Tetrahedron Letters 50 (2009) 6684–6686

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A simple method for the conversion of carboxylic acids into thioacids with Lawesson's reagent

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ARTICLE INFO

Article history:
Received 1 September 2009
Revised 12 September 2009
Accepted 15 September 2009
Available online 19 September 2009

ABSTRACT

A one-step protocol for the conversion of carboxylic acids to thioesters, using Lawesson's Reagent, has been developed.

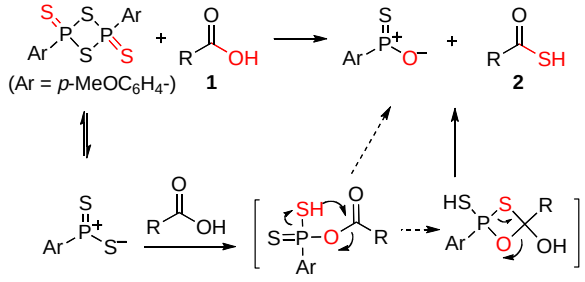
Thioacids represent a well-established and versatile class of organic compounds. Due to their nucleophilicity, thioacids have found broad applications, for instance the synthesis of thiols and thioesters[1] as well as in reactions with azides and nitrosulfonamides.[2,3] The recognition that thioacids are not only exploitable nucleophiles, but also can function as overall acylating agents under mild conditions, has enabled the development of a number of new methods for the construction of simple amides, as well as amide bonds in the context of peptide ligations.[4]

In the course of a current program directed toward the synthesis of glycopeptides (and glycoproteins),[5] we recently disclosed several strategies which use thioacids as the coupling partners.[6] The value of such methods depends on the accessibility of the thioacids. We have now directed our efforts to the development of a new and practical protocol for the selective installation of thioacid functionality.

Among the current methods for synthesizing thioacids, three are most commonly used. One involves pre-formation of activated carboxylic acids, which are converted to thioacids by reaction with hydrosulfide (HS) anion.[7] Another involves prior coupling of the carboxylic acid with either HSFmoc, HSTrt, or HSTmob. Removal of the protecting group releases the target thioacid.[8] Finally, Boc solid phase peptide synthesis (SPPS) with a thioester solid support can be applied to the preparation of large peptide thioacids.[9] The major limitations of these approaches include the toxicity of H_2S, required recourse to activating agents, current commercial unavailability of HSFmoc and HSTmob, and the inconvenience factors associated with a multistep protocol to accomplish a simple –OH to –SH interconversion. We describe herein the development of a new and efficient one-step synthesis of thioacids from the corresponding carboxylic acids, using Lawesson's reagent (LR).

Lawesson's reagent is commercially available, inexpensive, and widely used in organic synthesis, particularly for the transformation of a carbonyl functional group to its thiocarbonyl counterpart.[10] Remarkably, there had been no systematic study investigating the preparation of thioacids by direct reaction between carboxylic acid and LR. As outlined in Scheme 1, we postulated that, perhaps, a carboxylic acid (**1**) could react with LR in a manner analogous to that observed in reaction with alcohols, through a 'Wittig-like' mechanism, to provide the corresponding thioacid (**2**).[11]

Accordingly, we initiated a model study with benzoic acid (**3**, Table 1). In practice, no thioacid was observed when **3** was treated with LR (0.55 equiv) at RT in DCM for 3 h (entry 1). Even when the reaction was run overnight (entry 2), only trace amounts of thiobenzoic acid **4** were observed. Since microwave (MW) treatment is often employed for the rapid preparation of thiocarbonyl compounds with LR,[12] we wondered whether it might help to facilitate the desired transformation. Indeed, the conversion of **3**→**4** was accomplished efficiently within 10 min under MW conditions at 100 °C, in 76% yield (entry 3). A preliminary screening of conditions revealed that solvents, such as DCM, $CHCl_3$, and CH_3CN, promote thioacid formation with high levels of efficiency (entries 3, 5, and 6).



Scheme 1. Proposed mechanism for thioacid formation with LR.

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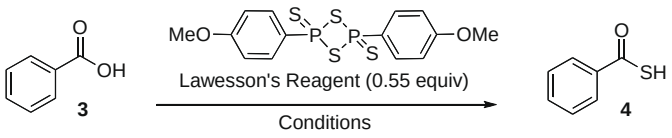
doi:10.1016/j.tetlet.2009.09.080

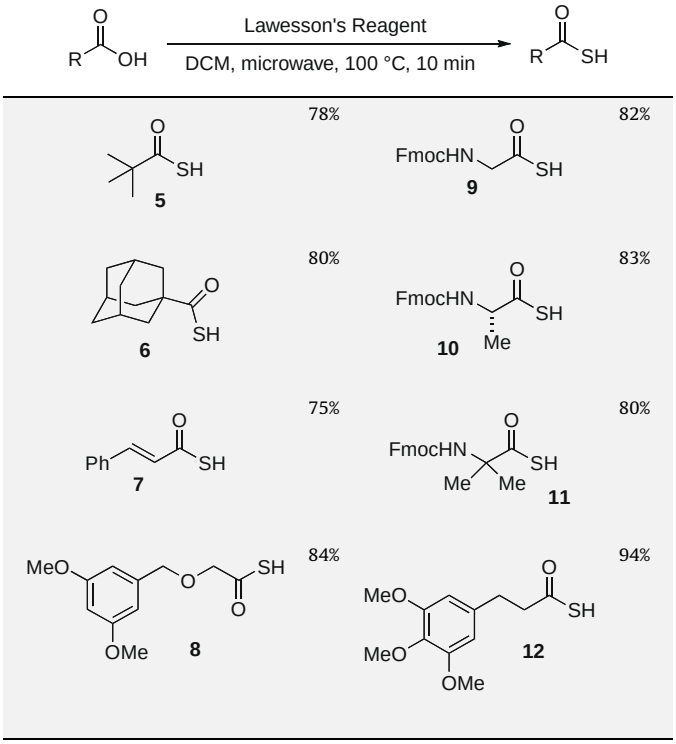
Table 1



Entry	Conditions	Yield (%)
1	DCM, rt, 3 h	NR[a]
2	DCM, rt, overnight	Trace
3	DCM, microwave, 100 °C, 10 min	76
4	THF, microwave, 100 °C, 10 min	46
5	$CHCl_3$, microwave, 100 °C, 10 min	73
6	CH_3CN, microwave, 100 °C, 10 min	77

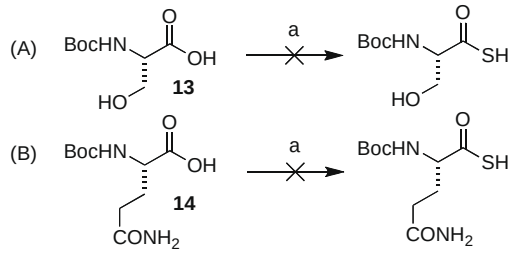
[a] NR = no reaction.

Table 2

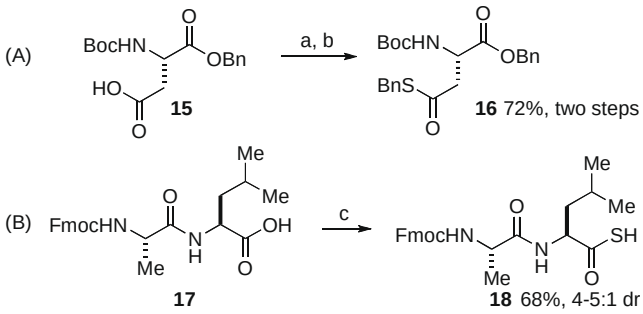


Encouraged by these preliminary results, we next explored the scope of the reaction (Table 2). We found that not only aliphatic thioacids (**8** and **12**), but also cinnamic thioacid (**7**) and hindered thioacids (**5**, **6**, and **11**) were produced under the conditions described above, in serviceable yields. Furthermore, excellent chemoselectivity was observed in the preparation of amino thioacids (**9**, **10**, and **11**). Thus, when 0.55 equiv of LR was used, the Fmoc protecting group was retained. However, reaction of substrates **13** and **14,** possessing more reactive alcohol and primary amide functionalities, respectively, did not yield the desired products (Scheme 2). While the specific reasons for this failure are presently unclear, conceivably, the primary alcohol and primary amides may be competing with the carboxylic acid functionality during the course of the reaction with LR. Alternatively, these functional groups might interdict mechanistic intermediates.

With this new method in hand, we sought to explore its potential applications to the preparation of synthetically valuable thioesters and peptidic thioacids. As illustrated in Scheme 3, an aspartic thioester (**16**) was efficiently prepared from aspartic acid (**15**)



Scheme 2. Reagents and conditions: (a) DCM, LR, MW, 100 °C, 10 min.



Scheme 3. Reagents and conditions: (a) DCM, MW, LR 100 °C; (b) BnBr, K_2CO_3, THF/MeOH, rt; (72%, two steps); c) LR, DCM, rt, 24 h; (68%, 4–5:1 dr).

through a 'two-step' procedure, in 72% overall yield. When dipeptide **17** was subjected to LR at rt overnight,[13] the corresponding thioacid **18** was obtained, with its internal amide bond intact. However, significant epimerization (possibly resulting from in situ oxazolone formation) was observed.

In summary, a practical new method for the synthesis of thioacids with LR has been developed. This method has been found to be generally useful for the preparation of a wide variety of thioacids. The reaction demonstrates good chemoselectivity for a number of functional groups, such as arenes, olefins, carbamates, esters, and amides. It has been successfully demonstrated in the context of the preparation of thioester **16**. Although our preliminary results indicate that epimerization may be a problem for the preparation of peptidic thioacids such as **18**, solutions to this issue are being pursued. Application of these new capabilities will be described in due course.

Acknowledgments

Support was provided by the NIH (CA103823 to S.J.D.). P.N. thanks the National Institutes of Health for a Ruth L. Kirschstein postdoctoral fellowship (CA125934-02). We thank Professor W. F. Berkowitz for helpful discussions. Special thanks to Ms. Rebecca Wilson for editorial consultation. We acknowledge Ms. Dana Ryan for assistance with the preparation of the Letter. We thank Dr. George Sukenick, Ms. Hui Fang, and Ms. Sylvi Rusli of the Sloan-Kettering Institute's NMR core facility for mass spectral and NMR spectroscopic analysis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.080.

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13. When the reaction was carried out under the microwave conditions, extensive decomposition of the starting material, **17**, and a low yield of **18** were observed. It is highly possible that the internal amide group may be competing with the carboxylic acid functionality during the course of the reaction with LR under the microwave conditions. However, the corresponding reaction was found to proceed at room temperature, albeit at a slower rate. There is a possibility that the superior reactivity of **17** at room temperature is facilitated by the intermediacy of the oxazolone. Further studies, which will shed some light into the origins of this effect, will be reported in a due course.