

Organic & Supramolecular Chemistry

DBU-Mediated Intermolecular 5-exo-dig Cyclization of Propargyl Alcohols and Carbon Disulfide to [1,3]-Oxathiole-2-thiones

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5-exo-dig is a versatile Baldwin tool to predict and make useful heterocyclic compounds from nucleophiles and electrophiles. In order to aid this, a novel metal-free method is proposed to produce [1,3]-oxathiole-2-thiones from a readily synthesized propargyl alcohols and easily accessible carbon disulfide, where

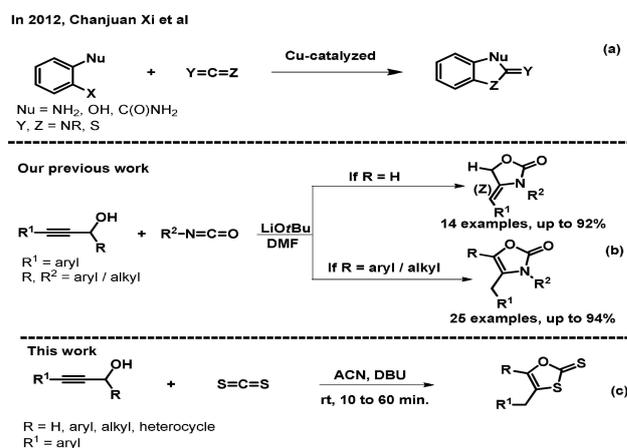
both secondary and primary propargyl alcohols are compatible to this methodology. This procedure is simple, versatile, atom economy and functional group tolerance resulting in moderate to excellent yields. Finally, the process was screened on different mode of reaction operation.

Introduction

The 5-exo-dig cyclization^[1] is commonly encountered methodology for making regio-specific five-membered cyclic compounds: till date, huge number of heterocyclic compounds^[2] have been synthesized *via* Baldwin rule under metal catalytic conditions. However metal mediated 5-exo-dig cyclization of sulfur containing moiety is inefficient as it poisons the catalysis quickly. Thus metal-free approach is more appropriate for making sulfur containing heterocyclic compounds, such as [1,3]-oxathiole-2-thione. [1,3]-Oxathiole-2-thione is a unique molecule due to its wide spread applications in graft terpolymerization, cationic polymerization/depolymerization,^[3] coatings, sealants, primers, and adhesion promoters of various metallic and non-metallic materials.^[4] Additionally, organic molecules bearing such subunits have also shown significant pharmaceutical or biochemical activities.^[5] Despite its vital application in chemical industries, there is a critical demand to find simple straight forward reactions to make a variety of substituted [1,3]-oxathiolane-2-thione derivatives.

In general, sulfur containing heterocycles are easily synthesized from carbon disulfide (CS₂): representative examples are isothiocyanate, di (or) trithiocarbonates,^[6] dithiocarbamates,^[7] mercaptobenzothiozoles, thiourea and triazole.^[8] The central carbon of heteroallene (CS₂) is an effective electrophile and could easily be coupled with nucleophiles, such as amine,

alcohol and epoxide, on other hand the neighboring sulfur atom becomes nucleophile which might involve in substitution or cyclization reaction.^[9] The domino cyclization^[10] of CS₂ with any of the following compounds, o-halobenzenamines, o-halophenols and o-halobenzamides, deliver benzo-heterocyclic compounds (Scheme 1, a). Here, either alkyne or alkynol is an



Scheme 1. Summary of previous and present works

alternate and versatile reagent for o-halophenol to synthesis cyclic compounds due to its dual nature, both electrophilic and nucleophilic. A number of reports are published on the cyclization of alkyne via 5-exo-dig: for example silver-mediated radical^[11] cyclization of 2-alkynylbenzonitriles produced phosphinylated 1-indenones and enediynes, a similar method also produced benzofulvenes.^[12] Likewise, Pd-catalyzed 5-exo-dig cyclization of alkyl amine^[13] with acid chloride offered excellent yield of switchable oxazolines and oxazoles. Similarly, unsubstituted propargyl alcohols^[14] are heavily used in cyclization due to their ease rearrangement of terminal alkyne, whereas

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only few reports are found on internal propargyl alcohols.^[15] However, till date, no research was carried out by treating internal propargyl alcohols^[16] with CS₂ for synthesizing valuable moieties.

In 2016, we have reported the synthesis of oxazolone-2-ones (Scheme 1, b)^[17] from propargyl alcohols and isocyanate via coupling and 5-*exo*-dig cyclization. Thus, exploring the same methodology on carbon disulfide for synthesizing valuable moieties is of great interest. Here we are disclosing, the DBU base mediated nucleophilic substitutional reaction of propargyl alcohol with carbon disulfide to synthesis [1,3]-oxathiolane-2-thiones (Scheme 1, c).

Results and Discussion

In order to optimize the reaction conditions, 1,3-diphenyl-prop-2-yn-1-ol (**1a**) was taken as the model substrate (Table 1).

Table 1. Reaction optimization					
Entry	Solvent	Base	Temp (°C)/t (h)	% yield of 2a ^a	% yield of 3a ^a
1	DCM	DBU	rt / 1	40	5
2	DCM	DBN	rt / 1	48	10
3	DCM	DABCO	rt / 1	0	0
4	DCM	DABCO	rt / 17	0	0
5	DCM	DIPEA	rt / 1	0	35
6	ACN	DBU	rt / 0.1	88	0
7	DMF	Na ₂ CO ₃	rt / 15	0	0
8	DMF	K ₂ CO ₃	rt / 15	0	46
9	DMF	Cs ₂ CO ₃	rt / 15	0	42
10	DMF	LiOH	rt / 1	15	0
11	DMF	NaOH	rt / 1	22	0
12	DMF	KOH	rt / 0.5	10	0
13	DMF	NaH	rt / 0.5	23	0
14	DMF	NaOEt	45 / 0.5	0	85
15	DMF	NaO ^t Bu	45 / 0.5	0	78
16	DMF	KO ^t Bu	45 / 0.5	25	0
17	DMF	LiO ^t Bu	45 / 0.5	39	0

^aYields of isolated products. DCM=Dichloromethane, ACN=Acetonitrile, DMF=N,N-Dimethyl-formamide, DIPEA=Diisopropyl ethyl amine, DBU=1,8-Diazabicyclo[5.4.0]undec-7-ene, DBN=1,5-Diazabicyclo[4.3.0]non-5-ene, DABCO=1,4-Diazabicyclo[2.2.2]octane, Na₂CO₃=Sodium carbonate, K₂CO₃=Potassium carbonate, Cs₂CO₃=Cesium carbonate, NaOH=Sodium hydroxide, LiOH=Lithium hydroxide, KOH=Potassium hydroxide, NaOEt=Sodium ethoxide, NaO^tBu=Sodium tertiary butoxide, KO^tBu=Potassium tertiary butoxide, LiO^tBu=Lithium tertiary butoxide, NaH=Sodium hydride, rt=room temperature, t=time, h=hour, Temp=temperature.

Initially, it is treated with CS₂ in dichloromethane (DCM) solvent with different organic bases like DBU, DBN, DABCO and DIPEA, where the first two bases only yielded less than 50% of **2a** (Table 1; Entries: 1, 2) and more decomposition was observed when the reaction mixtures were kept overnight. No reaction was noticed when treating with DABCO (Table 1; Entries: 3, 4)

and the reaction with DIPEA offered 35% of **3a** (Table 1; Entry: 5). However, when having DBU as base and changing the solvent as ACN delivered 88% of **2a** (Table 1; Entry: 6). Instead of organic bases, inorganic carbonate bases in DMF solvent were tested and no product of **2a** observed (Table 1; Entries: 7–9). The reaction with metal hydroxide and hydride bases, LiOH, NaOH, KOH and NaH, have only yielded traces of **2a** (Table 1; Entries: 10–13). When treated with NaOEt and NaO^tBu, no cyclized compound was formed (Table 1; Entries: 14, 15). Finally, KO^tBu and LiO^tBu yielded 25% and 39% of **2a**, respectively (Table 1; Entries: 16–17). Thus, the reaction conditions specified in Entry 6, having DBU as base and ACN as solvent can be adjudged as the best optimum reaction conditions.

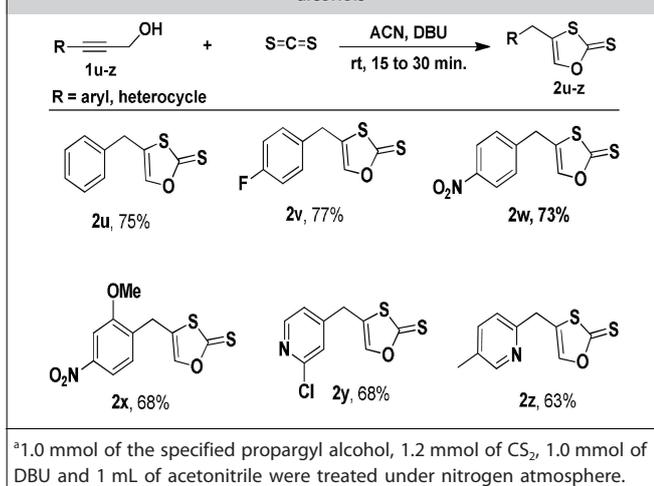
Having the optimum reaction conditions (Table 1; Entry: 6), the reactions between secondary propargyl alcohols and carbon disulfide were focused to synthesis [1,3]-oxathiole-2-thiones (Table 2). At first, **1a** treated with CS₂ under optimum

Table 2. Synthesis of [1,3]-oxathiole-2-thiones from secondary propargyl alcohols ^a				
R = aryl, alkyl, heterocycle R ¹ = aryl				

^a1.0 mmol of the specified propargyl alcohol, 1.2 mmol of CS₂, 1.0 mmol of DBU and 1 mL of acetonitrile were treated under nitrogen atmosphere.

reaction condition delivered 85% of **2a** and the reactions with mono to tri-fluoro substituted aryl propargyl alcohols also observed a relatively equivalent yield of the desired products **2b–2e**. The *p*-chloro or *p*-chloro and *p*-fluoro substituent carrying propargyl alcohols were also efficient and the respective reactions completed with very good yields of **2f–2g**. Similarly, the 2-chloro-5-nitro attached aryl near to –OH group were undergoing 5-*exo*-dig cyclization with CS₂ and producing

Table 3. Synthesis of [1,3]-oxathiole-2-thiones from primary propargyl alcohols^a



very good yields of **2h**^[18]-**2i**. The different positional bromo derivatives also offered equally good yield of the respective compounds (**2j**, **2k** and **2l**). Like electron deficient secondary propargyl alcohols, the electron rich compounds, 3-(4-Fluorophenyl)-1-(2-methoxy-phenyl)-prop-2-yn-1-ol and 3-[3-(4-Fluorophenyl)-1-hydroxy-prop-2-ynyl]-benzoic acid methyl ester, yielded 68% of **2m** and 72% of **2n**. Following the successful synthesis of different aromatic [1,3]-oxathiole-2-thiones, the reactions between CS₂ and the pyridine-substituted propargyl alcohols were studied. Electron deficient, neutral and electron rich heterocyclic propargyl alcohols adhered to the optimum reaction conditions afforded fairly good yields of **2o**-**2s**, which highlights no significant electronic effect. Finally, Aryl alkyl substituted propargyl alcohol; 4-Methyl-1-phenyl-pent-1-yn-3-ol was successfully coupled with CS₂ delivered 70% of **2t**.

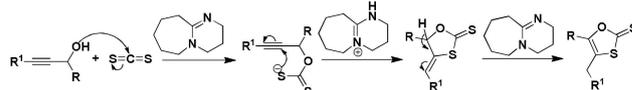
After the above successful synthesis of [1,3]-oxathiole-2-thiones from secondary propargyl alcohols and CS₂, the turn is to demonstrate the synthesis of heterocyclics from primary propargyl alcohols and CS₂ by employing the same optimum reaction conditions which was used for **1a** and CS₂.

The un-substituted and mono-substituted primary propargyl alcohols, 3-Phenyl-prop-2-yn-1-ol and 3-(4-Fluoro-phenyl)-prop-2-yn-1-ol, were separately treated with CS₂ yielded ~75% of **2u** and **2v**, respectively, whereas the nitro-substituted and nitro, methoxy-substituted 3-phenylprop-2-yn-1-ol offered 73% of **2w**^[19] and 68% of **2x**. Finally, electron withdrawing and electron donating substituent attached pyridine propargyl alcohols delivered moderate yields of **2y** and **2z**. At the end, the reaction was carried out in different mode of reaction operation conditions, as pointed in Table 4, and the yields are also captured. The reaction mass was charring in microwave irradiation and Sonicator, whereas clean reaction noticed while exploiting parallel synthesizer with or without nitrogen atmosphere and the open round bottom flask.

The possible reaction mechanism of product: The DBU initially de-protonates the OH of the propargyl alcohol and then the corresponding anion attacks the carbon of CS₂;

Table 4. Screening of different mode of reaction operational conditions

Entry	Reaction operation condition	Temperature/ Time	Product	Yield (%)
1	Microwave irradiation	rt/5 min.	2a/2u	10/5
2	Sonicator	rt/10 min.	2a/2u	32/14
3	Parr shaker without nitrogen atmosphere	rt/30 min.	2a/2u	76/71
4	Parallel synthesizer with nitrogen atmosphere	rt/30 min.	2a/2u	72/63
5	Parallel synthesizer without nitrogen atmosphere	rt/30 min.	2a/2u	70/60
6	Open round bottom flask	rt/30 min.	2a/2u	68/64



Scheme 2. Possible reaction mechanism

subsequently the sulfur anion of CS₂ cyclizes (5-*exo*-dig) with the triple bonded carbon-2, and then carbon-3 carbanion captures the proton formed 4-alkene-1,3-oxathiolane-2-thione as intermediate. The *exo*-cyclic double bond is rearranged into the cyclic ring forming [1,3]-oxathiole-2-thione. The earlier research by authors, i.e., synthesis of oxazolone-2-ones¹⁷ by reacting heteroallene (isocyanate) with secondary propargyl alcohol evolved via coupling, cyclization and rearrangement of *exo*-cyclic double bond whereas primary propargyl alcohol only undergoes for coupling and cyclization. However, interestingly in CS₂ both the propargyl alcohols undergoes the coupling, 5-*exo*-dig cyclization and *exo*-cyclic double bond migration to reach [1,3]-oxathiole-2-thiones.

Conclusions

We have established a novel metal free straight forward synthesis of [1,3]-oxathiole-2-thiones from readily prepared propargyl alcohols using easily and cheaply available reagents CS₂ and DBU, and the optimised process was tested on different mode of operational conditions instead of traditional round bottom flask reaction. This atmospheric temperature and non-hazardous solvent reactions were producing very good yields of different substituted [1,3]-oxathiole-2-thiones, and there is no considerable impact of electronic effects and aryl or heteroaryl substituent effects on the reaction yields.

Supporting information Summary

Detailed experimental procedures and spectroscopic data, copies of ¹H and ¹³C NMR spectra of all compounds and ortep for **2h** and **2w** are included in the supporting information.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Carbon disulfide · Double bond rearrangement · 5-exo-dig · [1,3]-Oxathiole-2-thione · Propargyl alcohol

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- [19] CCDC 1812465 (2 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif)

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