF ₃	1g 4g		53	76
8	R ¹ = 4-CO ₂ CH ₃	1h 4h		61	75
9	R ¹ = 4-CN	1i 4i		53/66 ^[f]	58
10	R ¹ = 4-NO ₂	1j 4j		35/54 ^[f]	33
11	R ¹ = 3-NO ₂	1k 4k		44/74 ^[f]	47
12	R ¹ = 4-OCH ₃	1l 4l		18	82
13	R ¹ = 3-OCH ₃	1m 4m		74	80
14	R ¹ = 2-OCH ₃	1n 4n		70	88
15	R ¹ = 2-SCH ₃	1o 4o		38	61
16		1p 4p		29	50
17	NH ₂ CN	1q 4q		54	67
18		1r 4r		65	71
19		1s 4s		65	83
20		1t 4t		46	70
21 ^[g]		1u 4u		28/41 ^[f]	33
22		1v 4v		52	77
23		1w 4w		49	57

[a] Reaction conditions: **1a** (1.7 mmol), **2a** (1.0 mmol), **3a** (2.5 mmol), CuI (1 mol %), 2-MeTHF (2.5 mL), 4 Å MS (300 mg), 75 °C, 20 h, air.

[b] Yield of the isolated product. [c] No MS were used. [d] Yield of a reaction carried out on a 10 mmol scale: 75 %. [e] When no CuI was added, **4a** was obtained in 63 % yield. [f] The reaction was carried out under the conditions described in [a], but with **3a** (3.3 mmol), CuI (2.5 mol %). No MS were used. [g] A lower yield was observed owing to the poor solubility of **1u**.

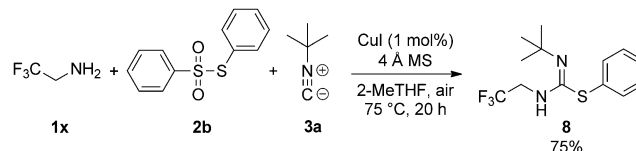
isocyanides are compatible with both electron-rich and electron-poor anilines (Table 3, entries 1–3, 7–10, and 11–13). Interestingly, *N*-benzyl-*N'*-(4-cyanophenyl)-*S*-methylisothiourea (**5i**) is a precursor for a superpotent sweetener (see Scheme S9).^[9a,22] The protocol also allows different functional groups in the isocyanide, such as an ether (substrate **3c**), an ester (substrates **3d,e,k**), or a carbamate group (substrate **3j**) (Table 3, entries 4–6, 16, and 17).

Notable is the reaction of methyl isocyanoacetate (**3e**), which features an acidic methylene functionality (Table 3, entry 6). When two methyl groups were present at the α -position of this isocyanide (substrate **3k**), **7** was isolated in

high yield (Table 3, entry 17).^[23] Compound **7** is formed from the initial reaction product **5q** by lactamization (Thorpe–Ingold). We were pleased to find that aromatic isocyanides were also well tolerated (Table 3, entries 18–20), which is not self-evident because these compounds readily polymerize.^[16a]

Besides **2a**, other aliphatic sulfonylating reagents were tested with **1a** and **3a** as coupling partners (Table 4). *S*-Butyl butanethiosulfonate (**2b**) was transformed into *S*-butyl-*N*-*tert*-butyl-*N'*-phenylisothiourea (**6a**) in 75 % yield (Table 4, entry 1). Even challenging reagents, such as the cysteine-derived thiosulfonate **2d**, were tolerated well (Table 4, entry 3). Aromatic sulfonylating reagents can also be used under the standard reaction conditions. *S*-Phenyl benzene-thiosulfonate (**2e**) was selected as a representative reagent and smoothly afforded *N*-*tert*-butyl-*N'*,*S*-diphenylisothiourea (**6c**) in 96 % yield (Table 4, entry 4). We were pleased to find that aromatic thiosulfonates are also compatible with primary and secondary isocyanides (Table 4, entries 5–7), as was observed for the aliphatic reagents (Table 3). Even mixed thiosulfonates based on thiomethanesulfonic acid can be successfully used, as exemplified by *S*-butyl methanethiosulfonate (**2c**) and *S*-(4-chlorophenyl) methanethiosulfonate (**2f**) (Table 4, entries 2 and 8).

Aliphatic amines were also tested as potential reagents (Scheme 3). Whereas propylamine ($pK_a = 10.6$) and morpholine ($pK_a = 8.4$) did not react, the reaction of β,β,β -trifluoroethylamine (**1x**; $pK_a = 5.7$) afforded the target product **8** in 75 % yield without any further optimization. It therefore seems that the protocol is suitable for amines with a pK_a value up to approximately 7.^[24]


Scheme 3. Use of β,β,β -trifluoroethylamine.

A proposal for the reaction mechanism is presented in Scheme 4. First, *tert*-butyl isocyanide (**3a**) complexed to CuI reacts with *S*-methyl methanethiosulfonate (**2a**) to form *S*-methylated *tert*-butyl isothiocyanate **I/II**. This step is facilitated by CuI acting as a Lewis acid. Intermediate **I/II** then reacts with aniline to generate the desired isothiourea and

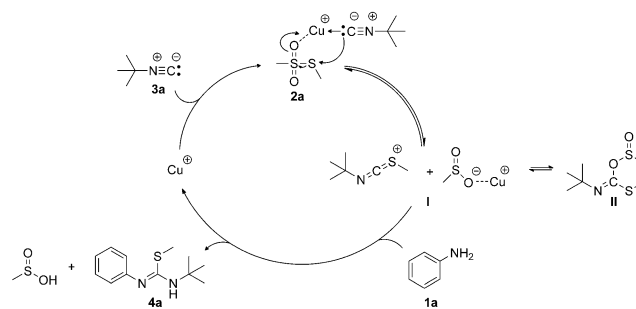

Scheme 4. Proposed mechanism.

Table 3: Scope of the reaction with respect to the isocyanide.^[a]

Entry	R ¹	R ²	Product	Yield [%] ^[b]
1	4-Cl	<i>n</i> Pn (3 b)	5 a	89 ^[c]
2	4-CO ₂ CH ₃	<i>n</i> Pn (3 b)	5 b	65 ^[c]
3	2-OMe	<i>n</i> Pn (3 b)	5 c	57
4	4-H		5 d	40
5	4-Cl		5 e	90
6	4-Cl		5 f	76
7	4-Cl	Bn (3 f)	5 g	65 ^[c]
8	4-CO ₂ CH ₃	Bn (3 f)	5 h	63 ^[c]
9	4-CN	Bn (3 f)	5 i	50 ^[c]
10	2-OMe	Bn (3 f)	5 j	71
11 ^[d]	4-Cl	<i>i</i> Pr (3 g)	5 k	65 ^[c]
12 ^[d]	4-CO ₂ CH ₃	<i>i</i> Pr (3 g)	5 l	69 ^[c]
13 ^[d]	2-OMe	<i>i</i> Pr (3 g)	5 m	70
14	4-Cl		5 n	71
15	4-Cl	Cy (3 i)	5 o	86 ^[c]
16	4-H		5 p	48
17	4-Cl		 7	82 ^[f]
18	4-H		5 r	70
19	4-H	4-MeOC ₆ H ₄ (3 m)	5 s	44
20	4-Cl		5 t	81

[a] Reaction conditions: **1** (1.7 equiv), **2 a** (1.0 equiv), **3 a** (2.5 equiv), CuI (1 mol%), 2-MeTHF (2.5 mL per mmol of **2 a**), 4 Å MS (300 mg per mmol of **2 a**), 75 °C, 20 h, air. [b] Yield of the isolated product. [c] Yield without molecular sieves: 76% (**5 a**), 62% (**5 b**), 51% (**5 g**), 51% (**5 h**), 65% (**5 k**), 70% (**5 l**), 44% (**5 o**). [d] The reaction was carried out in a sealed vial. [e] Yield on a 10 mmol scale: 45%. [f] Compound **5 q** was not isolated.

methanesulfinic acid. A transition-metal-catalyzed insertion of the isocyanide into a Cu–S or Cu–N bond does not seem to be involved, as the desired coupling is promoted by a variety of other transition metals in different oxidation states (Table 1, entries 14–21) as well as Lewis acids that are not based on transition metals (BF₃ and B(C₆F₅)₃; Table 1, entries 22 and 23). On the basis of the better performance of CuI as compared to more Lewis acidic Cu complexes and classical Lewis acids, a precomplexation of isocyanide with Cu to bring the isocyanide close to the sulfonyl group is considered.^[25] A radical reaction was excluded, as **4 a** was obtained in similar yield when a radical inhibitor was added

(see Scheme S4).^[21] An initial reaction of the (hetero)aromatic amine **1** with the thiosulfonate **2** or isocyanide **3** was also considered as the first step of the mechanism. However, no reaction occurred upon mixing **1 h** with **2 a** or **1 h** with **3 a** under the optimal reaction conditions (see Schemes S5 and S7).^[21] On the other hand, mixing of **2 a** and **3 a** resulted in the formation of a new compound whose ¹H NMR spectrum could be in accordance with **I/II** (Scheme 5). Moreover, addition of **1 h** to a premixed solution of **2 a** and **3 a** yielded the target compound **4 h** in 54% yield (Scheme 6).

The role of the MS does not seem to be the scavenging of H₂O from the reaction mixture, as dried 2-MeTHF was used for the reactions, which were carried out with a drying tube on top of the reflux condenser. The effect of 4 Å MS (Na₁₂[(AlO₂)₁₂(SiO₂)₁₂]:xH₂O) can be rationalized by a partial exchange of Na⁺ for Cu⁺ to form a more active catalyst. Cu⁺ zeolites are known to be Lewis acid catalysts.^[26] As the three-component reaction also proceeds in the absence of CuI and MS (Table 1, entry 24; see also Table S6), albeit in substantially lower yield, a simultaneous uncatalyzed reaction involving the insertion of the isocyanide into S-methyl methanethiosulfonate probably also takes place.

In conclusion, we have developed a novel three-component reaction between readily available isocyanides, thiosulfonates, and (hetero)aromatic amines to afford isothioureas in a single synthetic step. This new strategy offers a more sustainable and direct alternative for the synthesis of S-alkyl and S-aryl isothioureas in comparison to classical approaches. Especially S-aryl isothioureas are difficult to obtain by other methods. Although isothioureas can be obtained without the addition of a catalyst, the addition of CuI and 4 Å MS is generally required for the products to be obtained in high yield. Around 90% of the isothioureas reported in this study are hitherto unknown compounds, thus justifying the synthetic potential of this procedure.

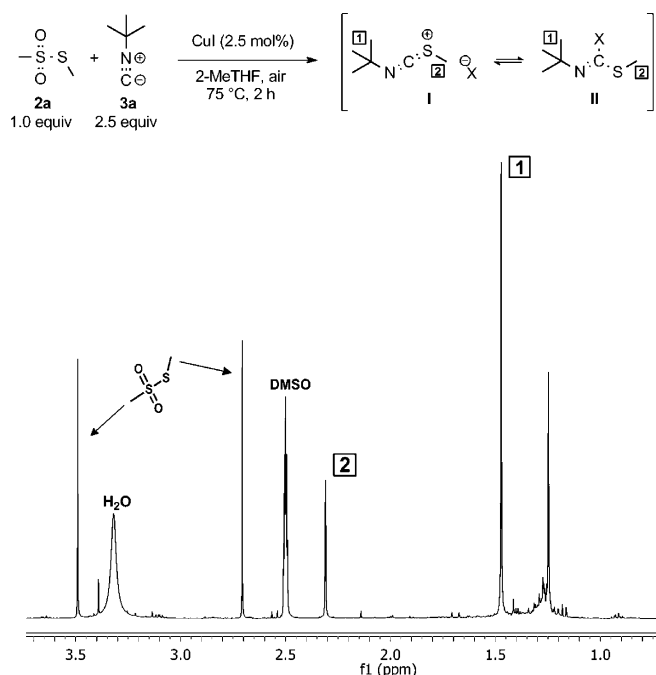
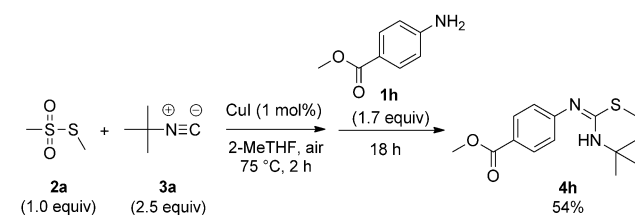
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Table 4: Scope of the reaction with respect to the thiosulfonate.^[a]

Entry	R ¹	R ²	R ³	Product	Yield [%] ^[b]
1	<i>n</i> Bu	<i>n</i> Bu	(2b)	6a	75
2	Me	<i>n</i> Bu	(2c)	6a	77
3			(2d)	6b	85
4	Ph	Ph	(2e)	6c	96 ^[c]
5 ^[d]	Ph	Ph	(2e)	6d	89
6	Ph	Ph	(2e)	6e	90
7	Ph	Ph	(2e)	6f	94
8	Me	4-ClC ₆ H ₄	(2f)	6g	84 ^[c]

[a] Reaction conditions: **1** (1.7 equiv), **2** (1.0 equiv), **3** (2.5 equiv), Cul (1 mol%), 2-MeTHF (2.5 mL per mmol of **2a**), 4 Å MS (300 mg per mmol of **2a**), 75 °C, 20 h, air. [b] Yield of the isolated product. [c] Yield without molecular sieves: 66% (**6c**), 63% (**6g**). [d] The reaction was carried out in a sealed vial.


Scheme 5. ¹H NMR spectrum obtained after mixing **2a** with **3a**. DMSO = dimethyl sulfoxide.

Scheme 6. Synthesis of **4h** through a one-pot two-stage procedure.

Keywords: copper catalysis · isocyanides · isothioureas · Lewis acids · molecular sieves

- [1] "Phenoxyphenylthioureas": J. Drabek, M. Böger, FR2465720A1, **1980**, and 4.939.257, **1988**.
- [2] A. Nicholson, J. D. Perry, A. L. James, S. P. Stanforth, S. Carnell, K. Wilkinson, C. M. Anjam Khan, A. De Soyza, F. K. Gould, *Int. J. Antimicrob. Agents* **2012**, 39, 27–32.
- [3] a) S. Harusawa, K. Sawada, T. Magata, H. Yoneyama, L. Araki, Y. Usami, K. Hatano, K. Yamamoto, D. Yamamoto, A. Yamatodani, *Bioorg. Med. Chem. Lett.* **2013**, 23, 6415–6420; b) E. P. Istyastono, S. Nijmeijer, H. D. Lim, A. van de Stolpe, L. Roumen, A. J. Kooistra, H. F. Vischer, I. J. P. de Esch, R. Leurs, C. de Graaf, *J. Med. Chem.* **2011**, 54, 8136–8147.
- [4] G. Thoma, M. B. Streiff, J. Kovarik, F. Glickman, T. Wagner, C. Beerli, H.-G. Zerwes, *J. Med. Chem.* **2008**, 51, 7915–7920.
- [5] C. Ma, A. Wu, Y. Wu, X. Ren, M. Cheng, *Arch. Pharm. Chem. Life Sci.* **2013**, 346, 891–900.
- [6] S. Mohan, P. S. Kerry, N. Bance, M. Niikura, B. M. Pinto, *Angew. Chem. Int. Ed.* **2014**, 53, 1076–1080; *Angew. Chem.* **2014**, 126, 1094–1098.
- [7] J. E. Taylor, S. D. Bull, J. M. J. Williams, *Chem. Soc. Rev.* **2012**, 41, 2109–2121.
- [8] K. Srinivas, P. S. Prathima, K. Balaswamy, B. Sridhar, M. M. Rao, *Catal. Sci. Technol.* **2012**, 2, 1180–1187.
- [9] For reviews, see: a) A. R. Katritzky, B. V. Rogovoy, *Arkivoc* **2005**, 4, 49–87; b) T. R. M. Rauws, B. U. W. Maes, *Chem. Soc. Rev.* **2012**, 41, 2463–2497; c) C. Alonso-Moreno, A. Antiñolo, F. Carillo-Hermosilla, A. Otero, *Chem. Soc. Rev.* **2014**, 43, 3406–3425.
- [10] For a radical approach towards *N*-acyl isothioureas from *N*-acyl cyanamides, see: G. Maestri, M.-H. Larraufie, C. Ollivier, M. Malacria, L. Fensterbank, E. Lacôte, *Org. Lett.* **2012**, 14, 5538–5541.
- [11] For HFR rating (health, flammability, reactivity), see: <http://www.big.be>.
- [12] For a procedure involving arynes that generally yields a mixture of benzamidines and *S*-aryl isothioureas, see: K. Biswas, M. F. Graeney, *Org. Lett.* **2011**, 13, 4946–4949.
- [13] For selected examples, see: a) K. Fujiki, N. Tanifuji, Y. Sasaki, T. Yokoyama, *Synthesis* **2002**, 343–348; b) N. Iranpoor, H. Firouzabadi, A.-R. Pourali, *Synlett* **2004**, 347–349; c) N. Iranpoor, H. Firouzabadi, A.-R. Pourali, *Phosphorus Sulfur Silicon Relat. Elem.* **2006**, 181, 473–479; d) L. Gaigai, L. Miaochang, C. Jiuxi, D. Jinchang, G. Wenxia, W. Huayue, *Chin. J. Chem.* **2012**, 30, 1611–1616; e) M. Kirihaara, S. Naito, Y. Nishimura, Y. Ishizuka, T. Iwai, H. Takeuchi, T. Ogata, H. Hanai, Y. Kinoshita, M. Kishida, K. Yamazaki, T. Noguchi, S. Yamashoji, *Tetrahedron* **2014**, 70, 2464–2471; f) N. Taniguchi, *Eur. J. Org. Chem.* **2014**, 5691–5694.
- [14] For methods starting from other sulfur reagents, see: a) P. Laszlo, A. Mathy, *J. Org. Chem.* **1984**, 49, 2281; b) F. Chemla, P. Karoyan, *Org. Synth.* **2004**, 10, 546–548.
- [15] A. Porcheddu, G. Giacomelli, M. Salaris, *J. Org. Chem.* **2005**, 70, 2361–2363.

- [16] a) *Isocyanide Chemistry: Applications in Synthesis and Material Science* (Ed.: C. Nenajdenko), Wiley-VCH, Weinheim, **2012**; b) A. V. Gulevich, A. G. Zhdanko, R. V. A. Orru, V. G. Nenajdenko, *Chem. Rev.* **2010**, *110*, 5235–5331.
- [17] For selected examples of the reaction of Lewis acid activated substrates with isocyanides, see: a) M. Tobisu, A. Kitajima, S. Yoshioka, I. Hyodo, M. Oshita, N. Chatani, *J. Am. Chem. Soc.* **2007**, *129*, 11431–11437; b) C.-H. Lei, D.-X. Wang, L. Zhao, J. Zhu, M.-X. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 4708–4711.
- [18] For reviews, see: a) T. Vlaar, E. Ruijter, B. U. W. Maes, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2013**, *52*, 7084–7097; *Angew. Chem.* **2013**, *125*, 7222–7236; b) G. Qiu, Q. Ding, J. Wu, *Chem. Soc. Rev.* **2013**, *42*, 5257–5269; c) S. Lang, *Chem. Soc. Rev.* **2013**, *42*, 4867–4880.
- [19] For selected recent examples, see: a) B. Liu, H. Gao, Y. Yu, W. Wu, H. Jiang, *J. Org. Chem.* **2013**, *78*, 10319–10328; b) J. V. Geden, A. K. Pancholi, M. Shipman, *J. Org. Chem.* **2013**, *78*, 4158–4164; c) G. Qiu, X. Qiu, J. Liu, J. Wu, *Adv. Synth. Catal.* **2013**, *355*, 2441–2446; d) Z. Hu, J. Wang, D. Liang, Q. Zhu, *Adv. Synth. Catal.* **2013**, *355*, 3290–3294; e) F. Ji, M.-f. Lv, W.-b. Yi, C. Cai, *Adv. Synth. Catal.* **2013**, *355*, 3401–3406; f) V. N. Bochatay, P. J. Boissarie, J. A. Murphy, C. J. Suckling, S. Lang, *J. Org. Chem.* **2013**, *78*, 1471–1477; g) T.-H. Zhu, X.-P. Xu, J.-J. Cao, T.-Q. Wei, S.-Y. Wang, S.-J. Ji, *Adv. Synth. Catal.* **2014**, *356*, 509–518.
- [20] For selected examples from our research groups, see: a) G. Van Baelen, S. Kuijter, L. Rýček, S. Sergeyev, E. Janssen, F. J. J. de Kanter, B. U. W. Maes, E. Ruijter, R. V. A. Orru, *Chem. Eur. J.* **2011**, *17*, 15039–15040; b) T. Vlaar, R. C. Cioc, P. Mampuy, B. U. W. Maes, R. V. A. Orru, E. Ruijter, *Angew. Chem. Int. Ed.* **2012**, *51*, 13058–13061; *Angew. Chem.* **2012**, *124*, 13235–13238; c) V. Estévez, G. Van Baelen, B. H. Lentferink, T. Vlaar, E. Janssen, B. U. W. Maes, R. V. A. Orru, E. Ruijter, *ACS Catal.* **2014**, *4*, 40–43.
- [21] See the Supporting Information.
- [22] S. Nagarajan, M. S. Kellogg, G. E. Dubois, *J. Med. Chem.* **1996**, *39*, 4167–4172.
- [23] Such compounds have shown biological activity: H. Elokda, T. Sulkowski, D. Cochran, M.-L. McKean, E. Quinet, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1791–1794.
- [24] *Handbook of Chemistry and Physics* (Ed.: W. M. Hayes), CRC, Boca Raton, FL, **2010**.
- [25] The synthesis of formamidines by the treatment of amines with isocyanides under Cu catalysis in a reaction involving the insertion of an isocyanide (complexed to Cu) into the N–H bond has been reported: T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, H. Yoshioka, *Tetrahedron Lett.* **1966**, *7*, 6121–6124. We thank a referee for bringing this work to our attention.
- [26] T. Boningari, A. Olmos, B. M. Reddy, J. Sommer, P. Pale, *Eur. J. Org. Chem.* **2010**, 6338–6347.