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CF_3SO_2Na-Mediated, UV-Light-Induced Friedel–Crafts Alkylation of Indoles with Ketones/Aldehydes and Bioactivities of Products

Tianbao Yang,[‖] Huiai Lu,[‖] Yixuan Shu, Yifeng Ou, Ling Hong,* Chak-Tong Au, and Renhua Qiu*

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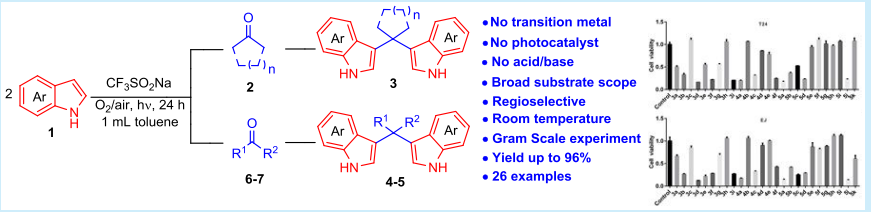
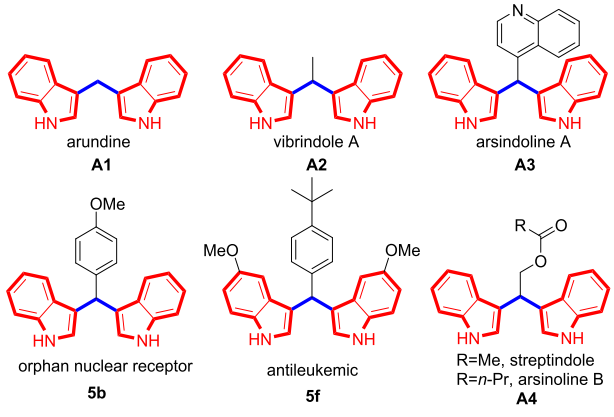


ABSTRACT: A concise, one-step route to produce 3,3′-diindolylmethanes (DIMs) from simple indoles and ketones or aldehydes is reported. The key step is the ready formation of indole derivatives that involves the in situ conversion of CF_3SO_2Na reagent to $\cdot CF_3$ under oxygen or air (1.0 atm) and UV irradiation. It is disclosed that most of the obtained DIMs show anticancer activities in human bladder cancer cell lines EJ and T24.

Indole moieties are common in a great number of pharmaceuticals and biologically important natural products.[1] It is especially so for the diindolylmethane derivatives (DIMs),[2] which exhibit a wide range of bioactivities, such as antileishmanial,[3] antistaphylococcal,[4] and anticancer.[5] For example (Scheme 1), 3,3′-diindolylmethane (**A1**) is a novel

Scheme 1. Biologically Active DIMs



preventive for breast cancers and has been used in therapeutic treatment,[6] and 3,3′-((4-methoxyphenyl)methylene)bis(1*H*-indole) (**5b**) could serve as an orphan nuclear receptor.[7] Furthermore, vibrindole A (**A2**) is useful for the treatment of fibromyalgia, chronic fatigue, and irritable bowel syndrome.[8] As for natural products, arsindoline A (**A3**)[9] and arsinoline B (**A4**)[10] from a marine-derived bacterium strain CB101 and their analogues have been reported.[11]

Because of their biological potential, DIMs have received much attention in organic synthesis, and several highly efficient methods have been developed for their production.[12−14] One of them is the Cu-catalyzed cross-coupling of asymmetry substituted indole (Scheme 2a).[12d] By means of organocatalysis, Huo et al.[12e] developed a synthetic method to generate DIMs from sodium triphenylphosphine-*m*-sulfonate (TPPMS) and CBr_4 (Scheme 2b). Later, Toy et al.[12a] used a novel approach of "halogen bond donor" to catalyze Friedel–Crafts reactions of indoles with aldehydes and ketones for the direct production of DIMs. Moreover, a concise method has been realized with specific active starting materials for the synthesis of DIMs at 80−100 °C without the need of a catalyst (Scheme 2c).[12b,c] In recent years, photocatalysis has been demonstrated to be an effective approach for the construction of useful organic skeletons under mild conditions. The first Rh-6G-catalyzed and photoinduced aerobic oxidative cross-coupling of indoles to DIMs was achieved by Zhang et al. using active glycine derivatives (Scheme 2d).[9] Nonetheless, most of the existing methods involve the use of a transition metal, an acid or a base, a Lewis acid, or substrate activation. Thus a simple, mild, and general protocol to afford DIMs is meaningful.

Herein we demonstrate a highly efficient method for the synthesis of DIMs from simple indoles and aldehydes or ketones directly using easily handled, greatly abundant, and

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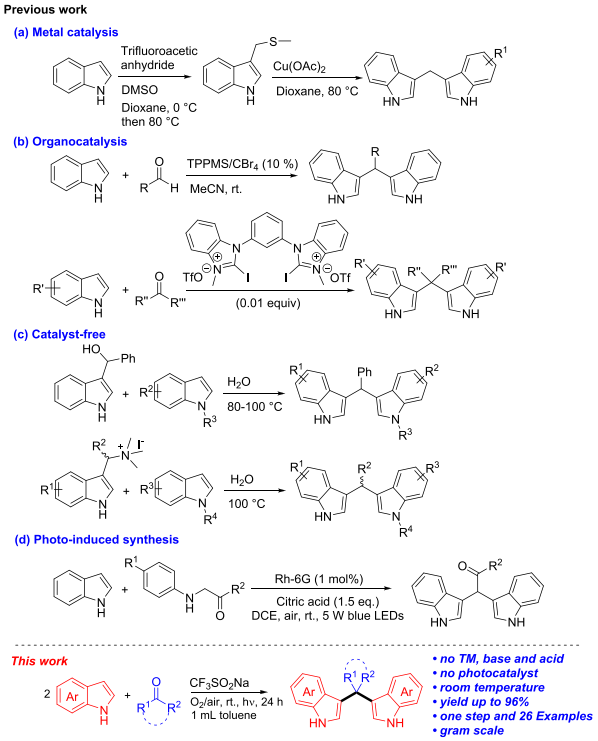
Scheme 2. Synthetic Approaches toward DIMs

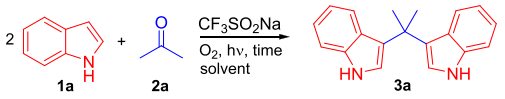


commercially available neutral salt CF_3SO_2Na as a mediator. The reaction is conducted at room temperature under UV irradiation and 1 atm pressure. The method does not involve any use of a transition metal, photocatalyst, base, or acid. It shows a broad substrate scope and gram-scalable ability. It is noted that most of the obtained DIMs show anticancer activities in human bladder cancer cell lines EJ and T24. Finally, a possible mechanism is proposed for the synthesis.

We first attempt to synthesize 3,3′-(propane-2,2-diyl)bis-(1*H*-indole) **3a** by treating a mixture of indole **1a** with acetone **2a** (1.0 mL, also as a solvent) and 1.0 equiv of CF_3SO_2Na under UV irradiation in an oxygen atmosphere, and the yield of **3a** is 57% (Table 1, entries 1−4). Next, we optimize the amount of CF_3SO_2Na, and 2.0 equiv of the salt is the best (63%, entry 5). Afterward, the reaction is carried out at room temperature by adding 5.0 equiv of acetone **2a**, and the **3a** yield is 77% at 19 h (entry 10) and 81% at 24 h (entry 11). The reaction does not take place without light or oxygen (entries 12 and 13). When the reaction is conducted in air (1 atm), the yield is low (34%, entry 14). In addition, in the absence of CF_3SO_2Na, there is no reaction (entry 15). The X-ray structure of **3a** is shown in Scheme 3.

Adopting the optimized conditions, we explored the scope of the substrates (Scheme 3). With the attachment of the electron-deficient fluorine atom on the indole, there is an apparent decrease in reactivity (**3b**, 17%), plausibly due to the lowering of the electron density of aromatic rings. In the case of introducing a 5-methoxy group on the indole, the product yield increases to 49% (**3c**). The insertion of a cyano group results in a good product yield (**3d**, 84%). With 5-NO_2 and 6-NO_2 groups on the rings, the yields of products **3e** and **3f** are significantly different, 70 and 38%, respectively. In the case of having a 7-methoxy group on the rings, the yield of **3g** is 55%. As for alkyl ketones, cyclopentanone and cyclohexanone give **3h** and **3i** in 40 and 30% yield, respectively. Compared with

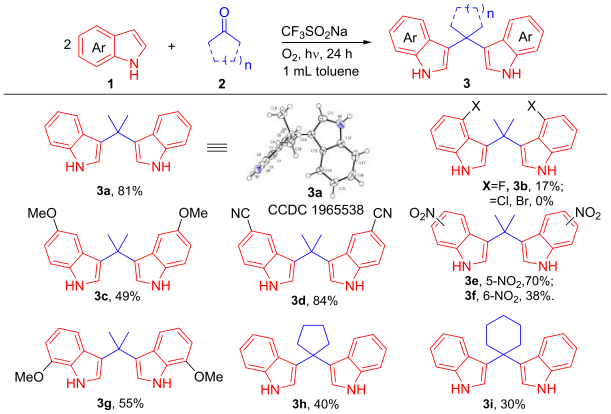
Table 1. Optimization of Reaction Conditions for 3a[a]



entry	**2a** (equiv)	CF_3SO_2Na (equiv)	time (h)	yield (%)
1	46	0.1	24	36[b]
2	46	0.5	24	44[b]
3	46	0.7	24	61[b]
4	46	1	24	57
5	46	2	24	63
6	1	2	19	36[b]
7	2	2	19	60[b]
8	3	2	19	60[b]
9	4	2	19	59
10	5	2	19	77
11	5	2	24	81
12	5	2	24	NR[c]
13	5	2	24	NR[d]
14	5	2	24	34[e]
15	5	2	24	NR[f]

[a]Reaction conditions: indole **1a** (0.3 mmol, 1.0 equiv), acetone **2a** (1.5 mmol, 5.0 equiv), CF_3SO_2Na (0.6 mmol, 2.0 equiv), toluene (1.0 mL, 0.3 M), O_2 (1.0 atm), UV irradiation (350−380 nm, 26 W lamp), rt, 24 h; isolated yield. [b]GC yield. [c]No light. [d]N_2 atmosphere. [e]Air atmosphere. [f]No CF_3SO_2Na.

Scheme 3. Substrates Scope with Alkyl Ketone[a]



[a]Reaction conditions: indole **1** (0.3 mmol, 1.0 equiv), ketone **2** (1.5 mmol, 5.0 equiv), CF_3SO_2Na (0.6 mmol, 2.0 equiv), toluene (1.0 mL, 0.3 M), O_2 (1.0 atm), UV irradiation (350−380 nm, 26 W lamp), rt, 24 h; isolated yield.

the previous protocol,[14a] our approach gives a better yield of **3a** (81%). (The yield of using $Bi(NO_3)_3{\cdot}5H_2O$ as the catalyst is 67%.)

Aromatic ketones are also well adopted in this reaction (Scheme 4). Acetophenones with bromine and iodine show similar reactivities (**4a−c**, 58−62%). Acetonaphthones with methyl sulfide and naphthyl groups give **4d** and **4e** in much lower yield (31 and 26%, respectively). With the thiophene derivative, the yield of **4f** is 36%, but in the cases of furan and pyrrole, there is no yield of any product. However, our system provides excellent selectivity for **4a**,**b**. Nonetheless, when HCl was used, the yields of **4a** and **4b** become 37 and 53%, respectively, with two side products.[13]

Compared with the ketones that are less reactive, the aldehydes show much higher efficiency. No matter whether an

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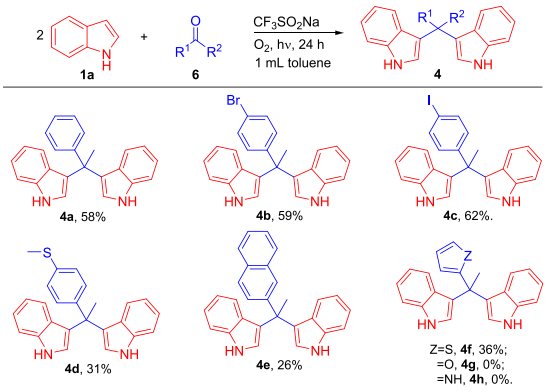
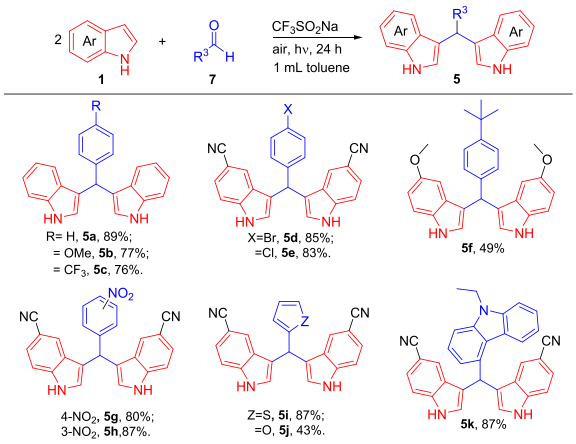
Scheme 4. Substrates Scope with Aromatic Ketones[a]



[a]Reaction conditions: indole **1a** (0.3 mmol, 1.0 equiv), ketone **6** (1.5 mmol, 5.0 equiv), CF_3SO_2Na (0.6 mmol, 2.0 equiv), toluene (1.0 mL, 0.3 M), O_2 (1.0 atm), UV irradiation (350−380 nm, 26 W lamp), rt, 24 h; isolated yield.

electron-donating or an electron-withdrawing group is attached on the aromatic rings (e.g., methoxy, bromine, chlorine), the aldehydes readily give DIMs in good yield under an air atmosphere (**5a**−**e**, 76−89%) (Scheme 5). 3-Nitrobenzaldehyde and 4-nitrobenzaldehyde could also participate in this reaction (**5g**,**h**, 80−87%). As for heteroaryl aldehydes such as thiophene-2-carbaldehyde, furfural, and 9-ethyl-9*H*-carbazole-4-carbaldehyde, **5i**, **5j**, and **5k** are produced in 87, 43, and 87% yield, respectively. Notably, if the reaction of these aldehydes was conducted under an O_2 atmosphere, then there would be many side products, and the corresponding yields would be much lower.

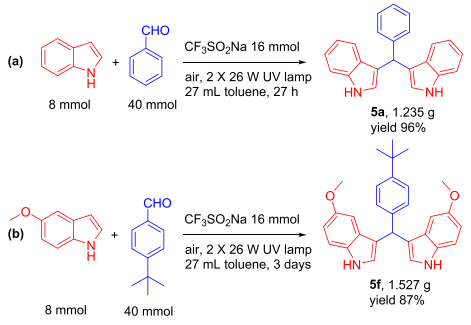
Scheme 5. Substrate Scope with Aldehydes[a]



[a]Reaction conditions: indole **1** (0.3 mmol, 1.0 equiv), aldehyde **7** (1.5 mmol, 5.0 equiv), CF_3SO_2Na (0.6 mmol, 2.0 equiv), toluene (1.0 mL, 0.3 M), air (1.0 atm), UV irradiation (350−380 nm, 26 W lamp), rt, 24 h; isolated yield.

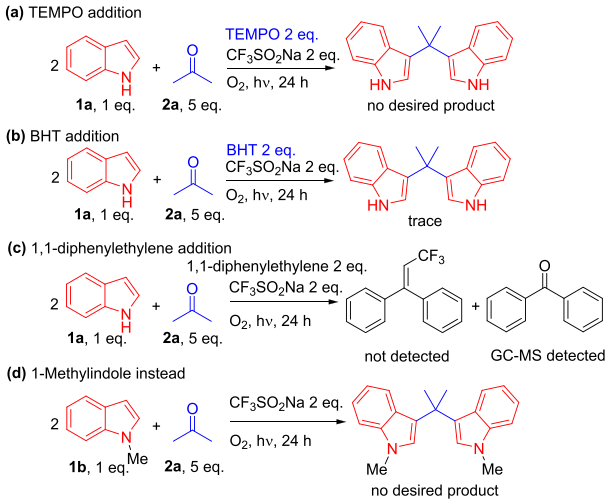
The product bis(indolyl)methanes **5a** is an antioxidant that can scavenge the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical by donating an electron.[15] It was reported that **5f** is a potent apoptogenic agent in leukemic cells through the inhibition of MAPK signaling and the suppression of the intrinsic and possibly caspase-independent apoptotic pathways.[16] To illustrate their potential for practical application in terms of facile fabrication, **5a** and **5f** were synthesized on a gram scale. It was demonstrated that they can be successfully prepared in 96 (1.24 g) and 87% (1.53 g) yield, respectively (Scheme 6).

Scheme 6. Gram-Scale Experiment



To reveal the synthetic mechanism, we did a series of control experiments. First, 2.0 equiv of 2,2,6,6-tetramethylpiperidinooxy (TEMPO) or butylated hydroxytoluene (BHT) was added to the reaction system under standard conditions, and there was no or only a trace amount of desired product, respectively (Scheme 7a,b). It is envisioned that 1,1-diphenylethylene does not capture the CF_3 radical but rather diverts the reaction to form benzophenone, as detected by GC−MS (Scheme 7c). Therefore, we speculate that there is the generation of a highly active $\cdot CF_3$ radical. When the N−H bond of the simple indole was replaced with an *N*-methyl bond, there was no detection of the expected product (Scheme 7d). The result indicates the necessity of the N−H bond for the ready conversion of the generated nitrogen radical to a carbon radical through a 1,3-H shift.

Scheme 7. Control Experiments



On the basis of the results of the control experiments and those of the literature,[17] we proposed a possible mechanism, as illustrated in Scheme 8. At the beginning, upon UV irradiation, CF_3SO_2Na is oxidized to generate $\cdot CF_3$ radical under an O_2-containing atmosphere,[18] and $\cdot CF_3$ attacks the amino hydrogen of indole to form nitrogen radical **A** and CF_3H.[19] By a 1,3-H shift (detected by ^{19}F NMR; see the SI), radical **A** readily isomerizes to carbon radical **B**. Then, radical **B** reacts with acetone to generate oxygen radical **C**, which reacts with

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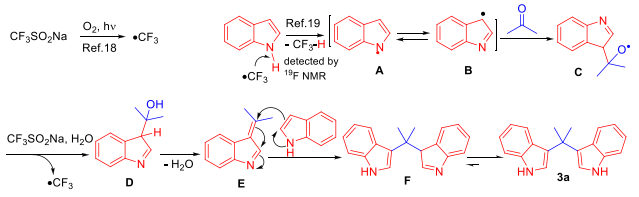
Scheme 8. Possible Reaction Mechanism



CF_3SO_2Na and H_2O to generate $\cdot CF_3$ and active indole **D**. Indole **D** can undergo β-elimination to generate intermediate **E**, whereas the other indole reacts with intermediate **E**[20] to form intermediate **F**, which isomerizes to produce **3a**.

It was demonstrated before that DIMs are heterocyclic compounds possessing high bioactivities;[2−5] we hence screened the compounds for anticancer activities in human bladder cancer cell lines T24 and EJ using the CCK-8 assay. It was found that compounds **3b**, **3d**, **3f**, **3i**, **4a**, **4c**, **4f**, **5a**, **5b**, **5d**, and **5j** can reduce >50% of the viability of the cancerous cell line (Figure 1). A further investigation of their bioactivities, especially those of **3d**, **4a**, **5a**, and **5j**, is underway in our laboratory. (For details of bioactivity experiments, see the SI.)

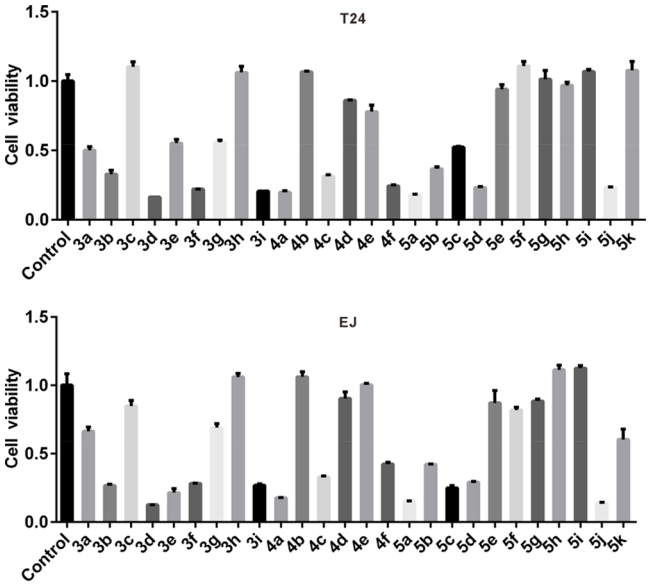


Figure 1. Anticancer activities of DIMs in human bladder cancer cell lines EJ and T24.

In summary, a concise and mild method without the need for a base, acid, or photocatalyst is developed to synthesize DIMs under UV irradiation and an oxygen or air atmosphere. The key step is the ready formation of indole derivatives involving the in situ generation of $\cdot CF_3$ from readily available CF_3SO_2Na. In addition, a variety of ketones and aldehydes are well tolerated in this protocol, and the condensation adducts are obtained with high regioselectivity. The yield of the gram-scale synthesis could be up to 96%, and most of the obtained DIMs exhibit anticancer activities in human bladder cancer cell lines EJ and T24.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04272.

Detailed experimental procedures, compound characterization data, and NMR spectra (PDF)

Accession Codes

CCDC 1965538 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Ling Hong − *Huazhong University of Science and Technology, Wuhan, P. R. China*; Email: lhong@mail.hust.edu.cn

Renhua Qiu − *Hunan University, Changsha, P. R. China*; orcid.org/0000-0002-8423-9988; Email: renhuaqiu@hnu.edu.cn

Other Authors

Tianbao Yang − *Hunan University, Changsha, P. R. China*

Huiai Lu − *Huazhong University of Science and Technology, Wuhan, P. R. China*

Yixuan Shu − *Huazhong University of Science and Technology, Wuhan, P. R. China*

Yifeng Ou − *Hunan University, Changsha, P. R. China*

Chak-Tong Au − *Hunan Institute of Engineering, Xiangtan, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.9b04272

Author Contributions

‖T.Y. and H.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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