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Methyl chlorothioformate as a convenient reagent for thionoester synthesis†

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A promising reagent for introducing the methyl thionoester function into organic molecules through a straightforward synthetic sequence based on common magnesium organics is proposed. A scalable procedure for its production is elaborated. The potential of the reaction, along with its advantages/simplicity, convenience, and effectiveness, is demonstrated and discussed.

Introduction

Thionoesters are the thiocarbonyl analogues of esters and possess unique reactivity. The difference in the reactivity of thionoesters and classical esters is explained by the difference in C = X double bond energy (the C=O bond is almost 50 kcal mol^{-1} more robust than the C=S bond),[1] higher polarisability of sulfur compared with oxygen and the significant influence of the C=S function on the reactivity of the leaving group at the Csp^2 carbon atom.[2] This difference allows for unique functional group transformations, such as the reduction of thionoesters to ethers,[3] the addition of organolithium with a subsequent reduction to modified branched ethers,[4] and dethiofluorination to difluoroalkyl ethers,[5] including the possibility of radiotracer production,[6] and, in some cases, usage in Newman–Kwart-like rearrangement, leading to rare thiols.[7] Additionally, thionoesters are valuable and irreplaceable C1-synthons[8] and dipolarophiles[9] for the synthesis of sulfur-containing heterocycles (Fig. 1). However, the synthetic potential of these compounds has not yet been fully revealed owing to their limited availability, especially in large quantities. Generally, synthetic methodologies can be divided into four categories: **A–D**. Category **A** is based on the sulfo-hydrolysis of imino esters with H_2S in pyridine,[10] which has a drawback of forming thioamides as side products. Next, category **B** is based on the thionation of esters by P_4S_{10} with different modifications.[11] However, such procedures still require harsh reaction conditions, which limit the diversity of substrates and the scale of synthesis. Category **C**, which is the largest category, uses alcohols for thioacylation,[12] including Pd-catalysed.[13] These processes require multiple non-trivial additional synthetic steps to prepare activated precursors. Among such protocols, the Newton base-catalyzed transesterification of thionoesters seems the most promising owing to the possibility of keeping on stock only corresponding methyl thionoesters as "surrogates" of all other esters.[14] Category **D**, which is rare, is based on C–C bond creation using C-nucleophiles and electrophilic counterparts with a thionoester function. Among recent protocols, the Ni-catalyzed cross-coupling of organozinc reagents and thiocarbonyl-containing starting materials could be highlighted.[15] Inspired by Newton's transesterification and the possibility of C–C bond creation, we decided to develop a convenient and scalable method for methyl thionoesters from readily available starting materials. Methyl chlorothioformate was selected as the electrophilic counterpart. Except for the "neglected" Delepine report from 1911 without experimental details,[16] only Pd-catalyzed thioacylation of mono-substituted alkynes with methyl chlorothioformate was described for this type of process.[17] Moreover, only phenyl chlorothioformate was used for thionoester synthesis in the reaction with PhMgBr[18] and the $AlCl_3$-catalyzed acylation of arenes.[19] We report preliminary and essential results for the TM-free synthesis of thionoesters from methyl chlorothioformate and commonly used Li, Mg and Zn organometallics. Such a protocol has considerable potential to significantly increase the diversity and availability of this rare class of compounds on a 10–100 gram scale, with a possibility for further scale-up.

Results and discussion

Since methyl chlorothioformate is commercially unavailable in multi-gram quantities at a reasonable price, we decided to develop a convenient protocol for its synthesis from $CSCl_2$ and MeOH. The optimal conditions (for the optimization protocol see ESI†) are the mixing of $CSCl_2$ and MeOH in Et_2O at 0 °C,

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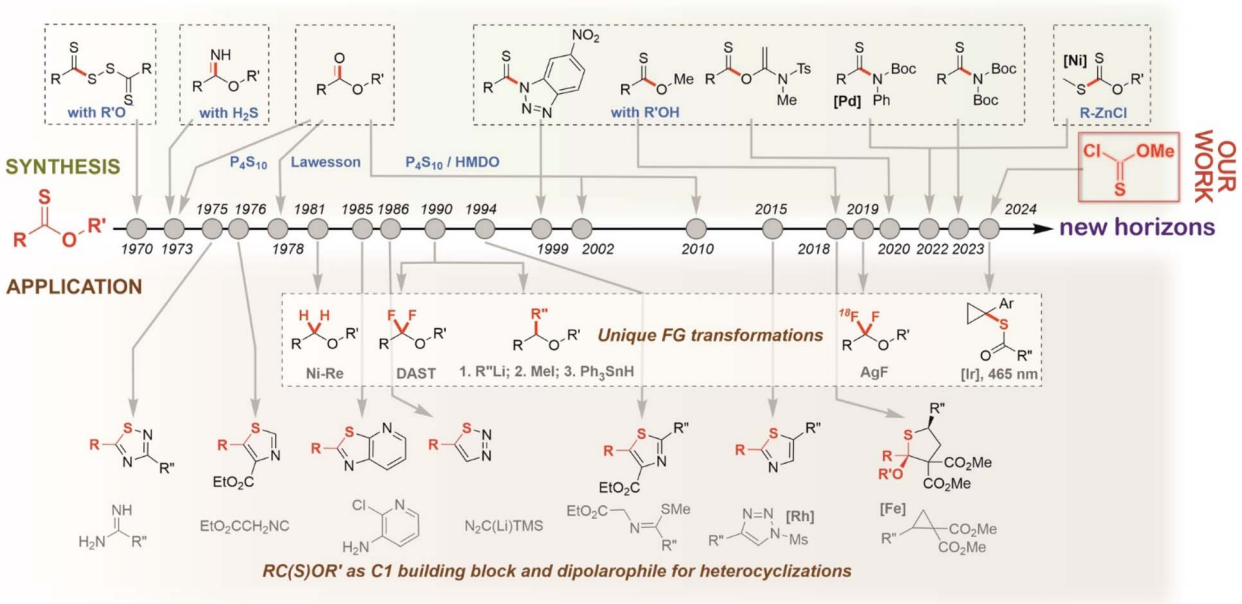
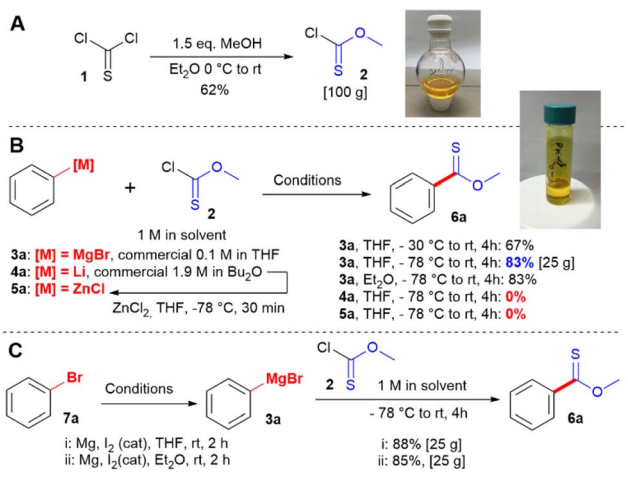


Fig. 1 The selected method of synthesis and applications of thionoesters.

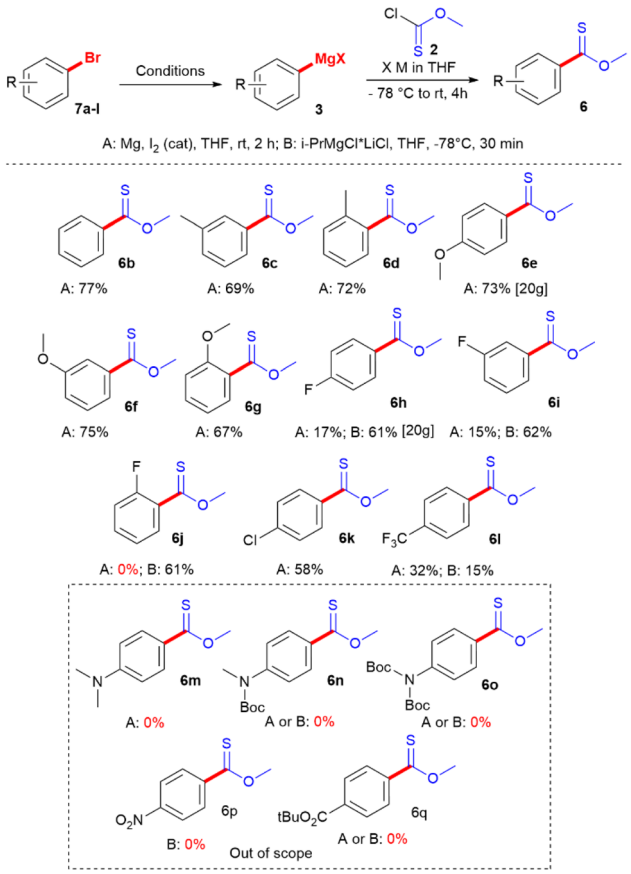
leading to methyl chlorothioformate **2**, which is isolated and purified by distillation at 0.5 bar in 62% yield on a 100 g scale from one synthetic run (Scheme 1A). It is crucial that while producing **2**, we avoid expensive and uncomfortable synthetic, separation and purification techniques, which make the protocol very attractive for further optimization process.

Then, we checked the reaction of compound **2** with commercially available PhMgBr **3a**, PhLi **4** and PhZnCl **5** prepared by transmetallation of PhLi with $ZnCl_2$ in THF.[20] The reaction of **2** with PhMgBr was successful at −78 °C, giving the target thionoester **6a** in 83% preparative yield. This procedure is easily scaled up to 25 g of the final product from one synthetic run. However, using corresponding Li or Zn derivatives does not lead to the formation of the desired product. In the case of Zn derivatives, thioacylation does not proceed. Meanwhile, in the case of Li derivatives, a complex mixture of products was formed (Scheme 1B). These data are in accordance with Nicolaou's results regarding the reaction ability of cyclic thionoester towards organometallics. Here, it was shown that the addition of organomagnesium reagents (except allyl magnesium bromide) resulted in excellent yields. In contrast, reagent organolithium reacts poorly.[4] Therefore, organomagnesium C-nucleophiles appeared to be the optimal substrates for the synthesis of thionoesters from chlorothioformates. Assuming a lack of commercial availability of diverse aryl magnesium compounds, we also checked the synthesis of the desired thionoester, starting with bromides. We obtained a comparable result on the model synthesis of thionoester **6a** by generating it from phenyl bromide **7a** or using commercial PhMgBr (Scheme 1C).

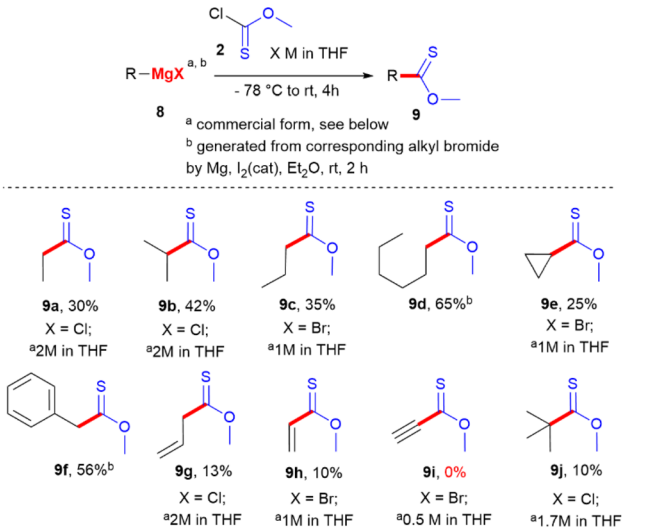


Scheme 1 Scale-up synthesis of methyl chlorothioformate and validation of the introduction procedure (A) synthesis of methyl chlorothioformate; (B) optimization of the organometallic source; (C) optimization of the synthetic procedure.

Unexpectedly, the fluorine-based aryl bromides **6h** and **i** afforded extremely low yields, and in the case of 1-bromo-2-fluorobenzene **6j**, the product was undetected. To solve this problem, we checked the milder bromine/magnesium exchange using turbo-Grignard reagent iPrMgCl·LiCl at lower



Scheme 2 The scope and limitations of the method for aryl-containing substrates.



Scheme 3 Expansion to aliphatic substrates.

temperatures.[21] Such changes in methodology for generating organomagnesium species significantly improved the preparative yields of products **6h–j**, achieving up to 62%. This procedure is also helpful for scaling up to multi-gram quantities.

Unfortunately, our preliminary attempts to use bromides bearing masked protected functional groups as substrates still failed. We attempted to use the Grignard reagent obtained from 4-bromo-*N*,*N*-dimethylaniline **7m** in the reaction, but the desired product **6m** was not observed. This could probably be explained by the incompatibility of chlorothioformates with tertiary amines owing to the formal dealkylation reaction.[22] To avoid such a side process, we attempted mono- and di-Boc derivatives **7n** and **o** in the reaction to generate both variants of organomagnesium intermediates, but all attempts failed. Using nitro derivative **7p** *via* turbo-Grignard-mediated bromine/magnesium exchange also did not lead to the target products. Unexpectedly and still unclear were the unsuccessful attempts to use *t*-Bu-protected benzoic acid derivative **7q** in both protocols (Scheme 2), we also tested aliphatic organomagnesium derivatives in the reaction. We selected a set of commercially available alkyl-based Grignard reagent **8a–c** and Grignard reagent **8e**. The desired products were formed in the reaction from low to moderate preparative yields in all cases. The worst result was observed for allyl magnesium chloride **8g** (commercial, 2 M in THF), which afforded the desired compound with only 13% after isolation (Scheme 3). Nevertheless, the efficient separation/purification steps and use of common, non-expensive starting materials make these results reasonable and promising.

These results also agree with Nicolaou's results regarding the reaction ability of cyclic thionoester towards allyl magnesium species.[4] Despite low yield, the method remains attractive for the synthesis of alkyl thionoesters owing to the simplicity of the procedures and easy accessibility of starting materials. Besides commercially available Grignard reagents, we tested the protocol by adding the *in situ* generation of organomagnesium species in Et_2O from alkyl bromides. In the case of *n*-butyl (**8d**) and benzyl bromide (**8f**), the approach gives better results (65% for **9d** and 56% for **9f**) than with commercial organometallics. Notably, in the reaction, our attempts to use the commercial Norman reagent **8h**, Iotsich reagent **8i**, or Grignard reagent **8j** failed. In the case of compounds **8h** and **8j**, the desired products **9h** and **9j** were detected at only 10% of the mixture after isolation; meanwhile, in the case of compound **8i**, product **9i** was not detected at all.

Conclusions

In summary, we translated methyl chlorothioformate from a rare to a promising common reagent by developing a preparative, scalable procedure for its production and understanding of the stability and storage conditions. We significantly improved the transition-metal-free crosscoupling of organomagnesium reagents and methyl chlorothioformate to access an array of methyl thionoesters. The synthesis of starting methyl chlorothioformate was optimized and scaled up to 100 g from 1 synthetic run. The coupling protocols were scaled up to 25 g from 1 synthetic run. It was shown that organomagnesium reagents are the optimal C-nucleophiles for this transformation. The lithium-based substrates appeared over-reactive towards methyl chlorothioformate, leading to complex reaction

mixtures. Meanwhile, zinc-based reagents appeared insufficiently reactive. The preliminary scope of the reaction was investigated. Broad examples of commercial and on-site prepared aryl and alkyl Grignard reagents were used. Among aryl reagents, the reagents bearing dialkylamino- or protected carboxyl functions are out of scope, as well as Norman and Iotsich reagents.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

Mykhailo O. Pashko: methodology, validation, formal analysis, investigation Kiril V. Pashkov: validation, formal analysis, resources, investigation Dmitriy S. Granat: methodology, formal analysis, investigation, resources, data curation, supervision Yurii L. Yagupolskii: conceptualization, methodology, formal analysis, supervision Serhiy V. Ryabukhin: conceptualization, funding acquisition, methodology, supervision, writing–review & editing, visualization Dmytro M. Volochnyuk: conceptualization, methodology, writing–original draft, visualization, supervision, project administration.

Conflicts of interest

There are no conflicts to declare.

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