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Copper-catalyzed synthesis of 2-sulfenylindoles from indoline-2-thiones and aryl iodides

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ABSTRACT

A novel and efficient method for synthesis of 2-sulfenylindole *via* copper-catalyzed coupling reaction of indoline-2-thiones with aryl iodides has been developed. A series of N-substituted and N-free 2-sulfenylindole were obtained in high yields. Furthermore, the method was employed to synthesis of benzothieno[2,3-b]indoles from indoline-2-thiones with 1,2-diiodobenzene in the presence of CuI and $Pd(OAc)_2$ as catalysts.

Sulfenylindoles[1], categorized as significant derivatives of indoles, are broadly found in bioorganic and medicinal chemistry with application in drug discovery and development for the treatment of various diseases (Figure 1), such as HIV,[2] cancer,[3] vascular,[4] respiratory disorders,[5] heart disease,[6] and allergies.[7] Consequently, many efficient methods were developed for the synthesis of sulfenylindoles.[8] Among them, the direct sulfenylation of indoles is an efficient and common strategy.[9] Due to the nucleophilic of indoles, the thioethers can be easily introduce in the 3-position of indoles and a variety of sulenylating reagents such as sulfenyl halide,[10] disulfides,[11] thiols,[12] arylsulfonyl chorides,[13] arylsulfonyl hydrazides,[14] sulfonium salts,[15] sulfinic acids[16] were smoothly coupled with indoles to 3-sulfenylindoles. However, the synthesis of 2-sulfenylindole was limited applying this protocol. The classic method to 2-sulfenylindole was used acid-catalyzed rearrangement of 3-sulfenylindole[17] and the sulfenylation of 2-lithioindoles.[18] Recently, Cossy and coworkers have found TFA-promoted direct C-H sulfenylation at C2 position of non-protected indoles for the synthesis of 2-sulfenylindoles.[19] Nevertheless, these methods suffer from use of strong acids and strong bases, incompatible with various functional groups. Thus, it is highly desirable to provide efficient and facile strategy for the preparation of 2-sulenylindoles.

Indole-2-thiones are an efficient synthon to construct 2-sulfenylindoles.[20] However, they are commonly used to synthesize the 2-alkyl thiolester indoles. Herein, we would like to disclose a useful application of indole-2-thones for the production of 2-sufenylindoles (Scheme 1).

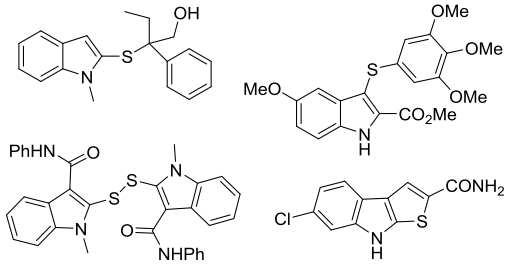
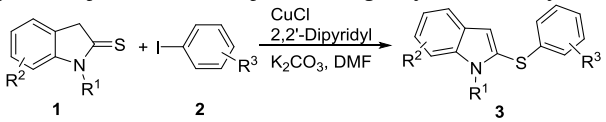


Figure 1 Representative examples of biologically active sulfenylindoles



Scheme 1 Method for preparation of 2-sulenylindoles

Initially, the coupling reaction of N-methylindoline-2-thione with iodobenzene was selected for optimization of reaction conditions, and the results are summarized in Table 1. Our investigation started by an attempted thiolation of N-methylindoline-2-thione with iodobenzene in DMF at 120 ^{o}C in the presence of CuI as the catalyst, and the desired product **3a** was isolated in 80% yield (entry 1). This result encouraged us to develop an efficient catalytic system to synthesize 2-sulfenylindoles from indoline-2-thiones and aryl iodides. A variety of copper catalysts, such as CuCl, CuBr, $Cu(OAc)_2$, $CuCl_2$, were screened and the results indicated that the catalyst of CuI is the best for this coupling reaction yet (entries 2-5). Without the copper catalyst, the desired product could not be isolated (entry 6). Subsequently, the effects of ligands were checked, and 2,2'-bipyridine was found to be an efficient ligand (entries 7-10). The effects of base (including K_3PO_4, KOAc, KF, and ^{t}BuOK) and solvent (including DMSO, CH_3CN and toluene) were examined. K_2CO_3 was found to give the best result and

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