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Copper-II mediated tandem reaction between aromatic ketones and 2-aminobenzenethiol for the synthesis of 2-aroylbenzothiazoles

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ABSTRACT

A novel copper (II) mediated tandem reaction was developed for the synthesis of 2-aroylbenzothiazoles from readily available aryl-alkyl ketones in the presence of oxygen in ethanol. This method is mild, operationally simple, makes the use of inexpensive $CuBr_2$ as mediator and affords the corresponding 2-aroylbenzothiazoles in moderate to good yield.

Benzothiazole moieties have gained interest because of their widespread applications not only in medicinal chemistry but also in agrochemicals, industrial dyes and functional material.[1] Among them 2-substituted aroyl benzothiazoles are one of the most important class of heterocycles, with wide range of biological activities such as antitumor, antidiabetic, and antiviral.[2] Besides this, their potential has also been explored as fatty acid amide hydrolase inhibitor, prolyl carboxy peptidase inhibitor,17β hydroxysteroid dehydrogenase inhibitor.[2]

2-acylbenzothiazoles are seldom synthesized as it is difficult to introduce acyl group at 2-position of benzothiazoles. Generally, 2-acylbenzothiazoles are synthesized by metallation of benzothiazoles with n-butyllithium or other lithium reagents at -78^{o}C, followed by reaction with suitable electrophile. Overall, these reactions require multiple step and highly reactive lithium salts making it imperative to maintain very low temperature.[2, 3] Only few methods have been reported for the synthesis of 2-acylbenzothiazole as compared to 2-arylbenzothiazoles.[4] Among them, only one method is reported for the synthesis of 2-acylbenzothiazole from acetophenone and 2-aminobenzenethiol, where iodine was used to promote oxidative functionalization of the sp^3 C-H bond of 2-arylalkyl ketones in presence of DMSO as an oxidant.[5a] In another method, one pot strategy was applied, where styrene or arylacetylene in presence of I_2/IBX in DMSO was heated for 2-3 hours and after addition of 2-aminobenzenethiol, final product 2-acylbenzothiazole was isolated. In this, it was postulated that styrene or arylacetylene was first converted into phenacyl iodine in presence of I_2 and IBX in DMSO, where IBX in DMSO acted as an oxidizing agent, while I_2 as an additive. Further this phenacyl iodine in presence of DMSO gets converted into phenylglyoxal or hydrated hemiacetal. After formation of phenylglyoxal or hydrated hemiacetal, 2-aminobenzenethiol was added and 2-acylbenzothiazole was isolated as a final product. Similarly, 2-hydroxy-1-phenyl ethanone and 2-hydroxy-aromatic ketones in presence of I_2/IBX in DMSO were first converted into phenylglyoxal and then treated with 2-aminobenzenethiol to get the final product.[5b]

It is also reported that, 2-acylbenzothiazole was obtained when acetophenone, reacted with benzothiazole in DMSO, in the presence of reagents like $FeCl_3.6H_2O$ with $K_2S_2O_8$;[5c] $FeCl_3.6H_2O$ with ligand;[5d] copper (I) iodide[5e] and iodine with KOH.[5f] But in case of $FeCl_3.6H_2O$ with $K_2S_2O_8$ non-selective 2-acyl and 2-arylbenzothiazoles products were obtained.

All the above methods have employed DMSO as an oxidant which played a crucial role in transforming acetophenone or haloacetophenone into phenylglyoxal a key intermediate (Kornblum Oxidation) to obtain the final product 2-acylbenzothiazole.

Although many of these methods provides efficient route to 2-acylbenzothiazoles but they require DMSO as a oxidant, harsh reaction condition like high reaction temperature, long reaction times and tedious workup procedure. Thus, the development of novel reaction system under mild reaction condition is necessary.

Transition-metal-catalyzed domino reactions have gained lot of interest in the area of research due to their ability to shorten reaction procedures, reduce wastes and use of mild conditions. Amongst them copper salts are relatively inexpensive, easy to handle, possess low toxicity and exhibit good functional tolerance.[6] Herein, we describe the novel system for synthesis of

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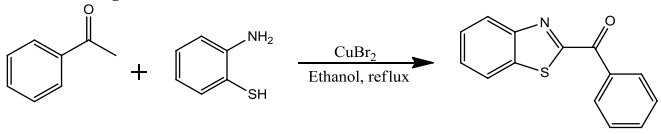
2-acylbenzothiazoles and their derivatives from aryl ketones and 2-aminobenzenethiols via copper salt mediated tandem reaction in presence of ethanol as a solvent.



Scheme 1. Synthesis of 2-acyl benzothiazoles

We initiated the present study with acetophenone and 2-aminobenzenethiol as model substrate in the presence of different copper salts in ethanol as a solvent at reflux temperature for 12 hours (Scheme 1) It was observed, that only Cupric bromide (1.5 equivalent) gave the desired product 2-acylbenzothiazole in 40% yield. No reaction was observed below 1.5 equivalent of $CuBr_2$, while use of 2 equivalent of $CuBr_2$ resulted into desired product 2-acylbenzothiazole in 75% yield along with traces of 2-arylbenzothiazole as a side product. Further increase in the amount of $CuBr_2$ did not influence the yield. Attempt was made to improve the yield of desired product and hence along with 1.5 equivalent of $CuBr_2$ various co-oxidants like $K_2S_2O_8$, H_2O_2, TBHP, Oxone, mCPBA were examined, but no significant change in the yield of the desired product was found. Finally, the reaction was conducted in the presence of oxygen atmosphere wherein 86% of the desired product was obtained without the formation of any side product. After optimizing the reaction conditions, it was observed that after 8 hrs under oxygen atmosphere in presence of 1.0 equivalent of $CuBr_2$ the desired product was obtained in good yield without any side product. Other copper salts under identical condition proved to be unsuccessful (Table 1).

Table 1. Optimization of the reaction conditions. [a]

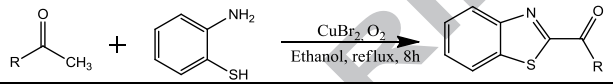
Entry	Copper salt	Co-oxidant	% Yield[b]
1	$CuBr_2$ (1.0)	---	NR
2	$CuBr_2$ (1.5)	---	40
3	CuCl (2.0)	---	NR
4	CuBr (2.0)	---	NR
5	CuI (2.0)	---	NR
6	Cu $(OAc)_2$ (2.0)	---	NR
7	$CuBr_2$ (2.0)	---	75
8	$CuBr_2$ (1.5)	Oxone	40
9	$CuBr_2$ (1.5)	$K_2S_2O_8$	40
10	$CuBr_2$ (1.5)	aq. TBHP	45
11	$CuBr_2$ (1.5)	m-CPBA	44
12	$CuBr_2$ (1.5)	aq. H_2O_2	42
13	$CuBr_2$ (1.5)	Oxygen	86
14	$CuBr_2$ (1.0)	Oxygen	86
15	$CuBr_2$ (0.5)	Oxygen	40

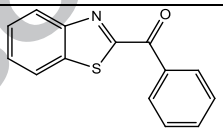
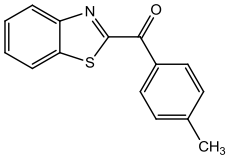
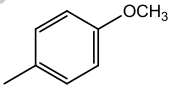
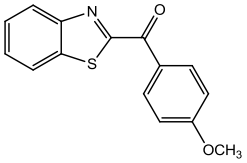
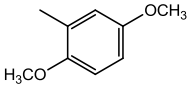
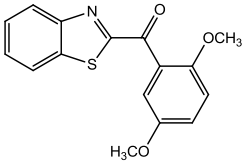
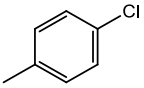
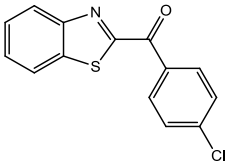
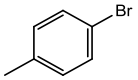
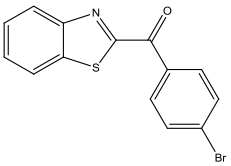
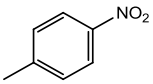
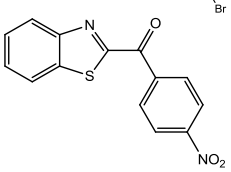
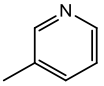
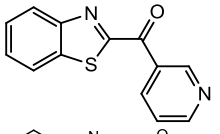
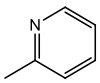
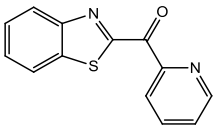
[a] Reaction conditions: 2-aminobenzenethiol (1.2mmol), acetophenone (1.0 mmol), in ethanol at reflux temperature for 8-12h. [b] Isolated yields of 2-acyl benzothiazole after column chromatography. [c] NR : no reaction

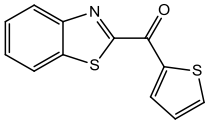
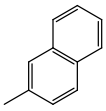
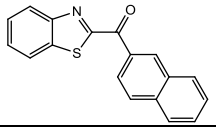
Further we screened various solvents under optimized reaction conditions and it was interesting to know that no product was obtained in non polar solvents like toluene, 1,4-Dioxane, DCM and $CHCl_3$ whereas in polar aprotic solvents such as DMF,THF, ACN a trace amount of desired product was formed. In case of polar protic solvents such as ethanol and water, maximum yield was obtained in ethanol as compared to water (40%) and hence ethanol was chosen as suitable solvent for this reaction.

With this optimized conditions in hand, scope of both aromatic and hetroaromatic ketones were established and results are presented in Table 2. It was noted that both electron donating and withdrawing groups are suitable for this transformation to get the corresponding product in moderate to good yield (Table 2, entries 2-7). Under this reaction condition, groups like methoxy were stable (Table 2, entries 3-4). Hetroaromatic groups also afforded moderate to good yield (Table 2, entries 8-10). Bulkier substituent such as naphthyl was also well tolerated under this reaction condition (Table 2, entry 11).

Table 2. Scope of aryl methyl ketones [a]



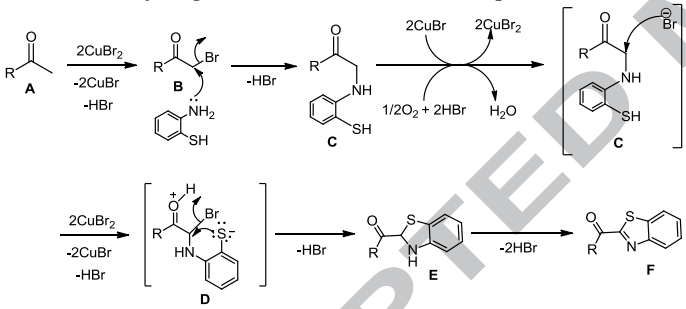
Entry	R	Product[b]	Yield (%)[c]
1			86
2			83
3			85
4			62
5			82
6			78
7			62
8			75
9			80

10			78
11			70

[a] Reaction conditions : 2-aminobenzenethiol (1.2 mmol), aryl-alkyl ketones (1.0 mmol), $CuBr_2$ (1.0 mmol) in ethanol at reflux temperature for 8h under Oxygen atmosphere. [b] Structures were confirmed by comparison of their NMR spectra, Mass spectra and melting points with literature data. [c] Isolated yields after column chromatography.

It was observed that in case of aliphatic ketones, such as methyl ethyl ketone; isobutyl-2-methyl ketone, no desired products were obtained. It was also observed that, substituted 2-aminothiophenol like 2-amino-4-chlorobenzenethiol also reacted with acetophenone to afford the desired product 5-chloro-1, 3-benzothiazol-2-yl(phenyl)methanone in 75% yield.

A plausible reaction mechanism for the tandem reaction is illustrated in Scheme 2. In the first step, bromination of aryl-alkyl ketones (A) gives α-bromoketones (B).[7a] Later nucleophilic substitution of amines with α-bromoketones (B) generates α-aminoketones (C).[7b] Further, bromination of α-aminoketones (C) leads to intermediate (D).[4h, 7c] Subsequent intramolecular nucleophilic attack by thiol leads to ring closure, generating intermediate (E). Finally, the intermediate (E) undergoes oxidative dehydrogenation to afford the desired product.



Scheme 2. Plausible reaction mechanism

In conclusion, we have developed simple, mild and efficient aerobic, copper-II mediated tandem protocol for the synthesis of 2-aroylbenzothiazoles. The protocol uses inexpensive copper salt, economic and environmentally friendly oxygen as the oxidant along with readily available aryl alkyl ketones as a starting material. Various functional groups were well tolerated leading to moderate to good yield. Absence of DMSO as a solvent suggests that the reaction follows a distinct path from Kornblum oxidation of alpha haloketones.

Acknowledgment

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Supplementary data

Experimental procedure and spectral data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016

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8. **General Procedure for preparation of 2- aroylbenzothiazoles**
A mixture of aryl-alkyl ketones (1.0 mmol), 2-aminobenzenethiol (1.2 mmol) and $CuBr_2$ (1.0 mmol) was stirred in ethanol. The reaction mixture was bubbled with oxygen (balloon) and was heated to reflux temperature for 8 hours. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with water, and then extracted with ethyl acetate. The organic extract was washed with $Na_2S_2O_3$ solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude product. The product was then purified with silica gel column chromatography (Hexane-EtOAc).

Graphical Abstract

Copper-II mediated tandem reaction between aromatic ketones and 2-aminobenzenethiol for the synthesis of 2-aroylbenzothiazoles

Jaishree K. Mali, Devidas A. Mali, Vikas N. Telvekar*

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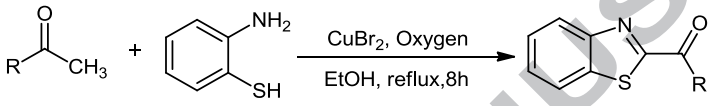

Highlights

- Tandem one step reaction for the synthesis of 2-aroylbenzothiazoles is developed
- Inexpensive, non-toxic, readily available copper (II) bromide is used as a mediator
- Absence of DMSO as a solvent, suggests that the reaction follows distinct path from Kornblum oxidation
- Desired products were obtained in moderate to good yields using a simple work-up procedure