HETEROCYCLES, Vol. 97, No. 1, 2018, pp. 163 - 169. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 5th February, 2018, Accepted, 14th March, 2018, Published online, 23rd March, 2018
DOI: 10.3987/COM-18-S(T)33

2-IODOIMIDAZOLINIUM SALT-CATALYZED FRIEDEL–CRAFTS REACTION: SYNTHESIS OF BIS(INDOLYL)METHANE ALKALOIDS

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Abstract – 2-Iodoimidazolinium salt-catalyzed Friedel–Crafts reactions of indoles with aldehydes were developed. Under mild reaction conditions, various bis(indolyl)methane derivatives, an important class of indole alkaloids, were obtained in good to high yields.

Bis(indolyl)methanes (BIMs) are a group of alkaloids with basic skeletons comprised of two indol-3-yl groups bridged with a single methyl carbon (Figure 1).[1] BIM alkaloids have various important biological properties,[2] such as antifungal,[3] antiinflammatory,[4] antibacterial,[5] and anticancer[6] activities. In addition, oxidized BIMs are often utilized as dyes and colorimetric chemosensors.[7] Owing to their versatile biological activities, there has been considerable interest in the synthesis of BIM derivatives. Lewis or Brønsted acids have traditionally been employed as catalysts to promote the electrophilic substitution of indoles with various carbonyl compounds.[8] A variety of organo-,[9] transition metal,[10] photoredox,[11] ionic

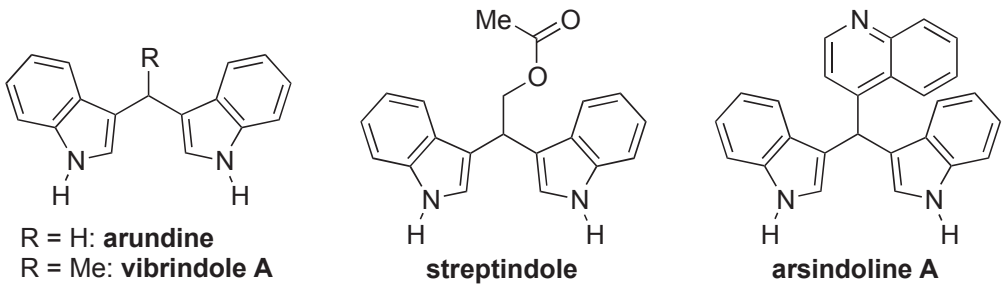


Figure 1. Bis(indolyl)methane (BIM) derivatives isolated from natural sources

liquid,[12] and nanomaterial[13] catalysts have also been reported. However, some of the reported methods suffer certain disadvantages such as requiring a high catalyst loading, expensive or highly toxic catalysts, harsh reaction conditions, and tedious workup procedures. Therefore, the development of more sustainable and mild protocols for the preparation of BIMs that circumvent the aforementioned drawbacks is desirable.

Halogen bond is the directional interaction between a covalently bound halogen atom and a Lewis base.[14] Although the interaction is mainly employed in the field of crystal engineering,[15] halogen–bond donors have recently begun to be utilized in synthetic organic chemistry as organic Lewis acid catalysts.[16] In fact, the activation of carbonyl compounds such as lactones,[17] α,β-unsaturated ketones,[18] iodonium ylides,[19] or arylaldehydes[20] by halogen–bond donor catalysts has been reported (Figure 2). In conjunction with our ongoing efforts in the realm of halogen–bond catalysis,[21] herein, we report the halogen–bond donor-catalyzed Friedel-Crafts reaction of indoles for the synthesis of BIM derivatives (Scheme 1).

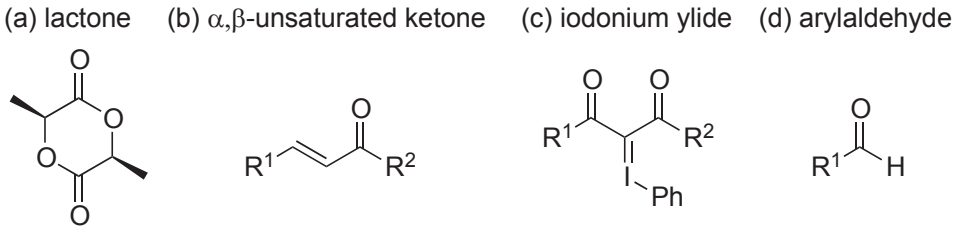
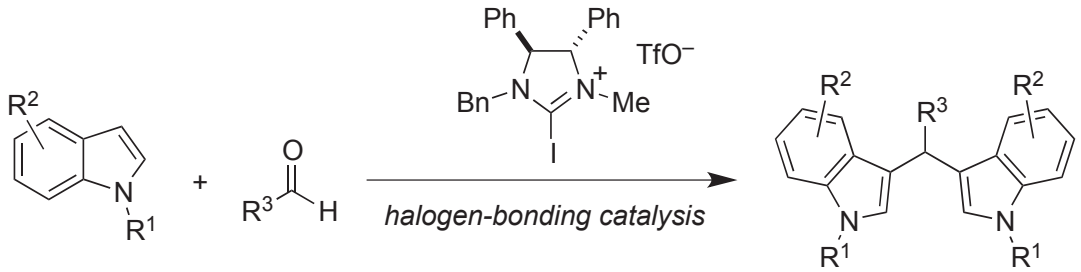


Figure 2. Carbonyl compounds activated through halogen bonds

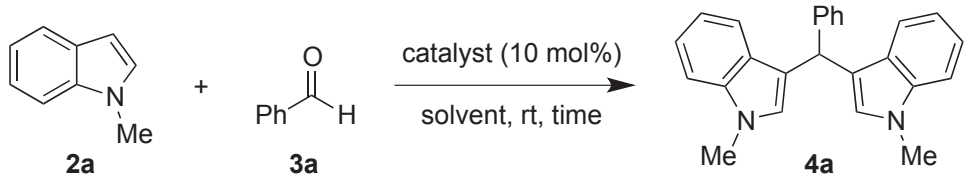


Scheme 1. Halogen–bond donor catalyzed Friedel–Crafts reaction for the synthesis of BIM derivatives

To begin our studies, we chose 1-methylindole **2a** and benzaldehyde **3a** as model substrates. When neutral halogen–bond donor **1a** was applied in chloroform, target BIM **4a** was not obtained (Table 1, entry 1). In contrast, cationic halogen–bond donors **1b**,[22] **1c**,[23] and **1d**[22] smoothly promoted the reaction, and 2-iodoimidazolinium salt **1d** gave product **4a** in 95% yield (entries 2-4). With the best catalyst **1d** in hand, the effect of solvent was investigated (entries 5-9). Dichloromethane gave a slightly lower yield

than chloroform (entry 5), whereas toluene and methanol resulted in moderate yields (entries 6 and 7). Notably, when the reaction was conducted in methanol, the dimethyl acetal derived from **3a** was detected. The use of coordinating solvents such as acetonitrile and THF reduced the yields of the products (entries 8 and 9), which suggested that they disturbed the halogen–bonding interaction between the catalyst and substrates or reaction intermediate. In the absence of **1d** in chloroform, no product was obtained (entry 10).

Table 1. Optimization of reaction conditions



2a 2.1 equiv + **3a** 1 equiv → **4a**

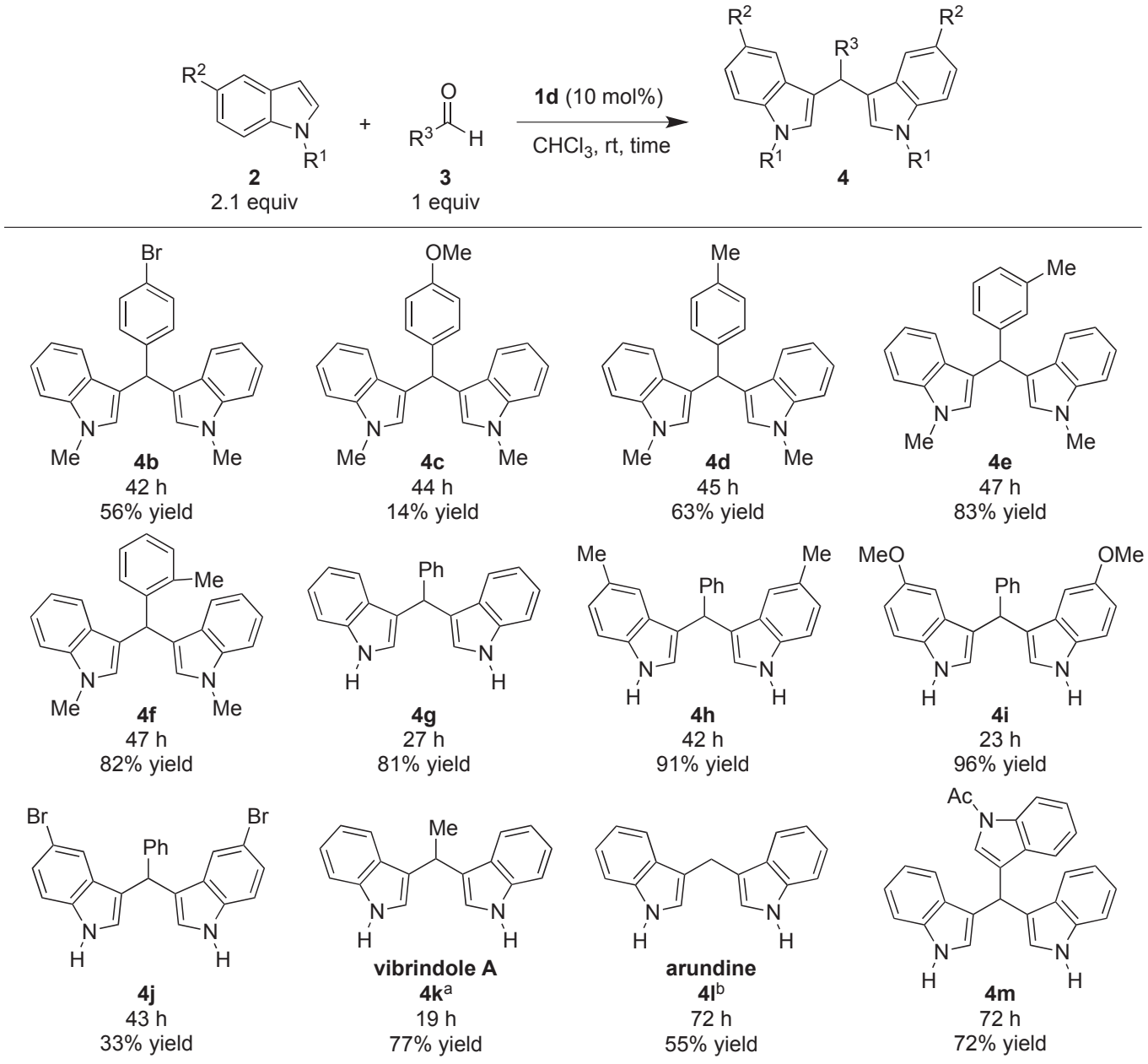
1a **1b** **1c** **1d**

entry	catalyst	solvent	time (h)	yield (%)[a]
1	**1a**	$CHCl_3$	48	NR
2	**1b**	$CHCl_3$	48	14
3	**1c**	$CHCl_3$	48	60
4	**1d**	$CHCl_3$	26	95
5	**1d**	CH_2Cl_2	26	92
6	**1d**	toluene	26	68
7	**1d**	MeOH	26	67
8	**1d**	MeCN	26	31
9	**1d**	THF	26	48
10	none	$CHCl_3$	26	NR

[a]Isolated yield.

With the optimal reaction conditions in hand, next we investigated the substrate scope of the halogen–bond donor-catalyzed Friedel-Crafts reaction. *p*-Bromo, *p*-methyl, *m*-methyl, and *o*-methyl substituted benzaldehydes gave the products (**4b**, **4d**, **4e**, and **4f**) in moderate to good yields, whereas *p*-methoxy-benzaldehyde gave the desired product **4c** in only 14% yield. NH-free indole was also viable, giving the corresponding product **4g** in 81% yield. Electron-rich indoles showed excellent reactivity, producing the target compounds in high yields (**4h** and **4i**). Electron-deficient indoles were well tolerated and gave the product **4j** in a moderate yield. To our delight, acetaldehyde and formaldehyde gave the natural products vibrindole A **4k**[1] and arundine **4l**,[1] respectively. Tris(indolyl)methane **4m**, which shows cytotoxic

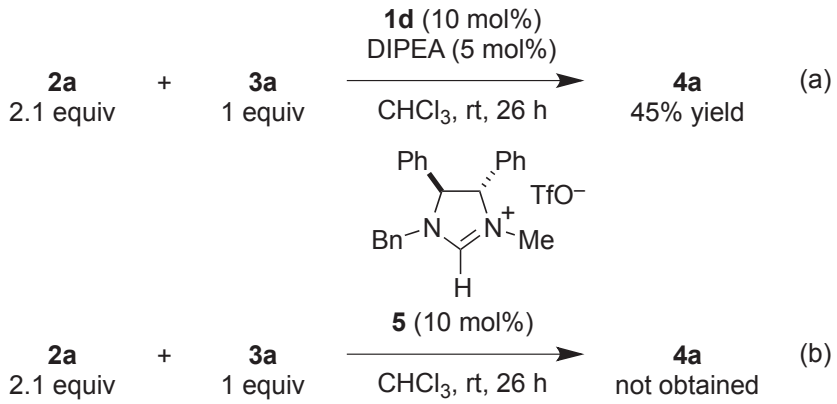
activities,[24] was obtained in a good yield using *N*-acetylated 3-formylindole.



[a]The reaction was conducted with 1.2 equiv. of acetaldehyde and 2 equiv. of indole.
[b]The reaction was conducted with 1.2 equiv. of formaldehyde and 2 equiv. of indole.

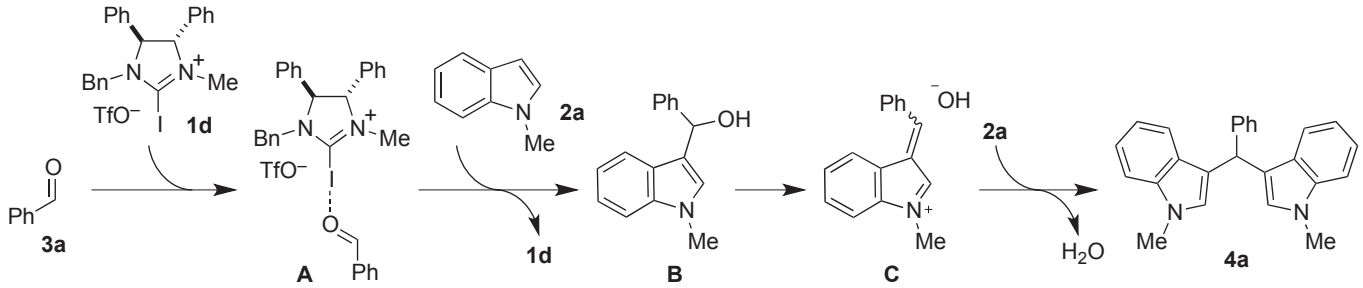
Scheme 2. Substrate scope of halogen–bond donor catalyzed synthesis of BIMs

To rule out the possibility of hidden Brønsted acid catalysis,[25] which could be generated from hydrolysis of the halogen–bond donor, an acid scavenger was added to the reaction (Scheme 3a). Even in the presence of 5 mol% of DIPEA, the product was obtained in 45% yield. And the reaction using an iodine-free imidazolinium salt **5** did not give **4a** at all (Scheme 3b). These results suggested that the halogen–bond donor, not the hidden Brønsted acid, was the true active species.



Scheme 3. Mechanistic studies

Based on the mechanistic studies, plausible reaction pathway is shown in Scheme 4. First, halogen–bond donor **1d** coordinate to aldehyde **3a** to give complex **A**. Then, first addition of indole **2a** produce indolylmethanol **B**. From the intermediate, iminium salt **C** is generated. And, finally, second addition of **2a** gives target compound **4a**. Halogen–bond donor **1d** might also promote the formation of **C** by coordinating to the hydroxy group of **B**.



Scheme 4. Plausible reaction pathway

In conclusion, we developed a halogen–bond donor-catalyzed Friedel-Crafts reaction of indoles with aldehydes. The synthesis of a variety of bis(indolyl)methanes and a tris(indolyl)methane was achieved under mild reaction conditions. The results of mechanistic studies suggested that the halogen–bond donor, not the hidden Brønsted acid, was the true active species.

ACKNOWLEDGEMENTS

This work was financially supported by JSPS KAKENHI (15K18841).

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