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Solvent-free synthesis of bis(indolyl)methanes catalyzed by CAN

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Abstract: Indoles and carbonyl compounds undergo a rapid electrophilic substitution reaction in the presence of a catalytic amount of CAN, under solvent-free conditions, to afford the corresponding bis(indolyl)methanes in excellent yields.

Keywords: Bis(indolyl)methanes; Solvent-free conditions; Ceric ammonium nitrate; CAN

Introduction

Indole fragments are featured wide variety of pharmacologically and biologically active compounds [1]. Bis(indolyl)methanes are common components of bioactive metabolites of terrestrial and marine origin [2]. A few bioactive members of these compounds like Vibrindole-A and others have also been isolated from natural sources [3] and are generally found to be of pharmaceutical interest in a variety of therapeutic areas [1]. These compounds have received considerable attention over the past years due to their wide occurrence in various natural products possessing biological activity [2b,4] and usefulness for drug design [1]. Bis(indolyl)methanes are most active cruciferous substances for promoting beneficial estrogen metabolism and inducing apoptosis in human cancer cells [5]. A simple and direct method for the synthesis of bis(indolyl)methanes is the reaction of indole with aldehydes. A wide variety of reaction conditions have been published for the synthesis of bis(indolyl)methane derivatives in solution, on solid phase and under solvent-free conditions. Several catalyst including lanthanide triflate [6] $Dy(OTf)_3$ [7], $InCl_3$ [8], PPh_3-$HClO_4$ [9], montmorilonite K-10 [10], NBS [11], I_2 [12], $KHSO_4$ [13], $RE(PFO)_3$ [14], InF_3 [15], $ZrOCl_2$ [16], $ZrCl_4$ [17] and acidic ionic liquid [18] were found to promote the reaction.

However, there are always some drawbacks with these procedures such as long reaction times, high catalyst loading, and use of an additional ultrasound or microwave oven. Therefore, the development of more efficient and green methods for the preparation of these kinds of compounds is still an active ongoing research area. Recently, ceric ammonium nitrate, CAN, has been introduced as a mild and efficient catalyst for various organic transformations [19]. The reaction of indoles with carbonyl compounds catalyzed by CAN which afford the bisindolymethane derivatives has been reported recently. However, the reactions must be performed using the toxic CH3CN as the solvent under the protection of N_2 atmosphere [20] or under ultrasonic irradiation [21]. As a part of our ongoing program in developing various new synthetic transformations using inexpensive and eco-friendly materials as catalyst [22-26], herein we wish to report an efficient procedure for the preparation of bis(indolyl)methanes using a catalytic amount of CAN at 120°C under solvent-free conditions (Scheme 1).

Results and Discussion

Our initial studies were focused on the optimization of the reaction conditions for the synthesis of bis(indolyl)methanes. 4-Nitrobenzaldehyde and indole were chosen as model substrates. The reaction in the presence of 0.07 mmol CAN at 120°C, in the absence of solvent, afforded the corresponding product in 87% yield. Lower catalyst loading could be used with only a marginal drop in reaction rate. With the optimized reaction conditions, we next studied the reaction of a series of aldehydes with indole derivatives. The results are shown in Table 1.

The investigations showed that not only aldehydes but also ketones could undergo the above electrophilic substituted reaction efficiently to afford the corresponding products in very short reaction times and

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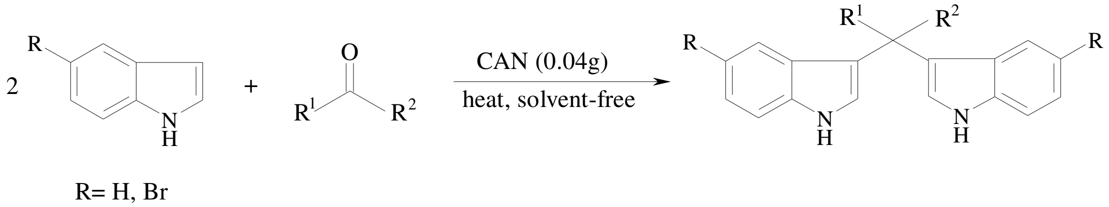
in good yields. The obtained results revealed that the nature of substitution on aromatic rings of aldehydes and indoles have no considerable effect on the times and yields. In all cases the reactions are completed in short reaction times and the pure products are obtained in very high yields.



Scheme 1

The present procedure is superior in comparison with CAN-catalyzed reaction of (1H-indol-3-yl)(alkyl) methanol with indoles in ethanol under ultrasonic irradiation [21] which requires longer reaction times, (2-5h) and an additional ultrasonic waves. On the other hand, in comparison to the other reported article for the synthesis of bis(indolyl)methanes in the presence of CAN in acetonitrile under nitrogen atmosphere [20], solvent-free synthesis of bis(indolyl)methanes was found to be an excellent choice in terms of reaction condition.

Table1. Solvent-free synthesis of bis(indolyl)methane derivatives catalyzed by CAN

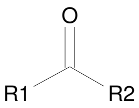
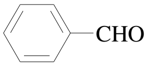
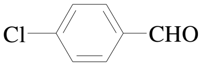
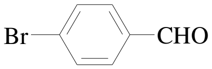
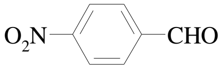
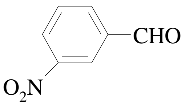
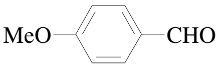
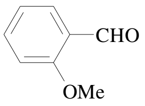
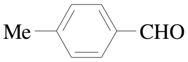
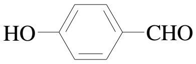
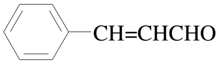
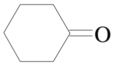
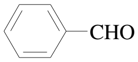
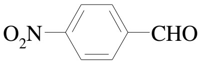
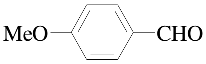
Entry	R		Time (min)	Yield(%)^{a,b}	M.P.(°C)	
					Found	Reported
1	H		5	91	124-126	125-127[27]
2	H		10	90	87-89	77-81[28]
3	H		5	89	136-138	
4	H		15	87	245-246	220-222[20]
5	H		15	86	261-263	265-266[27]
6	H		15	88	195	191-193[27]
7	H		5	90	131-133	134-136[17]

Table 1. Continued

8	H		5	92	96-98	94-96[30]
9	H		8	92	119-121	122-124[20]
10	H		40	70	94-96	99[29]
11	H		15	85	150	116-118[30]
12	Br		5	90	250	
13	Br		5	91	135-136	
14	Br		5	87	220-222	

[a] All products are well characterized by FT-IR, ^{1}H-NMR, Mass and melting point.

[b] Yields refer to isolated products.

Conclusion

In conclusion, we have reported a highly efficient and easy access method for the synthesis of biological significance bis(indolyl)methanes. Our method has several advantages including very short reaction times, mild conditions, excellent yields, use of an inexpensive and non-toxic catalyst, simple operation and work-up. Additionally, the protocol does not require volatile and hazardous organic solvents and an additional ultrasound or microwave oven. The elimination of the solvent has obvious environmental benefits in regard to the depletion of solvent waste; the simplicity and efficiency of the overall process.

Experimental Section

All the chemicals were purchased from Merck Company. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ^{1}H-NMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. All products were well characterized by their physical and spectral data.

Preparation of bis(indolyl)methanes:

General procedure

A mixture of an appropriate aromatic aldehyde (1mmol), 2mmol of indole derivative and 0.07 mmol of CAN (0.04 g) was heated at 120°C. The progress of the reaction was monitored by TLC. Upon completion of the reaction, mixture was poured into water and the precipitated solid was collected and washed with distilled water (20 mL). The crude mixture was purified by flash column chromatography (EtOAc/petroleum ether 1:4) or recrystallization from an appropriate solvent to afford the pure product. The results are summarized in Table 1.

Spectral and physical data for new compounds:

Entry 12: IR (KBr): 775, 1015, 1215, 1450, 1594, 3069, 3417 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.77 (s, 1H), 6.67 (s, 2H), 7.23-7.31 (m, 11H), 8.00 (s, 2H, NH).

Entry 13: IR (KBr): 792, 1344, 1388, 1599, 2973, 3416 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.8 (s, 1H), 6.66 (d, J=1.58 Hz, 2H), 7.28 (d, J=7.2 Hz, 2H), 7.44 (s, 2H), 7.66 (d, J=7.2 Hz, 2H), 8.07-8.13 (m, 4H), 8.4 (s, 2H, NH).

Entry 14: IR (KBr): 681, 1026, 1091, 1245, 1297, 1424, 1610, 2838, 2957, 3425 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.83 (s, 3H), 5.8 (s, 1H), 6.8 (d, J=1.27, 2H), 6.81 (d, J=8.6 Hz, 2H), 6.86 (d, J=8.6Hz, 2H), 7.44(m, 4H), 7.68(s, 2H), 8.29 (s, 2H, NH); MS (m/z): 508, 305, 208, 192, 165, 118, 102, 43.

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