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A Novel Method for Synthesis of Bis(indolyl)methanes Using 1,3-Dibromo-5,5-dimethylhydantoin as a Highly Efficient Catalyst Under Solvent-free Conditions

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The reactions of indole with carbonyl groups have been efficiently carried out in the presence of catalytic amounts of 1,3-dibromo-5,5-dimethylhydantoin under solvent-free conditions and corresponding bis(indolyl)-mathanes were obtained in good to excellent yields. Synthesis of di[bis(indolyl)methyl]benzene was also accomplished by this catalyst. Furthermore, chemoselective conversion of aromatic aldehydes to their corresponding bis(indolyl)methanes in the presence of aliphatic aldehydes or ketones was achieved by this method.

Key Words : Bis(indolyl)methane, Indole, 1,3-Dibromo-5,5-dimethylhydantoin, Carbonyl group

Introduction

Indole and its derivatives have attracted much interest in recent century due to their extensive biological activities.[1] Bis(indolyl)methanes are one of the most important group of indole derivatives which are found in cruciferous plants and marine sources.[2] These compounds have shown some different pharmaceutical activities such as anticancer,[3] antihyperglycemic, antiviral and antimicrobial properties[4] and are known as a promoter of estrogen metabolism.[5] Therefore, the synthesis of these moieties has received much attention during the last years. A simple and direct method for the synthesis of bis(indolyl)methanes is the condensation of 2 equv. of indole with the carbonyl groups. Various Brönsted acids,[6-8] Lewis acids,[9-11] heterogeneous acidic catalyst,[12] ionic liquid,[13] and some other catalysts have been applied for this synthesis. Although some of these protocols are valuable, most of them suffer from one or more drawbacks including long reaction times, low yields of products, harsh reaction conditions and use of expensive and/or toxic catalysts and solvents. Therefore, there is a strong demand for a mild, clean and highly efficient procedure for the synthesis of this worthy moiety.

1,3-Dibromo-5,5-dimethylhydantoin (DBDMH) is an N-halo reagent which has found widespread applications in industrial processes due to its economic advantages.[14] DBDMH is a well known brominating and oxidating agent that has recently gained special attention as a highly efficient, commercially available and inexpensive homogeneous catalyst.[14] However, in the following of our interest on the application of N-halo reagents in organic synthesis,[15-18] we wish to report the preparations of bis(indolyl)methanes from reactions of indole and carbonyl groups in the presence of DBDMH.

Experimental

All materials are commercial reagent grade and were obtained from Merck Co. IR spectra were recorded on a Shimadzu FT-IR 8440S spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AVANCE 400 and 500 MHz spectrometer and $CDCl_3$ was used as NMR solvent. Melting Points were taken on a Bamstead Electrothermal apparatus. Silica gel (70-230 mesh) was used for column chromatography. Elemental analysis was performed using a Heraeus CHN-O-Rapid analyzer.

General Procedure for the Synthesis of Bis(indolyl)-methanes. A mixture of carbonyl compound (1 mmol), indole (2 mmol) and DBDMH (0.05 mmol) was stirred at 50 °C under solvent-free condition for appropriate time according to Table 1. The progress of the reaction was monitored by TLC (eluent:*n*-hexane/EtOAc = 4:1). The reaction mixture was cooled to room temperature and purified by column chromatography to afford corresponding bis(indolyl)methane in good to excellent yield (Table 1).

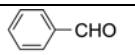
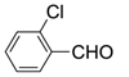
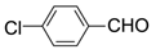
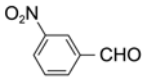
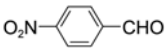
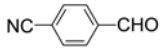
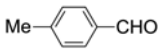
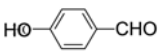
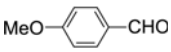
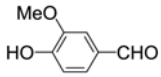
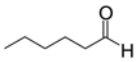
Procedure for the Synthesis of *p*-Di[bis(indolyl)methyl]benzene. To a mixture of terephthalaldehyde (1 mmol) and indole (4 mmol), was added the catalyst (0.1 mmol) and stirred at 50 °C for 90 min. After completion of the reaction as indicated by TLC (eluent:*n*-hexane/EtOAc = 4:1), the crude product purified by column chromatography (87%).

3,3'-Bis-indolyl-(4-cyanophenyl)methane (3f). mp 120-122 °C; IR (KBr): 3430, 3045, 2930, 2250, 1610, 1560, 780; ^{1}H NMR ($CDCl_3$) δ 6.00 (s, 1H), 6.68 (s, 2H), 7.00-7.05 (m, 4H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.99 (s, 2H, NH), 8.14 (d, *J* = 8.6 Hz, 2H); Anal. Calcd. For [$C_{24}H_{17}N_3$]: C, 82.97; H, 4.88; N, 12.15. Found: C, 83.00; H, 4.90; N, 12.10%.

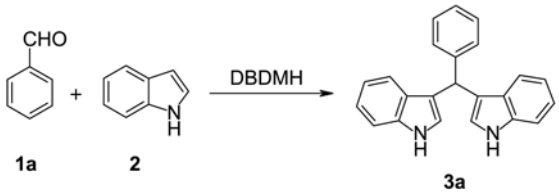
Results and Discussion

The catalytic synthesis of bis(indolyl)methane was studied in the reaction of benzaldehyde and indole in the presence of different amounts of DBDMH (Scheme 1). The best molar ratio of benzaldehyde: indole: DBDMH was found to be 1:2:0.05 at 50 °C under solvent-free conditions and 3,3-

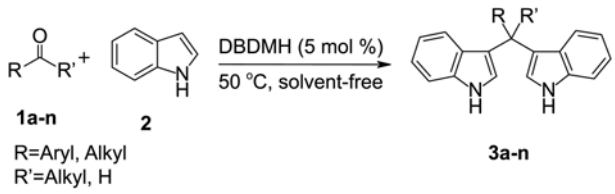
Table 1. DBDMH catalyzed synthesis of bis(indolyl)methanes from indole and carbonyl compounds

Entry	Carbonyl compound		Product	Time (min)	Yield[a] (%)	mp (°C)[Ref.]	Lit. mp (°C)[Ref.]
1		**1a**	**3a**	50	90	140-142	140-142[21]
2		**1b**	**3b**	40	85	73-75	74-76[21]
3		**1c**	**3c**	35	90	74-76	78-80[21]
4		**1d**	**3d**	40	90	219-221	220-222[21]
5		**1e**	**3e**	30	95	218-220	217-219[21]
6		**1f**	**3f**	32	90	120-122	
7		**1g**	**3g**	80	75	93-95	95-97[21]
8		**1h**	**3h**	45	84	121-123	119-121[21]
9		**1i**	**3i**	45	80	180-182	186-188[21]
10		**1j**	**3j**	90	70	219-221	222[10]
11		**1k**	**3k**	70	75	90-92	92[22]
12		**1l**	**3l**	80	70	65-66	68-70[22]
13		**1m**	**3m**	140	80	61-63	64-66[22]
14		**1n**	**3n**	120	85	160-162	163-165[21]

[a]Isolated yield.



Scheme 1

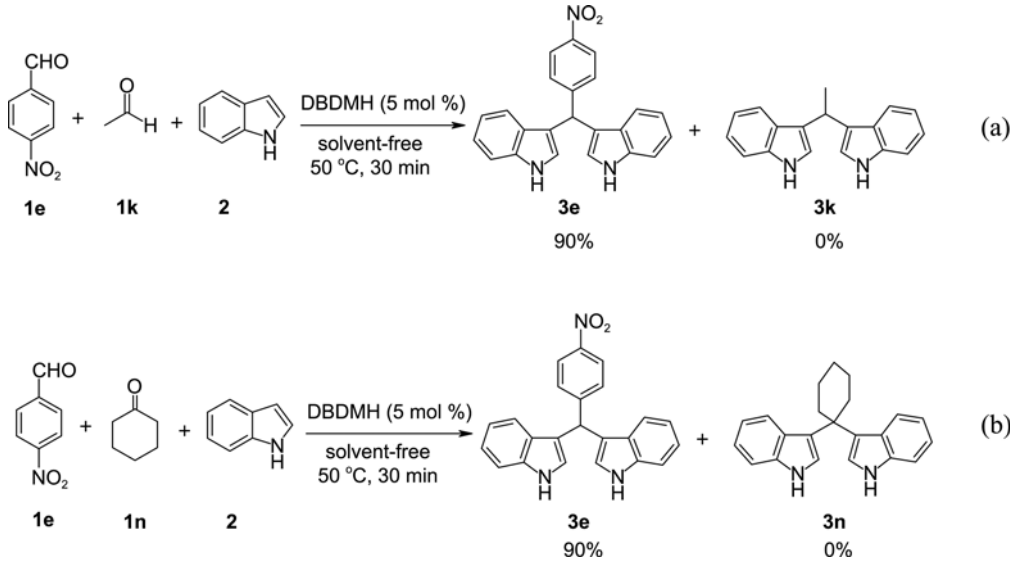


Scheme 2

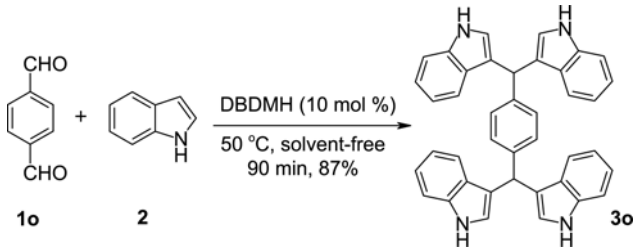
bis(indolyl)phenylmethane was obtained in 90% yield after 50 min (Table 1, entry 1). In order to show the role of DBDMH, the same reaction was carried out in the absence of catalyst which just resulted in 5% of the product after 10 hours. This result exhibit the high catalytic activity of DBDMH in the current transformation.

The generality of the procedure was evaluated by the reactions of various aromatic aldehydes with indole in the presence of DBDMH under optimized reaction conditions (Scheme 2, Table 1, entries 1-10) which give corresponding bis(indolyl)methanes in good to excellent yields. Electron-withdrawing substituents on aromatic ring reduced reaction times and increased product yields than electron-donating substituents. Furthermore, *p*-cyano derivative of bis(indolyl)-methane can be synthesized in high yield and short time by the current method (entry 6). This compound can be an interesting case because nitrile group can easily be converted to some organic compounds and some other functional groups.

We then examined the reactivity of aliphatic aldehydes and also ketones in this method. Reactions of these carbonyl groups with indole were satisfactorily performed by the current method but they needed longer times and afforded lower yields of products than aromatic aldehydes (Table 1, entries 11-14). However, low reaction activity of aliphatic aldehydes and ketones in the synthesis of bis(indolyl)-methanes encouraged us to investigate the selectivity of the present work. To this aim, equimolar mixtures of *p*-nitro-benzaldehyde and acetaldehyde and also *p*-nitrobenz-aldehyde and cyclohexanone were prepared and reacted with

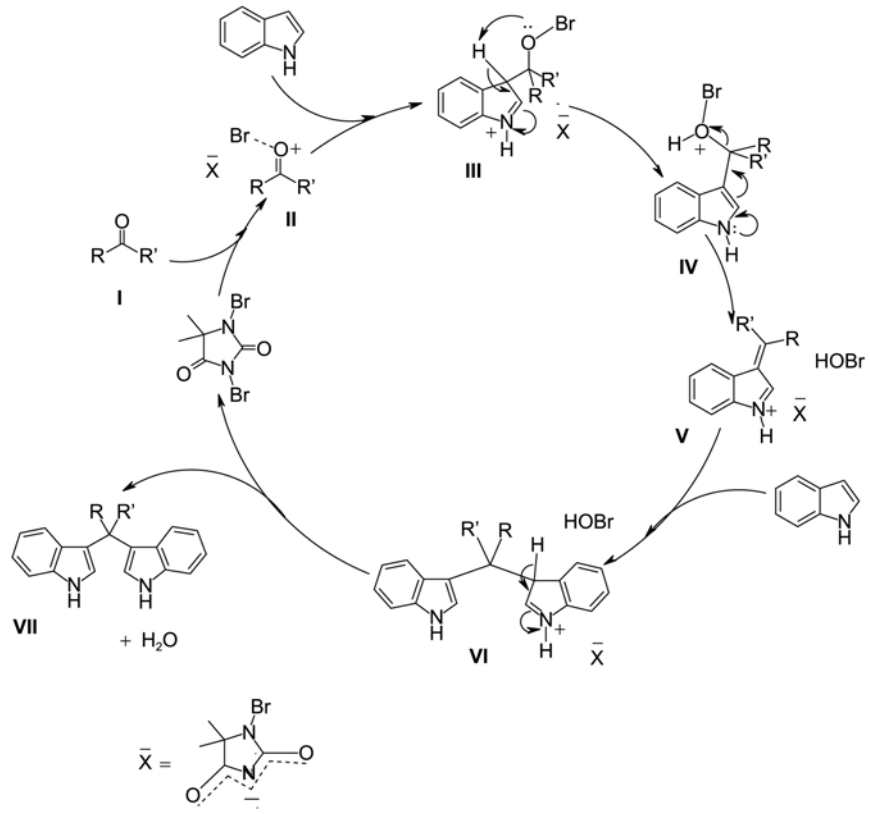


Scheme 3



Scheme 4

indole in the presence of DBDMH under optimum reaction conditions (Scheme 3). It was surprisingly observed that aromatic aldehyde produced corresponding bis(indolyl)-methane as major product in both reactions and another substrate remained intact in the reaction mixture. Therefore, the present method is potentially applicable for the chemo-selective conversion of aromatic aldehydes to corresponding bis(indolyl)methanes in the presence of aliphatic aldehydes and ketones.



Scheme 5

Table 2. Comparison of some other procedures with the present method for the synthesis of 3,3'-bis(indolyl)phenylmethane from benzaldehyde and indole

Entry	Catalyst	Solvent	Time	Yield (%)[Ref.]
1	DBDMH (5 mol %)	no solvent	50 min	90
2	$Dy(OTf)_3$ (2 mol %)	Ionic liquid	1 h	98[19]
3	TiO_2 (20 mol %)	no solvent	3 h	98[20]
4	$SbCl_3$ (10 mol %)	CH_3CN	30 min	96[10]
5	AcOH (1 mL)	no solvent	30 min	84[8]
6	$RuCl_3{\cdot}3H_2O$	C_6H_6	30 min	92[11]
7	$In(OTf)_3$ (5 mol %)	CH_3CN	25 min	71[23]
8	$Ln(OTf)_3$ (10 mol %)	$EtOH/H_2O$	12 h	95[24]

Furtheremore, di[bis(indolyl)methyl]benzene can be achieved by this method. The reaction of terephthalaldehyde with 4 equiv. of indole was performed in the presence of DBDMH (10 mol %) under optimized conditions and *p*-di[bis(indolyl)methyl]benzene produced in 87% yields after 90 min (Scheme 4).

The preparation of bis(indolyl)methane induced by DBDMH can be rationalized by the following mechanism (Scheme 5). Initially, the carbonyl group of aldehyde or ketone is activated by brominium ion. Then, nucleophilic attack of indole to activated carbonyl group **II** produces azafulvenium salt **V**. The formation of azafulvenium salt confirms by selectivity of the reaction as aromatic aldehydes can produce a stable conjugated system in azafulvenium salt but aliphatic aldehydes can't, so, aromatic aldehydes react faster than aliphatic ones. And finally, nucleophilic attack of second indole to **V** lead to the corresponding bis(indolyl)methane **VII** and the catalyst return to the next catalytic cycle.

In Table 2, we compared our method with some other reported procedures for the synthesis of bis(indolyl)phenylmethane. Results show the preference of the current method in terms of easy availability, cheapness and activity of the catalyst, reaction rate and solvent toxicity with those reported in the literatures.

Conclusions

In conclusion, we have developed a simple, novel and efficient procedure for the synthesis of bis(indolyl)methanes using DBDMH. Chemoselectivity, short reaction times, high yields of products and absence of solvent are significant preferences of the present work to the previous ones. Furthermore, using green catalyst with highlighted properties such as commercially availability, easily handling, insensitivity to air and moisture, and cheapness, is one of the main advantages of the current work.

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