



Pergamon

Tetrahedron Letters 41 (2000) 1627–1630

TETRAHEDRON
LETTERS

A new method of forming resin bound thioesters and their use as ‘traceless’ linkers in solid phase synthesis

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Received 19 November 1999; accepted 16 December 1999

Abstract

Resin bound thioesters can be prepared by heating thioamides in aqueous DMF with Merrifield resin in the presence of sodium iodide. These thioamides can be cleaved to give alcohols, ketones and lactones by a variety of methods. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: combinatorial chemistry; lactones; solid phase synthesis; thioamide; thioester.

Thioesters are activated carboxylic acid derivatives which exhibit acylating properties similar to those of acid anhydrides.¹ Usually prepared by condensation of a thiol and an acid chloride, they have found widespread application in synthetic chemistry as precursors to aldehydes, ketones, acids, esters, lactones, amides, lactams and heterocycles.² Surprisingly, in view of the diverse chemistry this functional group offers, it has attracted scant interest from combinatorial chemists.³ This may be attributed to a number of factors including the limited availability of methods to prepare resin bound thioesters and practical difficulties associated with resin bound acid chlorides.^{3–5} In this communication we present a new method for synthesising thioesters on a solid support and show how these materials may serve as precursors of 1°-alcohols, 3°-alcohols, ketones and lactones (Scheme 1).



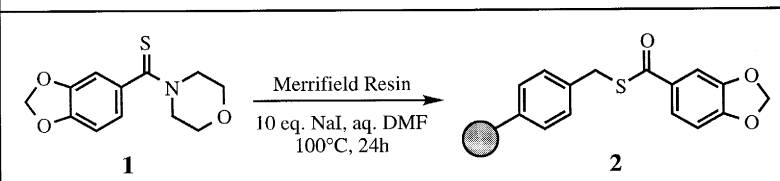
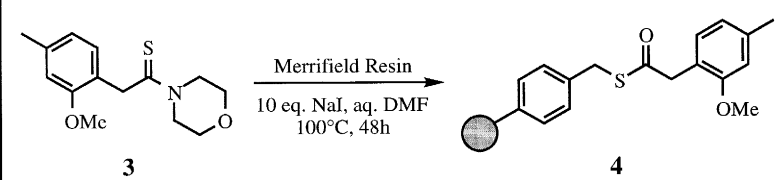
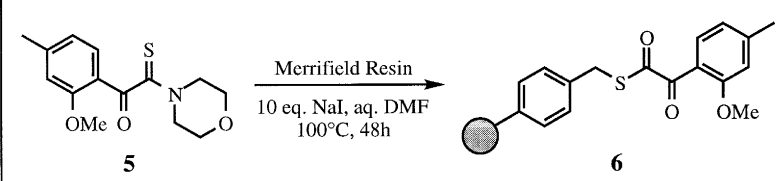
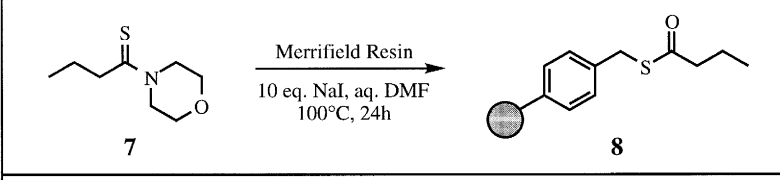
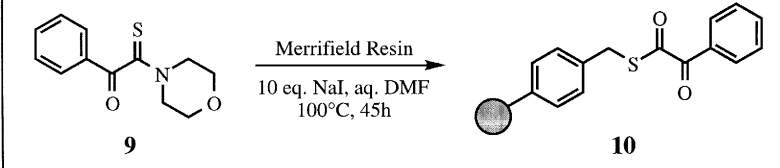
Scheme 1.

The method used to generate resin bound thioesters involved heating aqueous DMF solutions of a thioamide with sodium iodide and Merrifield resin.⁶ These conditions differ from those used in solution phase chemistry.^{7,8} In particular, the inclusion of NaI and use of a higher boiling solvent were necessary

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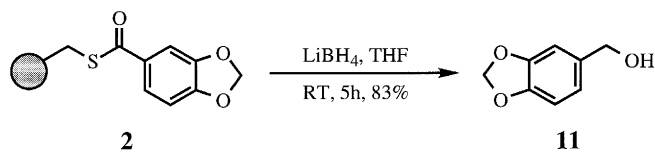
to achieve reasonable loadings (estimated to be 40% of the theoretical maximum)⁹ in an acceptable time frame. Importantly, the reaction had broad scope and was used to access resin-bound aromatic, aliphatic and α -ketothioesters. Characterisation by ATR reflectance infra-red spectroscopy was also possible:¹⁰ in each case a strong carbonyl stretching frequency was observed within 5 cm^{-1} of those data reported for the corresponding *S*-benzylthioester (Table 1).^{7,11}

Table 1
Formation of resin supported thioesters from thioamides

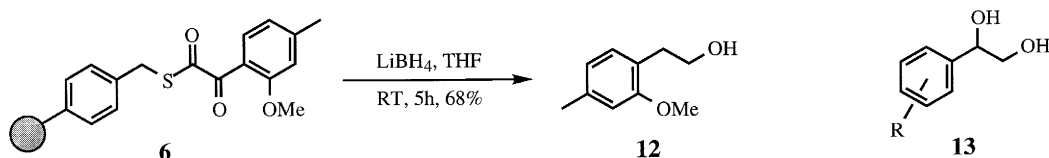
Reactions and Conditions	IR C=O stretch(es) of product
 <p>1 $\xrightarrow[10\text{ eq. NaI, aq. DMF, } 100^\circ\text{C, 24h}]{\text{Merrifield Resin}}$ 2</p>	<p>1656 cm⁻¹ the corresponding <i>S</i>-Bn thioester exhibited 1656 cm⁻¹ (CHCl₃)⁷</p>
 <p>3 $\xrightarrow[10\text{ eq. NaI, aq. DMF, } 100^\circ\text{C, 48h}]{\text{Merrifield Resin}}$ 4</p>	<p>1685 cm⁻¹ the corresponding <i>S</i>-Bn thioester exhibited 1687 cm⁻¹ (trace CDCl₃)⁷</p>
 <p>5 $\xrightarrow[10\text{ eq. NaI, aq. DMF, } 100^\circ\text{C, 48h}]{\text{Merrifield Resin}}$ 6</p>	<p>1725 & 1675 cm⁻¹ the corresponding <i>S</i>-Bn thioester exhibited 1735 and 1670 cm⁻¹ (solid)^{7,10}</p>
 <p>7 $\xrightarrow[10\text{ eq. NaI, aq. DMF, } 100^\circ\text{C, 24h}]{\text{Merrifield Resin}}$ 8</p>	<p>1683 cm⁻¹ the corresponding <i>S</i>-Bn thioester exhibited 1680 cm⁻¹ (neat)¹¹</p>
 <p>9 $\xrightarrow[10\text{ eq. NaI, aq. DMF, } 100^\circ\text{C, 45h}]{\text{Merrifield Resin}}$ 10</p>	<p>1720 & 1674 cm⁻¹</p>

Several methods for cleaving resin bound thioesters were investigated. The known reduction of these materials with lithium borohydride produced the expected alcohols in good yield (e.g. Scheme 2).^{3,13} Interestingly, the resin bound α -ketothioester **6** underwent over-reduction with lithium borohydride to give alcohol **12** rather than the expected diol **13** (Scheme 3).

Reactions with organometallic reagents likewise gave rise to some unexpected observations. For example, it has been reported that resin bound thioesters react with Grignard reagents to give ketones.¹²

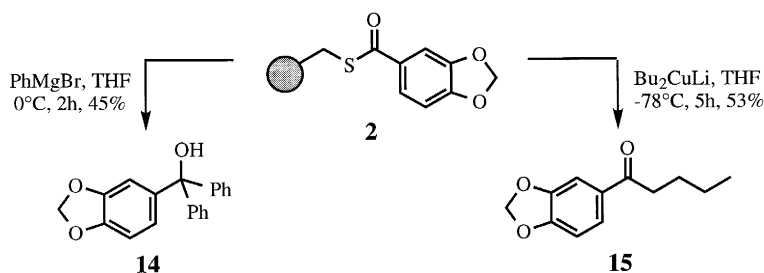


Scheme 2.



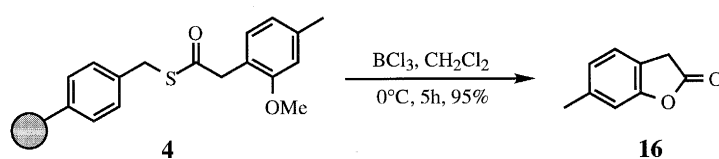
Scheme 3.

In our study, 3°-alcohols were produced when resin linked thioesters such as **2** were treated with phenylmagnesium bromide while ketones were produced when these substrates were exposed to organocopper reagents (Scheme 4).¹³



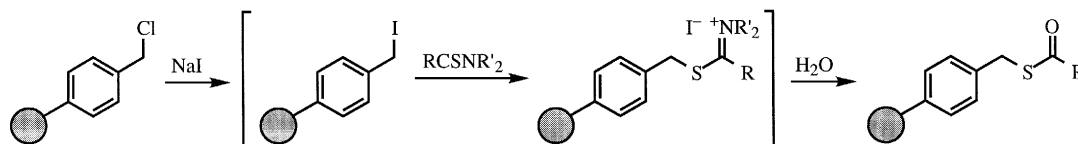
Scheme 4.

Cleavage of thioester **4** to benzofuranone **16** was also accomplished in excellent yield using boron trichloride. Though the scope of this reaction is limited, it provides an interesting method for substrate cleavage that has little precedent in the literature (Scheme 5).^{8,14}



Scheme 5.

In conclusion, we have developed a new method of preparing resin bound thioesters that is simple to effect and broad in scope. It proceeds through sequential activation of Merrifield resin, *S*-alkylation of a thioamide and hydrolysis of the resulting salt (Scheme 6).^{6,7} Additionally, we have shown that these materials cleave readily to give alcohols with lithium borohydride and Grignard reagents and ketones with organocuprates. The release of benzofuranone **16** when **4** was exposed to boron trichloride is similarly noteworthy.



Scheme 6.

Acknowledgements

The authors thank Rhône-Poulenc Rorer and the EPSRC for their financial support through the CASE studentship scheme. We also thank Matthew Lucas and Helen Russell for their help and interest in this work.

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