A Mild and Versatile Synthesis of Thioamides

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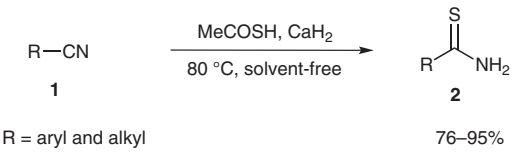
Abstract: Aliphatic and aromatic nitriles react with thioacetic acid in the presence of calcium hydride to give the corresponding thioamides in good to excellent yields. The examples studied include haloaryl nitriles in which the halogen is facile towards S_NAr reactions under other conditions.

Key words: thioamides, nitriles, thioacetic acid, calcium hydride



Scheme 1 Synthesis of thioamides from various nitrilies **2a–w**

Aromatic and aliphatic thioamides are regarded as versatile intermediates in organic synthesis.[1] They are the key intermediates in the synthesis of molecules which are of varied utilities such as pesticides[2] and pharmaceuticles.[3–5] Many methods are available in the literature for the synthesis of thioamide. They are synthesized either from the corresponding amides using Lawesson reagent,[5c] or from the corresponding nitriles using alkali metal hydrogen sulfide or ammonium sulfide under high pressure.[6] In addition reagents such as phosphorus decasulfide,[7] thioacids,[8] thioacetic acid in combination with Lewis acid,[9a] thioacetic acid in benzylamine,[9b] thioacetamide,[10] DowexSH,[11] *O*-dialkyldithiophosphates,[12] diphenylphosphinodithioacids,[13] sodium trimethylsilanethiolate,[14] sodium hydrosulfide hydrate and diethyl amine hydrochloride,[15] sodium hydrosulfide hydrate and magnesium chloride hexahydrate,[16] and $(P_4S_{11})Na_2$,[17,18] are also widely used in their synthesis from the corresponding nitriles. In special cases, thioamides are synthesized using elemental sulfur in the presence of morpholine[19a] and ammonium sulfide[19b] under microwave conditions.

As part of our current research program, we were in need of halogen-substituted aromatic thioamides. When some of the halogen substituted aryl nitriles were reacted with phosphorous pentasulfide or others sulfide-based reagents they resulted in various side products and required product formed in less than 10% yield. We tried to explore a condition which tolerates most of the functional groups.

One of the published methods utilized thioacetic acid in the presence of Lewis acid or light, but it is not compatible with other acid-sensitive groups such as acetals or *tert*-butyl esters. We observed that under basic conditions thioacetic acid could bring about desired transformation of nitriles to thioamide without any noticeable side reactions (Scheme 1).

Attempts to use other bases, such as carbonates or hydroxides of other alkali or alkaline earth metals, resulted in various byproducts, and their general applicability was minimal as other functional groups got affected. For example, thioacetic acid in the presence of sodium hydroxide resulted in the decomposition of ethyl cyanoacetate and no thioamide was observed.

In this paper we report a simple and efficient synthesis of a wide variety of thioamides which were synthesized from the corresponding nitriles. The nitrile compounds reacted with excess thioacetic acid in the presence of calcium hydride at 80 °C to afford good to excellent yields of respective thioamides within a short reaction time of 1.0–1.5 hours (Table 1).[20] In Scheme 2 we had depicted a plausible mechanism for this reaction. Calcium hydride reacts with thioacetic acid, resulting in the formation of nucleophilic calcium thiolate which attacks the nitrile group. Subsequent aqueous workup hydrolyzes this intermediate resulting in the thioamides.

It is worth mentioning that the same process was successfully extended to the synthesis of other halo-substituted thioamide derivatives; for example, halo-substituted benzonitriles reacted smoothly under the specified conditions to afford excellent yields of 92%, 86%, and 90%, respectively (entries 2–4 Table 1). These halo benzonitriles normally give rise to halogen-displaced side products with sulfide reagents. Additionally, substituted benzyl cyanides (entries 5–7, 9, and 10) also gave the corresponding thioamides **2e–g**,**i**,**j** in good to excellent yields. The pyridonitriles (entries 12–14) also gave the corresponding carbothioamides in excellent yields. It is interesting to note that the yields are usually in the range of 50–60% by using Lawesson reagent[21] or by using hydrogen sulfide–triethyl amine combination over 15–20 hours.[21] Similarly, thiophene-3-carbonitrile also gets converted into thiophene-3-thioamide **2o** (entry 15) in 85% yield. The methodology is widely applicable to aliphatic moieties as well. For example, aliphatic nitriles **1r–w** gave the corresponding thioamides **2r–w** in very good yields. The conditions tolerated easily hydrolyzable groups such as

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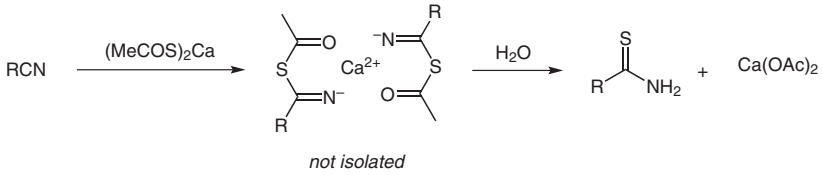
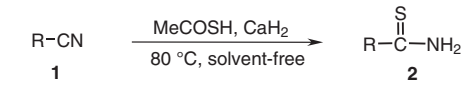


Scheme 2 Plausible mechanism

esters. Ethyl cyanoacetate, for example, afforded a good yield of ethyl 3-amino-3-thioxopropanoate **2s** without affecting the ester group.

Table 1 Conversion of Nitriles to Thioamides in the Presence of Thioacetic Acid



R = aryl and alkyl

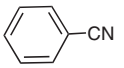
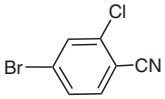
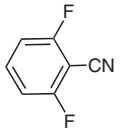
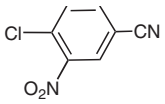
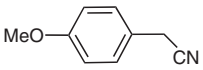
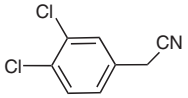
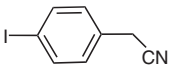
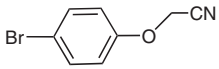
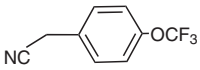
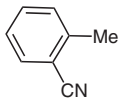
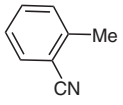
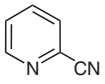
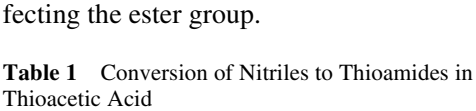
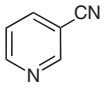
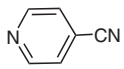
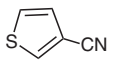
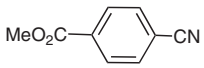
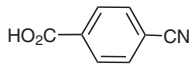
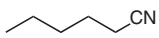
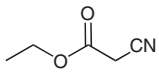
Entry	Nitrile	Product	Time (h)[a]	Yield (%)[b]
1		**2a**[22a]	1.0	95
2		**2b** (new)	1.0	92
3		**2c**[22b]	1.0	86
4		**2d** (new)	1.0	90
5		**2e**[22c]	1.5	94
6		**2f** (new)	1.5	90
7		**2g** (new)	1.0	95
8		**2h**[22d]	1.5	87
9		**2i** (new)	1.25	85
10		**2j**[22e]	1.25	90
11		**2k**[22f]	1.25	92
12		**2l**[22f]	1.5	88

Table 1 Conversion of Nitriles to Thioamides in the Presence of Thioacetic Acid (continued)



R = aryl and alkyl

Entry	Nitrile	Product	Time (h)[a]	Yield (%)[b]
13		**2m**[22f]	1.5	90
14		**2n**[22f]	1.5	92
15		**2o**[22g]	1.0	85
16		**2p**[22h]	1.0	92
17		**2q**[22i]	1.0	89
18		**2r**[22j]	1.0	76
19		**2s**[22k]	1.25	88
20		**2t** (new)	1.0	84
21		**2u**[22l]	1.0	80
22		**2v** (new)	1.0	87
23	MeCN	**2w**[22m]	1.0	80[c]

[a] Reactions were monitored by LC-MS, GC,[c] and TLC analysis.
[b] Yields refer to the isolated pure products after flash chromatography.
[c] Reaction was carried out at 50 °C.

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(20) **General Procedure for the Synthesis of Thioamide**
To a mixture of aryl nitrile (1 equiv) and CaH_2 (1 equiv) was taken in a two-necked 50 mL round-bottomed flask, and the content was cooled to 0 °C and added thioacetic acid (1.5 equiv). After stirring for 15 min the reaction mixture was heated in an oil bath at 80 °C for the given period of time (Table 1). After the completion of the reaction, the contents were cooled to r.t., 50% aq EtOAc (2 × 10 mL) was added and stirred for some time till the layers separated. Extraction was done once again with EtOAc, and the combined organic layer was filtered through Celite pad, and concentrated under reduced pressure to get the crude product. It was then purified by crystallization using PE and EtOAc (9:1). All the novel products were characterized by NMR and MS analysis.
4-Bromo-2-chlorobenzenecarbothioamide (2b)
^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.31 (d, 1 H), 7.50 (q, 1 H), 7.75 (s, 1 H), 9.73 (br s, 1 H), 10.23 (br s, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 126.5, 129.1, 129.7, 133.3, 136.6, 141.3, 188.5 ppm. Anal. Calcd (%) for $C_7H_5BrClNS$: C, 33.56; H, 2.01; N, 5.59. Found: C, 33.54; H, 2.22; N, 5.55. MS: *m/z* = 251.0 [M$^+$].
4-Chloro-3-nitrobenzenecarbothioamide (2d)
^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.8 (d, 1 H), 8.1 (d, 1 H), 8.5 (s, 1 H), 9.8 (br s, 1 H), 10.2 (br s, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 124.7, 128.0, 131.8, 132.4, 139.6, 147.2, 196.5 ppm. Anal. Calcd (%) for $C_7H_5ClN_2O_2S$: C, 33.81; H, 2.33; N, 12.93. Found: C, 33.76; H, 2.38; N, 12.96. MS: *m/z* = 214.9 [M$^+$].
2-(3,4-Dichlorophenyl)ethanethioamide (2f)
^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.8 (s, 2 H), 7.2 (d, 1 H), 7.5 (s, 1 H), 7.6 (d, 1 H), 9.4 (s, 1 H), 9.5 (s, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 50.5, 129.6, 129.8, 130.6, 131.1, 131.2, 138.8, 204.9 ppm. Anal. Calcd (%) for $C_8H_7Cl_2NS$: C, 43.65, H, 3.21, N, 6.36. Found: C, 43.76, H, 3.28, N, 6.34; MS: *m/z* = 219.9 [M$^+$].
3-(4-Iodophenyl)propanethioamide (2g)
^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.7 (s, 2 H), 7.1 (d, 2 H), 7.6 (d, 2 H), 9.3 (br s, 1 H), 9.4 (br s, 1 H) ppm. ^{13}C NMR: (100 MHz, DMSO-d_6): δ = 50.7, 93.0, 131.6, 137.3, 137.6, 205.4 ppm. Anal. Calcd (%) for C_8H_8INS: C, 34.67; H, 2.91; N, 5.05. Found: C, 34.65; H, 2.98; N, 5.11. MS: *m/z* = 277.8 [M$^+$].
2-[4-(Trifluoromethoxy)phenyl]ethanethioamide (2i)
^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.8 (s, 2 H), 7.2 (d, 2 H), 7.4 (d, 2 H), 9.4 (br s, 1 H), 9.5 (br s, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 50.5, 116.7, 131.0, 131.3, 136.8, 137.3, 147.6, 147.7, 205.4 ppm. Anal. Calcd (%) for $C_9H_8F_3NOS$: C, 45.95; H, 3.43; N, 5.95. Found: C, 45.98; H, 3.48; N, 5.98. MS: *m/z* = 235.8 [M$^+$].
Propanethioamide (2t)
^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.2 (t, 3 H) 2.6 (q, 2 H), 7.2 (s, 1 H), 8.0 (s, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 15.0, 42.1, 208.6 ppm. Anal. Calcd (%) for C_3H_7NS: C, 40.41; H, 7.91; N, 15.71. Found: C, 40.45; H, 7.98; N, 15.78. GC-MS: *m/z* = 89.1 [M$^+$].
2,2-Dimethylpropanethioamide (2v)
^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.3 (s, 9 H) 7.0 (br s, 1 H), 7.7 (br s, 1 H) ppm. ^{13}C NMR: (100 MHz, DMSO-d_6): δ = 32.5, 48.8, 221.8 ppm. Anal. Calcd (%) for $C_5H_{11}NS$: C, 51.23; H, 9.46; N, 11.95. Found: C, 51.31; H, 9.48; N, 11.98. MS: *m/z* = 118.0 [M$^+$].
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