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Efficient copper-catalyzed synthesis of C3-alkylated indoles from indoles and alcohols

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ABSTRACT

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ARTICLE INFO

Keywords: Alkylation of indole Cu catalysis Hydrogen borrowing Indole functionalization Sustainable process A highly efficient copper(II) catalyst system for alkylation of indoles with alcohols *via* hydrogen borrowing method has been developed to afford C3-alkylated indoles in good to excellent yields. $Cu(OAc)_2$ in the combination with dppm ligand has been found to be the most suitable catalyst system for this alkylation reaction.

1. Introduction

The indole framework is one of most popular heterocycles found in many important drugs, agrochemicals, advanced functional materials and bioactive natural products [1]. Especially, the indole structure has been identified as an important pharmacophore in medicinal chemistry research with representation in over 3000 natural products and 40 medicinal agents [2,3]. The construction of indole structure from simple building blocks based on the cyclization reactions in the absence or presence of metal catalysts has been well established [4-6]. On the other hand, the development of new synthetic methods for the direct functionalization of indoles has gained much attention [7]. The most common method for the direct alkylation of indoles is the Friedel-Crafts reaction using alkyl halides and Lewis acid catalysts [8]. However, this approach gives some drawbacks relating to the use of stoichiometric amounts of hazardous alkyl halides and Lewis acids, over alkylations, and poor regioselectivity [8]. It also forms a large amount of salt wastes which need to be treated after reaction. Recent advances in the development of new Brönsted acids and organocatalysts have provided greener processes for the direct functionalization of indoles [9-12]. High catalyst loadings (up to 20 mol%) were often required to give alkylated products in very good yields. Therefore, the development of more efficient and green alkylation methods using non-hazardous and less expensive starting materials would be highly beneficial for exploring future sustainable processes. Recently, hydrogen borrowing methodology is an alternative approach to the classical alkylation processes as non-toxic and easily available alcohols are used as alkylating reagents and the sole by-product is water [13–15]. In term of green and sustainable processes, this method provides the minimization of hazardous wastes and the avoidance of using toxic and expensive alkyl halides. Most popular catalysts for hydrogen borrowing processes are relied on expensive metals such as Ru, Ir, Rh, etc [13–15]. In recent years, these catalysts have been gradually replaced by earth-abundant metals (Co, Mn, Fe, etc.) in the combination with well-designed multidentate ligands [16,17].

Due to these significant reports in hydrogen borrowing method, the direct transition metals-catalyzed alkylation reactions of indoles using alcohols were disclosed. C3-alkylated indole has been commonly known as the main product. The catalytic cycle for the formation of C3-alkylated indole undergoes *via* three main steps: *i*) the dehydrogenation of alcohol to form aldehyde and metal-hydride species in the presence of metal catalyst, *ii*) the formation of alkylideneindolenine by the reaction of indole with aldehyde, *iii*) the hydrogenation of alkylideneindolenine intermediate by metal-hydride species to form desired product and regenerate metal catalyst for the next catalytic cycle (Scheme 1) [18–20]. In fact, C3-alkylated indole products could be formed in high yield and selectivity in the use of several expensive transition metal catalysts such as Pt [18], Pd [19,20], Ru [19,20] and Ir

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Scheme 1. Direct transition metal-catalyzed alkylation of indoles with alcohols via hydrogen borrowing method.

[21–25]. Interestingly, Piersanti et al. applied successfully Ir-catalyzed alkylation of indoles with amino alcohols in the synthesis of bioactive natural alkaloids such as Psilocin, Bufotenin, Serotonin and their derivatives [26]. In the recent development of practical alkylation processes of indoles with alcohols using base metals as catalysts, the first iron(II)-phthalocyanine catalyzed alkylation of indoles with alcohols was reported in moderate to very good yields [27]. One year later, cyclopentadienone iron carbonyl complexes were found to be highly efficient catalysts for the alkylation of indoles with a series of alcohols [28,29]. In 2017, Liu et al. described a highly convenient Co-based catalytic system by combination of $Co(BF_4)_2.6H_2O$ salt, a tetradentate phosphine ligand $P(CH_2CH_2PPh_2)_3$, for the methylation of indole with methanol [30]. To the best of our knowledge, until now, there are no

reports on Cu-catalyzed alkylation of indoles with alcohols *via* hydrogen borrowing approach. Herein, we are reporting a highly efficient Cu (OAc)₂/dppm catalyst system for alkylation of indoles with alcohols *via* hydrogen borrowing pathway to give C3-alkylated indoles in high yields.

2. Experimental section

General information: Readily available chemicals and solvents were used in this research without further purification. Products purification was performed on silica gel by column chromatography, technical-grade solvents were used. Reactions were put in magnetic stirrer and monitored by thin layer chromatography using Merck Silica Gel 60 F254 TLC

Table 1

Optimization of the reaction conditions for the Cu-catalyzed alkylation of indole with benzyl alcohol.

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17 Cu(OAc) ₂ KOH (1.0) dppm 83 ^b 18 Cu(OAc) ₂ KOH (2.0) dppm 99 19 Cu(OAc) ₂ KOH (2.0) dppm 99 ^c	16	Cu(OAc) ₂	K_2CO_3 (1.0)	dppm	_
18 Cu(OAc) ₂ KOH (2.0) dpm 99 19 Cu(OAc) ₂ KOH (2.0) dpm 99 ^{c)}	17	Cu(OAc) ₂	KOH (1.0)	dppm	83 ^{b)}
19 $Cu(OAc)_2$ KOH (2.0) dppm 99^{c}	18	Cu(OAc) ₂	KOH (2.0)	dppm	99
	19	Cu(OAc) ₂	KOH (2.0)	dppm	99 ^{c)}
20 Cu(OAc) ₂ KOH (2.0) dppm 72^{u_1}	20	$Cu(OAc)_2$	KOH (2.0)	dopm	72 ^{d)}
21 Cu(OAc) ₂ KOH (2.0) doppm 66°	21	$Cu(OAc)_2$	KOH (2.0)	dppm	66 ^{e)}
22 Cu(OAc) ₂ KOH (2.0) $ 35^{c}$	22	$Cu(OAc)_2$	KOH (2.0)		35 ^{c)}
23 Cu(OAc) none dnom _	23	Cu(OAc)	none	dnnm	_
24 _ KOH(2,0)	20	-	KOH (2.0)		_

Reaction conditions: Indole (0.5 mmol), benzyl alcohol (0.5 mL), Cu precursor (5 mol%), ligand (5 mol%), base (2 equiv.). Reaction was performed under argon; ^{a)} Isolated yields; ^{b)} Using 1 mol% Cu(OAc)₂, 1 mol% dppm; ^{c)} Reaction was completed in 6 h; ^{d)} Reaction was carried out in 6 h using 0.3 mL BnOH; ^{e)} Reaction was carried out at 150 °C in 6 h.

Table 2

Scope of Cu-catalyzed alkylation of indoles using alcohols^a).



plates. NMR spectra of products were measured in the CDCl₃ solvent using a cryoprob on a Bruker Avance 500 (500 MHz, ¹H NMR; 126 MHz, ¹³C NMR). Chemical shifts (δ) are given in parts per million (ppm) in the comparison to tetramethylsilane (TMS) for ¹H and ¹³C NMR spectra and also calibrated using the solvent residual peak. Multiplicities of spectra using MNova software are reported as following: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal or as a combination of them. Coupling constants (*J*) are reported in Hertz (Hz).

General procedure for the synthesis of compounds 1-18: A mixture of indole (0.5 mmol, 58.6 mg), Cu(OAc)₂ (4.54 mg, 5 mol%), dppm (9.6 mg, 5 mol%), KOH (56 mg, 2 equiv.) and benzyl alcohol (0.5 mL, about 5 mmol) were charged in a pressure tube under argon. The pressure tube was immersed in a pre-heated oil bath at 160 °C and stirred for 12 h. After cooling, the reaction mixture was filtered over a plug of Celite with hot water to eliminate the benzaldehyde and the excess of benzyl alcohol. Ethyl acetate was added into the organic phase and this mixture was dried by sodium sulfate (Na₂SO₄). The concentrated residue was purified by column chromatography (Hexane/ethyl acetate).

3. Results and discussion

Our first optimization studies for the alkylation of indole using benzyl alcohol as alkylating reagent showed that homogeneous copper catalysts obtained *in situ* from copper salts in the combination with a

phosphine ligand could catalyze the formation of C3-alkylated indole at 160 °C under argon. Our initial screenings using a catalytic amount of Cu(OAc)₂ (5 mol%) and a monodentate ligand (such as PPh₃, Xphos) in the presence of KOH base only gave the desired product in moderate yields, as presented in Table 1 (entries 1,2). Interestingly, under this condition, the yield was improved to 74 % in the employment of Xantphos, a bidentate ligand at 160 °C (Table 1, entry 3). Based on this good result, we would continue to examine a series of bidentate ligands (dpePhos, dppf, BINAP). In these reactions, the combination of Cu (OAc)₂ and BINAP ligand seemed to be a promising catalyst system which gave 85 % isolated yield of desired product (entry 6). In order to find the most suitable ligand for this reaction, other bidentate ligands such as dppp, dppe, dppm were also examined. Up to 92 % isolated yield of alkylated indole was achieved when the dppm ligand was employed (entry 9). Further examinations using common copper catalyst precursors (CuBr₂, CuCl₂ and CuI; entries 10-12) resulted in inferior results compared to that of Cu(OAc)₂ and this condition was selected as the catalyst precursor for further investigations using different bases. Several other bases such as NaOH, KOt-Bu, K₃PO₄, K₂CO₃ did not provide a better yield than our optimized experiment using KOH base (entries 13-16). Interestingly, when the catalyst loading was reduced to 1 mol%, we still obtained 83 % yield of desired product (entry 17). We continued with further optimization by increasing KOH amount to 2

equiv., quantitative yield of alkylated product was achieved under



Scheme 2. Control experiment.



Scheme 3. Plausible catalytic cycle for the alkylation of indoles with alcohols *via* hydrogen borrowing pathway.

optimized condition. In fact, the alkylation reaction was completed and gave 99 % yield of product after only 6 h reaction (entry 19). Then we reduced reaction temperature to 150 °C under optimized condition, the yield dropped to 66 % (entry 21). When we reduced the amount of BnOH (using 0.3 mL), we obtained lower product yield (72 %) (entry 20). This issue could be explained by when performing reaction at high temperature (160 °C), BnOH (as solvent) slowly evaporated and condensed on the wall of pressure tube and we realized that an excess amount of BnOH is required to provide enough Cu-H active species to completely reduce benzylideneindolenine intermediate to product. Then, we are interested in investigating the true role of catalyst and base, several control experiments were carried out. Notably, without the attention of Cu catalyst, only trace amount of product was observed in the presence of base (entry 24). We also realized that base played an important role in this reaction, in fact, this alkylation reaction did not run in the absence of base (entry 23).

Next, we opened the substrate scope of this Cu-catalyzed alkylation of indoles with different alcohols. For this purpose, reactions were carried out at 160 °C for 12 h compared to the optimized condition (Table 1, entry 19) to ensure complete conversion even when less reactive aliphatic alcohols were used. In general, the alkylation of indoles with benzylic alcohol derivatives were examined which gave moderate to excellent yields (Table 2). In case of alkylation reaction using fluorinated and trifluoromethylated benzyl alcohols, moderate yields of desired products were obtained (compounds 7-9). Notably, more challenging aliphatic alcohols could be used as alkylating reagents in the reaction of indole which afforded to good yields of alkylated products in 24 h (compounds 10-12). Interestingly, the alkylation of substituted indoles with benzyl alcohol *via* hydrogen borrowing strategy giving the corresponding products. In fact, the alkylation of 5-methoxyindole using benzyl alcohol gave desired product in 84 % yield (compound 13). Fluorinated indoles could also be used as starting materials resulted in 87 % and 40 % yields, respectively (compounds 14, 15). The alkylation of 6-bromoindole and 7-methylindole with benzyl alcohol afforded to corresponding products in 85 % and 95 % isolated yields, respectively (compound 16, 17). Unfortunately, when N-methylindole was used in the alkylation with benzyl alcohol, no trace amount of desired product was observed under standard condition. From this result, we believe that the N-methylated benzylideneindolenine intermediate was unable to form during the course of reaction using N-methylindole.

In order to understand about the hydrogen borrowing mechanism of this alkylation, we decided to choose a reaction mixture of indole, benzaldehyde and 3-methylbenzyl alcohol under standard condition (Scheme 2). After 12 h reaction, we isolated hydrogen transferred product 1 in 55 % yield, alkylated product 2 in 20 % yield and small amount of 3-methylbenzaldehyde 2a (32 % yield). It means that Cu-H species could be formed and then reduced 3-benzylidene-3*H*-indole intermediates to form both products 1, 2 (see a proposed catalytic cycle in Scheme 3). From this interesting result, we could confirm the true hydrogen borrowing mechanism which occurred in our copper catalyst system.

A plausible mechanism is proposed in Scheme 3 relying on our results (Table 1, Scheme 2) and previous research on copper catalyzed reactions. First, the *insitu*-formed copper complex I could react with potassium alkoxide to give copper alkoxide (intermediate II) which subsequently generate copper hydride complex (intermediate III) and an aldehyde. Then, in the presence of KOH, this aldehyde reacted with indole molecule to form 3-benzylidene-3*H*-indole which easily coordinate to copper hydride (III) to afford intermediate IV. Next, the hydride transfer step from copper hydride to indole ring occurred to give intermediate V which further reacted with potassium alkoxide to form the alkylated product and regenerate copper alkoxide (intermediate II) for the next catalytic cycle. Actually, a bidentate ligand (such as dppm) played a crucial role by stabilizing copper intermediates.

4. Conclusion

Herein, we have disclosed a practical and highly efficient homogeneous $Cu(OAc)_2/dppm$ catalyst system for the direct alkylation of indoles using alcohols. The chemoselective C3-monoalkylation of indoles with alcohols (including challenging aliphatic alcohols) was achieved in good to excellent yields. This practical procedure using simple copper catalyst system could be useful for preparing complex indoles containing various functional groups and exploring potential applications in medicinal chemistry and fine chemical industry. Further experimental studies in the combination with DFT calculation to understand mechanistic insights are currently carried out in our group.

Reaction conditions: ^{a)} Indole (0.5 mmol), benzyl alcohol (0.5 mL), Cu (OAc)₂ (5 mol%), dppm ligand (5 mol%), base (2.0 equiv.). Reactions were carried out under argon; ^{b)} Reactions were prolonged to 24 h.

CRediT authorship contribution statement

Ngoc-Khanh Nguyen: Methodology, Investigation. Duong Ha Nam: Investigation. Ban Van Phuc: Validation. Van Ha Nguyen: Writing - original draft, Validation. Quang Thang Trinh: Visualization, Investigation. Tran Quang Hung: Supervision, Validation. Tuan Thanh Dang: Supervision, Project administration, Writing - review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.mcat.2021.111462.

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