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Thioimides: New Reagents for Effective Synthesis of Thiolesters from Carboxylic Acids

Adam Henke and Jiri Srogl*

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nam. 2, 166 10, Prague, Czech Republic

jsrogl@uochb.cas.cz

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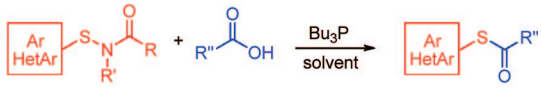
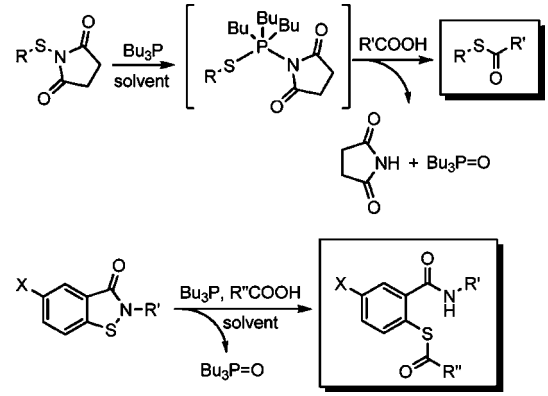


R= aryl, alkyl
R'= alkyl, aryl, acyl
R"= alkyl, aryl, heteroaryl

Thioimides and carboxylic acids are used as the precursors for the convenient synthesis of thiolesters in the phosphine mediated process. Cyclic and acyclic thioimides show equal efficiency, furnishing the desired thiolesters in good to excellent yields. The general, highly efficient transformation tolerates various functional groups and the resulting thiolesters are obtained in high purity after a simple separation. The reaction scope has been demonstrated on the preparation of several highly functionalized target molecules.

The importance of the acyl synthone role in organic chemistry has been undisputed. The high-energy acyl reagents, chlorides and anhydrides, have been traditionally used in a wide range of synthetic transformations.[1] Such highly reactive reagents have, however, necessitated certain strict requirements for handling and synthetic use. With the growing complexity of synthetic targets, the organic synthesis had to respond to the demand for acyl carriers that could be more compatible with extensively challenging reaction conditions. Following the biological chemistry example, such a class of acyl substrates, which would fulfill increasingly more rigorous synthetic demands on chemical selectivity, has been found in thiolesters.[2] Due to their stability and chemical tolerance they have since become an indispensable part of the synthetic arsenal. They have found use in a variety of organic transformations such as aldehyde[3] and ketone[4] synthesis and peptide chemistry,[5] to name just a few of the most typical examples of their application.

SCHEME 1. Proposed Mechanism of Thiolester Formation from Thioimide and Carboxylic Acid



Complementing the numerous pathways for the preparation thiolesters,[6] traditionally starting from acyl halides, we want to introduce a method that is chemically mild and uses readily available substrates. The preparation is, needless to say, highly tolerant to various functional groups.

Our method uses carboxylic acids and aryl (alkyl) thioimides as substrates in the trialkylphosphine mediated process (Scheme 1). Aryl(alkyl)mercapto, *N*-acyl moieties used as the reaction substrates, are not newcomers to synthetic chemistry. They are readily accessible crystalline compounds and stable under ambient conditions. Both the acyclic S,N and cyclic substrates have been prepared via the literature protocols.[7]

Mechanistically, the reaction starts, like the analogous disulfide version,[8] with the insertion of phosphine into the S,N bond of thioimide. The resulting pentavalent phosphorus intermediate reacts further with carboxylic acid, which replaces thiolate funcionality at the phosphorus center. The acivated acyl species is, in return, attacked by the nucleophilic thiolate,[8c] forming eventually the desired thiolester, imide, and phosphine oxide. When no carboxylic acid is present, products of simple reduction—thiol and imide—are the sole reaction results. In the cyclic version, the imide pendant is a part of the molecule while in the acyclic version succinimide is produced and eventually precipitates out of the reaction mixture.

Although, formally, our chemistry is similar to the reaction of disulfides and carboxylic acids, it offers fundamental synthetic advantages: Contrasting with the former reaction, where half of the disulfide is lost to the detrimental thiolate byproduct,

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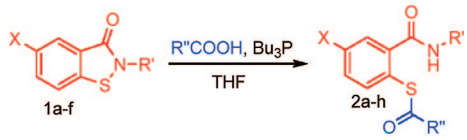
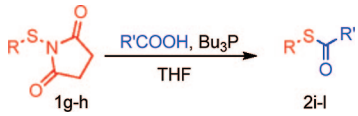
TABLE 1. Reaction of Cyclic Thioimide and Carboxylic Acid



	X	R′	R″	yield (%)
2a	NO_2	2,6-$Me_2C_6H_3$	thiophen-2-yl	76
2b	NO_2	$HOCH_2CH_2$	3,7-dimethyloct-6-enyl	85
2c	NO_2	allyl	2Cl-3-NO_2Ph	92
2d	NO_2	allyl	2-HO-3-MePh	63
2e	NO_2	*i*-Pr	PhCH=CH	84
2f	NO_2	*i*-Pr	Ph	95
2g	NO_2	2-HOPh	Ph	70
2h	PhCONH	Ph	Ph	78

TABLE 2. Reaction of Acyclic Thioimide and Carboxylic Acid



	R	R′	yield (%)
2i	4-MePh	Ph	89
2j	4-MePh	pyridin-3-yl	79
2k	4-MePh	H	58
2l	4,6-dimethylpyrimidin-2-yl	2-I-Ph	91

which can be, unfortunately, the source of significant side reactions and in any case, must be eventually separated from the product, in our setting desired thiolesters are obtained from the reaction mixture in near analytical purity after a simple workup. To illustrate this advantage we synthesized derivatives **2b**, **2e**, and **2k** which, due to their functionality, would be hard to obtain otherwise.

The wide variety of functional groups tolerated by our reaction conditions illustrates the generality of our method and demonstrates its chief advantage over classical ones (see Tables 1 and 2).

Great chemical tolerance is granted by the fact that acyl activation is accomplished by in situ oxidative means and no basic component is needed for scavenging of the acid, typically produced in acyl chloride/anhydride based methodes (Scheme 2).[1]

While the tributyl phosphine is used as the typical reaction mediator, we have also investigated a clever concept of phosphine salts, introduced by Fu.[9] To our surprise, in our case tributylphosphonium tetrafluoroborate did not require any external proton scavenger, whereas in the previous work the implicit presence of a base was crucial.[9] Presumably, the coordination of the proton to imide carbonyl facilitated liberation

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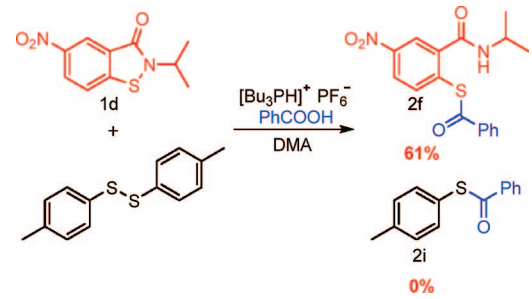
SCHEME 2. Reactivity Comparison of Thioimide and Disulfide in Thiolester-Forming Reaction



of phosphine moiety followed by the ensuing thiolester forming reaction. In fact, the reaction rate enhancement we observed in the case of phosphonium complex-mediated thiolesterification is strongly supportive to the intrinsic proton−carbonyl coordination and consequent activation of S−N bond of thioimide. We have demonstrated this reactivity differentiation on the reaction of substrate **1d** in the presence of disulfide. While the disulfide remained intact, thioimide, due to the acidic activation, reacted prominently, giving the desired thiolester **2f** in good yield

Overall, we have presented a general, mild, and convenient method for the preparation of thiolesters. We have shown that the method is highly tolerant to a wide variety of functional groups. By using our chemistry, we synthesized target molecules hardly attainable by other means, which could be, in our setting, prepared in good to excellent yields. We also bring to attention the thioimide as a synthetic equivalent of disulfides which, unlike the latter, can be tuned by simple chemical means. The results, the reaction scope and limitations, are demonstrated on a variety of synthetically useful targets.

Experimental Section

General Procedure for the Synthesis of Thiolesters from Thioimides and Carboxylic Acids. Thioimide (2.00 mmol) and corresponding carboxylic acid (1.20 mmol) were dissolved in dry THF (10 mL) under argon. Bu_3P (1.1 mmol) was added dropwise to the reaction mixture. After addition of the phosphine the reaction mixture was stirred for another 10 min. The mixture was then quenched with ice cold 5% hydrochloric acid (cca 50 mL), stirred for additional 2−3 h, and then filtered. After crystallization the desired product was obtained analytically pure.

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Supporting Information Available: A complete description of all of the experimental procedures as well as the characterization of all of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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