



Mukaiyama Reagent: Novel One-Pot System for the Synthesis of 1,3-Oxathiolan-5-one

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Abstract

A new application of mukaiyama reagent for the simple conversion of aldehyde and mercaptoacetic acid into the corresponding 1,3-oxathiolan-5-one is described. The transformation can be achieved in DMF and the method provides rapid and easy access to 1,3-oxathiolan-5-one compounds in good to excellent yields without any chromatographic purification.

Keywords: 1,3-oxathiolan-5-one, Mukaiyama reagent, One pot synthesis.

Introduction

1,3-oxathiolan-5-ones represent high value class of compounds in organic chemistry area, which has a wide range of biological properties. They are also used as an intermediates in the synthesis of many bioactive compounds.¹ The derivatives of 2-(hydroxyl-methyl)- 1,3-oxathiolan-5-ones can be used as building blocks for the preparation of the oxathiolanyl-nucleoside Coviracil²⁻⁴. 1,3-oxathiolan-5-ones have posses wide range of biological activities such as antiviral,⁵ anticonvulsant,⁶ antiulcer⁷ and antifungal activity.⁸ In addition, they also showed anti-HIV and anti-HBV activity,⁹ and oxathiolanes act both as agonists¹⁰⁻¹² and antagonists on muscarinic receptors. 1,3-oxathiolan-5-ones uses as herbicides,¹³ plant growth regulators,¹⁴ or enzymes inhibitors¹⁵.

1,3-oxathiolan-5-ones were synthesized one pot condensation of carbonyl compound and mercaptoacetic acid using PTSA¹⁶ or two step synthesis using ZnCl_2 ¹⁷. 2-Methyl-2-phenyl-1,3-oxathiolan-5-ones is prepared form acetophenone and mercaptoacetic acid in good yields using LiBr as a catalyst.¹⁸ 1,3-oxathiolan-5-ones was also prepared by using dimethyltin-diiodide-HMPTA complex¹⁹ and molecular iodine in [bmim][BF₄]²⁰. These types of reagents have some limitations such as high temperature, longer reaction time, and corrosive, expensive, hazardous reaction condition as well as chromatographic purification requires.

Materials and Methods

All reagents were purchased from commercial suppliers and used without further purification. Dry DMF and diethyl ether were purchased from Aldrich and were used as such. All reactions were run in oven-dried round bottom flask containing a Teflon-coated stir bar and sealed with septum. Analytical thin layer chromatography was carried out on silica pre-coated glass

plates (Silica gel 60 F254, 0.25 mm thickness) and visualized with UV light at 254 nm. ¹H NMR spectra were recorded on Bruker 400-MHz Ultrashield Advance II 400 model (400 and 100 MHz, respectively) at ambient temperature with CDCl₃ or DMSO-d₆ as solvents. Data for ¹H are recorded as follows: δ chemical shift (ppm), multiplicity (s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet), coupling constant (Hz), integration. Spectra were referenced internally to the residual proton resonance in CDCl₃ (δ 7.26 ppm), DMSO-d₆ (δ 2.50 ppm) or with tetramethylsilane (TMS, δ 0.00 ppm) as the internal standard. Chemical shifts (δ) were reported as part per million (ppm) in δ scale downfield from TMS. Liquid chromatography/mass spectrometry (LC/MS) data was obtained to verify molecular mass and analyze purity of products. The specifications of the LC/MS instrument are the following: Electrospray (+) ionization, mass range of 100-1000 Da, 20V cone voltage, Acquity BEH C-18 column (2.1 x 100mm, 1.7 μ m), and gradient mobile phase consisting of 5 mM ammonium acetate in water and acetonitrile, and a flow rate of 0.5 mL/min.

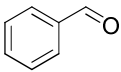
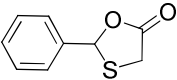
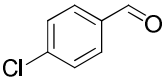
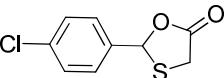
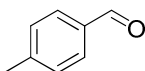
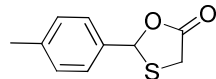
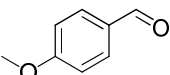
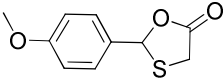
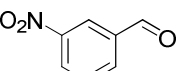
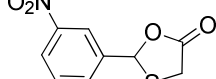
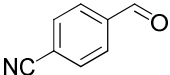
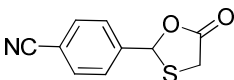
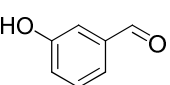
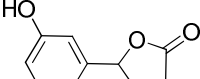
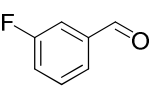
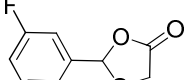
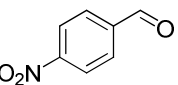
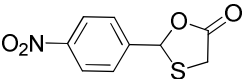
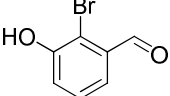
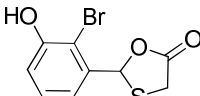
Experimental procedure for the synthesis of 1,3-oxathiolan-5-one: A 50 mL RBF equipped with magnetic stirring bar under nitrogen atmosphere was charge with aldehyde (200 mg scale) (1.0 mmol), mercaptoacetic acid (1.1 mmol), then DMF (10 mL) was added via syringe at room temperature and the mixture was stirred for 5 min. Triethyl amine (1.5 mmol) was then added to the above reaction followed by addition of mukaiyama reagent (1.5 mmol).

The reaction was stirred at room temperature for 0.5-1.5 h when TLC showed complete conversion of starting aldehyde. The reaction mixture was quenched by ice water to occur solid. The resulting solid was collected by filtration and washed with ice water. The solid was then washed with ice cooled diethyl ether to afford 1, 3-oxathiolan-5-ones.

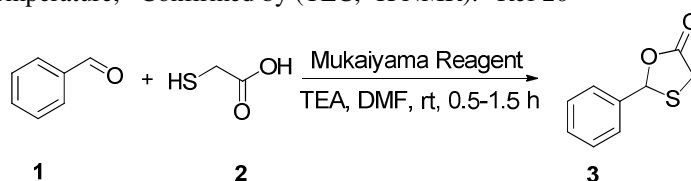
2-Phenyl-1,3-oxathiolan-5-one (Table-1, Entry 1): (326 mg, 96 %) as a white solid, R_F 0.5 (1:9 ethyl acetate–hexane); δ_H (400 MHz; $CDCl_3$) 7.40-7.47 (5H, m), 6.47 (1H, s), 3.87 (1H, d, $J=16.4$), 3.76 (1H, d, $J=16.8$); LCMS: m/z $[M+]$ calculated for $C_9H_8O_2S$: 180.91, found: 181.22.

2-(4-Chlorophenyl)-1,3-oxathiolan-5-one (Table-1, Entry 2): (290 mg, 95 %) as a white solid, R_F 0.6 (1:9 ethyl acetate–hexane); δ_H (400 MHz; $CDCl_3$) 7.39 (4H, d, $J=2.4$), 6.40 (1H, s), 3.86 (1H, d, $J=16.4$), 3.75 (1H, d, $J=16.4$); LCMS: m/z $[M+]$ calculated for $C_9H_7ClO_2S$: 214.99, found: 215.03.

Table-1
Synthesis of 1,3-oxathiolan-5-one derivatives ^{a,b}

Entry	Aldehyde	Time (h)	Product	Yield (%)
1		0.5		96 ^c
2		0.5		95 ^c
3		1.0		88
4		1.0		86
5		1.5		89
6		1.5		85
7		1.5		80
8		1.0		83
9		1.0		87
10		1.5		81

^a Reaction condition: 1.0 mmol of aldehyde, 1.1 mmol of mercaptoacetic acid, 1.5 mmol of mukaiyamaa reagent and 1.5 mmol of triethyl amine in DMF at room temperature, ^b Confirmed by (TLC, 1H NMR). ^c Ref 20



Scheme-1
Proposed approach to the synthesis of 1,3-oxathiolan-5-one

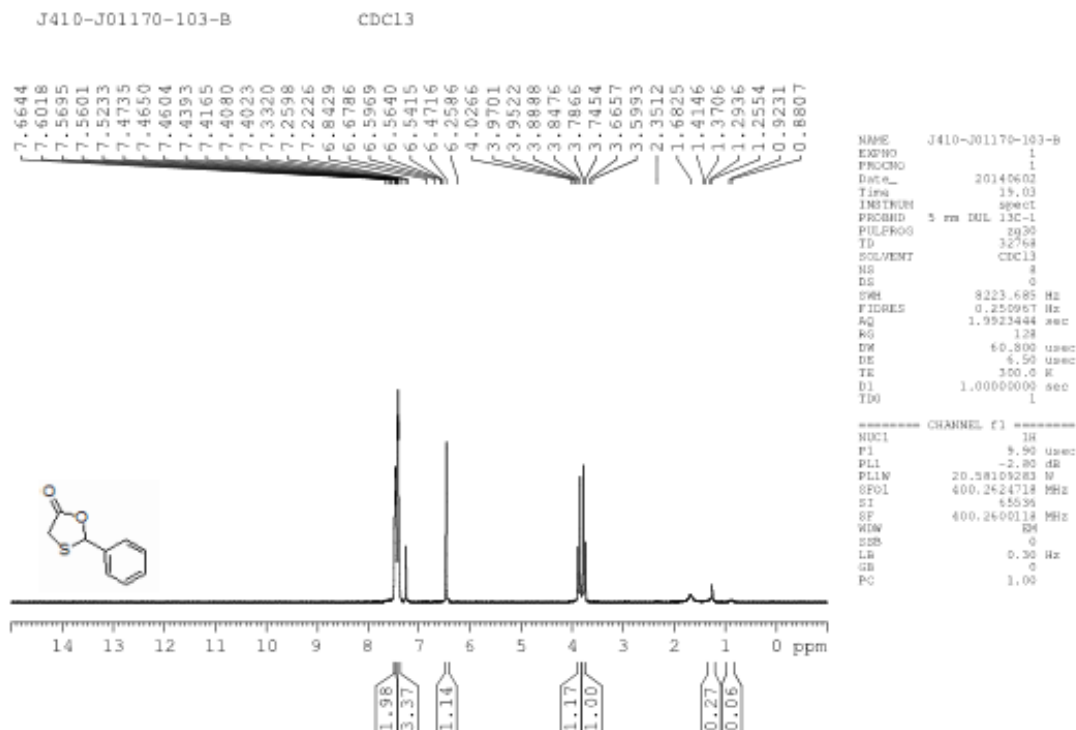


Figure-1
Proton NMR of 2-Phenyl-1,3-oxathiolan-5-one

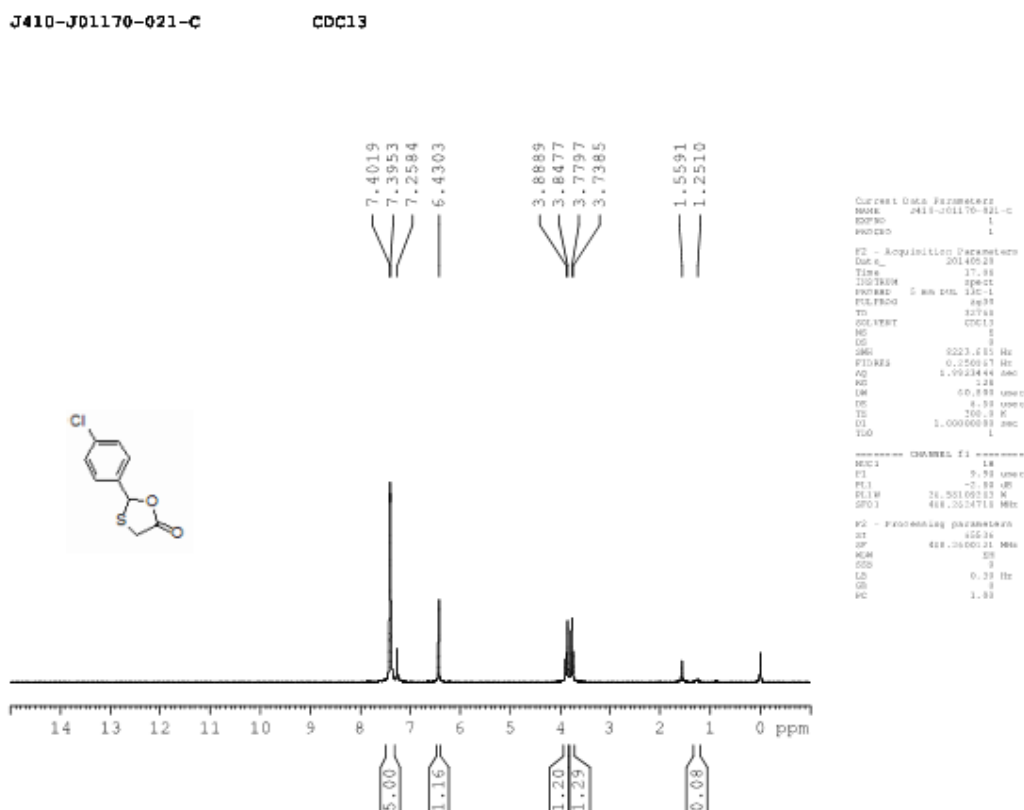


Figure-2
Proton NMR of 2-(4-Chlorophenyl)-1,3-oxathiolan-5-one

Results and Discussion

We believe a different procedure for 1,3-oxathiolan-5-ones synthesis from aldehydes and mercaptoacetic acid using Mukaiyama reagent to avoid by-product and are easily separable from the product. Mukaiyama reagent is one such efficient alternative as it is soluble in most organic. Mukaiyama reagent is an excellent reagent which activate of carboxylic acids to form esters, amides and lactones²¹⁻²³. Mukaiyama reagent keeps the same high reactivity as the other reagents used for the synthesis of esters, amides and lactones. At the same time, it provides simple and quick removal of pyridinium salt and its pyridine making the isolation of desired product much easier. Activation of carboxylic acid is rapid, and is typically complete in less than five minutes. This active ester is then reacting with alcohol to form the ester. Mukaiyama reagent has been used for the synthesis of 1, 3-oxathiolan-5-one because it is easily available, nontoxic and cheap and can be separated easily from the product. In this article, we describe mukaiyama reagent is novel system for 1,3-oxathiolan-5-one synthesis using one pot condensation of aldehyde and mercaptoacetic acid. The reactions are quick and no work up requires which makes it clean and excellent alternative to other procedures and is feasible for parallel synthesis of large number of compounds. At initial stage, we started our work using benzaldehyde, thioglycolic acid and triethylamine keeping in mind that mukaiyama reagent may provide assistance in removal of water in the final step of the condensation to afford 1,3-oxathiolan-5-one compound. In a general, the reaction of mercaptoacetic acid and benzaldehyde using mukaiyama reagent and triethyl amine in DCM afforded 1,3-oxathiolan-5-one in 46% yield. After the success in DCM, we tried various solvents and the results are shown in Table-2.

Table-2
Effect of various solvents^{a,b}

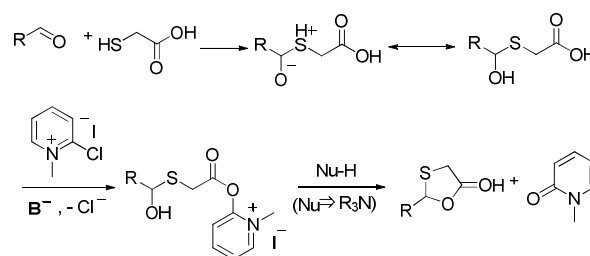
Entry	Solvent	Time (h)	Yields (%)
1	DCM	12	46
2	DCE	15	32
3	CAN	16	30
4	THF	10	55
5	DMF	0.5	96

^a yields are after purification of the compounds, ^b Confirmed by (TLC, ¹H NMR).

The reaction was very slow in DCM and only 46% product formation was observed. Lower yield of product were obtained when DCE, ACN and THF was used as solvent. This suggests that DCM, DCE, ACN and THF are not suitable solvents for the preparation of 1,3-oxathiolan-5-one. The reaction yields were

the excellent when DMF was used as solvent. The easy availability, low cost and no purification added advantage and was the solvent of choice for the further reactions (Scheme-1). After getting the result, we generalized the reaction using different aldehydes and observed the corresponding products in excellent yields (Table-1). The scope of the reaction was tested by treating benzaldehyde, mercaptoacetic acid and triethyl amine using mercaptoacetic acid in DMF at room temperature (Table-1, Entry-1). The reaction was very clean at room temperature and completed within 0.5 h. Different aldehyde reacted with mercaptoacetic acid in the presence of mukaiyama reagent and triethyl amine in DMF to give corresponding 1,3-oxathiolan-5-one with best yields (Table-1)²¹. In all cases, the reaction proceeded fast with high efficiency. Therefore mukaiyama reagent is an excellent reagent for the synthesis of 1,3-oxathiolan-5-one. The proposed reaction mechanism is shown (Scheme-2) and the results obtained hereby mentioned (Table-1).

The attack of nucleophilic thiol group on electrophilic carbon of carbonyl group is slight exothermic and the rate determining step in the synthesis 1,3-oxathiolan-5-one. Second step is highly exothermic. As the first step was completed, triethyl amine and mukaiyama reagent were added to the reaction mixture. At this stage mukaiyama reagent was completely insoluble in reaction mixture. After short time exotherm observed and the solubility of mukaiyama reagent was increases. Finally the clear solution indicates the completion of reaction. We tried the reaction at cooling, but it will take time to complete.



Scheme-2

Proposed mechanism of the reaction of the one-pot synthesis of 1,3-oxathiolan-5-one derivatives using mukaiyama reagent

Conclusion

Mukaiyama reagent is nontoxic and easy to handle; that is why it is an excellent reagent for the synthesis of 1,3-oxathiolan-5-one in a short time, without heating and any chromatographic purification. It will be interesting to observe that these modifications can be utilized as potent therapeutic agents in future.

Acknowledgment

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