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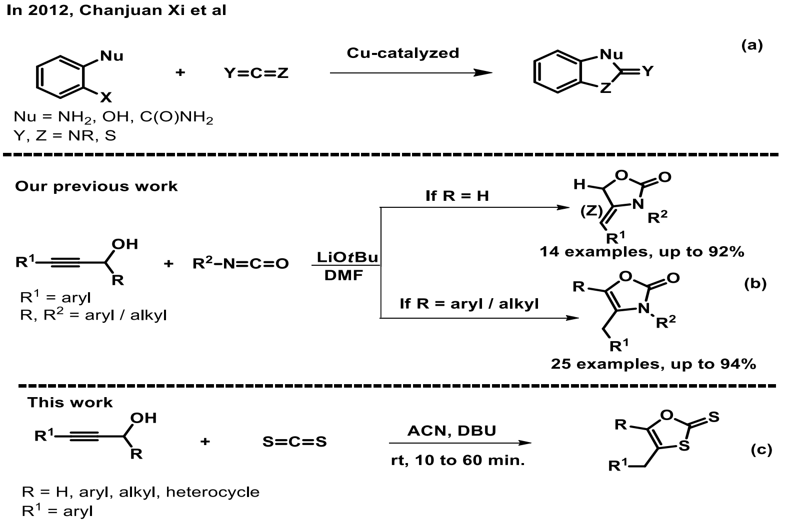
DBU-Mediated Intermolecular 5-exo-dig Cyclization of Propargyl Alcohols and Carbon Disulfide to [1,3]-Oxathiole-2-thiones

Sebastian Antony Savarimuthu,*[a] Devarajan Gnanaprakasi Leo Prakash,*[b] Selvaraj Augustine Thomas[a] and Thirumanavelan Gandhi[c]

Abstract: 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.



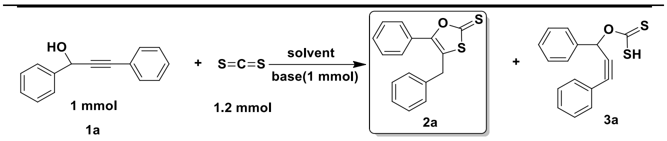
Scheme 1: Summary of previous and present works

In general, sulfur containing heterocycles are easily synthesized from carbon disulphide (CS_2): representative examples are isothiocyanate, di (or) trithiocarbonates,[6] dithicarbamates,[7] mercaptobenzothiozoles, thiourea and triazole.[8] The central carbon of heteroallene (CS_2) 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 CS_2 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 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, un-substituted propargyl alcohols[14] are heavily used in cyclization due to their ease rearrangement of terminal alkyne, whereas 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 CS_2 for synthesizing valuable moieties.

In 2016, we have reported the synthesis of oxazolon-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 disulphide 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

Table 1: Reaction optimization

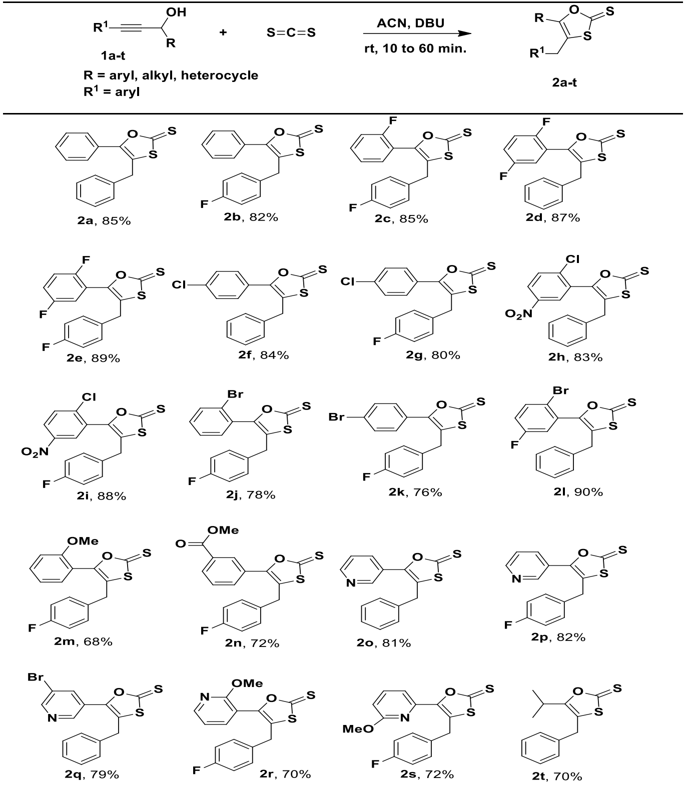


Entry	Solvent	Base	Temp (°C)/t (h)	% yield of **2a**[a]	% yield of **3a**[a]
1	DCM	DBU	rt / 1	40	5
2	DCM	DBN	rt / 1	48	10
3	DCM	DABCO	rt / 1	0	0
4	DCM	DABCO	rt / 17	0	0
5	DCM	DIPEA	rt / 1	0	35
6	ACN	DBU	rt / 0.1	88	0
7	DMF	Na_2CO_3	rt / 15	0	0
8	DMF	K_2CO_3	rt / 15	0	46
9	DMF	Cs_2CO_3	rt / 15	0	42
10	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

[a]Yields of isolated products. DCM = Dichloromethane, ACN = Acetonitrile, DMF = N,N-Dimethyl-formamide, DIPEA = Diisoprophyl 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, Na_2CO_3 = Sodium carbonate, K_2CO_3 = Potassium carbonate, Cs_2CO_3 = Cesium carbonate, NaOH = Sodium hydroxide, LiOH = Lithium hydroxide, KOH = Potassium hydroxide, NaOEt = Sodium ethoxide, NaO^{t}Bu = Sodium tertiary butoxide, KO^{t}Bu = Potassium tertiary butoxide, LiO^{t}Bu = Lithium tertiary butoxide, NaH = Sodium hydride, rt = room temperature, t = time, h = hour, Temp = temperature.

In order to optimize the reaction conditions, 1,3-diphenyl-prop-2-yn-1-ol (**1a**) was taken as the model substrate (Table 1). Initially, it is treated with CS_2 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^{t}Bu, no cyclized compound was formed (Table 1; Entries: 14, 15). Finally, KO^{t}Bu and LiO^{t}Bu 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.

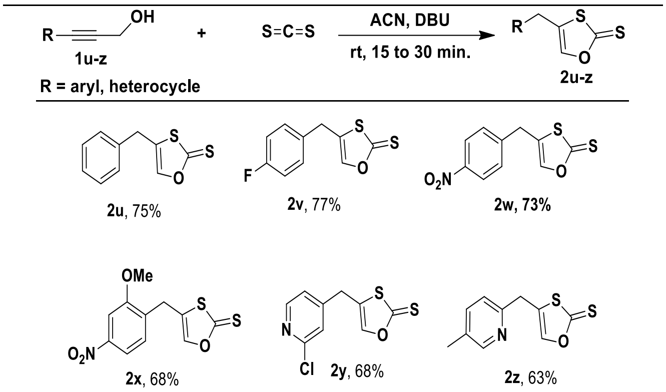
Table 2: Synthesis of [1,3]-oxathiole-2-thiones from secondary propargyl alcohols[a]



[a]1.0 mmol of the specified propargyl alcohol, 1.2 mmol of CS_2, 1.0 mmol of DBU and 1 mL of acetonitrile were treated under nitrogen atmosphere.

Having the optimum reaction conditions (Table 1; Entry: 6), the reactions between secondary propargyl alcohols and carbon disulphide were focused to synthesis [1,3]-oxathiole-2-thiones (Table 2). At first, **1a** treated with CS_2 under optimum 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 CS_2 and producing 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-Fluoro-phenyl)-1-(2-methoxy-phenyl)-prop-2-

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



[a]1.0 mmol of the specified propargyl alcohol, 1.2 mmol of CS_2, 1.0 mmol of DBU and 1 mL of acetonitrile were treated under nitrogen atmosphere.

yn-1-oland3-[3-(4-Fluoro-phenyl)-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 CS_2 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 CS_2 delivered 70% of **2t**.

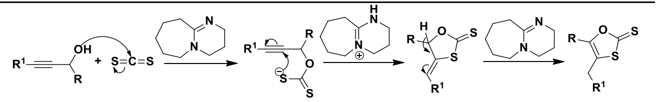
After the above successful synthesis of [1,3]-oxathiole-2-thiones from secondary propargyl alcohols and CS_2, the turn is to demonstrate the synthesis of heterocyclics from primary propargyl alcohols and CS_2 by employing the same optimum reaction conditions which was used for **1a** and CS_2.

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 CS_2 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.

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

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 CS_2; subsequently the sulphur anion of CS_2 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]-oxathiolane-2-thione. The earlier research by authors, i.e., synthesis of oxazolon-2-ones[17] 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 CS_2 both the propargyl alcohols undergoes the coupling, 5-*exo*-dig cyclization and *exo*-cyclic double bond migration to reach [1,3]-oxathiolane-2-thiones.



Scheme 2: Possible reaction mechanism

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 CS_2 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]-oxathiolane-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 ^{13}C NMR spectra of all compounds and ortep for **2h** and **2w** are included in the supporting information.

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

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[18] CCDC 1812466 (**2h)** 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

[19] CCDC 1812465 (**2w)** 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