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ARTICLE

An Investigation Towards 2,3-Dichloro-5,6-dicyanobenzoquinone Catalyzed Cross-Dehydrogenative Coupling Reactions of Thio-β-lactams/Thioethanoates with Aliphatic/Aromatic Nucleophiles

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ABSTRACT

An investigation towards 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)-catalyzed cross-dehydrogenative coupling (CDC) reactions of *trans*-3-phenylthio/benzylthioazetidin-2-ones (**1a,b**) and ethyl-2-phenylthioethanoates (**5**) with aliphatic/aromatic nucleophiles is described. A series of reaction conditions were chosen to obtain the monosubstituted and disubstituted β-lactams. However, CDC reactions of β-lactams with different aliphatic/aromatic substrates resulted into unidentified products whereas ethyl-2-phenylthioethanoates (**5**) underwent the CDC reaction to give the desired α-substituted ethyl-2-phenylthioethanoates (**7**). Also, a plausible mechanism for the cross coupling of ethyl-2-phenylthioethanoates (**5**) with nucleophiles is described.

KEYWORDS

Cross-dehydrogenative coupling, C-H activation, Copper catalyst, β-Lactams, Nucleophile, Oxidation.

INTRODUCTION

In the modern era of synthetic organic chemistry, formation of C-C or C-X (X = N, O, S) bonds using cross dehydrogenative coupling (CDC) reaction has evolved as an imperative methodology for the synthesis of complex molecules, being operationally simple, atom-economic, efficient and avoids any pre-functionalization of the substrate [1]. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) serves as a versatile strong quinonoid oxidizing agent [2], which has been employed for a number of chemical transformations including deprotections, cleavage of linker molecules from solid support, aromatizations, oxidative cyclizations, biaryl constructions, introduction of unsaturations, acetal formations and direct cross dehydrogenative coupling (CDC) reactions. The use of DDQ as an oxidant in the CDC reactions is well explored. The presumably dormant C-H bonds can be selectively functionalized by employing the CDC strategy [3]. Despite significant advancement in the C-H functionalization adjacent to nitrogen and oxygen [4-9], CDC of sulfur containing substrates is not much explored [10]. In a recent report by Xiao and coworkers [11], a combination

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of DDQ and copper salts efficiently promoted the cross coupling of thioacetals (**A**) with equimolar amounts of alcohol to generate 2-alkoxy-2-aryl-1,3-dithiolanes (**B**) (Fig. 1).

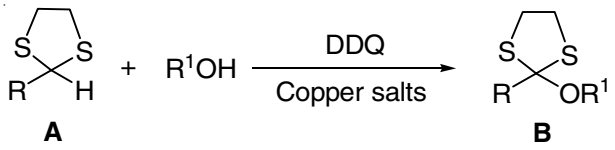


Fig. 1. CDC reaction of thioacetals with alcohols

Liu and coworkers [2] reported that DDQ could be used as a catalytic oxidant with MnO_2 serving as the stoichiometric oxidant for the cross-coupling of C-H bonds adjacent to oxygen atom with acetophenone. The direct coupling of sp^3 α C-H bonds of α-amino acid derivatives (particularly esters) with C-H bonds of various nucleophiles is well documented in the literature [12]. However, the direct cross-coupling of the corresponding sulfur analogues (thio esters) with nucleophiles has not been explored till yet.

β-Lactams have been considered a priveledged structure in chemical, pharmaceutical and material industries [13]. These are administered because of their safety profile, wide spectrum of activity and reliably consistent clinical efficacy. Our research group has been actively engaged in the synthetic β-lactam chemistry [14]. For example, novel β-lactam precursors, 3-thio/seleno-β-lactams and their Lewis acid mediated functionalizations, stereoselective *cis*- and *trans*-3-alkoxy-β-lactams, spirocyclic-β-lactams, α-keto-β-lactams, bicyclic-β-lactams, novel 4-pyrazolyl-β-lactams, 4-pyrazolylspirocyclic-β-lactams and (*E*)- and (*Z*)-3-allylidene-β-lactams are reported by us. Suitably substituted β-lactams occur in natural products, pharmaceuticals and materials in wide abundance. Therefore, it becomes highly desirable to synthesize these molecules by direct C-H functionalization. Keeping in view the work of Xiao and co-workers [11], herein, we report the studies towards the direct DDQ mediated oxidative functionalization of C-H bonds adjacent to sulfur in 3-phenylthio/benzylthio-β-lactams (**1a,b**) and thioesters (**5**), featuring C-H activation with inexpensive CuI catalyst.

EXPERIMENTAL

^{1}H NMR (400 MHz and 300 MHz), ^{13}C NMR (100 MHz and 75 MHz) were recorded using BRUKER or JEOL 400 MHz and 300 MHz NMR spectrometers. Infrared spectra were recorded using Perkin-Elmer Model 1430 spectrophotometer with potassium bromide (KBr) plates or Nujol with NaCl optic plates and are reported in cm^{-1}. The elemental analysis (C, H, N) was carried out using a Perkin-Elmer 2400 elemental analyzer. Column chromatography was performed using Merck Silica Gel (60-120 mesh) and eluted with ethyl acetate: hexanes mixtures. Thin-layer chromatography (TLC) was performed using Merck Silica Gel G. For visualization, TLC plates were stained with iodine vapours. Melting points were determined with a Thomas-Hoover capillary melting point apparatus. The reactions were carried out under dry and deoxygenated nitrogen atmosphere. Acetophenone (CDH), indole, allyltrimethyl silane, propargyl alcohol (Sigma Aldrich) and all other commercially available compounds/reagents/solvents were of reagent grade quality and used without any further purification. Chloroform was dried and distilled over anhydrous phosphorus pentoxide.

General procedure for the cross-coupling reactions: A mixture of β-lactam/thioester (0.5 mmol), nucleophile (0.5 mmol), CuI catalyst (10 mol %) and DDQ (1.0 mmol) in dry $CHCl_3$/neat conditions was stirred at room temperature/refluxed. The progress of the reaction was monitored by TLC. After completion, the solvent was removed under vacuum and the crude product was purified by column chromatography using silica gel eluting with ethyl acetate:hexane.

The spectroscopic data of ethyl 2-(methoxy)-2-phenylthioethanoate (**7a**) [15], ethyl 2-(prop-2-ynyloxy)-2-phenylthioethanoate (**7b**) [16], ethyl 2-(allyl)-2-phenylthioethanoate (**7c**) [11] have been reported previously in the cited reference.

RESULTS AND DISCUSSION

Cross dehydrogenative coupling of thio-β-lactams with nucleophiles: In our previous studies towards the C-3 functionalization of β-lactams [11-16], the substrate *cis*-3-chloro-3-phenyl/benzylthio/seleno-β-lactams (**2a-d**) were synthesized by stereospecific chlorination of *trans*-3-phenyl/benzylthio/seleno-β-lactams **1a-d** (Fig. 2). Compound **2** were further transformed to disubstituted/monosubstituted β-lactams **3/4** on reaction with aliphatic, aromatic or heterocyclic nucleophiles (Fig. 2) [14-16]. However, in these studies, some of the starting substrates such as *cis*-3-chloro-3-benzylseleno-β-lactams (**2d**) were obtained in much lower yields (24 %).

Therefore, keeping in view the work of Xiao and co-workers [11] and the exclusion of the required chloro-β-lactam (**2**), it was envisaged to carry out the direct functionalization of compound **1** using CDC methodology. The CDC of *trans*-3-phenylthio/benzyl thio-β-lactams (**1a,b**) with aliphatic, aromatic and heterocyclic nucleophiles was studied employing

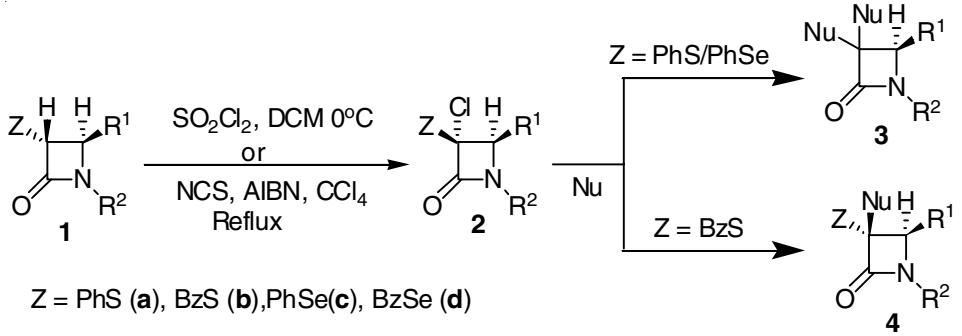
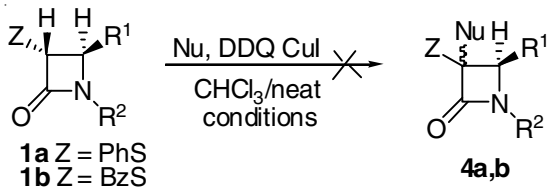


Fig. 2. Lewis acid mediated C-3 functionalization of *cis*-3-chloro-β-lactams (**2**)

DDQ as an oxidant (**Scheme-I**). The reactions were carried out in chloroform heated at reflux, at room temperature or under neat conditions. The results of the individual reactions are tabulated in Table-1.



Scheme-I: CDC of β-lactams (**1a,b**) with nucleophiles

Initially, we examined the CDC reaction of *trans*-3-phenylthio-β-lactam (0.5 mmol) **1a** with methanol (0.5 mmol) in $CHCl_3$, in the presence of 0.5 mmol DDQ at room temperature, under metal free conditions (Table-1, entry 1). However, no cross coupled product **4a** was detected. Even employing CuI (10 mol %) as the metal catalyst in chloroform at room temperature (Table-1, entry 2) or under reflux conditions (Table-1, entry 3) does not afford the cross coupled products. Further, the analogous reaction at room temperature under neat conditions, did not result into the coupled product either (Table-1, entry 4).

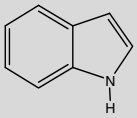
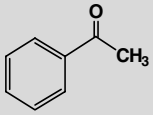
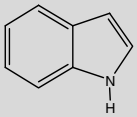
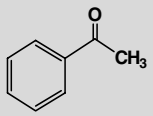
Similarly, the cross-couplings of 3-benzylthio-β-lactam (**1b**) with methanol in $CHCl_3$ at room temperature/reflux conditions or under neat conditions using DDQ as an oxidant, CuI as metal catalyst were unsuccessful (Table-1, entries 9-11). The TLC analysis of the crude reaction mixture did show the formation of more polar product(s). Upon column chromatographic purification, complex product(s) were separated which were completely unidentifiable by the spectroscopic techniques.

To investigate the scope and limitations of the oxidation, we carried out a systematic study of the DDQ catalyzed CDC of β-lactams (**1a,b**) with indole (Table-1, entries 5,7) and acetophenone (Table-1, entries 6,8). No cross coupled products **4** were observed however, the unreacted starting substrates (β-lactam and indole/acetophenone) were recovered as such after column chromatographic purification.

Cross dehydrogenative coupling of ethyl-2-phenylthioethanoates 5 with nucleophiles: In our earlier methodology [15,16], we have synthesized α-substituted 2-phenylthioethanoates (**7**) (Fig. 3), as β-lactam precursors from 2-chloro-2-phenylthioethanoates (**6**) using our reported procedure.

Further, following Xiao and co-workers CDC methodology [11], on alternate substrate, it was envisaged to synthesize various α-substituted 2-phenylthioethanoates (**7**) *via* DDQ

TABLE-1
DDQ CATALYZED CDC REACTIONS OF β-LACTAMS (**1a,b**) WITH NUCLEOPHILE[a]

Entry	1	R^1	R^2	Nucleophile	Solvent	Temperature (°C)	Catalyst
1	**1a**	$C_6H_4.OCH_3$ (4)	$C_6H_4.OCH_3$ (4)	CH_3OH	$CHCl_3$	Room temperature	–
2	**1a**	$C_6H_4.OCH_3$ (4)	$C_6H_4.OCH_3$ (4)	CH_3OH	$CHCl_3$	Room temperature	CuI
3	**1a**	$C_6H_4.OCH_3$ (4)	$C_6H_4.OCH_3$ (4)	CH_3OH	$CHCl_3$	61	CuI
4	**1a**	$C_6H_4.OCH_3$ (4)	$C_6H_4.OCH_3$ (4)	CH_3OH	Neat	Room temperature	CuI
5	**1a**	$C_6H_4.OCH_3$ (4)	$C_6H_4.OCH_3$ (4)		$CHCl_3$	61	–
6	**1a**	$C_6H_4.OCH_3$ (4)	$C_6H_4.OCH_3$ (4)		$CHCl_3$	Room temperature	–
7	**1b**	C_6H_5	$C_6H_4.OCH_3$ (4)		$CHCl_3$	61	–
8	**1b**	C_6H_5	$C_6H_4.OCH_3$ (4)		Neat	61	–
9	**1b**	C_6H_5	$C_6H_4.OCH_3$ (4)	CH_3OH	$CHCl_3$	Room temperature	CuI
10	**1b**	C_6H_5	$C_6H_4.OCH_3$ (4)	CH_3OH	Neat	Room temperature	–
11	**1b**	C_6H_5	$C_6H_4.OCH_3$ (4)	CH_3OH	$CHCl_3$	61	CuI

[a]Reaction conditions: **1a,b** (0.5 mmol), nucleophile (0.5 mmol), CuI (10 mol %) and DDQ (0.5 mmol)

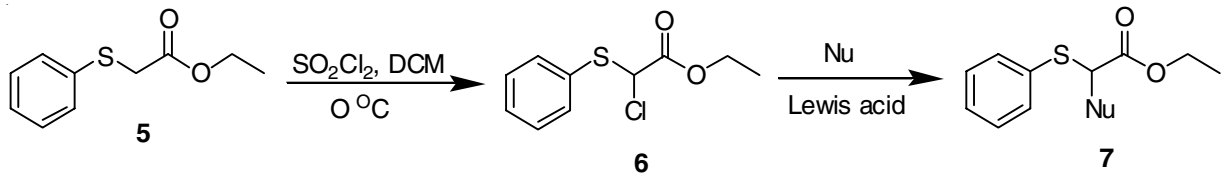
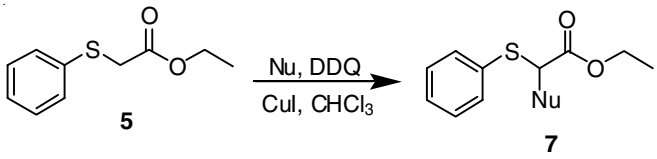


Fig. 3. Synthesis of C-2 nucleophile substituted 2-phenylthioethanoates (**7**)

mediated oxidative cross coupling of 2-phenylthioethanoates (**5**) and appropriate nucleophiles under CuI catalysis (**Scheme-II**).



Scheme-II: CDC of 2-phenylthioethanoates (**5**) with nucleophile

Initially, ester **5** (0.5 mmol) was treated with 0.5 mmol of methanol in chloroform in the presence of oxidant DDQ (0.5 mmol), CuI (10 mol %) as metal catalyst at room temperature (Table-2, entry 1). The coupled product ethyl 2-(methoxy)-2-phenylthioethanoate (**7a**) was obtained in 17 % yields. Similar reactions carried out in chloroform under reflux conditions improved the reaction yields (20 %) (Table-2, entry 2).

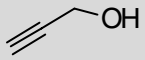
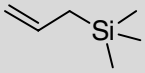
We further extended the scope of this methodology to the use of propargyl alcohol and allyltrimethylsilane as coupling partners (nucleophiles). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) mediated oxidative cross coupling reaction of ethyl-2-phenylthioethanoate **5** and propargyl alcohol/allyltrimethysilane was performed under chloroform reflux conditions with CuI catalysis (Table-2, entries 3, 4). Work-up and column chromatographic purification successfully gave the coupled products ethyl 2-(prop-2-ynyloxy)-2-phenylthioethanoate (**7b**) and ethyl 2-(allyl)-2-phenylthioethanoate (**7c**) in 23 % and 21 % isolated yields respectively.

A plausible mechanism for the CDC of ethyl-2-phenylthioethanoate (**5**) and nucleophile is depicted in Fig. 4. It is proposed that a single electron transfer (SET) from Cu(I) salt to DDQ generates the DDQ radical anion **A**. Abstraction of a hydrogen atom (sp^3 α C-H bond adjacent to sulfur) from the thioester molecule **5** forms the radical species **B** and $[Cu(II)DDQ\text{-}H]^+$. Subsequent oxidation of **B** through SET to $[Cu(II)DDQ\text{-}H]^+$ would afford thiocarbenium **C** and [Cu(I)DDQ-H]. [Cu(I)DDQ-H] abstracts a proton from the nucleophile (NuH) to form the activated nucleophile (Nu^-) which subsequently attacks the sulfonium cation **C** to generate the coupled product **7**, DDQ-HH and regenerates the Cu(I) catalyst.

Conclusion

In conclusion, studies have been performed towards the DDQ catalyzed cross coupling reactions of *trans*-3-phenylthio/3-benzylthioazetidin-2-ones and ethyl-2-phenylthioethanoates with aliphatic/aromatic nucleophiles. Merging DDQ with cuprous iodide proved to be effective for the cross-coupling of

TABLE-2
DDQ CATALYZED CDC REACTIONS OF THIOESTER (**5**) WITH NUCLEOPHILE[a]

Entry	Nucleophile	Solvent	Temperature (°C)	Catalyst	**7** (% yield)
1	CH_3OH	$CHCl_3$	Room temperature	CuI	**7a** 17 %
2	CH_3OH	$CHCl_3$	61	CuI	**7a** 20 %
3		$CHCl_3$	61	CuI	**7b** 23 %
4		$CHCl_3$	61	CuI	**7c** 21 %

[a]Reaction conditions: **5** (0.5 mmol), nucleophile (0.5 mmol), CuI (10 mol %) and DDQ (0.5 mmol)

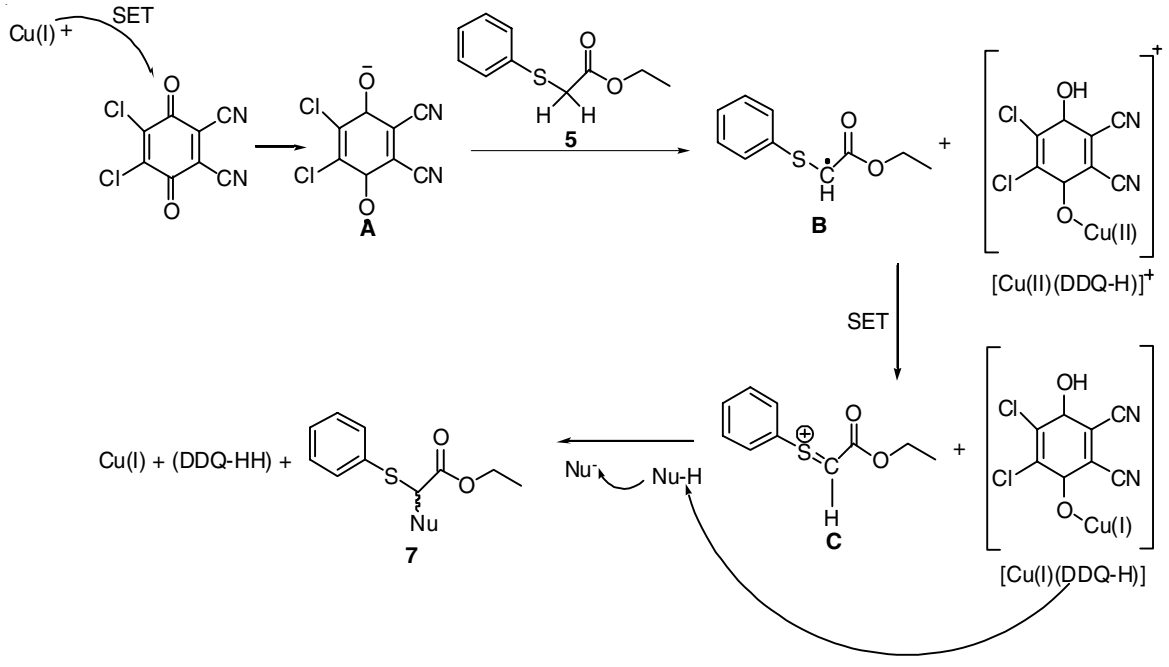


Fig. 4. Plausible mechanism for the CDC of thioester **5** with nucleophiles

ethyl-2-phenylthioethanoates and nucleophiles under mild conditions. Further elaboration of this work with appropriately active substrate and reagents is underway in our laboratory.

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