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An efficient synthesis of bis(indolyl) methanes under solvent free condition using Silica supported Chloroacetic Acid as reusable Catalyst

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ABSTRACT

Silica supported chloroacetic acid has been utilized as an efficient and an environmentally friendly heterogeneous, reusable catalyst for the coupling of aromatic aldehyde and indole to produce bis(indolyl)methanes under solvent free condition. The significances of this protocol are mild reaction condition, excellent yield and simple work up procedure.

Key words: Indole, aromatic aldehyde, bis(indolyl)methanes, silica supported chloroacetic acid, solvent-free reaction.

INTRODUCTION

In the chemical sciences, there emerges a need to carve benign synthetic pathways that in simultaneity of being high yielding are safe and simple also exhibiting high atom efficiency and thereby abridging the steps with no waste[1]. Removal of organic solvents from chemical synthesis proves vital and marches towards renovation in chemical technologies. Meritorious aspects of solvent-free reaction in regards of those in molecular solvents include i) no reaction medium to collect, purify, and recycle, (ii) the compounds formed are often sufficiently pure to circumvent extensive purification using chromatography, and in some cases the recrystallization is superfluous, (iii) reactions are converted to rapid one, sometimes reaching substantial completion in several minutes thereby outwitting the hours needed with that of organic solvents, (v) There seldom occurs need for specialized equipment, (vi) Significant lowering in energy consumption. Thus, constructing such solvent-free protocols is not only environmentally benign but also ensuring economical feasibility[2].

As a result of candid applications in material science[3], agrochemicals[4], pharmaceuticals[5], Indole derivatives prove to be prestigious. Indole and its derivatives reveal themselves as relevant intermediates in organic synthesis and depict various physiological and pharmacological properties[6], beneficial estrogen metabolism promoter[7], inhibitor for human prostate cancer

cells[8], radical scavengers[9], antiviral agents[10] and photo physical properties[11]. Bis(indolyl)methanes and its derivatives constitute bioactive metabolites of terrestrial and marine origin[12]. Generally, electrophilic substitution reaction of Indole with carbonyl compounds results azafulvanium salts which irrefutably undergo further addition with second molecule of Indole to offer bis(indolyl)methanes[13]. Both protic acids as well as Lewis acids are known to promote this reaction [14-31]. Although these methods are suitable for many synthetic conditions, many of these are associated with several drawbacks, which include the requirement of large or stoichiometric amount of catalysts due to their deactivation by nitrogen containing reactants, low yields, long reaction times, high reaction temperatures, expensiveness of catalysts, exhausting workup and generation of environmentally perilous waste material as a result of their extraction procedures.

As a result of serenity of Indole and bis(indolyl) methane derivatives, there emerges a consistent demand for developing a novel synthetic methodologies in this area. Also the high catalytic activity, low toxicity, moisture, and air tolerance, their recyclability and particularly low price make the use of solid supported reagents attractive alternatives to conventional Lewis acids and triflates [32]. Although the catalytic applications of solid supported reagents for organic synthesis have been well established, there is no report on the use of silica supported chloroacetic acid. Thereby in our ongoing endeavor to establish clean and ecofriendly synthetic methodologies [33], we report silica supported chloroacetic acid (0.1 mmol) as a reusable catalyst for the synthesis of bis(indolyl)methanes under solvent-free condition.

MATERIALS AND METHODS

All chemicals and solvents were reagent grade and used as purchased without any further purification. Analytical thin-layer chromatography was performed on percolated silica gel 60-F 254 plates. The data found were in consistent with the proposed structure. IR spectra on KBr disks were recorded on a Shimadzu IR-470 FT-IR spectrophotometer. The routine nuclear magnetic resonance spectra were taken in CDCl_3 using a Bruker 300 MHz spectrophotometer with TMS as an internal standard. Chemical shift δ was given in ppm relative to TMS and compared with reported literature values. Elemental analysis was done Melting points were determined in an open capillary tube and were found to be uncorrected.

Preparation of the catalyst:

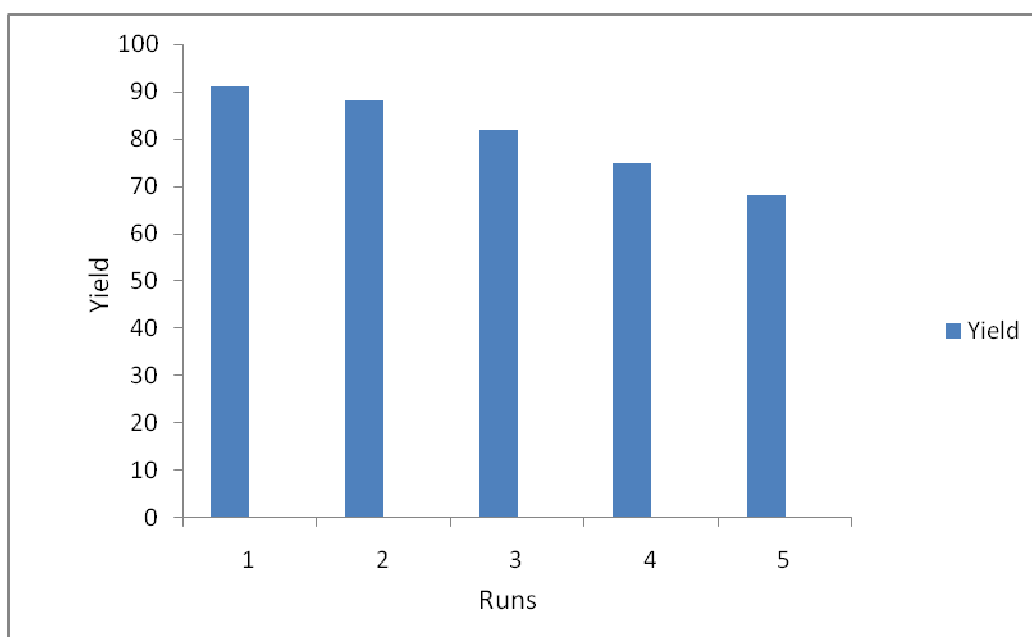
ClCH_2COOH (1.025 g, 12.5 mmol) was added to a suspension of silica gel (23.75 g, 230–400 mesh) in chloroform (75 mL). The mixture was concentrated and the residue dried under vacuum at 100°C for 72 h to afford $\text{SiO}_2\text{-ClCH}_2\text{COOH}$ (0.5 mmol g^{-1}) as a free flowing powder.

General Procedure for the preparation of compound 3:

A mixture of Indole (1mmol) and benzaldehyde (1 mmol) in round bottom flask was stirred at room temperature in presence of silica supported chloroacetic acid (0.1mmol) as catalyst for appropriate time (table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with chloroform (5 mL) and the catalyst was allowed to settle. The supernatant chloroform layer was decanted off, the catalyst washed with chloroform (2 mL) and the combined chloroform layers were concentrated under reduced pressure to afford almost pure product, which was further purified by recrystallization from ethanol and purified by column chromatography (silica gel, ethyl acetate: pet ether = 1:9) The recovered catalyst was activated by heating at 100°C under vacuum for 1 h and reused for the synthesis of bis(indolyl)methane from fresh benzaldehyde (1 mmol), affording a 88 % yield after 13 min. The recovered catalyst, after activation, was reused for synthesis of bis(indolyl)methane from fresh benzaldehyde (1

mmol) affording 82%, 75% and 68 % yields, respectively, in 18, 25 and 40 min. These results are summarized in **Figure I**.

Figure I: Recyclability of the Catalyst



Spectral Data of some selected compounds.

3,3'-(phenylmethanediyl)bis(1H-indole) (3a)

IR (KBr): 3402 (N–H) cm^{-1} ; ^1H NMR (CDCl_3 , TMS): d 5.86 (s, 1 H), 6.66 (s, 2 H), 7.11 (t, 2 H, $J = 6.9$ Hz), 7.14–7.22 (m, 3 H), 7.28–7.31 (m, 2 H), 7.35–7.42 (m, 6 H), 7.93 (br s, NH) ppm; ^{13}C NMR (CDCl_3 , TMS): d 31.6, 110.9, 111.9, 118.4, 119.5, 121.2, 124.0, 126.3, 127.1, 128.5, 128.6, 137.0, 145.2 ppm. Elemental analysis, Molecular Weight: 322.40, Calculated: C, 85.68; H, 5.63; N, 8.69, Found : C, 85.59; H, 5.60; N, 8.64.

3,3'-(4-methylphenyl)methanediyl]bis(1H-indole) (3b)

IR (KBr) 3411, 3054, 1599, 1455 cm^{-1} , ^1H NMR (CDCl_3 , 300MHz) δ 2.3 (s, 3H, -CH₃), 5.8 (s, 1H, -CH), 6.6 (s, 2H, Ar-H), 6.97.4 (m, 14H, ArH), 7.8 (bs, 2H), ^{13}C NMR (CDCl_3 , 300MHz) δ 21, 39, 110, 119.17, 119.92, 119.95, 123.53, 127.12, 128.58, 128.90, 135.46, 136.71, 141. Elemental analysis, Molecular Weight: 336.42, Calculated: C, 85.68; H, 5.99; N, 8.33, Found : C, 85.57; H, 5.89; N, 8.27.

3,3'-(4-methoxyphenyl)methanediyl]bis(1H-indole) (3c)

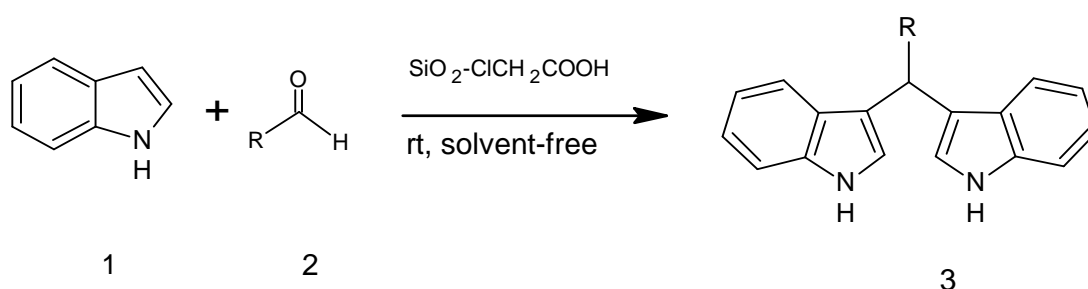
^1H NMR (CDCl_3 , 300MHz)- δ 3.7 (s, 3H, -OMe), 5.8 (s, 1H, -CH), 6.654 (s, 2H, Ar-H), 6.658–7.375 (m, 13H, Ar-H), 7.385 (bs, 2H, NH₂). ^{13}C NMR (CDCl_3 , 300MHz) δ 32.6, 39.3, 55.2, 109.0, 113.6, 118.6, 118.7, 120.1, 121.4, 127.5, 128.2, 129.6, 136.7, 137.5, 157.9, Elemental analysis, Molecular Weight: 352.42, Calculated: C, 81.79; H, 5.72; N, 7.95, Found : C, 81.76; H, 5.68; N, 7.90.

3,3'-(3,4-dimethoxyphenyl)methanediyl]bis(1H-indole). (3l)

^1H NMR (CDCl_3 , 300MHz)- δ 3.7 (s, 3H, -OMe), 3.8 (s, 3H, -OMe), 5.8 (s, 1H, -CH), 6.653 (s, 2H, Ar-H), 6.656–7.41 (m, 13H, Ar-H), 7.8 (bs, 2H, NH₂). Elemental analysis, Molecular Weight: 382.45, Calculated: C, 78.51; H, 5.80; N, 7.32, Found : C, 78.49; H, 5.77; N, 7.28.

RESULTS AND DISCUSSION

Initially, a blank reaction was carried out using indole and benzaldehyde in 2:1 proportion under solvent free condition in round bottom flask with constant stirring at room temperature, but the result proved to be abortive. Thus, desperately we subjected the similar reaction of indole and benzaldehyde in 2:1 proportion supplemented with similar conditions assisted with silica supported chloroacetic acid as catalyst. For our astonishment the reaction proceeds rapidly resulting in the formation of predicted product in opulent yield (**Scheme I**).



Scheme I: Synthesis of bis(indolyl)methane 3 from indole 1 and aromatic aldehyde 2.

A series of experiments were carried out varying the amounts of silica supported chloroacetic acid to optimize the catalytic amount required. 0.01 mmol of Silica gel supported Chloroacetic acid was found to be adequate to catalyze the reaction, but it offered 70 % yield of bis(indolyl)methanes in 45 min. 0.05 mmol and 0.1 mmol of silica gel supported chloroacetic acid as catalyst resulted in same but excellent yield in 25 min and 10 min respectively. Use of just 0.1 mmol was sufficient to drive the reaction forward; larger amounts of the catalyst did not improve the results.

Next, the conversion of benzaldehyde to the corresponding bis(indolyl)methanes was carried out at room temperature in the presence silica gel supported chloroacetic acid (0.1 mmol) using various solvents such as chloroform (45%), dichloromethane (50%), acetonitrile (80%), and tetrahydrofuran (40%). However, the best yield of product (91%) was obtained under solvent-free conditions. The reusability of silica gel supported chloroacetic acid was examined with benzaldehyde as a model substrate and the results are presented in the experimental procedure. The nature of the substituents on the aromatic ring did not show strongly obvious effects in terms of yields under the present reaction conditions. Various functional groups were tolerated under the present conditions, for example, Me, Cl, OMe, and NO₂. Acid sensitive substrates like furyl aldehyde (entry 3g) gave the corresponding bis(indolyl)methane in excellent yield without any side reactions, which are normally encountered under acidic conditions. Also whenever position 3 of indole is blocked (entry 3m), the electrophilic attack takes place through position 2 to give the corresponding bis(indolyl)methane in excellent yield. To check the versatility of this method a series of substituted benzaldehyde and other heterocyclic aldehydes were subjected to the reaction and results are summarized in table I.

The efficiency of silica supported chloroacetic acid catalyst was also compared with some of those reported in the literature (**Table II**). As it is seen in addition to having the general advantages attributed to the solid supported catalysts, silica supported chloroacetic acid has a good efficiency compared to other recently reported catalysts.

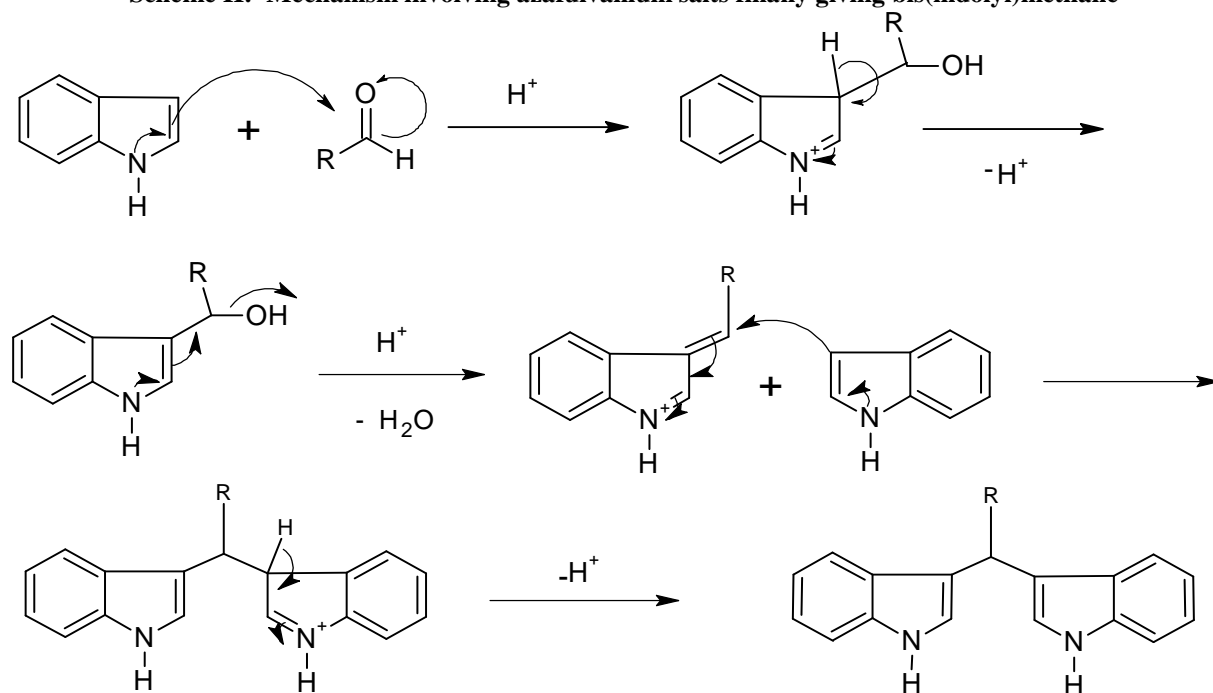
A plausible mechanism for the synthesis of bis(indolyl)methanes under silica supported chloroacetic acid as catalyst is shown in (**Scheme II**).

Table I. Synthesis of bis(indolyl)methanes using silica supported chloroacetic acid under solvent- free condition ^a

Entry	R	Time in min.	Yield(%) ^b
3a	C ₆ H ₅	10	91[19]
3b	4-MeC ₆ H ₄	8	92[14]
3c	4-OMeC ₆ H ₄	9	91[26]
3d	4-O ₂ NC ₆ H ₄	12	89[19]
3e	3-O ₂ NC ₆ H ₄	11	90[31]
3f	2-O ₂ NC ₆ H ₄	14	88[34]
3g	2-furyl	11	87[31]
3h	4-HOC ₆ H ₄	12	91[21]
3i	3-HOC ₆ H ₄	10	87[34a]
3j	4-ClC ₆ H ₄	13	86[26]
3k	2-ClC ₆ H ₄	15	87[26]
3l	3,4-(OMe) ₂ C ₆ H ₃	8	90[27]
3m	Indole3-acetic acid	15	88[34b]

^a: all the products are characterized by IR, ¹H NMR and were identified by comparison of their physical and spectral data with those of the authentic samples, ^b: yield of isolated products

Scheme II: Mechanism involving azafulvanium salts finally giving bis(indolyl)methane

Table II: Comparison of the catalytic efficiency of SiO₂-ClCH₂COOH against other reported catalysts for the conversion of benzaldehyde into bis(indolyl)methanes

Entry	Cat./solv./temp.(^o C)	Time (min)	Yield (%)
1	LiClO ₄ /MeCN/r.t.	150	95[14]
2	HClO ₄ -PPh ₃ /MeCN/r.t.	30	61[16]
3	Zeokarb-225/MeCN/r.t.	450	95[19]
4	La(PFO) ₃ /MeCN/r.t.	30	90[22]
5	SiO ₂ -ZrOCl ₂ -8H ₂ O/solvent-free/50	40	84[23]
6	AlPW ₁₂ O ₄₀ /MeCN/r.t.	15	92[24]
7	SiO ₂ -P ₂ O ₅ /solvent-free/r.t.	30	94[26]
8	Oxone/MeOH/r.t.	10	91[28]
9	Cellulose sulfuric acid/solvent-free/r.t	15	96[30]
10	Ps-AlCl ₃ /MeCN/reflux	60	95[31]
11	SiO ₂ -ClCH ₂ COOH/solvent-free/r.t.	10	91

CONCLUSION

In summary, it can be concluded that silica supported chloroacetic acid is an efficient and excellent catalyst for the synthesis of the synthesis of bis(indolyl)methanes from various aromatic aldehydes and indole in high yields under solvent-free and mild conditions in short reaction time using silica supported chloroacetic acid as catalyst. The mild reaction condition, rapid reaction rate, simple work up procedure, solvent free protocol, excellent product yield and reusable catalyst makes this method superior to existing synthetic route.

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