Tetrahedron Letters 53 (2012) 2712-2714

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Conjugate addition of unactivated thiols to α , β -unsaturated ketones catalyzed by a bifunctional rhenium(V)–oxo complex

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ARTICLE INFO

ABSTRACT

Article history: Received 16 February 2012 Revised 8 March 2012 Accepted 20 March 2012 Available online 26 March 2012

Keywords: Rhenium Conjugate addition Thiols Bifunctional Catalytic

Conjugate addition reactions are one of the most important synthetic tools for strategic bond formation. The conjugate addition of thiols to α,β -unsaturated ketones provides access to β -sulfanyl ketones. The synthetic utility and medicinal properties of these compounds have been the subject of numerous reports. Recently, βaryl-β-sulfanyl ketone analogs were found to have antiproliferative activity in a number of breast cancer cell lines.¹ In addition, these functional scaffolds have been reported to have antiviral activity.² The synthetic utility of β -sulfanyl ketones has been demonstrated in their application as alkene protecting groups.^{3,4} They have also been used as β -acylvinyl cation precursors⁵ and homoenolate equivalents.⁶ Pioneering efforts to synthesize β -sulfanyl ketones through the conjugate addition of thiols to enones include the use of catalytic Brønsted acids and bases⁷⁻¹³ and Lewis acids such as Bi³⁺ and In³⁺ salts.¹⁴⁻¹⁶ In pursuit of a general method for the conjugate addition of thiols to α , β -unsaturated ketones, we envisioned the use of a bench-top stable, bifunctional rhenium(V)oxo complex as a catalyst for the transformation. It is proposed that the Lewis acidic metal center will activate the enone while the Brønsted basic oxo ligand will facilitate proton transfer. The application of these complexes to this transformation also provides an opportunity to tune reactivity and selectivity of the catalyst through modifications of the associated ligands.

The development of a highly efficient and practical method for the conjugate addition of thiols to α , β -unsaturated ketones is described. After a brief catalyst screen,¹⁷ commercially available,

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air- and moisture-tolerant Re(V)-oxo complex **1** was identified as a catalyst for the reaction. Complex **1** displays several convenient properties that increase its practical value. The complex requires no special handling and no efforts need to be made to exclude oxygen or water from the reaction. Upon completion of the reaction, the catalyst can be triturated and removed by filtration, thus eliminating the need for aqueous extraction, which is typically required for reactions facilitated by Brønsted acids and bases.

ReOCl₃(OPPh₃)(S(CH₃)₂) has been found to be an efficient bifunctional catalyst for the 1,4-addition of thi-

ols to α,β -unsaturated ketones. The addition of thiophenol derivatives and alkyl thiols proceeds under

mild reaction conditions without pre-activation of the thiol or exogenous base. Reactions of aryl, alkyl,

and cyclic enones produce the corresponding β -sulfanyl ketones in good to excellent yield.

O CI ... || ...CI Re OPPh₃ 1

We first investigated the addition of 4-methylbenzenethiol (1.2 equiv) to 4-phenyl-3-buten-2-one (**2**) in the presence of 2 mol % of **1** under ambient conditions (Eq. 1). The reaction proceeded at room temperature, in ethyl acetate (2.0 M) without pre-activation of the thiol or addition of exogenous base. Gratifyingly, β -phenyl- β -sulfanyl ketone **3** was isolated in 85% yield. The reaction also proceeded with similar yields in diethyl ether and dichloromethane but was less efficient in aromatic solvents, such as toluene. Only modest product yields were observed when the reaction was run in hexanes. Because of its industrial and environmental advantages,¹⁸ ethyl acetate was utilized as the solvent for this method.





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The addition of 4-methylbenzenethiol to aryl and alkyl substituted α , β -unsaturated ketones is summarized in Table 1.¹⁹

Electron rich and electron deficient 4-aryl-3-buten-2-one derivatives reacted very well (Table 1, entries 1 and 2) providing the corresponding thioethers in high yield (83–89%). Substrates bearing heteroaromatic substitution at the β -position performed comparably well (entry 3, 88% yield). Aromatic substitution was not required for reactivity as evidenced by alkyl substituted enone **4d** (entry 4, 85%). Of particular note, the conjugate addition to mesityl oxide (**4e**) readily provided the corresponding tertiary thioether **5e** in excellent yield (97%). In addition to the substrates listed in Table 1, this catalytic conjugate addition reaction was able to be extended to cyclic enones. The addition of 4-methybenzenethiol to cyclohexenone readily provided thioether **6** in 75% yield (Eq. 2).

$$\begin{array}{c}
0 \\
1.2 \text{ equiv p-MePhSH}\\
2.0 \text{ mol}\% 1 \\
2.0 \text{ M in EtOAc}\\
\text{rt, 4 h}
\end{array}$$

$$\begin{array}{c}
0 \\
S \\
S \\
6.75\% \text{ yield}
\end{array}$$

$$(2)$$

The tolerance of the reaction to changes in the electronic structure of the thiophenol derivative was examined using 4-phenyl-3butene-2-one (**2**) as the model substrate. Electron-rich thiophenol **7a** was (Table 2, entry 1) readily added to enone **2** to give the corresponding thioether in 97% yield. Electron-deficient thiophenols were only slightly less reactive leading to the formation of thioethers **8c-e** in very good yield (75–91%, entries 3–5). Notable is the tolerance of the reaction to the presence of halide substitution on the aromatic ring, thus providing thioethers with a handle for additional synthetic manipulation.

Aryl substituted enones, as represented by enone **2**, are tolerated by a number of thioconjugate addition methods.^{16,20} Therefore, when addressing the generality of conjugate addition reactions involving thiophenol derivatives, mesityl oxide (**4e**) was also examined. A similar trend in reactivity to those described above was observed for the addition of electron-rich (Table 3, entry 1) and electron-deficient (entries 3–5) thiophenol derivatives to mesityl oxide. The corresponding tertiary thioethers were isolated in good to excellent yield (78–93%).

The reactivity of alkyl thiols in the conjugate addition was examined using dodecanethiol. The addition to 4-phenyl-3-butene-2-one and mesityl oxide proceeded under the standard reac-

Table 1

Addition of 4-methylbenzene thiol to differentially substituted enones



Entry	R ₁	R ₂	R ₃		Yield (%)	
1	4-OCH ₃ -Ph	Н	CH₃	4a	83	5a
2	4-ClPh	Н	CH ₃	4b	89	5b
3	Thiophene	Н	CH ₃	4c	88	5c
4	Pentyl	Н	CH ₃	4d	85	5d
5	CH ₃	CH_3	CH_3	4e	97	5e
6	Ph	Н	Ph	4f	69	5f

Table 2

Addition of thiophenol derivatives to 4-phenyl-3-buten-2-one



Table 3

Addition of thiophenol derivatives to mesityl oxide

CH ₃ O H ₃ C CH	H ₃ + R 1.2 equiv 7a-e	2.0 M in F 2.0 mol rt, 2-6	EtOAc % 1 8 h H ₃ C	S O CH ₃ ^{3C} 9a-e
Entry	R		Yield (%)	
1	OCH ₃	7a	78	9a
2	Н	7b	82	9b
3	Cl	7c	93	9c
4	Br	7d	88	9d
5	NO ₂	7e	78	9e

tion conditions. Thioethers **10** and **11** were isolated in good yield, 80% and 78%, respectively (Eqs. 3 and 4). This is a notable improvement on a previously reported yield for **11** of 52%, which was obtained under acid catalyzed conditions.²¹ To date, we have encountered no structural limitation with regard to the thiol.

$$\begin{array}{c} O \\ Ph \\ \hline \\ CH_{3} \\ H_{3}C \\ \hline \\ CH_{3} \\ CH_{3} \\ \hline \\ CH_{3} \\ CH_{3}$$

A reaction mechanism is proposed for the conjugate addition of unactivated thiols to α , β -unsaturated ketones catalyzed by Re(V)– oxo complex **1**, illustrating how this bifunctional Re–oxo complex is especially suited for this reaction (Scheme 1). We hypothesize that catalytic reaction proceeds through Lewis acid activation of the enone by the metal center following ligand dissociation. Addition of the thiol and proton transfer leads to the generation of a putative rhenium–enolate. Tautomerization regenerates the oxo ligand and facilitates the release of the product closing the catalytic cycle. The generation of rhenium–enolate creates the possibility that this proposed intermediate may add to another equivalent of enone; no such products were observed.²²

In conclusion, Re(V)–oxo complex **1** has been shown to be a versatile catalyst for the conjugate addition of unactivated thiols to α , β -unsaturated ketones. A wide range of enones and thiols were found to be reactive under the mild reaction conditions. Elaboration of this reaction, including the pursuit of enantioselective additions, is currently underway in our laboratories and will be reported in due time.



Scheme 1. Proposed catalytic cycle.

Acknowledgments

We gratefully acknowledge the University of Richmond and the Thomas F. and Kate Miller Jeffress Memorial Trust for financial support. We thank Dr. Wade Downey for many helpful discussions.

Supplementary data

Supplementary data associated with this article can be found, in version. at http://dx.doi.org/10.1016/j.tetthe online let.2012.03.075. These data include MOL files and InChiKeys of the most important compounds described in this article.

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