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Original scientific paper

Polystyrene-supported aluminum chloride as an efficient and reusable catalyst for condensation of indole with various carbonyl compounds

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Abstract: Crosslinked polystyrene-supported aluminum chloride (PS–$AlCl_3$) is a stable, recyclable and environmental friendly heterogeneous catalyst for the condensation of indole with aldehydes and ketones to afford diindolylmethanes. In addition, PS–$AlCl_3$ shows satisfactory selectivity in the reaction of mixtures of an aldehyde and a ketone with indole. Although $AlCl_3$ is a water sensitive, corrosive and environmentally harmful compound, PS–$AlCl_3$ is a stable and water-tolerant species. The mild reaction conditions, short reaction times, easy work-up, high to excellent yields, chemoselectivity, reuse of the catalyst for at least ten times without significant change in its catalytic activity, low cost, and easy preparation and handling of the polymeric catalyst are obvious advantages of the present method.

Keywords: bis-indolylmethanes; indole; polystyrene; aluminum chloride.

INTRODUCTION

Indole and its corresponding compounds have been identified as an important category of heterocyclic compounds in medicinal chemistry.[1,2] Among different indole derivatives, diindolylmethanes are known as a privileged group because of their representation in natural products[3] and extensive applications in pharmaceuticals.[4] Diindolylmethanes, which are found in marine sponges,[5,6] are effective in the prevention of cancer due to their ability to modulate cancer-causing estrogen metabolites.[7] Synthetically, the reaction of indole with aldehydes or ketones produces azafulvanium salts, which further react with another indole molecule to form bis-indolylmethanes.[8] A great number of methods have been reported in the literature for the preparation of bis-indolylmethanes in which protic acids,[9] as well as Lewis and other acids, such as $LiClO_4$,[10] montmoril-

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lonite K10,[11] $HClO_4$ (TPP),[12] $CeCl_3 \cdot 7H_2O$,[13] amberlyst-15,[14] $KHSO_4$,[15] zeokarb-225,[16] polyindole salt,[17] La(PFO)$_3$,[18] PEG-supported sulfonic acid,[19] $ZrOCl_2 \cdot 8H_2O$/silica gel[20] and heteropolyacids,[21,22] are employed. Ionic liquids in conjugation with In(OTf)$_3$ or $FeCl_3 \cdot 6H_2O$[23] were also reported to be useful media for this transformation. Although these methods were appropriate, many of them are associated with several drawbacks, including the requirement of large or stoichiometric amount of catalysts due to their deactivation by the nitrogen--containing reactants, low yields, long reaction time, expensive catalysts, exhausting wor-kup and the generation of environmentally perilous waste material as a result of the required extraction procedures.

Due to their wide range of biological, industrial and synthetic applications, the preparation of bis-indolylmethanes has received renewed attention of researchers interested in the discovery of improved protocols. In continuation of ongoing research on the use of heterogeneous polystyrene-supported aluminum chloride as a Lewis acid catalyst in organic reactions[24–26], herein this polymeric catalyst is introduced for the efficient electrophilic substitution of indole with a variety of carbonyl compounds.

EXPERIMENTAL

All chemicals were purchased from Merck or Fluka. Polystyrene (8 % divinylbenzene, prepared *via* suspension polymerization using polyvinylpyrrolidone 90 K as the suspension agent, grain size range: 0.25–0.6 mm) was obtained from the Iran Polymer and Petrochemical Institute. All products are known compounds and were identified by comparison of their physical and spectral data with those of authentic samples. The capacity of the catalyst was determined by the Mohr titration method and atomic absorption technique using a Philips atomic absorption instrument. Reaction monitoring and purity determination of the products were accomplished by TLC on silica-gel polygram SILG/UV254 plates. The IR spectra were recorded on a Shimadzu FTIR-8300 spectrophotometer, ν_{max} in cm^{-1}. The ^{1}H-NMR (250 MHz) and ^{13}C-NMR (62.5 MHz) were recorded on a Bruker Advanced DPX-250, FT-NMR spectrometer, δ in ppm. The mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX instrument. Microanalyses were performed on a Perkin-Elmer 240-B microanalyzer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

Preparation of PS–AlCl$_3$

Anhydrous $AlCl_3$ (4.5 g) was added to polystyrene (8 % divinylbenzene, 3.5 g) in carbon disulfide (25 mL) as the reaction medium. The mixture was stirred using a magnetic stirrer under reflux condition for 50 min, cooled and then water (40 mL) was cautiously added to hydrolyze the excess $AlCl_3$. The mixture was stirred until the deep orange color disappeared and the polymer became light yellow. The polymer beads were filtered and washed with water (350 mL) and then with acetone and diethyl ether. The polymer was dried in a vacuum oven for 12 h at room temperature. The capacity of the polymeric catalyst based on its chloride content was 0.40 mmol $AlCl_3$/g catalyst.[24-26]

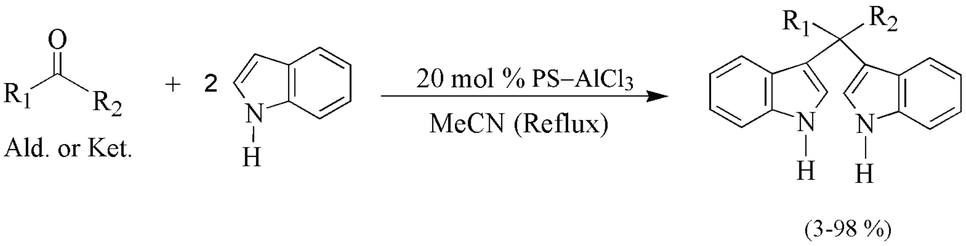
General procedure for the condensation of carbonyl compounds with indole

In a round bottom flask (25 mL) equipped with a condenser and a magnetic stirrer, a solution of the required carbonyl compound (1.0 mmol) and indole (2.0 mmol) in 10 mL MeCN was prepared. PS–$AlCl_3$ (0.20 mmol) was added to the solution and the reaction mixture was stirred magnetically under reflux conditions. The progress of the reaction was followed by TLC. After completion of the reaction, the catalyst was filtered off and washed with Et_2O (2×15 mL) and the filtrate concentrated on a rotary evaporator under reduced pressure to give the desired product. When required, the products were purified by column chromatography so as to afford the pure bis-indolylmethanes. The spent catalyst from different experiments was washed with Et_2O, dried and used again.

RESULTS AND DISCUSSION

PS–$AlCl_3$ was prepared by addition of anhydrous $AlCl_3$ to polystyrene (8 % divinylbenzene) in carbon disulfide under reflux conditions. The Mohr titration method[27] and the atomic absorption technique were employed to determine the capacity. The capacity of the polymeric catalyst was 0.40 mmol $AlCl_3$ per gram of catalyst. Although $AlCl_3$ is a water sensitive, corrosive and environmentally harmful compound, PS–$AlCl_3$ is a stable and water tolerant species (as a bench-top catalyst). This catalyst is easy to prepare, stable, storable in air for a long time without any change, easily recycled and reused without appreciable loss of activity.

In order to optimize the reaction conditions, PS–$AlCl_3$ was employed as the catalyst for the condensation of indole and benzaldehyde in different solvents, *i.e.*, MeCN, THF, CH_2Cl_2, EtOH, toluene, Et_2O and cyclohexane. Acetonitrile proved to be the best medium. It was found that 0.20:1.0:2.0 mmol ratio of catalyst/benzaldehyde/indole was sufficient to obtain the desired diindolylmethanes in 95 % yield within 1 h under reflux conditions (Scheme 1).



Scheme 1.

Next, (PS–$AlCl_3$)-catalyzed electrophilic substitution reactions of indole with a variety aldehydes and ketones were performed to better understand the generality of this method (Table I).

As can be seen in Table I (entries 1–16), aromatic, aliphatic and heterocyclic aldehydes underwent electrophilic substitution reaction with indole effectively to afford a wide range of substituted diindolylmethanes. Substrates with an electron-withdrawing substituent gave excellent yields in comparison with those carrying an electron-donating group, but the difference in time was not significant (entries 2–10). Both *o*-substituted and *p*-substituted aromatic aldehydes gave high yields. It was also found that the reaction of terephthalaldehyde (entry 16) with 4 equivalents of indole proceeded rapidly under similar conditions to afford *p*-bis-(diindolylmethyl)benzene in high yield (Scheme 2).

TABLE I. PS–$AlCl_3$ catalyzed synthesis of diindolylmethane derivatives (all reactions were performed under reflux in CH_3CN. Ratio of catalyst/carbonyl compound/indole was 0.20:1.0:2.0)

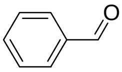
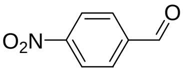
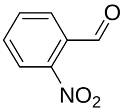
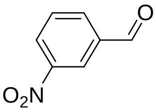
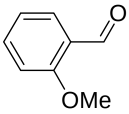
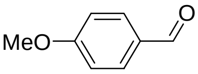
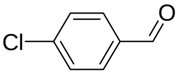
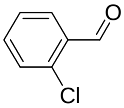
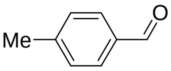
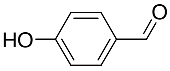
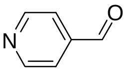
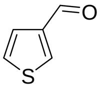
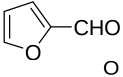
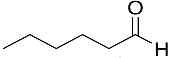
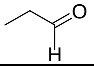
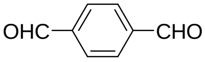
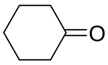
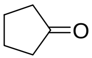
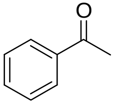
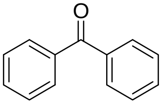
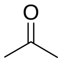
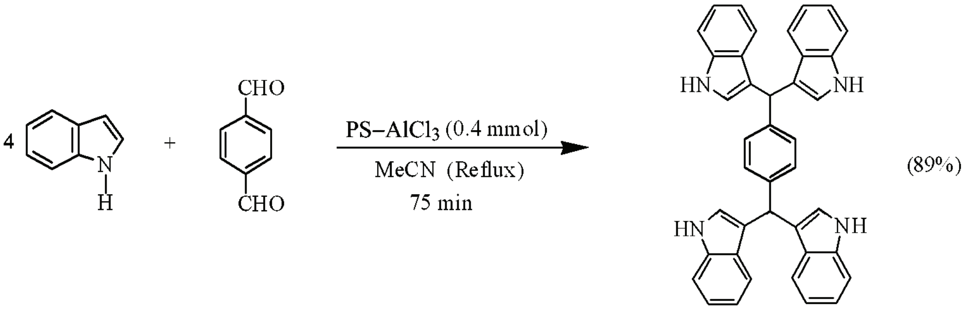
Entry	Carbonyl compound[a]	Time, min	Yield, %[b]	References for known compounds
1		60	95	28
2		80	98	16
3		80	90	28
4		65	93	29
5		75	85	18
6		75	89	28
7		80	93	28
8		30	83	28
9		50	89	10
10		55	85	17
11		75	89	29
12		65	90	30
13		80	87	28
14		120	79	10
15		120	75	15

TABLE I. Continued

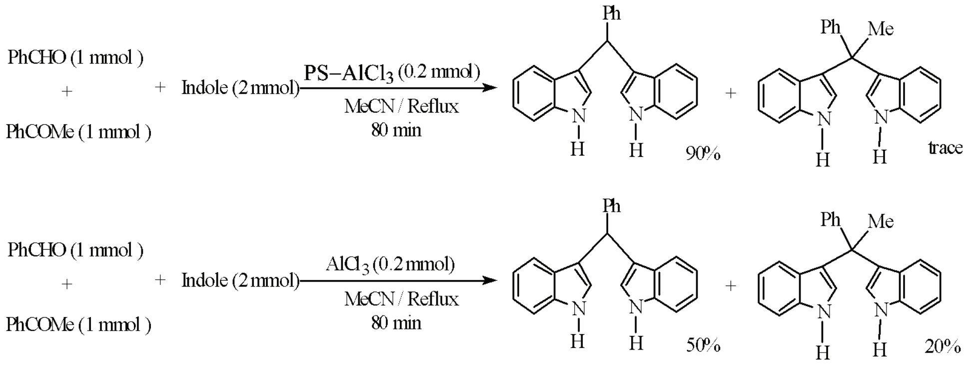
Entry	Carbonyl compound^a	Time, min	Yield, %^{b}	References for known compounds
16		75	89	28
17		150	76	28
18		200	65	28
19		220	3	28
20		240	0	–
21		240	55	31

[a] All products are known compounds and were identified by comparison of their physical and spectral data with those of the corresponding authentic sample; [b] isolated yields



Scheme 2.

Ketones required a longer reaction time and were obtained in moderate yields (entries 17–21). This striking difference in reactivity prompted an investigation of the applicability of the present method for the chemoselective electrophilic substitution reaction of indole with aldehydes and ketones. Thus, equimolar mixtures of aldehydes and ketones were allowed to react with indole in the presence of PS–AlCl$_3$. As shown in Scheme 3, the catalyst was able to discriminate between aldehydes and ketones. The observed chemoselectivity of PS–AlCl$_3$ makes it suitable for the selective reaction of aldehydes in the presence of keto carbonyl functions and hence it can be employed in the synthesis of complex molecules by multistep processes. The chemoselectivity of PS–AlCl$_3$ toward aldehydes and ketones is presumably due to its mild catalytic activity and also to the difference in bulkiness of the carbonyl compounds. It is noteworthy that PS–AlCl$_3$ showed a higher chemoselectivity than that of AlCl$_3$ in the reaction of indole with a mixture of aldehyde and ketones (Scheme 3). This is probably due to the higher reactivity of $AlCl_3$, *i.e.*, stronger Lewis acidity, and therefore lower selectivity.



+ Several unindetified products

Scheme 3.

Representative spectral data of some of the obtained compounds are given below.

*3,3'-(Phenylmethylene)bis-1*H*-indole (entry 1).* Pink solid. Yield: 95 %; m.p. 141–143 °C (Lit.[28] 140–142 °C). IR (KBr, cm^{-1}): 3402, 3051, 1618, 1600. ^{1}H-NMR (250 MHz, $CDCl_3$, δ / ppm): 5.86 (1H, *s*, C–H), 6.66 (2H, *s*, C–H), 7.11 (2H, *t*, ArH, J = 6.9 Hz), 7.14–7.22 (3H, *m*, ArH), 7.28–7.31 (2H, *m*, ArH), 7.35–7.42 (6H, *m*, ArH), 7.93 (2H, *broad* NH). ^{13}C-NMR (60 MHz; $CDCl_3$, δ / ppm): 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.

*3,3'-[(2-Nitrophenyl)methylene]bis-1*H*-indole (entry 3)*. Yellow solid. Yield: 90 %; m.p. 140–142 °C (Lit.[28] 139–141 °C). ^{1}H-NMR (250 MHz; $CDCl_3$, δ / ppm): 5.24 (1H, *s*, ArCH), 6.55 (2H, *s*, ArH), 7.10–7.87 (12H, *m*, ArH), 8.36 (2H, *broad d*, 2×NH, J = 8.6 Hz). ^{13}C-NMR (60 MHz, $CDCl_3$, δ / ppm): 34.9, 111.5, 111.6, 119.5, 120.7, 121.9, 122.2, 124.3, 126.8, 129.6, 131.2, 132.6, 134.2, 136.8, 149.7.

*3,3'-(2-Furanylmethylene)bis-1*H*-indole (entry 13)*. Brown solid. Yield: 87 %; m.p. 317–319 °C (Lit.[28] 316–318 °C). IR (KBr, cm^{-1}): 3410, 1712, 1450. ^{1}H-NMR (250 MHz, $CDCl_3$, δ / ppm): 5.97 (1H, *s*, ArCH), 6.90 (2H, *s*, ArH), 7.08–7.43 (11H, *m*, ArH), 8.00 (2H, *broad*, 2×NH). ^{13}C-NMR (60 MHz, $CDCl_3$, δ / ppm): 34.8, 106.5, 110.2, 111.3, 112.2, 118.0, 119.3, 119.7, 121.7, 124.3, 126.3, 135.9, 142.0.

*3,3',3",3'"-(1,4-Phenylenedimethylidyne)tetrakis-1*H*-indole (entry 16, Scheme 2)*. Pink solid. Yield: 89 % ; m.p.193 °C (dec.) (Lit.[28], 191 ° C). ^{1}H-NMR (250 MHz, $CDCl_3$, δ / ppm): 5.87 (2H, *s*, ArCH), 6.54 (4H, *s*, ArH), 7.09–7.18

(8H, *m*, ArH), 7.28–7.41 (12H, *m*, ArH), 8.14 (4H, *broad*, 4×NH). ^{13}C-NMR (60 MHz, $CDCl_3$, δ / ppm): 30.7, 111.8, 117.9, 118.1, 119.4, 121.1, 124.0, 126.6, 127.9, 137.0, 142.7.

The feasibility of recycling the catalyst was also examined. After completion of the reaction of indole with benzaldehyde, the polymer was filtered and washed with diethyl ether, dried in a vacuum oven at room temperature for 12 h and reused for the reaction of indole with the same or different aldehydes. As is shown in Table II, the efficiency of the recycled catalyst had not changed appreciably after ten cycles.

TABLE II. Comparison of the efficiencies of the recycled catalyst in the condensation of indole with benzaldehyde within 60 min

Entry	No. of cycles	Yield, %[a]
1	0	95
2	1	90
3	2	90
4	3	90
5	4	85
6	5	85
7	6	85
8	7	85
9	8	85
10	9	85

[a]Isolated yields

A comparison of the efficiency of the PS–$AlCl_3$ catalyst with some of those reported in the literature is given in Table III. As can be seen, in addition to having the general advantages attributed to polymeric supported catalysts, PS–$AlCl_3$ has a good efficiency compared to many of the other reported catalysts. The present procedure is superior in comparison with BF_3, Et_2O or $AlCl_3$ catalysts employed in the reaction of acetone with indole, which are reported to lead to the production of several unidentified products.[32–36]

TABLE III. Comparison of the efficiencies of a number of different reported catalysts with that of PS–$AlCl_3$ in the condensation of indole with benzaldehyde

Entry	Catalyst/solvent	Time, min	Yield, %[a]	Ref.
1	PS–$AlCl_3$/CH_3CN	60	95	–
2	$In(OTf)_3$/CH_3CN	25	71	23
3	$LiClO_4$/CH_3CN	120	80	10
4	$ZrOCl_2\cdot8H_2O$, solvent-free	40	84	20
5	$La(PFO)_3$/CH_3CN	30	90	18
6	$PPh_3\cdot HClO_4$/CH_3CN	30	61	12
7	$AlPW_{12}O_{40}$/CH_3CN	15	92	21
8	Zeokarb-225/CH_3CN	450	95	16

[a]Isolated yields

CONCLUSIONS

In conclusion, a highly efficient polymer-supported catalyst has been introduced for the reaction of indole with carbonyl compounds, to afford diindolylmethanes in good to excellent yields. Although $AlCl_3$ is a water sensitive, corrosive and environmentally harmful compound, PS–$AlCl_3$ is a stable and water tolerant species. The mild reaction conditions, short reaction times, easy work-up, high to excellent yields, chemoselectivity, reuse of the catalyst for at least ten times without significant change in its catalytic activity, low cost, and easy preparation and handling of the polymeric catalyst are the obvious advantages of the present method.

Acknowledgements. We gratefully acknowledge the partial support of this study by the Shiraz University and the Shahrekord University Research Council. In addition, the help of Mr. Gh. R. Nejabat in this work is appreciated.

ИЗВОД

АЛУМИНИЈУМ-ХЛОРИД НА ПОЛИСТИРЕНСКОМ НОСАЧУ КАО ЕФИКАСАН И ВИШЕКРАТНО УПОТРЕБЉИВ КАТАЛИЗАТОР У РЕАКЦИЈИ КОНДЕНЗАЦИЈЕ ИНДОЛА И РАЗЛИЧИТИХ КАРБОНИЛНИХ ЈЕДИЊЕЊА

BAHMAN TAMAMI[1], AMIR NASROLAHI SHIRAZI[1] и KAVEH PARVANAK BORUJENI[2]

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Алуминијум-хлорид везан за умрежени полистирен (PS–$AlCl_3$) је стабилан хетероген катализатор, подложан рециклирању и није штетан по животну средину. Ефикасан је као катализатор у реакцији кондензације индола са алдехидима и кетонима, при чему се добијају дииндолилметани. PS–$AlCl_3$ показује задовољавајућу селективност у реакцијама индола са смешом алдехида и кетона. Без обзира на то што је $AlCl_3$ осетљив према води, корозиван и штетан према животној средини, PS–$AlCl_3$ је стабилан и отпоран на присуство воде. Благи реакциони услови, кратко реакционо време, лака обрада реакционе смеше, висок до одличан принос реакција, хемоселективност, могућност вишеструке употребе катализатора до 10 пута без уочљивог губитка каталитичких својстава, ниска цена и лакоћа у припреми и руковању полимерног катализатора, очигледне су предности описаног поступка.

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