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CuBr₂-Catalyzed Synthesis of Bis(indolyl)methanes

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Abstract: Copper(II) bromide is found to be an efficient catalyst for the electrophilic substitution reaction of indole with aldehydes to afford the corresponding bis(indolyl)-methanes in good yields.

Keywords: Aldehydes, bis(indolyl)methanes, copper(II) bromide, indole

Development of bis(indolyl)alkane synthesis has been of considerable interest in organic synthesis because of bis(indolyl)alkanes' wide occurrence in various natural products possessing biological activity^[1] and usefulness for drug design.^[2] Bis(indolyl)methanes are most active cruciferous substances for promoting beneficial estrogen metabolism and inducing apoptosis in human cancer cells.^[3] Consequently, numerous methods have been reported for the preparation of bis(indolyl)methanes.^[4] Of these methods, the acidcatalyzed electrophilic substitution reaction of indoles with aldehydes is one of most simple and straightforward approaches for the synthesis of bis(indolyl)methanes. A variety of reagents such as acetic acid,^[5] InCl₃,^[6] In(OTf)₃,^[7] InF₃,^[8] Dy(OTf)₃,^[9] Ln(OTf)₃,^[10] LiClO₄,^[11] FeCl₃,^[12] I₂,^[13] NBS,^[14] KHSO₄,^[15] NaHSO₄ · SiO₂,^[16] PPh₃ · HClO₄ (TPP),^[17] CAN,^[18] zeolites,^[19] clay,^[20] H₃PMo₁₂O₄₀ · xH₂O,^[21] and 1-butyl-3-methylimidazolium tetrafluoroborate or 1-butyl-3-methylimidazolium hexafluorophosphate ionic liquids^[22] have been employed to accomplish this transformation. Recently, rare-earth perfluoroocanoates [RE(PFO)₃],^[23] trichloro-1,3,5-triazine,^[24] hexamethylenetetraamine-bromine,^[25] ion-exchange resin,^[26] and ionic

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liquids in conjunction with $In(OTf)_3$ or $FeCl_3 \cdot 6H_2O^{[27]}$ were also found to promote this reaction. However, some of the reported methods have the following drawbacks: for example, use of expensive reagents,^[7,9,10] longer reaction times,^[5,6,8,22] low yields of products,^[5,20b] and use of an additional microwave oven.^[12] Because of their wide range of biological, industrial, and synthetic applications, the preparation of bis(indolyl)methanes has received the renewed interest of researchers for the discovery of improved protocols and still awaits further development of milder and high-yielding products.

Copper(II) bromide is an important reagent not only for bromination^[28] but also a range of other reactions.^[29] It is significantly cheaper than known late transition-metal catalysts and tolerates a variety of functional groups. We found that $CuBr_2$ is an efficient catalyst for electrophilic substitution of indole with aldehyde or ketones. Here, we report a rapid and convenient procedure for the preparation of bis(indolyl)methanes from indole and aldehydes or ketones using a catalytic amount of $CuBr_2$ at room temperature (Scheme 1).

First, 4-chlorobenzaldehyde (1a) was chosen as a model for the reaction with indole. Compound 1a was treated with 2.0 equiv. of indole in the presence of 5 mol% (based on the amount of indole) of CuBr₂ at room temperature in various solvents (Table 1, entries 1–7). In CH₃CN, the reaction completed within 0.4 h to give bis(indolyl)methane **3a** in 95% yield. The reactions in CH₂Cl₂, AcOEt, MeOH, EtOH, DMF, and THF required longer reaction times and unreacted **1a** and indole remained. Next, the efficacy of various Lewis acids such as CuCl₂, Cu(OTf)₂, ZnCl₂, FeCl₃, AlCl₃, and CoCl₂ · 6H₂O was studied for this conversion. Among these Lewis acids, CuBr₂ was found to be superior in terms of conversion and reaction rates (Table 1). Although the reactions also proceeded with CuCl₂, long reaction times are typically needed to achieve comparable yields to those obtained with CuBr₂. Lower catalyst loading can be used with only a marginal drop in reaction rate (entry 8).

Having established reaction conditions, various aldehydes 1 were reacted with indole 2 to investigate the reaction scope, and several representative results are summarized in Table 2. Aromatic, aliphatic (entry **b**) and heterocyclic (entry **m**) aldehydes underwent smooth transformation to the



Scheme 1.

Entry	Solvent	Catalyst	Time (h)	Yield $(\%)^a$
1	CH ₃ CN	5% CuBr ₂	0.4	95
2	AcOEt	5% CuBr ₂	3	88
3	CH_2Cl_2	5% CuBr ₂	4	86
4	CH ₃ OH	5% CuBr ₂	4	81
5	C ₂ H ₅ OH	5% CuBr ₂	3	79
6	THF	5% CuBr ₂	10	76
7	DMF	5% CuBr ₂	15	37
8	CH ₃ CN	1% CuBr ₂	1	89
9	CH ₃ CN	5% CuCl ₂	1.5	94
10	CH ₃ CN	5% Cu(OTf) ₂	4	89
11	CH ₃ CN	5% ZnCl ₂	20	15
12	CH ₃ CN	5% BiCl ₃	4	86
13	CH ₃ CN	5% FeCl ₃	20	75
14	CH ₃ CN	5% AlCl ₃	8	90
15	CH ₃ CN	5% CoCl ₂ · 6H ₂ O	24	38

Table 1. Screening of the reaction conditions for the synthesis 3a

^aIsolated yields.

corresponding bis(indolyl)methanes in high to excellent yield in relatively short reaction times. It has been observed that the electronic properties of the aromatic ring have an effect on the rate of this electrophilic substitution reaction. The rate is accelerated if an electron-withdrawing group is present on the aromatic ring. The reaction of ketones with indole took longer when compared with aldehydes, and unreacted ketones and indole remained. Also, no any brominated side product was detected. It is also found that the reaction of terephetalaldehyde 4 with 4 equiv. of indole proceeded rapidly to give *p*-di(bis-indolylmethane)benzene 5 in similar conditions in high yield (Scheme 2).

In summary, the electrophilic substitution reaction of indole with aldehydes was successfully carried out in the presence of a catalytic amount of $CuBr_2$ at room temperature. This method offers several significant advantages such as high conversions, easy handing, cleaner reaction profiles, and short reaction times, which makes it a useful and attractive process for the rapid synthesis of substituted bis(indolyl)methanes.

EXPERIMENTAL

Melting points were determined using a X-4 apparatus and are uncorrected. NMR spectra were recorded on a Bruker-BZH-360/52 spectrometer using TMS as an internal standard. IR spectra were obtained using a FTS-135 spectrometer instrument. Mass spectra were recorded on a VG Micromass 7070H (70 eV) instrument. CHN analysis was recorded on MT-3 analyzer.

		т.	X 7' 11	Mp (°C)	
Entry	Substrate	(min)	$(\%)^a$	Found	Reported
a	сі-	24	95	76–77	77-81 ^[26]
b	Сно	80	85	68-70	70-72 ^[26]
c	СНО	30	94	123-125	125-127 ^[20b]
d	Ме	30	95	96-98	94-96 ^[27b]
e	Н3СО-СНО	40	92	190-192	187–189 ^[27b]
f	CHO CHO	35	90	100-102	97-99 ^[11]
g	но-Сно	40	89	124-125	122-124 ^[18]
h	MeO CHO	50	91	111-112	110-112 ^[19b]
i	Сі сно	25	94	72–74	72-74 ^[27b]
j		15	93	221-223	220-222 ^[26]
k	О2N	18	90	142-143	140-142 ^[20b]
1	CH(OAc) ₂	60	81	96-98	99 ^[5]
m	СНО	35	88	320-323	322 ^[25]
n		480	75	118-120	118-120 ^[11]
0	COCH3	480	38	189-190	190-192 ^[18]

Table 2. CuBr₂-catalyzed synthesis of bis(indolyl)methane derivatives

^aIsolated yield.

CuBr₂-Catalyzed Synthesis of Bis(indolyl)methanes



Scheme 2.

General Procedure

In a 50-mL, round-bottom flask, indole (2.0 mmol), aldehydes or ketone (1.0 mmol), and CuBr₂ (0.1 mmol) in MeCN were added with stirring at room temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was quenched with H₂O (5 mL) and extracted with EtOAc (3×10 mL), and combined organic layers were dried over Na₂SO₄, concentrated, and purified by column chromatography on SiO₂ with use of an ethyl acetate/hexane mixture as eluent; distillation of the solvent under reduced pressure gave pure products.

4-Chlorophenyl-3,3'-bis(indolyl)methane (**3a**): Pink solid. IR (KBr): 3411, 3055, 2923, 2848, 1617, 1417, 1337, 1089, 1013, 743 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ ppm: 5.86 (s, 1H, Ar-CH), 6.65 (s, 2H), 7.02 (t, 2H, J = 7.8 Hz), 7.18 (t, 2H, J = 7.8 Hz), 7.26–7.38 (m, 8H), 7.93 (br, s, 2H, NH). ¹³C NMR (75 MHz): 39.7, 111.4, 119.1, 119.5, 122.2, 123.8, 127.0, 128.5, 130.2, 131.9, 136.8, 142.8. EIMS: m/z (%): 356 (5, M⁺), 354 (15, M⁺-2), 244 (12), 186 (13), 172 (16), 138 (25), 116 (100). Anal. calcd. for C₂₃H₁₇ClN₂: C, 77.41; H, 4.80; Cl, 9.93; N, 7.85. Found: C, 77.52; H, 4.75; N, 7.89.

3,3'-Bisindoly(methyl)phenylmethane (**3p**): Coloress solid. IR (KBr): 741, 1010, 1336, 1455, 2848, 2923, 3053, 3410 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ ppm: 2.29 (s, 3H), 6.54 (s, 2H), 6.86 (t, J = 7.8 Hz, 2H), 7.06 (t, J = 7.8, 2H), 7.14–7.18 (m, 4H), 7.23–7.34 (m, 5H), 7.78 (br s, 2H, NH). ¹³C NMR (75 MHz, CDCl₃) δ ppm: 28.8, 43.7, 111.2, 118.9, 121.5, 122.1, 123.4, 124.7, 125.8, 126.5, 127.8, 128.1, 137.1, 148.1. EIMS: m/z (%) = 336 (86, M⁺), 243 (100), 245 (45), 220 (58), 77 (38). Anal. Calcd. for C₂₄H₂₀N₂: C, 85.68; H, 5.99; N, 8.33. Found: C, 85.56; H, 5.92; N, 8.40.

3,3',3",3"'-Tetraindoly(terepthalyl)dimethane (**5**•**2AcOEt**): Colorless solid, mp: 122–123 °C (Lit.^[13a]121–123°C). IR (KBr): 742, 776, 1295, 1455, 1720, 2849, 2920, 3052, 3411 cm⁻¹. ¹H NMR (300 MHz, acetone- d_6) δ ppm: 1.29 (t, J = 7.2 Hz, 6H, CH₃), 2.04 (s, 6H, CH₃), 4.04–4.09 (m, 4H, CH₂), 5.89 (s, 2H, Ar-CH), 6.81 (t, J = 7.8 Hz, 4H), 6.90 (t, J = 7.8 Hz, 4H), 7.05 (t, J = 7.8 Hz, 4H), 7.33–7.38 (m, 12H), 9.97 (br s, 4H, NH). ¹³C

NMR (75 MHz, acetone-*d*6) δ ppm: 14.4, 20.8, 40.8, 60.5, 112.1, 119.2, 120.0, 120.3, 121.9, 124.3, 124.5, 128.1, 129.2, 138.0, 143.4, 170.8. EIMS: m/z (%) = 566 (4, M⁺), 452 (12), 336 (68), 245 (12), 117 (8), 116 (100), 89 (50). Anal. calcd. for C₄₈H₄₆N₄O₄: C, 77.60; H, 6.24; N, 7.54. Found: C, 77.58; H, 6.30; N, 7.49.

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