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Bahman Tamami
Shiraz University

Amir Nasrolahi Shirazi
Chapman University, shirazi@chapman.edu

Kaveh Parvanak Borujeni
Shahrekord University

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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

BAHMAN TAMAMI^{1*}, AMIR NASROLAHI SHIRAZI¹
and KAVEH PARVANAK BORUJENI²

¹Department of Chemistry, Shiraz University, Shiraz 71454 and
²College of Science, Shahrekord University, Shahrekord 115, Iran

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Abstract: Crosslinked polystyrene-supported aluminum chloride (PS–AlCl₃) is a stable, recyclable and environmental friendly heterogeneous catalyst for the condensation of indole with aldehydes and ketones to afford diindolylmethanes. In addition, PS–AlCl₃ shows satisfactory selectivity in the reaction of mixtures of an aldehyde and a ketone with indole. Although AlCl₃ is a water sensitive, corrosive and environmentally harmful compound, PS–AlCl₃ 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 products³ 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 LiClO₄,¹⁰ montmoril-

* Corresponding author. E-mail: tamami@chem.susc.ac.ir
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Ionite K10,¹¹ HClO₄ (TPP),¹² CeCl₃·7H₂O,¹³ amberlyst-15,¹⁴ KHSO₄,¹⁵ zeo-karb-225,¹⁶ polyindole salt,¹⁷ La(PFO)₃,¹⁸ PEG-supported sulfonic acid,¹⁹ ZrOCl₂·8H₂O/silica gel²⁰ and heteropolyacids,^{21,22} are employed. Ionic liquids in conjugation with In(OTf)₃ or FeCl₃·6H₂O²³ 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 work-up 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 ¹H-NMR (250 MHz) and ¹³C-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–AlCl₃

Anhydrous AlCl₃ (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 AlCl₃. 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 AlCl₃/g catalyst.^{24–26}

General procedure for the condensation of carbonyl compounds with indole

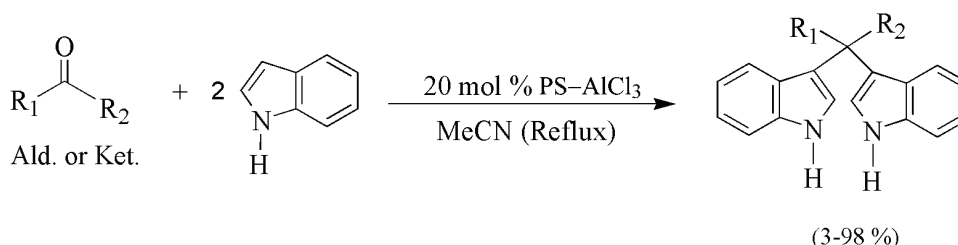
In a round bottom flask (25 mL) equipped with a condenser and a magnetic stirrer, a solution of the required carbonyl compound (1.0 mmol) and indole (2.0 mmol) in 10 mL MeCN

was prepared. PS-AlCl₃ (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 Et₂O (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 Et₂O, dried and used again.

RESULTS AND DISCUSSION

PS-AlCl₃ was prepared by addition of anhydrous AlCl₃ to polystyrene (8 % divinylbenzene) in carbon disulfide under reflux conditions. The Mohr titration method²⁷ and the atomic absorption technique were employed to determine the capacity. The capacity of the polymeric catalyst was 0.40 mmol AlCl₃ per gram of catalyst. Although AlCl₃ is a water sensitive, corrosive and environmentally harmful compound, PS-AlCl₃ 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-AlCl₃ was employed as the catalyst for the condensation of indole and benzaldehyde in different solvents, *i.e.*, MeCN, THF, CH₂Cl₂, EtOH, toluene, Et₂O 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-AlCl₃)-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-AlCl₃ catalyzed synthesis of diindolylmethane derivatives (all reactions were performed under reflux in CH₃CN. Ratio of catalyst/carbonyl compound/indole was 0.20:1.0:2.0)

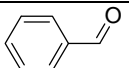
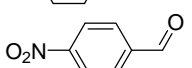
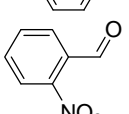
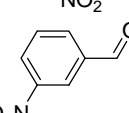
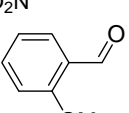
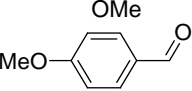
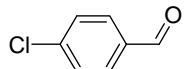
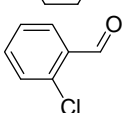
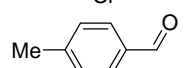
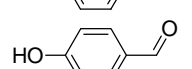
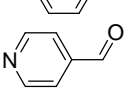
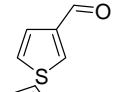
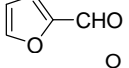
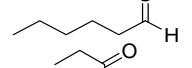
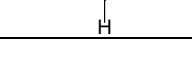

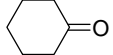

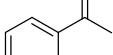
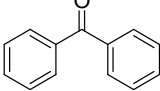

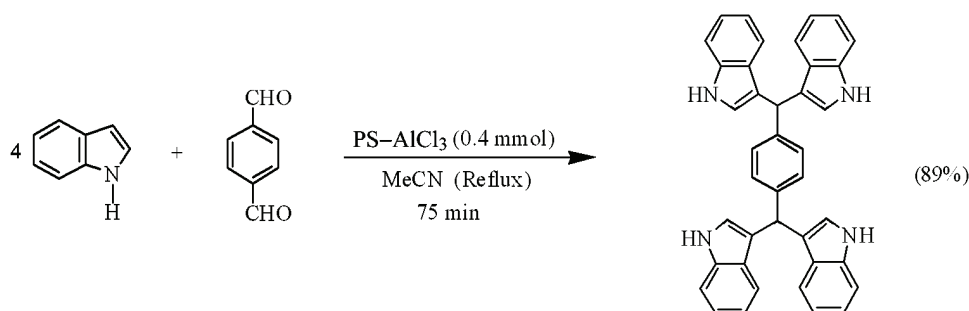
Entry	Carbonyl compound ^a	Time, min	Yield, % ^b	References for known compounds
1		60	95	28
2		80	98	16
3		80	90	28
4		65	93	29
5		75	85	18
6		75	89	28
7		80	93	28
8		30	83	28
9		50	89	10
10		55	85	17
11		75	89	29
12		65	90	30
13		80	87	28
14		120	79	10
15		120	75	15

TABLE I. Continued

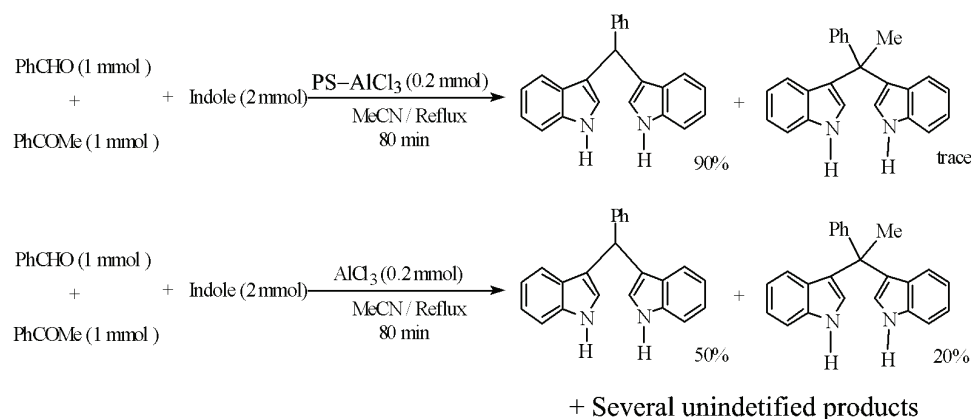
Entry	Carbonyl compound ^a	Time, min	Yield, % ^b	References for known compounds
16		75	89	28
17		150	76	28
18		200	65	28
19		220	3	28
20		240	0	–
21		240	55	31

^aAll products are known compounds and were identified by comparison of their physical and spectral data with those of the corresponding authentic sample; ^bisolated yields



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–AlCl₃. As shown in Scheme 3, the catalyst was able to discriminate between aldehydes and ketones. The observed chemoselectivity of PS–AlCl₃ 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–AlCl₃ 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–AlCl₃ showed a higher chemoselectivity than that of AlCl₃ in the reaction of indole with a mix-

ture 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.



Scheme 3.

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

3,3'-(Phenylmethylene)bis-1H-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. $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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-1H-indole (entry 3). Yellow solid. Yield: 90 %; m.p. 140–142 °C (Lit.²⁸ 139–141 °C). $^1\text{H-NMR}$ (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, $2\times\text{NH}$, $J = 8.6$ Hz). $^{13}\text{C-NMR}$ (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-1H-indole (entry 13). Brown solid. Yield: 87 %; m.p. 317–319 °C (Lit.²⁸ 316–318 °C). IR (KBr, cm^{-1}): 3410, 1712, 1450. $^1\text{H-NMR}$ (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, $2\times\text{NH}$). $^{13}\text{C-NMR}$ (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-Phenylenedimethyldiyne)tetrakis-1H-indole (entry 16, Scheme 2). Pink solid. Yield: 89 %; m.p. 193 °C (dec.) (Lit.²⁸, 191 °C). $^1\text{H-NMR}$ (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). ¹³C-NMR (60 MHz, CDCl₃, 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 re-used 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

^aIsolated yields

A comparison of the efficiency of the PS–AlCl₃ 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–AlCl₃ has a good efficiency compared to many of the other reported catalysts. The present procedure is superior in comparison with BF₃, Et₂O or AlCl₃ 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–AlCl₃ in the condensation of indole with benzaldehyde

Entry	Catalyst/solvent	Time, min	Yield, % ^a	Ref.
1	PS–AlCl ₃ /CH ₃ CN	60	95	–
2	In(OTf) ₃ /CH ₃ CN	25	71	23
3	LiClO ₄ /CH ₃ CN	120	80	10
4	ZrOCl ₂ ·8H ₂ O, solvent-free	40	84	20
5	La(PFO) ₃ /CH ₃ CN	30	90	18
6	PPh ₃ ·HClO ₄ /CH ₃ CN	30	61	12
7	AlPW ₁₂ O ₄₀ /CH ₃ CN	15	92	21
8	Zeokarb-225/CH ₃ CN	450	95	16

^aIsolated 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.

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ИЗВОД

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

ВАНМАН ТАМАМИ¹, АМИР НАСРОЛАНИ ШИРАЗИ¹ И КАВЕН ПАРВАНАК БОРУЈЕНИ²

¹Department of Chemistry, Shiraz University, Shiraz 71454 and ²College of Science,
Shahrekord University, Shahrekord 115, Iran

Алуминијум-хлорид везан за умрежени полистирен (PS-AlCl_3) је стабилан хетероген катализатор, подложен 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. Благо 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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