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Synthesis of bis(indolyl) methanes using aluminium oxide (acidic) in dry media

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Abstract

Heterogeneous catalyst aluminium oxide (acidic) is found to be an effective catalyst for the solvent-free condensation reaction of indole with aldehydes in microwave irradiation with shorter reaction time and higher yields.

Keywords: Aluminium oxide (acidic); Indole; Aldehydes; Bis(indolyl) methanes; Microwave irradiation; Dry media

In recent years, a large trend towards synthesis of bis(indolyl) methanes and their derivatives has attracted much attention due to their synthetic as well as biological applications [1]. Bis(indolyl) methanes are most active cruciferous substances for promoting beneficial estrogen metabolism and inducing apoptosis in human cancer cells [2].

Because of their wide occurrence as natural products and various biological activities, synthesis of these bis(indolyl) methanes has attracted attention. Recently, oxidized bis(indolyl) methanes containing a conjugated bis(indolyl) skeleton have acted as colorimetric sensors and chromogenic sensors [3]. Solvent-free reactions have been established an efficient technique for various organic reactions avoiding harmful solvents. The acid-catalyzed condensations of indole with carbonyl compounds have been of concern as a useful route for preparation of bis(indolyl) methanes. The protic acids [4] and Lewis acids [4] have been used in excess and drastic conditions. To abate the environmental pollution of the disposal of excess acids with the improvement of reaction condition a number of catalytic systems were used, which were rare earth perfluorooctanoate [$RE(PFO)_3$] [5], trichloro-1,3,5-triazine [6], hexamethylenetetramine-bromine [7], ion-exchange resin [8]. Ionic liquids in conjugation with $In(OTf)_3$ or $FeCl_3{\cdot}6H_2O$ [9] were also found to promote this reaction. Recently, phosphate zirconia [10], heteropoly acids [11], fluoroboric acid [12], amberlyst [13a], silica sulfuric acid [13b], $ZrOCl_2{\cdot}2H_2O/SiO_2$ [14], and protic solvents [15] were also reported to promote the synthesis of bis(indolyl) methanes.

However, many of these methods suffer from the drawback like use of expensive reagents [16–18], excess of catalyst [19], long reaction time [7,16,19] and low yield of products [23]. In order to develop a new method for the synthesis of bis(indolyl) methanes and to overcome all the problems on previous work of Posner et al., we use alumina (acidic) as a catalyst. The role of aluminium oxide as a heterogeneous catalyst on several organic reactions, such as

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oxidation, reduction and displacement reactions is known from the previous work of Posner et al. [20–23]. Keeping all these facts in mind, we go for synthesis of bis(indolyl) methanes using heterogeneous catalyst aluminium oxide (acidic) which gives clean, efficient and fast reactions.

1. Experimental

Melting points were determined in open capillaries and are uncorrected. The completion of reactions was monitored by TLC. IR spectra were recorded on a matrix of KBr with PerkinElmer 1430 spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on Varian NMR spectrometer, Model Mercury Plus (400 MHz), mass spectra [ES-MS] were recorded on a Water-Micro Mass Quattro-II. Microwave oven equipped with a turntable was used (LG Smart Chef MS-255R operating at 2450 MHz having maximum output of 900 W).

Aluminium oxide (acidic) (0.5 g) was added to a mixture of (2.0 mmol) indole and (1.0 mmol) aldehyde in a beaker and the reaction mixture irradiated in microwave at 450 W for appropriate time. The completion of the reaction was monitored by TLC. All compounds were characterized by spectral analysis.

3,3′-Bis(indolyl) phenylmethane **3a**: IR (KBr): 3478, 3019, 1601, 1522, 1456, 1419, 1215, 1093, 1017, 757, 669 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.89 (s, 1H), 6.67 (s, 2H), 7.09–7.58 (m, 13H), 7.94 (bs, 2H, NH); ES-MS *m*/*z* 322 (M^+).

2. Results and discussion

For the aforementioned reasons and in light of our general interest to synthesize bis(indolyl) methanes using various catalysts [24], in this paper, we report a simple procedure for the synthesis of bis(indolyl) methanes under solvent-free conditions using acidic aluminium oxide in microwave irradiation.

In order to study the optimization of reaction conditions for the synthesis of bis(indolyl) methanes, initially we have chosen various aluminium oxides for the condensation reaction of benzaldehyde and indole in the mole ratio of 1:2 as a standard example and we found that the reaction forward rapidly with acidic aluminium oxide rather than other catalysts (Table 1).

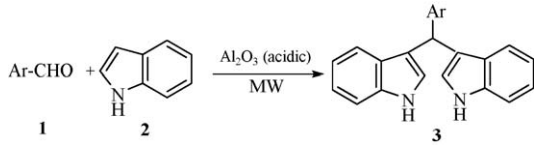
Then we performed a reaction with aluminium oxide (acidic) as catalyst (0.5 g) and carried out the reaction of benzaldehyde and indole in the mole ratio of 1:2 as a standard example (Scheme 1) in a domestic microwave oven at 450 W.

To explain the actual role of aluminium oxide (acidic) in the synthesis of bis(indolyl) methanes we explore probable mechanism of the reaction in Scheme 2.

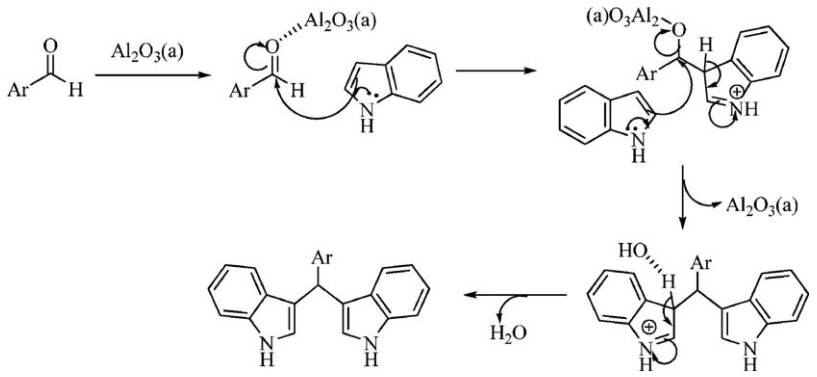
The reaction proceeded smoothly and the desired product (Table 2, entry **3a**) was obtained in high yield (97%) and in a shorter reaction time (5 min). The obtained results are encouraging results, we extended the procedure for the synthesis of different substituted bis(indolyl) methanes (**3a-l**) using substituted benzaldehydes and heterocyclic aldehydes. The results described in Table 2 indicate the scope and generality of the method. The reported method is

Table 1
Comparative study of catalysts using benzaldehyde as a substrate (**3a**).

Entry	Aluminium oxide	Time (min)	Yield (%)
1	Without	25	45
2	Neutral	20	60
3	Basic	25	55
4	Acidic	5	97



Scheme 1. Aluminium oxide (acidic) catalyzed solvent-free synthesis of bis(indolyl) methanes.



Scheme 2. Mechanistic role of aluminium oxide (acidic) in solvent-free synthesis of bis(indolyl) methanes.

Table 2
Characterization of bis(indolyl) methanes (**3a-l**).

Entry	Aromatic	Time (min)	M.P. (°C)[a]	Yield (%)
3a	C_6H_5	5	124–126	97
3b	4-Me C_6H_4	14	97–99	90
3c	4-Meo C_6H_4	15	191–193	89
3d	3,4-MeO C_6H_3	17	220–222	88
3e	4-Cl C_6H_4	6	104–105	95
3f	4-OH C_6H_4	18	123–125	88
3g	4-NO_2 C_6H_4	5	221–223	96
3h	3-MeO, 4-OH C_6H_3	10	111–113	88
3i	2-Pyridyl	11	137–139	91
3j	2-Furyl	19	319–321	85
3k	2-Thiophyl	16	278–280	86
3l	2-Piperanyl	17	98–99	90

[a] Melting points compared with physical data in Refs. [16–20].

efficient for various aromatic and heterocyclic aldehydes to obtain the bis(indolyl) methanes with yields greater than 85% (Table 2).

Aluminium oxide (acidic) is found to be the choice of catalyst for this reaction. Moreover, the reaction proceeded in the absence of catalyst to give the product in fewer yields (45%) over a prolonged period of time (25 min) as indicated in Table 1 (entry 1). In summary, we have demonstrated that aluminium oxide (acidic) can act as an efficient catalyst for the condensation reaction of aldehydes with indole under solvent-free condition using microwave irradiation through an environmentally acceptable process. The products were obtained in high yields and isolated very easily by dissolving the reaction mixture in dichloromethane to affect the separation of the catalyst. The dichloromethane layer was evaporated under reduced pressure. The crude product was recrystallized by using ethanol. All the prepared compounds were unequivocally characterized by their spectral analysis. In our next investigation we check the reusability of catalyst. For reusability experiment we have performed an experiment with same reaction condition considering benzaldehyde as a standard, the obtained results are illustrated in Table 3.

Table 3
The recycling of aluminium oxide (acidic) for benzaldehyde derivative.

Entry	Time (min)	Yield (%)[a]
0	12	92
1	14	90
2	16	87
3	20	85

[a] Isolated yields.

Aluminium oxide (acidic) has proved to be an efficient catalyst for the one pot synthesis of different bis(indolyl) methanes. The performed reaction gives excellent yields in shorter reaction time under solvent-free conditions using microwave irradiation. The method developed may find extensive use in combinatorial chemistry for the synthesis of different bis(indolyl) methanes.

3. Conclusions

Using aluminium oxide (acidic) the reaction goes through solvent-free and indicates the green concepts in organic synthesis with better yields and shorter reaction time.

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