Synthesis of Isothiocyanates by Reaction of Amines with Phenyl Chlorothionoformate via One-Pot or Two-Step Process

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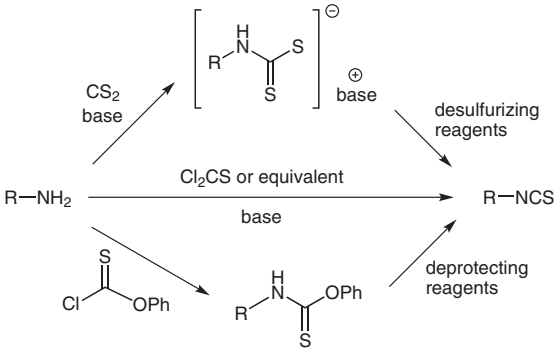
Abstract: A facile and efficient synthesis of isothiocyanates from amines is described. This method involves the reaction of amines with phenyl chlorothionoformate in the presence of solid sodium hydroxide by either a one-pot process or a two-step approach. The one-pot process is useful for preparing alkyl and electron-rich aryl isothiocyanates, whereas the two-step approach is more versatile, working very well not only for alkyl and electron-rich aryl isothiocyanates, but also for highly electron-deficient aryl and heterocyclic isothiocyanates.

Key words: isothiocyanates, phenyl chlorothionoformate, amine, one-pot process, two-step approach

Isothiocyanates are useful synthetic intermediates for the preparation of various sulfur- and nitrogen-containing organic compounds, especially for heterocycles.[1] Naturally occurring isothiocyanates have shown many interesting biological properties, such as antibacterial, antifungal, antimicrobial, and antioxidant activities.[2] Many synthetic isothiocyanates also have exhibited important biological activity.[3]

There are three main methods for the conversion of amines into the corresponding isothiocyanates (Scheme 1). The first method, the classical and traditional route, uses the treatment of amines with thiophosgene.[4] In order to avoid the use of toxic and volatile thiophosgene, many 'thiocarbonyl transfer' reagents[5] have been developed. However, many of these reagents are either commercial unavailable or very expensive, and they readily form thiourea byproducts, which limits the scope of application of these methodologies. The second method is the reagent-promoted desulfurylation of dithiocarbamic acid salts, which are generated in situ by the treatment of amines with carbon disulfide in the presence of a base, to give isothiocyanates.[6] However, almost all the of desulfurylating reagents are only suitable for preparation of alkyl isothiocyanates and electron-rich aryl isothiocyanates. The third method for the preparation of isothiocyanates, which was first reported by Burke in 2000, involves the reaction of amines with phenyl chlorothionoformate followed by deprotection of the resulting phenylcarbamothioates.[7] In this case, trichlorosilane and triethylamine were required for the deprotection, and limited examples were given. So far few methods have been reported for the preparation of isothiocyanates with highly electron-withdrawing or heterocyclic substituents. Therefore, the development of more efficient methods for the synthesis of isothiocyanates, particularly highly electron-deficient aryl isothiocyanates, is still a challenge in organic chemistry. Recently, we have found that the one-pot synthesis of isothiocyanates from amines and phenyl chlorothionoformate could be achieved in the presence of triethylamine but without using trichlorosilane.[8] However, the protocol is not suitable for a broad range of amines, especially for those with highly electron-deficient groups. As a part of our ongoing studies, we report herein an improved synthetic method for isothiocyanates that can be used for a broad range of substituents.



Scheme 1 Methods for conversion of amines into isothiocyanates

Using the preparation of phenyl isothiocyanate from aniline as a model reaction, we optimized the reaction conditions, including choice of different aryl chlorothionoformates, bases, and solvents; the results are summarized in Table 1. Firstly, the reactivity of various aryl chlorothionoformates was evaluated by performing the model reaction in dichloromethane and using triethylamine as the base (entries 1–4). The results showed that phenyl chlorothionoformate gave a slightly better yield than 4-methoxyphenyl, 4-fluorophenyl, or 4-chlorophenyl chlorothionoformate. Secondly, different inorganic bases (*t*-BuOK, Na_2CO_3, and Cs_2CO_3) and organic bases (Et_3N and pyridine) were studied (entries 1 and 5–10). It is interesting to note that different bases generated different products. As depicted in Scheme 2, when triethylamine

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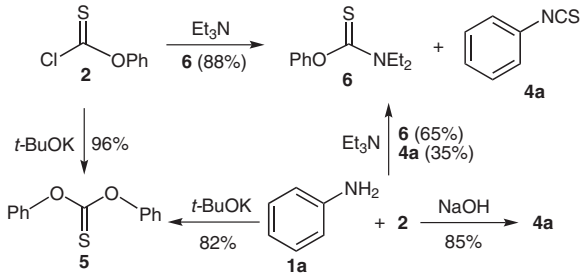
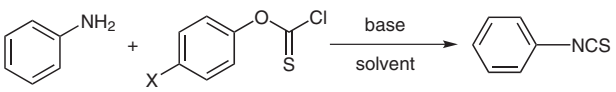
was employed phenyl isothiocyanate (**4a**) was obtained in 35% yield, but the major product was *O*-phenyl diethylcarbamothioate (**6**) in 65% yield. The formation of **6** probably resulted from the dealkylation[9] of triethylamine by phenyl chlorothionoformate (**2**). This result was further confirmed by the direct reaction of **2** with triethylamine without aniline. In this case, **6** was obtained in 88% yield. When potassium *tert*-butoxide was used as the base, the only isolated product was diphenyl carbonothioate (**5**) in 82% yield. Without the addition of aniline, the reaction of **2** with potassium *tert*-butoxide gave **5** almost quantitatively. Other bases, such as sodium carbonate, cesium carbonate, and pyridine, resulted in a very poor yield of **4a** (entries 6–8). To our delight, when solid sodium hydroxide was used as the base, **4a** was obtained in 85% yield and the reaction was complete within nine hours at room temperature (entry 9). However, the use of 1 M aqueous sodium hydroxide solution was not as effective as solid sodium hydroxide and resulted in a lower 59% yield (entry 10). Therefore, the product distribution and yields could be significantly influenced by the type, strength, and state of the base used in the reaction. Finally, the solvent effects were surveyed and the results are given in Table 1 (entries 9 and 11–13); dichloromethane is the best solvent compared to acetonitrile, tetrahydrofuran, and 1,4-dioxane. In addition, the use of excess phenyl chlorothionoformate (**2**) (from 1 equiv to 1.2 equiv) resulted in only a slight increase in the product yield (from 85% to 88%). Based on the results described above, the optimized reaction conditions for one-pot synthesis of isothiocyanates are: phenyl chlorothionoformate as the acylating reagent, solid sodium hydroxide as the base, dichloromethane as the solvent, and 1:1:3 molar ratio for amine/phenyl chlorothionoformate/sodium hydroxide.



Scheme 2 Different bases used for the reaction of phenyl chlorothionoformate with aniline (CH_2Cl_2, r.t.)

With the optimized conditions in hand, the scope and limitations of the one-pot synthesis of isothiocyanates from amines and phenyl chlorothionoformate in the presence of sodium hydroxide were examined (Table 2, method A). All alkylamines could be smoothly converted into the corresponding isothiocyanates in good to excellent yields (83–95%; entries 19–23). However, the electronic effect of the substituents on the aromatic ring has a significant influence on the reaction. For example, good yields (84–92%; entries 2–7) were obtained when electron-rich arylamines were employed; whereas the desired isothiocyanate products could not be detected from highly electron-deficient aryl amines (entries 8–10) and pyridin-3-amine (entry 24). Furthermore, halogenated arylamines afforded the corresponding isothiocyanates in only 21–51% yields (entries 11–17). For fused-ring naphthalen-1-amine, low reactivity was observed (49% yield; entry 18). Therefore, this one-pot process is not suitable for the preparation of electron-deficient aryl and heterocyclic isothiocyanates.

Table 1 Screening of Aryl Chlorothionoformate and Optimization of the Reaction Conditions for the Synthesis of Phenyl Isothiocyanate from Aniline[a]



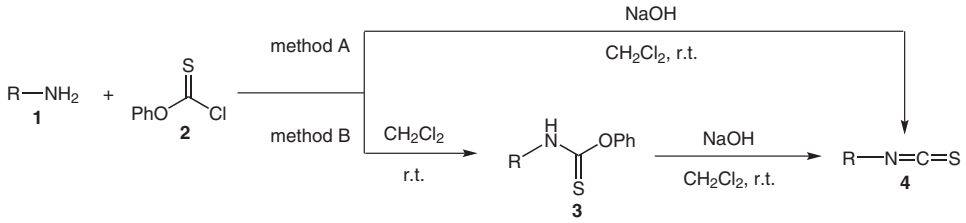
Entry	X	Base	Solvent	Yield[b] (%)
1	H	Et_3N	CH_2Cl_2	35
2	OMe	Et_3N	CH_2Cl_2	21
3	Cl	Et_3N	CH_2Cl_2	17
4	F	Et_3N	CH_2Cl_2	22
5	H	*t*-BuOK	CH_2Cl_2	3
6	H	pyridine	CH_2Cl_2	11
7	H	Na_2CO_3	CH_2Cl_2	27
8	H	Cs_2CO_3	CH_2Cl_2	37
9[c]	H	NaOH	CH_2Cl_2	85
10	H	aq NaOH[d]	CH_2Cl_2	59
11	H	NaOH	MeCN	10
12	H	NaOH	THF	22
13	H	NaOH	dioxane	39
14[c,e]	H	NaOH	CH_2Cl_2	88

[a] Reaction conditions: $PhNH_2$ (1.0 equiv), aryl chlorothionoformate (1 equiv), base (3.0 equiv), solvent, 0 °C, 1 h, then r.t., 48 h.
[b] Isolated yield after purification by column chromatography on silica gel.
[c] The reaction was completed in 9 h.
[d] 1 M NaOH aqueous solution was used.
[e] Phenyl chlorothionoformate (1.2 equiv) was used.

In order to overcome the obstacles in the preparation of isothiocyanates from inactive aromatic amines, different approaches to the reaction of 4-nitroaniline (**1h**) with phenyl chlorothionoformate (**2**) were investigated. As depicted in Scheme 3, by the one-pot process, diphenyl carbonothioate **5**, instead of 4-nitrophenyl isothiocyanate (**4h**), was observed. In this case, 4-nitroaniline (**1h**) did not take part in the reaction, which was confirmed by converting **2** into **5** in the absence of **1h**. According to the reaction mechanism, thiocarbamate **3** is the key intermediate, which can be prepared from the reaction of the amine with phenyl chlorothionoformate without base, and followed by decomposition of **3** to form the corre-

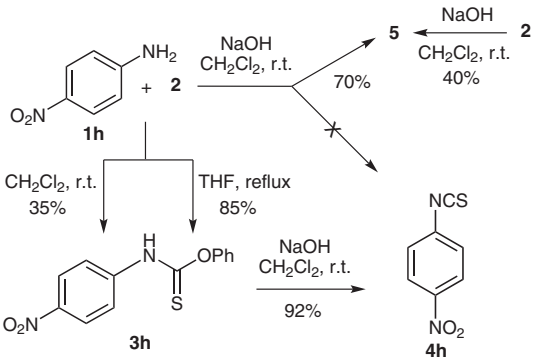
sponding isothiocyanates **4** using trichlorosilane/triethylamine[7] or triethylamine.[8] Hence, a two-step process for the synthesis of **4h** was studied (Scheme 3). In the first step, thiocarbamate **3h** was prepared in refluxing tetrahydrofuran in 85% isolated yield, whereas only 35% yield of **3h** was obtained when the reaction was performed in dichloromethane at room temperature. Fortunately, in the second step, upon treatment with solid sodium hy-

Table 2 Synthesis of Isothiocyanates from Primary Amines and Phenyl Chlorothionoformate



Entry	R	Method A[a]			Method B[b]			
					Step 1		Step 2	
		Time (h)	Product	Yield[c] (%)	Product	Yield[c] (%)	Product	Yield[c] (%)
1	Ph	9	**4a**	85	**3a**	91	**4a**	90
2	4-$MeOC_6H_4$	5	**4b**	84	**3b**	92	**4b**	92
3	3-$MeOC_6H_4$	18	**4c**	88	**3c**	97	**4c**	97
4	4-MeC_6H_4	14	**4d**	88	**3d**	99	**4d**	94
5	2-MeC_6H_4	16	**4e**	86	**3e**	95	**4e**	99
6	3,5-$Me_2C_6H_3$	24	**4f**	92	**3f**	93	**4f**	98
7	4-$Me_2NC_6H_4$	20	**4g**	85	**3g**	85	**4g**	96
8	4-$O_2NC_6H_4$	72	–	–	**3h**	35, 85[d]	**4h**	92
9	2-$O_2NC_6H_4$	72	–	–	**3i**	82[d]	**4i**	96
10	3-$O_2NC_6H_4$	72	–	–	**3j**	89	**4j**	93
11	4-FC_6H_4	72	**4k**	39	**3k**	87	**4k**	98
12	4-ClC_6H_4	72	**4l**	47	**3l**	94	**4l**	86
13	4-BrC_6H_4	72	**4m**	51	**3m**	94	**4m**	94
14	4-IC_6H_4	72	**4n**	24	**3n**	90	**4n**	94
15	2-ClC_6H_4	72	**4o**	28	**3o**	65	**4o**	99
16	3-BrC_6H_4	72	**4p**	32	**3p**	84	**4p**	94
17	2,4-$Cl_2C_6H_3$	72	**4q**	21	**3q**	62[d]	**4q**	99
18	1-naphthyl	18	**4r**	49	**3r**	93	**4r**	97
19	Bn	5	**4s**	95	**3s**	99	**4s**	97
20	2-furylmethyl	6	**4t**	83	**3t**	99	**4t**	94
21	2-thienylmethyl	5	**4u**	89	**3u**	96	**4u**	97
22	$(CH_2)_5Me$	6	**4v**	87	**3v**	93	**4v**	98
23	Cy	9	**4w**	83	**3w**	98	**4w**	99
24	3-pyridyl	72	–	–	**3x**	72	**4x**	85

[a] Method A: **1** (2.0 mmol), **2** (2.0 mmol, solid NaOH (6.0 mmol), anhyd CH_2Cl_2 (12 mL).
[b] Method B: 1. **1** (2.0 mmol), **2** (1.0 mmol), anhyd CH_2Cl_2 (5 mL), r.t., ~30 min; 2. **3** (1.0 mmol), solid NaOH (1.2 mmol), anhyd CH_2Cl_2 (5 mL), r.t., ~1 h.
[c] Isolated yield.
[d] The reaction mixture was refluxed in THF.



Scheme 3 Different approaches for the reaction of 4-nitroaniline with phenyl chlorothionoformate

droxide in dichloromethane, **3h** was smoothly converted into the corresponding isothiocyanate **4h** in 92% yield.

After the success in the synthesis of highly electron-deficient 4-nitrophenyl isothiocyanate (**4h**), the two-step protocol was employed for various kinds of amines and using solid sodium hydroxide as the deprotection reagent (Table 2, method B). In the first step, all of the intermediate thiocarbamates **3** could be conveniently prepared by reacting the amine with phenyl chlorothionoformate in dichloromethane at room temperature,[7] with the exception of thiocarbamates **3h**,**i**,**q** which were synthesized in refluxing tetrahydrofuran. During the course of second step, all of the thiocarbamates **3a**–**w** derived from aryl- and alkylamines could be smoothly deprotected by sodium hydroxide to afford the corresponding isothiocyanates **4a**–**w** with good to excellent yields (86%–99%). Compared to the one-pot process (method A), the two-step synthesis (method B) has obvious superiority for those aromatic amines with highly electron-deficient groups such as nitro and fluoro groups (Table 2, entries 8–11). Furthermore, higher reaction efficiency for halogenated aryl amines **1k**–**q** and fused-ring naphthalen-1-amine (**1r**) were obtained by method B (entries 11–18). Finally, the two-step approach also worked well for the heterocyclic substrate pyridin-3-amine (**1x**, entry 24). In this instance, 3-isothiocyanatopyridine (**4x**), which could not be prepared by the one-pot process and other previous methods, was obtained in 61% overall yield.

In summary, we have developed a facile and efficient method for the synthesis of isothiocyanates from amines and phenyl chlorothionoformate in the presence of solid sodium hydroxide via one-pot or two-step process. The one-pot approach is useful for alkyl and electron-rich aryl isothiocyanates, whereas the two-step method is efficient and versatile for synthesizing broad range of alkyl, aryl, and heterocyclic isothiocyanates, especially useful for the highly electron-deficient aryl and heterocyclic isothiocyanates.

^{1}H and ^{13}C NMR spectra were measured on 300, 400, and 500 MHz NMR spectrometers using TMS as the internal standard. LCMS and GCMS were recorded on a mass spectrometer by ESI and EI techniques, respectively. Melting points were measured with a micro-melting point apparatus and are uncorrected. TLC was performed on precoated silica gel 60 F_{254} plates. Flash column chromatography was performed with silica gel (300–400 mesh). All yields given refer to isolated yields. All chemical reagents were purchased from commercial sources and used as received.

Isothiocyanates 4 by the One-Pot Process; General Procedure (Method A)

To an ice-cold stirred soln of amine **1** (2.0 mmol) and powdered NaOH (6.0 mmol) in anhyd CH_2Cl_2 (10 mL) was added dropwise a soln of phenyl chlorothionoformate (**2**, 2.0 mmol) in anhyd CH_2Cl_2 (2 mL). The mixture was stirred at 0 °C for 1 h. The ice bath was removed, and the mixture was stirred at r.t. until completion (TLC and GC-MS monitoring). The reaction was quenched with H_2O (20 mL), and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were washed with brine (30 mL) and dried (anhyd Na_2SO_4). The solvent was concentrated in vacuo, and the crude products were purified by column chromatography (petroleum ether–EtOAc) to give the corresponding isothiocyanate **4**.

Isothiocyanates 4 by the Two-Step Process, Step 1, Synthesis of Thiocarbamates 3; General Procedure (Method B)

A mixture of amine **1** (2.0 mmol) and phenyl chlorothionoformate (**2**, 1.0 mmol) in CH_2Cl_2 (5 mL) was stirred at r.t. for ~30 min (TLC monitoring). When the reaction was complete, the mixture was filtered to remove the precipitate, and the filtrate was evaporated under reduced pressure. The residues were purified by flash column chromatography (petroleum ether–EtOAc) to give the corresponding thiocarbamates **3**.

***O*-Phenyl Phenylcarbamothioate (3a)**

White solid; yield: 208 mg (0.91 mmol, 91%); mp 141–143 °C (Lit.[10] 142–143 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.64 (m, 1 H), 7.38–7.45 (m, 5 H), 7.30 (t, *J* = 7.6 Hz, 2 H), 7.15 (d, *J* = 7.6 Hz, 2 H).

***O*-Phenyl (4-Methoxyphenyl)carbamothioate (3b)**

White solid; yield: 238 mg (0.92 mmol, 92%); mp 122–123 °C (Lit.[8] 122–123 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 8.4 Hz, 1 H), 7.42 (t, *J* = 7.2 Hz, 2 H), 7.29 (d, *J* = 7.2 Hz, 2 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 6.92 (t, *J* = 8.8 Hz, 2 H), 3.82 (s, 3 H).

***O*-Phenyl (3-Methoxyphenyl)carbamothioate (3c)**[11]

White solid; yield: 251 mg (0.97 mmol, 97%); mp 101–102 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.41 (m, 3 H), 7.33–7.28 (m, 2 H), 7.15 (d, *J* = 7.5 Hz, 2 H), 6.96 (s, 1 H), 6.77 (d, *J* = 7.5 Hz, 1 H), 3.81 (s, 3 H).

***O*-Phenyl *p*-Tolylcarbamothioate (3d)**

White solid; yield: 241 mg (0.99 mmol, 99%); mp 121–122 °C (Lit.[12] 120–122 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 7.2 Hz, 1 H), 7.43 (t, *J* = 7.5 Hz, 2 H), 7.31 (d, *J* = 7.5 Hz, 1 H), 7.19–7.14 (m, 5 H), 2.35 (s, 3 H).

***O*-Phenyl *o*-Tolylcarbamothioate (3e)**

White solid; yield: 231 mg (0.95 mmol, 95%); mp 114–115 °C (Lit.[13] 109.5–111.5 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.62 (m, 1 H), 7.48–7.36 (m, 3 H), 7.30–7.10 (m, 5 H), 2.41 (s, 3 H).

***O*-Phenyl (3,5-Dimethylphenyl)carbamothioate (3f)**
White solid; yield: 239 mg (0.93 mmol, 93%); mp 126–128 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (t, *J* = 7.8 Hz, 2 H), 7.30 (t, *J* = 7.5 Hz, 2 H), 7.15 (d, *J* = 7.8 Hz, 2 H), 6.98 (s, 1 H), 6.87 (s, 1 H), 2.33 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.9, 152.5, 137.9, 135.6, 128.3, 126.7, 125.4, 121.9, 121.5, 120.1, 118.8, 20.3.

MS (ESI): *m*/*z* = 258 ($M + H^+$, 100).

Anal. Calcd for $C_{15}H_{15}NOS$: C, 70.01; H, 5.87; N, 5.44; S, 12.46. Found: C, 69.89; H, 5.96; N, 5.38; S, 12.39.

***O*-Phenyl [4-(Dimethylamino)phenyl]carbamothioate (3g)**
Yellow solid; yield: 231 mg (0.85 mmol, 85%); mp 148–149 °C (Lit.[10] 130–132 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.39 (m, 3 H), 7.30–7.23 (m, 2 H), 7.17–7.12 (m, 2 H), 6.79–6.71 (m, 2 H), 2.96 (s, 6 H).

***O*-Phenyl (4-Nitrophenyl)carbamothioate (3h)**[11]
The reaction was performed in refluxing THF; yellow solid; yield: 233 mg (0.85 mmol, 85%); mp 135–136 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (t, *J* = 8.8 Hz, 2 H), 7.72 (d, *J* = 8.8 Hz, 2 H), 7.44 (t, *J* = 8.0 Hz, 2 H), 7.32 (t, *J* = 7.2 Hz, 1 H), 7.18 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.7, 153.6, 148.7, 147.4, 129.8, 129.4, 127.0, 125.1, 121.6.

***O*-Phenyl (2-Nitrophenyl)carbamothioate (3i)**
The reaction was performed in refluxing THF; yellow solid; yield: 225 mg (0.82 mmol, 82%); mp 95–97 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.03 (br s, 1 H), 8.82–8.80 (m, 1 H), 8.24 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1 H), 7.73–7.68 (m, 1 H), 7.49–7.43 (m, 2 H), 7.35–7.29 (m, 2 H), 7.17–7.14 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.2, 152.7, 138.5, 135.2, 133.4, 129.5, 126.7, 125.9, 125.1, 124.0, 122.6.

MS (ESI): *m*/*z* = 275 ($M + H^+$, 100).

Anal. Calcd for $C_{13}H_{10}N_2O_3S$: C, 56.92; H, 3.67; N, 10.21; S, 11.69. Found: C, 56.79; H, 3.76; N, 10.11; S, 11.62.

***O*-Phenyl (3-Nitrophenyl)carbamothioate (3j)**[11]
Yellow solid; yield: 244 mg (0.89 mmol, 89%); mp 114–115 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (dd, *J* = 8.1, 1.2 Hz, 1 H), 7.58–7.21 (m, 6 H), 7.16 (d, *J* = 7.8 Hz, 2 H).

***O*-Phenyl (4-Fluorophenyl)carbamothioate (3k)**
White solid; yield: 215 mg (0.87 mmol, 87%); mp 138–140 °C (Lit.[10] 136–138 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64–7.61 (m, 1 H), 7.46–7.30 (m, 4 H), 7.15–7.09 (m, 4 H).

***O*-Phenyl (4-Chlorophenyl)carbamothioate (3l)**
White solid; yield: 247 mg (0.94 mmol, 94%); mp 128–129 °C (Lit.[10] 128–129 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.64 (m, 1 H), 7.43 (d, *J* = 8.0 Hz, 2 H), 7.37–7.29 (m, 4 H), 7.14 (d, *J* = 8.4 Hz, 2 H).

***O*-Phenyl (4-Bromophenyl)carbamothioate (3m)**
White solid; yield: 289 mg (0.94 mmol, 94%); mp 124–125 °C (Lit.[10] 125–126 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.59 (m, 1 H), 7.52 (d, *J* = 8.4 Hz, 2 H), 7.44 (t, *J* = 7.5 Hz, 2 H), 7.31 (t, *J* = 7.5 Hz, 2 H), 7.15 (d, *J* = 6.9 Hz, 2 H).

***O*-Phenyl (4-Iodophenyl)carbamothioate (3n)**
White solid; yield: 319 mg (0.90 mmol, 90%); mp 164–166 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.75 (d, *J* = 8.1 Hz, 2 H), 7.64 (d, *J* = 8.4 Hz, 1 H), 7.44 (t, *J* = 7.8 Hz, 2 H), 7.31–7.26 (m, 2 H), 7.17 (d, *J* = 7.8 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 186.9, 153.0, 138.7, 137.8, 129.8, 126.4, 124.9, 123.5, 90.4.

MS (ESI): *m*/*z* = 356 ($M + H^+$, 100).

Anal. Calcd for $C_{13}H_{10}INOS$: C, 43.96; H, 2.84; N, 3.94; S, 9.03. Found: C, 43.85; H, 2.91; N, 3.88; S, 9.10.

***O*-Phenyl (2-Chlorophenyl)carbamothioate (3o)**
White solid; yield: 171 mg (0.65 mmol, 65%); mp 122–123 °C (Lit.[13] 119–121 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.41 (m, 3 H), 7.36–7.28 (m, 3 H), 7.21–7.14 (m, 3 H).

***O*-Phenyl (3-Bromophenyl)carbamothioate (3p)**[11]
White solid; yield: 258 mg (0.84 mmol, 84%); mp 122–124 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (s, 1 H), 7.37 (t, *J* = 7.8 Hz, 2 H), 7.29–7.14 (m, 4 H), 7.07 (d, *J* = 7.8 Hz, 2 H).

***O*-Phenyl (2,4-Dichlorophenyl)carbamothioate (3q)**
The reaction was performed in refluxing THF; white solid; yield: 184 mg (0.62 mmol, 62%); mp 102–103 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.55 (br s, 1 H), 7.48–7.41 (m, 3 H), 7.34–7.28 (m, 2 H), 7.17–7.12 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.2, 151.7, 131.8, 130.5, 128.4, 128.3, 127.9, 126.7, 125.6, 124.1, 121.5.

MS (ESI): *m*/*z* = 298 ($M + H^+$, 100).

Anal. Calcd for $C_{13}H_9Cl_2NOS$: C, 52.36; H, 3.04; N, 4.70; S, 10.75. Found: C, 52.21; H, 3.16; N, 4.61; S, 10.83.

***O*-Phenyl Naphthalen-1-ylcarbamothioate (3r)**[7]
Reddish solid; yield: 260 mg (0.93 mmol, 93%); mp 143–145 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14–7.78 (m, 3 H), 7.63–7.05 (m, 9 H).

***O*-Phenyl Benzylcarbamothioate (3s)**
White solid; yield: 241 mg (0.99 mmol, 99%); mp 76–77 °C (Lit.[12] 75–77 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.27 (m, 8 H), 7.13–7.06 (m, 2 H), 4.83 (d, *J* = 5.4 Hz, 1 H), 4.68 (d, *J* = 5.4 Hz, 1 H).

***O*-Phenyl (Furan-2-ylmethyl)carbamothioate (3t)**
White oil; yield: 231 mg (0.99 mmol, 99%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.38 (m, 3 H), 7.32–7.27 (m, 1 H), 7.11–7.08 (m, 2 H), 6.93 (br s, 1 H), 6.39–6.33 (m, 2 H), 4.82 (d, *J* = 5.4 Hz, 1 H), 4.67 (d, *J* = 5.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.4, 152.1, 148.2, 141.7, 128.2, 125.2, 121.7, 109.6, 107.8, 41.6, 39.8.

MS (ESI): *m*/*z* = 234 ($M + H^+$, 100).

Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00; S, 13.74. Found: C, 61.62; H, 4.86; N, 5.93; S, 13.69.

***O*-Phenyl (Thiophen-2-ylmethyl)carbamothioate (3u)**
White oil; yield: 239 mg (0.96 mmol, 96%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.38 (m, 2 H), 7.32–7.28 (m, 2 H), 7.15–7.06 (m, 3 H), 7.03–7.00 (m, 1 H), 6.91 (br s, 1 H), 4.99 (d, *J* = 5.1 Hz, 1 H), 4.84 (d, *J* = 5.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.3, 152.1, 137.3, 128.2, 126.2, 126.0, 125.2, 124.9, 121.7, 43.3, 41.5.

MS (ESI): *m*/*z* = 250 ($M + H^+$, 100).

Anal. Calcd for $C_{12}H_{11}NOS_2$: C, 57.80; H, 4.45; N, 5.62; S, 25.72. Found: C, 57.66; H, 4.58; N, 5.55; S, 25.79.

***O*-Phenyl Hexylcarbamothioate (3v)**
Yellow oil; yield: 221 mg (0.93 mmol, 93%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.36 (m, 2 H), 7.30–7.23 (m, 1 H), 7.11–7.07 (m, 2 H), 6.75 (br s, 1 H), 3.59 (dd, J_1 = 12.9 Hz, J_2 = 7.2 Hz, 1 H), 3.47 (dd, J_1 = 13.2 Hz, J_2 = 6.9 Hz, 1 H), 1.71–1.56 (m, 2 H), 1.36–1.26 (m, 6 H), 0.91 (t, J = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.4, 153.6, 153.1, 129.2, 126.1, 122.8, 45.9, 44.2, 31.4, 29.2, 28.4, 26.6, 22.5, 14.0.

MS (ESI): m/z = 238 (M + H$^+$, 100).

Anal. Calcd for $C_{13}H_{19}NOS$: C, 65.78; H, 8.07; N, 5.90; S, 13.51. Found: C, 65.66; H, 8.18; N, 5.82; S, 13.44.

***O*-Phenyl Cyclohexylcarbamothioate (3w)**
Yellow solid; yield: 230 mg (0.98 mmol, 98%); mp 128–129 °C (Lit.[12] 132 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.37 (m, 2 H), 7.30–7.23 (m, 1 H), 7.12–7.07 (m, 2 H), 4.16–3.87 (m, 1 H), 2.18–2.05 (m, 2 H), 1.81–1.15 (m, 8 H).

***O*-Phenyl Pyridin-3-ylcarbamothioate (3x)**
White solid; yield: 166 mg (0.72 mmol, 72%); mp 84–86 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.55–8.49 (m, 1 H), 7.59–7.55 (m, 1 H), 7.38–7.34 (m, 1 H), 7.27–7.21 (m, 2 H), 6.94–6.83 (m, 4 H), 6.02 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.8, 147.0, 146.5, 133.0, 129.7, 124.4, 120.6, 115.3.

MS (ESI): m/z = 231 (M + H$^+$, 100).

Anal. Calcd for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16; S, 13.92. Found: C, 62.44; H, 4.45; N, 12.21; S, 13.83.

Isothiocyanates 4 by the Two-Step Process, Step 2, Synthesis of Isothiocyanates 4; General Procedure (Method B)
A soln of thiocarbamate **3** (1.0 mmol) and powdered NaOH (1.2 mmol) in CH_2Cl_2 (5 mL) was stirred at r.t. for ~1 h (TLC monitoring). The reaction was quenched with H_2O (10 mL). The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), concentrated in vacuo, and purified by flash column chromatography (petroleum ether–EtOAc) to give the corresponding isothiocyanate **4**.

Isothiocyanatobenzene (4a)[8,14]
Colorless oil; yield: 122 mg (0.90 mmol, 90%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (t, J = 7.5 Hz, 2 H), 7.28 (d, J = 7.5 Hz, 1 H), 7.23 (d, J = 7.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 130.2, 128.5, 126.3, 124.7, 123.2.

MS (EI, 70 eV): m/z = 135 (M$^+$, 100).

1-Isothiocyanato-4-methoxybenzene (4b)[8,14b,c,15]
Yellow oil; yield: 152 mg (0.92 mmol, 92%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.17 (d, J = 9.0 Hz, 2 H), 6.85 (d, J = 9.0 Hz, 2 H), 3.81 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.5, 129.7, 127.0, 123.5, 114.8, 55.6.

MS (EI, 70 eV): m/z = 165 (M$^+$, 100).

1-Isothiocyanato-3-methoxybenzene (4c)[14c]
Yellow oil; yield: 160 mg (0.97 mmol, 97%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.17 (d, J = 9.0 Hz, 2 H), 6.85 (d, J = 9.0 Hz, 2 H), 3.81 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.3, 135.4, 132.1, 121.8, 118.2, 113.7, 111.1, 55.5.

MS (EI, 70 eV): m/z = 165 (M$^+$, 100).

1-Isothiocyanato-4-methylbenzene (4d)
White solid; yield: 140 mg (0.94 mmol, 94%); mp 25–26 °C (Lit.[14b] 25–27 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.13 (d, J = 8.5 Hz, 2 H), 7.10 (d, J = 8.5 Hz, 2 H), 2.34 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.5, 134.4, 130.1, 128.4, 125.5, 21.2.

MS (EI, 70 eV): m/z = 149 (M$^+$, 100).

1-Isothiocyanato-2-methylbenzene (4e)[6e,14b,c]
Yellow oil; yield: 148 mg (0.99 mmol, 99%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23–7.16 (m, 4 H), 2.38 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 134.0, 129.6, 128.6, 126.3, 125.9, 124.9, 120.8, 17.3.

MS (EI, 70 eV): m/z = 149 (M$^+$, 100).

1-Isothiocyanato-3,5-dimethylbenzene (4f)[16]
Yellow oil; yield: 160 mg (0.98 mmol, 98%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.90 (s, 1 H), 6.85 (s, 2 H), 2.29 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.4, 134.5, 130.8, 129.2, 123.4, 21.0.

MS (EI, 70 eV): m/z = 163 (M$^+$, 100).

4-Isothiocyanato-*N*,*N*-dimethylaniline (4g)
Yellow solid; yield: 171 mg (0.96 mmol, 96%); mp 67–69 °C (Lit.[6c] 69 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (d, J = 8.8 Hz, 2 H), 6.59 (d, J = 8.8 Hz, 2 H), 2.96 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.3, 129.6, 126.7, 121.8, 112.3, 40.3.

MS (EI, 70 eV): m/z = 178 (M$^+$, 100).

1-Isothiocyanato-4-nitrobenzene (4h)
White solid; yield: 166 mg (0.92 mmol, 92%); mp 108–109 °C (Lit.[14b] 109–110 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, J = 8.8 Hz, 2 H), 7.35 (d, J = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.9, 140.5, 138.0, 126.4, 125.3.

MS (EI, 70 eV): m/z = 180 (M$^+$, 100).

1-Isothiocyanato-2-nitrobenzene (4i)
White solid; yield: 173 mg (0.96 mmol, 96%); mp 75–77 °C (Lit.[15] 75–76 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (dd, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 1 H), 7.66–7.61 (m, 1 H), 7.45–7.39 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.5, 134.4, 129.5, 129.2, 127.2, 125.9, 121.4.

MS (EI, 70 eV): m/z = 180 (M$^+$, 100).

1-Isothiocyanato-3-nitrobenzene (4j)[6g]
White solid; yield: 167 mg (0.93 mmol, 93%); mp 59–61 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16–8.12 (m, 1 H), 8.08–8.07 (m, 1 H), 7.57–7.55 (m, 1 H), 7.54 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.8, 139.6, 133.2, 131.5, 130.5, 121.8, 120.7.

MS (EI, 70 eV): m/z = 180 (M$^+$, 100).

1-Fluoro-4-isothiocyanatobenzene (4k)[6e]
Yellow oil; yield: 150 mg (0.98 mmol, 98%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22–7.19 (m, 2 H), 7.04 (t, J = 8.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.2, 136.1, 127.4, 123.2, 116.8.

MS (EI, 70 eV): *m*/*z* = 153 (M^+, 100).

1-Chloro-4-isothiocyanatobenzene (4l)
White solid; yield: 145 mg (0.86 mmol, 86%); mp 42–44 °C (Lit.[14c] 42–43 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8.5 Hz, 2 H), 7.16 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 136.7, 132.9, 130.0, 129.8, 126.9.

MS (EI, 70 eV): *m*/*z* = 169 (M^+, 100).

1-Bromo-4-isothiocyanatobenzene (4m)
Yellow solid; yield: 200 mg (0.94 mmol, 94%); mp 57–59 °C (Lit.[6c] 50 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.5 Hz, 2 H), 7.09 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 136.9, 132.7, 130.5, 127.2, 120.8.

MS (EI, 70 eV): *m*/*z* = 213, 215 (M^+, 100).

1-Iodo-4-isothiocyanatobenzene (4n)[17]
Yellow solid; yield: 245 mg (0.94 mmol, 94%); mp 76–78 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.5 Hz, 2 H), 6.96 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.7, 136.9, 131.2, 127.4, 91.9.

MS (EI, 70 eV): *m*/*z* = 261 (M^+, 100).

1-Chloro-2-isothiocyanatobenzene (4o)[6e,g,i]
Colorless oil; yield: 167 mg (0.99 mmol, 99%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.40 (m, 1 H), 7.25–7.17 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.7, 131.8, 130.1, 129.8, 128.0, 127.6, 126.7.

MS (EI, 70 eV): *m*/*z* = 169 (M^+, 100).

1-Bromo-3-isothiocyanatobenzene (4p)[6e]
Colorless oil; yield: 200 mg (0.94 mmol, 94%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.32 (m, 2 H), 7.19–7.07 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.4, 131.7, 129.7, 129.4, 127.7, 123.3, 121.8.

MS (EI, 70 eV): *m*/*z* = 213, 215 (M^+, 100).

2,4-Dichloro-1-isothiocyanatobenzene (4q)
White solid; yield: 201 mg (0.99 mmol, 99%); mp 38–39 °C (Lit.[18] 37–42 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 2.1 Hz, 1 H), 7.21 (d, *J* = 2.4 Hz, 1 H), 7.18 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.9, 133.0, 132.6, 130.0, 128.6, 128.0, 127.1.

MS (EI, 70 eV): *m*/*z* = 203 (M^+, 100).

1-Isothiocyanatonaphthalene (4r)
White solid; yield: 179 mg (0.97 mmol, 97%); mp 56–58 °C (Lit.[19] 53–54 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 8.5 Hz, 1 H), 7.86 (d, *J* = 8.0 Hz, 1 H), 7.78–7.75 (m, 1 H), 7.62–7.54 (m, 2 H), 7.42–7.38 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 136.1, 134.0, 129.3, 128.4, 127.7, 127.5, 127.4, 127.1, 125.4, 123.4, 122.7.

MS (EI, 70 eV): *m*/*z* = 185 (M^+, 100).

(Isothiocyanatomethyl)benzene (4s)[6e,i,8,19]
Yellow oil; yield: 145 mg (0.97 mmol, 97%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (t, *J* = 7.0 Hz, 2 H), 7.35 (d, *J* = 7.0 Hz, 1 H), 7.31 (d, *J* = 7.0 Hz, 2 H), 4.71 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 134.3, 132.4, 129.0, 128.4, 126.8, 48.7.

MS (EI, 70 eV): *m*/*z* = 149 (M^+, 28), 91 (100).

2-(Isothiocyanatomethyl)furan (4t)[6g,14a]
Yellow oil; yield: 131 mg (0.94 mmol, 94%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.42 (m, 1 H), 6.38–6.34 (m, 2 H), 4.65 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.3, 143.2, 134.9, 110.6, 108.7, 41.9.

MS (EI, 70 eV): *m*/*z* = 139 (M^+, 17), 81 (100).

2-(Isothiocyanatomethyl)thiophene (4u)[20]
White oil; yield: 150 mg (0.97 mmol, 97%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (dd, *J* = 5.1, 1.2 Hz, 1 H), 7.05-7.04 (m, 1 H), 6.98 (dd, J_1 = 5.1 Hz, J_2 = 3.6 Hz, 1 H), 4.84 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.5, 134.4, 127.1, 126.6, 126.2, 3.8.

MS (EI, 70 eV): *m*/*z* = 155 (M^+, 12), 97 (100).

1-Isothiocyanatohexane (4v)[8]
Colorless oil; yield: 140 mg (0.98 mmol, 98%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.52 (t, *J* = 7.0 Hz, 2 H), 1.73–1.67 (m, 2 H), 1.45–1.39 (m, 2 H), 1.37–1.29 (m, 4 H), 0.91 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 129.3, 45.1, 31.0, 29.9, 26.2, 22.5, 14.0.

MS (EI, 70 eV): *m*/*z* = 143 (M^+, 10), 115 (100).

Isothiocyanatocyclohexane (4w)[6i,8,19]
Colorless oil; yield: 140 mg (0.99 mmol, 99%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.71–3.69 (m, 1 H), 1.94–1.86 (m, 2 H), 1.74–1.64 (m, 4 H), 1.51–1.38 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 129.5, 55.4, 33.2, 25.0, 23.2.

MS (EI, 70 eV): *m*/*z* = 141 (M^+, 68), 55 (100).

3-Isothiocyanatopyridine (4x)[21]
White oil; yield: 116 mg (0.85 mmol, 85%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.55 (d, *J* = 2.1 Hz, 1 H), 8.51 (dd, *J* = 4.8, 1.5 Hz, 1 H), 7.55–7.51 (m, 1 H), 7.34–7.30 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.6, 147.1, 139.2, 132.4, 129.6, 124.0.

MS (EI, 70 eV): *m*/*z* = 136 (M^+, 100).

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