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NBS was found to be an efficient catalyst for condensations of indoles with aldehydes or ketones in the absence of solvent.

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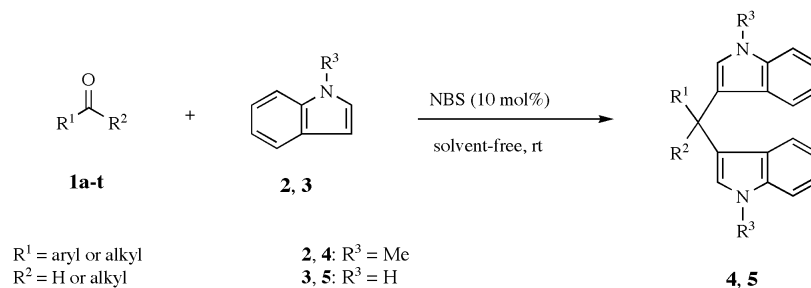
Introduction.

Condensations of indoles and carbonyl compounds proceed by acid catalysts to form bis(indolyl)methanes [1]. The acids utilized in this type of reactions are protic acids, for instance, hydriodic acid [2] and hydrochloric acid [3]. Lewis acids such as boron trifluoride [4], zinc chloride [5], lithium perchlorate [6] and lanthanide triflates [7] have also been used. Furthermore, photochemical reactions in the solid state between aldehydes and indole afford similar condensation products [8]. Recently, Karimi and coworkers have published that *N*-bromosuccinimide (NBS) is an effective catalyst for the conversions of carbonyl compounds to acetals [9], 1,3-dioxanes [10], and 1,1-diacetates [11] under neutral conditions. We report here that NBS is also effective as a catalyst for the condensations of indoles with aldehydes or ketones under solvent-free conditions at room temperature (Scheme 1 and Table 1).

reaction time (entry 4). Thereafter, **2** was utilized to carry out reactions with various aldehydes and ketones usually in the presence of 10 mol% NBS.

A series of substituted benzaldehydes **1b-g** were efficiently converted to the corresponding bis(indolyl)methanes **4** within several hours reaction time (entries 5-10), while *p*-*N,N*-dimethylaminobenzaldehyde **1h** has moderate reactivity (entry 11). Naphthaldehydes **1j,k** and 2-thiophenecarbaldehyde **1l** also revealed good reactivities (entries 13-15). However, 4-pyridinecarboxaldehyde **1m** has low reactivity to give monosubstituted carbinol **6m** as a major product and disubstituted product **4m** as a minor product after prolonged reaction time for 92 hours (entry 16). Aliphatic aldehydes such as hexanal **1o** and chloral **1p** formed the respective disubstituted products **4o** and **4p** in moderate and low yield, respectively, although long reaction times were required to complete the reactions (entries 20 and 21).

Scheme 1



Reactions of Carbonyl Compounds and Indoles

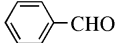
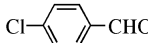
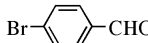

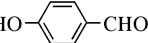

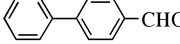
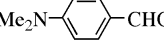
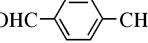
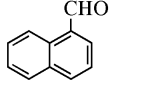
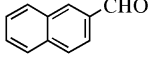
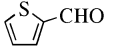
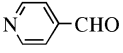
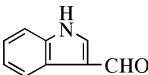
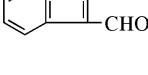
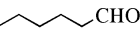
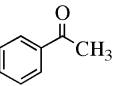
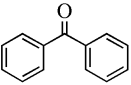
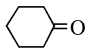
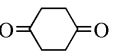
Results and Discussion.

Benzaldehyde **1a** reacted with *N*-methylindole **2** (2 equivalents) in the presence of only 1 mol% NBS to give bis(3-(*N*-methylindolyl))phenylmethane **4a** in quantitative yield after 10 hours reaction time (Table 1, entry 1). Increase of NBS to 5 and 10 mol% resulted in accelerating the reaction rate to 3 and 0.5 hours, respectively (entries 2 and 3). Indole **3** underwent similar condensation with **1a** in less reactivity than that of **2**, because of affording the corresponding product bis(3-indolyl)phenylmethane **5a** (78% yield) in the presence of 20 mol% NBS after 8 hours

On the other hand, ketones have lower reactivities than aldehydes. For instance, acetophenone **1q** was achieved in moderate yield in the presence of 20 mol% NBS after prolonged reaction time (entry 22). Benzophenone **1r** was recovered intact even 48 hours under similar reaction conditions (entry 23). Cyclohexanone has also moderate reactivity (entry 24).

When terephthalaldehyde was reacted with four times molar of **2** in the presence of 20 mmol% NBS, tetrasubstituted product **4i** was obtained in good yield (entry 12). Similarly, 1,4-cyclohexanedione gave tetrasubstituted product **4t** (entry 18).

Table 1
NBS catalyzed condensation of carbonyl compounds
and indoles in the absence of solvent

Entry	Carbonyl compound 1	1/2/NBS [1/3/NBS]	Reaction time (h)	Yield 4 [5] , (%)
1	a	1:2:0.01	10	95
2	a 	1:2:0.05	3	94
3	a	1:2:0.1	0.5	99
4	a	[1:2:0.2]	8	[78]
5	b 	1:2:0.1	6	96
6	c 	1:2:0.1	3	95
7	d 	1:2:0.1	3	85
8	e 	1:2:0.1	2	81
9	f 	1:2:0.1	3	89
10	g 	1:2:0.1	1	88
11	h 	1:2:0.2	22	68
12	i 	1:4:0.2	7	88
13	j 	1:2:0.1	4	87
14	k 	1:2:0.1	7	92
15	l 	1:2:0.1	1	92
16	m 	1:2.5:0.2	92	5; 6m, 36
17	n 	1:2:0.2	24	4; 7n, 31
18	n 	1:4:0.5	24	26; 7n, 38
19	n	[1:2:0.3]	29	[23]
20	o 	1:2:0.1	24	61
21	p CCl_3CHO	1:2:0.1	21	18
22	q 	1:2:0.2	22	59
23	r 	1:2:0.2	48	[a]
24	s 	1:2:0.1	5	65
25	t 	1:2:0.2	26	60

[a] No reaction.

Interestingly, reaction of indole-3-carbaldehyde **1n** with **2** gave tris(3-(*N*-methylindolyl)methane **7n** as a major product. The normal disubstituted product **4n** was obtained as a minor product. Although the formation mechanism of **7n** is not yet clear, the compound could be identified from the several spectral data. The reaction under the stronger condition using **2** (4 equivalents) and NBS (50 mol%) resulted in increasing the formation of **4n** and **7n** to 26% and 38% yield, respectively. Indole-3-carbaldehyde **1n** also reacted with indole **3** by NBS catalyst to afford tris(3-indolyl)methane **5n** in low yield. These results suggest that NBS might be a more efficient catalyst for the condensation reactions, because acid catalysts such as zinc chloride and *p*-toluenesulfonic acid did not cause any reaction between **1n** and indoles **2** and **3** under solvent-free conditions. In addition, these propeller type of compounds (**4n**, **7n**, **5n**) having three blades of indoles might have some possibility for supramolecular synthons, in fact several inclusion complexes of bis(indolyl)arylmethanes with solvent molecules were already reported [8].

At the present time, the actual role of NBS is not clear. As pointed out by Karimi *et al.* [9-11], NBS might act as a source for Br⁺ which activates the carbonyl group, or NBS probably generate small quantities of HBr or Br₂, which may be the actual catalysts for the reaction. Further study is necessary to confirm the mechanism.

In conclusion, NBS can be used as a mild and efficient catalyst for the preparation of bis(indolyl)methanes from aldehydes and ketones under solvent-free conditions.

EXPERIMENTAL

¹H nmr spectra were measured on a JEOL JNM-GSX270 spectrometer with tetramethylsilane as an internal standard. IR spectra were recorded on a JASCO FT/IR-300E spectrophotometer. Melting points (mp) were not corrected. Elemental analysis was carried out with a Yanaco CHN Corder MT-5. All the reagents were commercially available.

General Procedure for Solvent-free Reaction.

A mixture of carbonyl compound **1** (1 mmol) and *N*-methylindole **2** (2 mmol) was stirred with NBS (0.1 mmol) in the absence of solvent at room temperature in a vessel through a calcium chloride dry tube. After completion of the reaction (TLC), an aqueous solution of NaHCO₃ was added and the mixture was collected by filtration. When necessary, product was separated by silica gel column chromatography.

Spectral Data for Selected Compounds.

Bis(3-(*N*-methylindolyl))-3-indolylmethane (**4n**).

Compound **4n** was obtained as a white powder; mp 219-220 °C (from ethyl acetate); ir (KBr) 3401 (NH) cm⁻¹; ¹H nmr (300 MHz,

deuteriochloroform): δ 7.87 (s, broad, 1H, NH), 7.52-7.48 (m, 3H, Ar), 7.38-7.14 (m, 6H, Ar), 7.03-6.97 (m, 2H, Ar), 6.78 (d, J = 2.0, 1H, In), 6.63 (s, 2H, N-MeIn), 6.16 (s, 1H, CH), 3.66 (s, 6H, CH₃).

Anal. Calcd. for C₂₇H₂₃N₃: C, 83.25; H, 5.96; N, 10.79. Found: C, 83.09; H, 6.27; N, 10.51.

Tris(3-indolyl)methane (**5n**).

Compound **5n** was obtained as a white powder; mp 219-222 °C (from ethyl acetate); ir (KBr) 3425, 3392 (NH) cm⁻¹; ¹H nmr (300 MHz, deuteriochloroform): δ 7.88 (s, broad, 3H, NH), 7.50 (d, J = 7.5, 3H, Ar), 7.36 (d, J = 8.1, 3H, Ar), 7.16 (t, J = 7.5, 3H, Ar), 7.00 (t, J = 7.5, 3H, Ar), 6.77 (d, J = 2.0, 3H, In), 6.17 (s, 1H, CH).

Anal. Calcd. for C₂₅H₁₉N₃: C, 83.06; H, 5.31; N, 11.63. Found: C, 82.95; H, 5.59; N, 11.40.

Tris(3-(*N*-methylindolyl)methane (**7n**).

Compound **7n** was obtained as a white powder; mp 244-245 °C (from ethyl acetate); ir (KBr) no NH band; ¹H nmr (300 MHz, deuteriochloroform) δ 7.49 (d, J = 7.5, 3H, Ar), 7.31-7.17 (m, 6H, Ar), 6.99 (t, J = 7.5, 3H, Ar), 6.63 (s, 3H, N-MeIn), 6.16 (s, 1H, CH), 3.66 (s, 9H, CH₃); eims (20 eV): *m/z* 403 (M⁺, 100) 272 (100), 257 (21), 131 (21).

Anal. Calcd. for C₂₈H₂₅N₃: C, 83.34; H, 6.24; N, 10.41. Found: C, 83.11; H, 6.43; N, 10.29.

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