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Synthesis of bis-indolylmethanes catalyzed by oxone

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Abstract

Oxone (3.5 mol%) was found to be an effective catalyst for the condensation reactions of indoles with aldehydes to afford bis-indolylmethanes in good to excellent yields within 10–30 min. The method is simple and economic. The catalyst is found to be recyclable.

Keywords: Indole; Aldehyde; Bis-indolylmethane; Oxone

Bis-indolylmethanes [1] are important derivatives of indole and inhibit the proliferation of breast tumor cell [2,3]. Therefore, their syntheses have received an increasing attention. Several methods have been reported in the literature for the synthesis of bis-indolylmethanes. Protic acids [4] and Lewis acids [5,6] are known to promote these reactions. However, these procedures suffered from some limitations when several substrates are sensitive to protic acids. Most recently, a great effort has been made to find mild and clean procedure in the synthesis of bis-indolylmethanes and some catalytic systems have been developed, such as $LiClO_4$ [7], NH_4Cl [8], Zeolite [9] under solvent free conditions; $Fe(DS)_3$ [10], $Zr(DS)_4$ [11], $NaBAr^F{}_4$ [12], SDS [13], HMTAB [14] in aqueous medium; and $Dy(OTf)_3$ [15], $In(OTf)_3$ [16] and $La(PFO)_3$ [17] in ionic liquids. However, some of these methods suffered from some drawbacks such as high temperature [7,8,15], long reaction time [9,16,17], low yields [9,13], causing toxic wastes [7,12] and expensive ionic liquids [15–17]. Thus, there is still scope to develop simple and practical method for the synthesis of bis-indolylmethanes.

Oxone ($2KHSO_5·KHSO_4·K_2SO_4$), a strong and commercially available reagent, has been used for many organic transformations [18]. Herein, we report a rapid and convenient procedure for the preparation of bis-indolylmethanes using a catalytic amount of oxone in methanol at room temperature (Scheme 1).

1. Experimental

To optimize the stoichiometry of oxone with indole and aldehyde required for the reaction, 1,2-dimethylindole and p-methoxybenzaldehyde were taken as model, several experiments were examined with different ratios of oxone, the best result was obtained by the molar ratio 1:2:0.035 for p-methoxybenzaldehyde, 1,2-dimethylindole, and oxone. To

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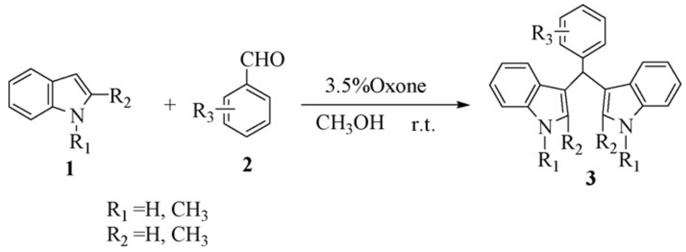


Scheme 1.

extend the scope of the reaction and to generalize the procedure, the reaction of series of aldehydes with indole were carried out and the results were summarized in Table 1.

1.1. General experimental procedure

To a mixture of indole (2.0 mmol) and aldehyde (1.0 mmol) in methanol (5 mL), oxone (0.035 mmol) was added. The mixture was stirred at room temperature for the appropriate time (see Table 1) until TLC showed that the reaction was complete. The insoluble oxone was then filtrated; water (15 mL) was added to filtrate to quench the reaction and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and then evaporated. The crude product was purified by silica-gel flash column chromatography and eluted with an ethyl acetate and hexane mixture to afford bis-indolylmethane. The insoluble oxone was filtrated and directly used in subsequent runs without further treatment.

The spectral (^{1}H NMR, IR, ^{13}C NMR, MS and EA) data of selected compounds are given below:

Compound **3a**: 3,3′-Bis(1,2-methyl-indolyl)-p-methoxyphenylmethane, Mp 197–199 °C. IR (KBr) (ν_{max}, cm^{-1}): 2933, 1610, 1509, 1472, 1365, 1339, 1247, 1173, 1031, 833, 748; ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 2.14 (s, 6H), 3.61 (s, 6H), 3.76 (s, 3H), 5.98 (s, 1H), 6.83–6.75 (m, 4H), 6.92 (d, 2H, J = 3.8 Hz), 7.04 (t, 2H, J = 7.6 Hz), 7.14 (d, 2H, J = 4.4 Hz), 7.2 (d, 2H, J = 4.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 157.7, 136.6, 136.2, 133.4, 129.9, 127.8, 119.9, 119.6, 118.5, 113.43, 108.3, 55.2, 38.9, 29.4, 10.7; LRMS (EI, 20 eV) *m/z* (%) 408 (M$^+$, 100); Anal. Calcd. for $C_{28}H_{28}N_2O$: C, 82.32; H, 6.91; N, 6.86. Found: C, 82.26; H, 6.99; N, 6.74.

Compound **3j**: 3,3′-Bis(1,2-methyl-indolyl)-1-naphtphenylmethane Mp 214–216 °C. IR (KBr) (ν_{max}, cm^{-1}): 2912, 1595, 1535, 1468, 1366, 1336, 1026, 802, 782, 739; ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 2.05 (s, 6H), 3.63 (s, 6H), 6.68 (s, 1H), 6.81 (t, 2H, J = 7.8 Hz), 6.97 (s, 2H), 7.07 (t, 3H, J = 7.8 Hz), 7.34-7.23 (m, 5H), 7.40 (t, 1H, J = 7.2 Hz), 7.77 (d, 1H, J = 3.6 Hz), 7.86 (d, 1H, J = 4 Hz), 8.01 (d, 1H, J = 4.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 139.9, 136.6, 133.7, 133.5, 132.3, 128.4, 128.1, 126.9, 126.6, 125.7, 125.3, 124.3, 120.0, 119.0, 112.0, 108.2, 37.0, 29.4, 10.4; LRMS (EI, 20 eV) *m/z* (%) 428 (M$^+$, 100); Anal. Calcd. for $C_{31}H_{28}N_2$: C, 86.87; H,6.58; N, 6.53. Found: C, 86.74; H, 6.67; N, 6.41.

2. Results and discussion

As shown in Table 1, Aromatic and heterocyclic aldehydes underwent smooth transformation to the corresponding bis-indolylmethanes 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 electron-donating substituents $–CH_2O_2$ and $–OCH_3$ (entries 7 and 9) required shorter reaction times than the electron-withdrawing counterparts $–NO_2$, –CN and –Cl (entries 6–4), but the aromatic aldehyde with electron-donating and electron-withdrawing groups and even heteroaromatic aldehyde have no significant effect on the reaction yields. It indicated that the oxone/CH_3OH catalytic system has wide functional group tolerance.

And another intention of our study was to investigate the reuse of oxone. After the reaction, oxone was filtrated and directly used in subsequent runs without further treatment. As shown in Table 2, the catalytic activities gradually decreased in the following cycles. However, even after three cycles, it still have moderate yields. It implied that the oxone/CH_3OH catalytic system can be reused at least three times without significant loss of activity.

Table 1
Oxone-catalyzed synthesis of bis-indolylmethanes derivatives.

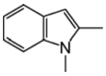
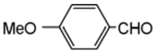
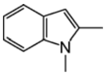
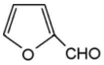
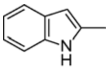
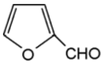
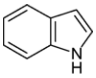
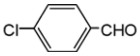
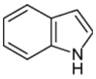
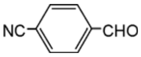
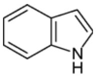
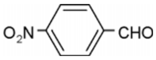
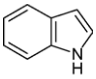
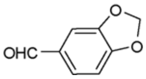
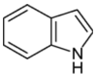
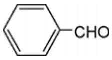
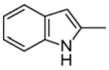
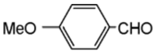
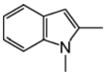
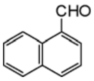
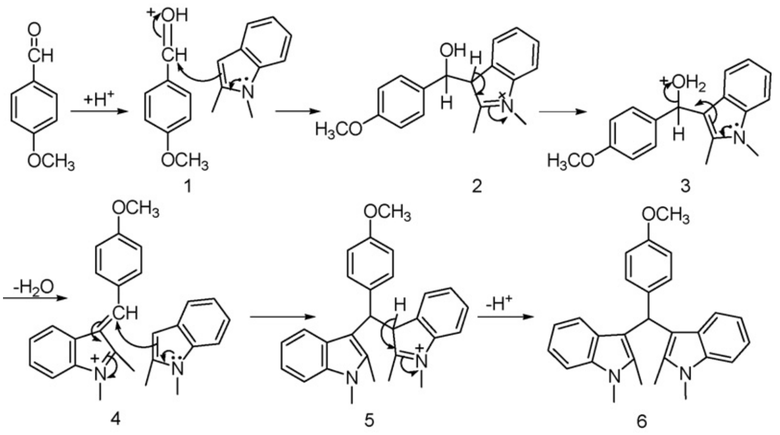
Entry	Indole	Aldehyde	Product	Time (min)	Isolated yield (%)
1			**3a**	10	94
2			**3b**	10	96
3			**3c**	10	94
4			**3d**	25	95
5			**3e**	25	88
6			**3f**	30	82
7			**3g**	10	98
8			**3h**	10	91
9			**3i**	10	95
10			**3j**	15	88

Table 2
Synthesis of 3,3′-bis(1,2-methyl-indolyl)-p-methoxybenzmethane (**3a**) in CH_3OH using recycled oxone.

Cycle	Time	Isolated yield (%)
0	10 min	94
1	4 h	92
2	12 h	88
3	24 h	86

According to the literature [8,9,13], we think that oxone catalyzed the reaction as a mild protic acid under methanol. With entry 1 as model, a possible mechanism for the reaction is sketched in Scheme 2. An aldehyde was first activated by proton and then carried out an electrophilic substitution at C-3 of an indole. After loss of water, an intermediate **4** was generated. The intermediate 4 was served as an electrophile to attack a second molecule of indole to form the product.



Scheme 2.

In conclusion, we have developed a general and facile method for the synthesis of bis-indolylmethanes using oxone as the catalyst. Such catalytic system deserves advantages including short reaction times (10–30 min), room temperature, high yields of products and the oxone is easy to recover and can be reused for at least three times.

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