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Innate synthesis of 1,3-oxathiolan-5-one derivatives & its antimicrobial potential

Deepak Kumar Kashyap[a,b*], Narva Deshwar Kushwaha[a,b], Jyotsna Gupta[a], Kamalesh K. Verma[b] and Mahesh Srivastav[b]

[a]*Department of Chemistry, NIMS University Sobha Nagar Jaipur (Rajasthan), India*
[b]*Department of Chemistry, Meerut College, Meerut (U.P.), India*

ABSTRACT

Hetrocyclic systems are one of the most important classes of organic compounds present in nature or synthesized in laboratory. These compound posses several interesting biological activity and are imployed in the treatment of various commonly occurring diseases. The biological significance of the 1, 3-oxathiolan-5-one derivative has promoted us to synthesize a series of its analogical derivative. In continuation of interest on the synthesis of 1,3-oxathiolan-5-one derivatives herein an easy, practical and efficient cost effective ,time saving procedure for the synthesis of 1,3-oxathiolan-5-one derivatives by using aromatic aldehyde, mercaptoacetic acid dehydrating/ cyclising agent. All the compounds have been screened for their antimicrobial activity against three Gram -ve bacteria (Eschericha Coli, Staphylococcus aureus and Klebsiella pneumoniae three Gram +ve(Seratia reticulata, Bacillus subtilis and Streptococcus pneumoniae) and two fungal strains (P. aeruginosa and C.albicans). In the primary screening, the compounds exhibited appreciable activity. The structures of the synthesized compounds 3a-3l have been established on the basis of elemental analysis and spectral data.

Key words: 1,3-oxathiolan-5-one, cyclocondensation reaction, antimicrobial activity

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INTRODUCTION

Heterocyclic systems are one of the most important classes of organic compounds present in nature or synthesized in laboratory. These compound posses several interesting biological activity. Indeed, one of the richest sources of diversity for the medicinal chemist are small heterocyclic rings, which in addition to often exhibiting biological activity, may serve as rigid scaffolds for further display of functionalities[1]. Oxathiolan-5-one derivatives are of great interest because they exhibit a broad spectrum of biological activities and are important heterocycles occurring in natural and medicinal molecules. They are intermediates in the synthesis of many bioactive compounds [2]. To exemplify, derivatives of 2-(hydroxy-methyl)-1, 3-oxathiolan-5-ones can be used as building blocks for the preparation of the oxathiolanyl-nucleoside Coviracil [3-5]. 1, 3-Oxathiolane/1, 3-oxathianes are one such class of heterocycles which have attracted much attention as they have been reported to possess a wide range of biological activities, including antiviral, [6] anticonvulsant, [7] antiulcer [8] and antifungal activity[9]. In addition, they also showed anti-HIV and anti-HBV activity [10] and oxathiolanes act both as agonists [11–13] and antagonists on muscarinic receptors. Cevimeline (*cis*-2-methylspiro [1, 3-oxathiolane-5, 3'-quinuclidine hydrochloride) is a selective M1 receptor agonist.

A brief overview of literature showed that various protocols have been developed for the synthesis of 1,3-oxathialane-5-one but they have various technical limitation such as long reaction time, difficult workup, and formation of over-oxidation products leading to lower yields, requirements of strong oxidizing agents, strong acidic or basic media, prolonged heating using benzene [14] and the catalysts p-toluenesulfonic acid (*p*-TSA) [15] the dimethyltin diiodide–HMPTA complex [16], use of expensive, toxic, and explosive LiBr [17], molecular iodine in [bmim][BF4] ionic liquid [18], zinc chloride [19]. Thus there is an inevitable need to develop an effective ,efficient and cost effective synthetic procedure for synthesizing 1,3-oxathiolan-5-one derivatives which should be capable to overcome the above mentioned limitations. In continuation of interest on the synthesis of 1,3-oxathiolan-5-one derivatives herein an easy, practical and efficient cost effective ,time saving procedure for the synthesis of 1,3-oxathiolan-5-one derivatives by using dehydrating/cyclising agent dicyclohexylcarbodimide (DCC). In a general reaction, treatment of aromatic aldehyde with mercaptoacetic acid in THF in the presence of triethylamine and DCC afforded 2- (substituted aryl or alkyl) - 1, 3-oxathiolan-5-one derivatives with higher yields.

EXPERIMENTAL SECTION

Chemistry

Melting points of all the compounds were determined in open capillary tubes and are uncorrected. Thin layer chromatography was performed using TLC silica gel 60 F_{254} Merck and spots were visualized by exposure to UV light. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker NMR (400 MHZ) spectrophotometer in using TMS as internal standard chemical shifts recorded ppm). The mass spectra of synthesised compounds were recorded on XEVO QTOF and Thermo LCQ Advantage Max Ion Trap spectrometers. Elemental microanalyses were performed on a Carlo-Erba 1108 CHN analyzer.

General procedure for compounds (1, 3-oxathiolan-5-one derivatives) 3a-3l:

To the ice cooled solution of appropriate aldehyde (1.0 mmol) in THF was added triethylamine (3.0 mmol) followed by addition of mercaptoacetic acid (3.0 mmol). After 5 min DCC(1.2mmol) was added to the reaction mixture at 0^{o}C and the reaction mixture stirred for an additional 60 min at room temp. DCU was removed by filtration and the filtrate was concentrated to dryness under reduced pressure to get a crude product that was purified by column chromatography on silica gel using hexane–ethyl acetate as eluent.

Table 1: Antimicrobial activity of synthesized 1,3-oxathiolan-5-one derivatives

Sample	Zone of Inhibition in mm							
	Bacterial Strain						Fungal Strain	
	E.Coli	*S.aureus*	*K.pneumoniae*	*S.reticulata*	*B.subtilis*	*S.pneumoniae*	*P.aeruginosa*	*C.albicans*
3a	15	8	6	15	14	10	4	4
3b	7	11	12	8	16	-	3	5
3c	3	7	-	-	14	11	8	7
3d	8	4	13	11	12	12	-	-
3e	**19**	**23**	**20**	**21**	**19**	**16**	12	9
3f	11	7	14	12	8	-	14	14
3g	8	-	4	16	-	9	11	12
3h	**18**	**24**	**19**	**22**	**21**	**17**	13	11
3i	12	10	8	7	6	8	**16**	**17**
3j	9	7	12	13	8	7	11	13
3k	4	3	-	-	11	13	7	12
3l	-	-	4	2	-	-	2	1
Ampicillin	22	30	22	25	22	20	19	21
DMF	-	-	-	-	-	-	-	-

Biological Screening:

All the synthesized compounds were subjected to antimicrobial screening at a concentration of 100µg/ml involving three Gram -ve bacteria (*Eschericha Coli*, *Staphylococcus aureus* and *Klebsiella pneumoniae*); three Gram +ve (*Seratia reticulata*, *Bacillus subtilis* and *Streptococcus pneumoniae*) and two fungal strains (*P. aeruginosa* and *C.albicans*) using Ampicillin as standard at the same concentration. The work, in reference, was carried out by Agar disc diffusion method [20]. The response of organisms to the synthesized compounds were measured in terms of zone of inhibition and compared with that obtained with standard.

A) Preparation of Mueller Hinton Agar (MHA) Media

Mueller Hinton Agar Media was used for antimicrobial screening and its composition is as:

Casein Acid Hydrolysate	17.50gm
Beef Heart Infusion	2.00gm
Starch, soluble	1.50gm
Agar	17.00gm

For preparing Mueller Hinton Agar (MHA) Media, 38gm of Mueller Hinton Agar No. 2 was dissolved in 1000ml distilled water. It was mixed properly and heated to boil to dissolve the medium completely. It was autoclaved at 15lbs pressure (121°C) for 15 minutes. It was than cooled and poured into sterilized plates. All the plates were kept for 4-5 hours in laminar airflow until the media got solidified. The plates were than kept in an incubator at 37°C.

B) Preparation of standard antibiotic solution

A solution (100µg/ml) of standard drug (Ampicillin) was prepared in sterile water.

C) Preparation of Test solution

10 mg of the synthesized compound(s) was dissolved in 10 ml of DMF. 1 ml of this solution was taken and diluted to 10 ml (with DMF) so that the concentration of the test solution became 100µg/ml.

D) Preparation of inoculums

For the preparation of inoculums, 5g of nutrient agar was dissolved in 100 ml of distilled water and the pH was adjusted at 7.2 ± 0.2. It was poured in test-tubes as per requirement and then sterilized by autoclaving at 121°C. A 24 hour old culture was used for the preparation of bacterial suspension. Likewise suspensions of all the organisms were prepared as per standard procedure.

E) Preparation of discs

Discs of 6-7 mm in diameter were punched from No. 1 Whattmann filter paper with sterile cork borer of same size. These discs were sterilized by keeping in oven at 140°C one hour. Standard and test solutions were added separately to these discs which were air dried later on.

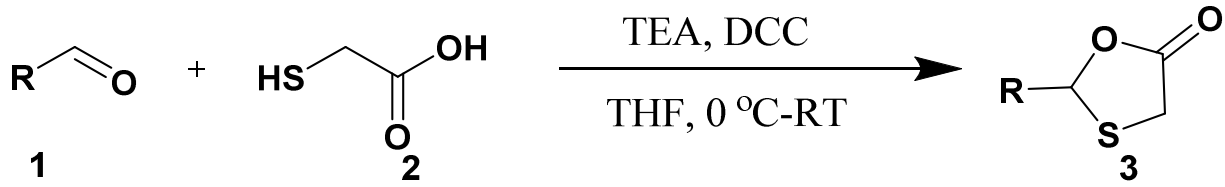
F) Method of testing

Inoculums were added to the prepared media plates and allowed to solidify. The previously prepared discs were carefully kept on the solidified media by using sterilized forceps. These petridishes were kept for one- hour diffusion at room temperature and then for incubation at 37°C for 24 hours in an incubator. The zones of inhibition after 24 hours were measured in millimeters. The results obtained are shown in Table 2 and Table 3

RESULTS AND DISCUSSION

In the present research work twelve 2- (substituted aryl or alkyl) - 1, 3-oxathiolan-5-one derivatives were synthesized by using aldehyde and mercaptoacetic acid and evaluated its antimicrobial potential.

In a general reaction, treatment of appropriate aryl or alkyl aldehyde with mercaptoacetic acid in THF followed by addition Triethylamine (TEA) and Dicyclohexylcarbodiimide (DCC) afforded substituted 1,3-oxathiolan-5-one in 92% yield (Scheme:1). Reaction required very short duration, 30 minutes for completion of reaction and gave better yield as compared to conventional synthesis.

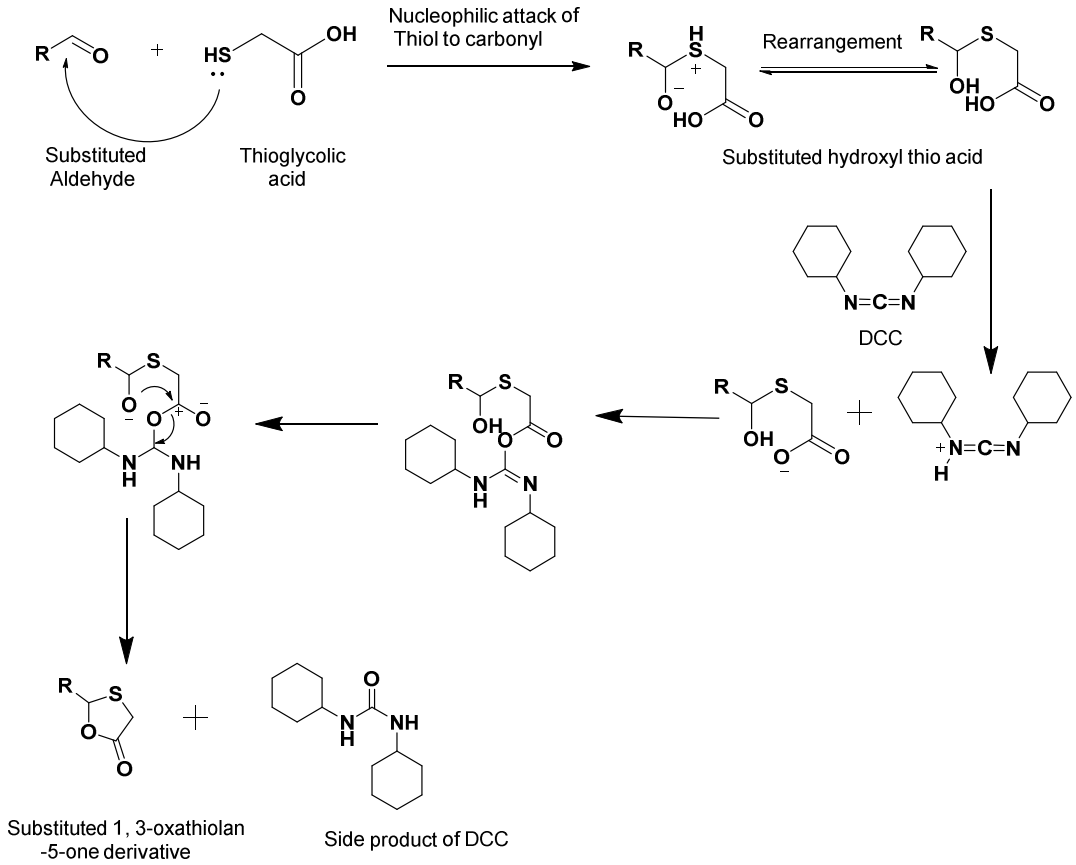


R= Phenyl,Substituted phenyl, Substituted pyridyl,cycloalkyl

Scheme-1: General scheme for the Synthesis of title compound

This cyclocondensation reaction is two-step reaction. The first step involves nucleophilic attack of thiol group of thioglycolic acid on carbon oxygen double bond of carbonyl group of substituted aldehydein the presence of triethylamine (TEA) giving the intermediate Substituted hydroxyl thio acid which on elimination of water molecule in the presence of dicyclohexy carbodiimide (DCC) gives substituted 1,3-oxathiolan-5-one derivatives and side product of DCC i.e. substituted dicyclohexyl urea which is insoluble in water as well as in organic solvent that can be easily removed by simple filtration. The suggested mechanism for cyclocondensation reaction shown in Scheme-2.

Scheme-2: The suggested mechanism for the formation of the title compounds

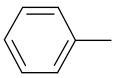
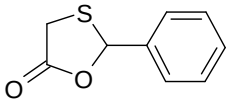
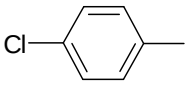
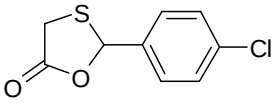
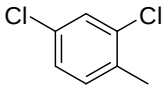
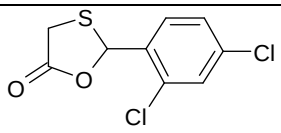
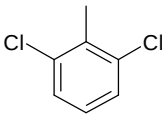
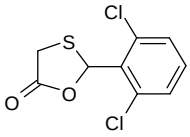
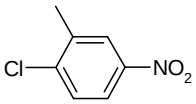
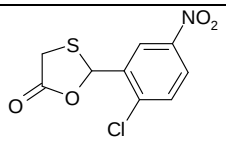
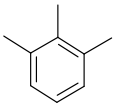
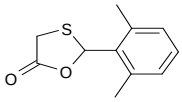
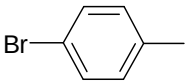
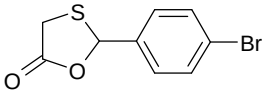
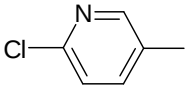
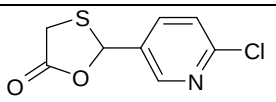
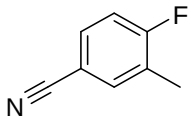
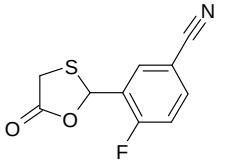
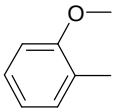
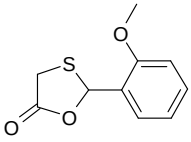
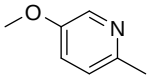
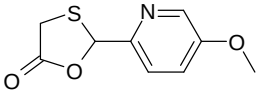
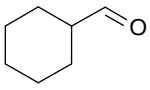
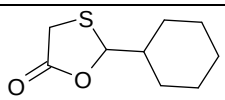


Moreover, in general, the desired compounds obtained in a single step with high yield. This has been noticed so far, that the modifications on 1,3-oxathiolan-5-one moiety could display valuable biological activities and these modifications can be utilized to develop potentially active agents in future. Thus, the many more modifications on 1,3-oxathiolan-5-one moiety needs to be continued. An effort was made to synthesize a novel series of 1,3-oxathiolan-5-one derivatives of pharmaceutical interest by condensing the substituted aldehyde and thioglycolic acid. Thus series of 1,3-oxathiolan-5-one were prepared by using above discussed methodology which are shown in Table:2.

The structures of the products **3a-3l** were established by spectral and elemental analysis. The structural elucidations of the products were based on their spectral (1H NMR and mass) data as given below.

2-phenyl-1, 3-oxathiolan-5-one (3a):
Analysis Calculated for **C9H8O2S**: C, 59.98 %; H, 4.47 %; O, 17.75 %; S, 17.79 %. Found: C, 59.99 %; H, 4.49 %; O, 17.78 %; S, 17.81 %. 1H-NMR (400 MHz, CDCl3, TMS / ppm) δ: 3.76 (1H, *d*, *J* = 16.4 Hz, CH2), 3.87 (1H, *d*, *J* = 16.4 Hz, CH2), 6.47 (1H, s, CH), 7.40-7.48 (5H, *m*,).MS (*m*/*z*): 181.

Table-2: Synthesis of 1, 3-oxathiolan-5-one derivatives

SN	Compound	R	Product	Molecular Formula	M.P. (°C)	Yield (%)
1	3a			C9H8O2S	88	86
2	3b			C9H7ClO2S	134	83
3	3c			C9H6Cl2O2S	169	88
4	3d			C9H6Cl2O2S	165	87
5	3e			C9H6ClNO4S	-	72
6	3f			C11H12O2S	138	90
7	3g			C9H7BrO2S	165	84
8	3h			C8H6ClNO2S	181	94
9	3i			C10H6FNO2S	184	77
10	3j			C10H10O3S	130	89
11	3k			C9H9NO3S	188	90
12	3l			C9H14O2S	81	91

2-(6-chloropyridin-3-yl)-1, 3-oxathiolan-5-one (3h):

Analysis Calculated for **C8H6ClNO2S**: C, 44.56 %; H,2.80 %; Cl, 16.44 %; N, 6.49 %; O, 14.84 %; S, 14.87 %. Found: C,44.58 %; H, 2.84 %; Cl, 16.47 %; N, 6.51 %; O, 14.86 %; S, 14.88 %. 1H-NMR (400 MHz, CDCl3, TMS/

ppm) δ: 3.78 (1H, *d*, *J* = 16.8 Hz, CH2), 3.90 (1H, *d*, *J* = 16.8 Hz, CH2), 6.48 (1H, s, CH), 7.41(1H, *d*, *J* = 8.4 Hz, CH), 7.797-7.824 (1H, *dd*, *J* = 2.4 Hz, CH), 8.47 (1H, *d* ,1H,).MS (*m*/*z*): 216.

All synthesized compounds have been screened for their antimicrobial potential. From the antimicrobial screening results it was observed that the presence of electron withdrawing group made the compounds to exhibit moderate to significant activity in comparison to standard drug Ampicillin. Compound **3e** and **3h** exhibited promising antibacterial activity while compound **3i** exhibited promising antifungal activity. However other compounds of the series also exhibited moderate to significant activity against the microorganisms as mentioned above.

CONCLUSION

We have innovated a relatively effective and efficient method for synthesizing 1, 3-oxathiolane-5-one by using simple and cost effective reagents. Due to the simplicity of the conditions, high yields and purity of the products, the above mentioned methodology should find utility in organic synthesis. In addition, this method is safer; it avoids the use of toxic or hazardous solvents. The results of antimicrobial screening of synthesized compound established the fact that 1, 3-oxathiolan-5-one substituted with various aldehydes (substituted) can be studied further to explore out newer antimicrobial compounds based on 1, 3-oxathiolan-5-one scaffold .

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