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Synthetic Methods

A Robust, Eco-Friendly Access to Secondary Thioamides through the Addition of Organolithium Reagents to Isothiocyanates in Cyclopentyl Methyl Ether (CPME)

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Dedicated to Professor Norbert De Kimpe on the occasion of his retirement

Abstract: The nucleophilic addition of widely available and variously functionalized organolithium reagents to isothiocyanates represents a straightforward, high-yielding, one-pot method to access secondary thioamides. The simple reaction conditions required and the broad scope (>50 cases examples) makes it a robust and reliable method to access both simple and complex thioamides, including enantiopure ones. Noxious and unpleasant-smelling sulfurating agents, usually employed in the literature established methods, are avoided during the whole synthetic procedure thus, rendering the protocol highly attractive, also for sustainability aspects.

Thioamides constitute a pivotal class of organic molecules, the chemo-, physico- and biological properties of which differ substantially from their corresponding oxoamide analogues.[1] The pronounced resonance stabilization in the thioamide moiety arising from the donation from the nonbonding nitrogen lone pair is increased by the high polarizability of the sulfur atom.[2] Unlike other thiocarbonyl derivatives, they present attractive features, such as stability, crystallizability, and the absence of unpleasant smells; thus, the combination of the chemical reactivity and the physical properties renders them highly valuable scaffolds across the chemical sciences.[3] Among the most striking advantages of using thioamides (in place of oxoamides), the feasibility of nucleophilic additions of reducing agents or organometallics to the electrophilic carbon (by the straightforward transformation into thioiminium salts) plays a prominent role, as showcased in elegant works by Murai and co-workers.[4]

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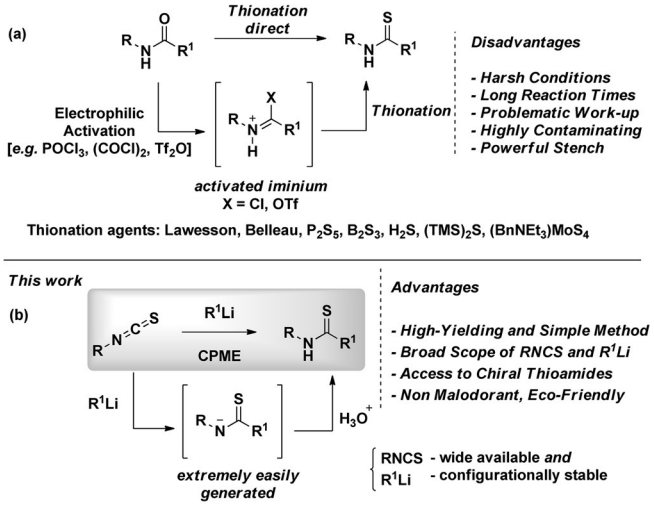
Compared to the extensive studies available on amide-link syntheses, conceptual approaches towards thioamides are rather limited.[5] In fact, despite the huge, non-discussed importance, the most common methods for the synthesis of thioamides still relies on thionation (direct or by previous electrophilic activation)[6] of carboxamides with sulfurating agents, such as the Lawesson's reagent (Scheme 1a).[7] The effectiveness of these



Scheme 1. Conceptually distinct approaches towards thioamides.

procedures is highly dependent on the harsh reaction conditions employed; in particular, the use of high-boiling-point solvents or even carcinogenic ones, such as hexamethylphosphoramide (HMPA), are frequently required to solubilize the sulfur source or to promote these long-time requiring reactions. Tedious work-up techniques and purifications, the persistent and powerful malodour together with the high toxicity of the reagents and chemoselectivity issues, severely limit the synthetic appeal of such non-uniformly high-yielding and expensive approaches. Sulfur incorporation through different techniques, such as the Willgerodt–Kindler reaction,[8] decarboxylative thioamidation,[9] and multicomponent reactions,[10] are often plagued by analogous drawbacks or by a limited functional-group tolerance.

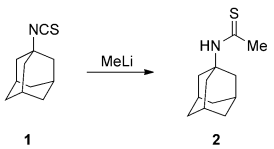
In this scenario, an alternative approach involving the addition of a carbon nucleophile to an extremely electrophilic iso-

thiocyanate can be envisaged. Although firstly illustrated by Worrall[11] and Gilman[12] in 1920s, the addition of organometallics to these electrophiles has not emerged as the method of choice for the synthesis of thioamides; unfortunately applications in organic synthesis are rare, thus obscuring the synthetic potential of the methodology.[13]

Considering the wide availability of both isothiocyanates and methods to prepare organolithium reagents (configurationally stable),[14] herein we report a robust protocol to prepare a broad series of thioamides, including enantiopure ones, through a simple nucleophilic addition (Scheme 1 b). Key features of the method are: 1) uniform efficiency under mild conditions, and high yields regardless of the nature of the two reacting partners used; 2) obtainment of the desired thioamides as the exclusive reaction products, thus simplifying the work-up and purification procedures; 3) absence of unpleasant odors during the whole reaction process; 4) use of cyclopentyl methyl ether[15] as the ideal reaction medium; and 5) retention of optical purity when chiral isothiocyanates and/or organolithium reagents are used.

Our investigations commenced by selecting the highly sterically hindered 1-adamantyl isothiocyanate **1** (Table 1) as the model substrate. Upon the addition of MeLi (2 equiv) in THF at 0 °C, the desired thioamide **2** was formed in a satisfactory isolated yield of 71% after a simple recrystallization (entry 1). Lowering the loading of the nucleophile to 1.5 or 1.0 equivalents decreased the yields, thus suggesting 2 equivalents as the ideal amount of the reactant (entries 1–3). Switching to a more apolar media, such as 2-MeTHF[16] and toluene (entries 4 and 5), benefited the reaction compared to polar solvents (entries 9 and 10). A further improvement and the best result was achieved by running the reaction in cyclopentyl methyl ether (CPME; entry 6),[15] which is an attractive alternative to classical ethereal solvents, such as THF and 1,4-dioxane.

Table 1. Model reaction optimization.[a]



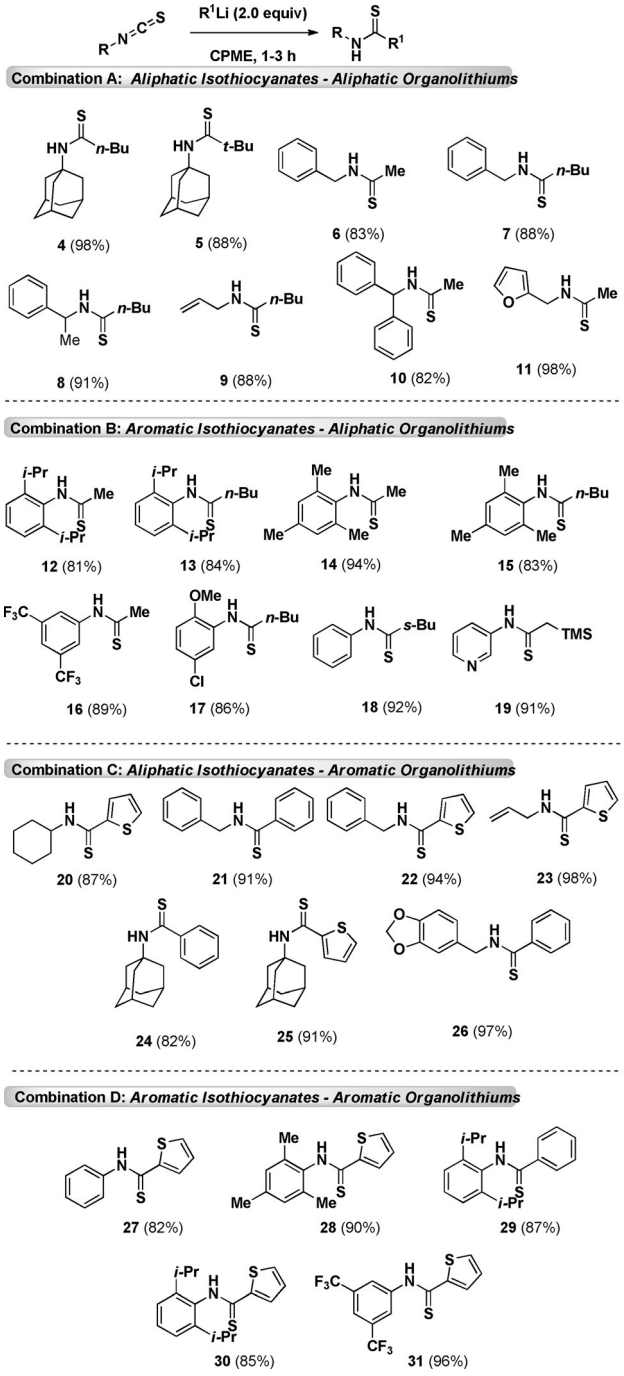
1 **2**

Entry	MeLi [equiv]	Solvent[b]	T [°C]/t [h]	Isolated yield [%]
1	2.0	THF	0/1	71
2	1.5	THF	0/1	65
3	1.0	THF	0/1	59
4	2.0	2-MeTHF	0/1	88
5	2.0	toluene	0/1	91
6	2.0	CPME	0/1	98
7	1.5	CPME	0/1	92
8	1.0	CPME	0/1	84
9	2.0	1,4-dioxane	0/1	75
10	2.0	Et_2O	0/1	81
11	2.0	CPME	rt/1	85

[a] See Experimental Section in the Supporting Information for details. [b] THF = tetrahydrofuran, 2-MeTHF = 2-methyltetrahydrofuran, and CPME = cyclopentyl methyl ether.

Increasing the temperature up to 23 °C (rt, entry 11), resulted in a lower efficiency, thus revealing 0 °C as the optimal temperature.

Once the optimal conditions for accessing thioamides from isothiocyanates and organolithium reagents were established, we next focused on the scope of the method. As presented in Scheme 2, the reaction of variously functionalized commercially available isothiocyanates with organolithium reagents afforded a wide range of thioamides (**4**–**31**) in very high yields after simple purification by recrystallization from CPME, thus

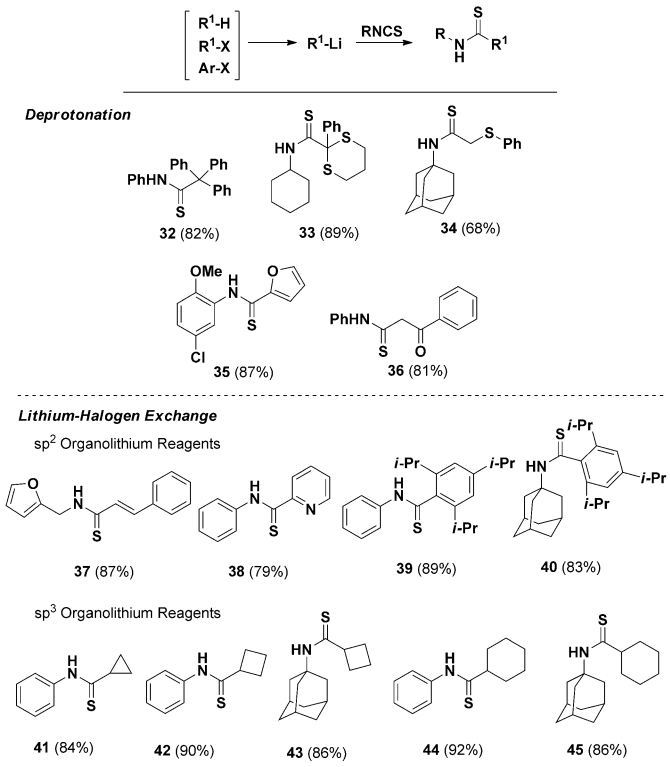


Scheme 2. Use of commercially available organolithium reagents in the syntheses of thioamides.

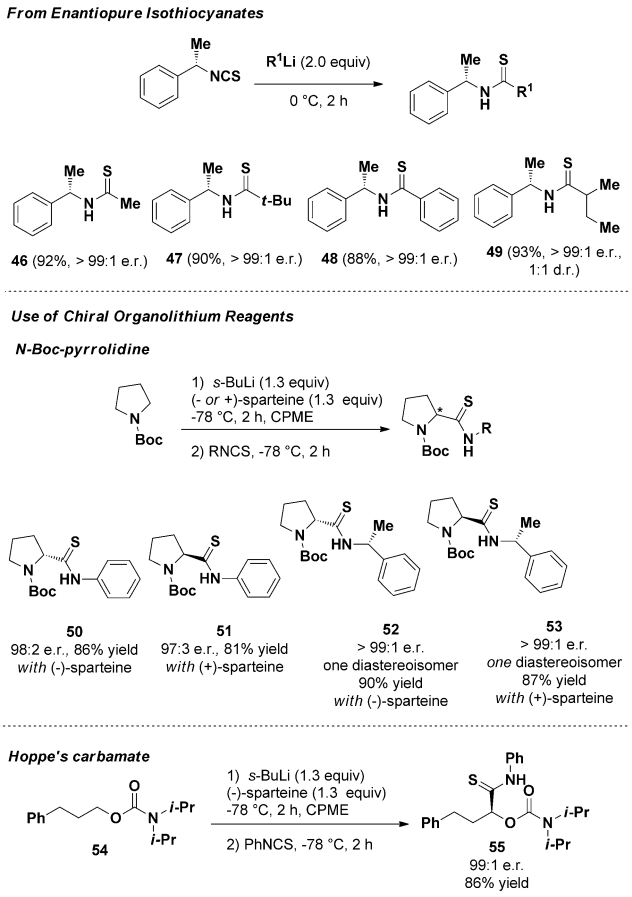
simplifying significantly the overall procedure. The observed reactivity is quite general, allowing the combination of reactions of both aliphatic and aromatic isothiocyanates with both types of organolithium reagents (combinations **A**–**D**). The steric hindrance on both sides of the reaction partners was perfectly tolerated and allowed to prepare sterically demanding thioamides (**4**, **5**, **12**–**15**, **24**, **25**, and **28**–**30**) in excellent yields. Analogously, (hetero)aromatic isothiocyanates containing different electron-donating or -withdrawing substituents were also viable and gave the corresponding products (**16**, **17**, and **31**). Allylic moieties (**9** and **19**) or heteroaromatic nuclei (**11**, **19**, **23**, and **26**) as substituents on the carbon-bearing isothiocyanates did not affect the feasibility of the process. The employment of a substituted alkyllithium (**19**) or heteroaryllithium (**20**, **22**, **23**, **25**, **27**, **28**, **30**, and **31**) species proceeded equally well. No enolization processes were detected during the addition of lithium reagents to isothiocyanates bearing acidic α-protons (**10**).

The wide availability of established methods to generate organolithium reagents permits further expansion of the versatility of the protocol.[17] As such, we employed two common accesses to such reagents, namely deprotonation and lithium–halogen exchange (Scheme 3). Triphenylmethane (**32**), a thioacetal (**33**), thioanisole (**34**), furan (**35**), or an enolate (**36**) served as excellent pronucleophiles regardless of the electronic and/or steric features on the isothiocyanate. A lithium–halogen exchange method was employed to generate sp^2 organolithium reagents; thus, the obtained styryllithium was smoothly added to a furyl-containing isothiocyanate to give the α,β-unsaturated thioamide **37** in high yield. Analogously, 2-lithiopyridine, which was obtained from the metalation of 2-bromopyridine, afforded compound **38** in 79% isolated yield. Of particular interest is the possibility to generate the highly sterically demanding 2,4,6-triisopropylphenyllithium, which was able to attack not only the simple phenylisothiocyanate yielding **39**, but also the 1-adamantyl congener, affording the thioamide **40**, which had not been previously reported. To the best of our knowledge, the latter represents one of the most bulky examples of thiocarbonyls known. The ease of addition was also evidenced by using sp^3 lithium species as the corresponding cyclopropyl, cyclobutyl or cyclohexyl derivatives (**41**–**45**). It is worth remarking the independence of the effectiveness from the nature of both organolithium reagents and isothiocyanates employed. This is evidently a big advantage compared to procedures based on thionation methods, the effectiveness of which is also influenced by the not always smooth availability of the starting amides.

Optically active isothiocyanates underwent the addition of highly basic alkyl- or aryllithium reagents in excellent yields without loss of the chirality (Scheme 4, **46**–**49**).[18] Importantly, chiral lithiated species performed equally well in the nucleophilic addition, as showcased by the use of *N*-Boc-substituted pyrrolidine[19] in the formation of **50**–**53**, as well as Hoppe's carbamate (**54**),[20] which resulted in the isolation of compound



Scheme 3. Use of organolithium reagents, generated by deprotonation or lithium–halogen exchange methods.



Scheme 4. Addition to enantiopure isothiocyanates and employment of enantioenriched organolithium reagents.

55. In both cases, the enantiopure α-oxo and α-amino functionalized carbanions were generated by (−)-sparteine-assisted deprotonation in CPME (98:2 to 99:1 e.r.).[21] The opposite enantiomers (**51** and **53**) could be prepared in analogous excellent enantiopurity by switching to (+)-sparteine. Finally, the addition of the generated chiral organolithium to an optically active isothiocyanate proceeded with an excellent diastereoselectivity (**52** and **53**). X-ray crystallography analyses of **50**, **52**, **53**, and **55** (Figure 1 and the Supporting Information) determined the absolute configuration of the newly formed carbon–carbon bond.

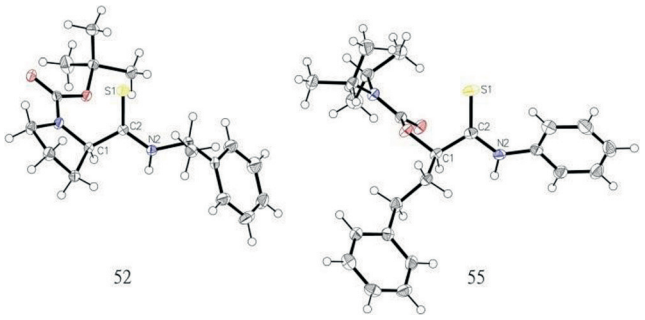
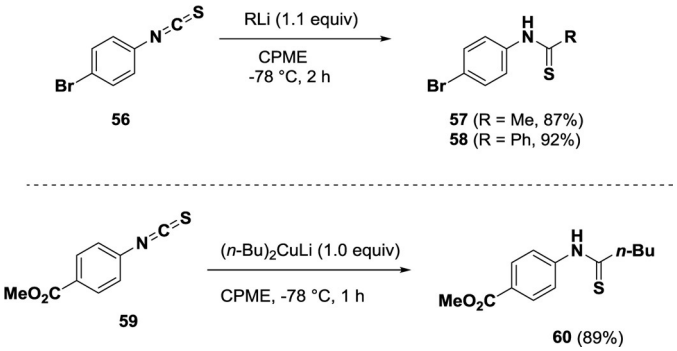


Figure 1. Molecular structures of **52** and **55** drawn with 50% displacement ellipsoids. According to the resulting chiral space group $P2_12_12_1$ for both, C_1 can be determined in *R* conformation ($Flack_{52} = -0.012(11)$, $Flack_{55} = 0.003(2)$). Details about X-ray structure analysis[24] and further results for **50** and **53** can be found in the Supporting Information.

It should be highlighted how this protocol shows superior performances in terms of both synthetic economy and efficiency compared to previously reported preparations of 2-substituted pyrrolidinyl thioamides, which are organocatalyst precursors. In fact, Lawesson's reagent mediated thionation of the corresponding oxoamides occurred with uniformly lower yields and in the case of compound **51** with dramatic erosion of the enantiopurity down to 26% *ee*.[22]

To gain a definitive proof of the robustness of the method, the chemoselectivity of the process was investigated. Pleasingly, the addition of MeLi or PhLi to 4-bromoisothiocyanate (**56**) proceeded with an exclusive attack at the heterocumulene moiety at −78 °C, leaving the exchangeable aromatic bromide completely unaffected (Scheme 5). The excellent electrophilicity of the isothiocyanate is also manifested in the chemoselective reaction with a mixed lithium–copper reagent [$(n\text{Bu})_2\text{CuLi}$].[23] This so-called Gilman reagent, presenting evidently a tamed nucleophilicity compared to a classical organolithium, is able to attack the isothiocyanate exclusively, regardless of the concomitant presence of an ester (**59**), providing the methoxycarbonyl-substituted thioamide (**60**).



Scheme 5. Study of the chemoselectivity.

In conclusion, we have reported a robust, highly efficient access to variously functionalized secondary thioamides through the addition of widely available or prepared organolithium reagents to isothiocyanates. The method is characterized by an excellent versatility, which renders it applicable to the synthesis of thioamides ranging from the simplest to sterically hindered and complex ones. Preservation of the enantiopurity when using chiral isothiocyanates or organolithium reagents further showcases its potential. A complete avoidance of noxious and unpleasant-smelling conventional thionating agents together with conducting the reaction in CPME maximizes the eco-compatibility of this otherwise limited synthetic process.

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Keywords: isothiocyanates · lithiation · nucleophilic addition · one-pot synthesis · thioamides

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[24] CCDC 1418885 (**50**), 1418884 (**52**), 1418887 (**53**), and 1418886 (**55**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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