

Ammonium monovanadate: a versatile and reusable catalyst for Friedel-Crafts alkylation and Michael addition of indoles

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ABSTRACT

Ammonium monovanadate (NH_4VO_3) has been devoted as an efficient, commercially available, eco-friendly and reusable catalyst for the synthesis of bis(indolyl)methanes (BIMs), oxindole derivatives and also Michael adducts of indoles at 50 °C under solvent-free conditions. The reusability of this solid acid catalyst in addition with its selectivity has also been examined.

Keywords: Indole, Isatin, α,β -Unsaturated compounds, Alkylation, Ammonium monovanadate.

1. Introduction

Indole is a 150 year-old heteroaromatic structure in chemistry [1]. During this period it is a privileged compound in pharmaceutical, fragrance, agrochemicals, pigment and material science [2,3]. Beside this, many natural compounds that derived from agricultural or animal sources, contain this motif [4].

According to this widespread applications, many class of functionalized indoles has been synthesized which possess physiological properties and contain medicinal applications [5,6]. In the mid-1950s indolic alkaloids such as reserpine which is one of the first drugs for treatment of central nervous system disease, has been synthesized [7]. In 1960s many indolyl alkaloids with antitumor [8], anti-inflammatory [9], tranquilizing [10], and antihypertensive [11] activities have been discovered. The most reactive position of this electron-rich heteroaromatic is C3 site. Different class of electrophiles can underwent the substitution with indoles.

Based on the electrophile nature, the reaction can be titled as Friedel-Crafts alkylation (condensation of indoles with carbonyl groups or isatins) and Michael addition (the nucleophilic attack of indole to an α,β -unsaturated compound).

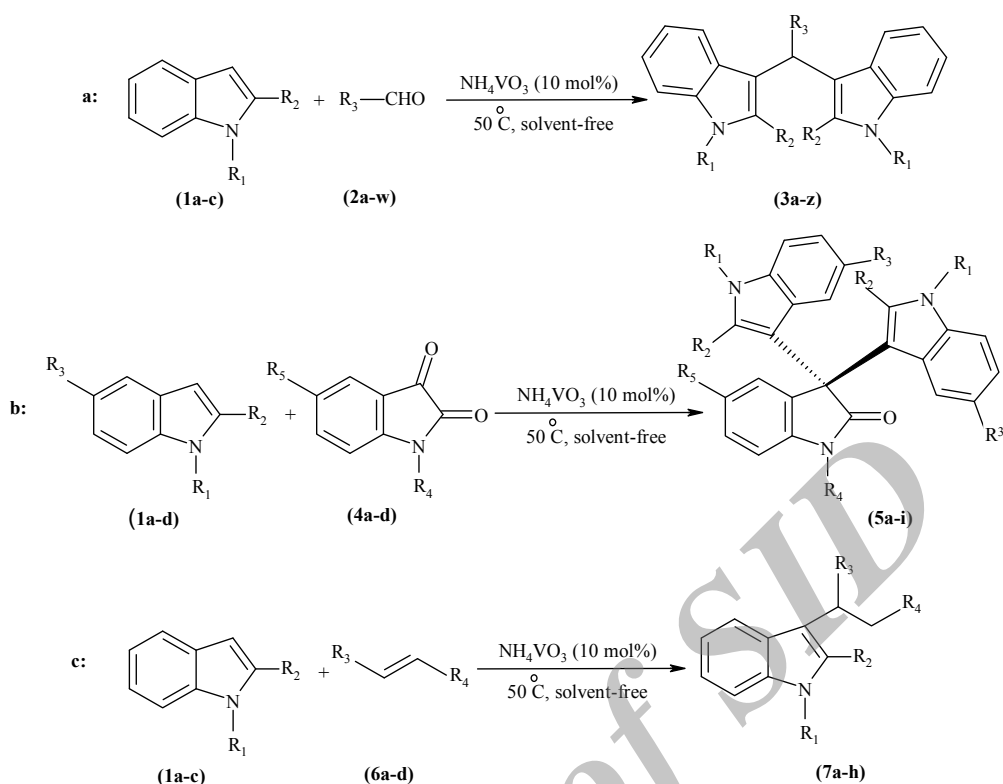
The products nominated as BIMs, oxindoles and Michael adducts. BIMs are important derivatives of indole and are known to promote beneficial estrogen metabolism and induce apoptosis in human cancer cell [12].

3,3-Bis(indolyl)oxindoles showed anti-protozoal, laxative and Antiproliferative properties [13-15]. Michael adducts have been known for more than 70 year [3]. They emerged as integral backbones of several antibacterial, antialgal and antimycotic agents [16]. Many procedures has been published for the synthesis of these classes of indoles due to various catalysts and/or new protocols [17-23].

Ammonium metavanadate (NH_4VO_3) is a water soluble, relatively non-toxic (LD_{50} dermal rat 2102 mg/kg) and inorganic acid [24]. Its solvation in water results in solutions contain moderate concentrations of hydrogen ions and have pH's of less than 7.0 [25]. It is a reagent used in analytical chemistry, the photographic and textile industry [24]. It catalyzes the reactions such as alkane oxidation [26], synthesis of α -hydroxyphosphonates [27], synthesis of α -aminophosphonates [28], oxidative aromatization of 2-cyclohexenones [29] and synthesis of coumarins [30].

In continuation of our research work on indole motif [31-38], herein we report NH_4VO_3 as an effective, commercial available and reusable catalyst for indole alkylation under solvent-free conditions at 50 °C (Scheme 1-a).

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Scheme 1. Reaction of indoles with aldehydes (a), isatins (b) and α,β -unsaturated compounds (c) catalyzed by ammonium monovanadate.

2. Experimental

2.1. General

Chemicals and solvents were purchased from Merck, Aldrich and Alfa Aesar and used without further purifications. *N*-Benzyloisatin is synthesized from isatin according to the reported procedure [39]. Melting points were determined using a Stuart Scientific apparatus and are uncorrected. Fourier transform infrared (FT-IR) spectra (KBr discs, $500\text{--}4000\text{ cm}^{-1}$) were recorded using a Bruker FTIR model Tensor 27 spectrometer. $^1\text{H-NMR}$ spectra were recorded in CDCl_3 solvent on a Bruker 500 MHz spectrometer. Mass spectra were obtained on Platform II spectrometer from Micromass; EI mode at 70 eV. Preparative layer chromatography (PLC) carried out on $20\times 20\text{ cm}^2$ plates, coated with a 1 mm layer of Merck silica gel PF254, prepared by applying the silica as slurry and drying in air. All the products were characterized by comparison of their spectroscopic data (IR, $^1\text{H-NMR}$ and Mass spectra) with those of the authentic samples in literature. Yields refer to isolated products.

2.2. General procedure for Friedel-Crafts alkylation of indoles with aldehydes or isatins

To a mixture of indoles **1a-d** (2 mmol) and aldehydes **2a-w** or isatins **4a-d** (1 mmol) at 50°C , 0.1 mmol NH_4VO_3 was added. After completion of the reaction

monitored by TLC, the reaction was quenched by adding EtOAc (10 mL) and filtered to separate NH_4VO_3 . The filtrate was evaporated and residue was purified utilizing short column chromatography (EtOAc and *n*-hexane as eluent) to obtain the pure products (**3a-z** and **5a-i**).

2.3. General procedure for Michael addition of indoles with α,β -unsaturated compounds

A mixture of indoles **1a-c** (1 mmol) and α,β -unsaturated compounds **6a-d** (1 mmol) and NH_4VO_3 (0.1 mmol) stirred at 50°C . The progress of the reaction was monitored by TLC. After completion, EtOAc (10 mL) was added and filtered. The solid residue washed with ethylacetate ($2\times 10\text{ ml}$). The solvent was evaporated and the residue purified by chromatography on silica gel (eluent: *n*-hexane-EtOAc) to afford the pure products **7a-h**. The spectral data of a selected compounds is given below.

Selected spectral data

4-(Di(1*H*-indol-3-yl)methyl)benzaldehyde (**9a**):

m.p.= $108\text{--}110^\circ\text{C}$ [31]. IR (KBr): $\bar{\nu} = 3441$ (N-H), 2969 (aldehydic CH), 2855 (aldehydic CH), 1694 (C=O), 733 (N-H) cm^{-1} . $^1\text{HNMR}$ (500 MHz, CDCl_3): $\delta = 5.96$ (s, 1H), 6.66 (s, 2H), 7.01 (t, $J = 7.5\text{ Hz}$, 2H), 7.18 (t, $J = 6.75\text{ Hz}$, 2H), 7.36 (t, $J = 7.25\text{ Hz}$, 4H), 7.51 (d, $J = 7.97\text{ Hz}$, 2H), 7.79 (d, $J = 7.88\text{ Hz}$, 2H), 7.98

(br s, 2H), 9.97 (s, 1H) ppm. EI-MS (m/e, %): (350 [M⁺], 31), (245, 26), (204, 33), (117, 100).

3-((4-(Di(1H-indol-3-yl)methyl)phenyl)(1H-indol-3-yl)methyl)-1H-indole (9b):

m.p.= 149-151 °C [31]. IR (KBr): $\bar{\nu}$ = 3428 (N-H), 2948, 738 (N-H) cm⁻¹. ¹HNMR (500 MHz, CDCl₃): δ = 5.69 (s, 2H), 6.06 (br s, 4H), 7.00 (t, *J* = 7.25 Hz, 4H), 7.12 (t, *J* = 7.50 Hz, 4H), 7.16-7.22 (m, 8H), 7.34 (d, *J* = 7.79 Hz, 4H) ppm. EI-MS (m/e, %): (566 [M⁺], 3), (207, 65), (117, 100).

3,3'-Bis(1H-indol-3-yl)-(3-methoxyphenyl)methane (3d):

m.p.= 149-151 °C [31]. IR (KBr): $\bar{\nu}$ = 3409 (N-H), 2936, 1601, 1453, 738 (N-H) cm⁻¹. ¹HNMR (500 MHz, CDCl₃): δ = 3.74 (s, 3H), 5.87 (s, 1H), 6.64 (s, 2H), 6.77-6.79 (m, 1H), 6.96 (t, *J* = 8.47 Hz, 2H), 7.01 (t, *J* = 7.48 Hz, 2H), 7.16-7.22 (m, 3H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 7.92 Hz, 2H), 7.86 (br s, 2H) ppm. EI-MS (m/e, %): (352 [M⁺], 32), (245, 31), (204, 18), (117, 100).

3,3'-Bis(1H-indol-3-yl)-(4-isopropylphenyl)methane (3i):

m.p.= 145-147 °C [31]. IR (KBr): $\bar{\nu}$ = 441 (N-H), 2969, 1606, 1455, 733 (N-H) cm⁻¹. ¹HNMR (500 MHz, CDCl₃): δ = 1.25 (d, *J* = 6.11 Hz, 6H), 2.9 (m, 1H), 5.87 (s, 1H), 6.66 (s, 2H), 7.02 (t, *J* = 7.18 Hz, 2H), 7.15 (t, *J* = 6.55 Hz, 2H), 7.19 (d, *J* = 7.29 Hz, 2H), 7.28 (d, *J* = 7.99 Hz, 2H), 7.35 (d, *J* = 8.11 Hz, 2H), 7.43 (d, *J* = 7.94 Hz, 2H), 7.83 (br s, 2H) ppm.

3,3'-Bis(1H-indol-3-yl)-2-methyl-1-phenylpropene (3r):

m.p.= 74-76 °C [31]. IR (KBr): $\bar{\nu}$ = 3452 (N-H), 3055, 1332, 1090, 733 (N-H) cm⁻¹. ¹HNMR (500 MHz, CDCl₃): δ = 2.04 (d, *J* = 11.35 Hz, 3H), 5.32 (s, 1H), 6.48 (s, 1H), 6.88 (s, 2H), 7.09 (t, *J* = 7.49 Hz, 2H), 7.16-7.41 (m, 9H), 7.64 (d, *J* = 7.92 Hz, 2H), 7.93 (br s, 2H) ppm. EI-MS (m/e, %): (362 [M⁺], 96), (347, 83), (245, 100), (117, 97).

3,3'-Bis(1H-indol-3-yl)-(5-methyl-2-furyl)methane (3t):

m.p.= 74-76 °C [31]. IR (KBr): $\bar{\nu}$ = 3420 (N-H), 1610, 1560, 1450, 1080, 730 (N-H) cm⁻¹. ¹HNMR (500 MHz, CDCl₃): δ = 2.26 (s, 3H), 7.05 (t, *J* = 7.47 Hz, 2H), 7.17 (t, *J* = 7.58 Hz, 2H), 5.88 (s, 1H), 5.89 (d, *J* = 6.77 Hz, 2H), 6.86 (s, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 7.93 Hz, 2H), 7.93 (br s, 2H) ppm. EI-MS (m/e, %): (326, 24), (283, 31), (209, 21), (117, 100).

3,3'-Bis(1-methyl-indol-3-yl)-(4-isopropylphenyl)methane (3y):

m.p.= 144-146 °C [31]. IR (KBr): $\bar{\nu}$ = 2926, 1611, 1482, 1324, 1117, 733 (N-H) cm⁻¹. ¹HNMR (500 MHz, CDCl₃): δ = 1.27 (d, *J* = 11.00 Hz, 3H), 1.27 (d, *J* = 11.13 Hz, 3H), 2.89-2.95 (m, 1H), 3.40-3.45 (m, 1H), 3.69 (s, 3H), 3.70 (s, 3H), 5.89 (s, 1H), 6.21 (s, 1H),

6.45 (s, 1H), 6.59 (s, 1H), 7.01-7.33 (m, 8H), 7.39 (t, *J* = 6.5 Hz, 2H), 7.43 (t, *J* = 8.00 Hz, 2H) ppm. EI-MS (m/e, %): (392, 43), (349, 7), (260, 35), (246, 36), (131, 100).

3,3'-Bis(1-methyl-indol-3-yl)-(4-fluorophenyl)methane (3z):

m.p.= 197-198 °C [31]. IR (KBr): $\bar{\nu}$ = 2936, 1608, 1485, 1222, 1095, 736 (N-H) cm⁻¹. ¹HNMR (500 MHz, CDCl₃): δ = 3.70 (s, 6H), 5.87 (s, 1H), 6.53 (s, 2H), 6.98 (t, *J* = 8.71 Hz, 2H), 7.02 (t, *J* = 9.64 Hz, 2H), 7.23 (t, *J* = 7.60 Hz, 2H), 7.31 (t, *J* = 6.99 Hz, 4H), 7.38 (d, *J* = 7.93 Hz, 2H) ppm. EI-MS (m/e, %): (368, 100), (273, 91), (128, 99).

4-(2-Methyl-Indol-3-yl)-4-phenyl-butan-2-one (7c):

m.p.= 73-75 °C [34]. IR (KBr): $\bar{\nu}$ = 3398 (N-H), 3025, 2915, 1708 (C=O), 1157, 730 (N-H) cm⁻¹. ¹HNMR (500 MHz, CDCl₃): δ = 2.01 (s, 3H), 2.38 (s, 3H), 3.33 (dd, *J* = 6.33 & 16.22 Hz, 1H), 3.45 (dd, *J* = 8.51 & 16.21 Hz, 1H), 4.87 (t, *J* = 7.36 Hz, 1H), 7.01 (t, *J* = 7.41 Hz, 1H), 7.08 (t, *J* = 7.51 Hz, 1H), 7.15 (t, *J* = 7.15 Hz, 1H), 7.21-7.26 (m, 3H), 7.31 (d, *J* = 7.62 Hz, 2H), 7.47 (d, *J* = 7.86 Hz, 1H), 7.79 (br s, 1H) ppm. EI-MS (m/e, %): (277, 80), (234, 48), (220, 100), (204, 78), (130, 91), (103, 90).

5-(2-methyl-Indol-3-yl)-1,3-diphenylpropane-1-one (7f):

m.p.= 80-81 °C [34]. IR (KBr): $\bar{\nu}$ = 3398 (N-H), 3065, 2904, 1678 (C=O), 1262, 736 (N-H) cm⁻¹. ¹HNMR (500 MHz, CDCl₃): δ = 2.39 (s, 3H), 3.89 (dd, *J* = 6.60 & 6.70 Hz, 1H), 3.95 (dd, *J* = 8.53 & 6.68 Hz, 1H), 5.09 (t, *J* = 7.00 Hz, 1H), 6.99 (t, *J* = 7.46 Hz), 7.05 (t, *J* = 7.05 Hz, 1H), 7.14 (t, *J* = 7.25 Hz, 1H), 7.25-7.20 (m, 3H), 7.37 (t, *J* = 8.11 Hz, 4H), 7.46-7.50 (m, 2H), 7.87 (d, *J* = 7.76 Hz, 2H), 7.79 (br s, 1H) ppm. EI-MS (m/e, %): (339, 21), (234, 7), (220, 57), (130, 97), (105, 94).

3. Results and Discussion

At first the condensation of 4-chlorobenzaldehyde with indole was chosen as a model to obtain the optimized reaction conditions (Table 1). The corresponding BIM **3j** was obtained in 70% yield after 40 min in the presence of 10 mol% NH₄VO₃ in the absence of solvent (Table 1, entry 1). Increasing the catalyst up to 0.3 mmol didn't affect the result (Table 1, entry 3). Performing the reaction in CH₃CN wasn't a suitable choice (entry 2). Thermal situations (entries 4 and 5) confirm that 50 °C is appropriate. For comparison the effectiveness of NH₄VO₃ was measured with respect to catalyst-free condensation under solvent-free conditions (entry 6). Finally the best results were gained in the presence of NH₄VO₃ (0.1 mmol) at an ambient temperature of 50 °C without any solvent media (entry 4).

Table 1. Conditions optimization in the reaction of indole (2 mmol) with 4-chlorobenzaldehyde (1 mmol) in the presence of NH_4VO_3 .

Entry	Condition	Time (min)	Yield ^a (%)
1	NH_4VO_3 (0.1 mmol)/ rt/ solvent-free	40	70
2	NH_4VO_3 (0.1 mmol)/ rt/ CH_3CN	80	70
3	NH_4VO_3 (0.3 mmol)/ rt/ solvent-free	40	75
4	NH_4VO_3 (0.1 mmol)/ 50 °C/ solvent-free	30	90
5	NH_4VO_3 (0.1 mmol)/ 100 °C/ solvent-free	25	90
6	50 °C/ solvent-free	80	45

^aIsolated yields.

In the next step, the general applicability of catalyst for condensation reaction was investigated (Table 2). It was observed that benzaldehyde and its activated derivatives as well as deactivated aromatic aldehydes gave their corresponding BIMs **3a-m** with indole in high yield.

Aliphatic aldehydes also underwent the condensation with indole in good yields (**3n-p**). The specialty of the catalyst has been perceived in condensation of unsaturated aldehydes such as 3-phenyl-2-propenal, 2-butenal and 2-methyl-3-phenyl-2-propenal with indole.

In these cases their corresponding BIMs obtained without any conjugate adducts (**3q-s**). 5-Methylfurfural, 1-naphthaldehyde and 9-anthracenecarbaldehyde condensed with indole successfully (**3t-v**). Arylaldehydes with 2-methylindole and 1-methylindole yielded the corresponding triarylmethanes **3w-z**. As can be seen, utilizing 1-methylindole the reaction time is a bit longer in comparison with 2-methylindole. 4-Methylacetophenone as a model keton failed to react with indole even after 5h.

Next we focused on the synthesis of other kinds of BIMs. Isatin has been chosen as another candidate to react with indole to form its related oxindole **5a** in 15 min by 85% yield (Table 3, entry 1). According to Table 3 other indoles with variant activated isatins alternated the condensation prosperously (**5b-h**). 3,3'-Bis(5-bromoindolyl)-indoline-2-one (**5i**) gained in condensation of isatin with 5-bromoindole in 78% yield.

In the next step to qualify the catalytic potential of NH_4VO_3 , the Michael addition of indole with 2-nitrovinylbenzene has been examined in the presence of 0.1 mmol of the catalyst at 50 °C under solvent-free conditions (Table 4, **7a**). This satisfactory result accrued to successful conjugate addition of 2-methylindol and 1-methylindole with indole to obtain **7e** and **7h**. Other α,β -unsaturated compounds such as 3-buten-2-one, 4-phenyl-3-buten-2-one and

1,3-diphenyl-2-propen-1-one in the reaction with indole, 1-methylindole and 2-methylindole yielded their Michael adducts **7b-7d** and **7g-7h** in 82-90%.

Another efficient and important aspect of this protocol, is the reusability of the recovered catalyst. For this reason, the NH_4VO_3 was recovered from the reaction mixture of 3,3'-Bis(1*H*-indolyl)-(4-chlorophenyl)methane (**3j**) by addition of EtOAc and filtering. The solid residue washed with further EtOAc and dried overnight at room temperature. This recovered catalyst reused and recycled with in four runs with almost no activity decrease. As could be seen in Table 2, the recovered NH_4VO_3 could catalyzed the condensation of indole and 7-chlorobenzaldehyde to obtain BIM **3j** within 90, 90, 88 and 85 % yield during 4 alternate separation and further usage (Table 2, compound **3j**). Subsequently as the final stage, the condensation of indole with Terephthalaldehyde (**8**) examined with indole (Scheme 2). Surprisingly the results confirm that even in the presence of 4 mmol of indole and/or 0.2 mmol of ammonium monovanadate, 4-[bis(indolyl)methyl]-benzaldehyde (**9a**) gained as the main product.

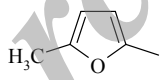
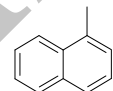
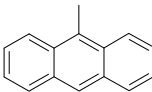
4. Conclusions

In summary, ammonium monovanadate has been extinguished as an effective, commercially available, low cost, almost eco-friendly and reusable solid acid catalyst which catalyzes the condensation of indoles with aldehydes and isatins to form triaryl methanes and oxindole derivatives in high yields. The applicability of the catalyst has also been confirmed in the Michael addition of indole with α,β -unsaturated compounds that yields their correspondence conjugate adducts successfully. Simple procedure associated with reusability and widespread efficiency of the catalyst are the highlighted points of this work.

Acknowledgment

I thank the Alzahra University for financial support.

Table 2. Condensation of indoles with aldehydes in the presence of NH_4VO_3 (0.1 mmol) at 50 °C under solvent-free conditions.

Compound	R ₁	R ₂	R ₃	Time (min)	Yield (%)	m.p. (°C) found	m.p. (°C) reported	Ref.
3a	H	H	C ₆ H ₅	15	88	121-123	123-125	[40]
3b	H	H	4-MeC ₆ H ₄	20	92	97-99	95-97	[23]
3c	H	H	4-MeOC ₆ H ₄	40	85	190-192	187-189	[23]
3d	H	H	3-MeOC ₆ H ₄	35	90	149-151	-	[31]
3e	H	H	2-MeOC ₆ H ₄	50	83	109-111	134-136	[43]
3f	H	H	4-NO ₂ C ₆ H ₄	60	90	229-231	221-223	[40]
3g	H	H	3-NO ₂ C ₆ H ₄	50	91	217-219	263-264	[43]
3h	H	H	2-NO ₂ C ₆ H ₄	70	85	106-108	139-141	[44]
3i	H	H	4-(CH ₃) ₂ CHC ₆ H ₄	40	92	145-147	-	[31]
3j	H	H	4-ClC ₆ H ₄	30	90, 90,88, 85 ^a	111-112	104-106	[43]
3k	H	H	2,4-Cl ₂ C ₆ H ₃	35	91	126-128	100-102	[42]
3l	H	H	3-BrC ₆ H ₄	35	93	145-147	189-191	[46]
3m	H	H	2-OHC ₆ H ₄	55	91	196-198	127	[41]
3n	H	H	C ₃ H ₇	70	85	77-79	64-66	[43]
3o	H	H	C ₆ H ₅ CH ₂ CH ₂	65	86	122-124	124-125	[34]
3p	H	H	C ₆ H ₅ CHCH ₂	60	87	163-165	72-73	[45]
3q	H	H	C ₆ H ₅ CH=CH	50	90	92-94	95-97	[43]
3r	H	H	C ₆ H ₅ CH=CCH ₃	70	88	74-76	-	[31]
3s	H	H	CH ₃ CH=CH	70	90	130-132	126-128	[44]
3t	H	H		75	85	74-76	-	[31]
3u	H	H		50	92	226-228	248-250	[23]
3v	H	H		65	70	243-245	240	[47]
3w	H	Me	4-MeC ₆ H ₄	40	92	92-94	174-176	[23]
3x	H	Me	2,4-Cl ₂ C ₆ H ₃	45	92	214-215	215-216	[31]
3y	Me	H	4-(CH ₃) ₂ CHC ₆ H ₄	100	86	144-146	-	[31]
3z	Me	H	4-FC ₆ H ₄	120	90	196-197	-	[31]

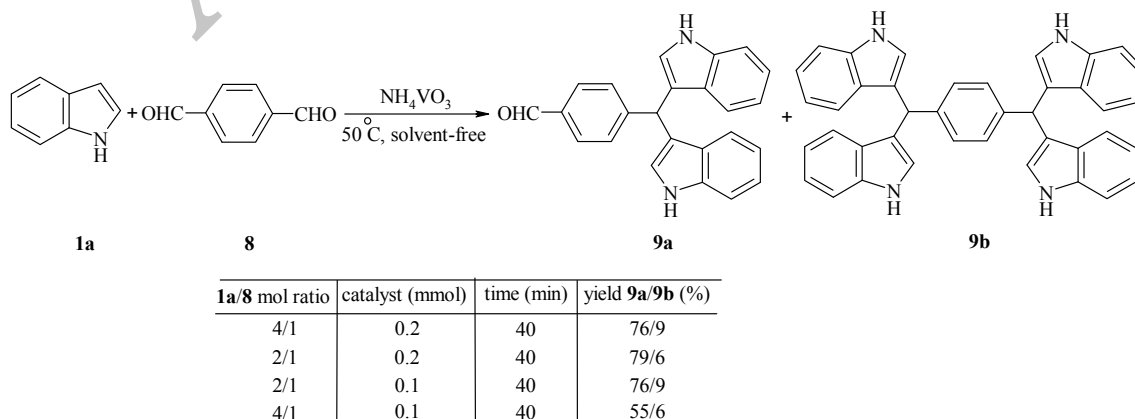
^aThe yield of reusability of the catalyst in 4 run.

Table 3. Condensation of indoles with isatins in the presence of NH_4VO_3 (0.1 mmol) at 50 °C under solvent-free conditions.

Compound	R ₁	R ₂	R ₃	R ₄	R ₅	Time (min)	Yield (%)	m.p. (°C) found	m.p. (°C) reported	Ref.
5a	H	H	H	H	H	15	85	313-315	312-314	[37]
5b	H	H	H	Me	H	20	81	287-289	291-293	[37]
5c	H	H	H	H	NO ₂	80	80	300-301	298-299	[37]
5d	H	H	H	CH ₂ C ₆ H ₅	H	120	78	262-264	288-289	[37]
5e	H	Me	H	H	H	20	90	275-277	291-293	[37]
5f	H	Me	H	Me	H	40	83	266-268	272-273	[37]
5g	H	Me	H	CH ₂ C ₆ H ₅	H	100	85	202-204	212-214	[37]
5h	Me	H	H	H	H	20	90	309-311	330-332	[37]
5i	Me	H	H	H	NO ₂	90	75	312-314	>300	[37]
5j	H	H	Br	H	H	50	78	307-310	310-311	[37]

Table 4. Michael addition of indoles with α,β -unsaturated compounds in the presence of NH_4VO_3 (0.1 mmol) at 50 °C under solvent-free conditions.

Compound	R ₁	R ₂	R ₃	R ₄	Time (min)	Yield (%)	m.p. (°C) found	m.p. (°C) reported	Ref.
7a	H	H	C ₆ H ₅	NO ₂	90	87	oil	viscous oil	[48]
7b	H	H	H	COCH ₃	40	83	86-87	71-72	[48]
7c	H	H	C ₆ H ₅	COCH ₃	160	82	73-75	-	[34]
7d	H	H	C ₆ H ₅	COC ₆ H ₅	180	84	60-62	125-127	[49]
7e	H	Me	C ₆ H ₅	NO ₂	150	90	96-98	94-96	[34]
7f	H	Me	C ₆ H ₅	COC ₆ H ₅	120	90	80-81	-	[34]
7g	Me	H	H	COCH ₃	100	88	oil	viscous oil	[48]
7h	Me	H	C ₆ H ₅	NO ₂	120	80	113-114	110-112	[32]

**Scheme 2.** Reaction of indole with Terephthalaldehyde catalyzed by ammonium monovanadate.

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