

Aluminumdodecatungstophosphate (AIPW₁₂O₄₀), a versatile and a highly water tolerant *green* Lewis acid catalyzes efficient preparation of indole derivatives

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Abstract

Aluminumdodecatungstophosphate (AIPW₁₂O₄₀) a highly water tolerant, *green* Lewis acid has been applied as an efficient catalyst for the preparation of indole derivatives as bis(indolyl)methanes from carbonyl compounds via Friedel–Crafts alkylation and 3-substituted indoles via Michael addition of indole to α,β -unsaturated carbonyl compounds in CH₃CN at room temperature.

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1. Introduction

The syntheses and the reactions of indoles have received much interest for over a century because a number of their derivatives occur in nature and show versatile biological activities [1]. 3-Position of indole is the preferred site for electrophilic substitution reaction and 3-substituted indoles are versatile intermediates for the synthesis of a wide range of indole compounds [2]. One of the simple and direct method for the synthesis of 3-substituted indoles involve the conjugate addition of them to α,β -unsaturated carbonyl compounds or reaction of 2 equiv. of indoles with the carbonyl group in the presence of either protic [3,4] or Lewis acids [5–7]. However, many Lewis acids are deactivated or sometimes decomposed by nitrogen containing reactants. Even when the desired reactions proceed, more than stoichiometric amounts of the Lewis acids are required because the acids are deactivated by the nitrogen atom of indoles [8]. The use of lanthanide triflates [6] applied for this purpose shows attractions. However, lanthanide triflates are rather expensive, thus their uses especially for the large-scale synthetic operation, may not be economical. For this reason, cheaper

Lewis acid catalysts that secure catalytic activity, low toxicity, high stability towards humidity, and air tolerance are desirable. Along this line and in continuation of our interest to explore new catalytic activities of H₃PW₁₂O₄₀ [9], and its salts [10], we now introduce AIPW₁₂O₄₀ which has been successfully applied for carbon–carbon bond formation between indole with carbonyl compounds or α,β -unsaturated ketones to produce bis-indolylmethanes or Michael adducts to give β -(3-indolyl) ketones under mild conditions in CH₃CN. AIPW₁₂O₄₀ is prepared from easily available cheap starting materials and being stable and tolerant towards humidity and air with low toxicity and is not a corrosive compound. The handling of the catalyst is easy and does not need especial precautions. AIPW₁₂O₄₀ could be considered as a modified AlCl₃. AlCl₃ is a water sensitive and corrosive compound and should be usually used in molar excess, in different reactions [10d].

2. Result and discussion

First, we studied the reaction of benzaldehyde with indole (1:2 molar ratios) in order to optimize the reaction conditions with respect to temperature, time, and the molar ratio of AIPW₁₂O₄₀ to the substrate. We found that 2 mol% of AIPW₁₂O₄₀ was sufficient to obtain the desired bis-indolylmethane in 92% yield within 15 min at room temperature in CH₃CN using benzaldehyde (Scheme 1).

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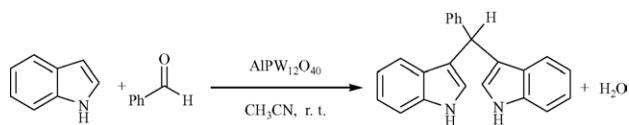


Table 1
Reaction of indole with benzaldehyde in the presence of different catalysts

Entry	Catalyst/solvent	Catalyst (mol%)	Time (h)	Yield (%)	Ref.
1	AIPW ₁₂ O ₄₀ /CH ₃ CN	2	15 min	92	
2	Ln(OTf) ₃ /EtOH·H ₂ O	10	12	95	[6e]
3	Dy(OTf) ₃ in ionic liquid	2	1	98	[6f]
4	In(OTf) ₃ /CH ₃ CN	5	25 min	71	[6g]
5	La(PFO) ₃ /EtOH	5	0.5	90	[6h]
6	LiClO ₄ /CH ₃ CN	10	5	90	[7f]
7	HY-Zeolite/CH ₂ Cl ₂	0.2 g	1	85	[3d]

In order to show the merit of AIPW₁₂O₄₀ in comparison with the other catalysts used for the similar reaction, we have tabulated some of the results in Table 1. As it is evident from the results, the required ratio for the most catalysts used for this purpose is >2 mol% and also the required reaction times are much longer (1–12 h).

A reasonable pathway for the reaction of indole with carbonyl compounds conducted in the presence of AIPW₁₂O₄₀ is presented by Scheme 2. The reaction most probably proceeds

via the formation of azafulvenium salt which undergoes further addition with the second indole molecule to afford bis(indolyl) methane derivatives [4].

However, aliphatic aldehydes and cyclohexanone needed longer reaction times with more molar ratios of the catalyst (Table 2, entries 8–10). We have found that the reaction of acetophenone with indole in the presence of this catalyst was not a straightforward reaction and after a prolonged reaction time most of the starting materials were remained intact. The reaction was then applied to structurally diverse aromatic and aliphatic carbonyl compounds with indoles. In the presence of this catalyst, both activated and deactivated aromatic aldehydes were converted to their corresponding bis-indolylmethanes in excellent yields (Table 2, entries 1–7, 11, 12).

Michael reactions promoted by Lewis acids have attracted much attention as one of the most important carbon–carbon bond-forming reactions in organic synthesis. In particular, they are totally atom-efficient procedures and thus are inherently *green* transformations [7]. The reaction of indole and 2-methyl indole with methyl vinyl ketone in the presence of a 0.2 mol% of AIPW₁₂O₄₀ proceeded well giving the β-(3-indolyl) ketones in excellent yields without formation of dimerization or polymerization products. Similarly, 2-methyl indole reacted well with cyclohexenone and cyclopentenone to give the corresponding β-(3-indolyl) ketones in high yields. The reactions proceeded smoothly at ambient temperature with high selectivity without producing N–C adduct or 1,2-addition products (Table 3, entries 1–3, Scheme 3). Although, the reaction of indole with cyclo-

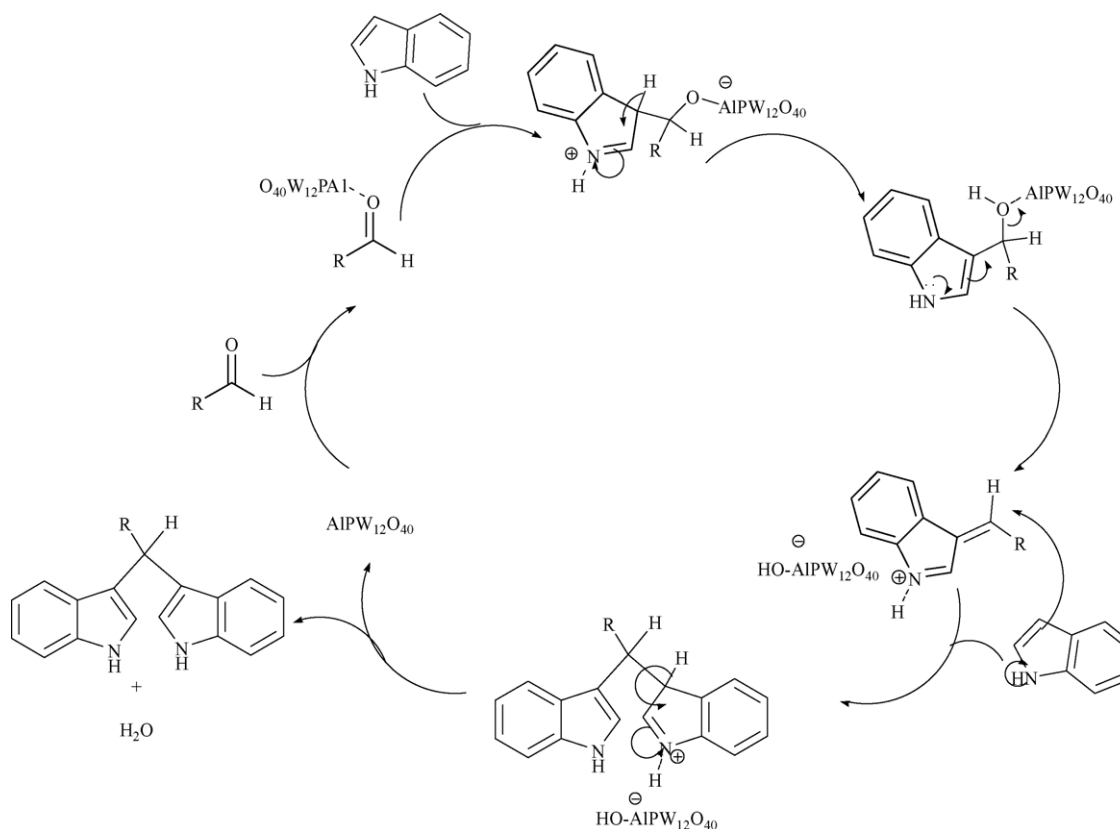


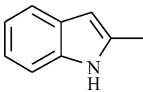

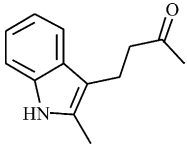
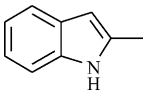
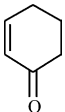
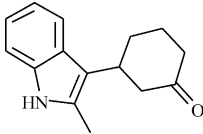
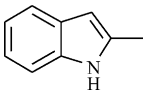
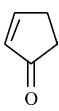
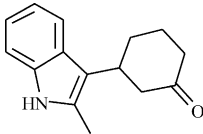
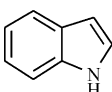

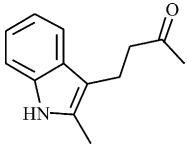
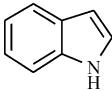
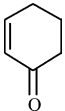
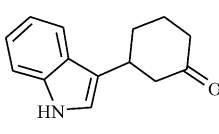
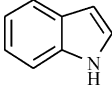

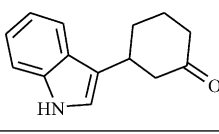
Table 2
Preparation of bis-indolylmethanes derivatives catalyzed by $\text{AlPW}_{12}\text{O}_{40}$ at room temperature from indoles

Entry	Indole	Carbonyl group	Product	Catalyst (mol%)	Time (min)	Yield (%) ^a	References for the known compound
1		X = H	X = H	2	15	92	[7f]
2		X = 4-Me	X = 4-Me	2	15	90	[7f]
3		X = 4-MeO	X = 4-MeO	2	25	89	[3d]
4		X = 4-OH	X = 4-OH	3	4 h	95	– ^b
5		X = 4-Cl	X = 4-Cl	2	30	91	[3d]
6		X = 4-NO ₂	X = 4-NO ₂	3	60	96	[3d]
7			X = 3-MeO, 4-OH	3	45	90	[3d]
8		CH ₃ CH ₂ CHO		7	2 h	83	[6h]
9			R = <i>n</i> -pentyl	7	5 h	78	[7f]
10				7	4 h	93	[7f]
11		X = H		2	20	94	[3d]
12		X = 4-OH	X = 4-OH	2	45	91	– ^b

^a Pure product was obtained after a short column chromatography except entries 8 and 9 that were purified by preparative plate chromatography. All products were identified by their IR, NMR, and MS spectra.

^b Spectral data and the elemental analysis are given in the experimental part.

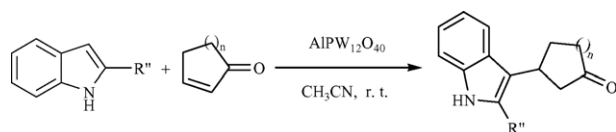
Table 3
Conjugative addition of indoles to α,β -unsaturated ketones in CH_3CN catalyzed by $\text{AIPW}_{12}\text{O}_{40}$ at room temperature

Entry	Indole	α,β -Unsaturated ketones	Product	Catalyst (mol%)	Time (min)	Yield ^a (%)	References for the known compound
1				0.2	10	97	[7h]
2				0.2	30	94	[7a]
3				0.2	45	91	[7a]
4				0.2	10	96	[7h]
5				7	2 h	67	[7h]
6				7	2 h	62	[7h]

^a Pure product was obtained after a short column chromatography except entries 5 and 6 that were purified by preparative plate chromatography. All products were identified by their IR, NMR, and MS spectra.

hexenone or cyclopentenone required higher molar ratios of the catalyst with longer reaction times and producing the adducts in lower yields (Table 3, entries 4–6).

In conclusion, we have developed a selective and efficient procedure for the C–C bond formation to produce indole derivatives. Preparation of bis(indolyl)methanes through the electrophilic substitution reactions of indoles with aldehydes and ketones and preparation of β -(3-indolyl) ketones via Michael addition of indoles to α,β -unsaturated ketones by using $\text{AIPW}_{12}\text{O}_{40}$ as a heterogeneous, and environmentally benign catalyst has been successfully performed. The procedure offers several advantages including mild reaction conditions, cleaner reactions, and high yields of the products as well as simple experimental and isolation procedures. All these, make this protocol a useful and an attractive procedure for the synthesis of indole derivatives.



3. Experimental

All solvents and reagents were purchased from Fluka or Merck chemical Companies. The products were purified by column or thick layer chromatography techniques. FT-IR spectra were recorded on a Shimadzu DR-8001 spectrometer. NMR spectra were recorded on a Bruker Avance DPX 250 MHz instrument. Mass spectra were recorded on a Shimadzu GC-MS-QP 1000PX. Melting points are not corrected.

3.1. General procedure for preparation of bis-indolylmethanes

A mixture of carbonyl compound (1 mmol), indole (0.234 g, 2 mmol) and $\text{AIPW}_{12}\text{O}_{40}$ (2–7 mol%) in acetonitrile (3 ml) was stirred at room temperature for the appropriate reaction time (Table 2). Acetonitrile (5 ml) was added to the reaction mixture and the solid $\text{AIPW}_{12}\text{O}_{40}$ was filtered. To the filtrate, silica gel (1 g) was added and after evaporation of the solvent a dark grayish solid mixture was obtained. Purification of the product was performed by a short column chromatography eluted with ethyl acetate/petroleum ether to give the desired product in high yields (Table 2).

3.2. 3,3'-Bis(indolyl)-4-hydroxyphenylmethane (Table 2, entry 4)

Pinkish powder; m.p. 210–211 °C; ¹H NMR (250 MHz, DMSO): δ (ppm) 9.65 (s, 2H, NH), 8.62 (s, H, OH), 7.29 (t, 4H, *J* = 7.7 Hz), 7.12 (d, 2H, *J* = 7.5 Hz), 7.00 (t, 2H, *J* = 7.6 Hz), 6.84 (t, 2H, *J* = 7.5 Hz), 6.67 (d, 4H, *J* = 8.75 Hz), 5.70 (s, 1H); ¹³C NMR (CDCl₃, 63 MHz) δ (ppm) = 160.5, 142, 140.6, 134.7, 132.2, 129, 126.3, 124.8, 124.6, 123.6, 120.3, 116.5, 44.8; MS (70 eV) *m/z* = 338 [*M*]⁺; Anal. Calcd. for (C₂₃H₁₈N₂O): C, 81.63; H, 5.36; Found: C, 81.65; H, 5.34.

3.3. 3,3'-Bis(2-methyl-indolyl)-4-hydroxyphenylmethane (Table 2, entry 12)

Pinkish powder; m.p. 237–239 °C; ¹H NMR (250 MHz, DMSO): δ (ppm) 9.65 (s, 2H, NH), 8.62 (s, H, OH), 7.17 (d, 2H, *J* = 7.5 Hz), 7.01 (d, 2H, *J* = 7.5 Hz), 6.71 (m, 4H), 6.50 (m, 4H), 5.64 (s, 1H), 1.85 (s, 6H); ¹³C NMR (CDCl₃, 63 MHz) δ (ppm) = 155.1, 135.1, 134.6, 131.9, 129.6, 128.6, 119.6, 118.8, 118, 114.8, 113., 110.1, 38.1, 12.1; MS (70 eV) *m/z* = 366 [*M*]⁺; Anal. Calcd. for (C₂₅H₂₂N₂O): C, 81.94; H, 6.05. Found: C, 81.91; H, 6.1.

3.4. General procedure for preparation of β-(3-indolyl) ketones

A mixture of carbonyl compound (1.1 mmol), indole (0.117 g, 1 mmol) and AlPW₁₂O₄₀ (0.2–7 mol%) in acetonitrile (3 ml) was stirred at room temperature for the appropriate reaction time (Table 2). Acetonitrile (5 ml) was added to the reaction mixture and the solid AlPW₁₂O₄₀ was filtered. To the filtrate, silica gel (1 g) was added and after evaporation of the solvent a dark grayish solid mixture was obtained. Purification of the product was performed by a short column chromatography eluted with ethyl acetate/petroleum ether (50/50) in 62–97% (Table 3).

3.5. 3-[3-(2-Methyl-Indolyl)]-cyclohexan-1-one (Table 3, entry 2)

¹H NMR (250 MHz, DMSO): δ (ppm) = 8.33 (s, 1H, NH), 7.59 (d, 1H, *J* = 7.75 Hz), 7.01 (d, 2H, *J* = 6.7 Hz), 7.07–6.98 (m, 2H), 3.2–3.1 (m, 1H), 2.99–2.88 (m, 1H), 2.48–2.36 (m, 3H), 2.23 (s, 3H), 2.19–2.08 (m, 1H), 1.93–1.88 (m, 2H), 1.75–1.65 (m, 1H); ¹³C NMR (CDCl₃, 63 MHz) δ (ppm) = 207.5, 130.8, 125.7, 122.1, 116, 114.1, 114, 108.6, 106.1, 43.5, 36.7, 32.6, 26.7, 21.4, 7.4; MS (70 eV) *m/z* = 227 [*M*]⁺; Anal. Calcd. for (C₁₅H₁₇NO): C, 79.26; H, 7.54. Found: C, 79.2; H, 7.51 [7a].

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