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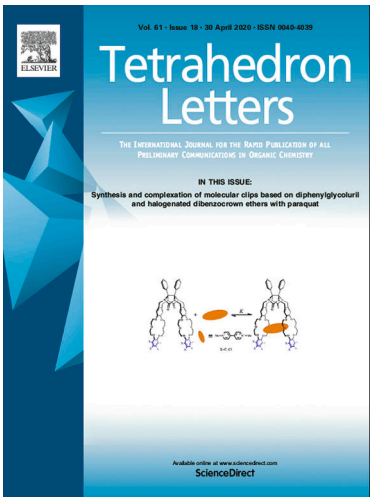

Copper catalyzed cyanomethylation reaction of 4-thiazolidinone

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Copper catalyzed cyanomethylation reaction of 4-thiazolidinone

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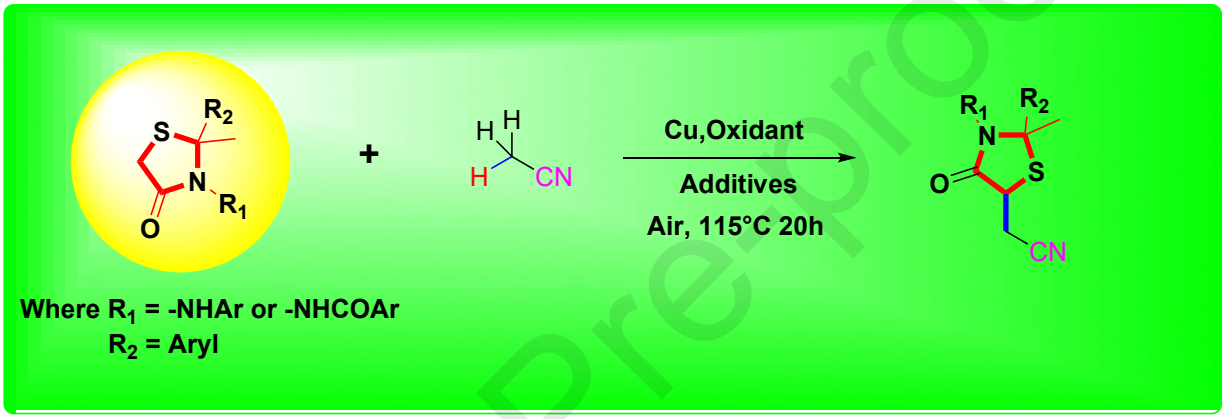
Graphical abstract:



Abstract:

An effective copper catalyzed Cross Dehydrogenative Coupling (CDC) reaction of 4-thiazolidinones with acetonitrile has been developed. The described strategy undergoes radical pathway by employing copper, oxidant and easily available acetonitrile as a cyanomethyl source. Various cyanomethylated 4-thiazolidinone derivatives were obtained easily and conveniently in moderate to good yield by employing this method. Substrate scope and optimization have been carried out appropriately. Optimization was carried out through different oxidants, catalyst and various additives.

Key words: 4-Thiazolidinones, Cross Dehydrogenative Coupling (CDC), Cyanomethylation, Copper catalyst.

Introduction:

From green chemistry point of view as well as from atom economic approach, the direct C-H functionalization methodology through cross dehydrogenative coupling (CDC) strategy or

oxidative coupling" has emerged as an impressive and versatile tool in the construction of carbon-carbon bond without any necessity of prefunctionalized substrate [1-10]. In the past few decades, significant progress has been noticed for CDC reactions of relatively inert C(sp^3)-H bond [11-14]. Traditionally, C-H bond activation reactions have been achieved by employing heavy transition elements like platinum, palladium, rhodium and ruthenium as heroic catalysts with the generation of some stoichiometric amounts of metal salts as waste.

Nowadays, copper-catalyzed dehydrogenative coupling reactions have attracted more attention owing to their lower cost and ease in handling [15-22]. Among them, the oxidative C(sp^3)-H activation of cheap and easily accessible acetonitrile has received great attention, as cyano group can be easily converted into other reactive functional groups like esters, carboxylic acids, amines, amides, tetrazoles, aldehydes and ketones etc.[23-24]. In addition to this, it plays an important role in pharmaceuticals [25-26], bioactive molecules [27-28] and in synthesizing the chemicals which owes unique character [29-30]. On the other hand,4-thiazolidinone scaffolds are potentially useful constructs that display a wide range of fascinating biological activities such as antimalarial [31], anti-HIV [32], anticancer [33], tuberculostatic [34], anti-inflammatory [35], antiarrhythmic [36], anticonvulsant [37], and antihistaminic [38]. Some of the representative nucleus is mentioned in Fig(1). In view of the pharmacological significance of 4-thiazolidinone and importance of cyano group, as well as our continuous efforts regarding this type of molecule [39-41],we were tempted to develop a novel heterocyclic building block which incorporates both these units in the single molecular framework.

Acetonitrile (CH_3CN) is a well recognized solvent and viewed as an inert chemical reagent. The pKa value of acetonitrile is 31.3 in DMSO, so it is quite difficult to use it as pronucleophile. Various approaches are available in which acetonitrile has been used directly as a cyanomethylating agent by activating C(sp^3)-H bond of methyl group. However, the direct installation of cyano group through cyanomethylation reaction via radical pathways are less explored [42-43] and also oxidative C-H functionalization nearby to the sulphur atom is less reported [44-46]. Previously, Wei Zhang's group has elegantly reported Cu-catalyzed cyanomethylation of substituted tetrahydroisoquinolines with acetonitrile (sp^3-sp^3 coupling) but it is beside to the N atom[47]. To the best of our knowledge, no examples have yet been reported for the CDC reaction of 4-thiazolidinone and acetonitrile. Here, for the first time, we have been reporting cyanomethylation of 4-thiazolidinone by making the use of copper catalyzed CDC reaction in the presence of TBPB as an oxidant and Cs_2CO_3 as an additive. The required

starting material 4-thiazolidinones were synthesized by the condensation reaction of various aryl hydrazide with different aryl ketones through Schiff base formation followed by cyclization with the help of thioglycolic acid. Slightly acidic C-H bond of the synthesized 4-thiazolidinones was chosen for functionalization with acetonitrile through CDC strategy. In past, our research group has developed C-alkynylation on the same C-H bond of 4-thiazolidinone through Cu catalyst and CDC strategy [48].

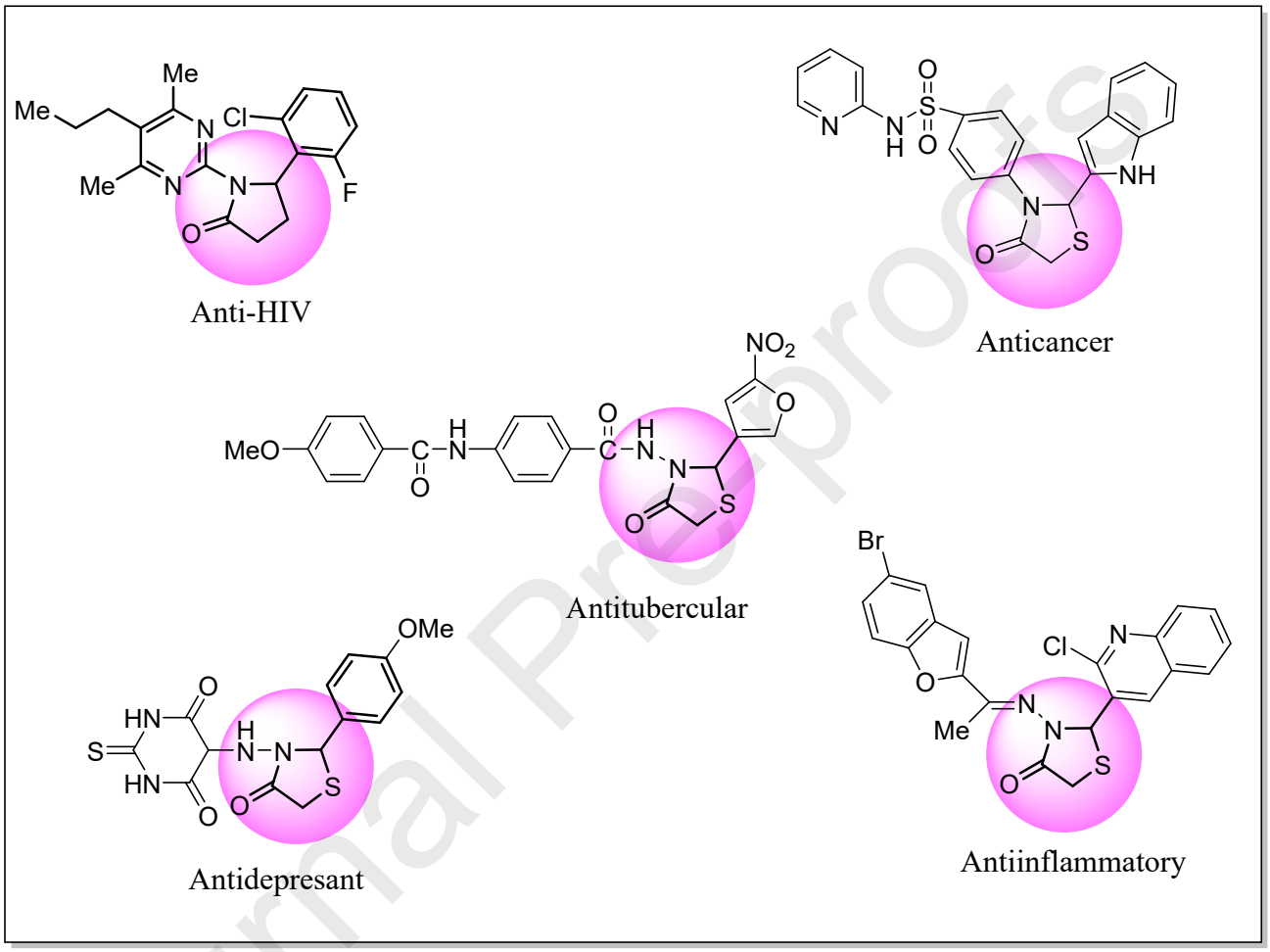
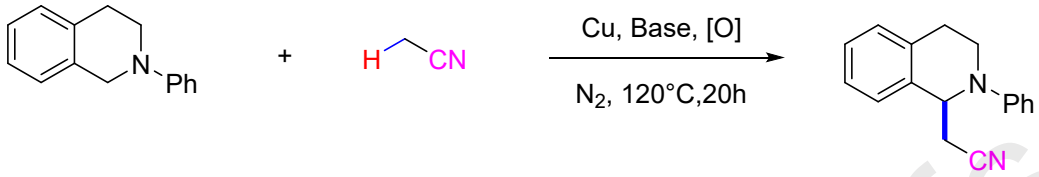


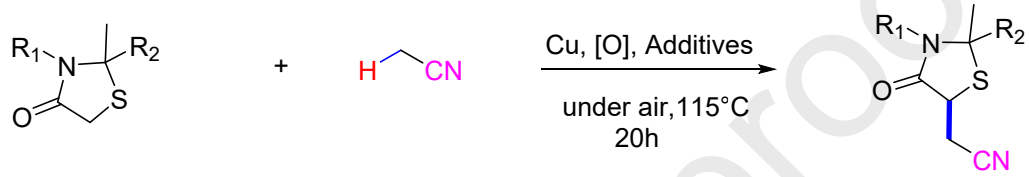
Figure 1. Selected representative biologically active 4-thiazolidinone containing molecules.

Scheme -1 Earlier work

Wei Zhang's Work



Present work



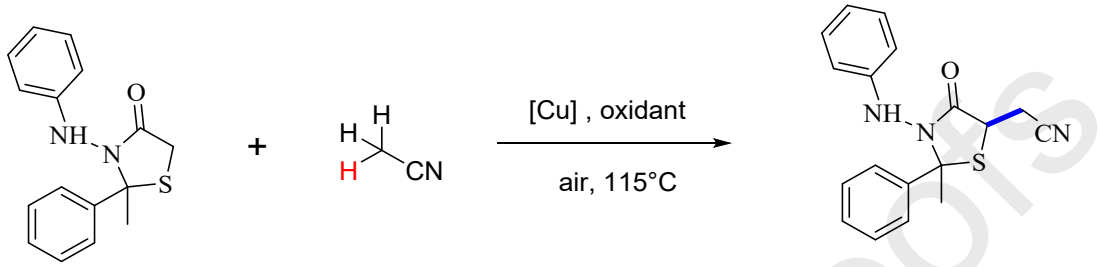
Where R^1 =**NHAr or -NHCOAr**
& R^2 =**Aryl**

Results and Discussion

In order to validate our hypothesis and to get preliminary idea about preferred optimized reaction condition, we strived with 2-methyl-2-phenyl-3-(phenyl amino) thiazolidin-4-one (1a) as a model substrate, which was reacted with 10 ml of easily available acetonitrile (2a) in the presence of oxidant along with catalyst and additive for 20 hour at 115°C under air atmosphere as a model reaction (Table-1). To obtain the desired product in appropriate proportion, we selected sequence of catalyst, oxidant as well as additives. Initially, we started with different copper(I) catalyst such as CuCl, CuI & CuOAc respectively with oxidants like potassium persulphate without any additive which gave the desired yield in very less proportion (Table-1, entries1-3). Switching to CuBr catalyst with same oxidant and using Na_2CO_3, K_2CO_3 & $NaHCO_3$ as an additive respectively increased the proportion of yield (Table-1, entries 4-6) and generated the idea that catalyst CuBr suits the best among other. Moreover, to achieve yield in adequate proportion, we exchanged oxidant potassium persulphate by TBHP and different additives like K_2CO_3, Li_2CO_3, NAH and Cs_2CO_3 but still remarkable increase in the quantity of yield was not observed. It was noticed that additive Cs_2CO_3 gave the best result compared to K_2CO_3, Li_2CO_3 & NaH (Table-1, entries 7-10). To our delight, when oxidant TBPB was used in place of TBHP, the yield was increased remarkably (Table-1, entry 11). Then, we shifted our attention and examined

copper (II) catalyst but the yield of the desired product was not increased (Table-1, entries 12-13). Furthermore, $Cu(OAc)_2$ with same additive and oxidant at 100 °C also fails to improve the proportion of yield (Table-1, entry 14). Finally, carrying out the reaction without oxidant or catalyst gave the yield in less proportion (Table-1, entries 15-16).

Table 1: Optimization of reaction conditions[a]



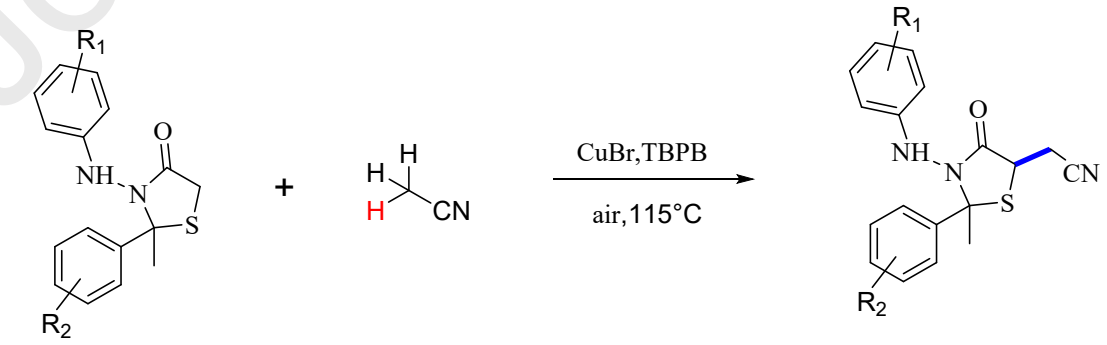
1a **2a** **3a**

Entry	Catalyst	Oxidant	CH_3CN	Additives	[b]Yield
1	CuCl	$K_2S_2O_8$	10ml	-	10%
2	CuI	$K_2S_2O_8$	10ml	-	14%
3	CuOAc	$K_2S_2O_8$	10ml	-	Trace
4	CuBr	$K_2S_2O_8$	10ml	Na_2CO_3	31%
5	CuBr	$K_2S_2O_8$	10ml	K_2CO_3	33%
6	CuBr	$K_2S_2O_8$	10ml	$NaHCO_3$	25%
7	CuBr	TBHP	10ml	K_2CO_3	41%
8	CuBr	TBHP	10ml	Li_2CO_3	40%
9	CuBr	TBHP	10ml	NaH	35%
10	CuBr	TBHP	10ml	Cs_2CO_3	58%
11	**CuBr**	**TBPB**	**10ml**	**Cs_2CO_3**	**76%**
12	$CuCl_2$	TBPB	10ml	Cs_2CO_3	40%
13	$CuCl_2.2H_2O$	TBPB	10ml	Cs_2CO_3	Trace
14	$Cu(OAc)_2$	TBPB	10ml	Cs_2CO_3	46%
15	CuBr	-	10ml	Cs_2CO_3	10%
16	-	TBPB	10ml	Cs_2CO_3	25%

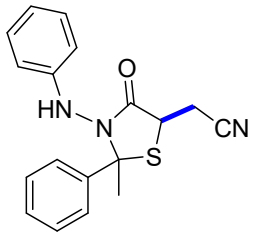
[a]Reaction Condition: 1a: (0.20 mmol), 2a: (10ml), catalyst: 10 mol%, oxidants: 3.0 equivalent & Additives: 1.5 equivalent, 20 hours, under air. [b]Isolated Yield.

With the optimized reaction condition in hand, to propose the generality of the transformation (Table 2 and 3), we moved our attention towards investigation of substrate scope with respect to coupling partner such as 2-methyl-2-phenyl-3-(phenylamino) thiazolidin-4-one (1a) with acetonitrile (2a). Initially, diverse 4-thiazolidinones were permitted to react with less acidic acetonitrile under optimized condition (Table-2). Both electron withdrawing and donating groups were well tolerated under optimized reaction condition in more or less proportion. Cyanomethylation of 4-thiazolidinone substrate without any substitution afforded 76 % yield (Table-2, entry **3a**). In addition, wide range of electron donating substituents present on R_1 and R_2 aromatic ring of 4-thiazolidinone also generated good to higher yield (Table-2, entries **3b-3e**). Whereas, electron withdrawing substituents present on R_1 and R_2 of aromatic ring lowered the desired yield (Table-2, entries **3f-3i).** Furthermore, the scope of different 4-thiazolidinone substrates of benzoylhydrazide were also examined under optimal condition (Table 3). It was observed that unsubstituted compound afforded 74% yield (Table 3, entry **3aa**). Herein, we also noticed that both electron donating and withdrawing group played a crucial role for this transformation. Electron donating group present on R_1' & R_2' of 4- thiazolidinone substrates of benzoyl hydrazide could increase the yield (Table-3, entries **3ab-3ae**) and electron withdrawing group lowered the yield (Table-3, entries **3af-3ai**). Next, we had examined the furan bearing 4-thiazolidinone of benzoylhydrazide with the standard condition, which also generated good yield (table 3, entry **3aj**) but not in higher proportion. Since, pyridine nucleus possess good biological acivity, reaction with pyridine containing 4-thiazolidinone was also conducted and related product was afforded in good amount. (table 3, entry **3ak**).

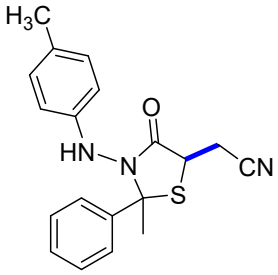
Table 2: Scope for the reaction of various 4-thaizolidinone of phenyl hydrazine.



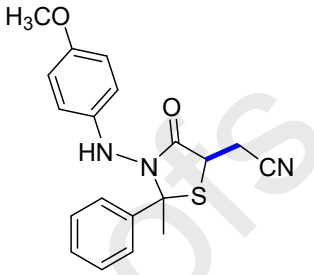
1 (a-i) **2** **3 (a-i)**



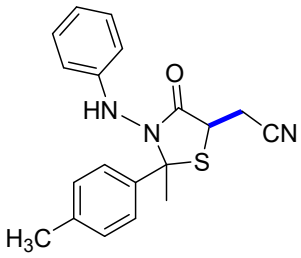
3a (76%)



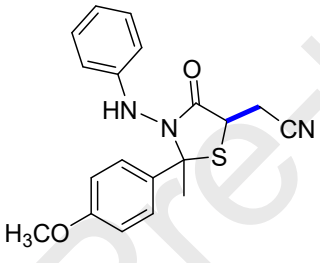
3b (78%)



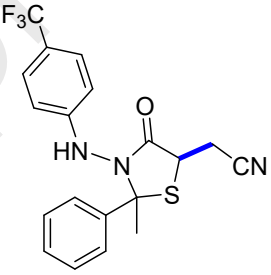
3c (80%)



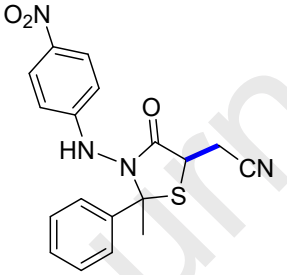
3d (77%)



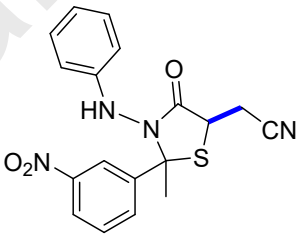
3e (76%)



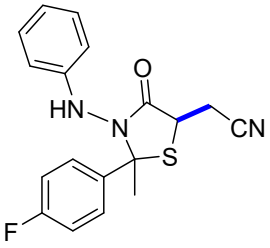
3f (69%)



3g (63%)

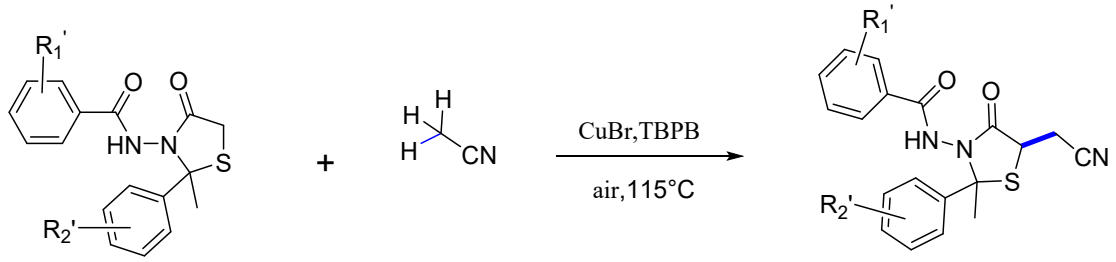


3h (64%)

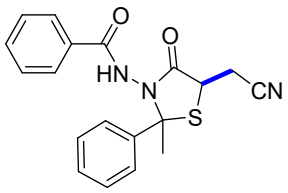


3i (67%)

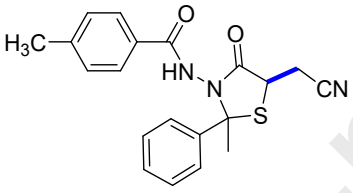
Table-3: Substrate scope of 4-thiazolidinones of benzoyl hydrazide



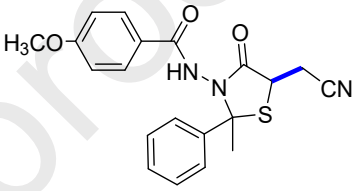
1a (a-k) **2** **3a (a-k)**



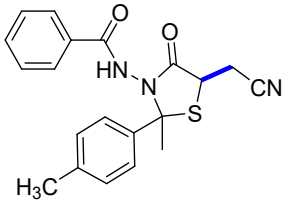
3aa (74%)



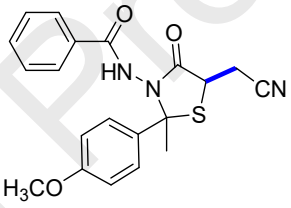
3ab (78%)



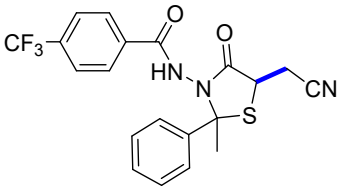
3ac (79%)



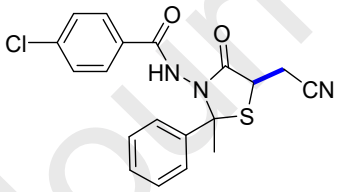
3ad (77%)



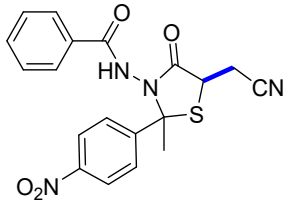
3ae (81%)



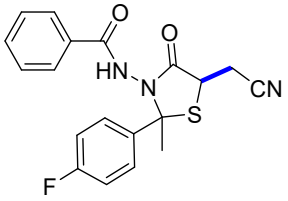
3af (68%)



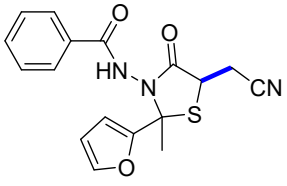
3ag (70%)



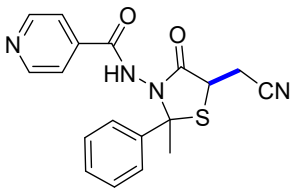
3ah (64%)



3ai (69%)



3aj (76%)



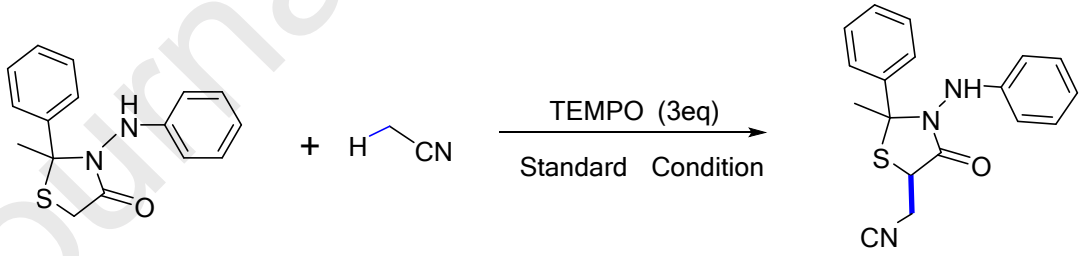
3ak (71%)

From Table-2 and 3, it can be said that optimized condition exhibits considerable functional group tolerance including -OH, -X, -OR, -NO_2 and -CF_3.

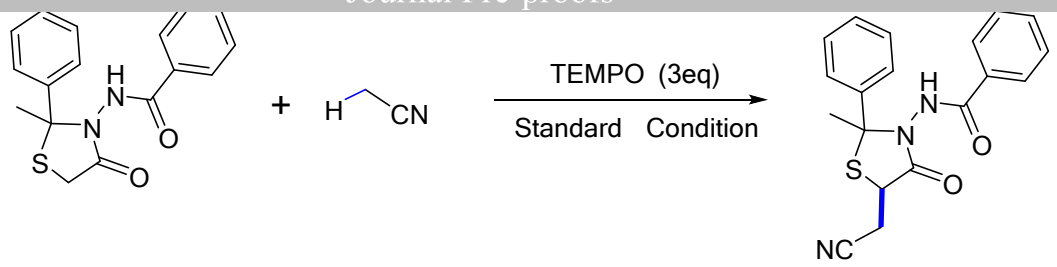
On the basis of experimental results and literature survey [49-51], a plausible mechanism has been proposed for compound **3a.** Initially, formation of active Cu (II) species **A** along with tert-butoxy radical or benzoate radical takes place through oxidation of CuBr by tert-butyl peroxy benzoate (TBPB) under the thermal condition. Then less acidic C(sp^3)-H bond of acetonitrile was abstracted by tert-butoxy or benzoate radical and generated cyanomethyl radical active species **B,** concominant elimination of tBuOH of PhCOOH**.** Then coordination-directed insertion of slightly acidic C-H bond of 4-thiazolidinone 1a with Cu (II) active species generated the metallacycle intermediate **C** with simultaneous formation of tBuOH or PhCOOH. After the formation of active species B and C, the formation of complex D takes place, which is followed by the free radical addition of species B & C. Finally, the desired cyanomethylated coupling product 3a was obtained by the reductive elimination with regeneration of Cu (I) species again.

Control experiment:

To get insight in the reaction pathway, control experiments were carried out for compound 1a and 1aa. When radical scavenger like 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added during cyanomethylation of 4-thaizolidinone under standard optimized condition for 20 h and the results revealed that cyanomethylation was fully inhibited since the compounds 3a and 3aa were not obtained. Therefore, a single-electron-transfer (SET) pathway was considered and presumed that cyanomethyl radical might act as an intermediate.



1a 2 3a, NR



1aa 2 3aa, NR

Plausible Mechanism:

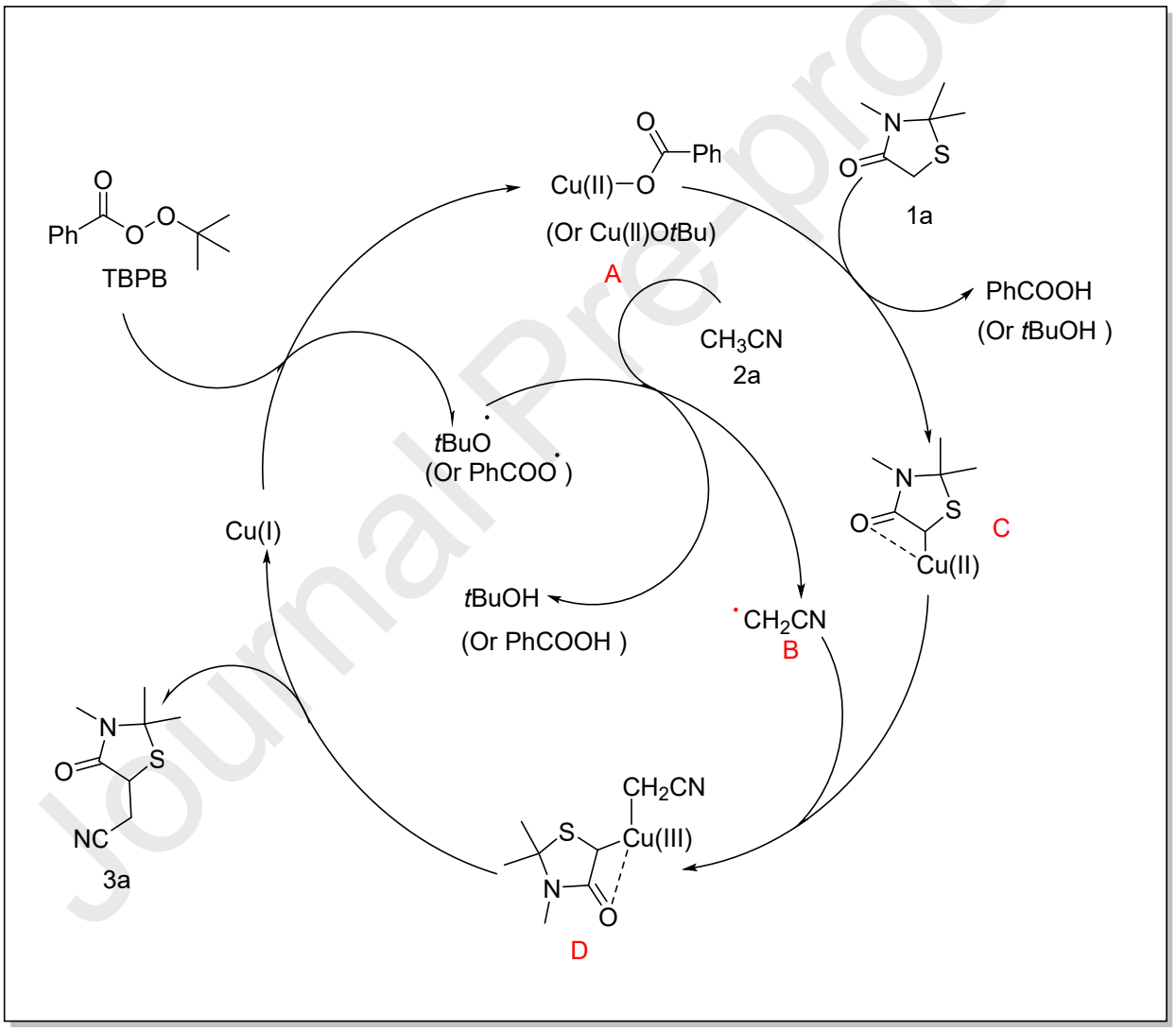


Figure-2. Plausible mechanism for cyanomethylation

Conclusion:

We have developed an efficient and prominent Cu catalysed cyanomethylation of C(sp^3)-H using diverse 4-thiazolidinones with acetonitrile. This methodology represents the cross dehydrogenative coupling (CDC) of C(sp^3)-H of 4-thiazolidinones adjacent to sulphur atom and C(sp^3)-H bond of acetonitrile. One pot synthesis, functional group tolerance and favourable in terms of atom economy make this protocol more interesting and promising. This strategy tolerates wide range of functional group and provides new example/insight into C-H functionalisation. This study would become more helpful in synthesizing other analogue derivatives which required functionalization of relatively inert C-H bond adjacent to sulphur atom.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

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