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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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