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SYNTHESIS OF BIS(INDOLYL) METHANES IN CATALYST- AND SOLVENT-FREE REACTION

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GRAPHICAL ABSTRACT



R : Phenyl, Alkyl; R': H, Phenyl, Alkyl

Abstract *Efficient synthesis of bis(indolyl) methanes by the reaction of indoles with various carbonyl compounds in the absence of catalyst and solvent afforded the corresponding bis(indolyl) methanes in excellent yields.*

Keywords Aldehydes; bis(indolyl) methanes; indole; solvent-free

INTRODUCTION

Simple, efficient, environmentally benign, and economically viable chemical processes or methodologies for widely used organic compounds are in great demand. Bis(indolyl) alkanes are a biologically useful class of organic compounds, and a large number of these indolyl methanes have been isolated from terrestrial and marine natural sources such as tunicates and sponges.^[1] For example, vibrindole A (3,3'-diindolyl ethane) exhibits antibacterial activity, and 3,3'-diindolyl methane has potent carcinogenic properties.^[2] Because of their wide occurrence as natural products and various biological activities, synthesis of these bis(indolyl) methanes have attracted attention. Recently, oxidized bis(indolyl) methanes containing a conjugated bis(indolyl) skeleton have acted as colorimetric sensors and chromogenic sensors.^[3] In addition, 1,1-bis(3'-indolyl)-1-(p-substituted phenyl) methanes

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containing p-trifluoromethyl (DIM-C-p-CF₃Ph), p-t-butyl (DIM-C-p-tBuPh), and p-phenyl (DIMC-p-C₆H₅Ph) substituents have been identified as belonging to a new class of peroxisome proliferator-activated receptors (PPAR) agonists that exhibit antitumorigenic activity.^[4] Various methods have been developed for their synthesis using Lewis acid catalysts such as LiClO₄,^[5] In(OTf)₃,^[6] Dy(OTf)₃,^[7] Sc(OTf)₃,^[8,9] ceric ammonium nitrate (CAN),^[10] ZrOCl₂,^[11] InCl₃,^[12] and AlPW₁₂O₄₀,^[13] ionic liquids,^[14] trichloro-1,3,5-triazine,^[15] potassium hydrogen sulfate,^[16] La(NO₃)₃ · 6H₂O,^[17] and Fe(DS)₃.^[18] However, many of these reported methods suffer from one or more disadvantages such as harsh experimental procedure and reagents that are expensive, moisture sensitive, or highly toxic in nature. A mild and efficient catalyst for the synthesis of bis(indolyl) methanes is highly desirable. Consequently, there is an opportunity for further development of mild conditions, increased variation of the components, and better yields. In this communication, we report a green protocol for the synthesis of bis(indolyl) methanes in the absence of catalyst.

RESULTS AND DISCUSSION

A wide variety of compounds were applied to the optimal reaction conditions to prepare a wide range of bis(indolyl) methanes (Scheme 1).

The results are summarized in Table 1. The reaction proceeded efficiently and smoothly at 80 °C in the absence of catalyst and absence of solvent, and the products were obtained in excellent yields. Furthermore, the reaction conditions are very mild, and no by-products were observed. Aromatic aldehydes reacted more rapidly than aliphatic aldehyde. The effect of electron deficiency and nature of the substituents on the aromatic ring showed some effect on this conversion. The nitro substituted aryl aldehydes required slightly longer reaction times than those of their simple and electron-rich counterparts to produce comparable yields (Table 1, entries 1-14). Electron-rich aldehydes such as anisaldehyde, piperonal, and veratraldehyde reacted rapidly with indole to give corresponding products in excellent yields within 40 min (Table 1, entries 3, 4, and 15). Aliphatic aldehydes such as n-hexanal, n-heptanal, and cyclohexane carboxaldehyd showed somewhat less reactivity (Table 1, entries 16–18). Substituted indoles reacted rapidly with any aldehydes with considerable yields (Table 1, entries 19, 20, and 21). Further, the reaction of ketones proceeded with more reaction time under the same reaction conditions, and the corresponding products were obtained in moderate yields (Table 1, entries 22-25).



Scheme 1. R: phenyl, alkyl; R': H, phenyl, alkyl.

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\mathbf{Yield}^{c} $(\%)$	92	06	8
Time (min)	40	40	40
$\operatorname{Product}^{b}$	Z-I Z-I	I D Z-I Z-I	₽ O Z-I Z-I
Indoles	Z-I	Z-I	Z-I
Aldehyde ^a	ਉ	OH HO	OMe
Entry	_	7	e

Table 1. Synthesis of bis(indolyl) methanes

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Table 1.	

Yield ^c (%)	06	8	85
Time (min)	40	50	70
$\mathbf{Product}^{b}$	IO-Z-I Z-I	m Z-I Z-I	
Indoles	Z-I	Z-I	Z-I
Aldehyde ^a	OHO CHO CHO CHO CHO CHO CHO CHO CHO CHO	о Н О Н О С Н О С Н О С Н О С Н О С Н О	CHO
Entry	~	Ø	10





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	Yield^c (%)	85	80	89
	Time (min)	120	120	120
Continued	$\operatorname{Product}^{b}$	Me	⁴ ⁴ z−1 z−1	H-Z-H
Table 1.	Indoles	Z-I	Z-I	Z-I
	$Aldehyde^{a}$	Me	Ч Ч Ч	H ₅ C ₂ CH ₃
	Entry	53	24	25

^{σ}The substrate was treated with indole (4 mmol) by stirring at 80°C in absence of solvent. ^bAll products were identified by their IR and ¹H NMR spectra. ^cIsolated yields after column chromatography.

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GENERAL EXPERIMENTAL PROCEDURE FOR BIS(INDOLYL) METHANES

A mixture of benzaldehyde (2 mmol) and indole (4 mmol) was stirred magnetically at 80 °C in the absence of solvent and the progress of the reaction was monitored by thin-layer chromatography (TLC). The completion of reaction confirmed with TLC. The product was dried over anhydrous Na_2SO_4 and then evaporated under vacuum to afford the crude product, which was further purified by column chromatography. In all the cases, the product obtained after the usual workup gave satisfactory spectral data.

SPECTRAL DATA FOR SELECTED COMPOUNDS

3,3'-Bisindolyl Phenylmethane (1b)

Pale red solid, yield 92%, mp 123–125; IR (KBr): 735, 1094, 1342, 1458, 1483, 2927, 2956, 3045, 3387 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 7.78 (br s, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.10–7.36 (m, 9H), 6.95 (t, *J* = 7.5 Hz, 2H), 6.46 (d, *J* = 1.8 Hz, 2H), 5.82 (s, 1H); ¹³C NMR (CDCl₃): 143.0, 136.2, 128.5, 128.6, 127.3, 126.5, 123.4, 121.3, 119.4, 119.0, 118.9, 111.3, 40.6.

3,3'-Bisindolyl-4-methoxylphenylmethane (3b)

Brown needles, yield 89%, mp 193–195; IR (KBr): 740, 780, 1015, 1090, 1132, 1341, 1450, 1607, 2922, 3052, 3386, 3422 cm^{-1} ; ¹H NMR (300 MHz, CDCl₃): $\delta = 7.90$ (br s, 2H), 6.9–7.9 (m, 12H), 6.4 (s, 2H), 6.1 (s, 1H), 3.95 (s, 3H), ¹³C NMR (CDCl₃): 39.4, 55.6, 102.3, 111.3, 119.7, 122, 123.8, 128.2, 129.9, 135.8, 136.8, 157.8; EIMS: m/z 352.

3,3'-Bisindolyl-4-dimethylaminophenylmethane (7b)

Pink solid, yield 91%, mp 168–170; IR (KBr): 740, 760, 1015, 1095, 1222, 1350, 1456, 1512, 2920, 3062, 3342, 3418, 3520 cm⁻¹; ¹H NMR (300 MHz, DMSO): 11.30 (br s, 2H), 8.30 (d, J = 2.0 Hz, 2H), 8.02 (dd, J = 8.8, 2.0 Hz, 2H), 7.50 (dd, J = 9.2, 1.6 Hz, 2H), 7.43 (d, J = 7.6 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.25 (d, J = 7.2 Hz, 1H), 7.20 (s, 2H), 6.23(s, 1H); ¹³C NMR (DMSO): 148.6, 145.2, 144.2, 133.1, 133.5, 132.6, 131.7, 130.2, 125.8, 121.4, 121.5, 117.3, 43.7; MS (ESI) m/z: 411.34.

3,3'-Bisindolyl-4-methylphenylmethane (8b)

Pale red solid, yield 90%, mp 95–98; IR (KBr): 742, 788, 999, 1090, 1225, 1340, 1457, 1508, 2925, 3056, 3386, 3420 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): 7.84 (br s, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.15 (dd, J = 7.6 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 7.00 (t, J = 7.2 Hz, 2H), 6.64 (s, 2H), 5.83 (s, 1H), 2.33 (s, 3H); ¹³C NMR (CDCl₃): 141.2, 136.5, 136.5, 129.2, 128.5,127.3, 123.4, 122.1, 120.2, 119.5, 119.2, 111.2, 40.2, 21.3.

3,3'-Bisindolyl-4-chlorophenylmethane (11b)

Pale solid, yield 86%, mp 74–76; IR (KBr): 743, 787, 1010, 1100, 1130, 1325, 1456, 1603, 2920, 3050, 3382, 3420 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 7.7 (br s, 2H), 7.3 (d, 2H, *J*=7.8), 7.01–7.15 (m, 8H), 6.86–6.97 (m, 2H), 6.35 (s, 2H), 5.73 (s, 1H); ¹³C NMR (CDCl₃): 44.4, 111.1, 112.2, 119.1, 120.4, 121.6, 122.8, 128.8, 130.7, 131.5, 135.9, 136.6.

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