The BF_3·OEt_2-Assisted Conversion of Nitriles into Thioamides with Lawesson's Reagent

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Abstract: A method for the thiolysis of nitriles by applying Lawesson's reagent and facilitated by the addition of boron trifluoride–diethyl ether complex is reported. The method opens an easy access to primary thioamides. Aromatic, benzylic, and aliphatic nitriles were converted into the corresponding thioamides in high to quantitative yields (even in unfavorable cases, e.g., *ortho*-substituted benzonitriles). The reaction was performed in 1,2-dimethoxyethane–tetrahydrofuran or toluene–diethyl ether solvent mixtures at 20–50 °C, and exhibited considerable selectivity in the case of multifunctional nitrile substrates, such as cyanomethyl *N*-acetylphenylalaninate, benzoylacetonitrile, 4-cyanobenzamide, 4-acetylbenzonitrile, or pent-3-enenitrile.

Key words: thioamides, nitriles, Lawesson's reagent, Lewis acid complex, sulfur-transferring reagents

The thiolysis of nitriles leading directly to thioamides remains an attractive synthetic transformation.[2] Thioamides are versatile synthetic intermediates in the preparation of heterocyclic compounds.[3] Furthermore, thioamide-based drugs are of increasing relevance in the treatment of multidrug-resistant tuberculosis.[4] The thionation of nitriles, amides, ketones, or esters has been known for a long time, mostly utilizing hydrogen sulfide,[5] ammonium and alkaline sulfides,[6] and phosphorus pentasulfide[7] as sulfur-transferring reagents. More recent approaches share the methodological goal of overcoming the inconveniencies of these methods due to the toxicity, malodorous properties, or moderate solubilities of these reagents. Especially, diphenylphosphinodithioic acid,[8] *O*,*O*-diethyl dithiophosphate,[9] thioacetic acid,[10] trimethylsilanethiolate,[11] or 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide[12] (commonly known as Lawesson's reagent; L.R.) and its analogues have found application as alternatives to phosphorus pentasulfide. Thionylations with Lawesson's reagent have become part of the standard repertoire of organic synthesis.[13] The commercially available reagent has been widely applied for the introduction of sulfur to carbonyl, amide, and, with some restrictions, ester functions. However, so far the thiolysis of nitriles with Lawesson's reagent has been restricted to a few special cases (thionation of alkylidenemalonitriles).[14]

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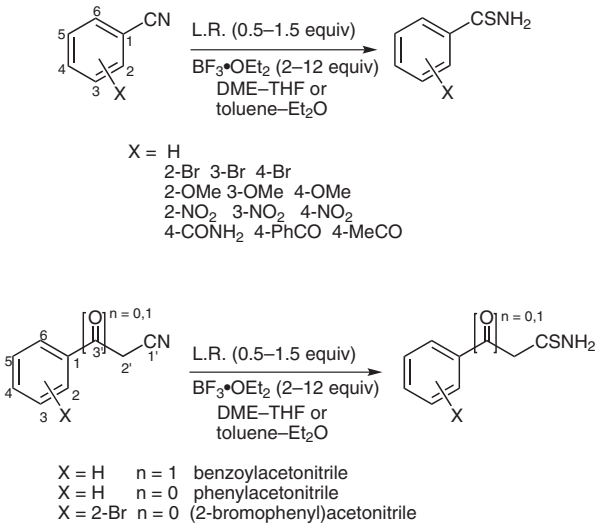
Intending the preparation of sulfur analogues of cyanomethyl esters of *N*-acetylated α-amino acids (e.g., used for aminoacylations of adenosine mononucleotides[15]) we initially focussed on the thionylation reactions of these substrates with Lawesson's reagent. Remarkably,[16] addition of boron trifluoride–diethyl ether complex to the reaction mixtures resulted in a significant increase in the susceptibility[17] of the cyanomethyl moiety towards thiolysis and led to exclusive and almost quantitative transformation of the nitrile group into the thioacetamide moiety, leaving the amide function of the *N*-acetyl group untouched. This pronounced nitrile activating effect was observed for all types of nitrile substrates investigated. The reaction system, Lawesson's reagent–BF_3·OEt_2, opened a simple and efficient route to primary thioamides.



Scheme 1 Examples for aromatic, benzylic, and homobenzylic nitriles as substrates in thioamide formation reactions using the L.R.–BF_3·OEt_2 system

Monosubstituted benzonitriles, homoaromatic phenylacetonitriles, and aliphatic nitriles were reacted with 0.5 to 1.5 equivalents of Lawesson's reagent in the presence of 0 to 12 equivalents of boron trifluoride–diethyl ether complex in different solvent mixtures (Table 1). Mixtures of 1,2-dimethoxyethane–tetrahydrofuran (2:1) and toluene–diethyl ether (7:1) were found to be suitable media for the transformation of nitriles into the corresponding primary thioamides.

Table 1 Influence of the Addition of $BF_3{\cdot}OEt_2$ on the Conversion of Nitriles into Primary Thioamides by Lawesson's Reagent for Different Solvent Mixtures and Reaction Conditions

Entry	Nitrile	Product	Yield (%)[a]				
			No $BF_3{\cdot}OEt_2$, DME–THF[b]	$BF_3{\cdot}OEt_2$ (2 equiv), DME–THF[c]	$BF_3{\cdot}OEt_2$ (12 equiv), DME–THF[d]	No $BF_3{\cdot}OEt_2$, toluene–Et_2O[e]	$BF_3{\cdot}OEt_2$ (12 equiv), toluene–Et_2O[f]
1	benzonitrile	**1**	8	61	80	7	75
2	2-bromobenzonitrile	**2**	<1	18	12	9	62
3	3-bromobenzonitrile	**3**	5	54	55	14	98
4	4-bromobenzonitrile	**4**	5	<1	42[g]	17	97
5	2-methoxybenzonitrile	**5**	2	12	8[g]	4	75
6	3-methoxybenzonitrile	**6**	12	23	87	10	96
7	4-methoxybenzonitrile	**7**	15	67	95	15	99
8	2-nitrobenzonitrile	**8**	<1	<5	15	<1	65
9	3-nitrobenzonitrile	**9**	8	53	77	13	88
10	4-nitrobenzonitrile	**10**	3	<1	70	8	95
11	phenylacetonitrile	**11**	–	–	40	–	76
12	(2-bromophenyl)acetonitrile	**12**	–	–	35	–	78
13	pentanenitrile	**13**	–	0	0	0	47[i]
14	pentanedinitrile	**14**	–	0	18[h]	0	92[j]

[a] Yields of isolated thioamides.
[b] Conditions: nitrile (1 mmol), L.R. (0.5 mmol), DME–THF (2:1, 28 mL), 50 °C, 14 h.
[c] Conditions: nitrile (1 mmol), L.R. (0.5 mmol), $BF_3{\cdot}OEt_2$ (2 mmol), DME–THF (2:1, 28 mL), r.t., 3 h.
[d] Conditions: nitrile (1 mmol), L.R. (1.5 mmol), $BF_3{\cdot}OEt_2$ (12 mmol), DME–THF (2:1, 68 mL), 50 °C, 14 h (unless otherwise noted).
[e] Conditions: nitrile (1 mmol), L.R. (1.5 mmol), toluene–Et_2O (10:1.5, 120 mL), 50 °C, 14 h.
[f] Conditions: nitrile (1 mmol), L.R. (1.5 mmol), $BF_3{\cdot}OEt_2$ (12 mmol), toluene–Et_2O (10:1.5, 120 mL), 50 °C, 14 h (unless otherwise noted).
[g] 50 °C, 36 h.
[h] 80 °C, 5 h, then r.t., 60 h.
[i] Conditions: nitrile (1 mmol), L.R. (1.5 mmol), $BF_3{\cdot}OEt_2$ (24 mmol), toluene–Et_2O (10:1.5, 120 mL), 50 °C, 36 h.
[j] Conditions: nitrile (1 mmol), L.R. (3 mmol), $BF_3{\cdot}OEt_2$ (24 mmol), toluene–Et_2O (10:1.5, 230 mL), 50 °C, 14 h.

Some aromatic nitriles show moderate reactivity towards Lawesson's reagent, a fact that has to our knowledge not been systematically investigated so far. In our control experiments we treated a variety of methoxy, bromo, and nitro derivatives of benzonitrile (Scheme 1) with Lawesson's reagent (see Table 1). Expectedly, after workup we found only small amounts of thioamides in our reaction mixtures after reaction times of 12 hours (at 50 °C). For the most reactive substrates, 3-bromobenzonitrile, 3-methoxy- and 4-methoxybenzonitrile, and 3-nitrobenzonitrile, the yields of the corresponding thioamides **3**, **6**, **7**, **9** obtained were in the range of 10–15% (Table 1, entries 3, 6, 7, 9). The lowest reactivities were observed for *ortho*-substituted benzonitriles (Table 1, entries 2, 5, 8). Essentially, the reactivities did not differ in 1,2-dimethoxyethane–tetrahydrofuran to toluene–diethyl ether solvent mixtures. Recovery of unreacted nitriles (70–99%), complementing the molar fractions of isolated thioamides, demonstrates the consistency of thioamide yield and nitrile reactivity. Homoaromatic and aliphatic nitriles were found to be unreactive towards Lawesson's reagent (Table 1, entries 11–14).

The addition of boron trifluoride–diethyl ether complex to the reaction mixtures led to a significant increase in thioamide formation under even milder reaction conditions. Thus, when aromatic nitriles were reacted with 0.5 equivalents of Lawesson's reagent in the presence of 2.0 equivalents of boron trifluoride–diethyl ether complex in 1,2-dimethoxyethane–tetrahydrofuran (2:1) at room temperature for three hours (Table 1, entries 1–10), substantial amounts of thioamides were isolated from the reaction mixtures (with exception of 4-bromo- and 4-nitrobenzonitrile, Table 1, entries 4 and 10). While under these conditions yields for the corresponding product thioamides were only average for most aromatic nitriles, the different reactivities of the chosen substrates towards thionylation are reflected clearly: the *meta*-derivatives of bromo- and nitrobenzonitrile, as well as 4-methoxy- and unsubstituted benzonitrile (Table 1, entries 3, 9, 7, 1) gave 50–70% yields of the corresponding thioamides. Generally, low

yields were found in the case of the *ortho*-substituted derivatives 2-bromo-, 2-methoxy- and 2-nitrobenzonitrile (Table 1, entries 2, 5, 8). Interestingly, only traces of products could be isolated from reaction mixtures of 4-bromo- and 4-nitrobenzonitrile after a reaction time of three hours at room temperature (Table 1, entries 4, 10). Aliphatic nitriles also proved to be unreactive under these conditions (Table 1, entries 13, 14). High levels of recovery of the unreacted nitrile substrate, regardless of the degree of conversion, indicated the high selectivity of the above transformations. Only traces of thioamides were found in reaction mixtures devoid of boron trifluoride–diethyl ether complex under otherwise similar reaction conditions (r.t., 3 h).

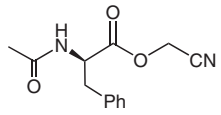
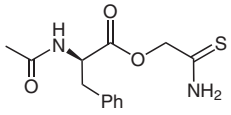
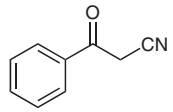
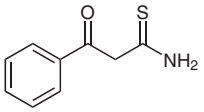
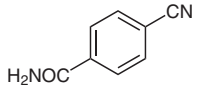
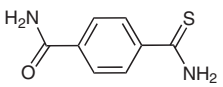
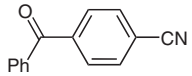
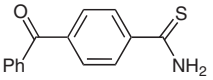
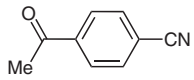
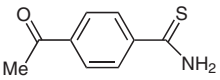
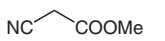
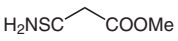
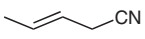
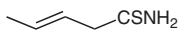
Increasing of the molar ratios of Lawesson's reagent (up to 1.5 equiv) and boron trifluoride–diethyl ether complex (up to 12 equiv) as well as raising the temperature (up to 50 °C) and increasing the reaction time (up to 36 h) led to further improvements in conversions (with the exceptions of 2-bromobenzonitrile and 2-methoxybenzonitrile, Table 1, entries 2 and 5). Generally, between 50% and 90% of the corresponding product thioamides were obtained from the reaction mixtures (Table 1, entries 1–9). Even homoaromatic phenylacetonitriles (Scheme 1) showed average reactivity under these stoichiometric conditions (Table 1, entries 11, 12), for pentanedinitrile 18% conversion into the corresponding dithioamide **14** was observed (Table 1, entry 14).

A more pronounced effect was obtained when using the two-component solvent mixture toluene–diethyl ether (7:1), by treating the respective nitrile with 1.5 equivalents of Lawesson's reagent and 12 equivalents of boron trifluoride–diethyl ether complex. All aromatic nitriles tested were converted into the thioamides in high yields (Table 1, entries 1–10). Benzylic nitriles and even aliphatic nitriles gave the corresponding thioamides in moderate to good yields under these reaction conditions (Table 1, entries 11–14).

The strong increase in reactivity of the nitrile function towards Lawesson's reagent by applying the Lewis acid complex boron trifluoride–diethyl ether complex was also illustrated by a series of reactions with multifunctional nitrile substrates (Table 2), showing functional groups such as ester, vinyl, carbonyl, and amide functionalities.

In analogy to certain aromatic nitriles, conventional thionation of the cyanomethyl ester of *N*-acetyl-L-phenylalanine with Lawesson's reagent, without addition of boron trifluoride–diethyl ether complex, revealed the susceptibility of the nitrile function of the cyanohydrin moiety[17] towards thiolysis. Due to partial thiolysis of the cyanomethyl group, the *N*-acetylphenylalanine ester **15** was present in the product mixtures (together with the cyanomethyl and 2-hydroxythioacetamide esters of *N*-thioacetylphenylalanine), albeit the yield for this product was below 30%. However, addition of six equivalents of boron trifluoride–diethyl ether complex to the reaction mixture yielded 89% of monothioamide **15** as the sole product (Table 2, entry 1), whereas the amide portion of the *N*-acetyl group remained untouched. In the interesting case of 4-cyanobenzamide (Table 2, entry 3) conventional thionation with Lawesson's reagent in 1,2-dimethoxyethane–tetrahydrofuran (2:1) (i.e., without addition of

Table 2 Yields and Selectivity of Thionylations of Multifunctional Nitrile Substrates by the System Lawesson's Reagent–$BF_3{\cdot}OEt_2$

Entry	Substrate	Product	Solvent[a]	Stoichiometry[b]	Temp (°C)	Time (h)	Yield[c] (%)
1		**15** 	A	1:0.8:6	40	4	89
2		**16** 	B	1:1.0:12	20	14	75
3		**17** 	A	1:0.7:24	20	3	73
4		**18** 	B	1:1.5:12	20	12	51
5		**19** 	B	1:1.5:12	20	12	70
6		**20** 	A	1:1.5:12	55	14	62
7		**21** 	B	1:1.5:12	20	14	45

[a] Solvent A: DME–THF (2:1, 68 mL); solvent B: toluene–Et_2O (7:1, 120 mL).
[b] Substrate (equiv)/L.R. (equiv)/$BF_3{\cdot}OEt_2$ (equiv).
[c] Isolated yield (mol%).

$BF_3{\cdot}OEt_2$) led to isolation of 4-cyanothiobenzoamide[18] as single product after three hours at 50 °C (45%), as a result of regioselective thionation of the aromatic amide moiety. However, this regioselectivity was reversed when 24 equivalents of boron trifluoride–diethyl ether complex were added to the reaction mixture; after three hours at room temperature the monothio derivative 4-(thiocarbamoyl)benzamide (**17**) was isolated exclusively in high yield.

High yields of the monothionylated products **18** and **19** were also found for 4-benzoyl- and 4-acetylbenzonitrile (Table 2, entries 4 and 5). Selective conversion of the nitrile group was also observed in the case of benzoylacetonitrile (Table 2, entry 2): thioamide **16** was isolated as the main product in good yield as a 1:1 mixture of the corresponding keto and enol forms.[19] No formation of 1,2,3-oxazaphosphorin-4-thione 2-sulfides[20] was observed.

Further examples of application of this method to functionalized nitriles are the conversions of methyl cyanoacetate and pent-3-enonitrile into the corresponding thioamides (Table 2, entries 6 and 7), giving access to the corresponding thioamides **20** and **21** in moderate yield.

In summary, we have demonstrated that the addition of boron trifluoride–diethyl ether complex to reaction mixtures of nitriles and Lawesson's reagent promotes the direct and smooth conversion of these substrates into their corresponding thioamides, which were found to be inaccessible if boron trifluoride–diethyl ether complex was omitted. High yields of thioamides were obtained even in the case of aliphatic nitriles or *ortho*-substituted aromatic nitriles. The reaction shows remarkable compatibility with a number of functional groups, such as benzoyl, acetyl, ester, amide, and vinyl moieties. Thus, the boron trifluoride–diethyl ether complex assisted conversion of nitriles into thioamides by Lawesson's reagent represents a considerable expansion of the applicability of this widely used and versatile sulfur-transferring reagent.[13]

All reactions were performed in anhydrous solvents under an argon atmosphere. THF, DME, Et_2O, and toluene were distilled from K and Na metal, respectively. MeCN was distilled from CaH_2. PE refers to petroleum ether (boiling range 60–95 °C). All reagents were purchased from commercial sources and used without further purification. Lawesson's reagent was purchased from Fluka. Nitrile samples were purchased from Aldrich (4-methoxybenzonitrile from Alfa Aesar). $BF_3{\cdot}OEt_2$ (content ~48% BF_3) was purchased from Merck and Aldrich. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Bruker Avance 400 spectrometer. Products were checked by ^{19}F and ^{31}P NMR spectroscopy for the absence of inorganic impurities. Melting points of thioamides were determined on a Leica Galen III melting point apparatus, after recrystallization ($CHCl_3$ or EtOAc unless otherwise noted). EI-MS spectra were measured on a Finnigan MAT 8230 mass spectrometer, ESI-MS spectra were measured on a Finnigan MAT 900S mass spectrometer. NanoESI-MS and MS/MS measurements (MeOH–5% aq HCO_2H, 1:1) were carried out on a QSTAR Elite hybrid mass spectrometer (Applied Biosystems, CA).

Cyanomethyl *N*-Acetyl-L-phenylalaninate (Table 2, Entry 1)

To a suspension of *N*-acetyl-L-phenylalanine (1.14 g, 5.5 mmol) in anhyd MeCN (8 mL) under an argon atmosphere was added freshly distilled Et_3N (2.06 mL) to obtain a clear soln. The soln was cooled on ice, chloroacetonitrile (1.46 mL, 19.5 mmol, 3.5 equiv) was added, and the mixture was stirred at 20 °C for 16 h (formation of a white precipitate). CH_2Cl_2 (120 mL) was added and the mixture was washed with 1 M $NaHSO_4$. The aqueous phase was extracted with another portion of CH_2Cl_2 (120 mL). The combined organic phases were washed with brine and dried ($MgSO_4$). After evaporation of the solvent, the material obtained was dried in vacuo. The crude material was pure enough for further transformations; white, feathery crystals; yield: 1.2 g (89%).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.13 (m, 5 H_{Ph}), 4.94–4.89 (ABX, 1 H, H_x2), 4.80–4.76 (d, *J* = 15.6 Hz, 1 H, COOCH_A), 4.70–4.66 (d, *J* = 15.6 Hz, 1 H, COOCH_B), 3.13 (ABX, 2 H, PhCH_2), 1.98 (s, 3 H, $COCH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 170.6, 135.4, 129.9, 129.5, 127.9, 114.2, 53.5, 49.3, 37.9, 23.3.

4-Methoxythiobenzamide (7); Typical Procedure for Thiolysis in DME–THF (2:1)

To a stirred soln of 4-methoxybenzonitrile (133 mg, 1.0 mmol) in DME (6 mL) and THF (3 mL) was added, under an argon atmosphere, $BF_3{\cdot}OEt_2$ (1.50 mL, 12 mmol) followed by 0.025 M Lawesson's reagent in DME–THF (2:1) (60 mL, 1.5 mmol) [prepared in an ultrasound cleaning bath at 50 °C]. The mixture was stirred overnight at 50 °C. After 14 h, $NaHCO_3$ (1.01 g, 12 mmol) was added and the mixture was stirred at r.t. for 20 min. After evaporation of the solvents the residue was dried in vacuo. The product **7** was purified by column chromatography (silica gel, PE–EtOAc, 1:1); yield: 159 mg (95%).

(2-Bromophenyl)thioacetamide (12); Typical Procedure for Thiolysis in Toluene–Et_2O (10:1.5)

To a stirred soln of (2-bromophenyl)acetonitrile (197 mg, 1.0 mmol) in toluene (105 mL) and Et_2O (15 mL) was added, under an argon atmosphere, $BF_3{\cdot}OEt_2$ (1.50 mL, 12 mmol) followed by solid Lawesson's reagent (606 mg, 1.5 mmol). The mixture was stirred at 50 °C overnight. After 14 h, $NaHCO_3$ (1.01 g, 12 mmol) was added and the mixture was stirred at r.t. for 20 min. After evaporation of ca. 75% of the total solvent volume, DME (10 mL) was added, followed by repeated evaporation of the solvent. The residue was dried in vacuo. The product **12** was purified by column chromatography (silica gel, PE–EtOAc, 1:1); yield: 180 mg (78%).

Reaction conditions for different substrates (reaction time, temperature, stoichiometry) and yields are listed in Tables 1 and 2. Products were purified by column chromatography (silica gel, PE–EtOAc, 1:1), except otherwise noted. For atom labeling see Scheme 1.

Thiobenzamide (1)

Pale yellow coating of fan-shaped aggregated needles; mp 118–19 °C (Lit.[2g] 116–117 °C).

NMR data are in agreement with literature data.[28]

2-Bromothiobenzamide (2)

Brown viscous oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.24 (br s, 1 H, CSNH), 7.58–7.56 (d, *J* = 7.6 Hz, 2 H, H3, H6), 7.36–7.32 (t, *J* = 7.7 Hz, 1 H, H5), 7.26–7.22 (t, *J* = 7.7 Hz, 1 H, H4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.3 (s, $CSNH_2$), 143.2 (s, C1), 133.6 (d, C3), 131.3 (d, C4), 130.0 (d, C6), 128.0 (d, C5), 117.5 (s, C2).

MS (EI, 70 eV): *m*/*z* (%) = 135.9 (100), 214.7/216.7 (20/20) [M^+].

3-Bromothiobenzamide (3)
Bright yellow needles; mp 120–21 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 1.8 Hz, 1 H, H2), 7.81–7.78 (d, *J* = 7.8 Hz, 1 H, H6), 7.67–7.64 (d, *J* = 8.0 Hz, 1 H, H4), 7.34–7.28 (t, *J* = 8.1, 7.8 Hz, 1 H, H5), 7.19 (br s, CSNH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.4, 141.5, 135.1, 130.4, 130.4, 125.8, 123.0.

MS (EI, 70 eV): *m*/*z* (%) = 154.8/156.8 (13/11), 181.8/183.8 (50/41), 214.7/216.7 (80/74) [M^+].

4-Bromothiobenzamide (4)
Citreous needles; mp 131–35 °C (Lit.[2b] 138–142 °C).

NMR data are in agreement with literature data.[2b]

2-Methoxythiobenzamide (5)
Yellow platelets; mp 105–108 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.06 (br s, 1 H, CSNH), 8.64–8.61 (dd, *J* = 8.0 Hz, 1 H, H6), 8.35 (br s, 1 H, CSNH), 7.49–7.44 (t, *J* = 8.0 Hz, 1 H, H4), 7.10–7.03 (t, *J* = 7.16 Hz, 1 H, H5), 6.97–6.95 (d, *J* = 8.44 Hz, 1 H, H3), 3.96 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.5, 156.7, 136.7, 134.1, 125.4, 121.6, 111.9, 56.5.

MS (EI, 70 eV): *m*/*z* (%) = 106.0 (72), 107.0 (19), 134.0 (100), 166.9 (81) [M^+].

3-Methoxythiobenzamide (6)
Dark yellow viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.40 (dd, *J* = 1.8 Hz, 1 H, H2), 7.30–7.28 (dd, *J* = 7.3 Hz, 1 H, H6), 7.25–7.20 (t, *J* = 8.0 Hz, 1 H, H5), 6.99–6.96 (dd, *J* = 8 Hz, 1 H, H4), 3.78 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.0, 159.9, 141.0, 129.9, 118.7, 118.5, 113.4, 55.9.

MS (EI, 70 eV): *m*/*z* (%) = 107.0 (17), 134.0 (89), 151.0 (16), 166.9 (100) [M^+].

4-Methoxythiobenzamide (7)
Pale yellow coating of fan-shaped aggregated needles; mp 144–148 °C (Lit.[8a,21] 145–147 to 148–149 °C).

NMR data are in agreement with literature data.[29]

2-Nitrothiobenzamide (8)
Pale yellow, crystalline solid; mp 99–104 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.92 (d, *J* = 8.1 Hz, 1 H, H6), 7.59–7.55 (t, *J* = 7.4 Hz, 1 H, H5), 7.47–7.44 (m, 2 H, H3, H4), 7.05 (br s, 1 H, CSNH).

^{13}C NMR (100 MHz, $CDCl_3$):[30] δ = 201.5, 145.8, 138.3, 133.5, 130.5, 128.9, 125.1.

MS (ESI, 4 kV, MeOH–MeCN): *m*/*z* (%) = 180.9 [M – H]$^-$.

3-Nitrothiobenzamide (9)
Orpiment yellow, granular power; mp 124–28 °C.

NMR data are in agreement with literature data.[29]

4-Nitrothiobenzamide (10)
Yellow, crystalline powder; mp 154–157 °C (Lit.[2b,8a,22b] 156–159 °C to 159–161 °C).

NMR data are in agreement with literature data.[29]

Phenylthioacetamide (11)
Colorless needles; mp 94–96 °C (Lit.[2g,5a,8a,22] 94–96 °C to 99–100 °C).

NMR data are in agreement with literature data.[29]

(2-Bromophenyl)thioacetamide (12)
Colorless, shiny platelets; mp 145–148 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.53 (dd, *J* = 8.0 Hz, 1 H, H3), 7.36–7.33 (dd, *J* = 7.6 Hz, 1 H, H6), 7.29–7.25 (t, *J* = 7.5 Hz, 1 H, H5), 7.15–7.11 (t, *J* = 7.6 Hz, 1 H, H4), 6.70 (br s, 1 H, CSNH), 4.17 (s, 2 H, H2′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.3, 135.5, 133.7, 132.2, 130.1, 128.6, 125.3, 52.2.

MS (EI, 70 eV): *m*/*z* (%) = 150.0 (100), 168.9/170.9 (5/4), 194.9/196.9 (6/6), 229/231 (<1) [M^+].

MS (NanoESI-MS/MS, +850 V): *m*/*z* (%) = 150.0, 169.0/170.9, 213.0/214.9, 229.9/231.9 [M^+].

Anal. Calcd for C_8H_8BrNS: C, 41.75; H, 3.50; N, 6.08; S, 13.93. Found: C, 41.90; H, 3.48; N, 6.05; S, 13.86.

Pentanethioamide (13)
Purified by column chromatography (PE–EtOAc, 2:1); white, waxy solid; mp 40–45 °C.

^{1}H NMR (400 MHz, $CDCl_3$):[31] δ = 7.40 (br s, 1 H, CSNH), 2.62–2.58 (t, *J* = 7.6 Hz, 2 H, H2), 1.69–1.61 (tt, *J* = 7.6, 7.4 Hz, 2 H, H3), 1.35–1.24 (tq, *J* = 7.4, 7.2 Hz, 2 H, H4), 0.87–0.83 (t, *J* = 7.2 Hz, 3 H, H5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.7 (s, $CSNH_2$), 44.8 (t, C2), 31.3 (t, C3), 22.4 (t, C4), 16.5 (t, C5).

MS (EI, 70 eV): *m*/*z* (%) = 117.0 (85) [M^+].

Pentanebis(thioamide) (14)
Purified by column chromatography (PE–EtOAc, 2:1); yellow coating of fan-shaped aggregated needles; mp 98–102 °C (Lit.[23] 120–121 °C, dec.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.98–2.95 (t, *J* = 6.0 Hz, 4 H, H2, H4), 1.98–1.89 (quint, *J* = 6.2 Hz, 2 H, H3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.2 (s, 2 $CSNH_2$), 40.7 (t, C2, C4), 20.4 (t, C3).

MS (NanoESI-MS/MS, +850 V): *m*/*z* (%) = 130.0, 145.0, 162.1 [M^+], 163.1 [M + H]$^+$.

2-Amino-2-thioxoethyl *N*-Acetyl-L-phenylalaninate (15)
Purified by column chromatography (PE–EtOAc, 1:4); white, feathery crystalline solid; mp 137–140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.12 (m, 5 H_{Ph}), 5.11–5.07 (d, *J* = 16.7 Hz, 1 H, $COOCH_A$), 4.86–4.81 (d, *J* = 16.7 Hz, 1 H, $COOCH_B$), 4.56–4.51 (ABX, 1 H, H_x2), 3.18–3.06 (ABX, 2 H, $PhCH_2$), 1.98 (s, 3 H, $COCH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.6 (s, $CSNH_2$), 172.0 (s, NH-*C*OMe), 170.9 (s, CO_2CH_2), 135.6 (s, C_{Ph}), 129.5 (d), 129.3 (d), 128.1 (d) (CH_{Ph}), 69.0 (t, OCH_2), 55.2 (d, $NHCHCO_2$), 37.3 (t, $PhCH_2$), 23.2 (q, $COCH_3$).

MS (NanoESI-MS/MS, +850 V): *m*/*z* (%) = 120.1, 162.1, 208.1, 281.2 [M + H]$^+$.

Anal. Calcd for $C_{13}H_{16}N_2O_3S$: C, 55.69; H, 5.75; N, 9.99; S, 11.44. Found: C, 55.53; H, 5.89; N, 9.85; S, 11.37.

2-Benzoylthioacetamide (16)
Purified by column chromatography (PE–EtOAc, 1:2); yellow crystalline powder ; mp 124–128 °C (Lit.[24] 133 °C). Mixture of keto (K) and enol forms (E) (1:1) in $CDCl_3$. (Orange solid from $CDCl_3$ soln).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.59 [s, 1 H, OH (E)], 8.81 (br s, 1 H, CSNH), 8.04–8.01 [d, *J* = 8.5 Hz, 2 H, H2, H6 (K)], 7.80–7.78 [d, *J* = 7.0 Hz, 2 H, H2, H6 (E)], 7.72 (br s, 1 H, CSNH), 7.66–7.62 [t, *J* = 7.4 Hz, 1 H, H4 (E)], 7.53–7.41 [m, 5 H, H3, H5 (K + E), H4

(K)], 6.50 (br s, 1 H, CSNH), 6.07 [s, 1 H, C(OH)=C*H* (E)], 4.49 [s, 2 H, $COCH_2$ (K)].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9 [s, $CSNH_2$ (E)], 195.9 [s, CO (K)], 194.6 [s, $CSNH_2$ (K)], 171.9 [s, *C*(OH)=C (E)], 135.8 [s, C1 (K)], 134.9 [s, C1 (E)], 134.4 [d, C4 (E)], 131.4 [d, C4 (K)], 128.9 (d), 128.7 (d) [C3, C5 (K + E)], 128.6 [d, C2, C6 (K)], 126.2 [d, C2, C6 (E)], 96.3 [d, C(OH)=*C*H (E)], 51.8 [t, CO*C*H_2 (K)].

MS (NanoESI-MS/MS, +850 V): *m/z* (%) = 77.0, 105.0, 146.1, 163.0, 180.0 $[M + H]^+$.

4-(Thiocarbamoyl)benzamide (17)
Purified by column chromatography (PE–EtOAc, 1:2); crystalline, 'fluorescent yellow' powder; mp 225–26 °C (nitrobenzene) (Lit.[25] 224–225 °C).

^1H NMR data are in agreement with literature data.[25]

^{13}C NMR (150 MHz, CD_3OD):[26] δ = 203.0 (s, $CSNH_2$), 171.4 (s, $CONH_2$), 144.3 (s, C1), 137.2 (s, C4), 128.4 (d, C2, C6), 128.4 (d, C3, C5).

MS (EI, 70 eV): *m/z* (%) = 146.0 (25), 147.0 (24), 164.0 (15), 180.0 (22) $[M^+]$.

MS (ESI, 4 kV, MeOH–MeCN): *m/z* (%) = 179.1 $[M - H]^-$.

4-Benzoylthiobenzamide (18)
Purified by column chromatography (PE–EtOAc, 3:2); lime yellow, crystalline powder; mp 145–150 °C.

NMR data are in agreement with literature data.[32]

4-Acetylthiobenzamide (19)
Yellow, crystalline powder; mp 170–73 °C (Lit.[27] 180–181 °C).

NMR data are in agreement with literature data.[26]

Methyl 3-Amino-3-thioxopropanoate (20)
Amber oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.80 (br s, 1 H, CSNH), 8.10 (br s, 1 H, CSNH), 3.86 (s, 2 H, CH_2), 3.77 (s, 3 H, $COOCH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.2 (s, $CSNH_2$), 170.3 (s, *C*OOMe), 53.1 (q, COO*C*H_3), 47.9 (t, CH_2)

MS (EI, 70 eV): *m/z* (%) = 73.9 (27), 74.9 (16), 101.9 (24), 132.9 (100) $[M^+]$.

Pent-3-enethioamide (21)
Purified by column chromatography (PE–EtOAc, 1:2); white felted needles; mp 59–64 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.20 (br s, 1 H, CSNH), 5.78–5.64 (dq, *J* = 15.3, 6.2 Hz, 1 H, $H4_{vinyl}$), 5.62–5.50 (ddt, *J* = 15.3, 6.7, 1.3 Hz, 1 H, $H3_{vinyl}$), 3.46–3.43 (d, *J* = 6.8 Hz, 2 H, H2), 1.78–1.75 (dd, *J* = 6.2, 1.2 Hz, 3 H, H5)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.5 (s, C1), 132.4 (d, C3), 125.0 (d, C4), 49.3 (t, C2), 18.4 (q, C1).

MS (EI, 70 eV): *m/z* (%) = 99.9 (14), 114.9 (70) $[M^+]$.

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