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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 Csp² 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-synthons⁸ and dipolarophiles⁹ 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 H₂S in pyridine,¹⁰ which has a drawback of forming thioamides as side products. Next, category B is based on the thionation of esters by P₄S₁₀ 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 PhMgBr¹⁸ and the AlCl₃-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 CSCL₂ and MeOH. The optimal conditions (for the optimization protocol see ESI†) are the mixing of CSCL₂ and MeOH in Et₂O at 0 °C,

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† Electronic supplementary information (ESI) available: Experiments and synthesis; spectral and analytical data for the synthesized compounds; copies of NMR spectra. See DOI: <https://doi.org/10.1039/d5ra01538c>



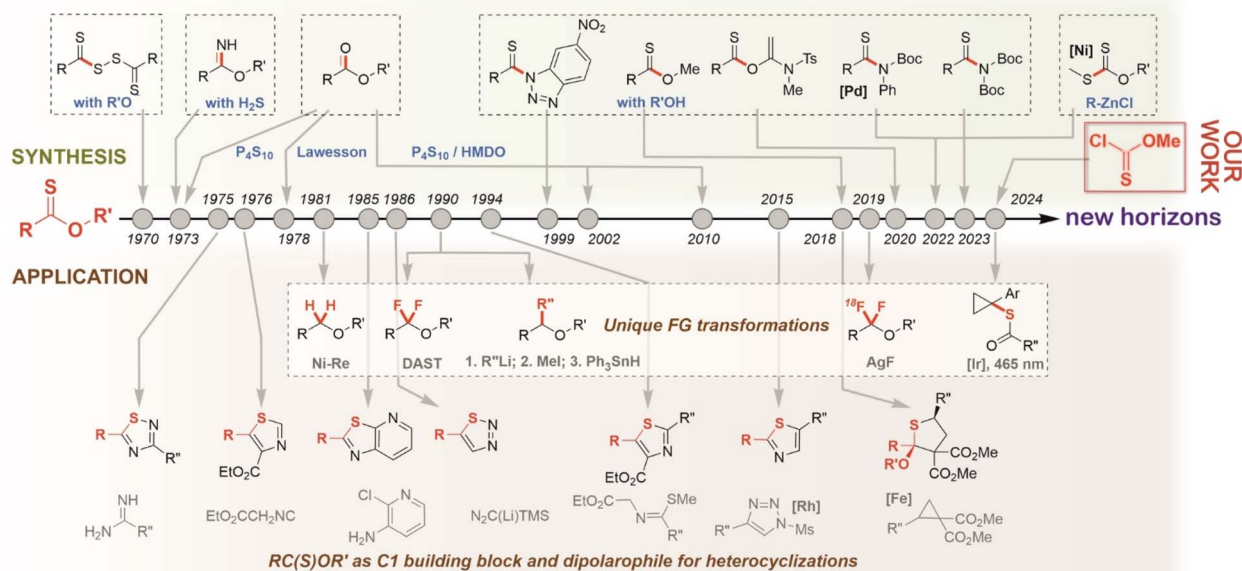


Fig. 1 The selected method of synthesis and applications of thioesters.

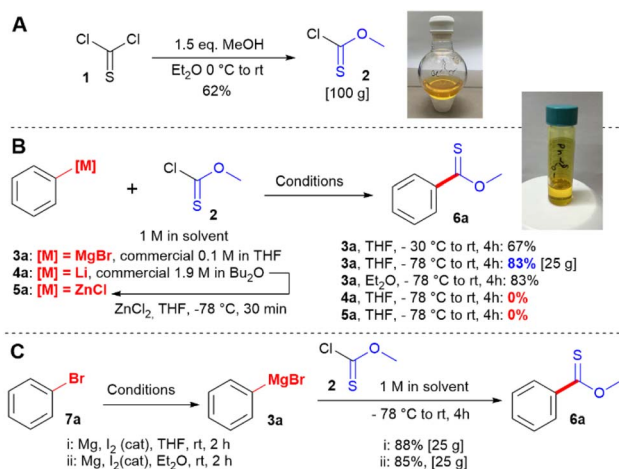
leading to methyl chlorothioformate **2**, which is isolated and purified by distillation at 0.5 bar in 62% yield on a 100 g scale from one synthetic run (Scheme 1A). It is crucial that while producing **2**, we avoid expensive and uncomfortable synthetic, separation and purification techniques, which 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 transmetalation of PhLi with ZnCl₂ in THF.²⁰ The reaction of **2** with PhMgBr was successful at -78 °C, giving the target thioester **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 thioester 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 thioesters from chlorothioformates. Assuming a lack of commercial availability of diverse aryl magnesium compounds, we also checked the synthesis of the desired thioester, starting with bromides. We obtained a comparable result on the model synthesis of thioester **6a** by generating it from phenyl bromide **7a** or using commercial PhMgBr (Scheme 1C).

The next step of the investigation was mini-screening aryl bromides, which can form the corresponding thioesters in the above-mentioned protocol. The "functional group free" aryl bromide **7a–i** was subjected to a developed protocol and possessed good preparative results, affording the desired thioester **6a–i** in 32–77% yields. In most cases, the procedure was easily scaled up to 20 g (Scheme 2). The moderate yields in our situation are not critical. Owing to easy separation and purification steps without the usage of expansive techniques, there is a broad potential for further scale-up of the protocol and elaboration of industrial regulations.

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 *i*PrMgCl·LiCl at lower



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.



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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