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Development of β-keto 1,3-dithianes as versatile intermediates for organic synthesis

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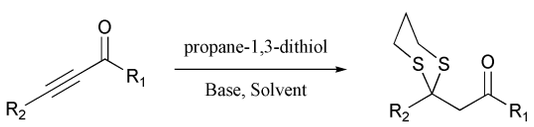
β-Keto 1,3-dithianes can be generated by the double conjugate addition of dithiols to propargylic ketones, esters and aldehydes in excellent yields. As masked 1,3-dicarbonyl systems these substrates can be converted to a range of functionalised oxygen-containing heterocycles that can be used in natural product synthesis.

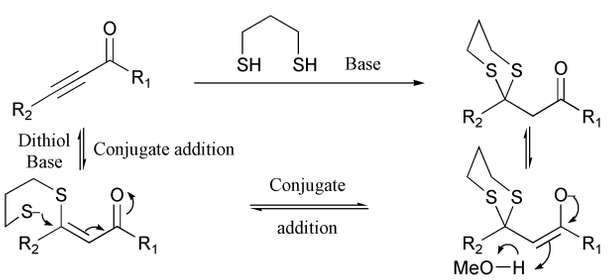
The generation of 1,3-oxygenated functionality in organic molecules is an important process of modern synthetic chemistry.[1] While there have been many advances in this area, and especially for the assembly of polyketide natural products, there remains a constant need to develop new methods for the introduction of 1,3-oxidation patterns with enantio- and diastereocontrol.[2]

We were interested in developing a general functionalised molecular unit from which we could generate a range of 1,3-substituted molecules. Here we report our initial studies on the facile double conjugate addition of dithiols to propargylic carbonyls to form a β-carbonyl dithiane. This intermediate provides a versatile platform for the preparation of heterocycles containing 1,3-oxidation arrangements.



Scheme 1

There are a number of methods available for the generation of β-keto 1,3-dithianes, although in some cases their synthesis is complicated and reported applications have therefore been limited.[3] Potentially, however, orthogonally protected dicarbonyl intermediates have wide ranging applications. We conceived that a dithiol would undergo a base mediated double conjugate addition to a propargylic ketone to generate the desired β-keto 1,3-dithiane (Scheme 1, 2).[4]



Scheme 2 Conjugate addition of a dithiol to propargylic ketones.

Initial investigations proceeded on the addition of propane-1,3-dithiol to alkyne **1a** to generate desired β-keto dithiane **2a** in an excellent yield. The optimal system involved the use of NaOMe in MeOH with either THF or CH_2Cl_2 as co-solvent. The scope of the reaction was investigated using a range of propargylic compounds (**1a**–**f**). Pleasingly, the dithiol additions worked in good to excellent yields, Table 1.† Ketones (entries 1, 3, and 4) and esters (entry 2) with a range of substituents were good substrates for this process.[5] In general, we found that the addition of the base to a solution of dithiol and the propargylic carbonyl at −10 °C and allowing the temperature to rise to 0 °C overnight gave optimal yield of product. Particularly noteworthy is the formation of dithiane **2e** from aldehyde **1e** (entry 5). This versatile aldehyde derivative was generated in good yield. The dithiol addition is amenable to large-scale production of dithiane adducts. For example, ethyl propiolate **1b** is converted to dithiane **2b** in 84% yield on a 0.1 mole scale. Dithiane **2f** is formed in modest yield from **1f** (entry 6). This product is probably formed by dithiol addition[6] to the alkyne followed by attack of methoxide on the resulting aldehyde and subsequent 1,4-Brook rearrangement.[7]

Table 1 Dithiol additions to propargylic ketones

Entry	Substrate[a]	Time/h	Yield (%)	Product
1	**1a**	16	94	**2a**
2[b]	**1b**	4	84	**2b**
3	**1c**	24	88	**2c**
4	**1d**	24	82	**2d**
5	**1e**	18	88	**2e**
6[c]	**1f**	18	48	**2f**

[a] *Reagents and conditions*: NaOMe (1.3 equiv.), propane-1,3-dithiol (1.1–1.3 equiv.), MeOH–CH_2Cl_2 (4 : 1, 0.05 M), −10 °C to 0 °C. [b] NaOEt, EtOH–CH_2Cl_2 are used. [c] NBu_4OH (1.3 equiv.), propane-1,3-dithiol, THF–MeOH, 0 °C.

More complex substrates are also amenable to this reaction. As part of our natural product synthesis programmes we required a number of poly-oxygenated 1,3-dicarbonyl compounds. The propargylic ketones were readily prepared by a two step procedure involving acetylide addition to an aldehyde and oxidation of the resulting propargylic alcohols. Table 2 shows the addition of dithiols to more complex substrates (**1g**–**i**), highlighting the compatibility of this reaction with a

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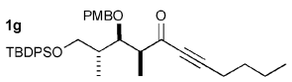
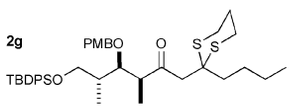
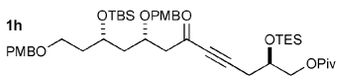
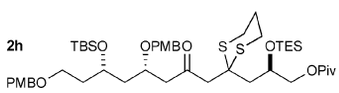
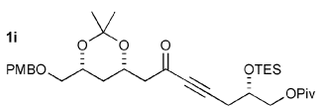
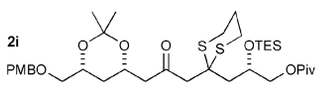
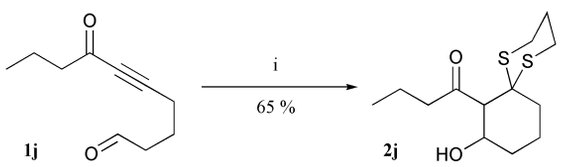
Table 2 Dithiol addition to complex propargylic ketones

Entry	Substrate[a]	Time/h	Yield (%)	Product
1		16	80	
2		16	90	
3		16	95	

[a] *Reagents and conditions*: NaOMe (1.3 equiv.), propane-1,3-dithiol (1.1 equiv.), MeOH–CH_2Cl_2 (4 : 1, 0.05 M), −10 to 0 °C.

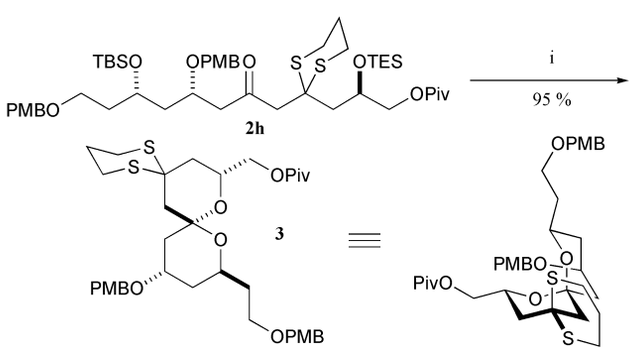
range of common protecting groups. Moreover, the stereochemical integrity of ketone **1g** is conserved in the formation of **2g** implying that this methodology is adaptable to molecules with base sensitive asymmetric centres.

We also investigated the addition to **1j**, a substrate that contains a second electrophilic site. Dithiol addition proceeded smoothly and was followed by intramolecular aldol reaction to form **2j** as a 3 : 1 (*syn–anti*) mixture of diastereomers in 65% yield. *This tandem process generates cyclic systems with high levels of functionality* (Scheme 3).



Scheme 3 Tandem dithiol-intramolecular aldol reaction.
Reagents and conditions: (i) NaOMe (1.3 equiv.), propane-1,3-dithiol (1.1 equiv.), MeOH–CH_2Cl_2 (3 : 1), 0 °C to rt, 14 h.

The conversion of the propargylic ketone unit to a β-keto 1,3-dithiane removes the rigid acetylene unit from the molecule permitting a range of cyclisation reactions. For example, treatment of **2h** with *p*-TsOH in MeCN–H_2O for 16 hours facilitated removal of the two silicon groups and subsequent cyclisation afforded spiroketal **3**. This sequence of reactions provided a model compound for the synthesis of the AB spiroketal unit of spongistatin 1 (Scheme 4).[8] Interestingly, the 1,3-dithiane



Scheme 4 Application to the synthesis of spiroketal **3**.
Reagents and conditions: (i) *p*-TsOH, MeCN–H_2O (4 : 1), 30 °C.

unit seems to have a significant effect on the cyclisation of **2h**. Cyclisation of the corresponding dione proved capricious,[9] *however, in the presence of the dithiane unit the cyclisation cleanly produced the desired spiroketal in excellent yield (95%)*.

In summary, we have developed an efficient method for the conjugate addition of dithiols to propargylic ketones, esters and aldehydes. The resulting β-carbonyl-dithianes are isolated in good to excellent yields across a range of substrates. The potential of these units as versatile platforms for the generation of 1,3-oxygenated structures is highlighted through the synthesis of spiroketal **3**. Functionalised dithianes (**2f**) can be accessed from a silyl substituted propargylic aldehyde (**1f**) and we have also reported a new tandem process that forms highly functionalised cyclic systems. We are currently exploring the application of these species in a number of synthesis programmes and these results will be reported in due course.

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Notes and references

† *General procedure*. NaOMe (1.3 equiv.) was added in one portion to a stirred solution of propargylic carbonyl compounds and propane-1,3-dithiol (1.1 equiv.) in MeOH–CH_2Cl_2 (4 : 1, 0.05 M) at approximately −10 °C (ice–acetone bath). The reaction mixture was stirred for 14 hours, allowing the temperature to rise to 0 °C. On completion the reaction was quenched by the addition of NH_4Cl solution and extracted with Et_2O. The organic fractions were washed (water and brine), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography.

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