Tetrahedron Letters 68 (2021) 152936

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Facile access to *bis*(indolyl)methanes by copper-catalysed alkylation of indoles using alcohols under air

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ARTICLE INFO

Article history:
Received 7 December 2020
Revised 1 February 2021
Accepted 11 February 2021
Available online 20 February 2021

Keywords:
Bis(3-indolyl)methane synthesis
Copper catalysis
Indole functionalization
Alkylation
Sustainable process

ABSTRACT

Bis(3-indolyl)methanes (BIM) are important and present in the structure of many alkaloid and bioactive compounds (anti-inflammatory, anticancer, antiobesity, antimicrobial, etc.). Herein, we have reported an air stable and convenient $Cu(OAc)_2$ catalyst for alkylation of indoles with alcohols to give *bis*(3-indolyl) methanes in very good yields.

Introduction

The indole structure is an important type of heterocycle present in many drugs, agrochemicals, advanced materials and bioactive natural products [1–22]. The indole moiety is an important pharmacophore in medicinal chemistry and occurs in over 3000 natural products and 40 drugs [2,3]. Notably, *bis*(3-indolyl)methanes (BIMs) are an important subgroup of indoles, due to their presence in the core structure of many pharmacologically important natural products (arundine, arsindoline A, barakacin, vibrindole A, etc. [2–22]. For example, arundine is known as a potential agent for the treatment of breast cancer [4]. Vibrindole A was successfully used in the treatment of irritable bowel syndrome, fibromyalgia and chronic fatigue [5]. In addition, BIM derivatives have found many applications in the exploration of new bioactive compounds (anticancer, anti-inflammatory, antiobesity, antimetastatic, antimicrobial, etc.) (Fig. 1) [13–21].

Conventional syntheses of indole derivatives rely on the cyclization of simple building blocks in the absence or presence of metal catalysts [7–16]. However, the formation of large molecules containing several indole moieties, requires other synthetic approaches [13,17–23]. Because of the importance of BIM derivatives in medicinal chemistry, the development of efficient pathways for their preparation has received much attention. Most reports are based on the reaction of indoles with aldehydes or ketones in the presence of Lewis or Bronsted acids [7–13]. As a consequence of the growing demand for green and sustainable processes, methods for the preparation of BIMs by direct transition metal-catalysed coupling reactions of indoles with alcohols have been described [24–30]. Grigg *et al.* reported the observation of BIM as a side product during their research in the Ir-catalysed alkylation of indoles with alcohols [24]. In 2012, Liu *et al.* described the preparation of BIM derivatives in good yields based on the Ru-catalysed alkylation reaction of indoles with benzylic alcohols [28]. One year later, the Ohta group demonstrated an efficient Ru-catalysed alkylation of indole with benzyl alcohols (24 h at 110 °C) [27]. Very recently, in 2020, Srimani and coworkers reported alkylation reactions of indoles with alcohols to afford either C3-alkylated products or BIMs by tuning reaction conditions [25]. In these reactions an acridine-derived ruthenium pincer complex was employed as the catalyst. Hikawa and Yokoyama developed an interesting Pd-catalysed domino reaction for the synthesis of BIMs involving C3–H benzylation of indoles and

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https://doi.org/10.1016/j.tetlet.2021.152936
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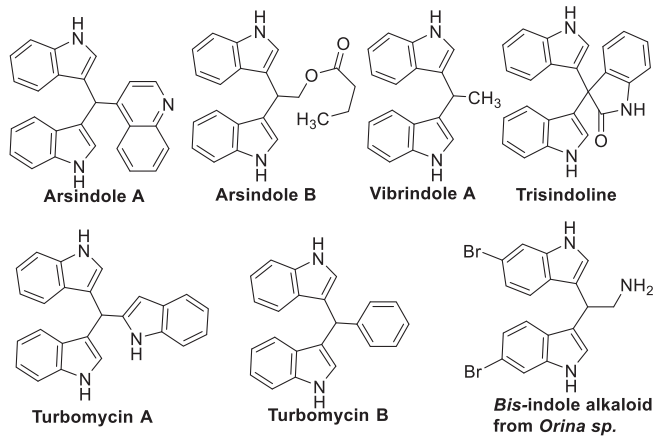


Fig. 1. Several natural alkaloids and pharmaceutically active compounds containing BIM derivatives.

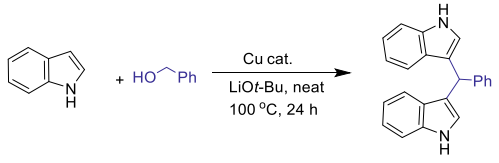
benzyl C—H functionalization in water [26]. In 2014, Sekar and coworkers described a practical $FeCl_2$/BINAM catalyst system in the combination with dicumyl peroxide oxidant which could be used for the preparation of BIMs in moderate yields [29]. Recently, Ni nanoparticles, supported on ionic liquid-functionalized magnetic silica, were found to be an efficient catalyst for the synthesis of BIMs under air [30]. In 2019, a convenient method for the preparation of BIMs by alkylation of indoles and alcohols using Fe_3O_4@-SiO_2@TPP-Cu as the photocatalyst under blue LED light irradiation was reported [31]. In general, the methods for preparation of BIM derivatives often require the use of expensive or well-designed catalysts under harsh reaction conditions which makes it difficult to find broad synthetic applications.

In order to develop a practical procedure for the preparation of BIM derivatives, we were interested in exploring direct alkylations of indoles using inexpensive alcohols as alkylating reagents and simple metal salts as the catalyst. Herein, we report, for the first time, a robust, ligand-free Cu-catalysed method for the convenient synthesis of *bis*(3-indolyl)phenylmethane derivatives under air.

Results and discussion

In order to optimize the reaction, we chose indole and benzyl alcohol as the key starting materials in the presence of several

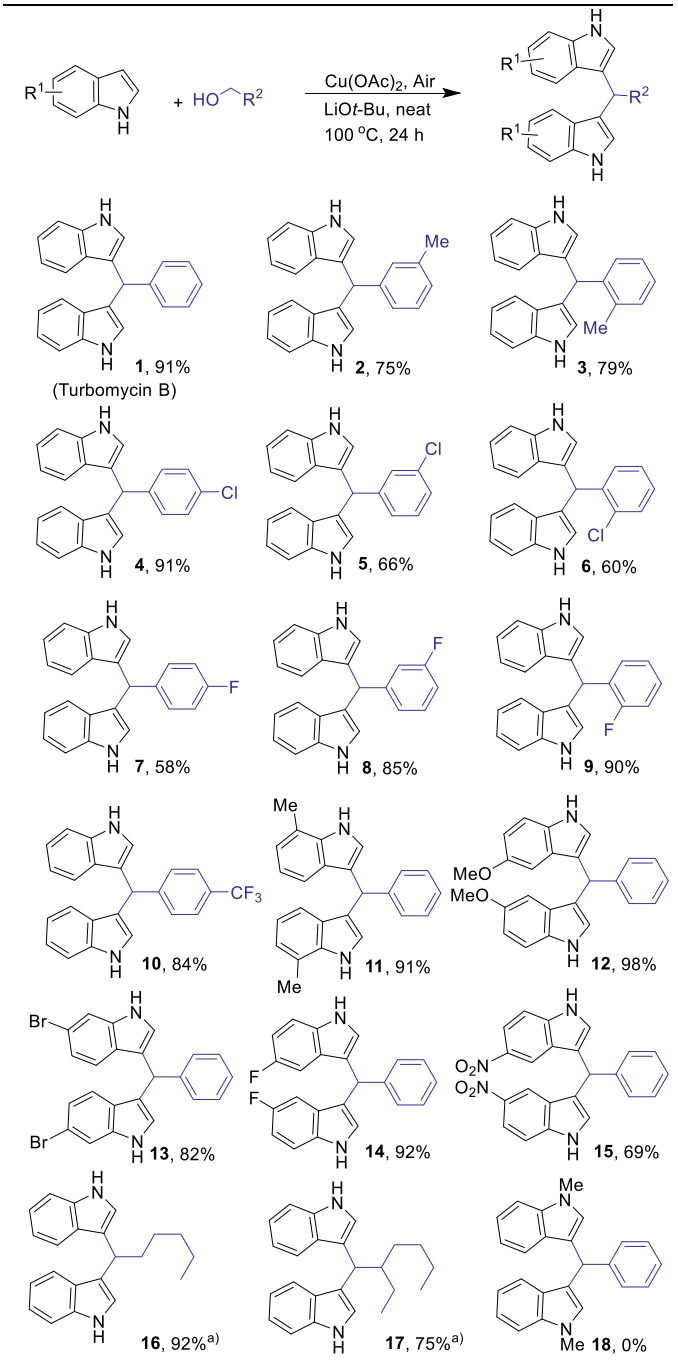
Table 1
Optimization of the reaction conditions for the synthesis of *bis*(3-indolyl) phenylmethane.



Entry	Catalyst (mol%)	Base (equiv.)	Yield (%)[a)]
1	CuCl (5)	KOH (1.0)	32
2	$CuCl_2$ (5)	KOH (1.0)	45
3	$Cu(OAc)_2$ (5)	KOH (1.0)	67
4	$Cu(OAc)_2$ (5)	KO*t*-Bu (1.0)	40
5	$Cu(OAc)_2$ (5)	LiO*t*-Bu (1.0)	96
6	$Cu(OAc)_2$ (1)	LiO*t*-Bu (1.0)	87
7	$Cu(OAc)_2$ (5)	–	–
8	–	LiO*t*-Bu (1.0)	9
9	$Cu(OAc)_2$ (5)	LiO*t*-Bu (1.0)	12[b)]

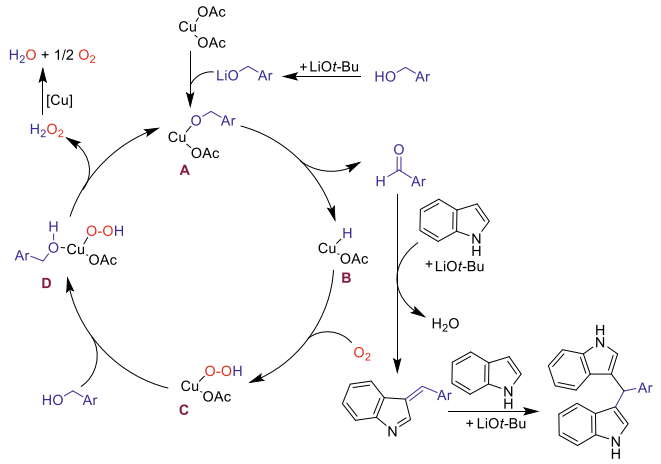
Reaction conditions: Indole (0.3 mmol), benzyl alcohol (0.9 mmol); [a)]Isolated yield. [b)] reaction was carried out under argon atmosphere.

Table 2
Scope in the synthesis of *bis*(3-indolyl)phenylmethanes.



Reaction condition: Indole (0.3 mmol), benzyl alcohol (0.9 mmol), $Cu(OAc)_2$ (5 mol %), base (1.0 equiv.); [a)] Reactions were carried out at 120 °C.

copper catalysts. After screening several conditions using homogeneous copper catalysts in combination with several ligands at high temperature (higher than 120 °C), we only obtained mixtures of hydrogen transferred product and *bis*(3-indolyl)phenylmethane (BIM). Interestingly, we observed that BIM could be often formed in higher selectivity at lower temperature. After having carried out several control experiments, we obtained promising yields of BIM product using only $Cu(OAc)_2$ as a single catalyst in the absence of any ligand under air (Table 1). CuCl and $CuCl_2$ catalysts were also examined which, however, did not give better yields of BIM



Scheme 1. Proposed catalytic cycle for the formation of BIM products.

product. Indeed, in the presence of $Cu(OAc)_2$ as catalyst (5 mol%), we achieved 67% yield of BIM product at 100 °C. Subsequently, we tried to improve the yield by changing the base. In fact, LiO*t*-Bu was found to be the most suitable base in this transformation which gave up to 96% yield of the desired product (Table 1, entry 5). Notably, up to 87% yield of product was obtained when a low catalyst loading (1 mol%) was employed (Table 1, entry 6). In order to gain some further insights in this transformation, additional control experiments were carried out. Firstly, we only observed trace amounts of product in the absence of base or catalyst (Table 1, entry 7, 8). Then, the role of oxygen as a key oxidant could be confirmed when we performed this reaction under argon atmosphere. In fact, the BIM product was only obtained in very low yield (12%) after 24 h reaction time (Table 1, entry 9). Under this condition, C3-alkylated indole was formed as a side product in 25% yield. Based on this result, we believe that oxygen serves as essential oxidant in this reaction.

With optimized conditions in hand, we further explored the scope of this reaction using various alcohols (Table 2). Firstly, a series of benzyl alcohols were used in the alkylation of indoles. A variety of BIM derivatives, with tolerance of both electron donating and withdrawing groups, were prepared in good to excellent isolated yields (Table 2). Indeed, the $Cu(OAc)_2$-catalysed alkylation reaction of indole with parent benzyl alcohol gave a better yield than those of indole with other benzyl alcohol derivatives. It is worth to be mentioned, that product **1** represents an antibiotic and natural product named turbomycin B [7]. Subsequently, reactions of substituted indole derivatives were studied which gave very good yields of the corresponding BIMs (Table 2, compounds **1**–**15**). Interestingly, when 5-methoxyindole was employed, up to 98% yield of BIM product was obtained (compound **12**). The reaction of 5-nitroindole, bearing to a strong electron withdrawing group, resulted in lower yield of BIM product **15**, due to lower nucleophilicity of the indole. The reactions of indole with aliphatic alcohols only gave desired BIM products in moderate yield under 100 °C. Therefore, we increased reaction temperature to 120 °C which gave correstponding products **16, 17** in higher yields (92% and 75%, respectively). Unfortunately, the alkylation of *N*-methyl indole with benzyl alcohol did not give any trace of BIM product **18**.

Basing on our experimental results (Table 1) and the existing literature reports [32–36], a plausible mechanism is proposed as depicted in Scheme 1. Firstly, in the presence of $Cu(OAc)_2$ catalyst and lithium alkoxide, benzyl alcohol is oxidized to form a copper-alkoxide (intermediate A) and benzaldehyde which subsequently reacts with indole to give 3-benzylidene-3*H*-indole. Next, in the presence of base (LiO*t*-Bu), nucleophilic addition of another indole molecule to 3-benzylidene-3*H*-indole takes place by a Michael-type reaction to afford the final BIM product. Ramon et al. showed by labelled experiments, that in the Cu-catalysed reaction of alcohols with amines hydrogen is transferred to the product [13]. Based on this result, we believe that intermediate A is converted to copper hydride (intermediate B) which easily reacts with oxygen to form a copper hydroperoxide complex (intermediate C). The formation of copper hydride and copper hydroperoxide complexes as intermediates was well studied in previous reports of related transformations [32–36]. In the absence of any ligand, the solvent (benzyl alcohol) can bind to the coordination free site of copper intermediate C to give intermediate D which is further converted to hydrogen peroxide to regenerate the copper alkoxide (intermediate A) for the next catalytic cycle.

Conclusion

Herein, we have reported a practical, robust and efficient method for the direct alkylation of indoles with alcohols under air. The products, BIM derivatives, represent important core structures in natural products and medicinal chemistry and were isolated in very good yields The reactions are based on the use of inexpensive $Cu(OAc)_2$ as homogeneous catalyst. The procedure is advantageous in comparison with previous methods which need to be carried out under inert gas atmosphere using expensive transition metal catalysts and ligands. Further experimental studies in combination with DFT calculations to better understand the mechanism of this reaction are currently carried out in our group.

Funding information

This research is funded by Vietnam National Foundation for Science and Technology Development (NAFOSTED) under grant number 104.01-2018.30.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152936.

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