Tetrahedron Letters 51 (2010) 290–292

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Double Michael addition of dithiols to acetylenic carbonyl compounds under the influence of molecular sieve and dimethyl sulfoxide

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ARTICLE INFO

Article history:
Received 18 September 2009
Revised 22 October 2009
Accepted 2 November 2009
Available online 5 November 2009

ABSTRACT

Double Michael addition of dithiols such as 1,3-propanedithiol and 1,2-ethanedithiol to α,β-acetylenic carbonyl compounds in the presence of molecular sieve and dimethyl sulfoxide proceeds very smoothly to afford the corresponding β-keto 1,3-dithianes and β-keto 1,3-dithiolanes, respectively, in good to high yields.

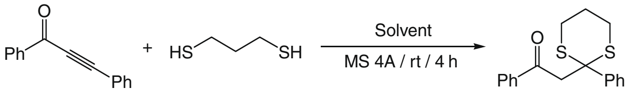
β-Keto cyclic dithioacetals, such as β-keto 1,3-dithiolanes and 1,3-dithianes, are well known as versatile synthetic intermediates.[1] For example, β-keto 1,3-dithianes can be converted to 1,3-dicarbonyl compounds by deprotection of the 1,3-dithiane moiety.[2]

A number of methods are available for generating β-keto 1,3-dithiolanes and β-keto 1,3-dithianes, including α-alkylation of carbonyl compounds with 1,3-dithiolane and 1,3-dithiane or its derivatives,[3] nucleophilic addition of 1,3-dithiane to epoxides followed by oxidation,[4] conjugate reduction of α-oxoketene dithioacetals,[5] and double Michael addition of 1,2-ethanedithiol and 1,3-propanedithiol to α,β-acetylenic carbonyl compounds.[6] The double Michael addition of dithiols needs a catalyst [Al_2O_3, n-Bu_3P, ionic liquid, $(MgCO_3)_4Mg(OH)_2$, and NaOMe][2,6] to proceed smoothly. Furthermore, some reactions must be carried out at a lower temperature.[6b,d] These conventional methods, therefore, have much room for improvement toward simpler operations and milder reaction conditions. For example, in the case of Al_2O_3-catalyzed double Michael addition, the activation of Al_2O_3 is unavoidable before use.

In recent years, dimethyl sulfoxide (DMSO) has received renewed attention as a polar solvent and a promoter of efficient organic reactions.[7] We developed several effective reactions in the presence of molecular sieves (MS) 4A in DMSO during the course of our intensive work. For example, cyanobenzoylation of aldehydes,[8] cyanocarbonation of aldehydes,[9] trifluoromethylation of carbonyl compounds,[10] Henry reaction,[11] and Knoevenagel reaction[12] were documented. Moreover, we investigated Michael addition in the presence of MS 4A in DMSO, and the desired reaction occurred readily to yield the corresponding 1,4-addition products.[13] These results suggested that a similar double Michael addition of dithiols could be performed in DMSO.

The reaction of 1,3-diphenyl-2-propyn-1-one with 1,3-propanedithiol was selected to optimize the reaction conditions. First, we tried double Michael addition of 1,3-propanedithiol (0.30 mmol) to 1,3-diphenyl-2-propyn-1-one (0.30 mmol) in the presence of MS 4A in various solvents (Table 1). We found that aprotic polar solvents (DMSO, dimethylformamide) were suitable for this reaction and 1-pheny-2-(2-phenyl-1,3-dithian-2-yl)ethan-1-one(**1a**) was obtained in 90% and 88% yields, respectively (entries 1 and 2). When using MeOH as a solvent, we obtained the desired product in moderate yield (entry 3). Dichloromethane, tetrahydrofuran, and hexane were found to be ineffective for this reaction (entries 4–6). We have already reported the silylation of alcohols with trialkylsilyl chloride under the influence of DMSO (3 equiv) in hexane without using a catalyst.[14] Therefore, we expected that the amount of DMSO could be reduced in hexane as a solvent. Thus, we investigated the equivalent of DMSO to 1,3-diphenyl-2-propyn-1-one in hexane (Table 2). We found that 5 equiv

Table 1
Effect of solvent[a]



1a

Entry	Solvent (2 mL)	Yield[b] (%)
1	DMSO	90
2	DMF	88
3	MeOH	45
4	CH_2Cl_2	4
5	THF	3
6	Hexane	5

[a] Reactions were carried out using 1,3-diphenyl-2-propyn-1-one (0.3 mmol) and 1,3-propanedithiol (0.3 mmol) in solvent in the presence of MS 4A (100 mg).
[b] Isolated yield of the purified product.

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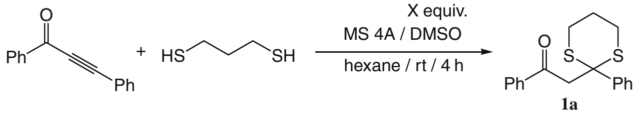
doi:10.1016/j.tetlet.2009.11.002

Table 2
Screening of the amount of DMSO[a]



1a

Enrty	X (equiv)	Yield[b] (%)
1	94 (2 mL)	90[c]
2	10	90
3	5	90
4	3	73

[a] Reactions were carried out using 1,3-diphenyl-2-propyn-1-one (0.3 mmol) and 1,3-propanedithiol (0.3 mmol) in hexane (2 mL) in the presence of MS 4A (100 mg).

[b] Isolated yield of the purified product.

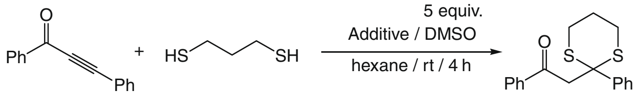
(1.5 mmol) of DMSO in hexane (2 mL) improved the yield of the desired product (entry 3).

Next, we tested double Michael addition in the presence of various dehydrating reagents as an additive (Table 3). When the experiment was performed without an additive, no reaction occurred (entry 1). On the other hand, the reaction in the presence of MS 4A (100 mg) proceeded very smoothly to yield the desired product in 90% yield (entry 3). Other additives such as MS 5A, MS 13X, Drierite, and $MgSO_4$ were less effective than MS 4A[15] (entries 4–7). A screening of the amount of MS 4A showed that double Michael addition proceeded smoothly, when MS 4A (150 mg) was used. The reaction with 1,2-ethanedithiol instead of 1,3-propanedithiol also occurred readily, producing the corresponding β-keto 1,3-dithiolane in good yields. However, thioacetalization of the carbonyl group could not be detected.

The scope of the present reaction was investigated using a variety of α,β-acetylenic carbonyl compounds (Table 4).[16,17] Double Michael addition of 1,2-ethanedithiol and 1,3-propanedithiol was uniformly successful for various α,β-acetylenic ketones (entries 1–8). The ketone having a trialkylsilyloxy group afforded the corresponding product in good yield (entry 5). Moreover, we found that α,β-acetylenic aldehyde and α,β-acetylenic ester also gave the corresponding adducts in good yields (entries 9 and 10).

We examined the addition reaction of 1,3-diphenyl-2-propyn-1-one with monothiol, *n*-BuSH, instead of dithiol; however, we obtained the single Michael adduct predominantly in 94% yield (Scheme 1). In addition, we could obtain the corresponding β-keto dithiane in larger scale after purification by recrystallization (10 mmol scale, Scheme 2). The detailed role of DMSO and MS 4A in not made clear at present, the combination of DMSO and MS 4A is indispensable for this double Michael addition.

Table 3
Effect of additive[a]



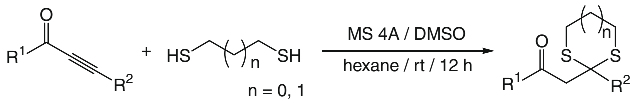
1a

Entry	Additive	Yield[b] (%)
1	None	Trace
2	MS 3A (100 mg)	86
3	MS 4A (100 mg)	90
4	MS 5A (100 mg)	5
5	MS 13X (100 mg)	42
6	Drierite (100 mg)	7
7	$MgSO_4$ (100 mg)	6
8	MS 4A (150 mg)	93
9	MS 4A (200 mg)	76

[a] Reactions were carried out using 1,3-diphenyl-2-propyn-1-one (0.3 mmol) and 1,3-propanedithiol (0.3 mmol) in hexane (2 mL) in the presence of DMSO (1.5 mmol).

[b] Isolated yield of the purified product.

Table 4
Double Michael addition to various α,β-acetylenic carbonyl compounds[a]

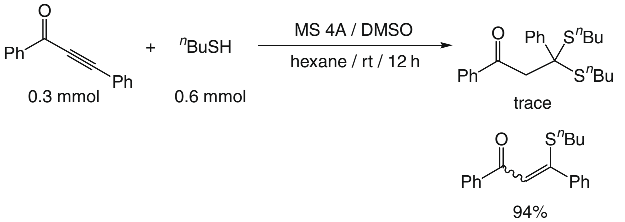


Entry	R^1	R^2	Yield[b] (%) (*n* = 0)	Yield[b] (%) (*n* = 1)
1	Ph	Ph	93	97
2	4-BrC_6H_4	Ph	63	88
3	4-MeC_6H_4	Ph	90	89
4	4-$MeOC_6H_4$	Ph	73	63
5	Ph	$CH_2OTBDMS$	83	63
6	2-Furyl	Ph	95[c]	89[c]
7	Me	Ph	86	74
8	Ph	*n*-Bu	72	61
9	H	Ph	72	55
10	EtO	H	64	44

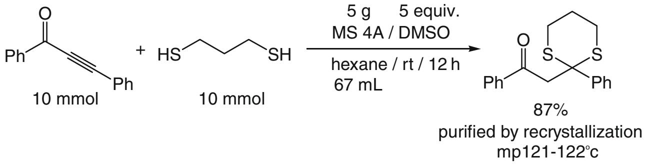
[a] The reactions were performed using α,β-acetylenic carbonyl compounds (0.3 mmol) and dithiols (0.3 mmol) in hexane (2 mL) in the presence of MS 4A (150 mg) and DMSO (1.5 mmol).

[b] Isolated yield of the purified product.

[c] The reaction was carried out in DMSO (2 mL).



Scheme 1. Michael addition of *n*-BuSH.



Scheme 2. Double Michael addition performed in a large scale.

In conclusion, we have developed a convenient double Michael addition of 1,3-propanedithiol and 1,2-ethanedithiol to α,β-acetylenic carbonyl compounds to give β-keto 1,3-dithianes and β-keto 1,3-dithiolanes, respectively. The reaction can proceed smoothly in hexane in the presence of MS 4A and DMSO. The reaction has the following synthetic advantages: (1) in contrast to known methods, this procedure does not need an additional base or Lewis acid, (2) a wide range of α,β-acetylenic carbonyl compounds can be employed, (3) not only 1,3-propanedithiol but also 1,2-ethanedithiol as a nucleophile are available, (4) this method is very simple, convenient, and practical, and (5) atom economy is extremely high.

Acknowledgment

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas ‘Advanced Molecular Transformations of

Carbon Resources' from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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16. Acetylenic carbonyl compounds were prepared according to the procedure reported in references: (a) Cox, R. J.; Ritson, D. J.; Dane, T. A.; Berge, J.; Charmant, J. P. H.; Kantacha, A. *Chem. Commun.* **2005**, 1037; (b) Journet, M.; Cai, D.; DiMichele, L. M.; Larsen, R. D. *Tetrahedron Lett.* **1998**, *39*, 6427.
17. Dehydrated DMSO was purchased from Wako Pure Chemical Industries and used without further purification. Typical experimental procedure is as follows: 1,3-propanedithiol (30 μL, 0.3 mmol) and DMSO (110 μL, 1.5 mmol) were added to a solution of 1,3-diphenyl-2-propyn-1-one (61.8 mg, 0.3 mmol) in hexane (2 mL) in the presence of MS 4A (150 mg) at room temperature under argon atmosphere. The resultant mixture was stirred for 12 h at room temperature and the reaction was quenched with a phosphate buffer (pH 7). The organic materials were extracted with AcOEt and dried over $MgSO_4$. The solvent was evaporated and 1-pheny-2-(2-phenyl-1,3-dithian-2-yl)ethan-1-one (89.5 mg, 97%) was isolated by thin-layer chromatography on silica gel (AcOEt/hexane = 1:5). The product gave satisfactory NMR and IR spectra.