Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2017, 9(13):112-117
(http://www.derpharmachemica.com/archive.html)

PMA-SiO_2: Heteropolyacid Catalysis for Michael Addition-Convenient Route to Substituted-3-Indoles

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ABSTRACT

Synthesis of 3-substituted indoles in a hassel-free, ecofriendly manner by treating indoles with α, β-unsaturated carbonyl or nitro compounds under acidic conditions to give good to excellent yields with shorter reaction durations are described. The catalyst is recyclable for three to four times without great loss in the activity.

Keywords: Phosphomolybdic Acid (PMA), Substituted indoles, α, β-unsaturated carbonyl compounds, α, β-unsaturated nitro compounds, Michael addition

INTRODUCTION

Heterocyclic chemistry is one of the quintessential branches of organic synthesis beaconing towards new scaffolds with medicinal values, new methodologies to the existing active principles etc. One among such skeletons is indole. It is perhaps the most common heterocycles in chemistry and its derivatives are obtained from coal pitch, variety of plants or by the bacterial decay of tryptophan in the intestine [1]. Indole derivatives serve as signaling chemicals in plants and animals, as nucleus building blocks (serotonin [2] (A) a crucial neurotransmitter in the central nervous system [3]), as antibacterial [4], antiviral [5], protein kinase inhibitors [6], anticancer agents [7], entheogens (psilocybin (B) causes perceptional changes), hormones (melatonin (C) regulates sleep and wakefulness), antidepressants (roxindole (D), bufotenin (E)), sumatriptan (F) for the treatment of migraine and ondansetron (G) for the suppression of nausea and vastly found in natural products such as alkaloids (*Corynanthe*, *Iboga*, and *Aspidosperma* alkaloids) [8-10], indigoids etc., which originate, either fully or partly, from bio-oxidation of indoles [11]. Maintaining their presence as privileged motifs in the biologically important structures demand the development of newer methods for the synthesis of 3-substituted indoles. Over indole moiety, important analogues with medicinal values are found to have the substitution at 3rd position with a two carbon fragment, has made most of it. It can be readily obtained by C-C bond formation in a Michael addition of an electron rich substrate (example: Indoles) on the α, β-unsaturated carbonyl or nitro compounds under acidic or basic conditions. They are atom efficient and thus are inherently green transformations (Figure 1) [11].

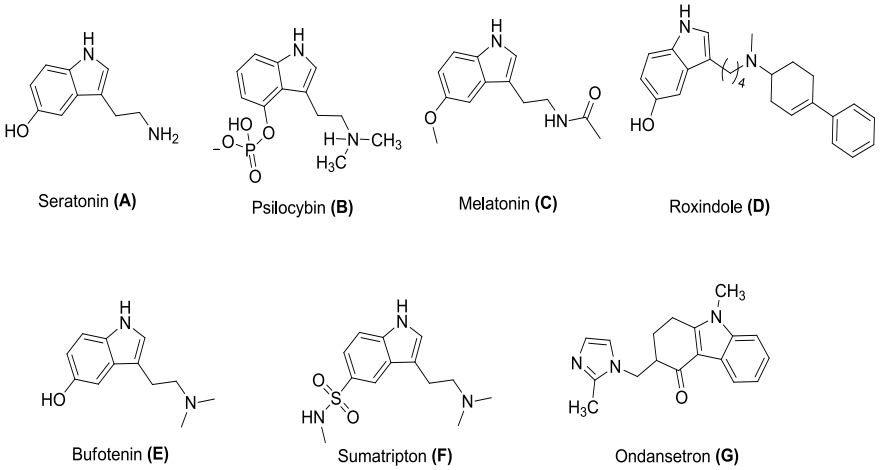
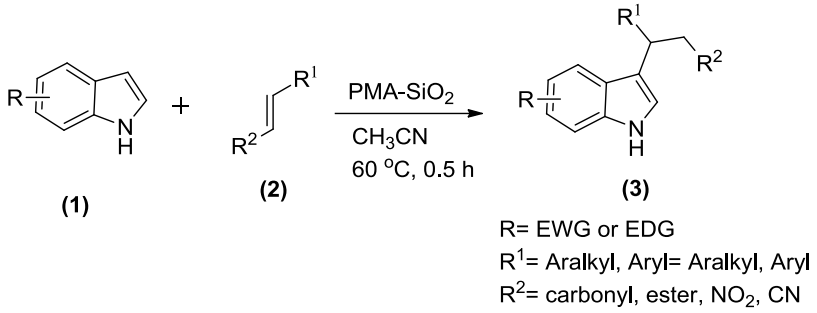


Figure 1: Examples of 3-substituted indoles based drugs

As different procedures are well documented that use protic [12-15], Lewis acids [16-22] and metal complexes [23-26] for the synthesis of substituted-3-indoles in a Michael manner, they suffer from strong acidic conditions, expensive reagents and longer reaction times, low yields of products and uneasy handling. Hence, the variations are attempted in developing a catalyst or a new method with the existing catalyst to optimize and standardize the effective conditions of synthesis. In this process, solid supported catalysts are contemplated due to their minimum stoichiometric presence, maximum surface area and easy separation followed by recyclability. The best support reported in the recent times is the silica with acid catalysts. Literature survey reveals that most of the catalysts developed in this way have one or the other drawback including the generation of bis(indolyl)methane as a side product [27]. Now-a-days heteropolyacids-Bronsted acids have attracted the attention of chemists as alternatives to the protic, Lewis acids and Phosphomolybdic Acid (PMA, $H_3PMO_{12}O_{40}$) a heteropoly acid is cogently a Bronsted acid catalyst used in various organic transformations such as in MCRs [28], enol ether formation [29], propargylation of alcohols attributing cleaner, greener and cost effective traits at low concentrations and temperatures. To overcome the aforementioned drawbacks and to come out with a better silica supported catalyst, a test report on silica supported PMA is presented in this article and verified its efficacy in the Michael reaction (Scheme 1) [30].



Scheme 1: Michael reaction

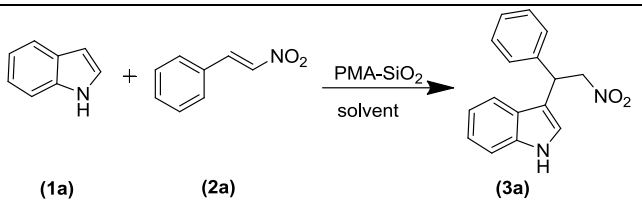
MATERIALS AND METHODS

Melting points are uncorrected and were obtained in open capillary tubes using sulphuric acid bath. Thin Layer Chromatography (TLC) checking was done on precoated sheets with silica gel GF-254 (Merck). Flash column chromatography was performed over silica gel (mesh 60 × 120) with hexane/ethyl acetate (7:3 ratio) combination as the eluent. ^{1}H-NMR and ^{13}C-NMR spectra were determined in Dimethyl Sulfoxide (DMSO-d_6) solution by using 400 and 100 MHz spectrometers respectively with Tetramethylsilane (TMS, δ=0.00) as internal standard and expressed in ppm. Coupling constants (J) are given in hertz. IR spectra were recorded using Perkin-Elmer model 1700 instrument in KBr phase. MS spectra were obtained on a mass spectrometer.

RESULTS AND DISCUSSION

In our study, indole (1 equivalent) was treated with unsaturated carbonyl or nitro compounds (1 equivalent) in the presence of PMA-SiO_2 (5 mol%) in various solvents to optimize and standardize the conditions better suitable for the synthesis. Out of all the tested solvents, acetonitrile (entry 7, Table 1) was found to be the suitable one giving maximum yields (96%) at reflux temperature in 0.30 min.

Table 1: Optimization conditions for the Michael addition



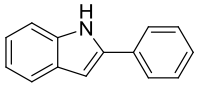
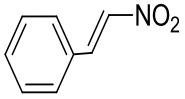
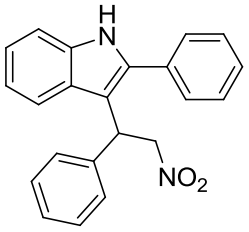
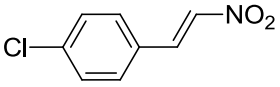
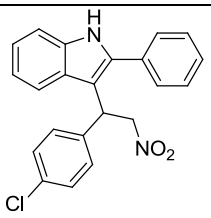
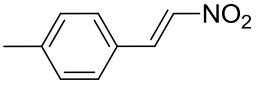
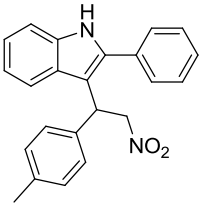
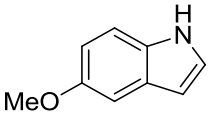
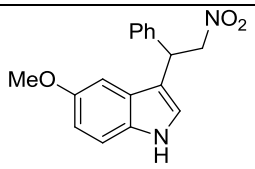
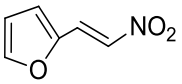
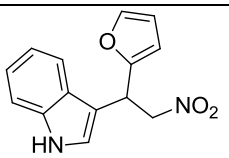
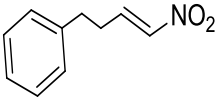
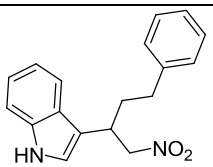
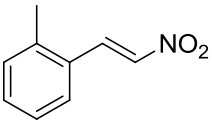
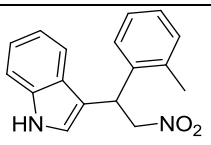
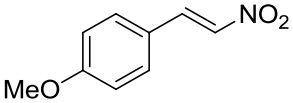
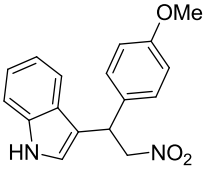
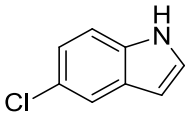
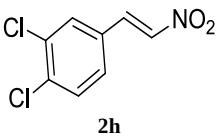
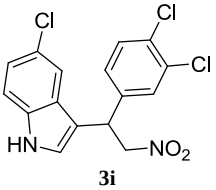
(1a) (2a) (3a)

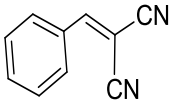
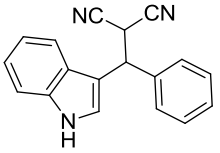
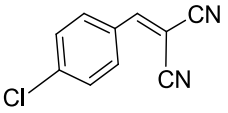
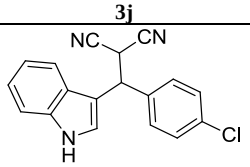
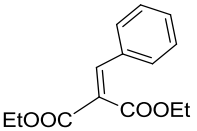
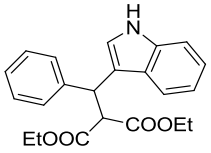
Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)[b]
1	THF	25	2	70
2	DCM	25	2	70
3	Toluene	25	2	70
4	EtOH	25	2	75
5	MeOH	25	1.5	75
6	CH_3CN	25	1.2	85
7	CH_3CN	60	0.5	96 (94, 92, 89)[c]

[a]All the reactions were carried out by using Indole 1a (1 equivalent), β-nitrostyrene 2a (1 equivalent), PMA-SiO_2 (5 mol%) in a solvent (5 ml) at 60°C; [b]Isolated yields; [c]Catalyst was reused for additional three runs and figures within parentheses indicate the corresponding yield for each run

To test the recyclability of the catalyst (PMA-SiO_2) used, it was recovered after every cycle by simple filteration and reused, wherein, the isolated yields (94%, 92% and 89%) at first, second, third and fourth cycle respectively) are an evidence for the fact that there is no substantial reduction in the catalytic activity. By adopting the procedure described in the experimental section 12 compounds were prepared and confirmed their structure spectroscopically (^{1}H-NMR, ^{13}C-NMR, Mass) (Table 2).

Table 2: PMA-SiO_2 catalyzed synthesis of 3-substituted indoles[a]

Entry	Substituted indoles (1)	α, β-unsaturated carbonyl or nitro compounds (2)	Product (3)	Yield(%)[b]
1	 **1a**	 **2a**	 **3a**	96
2	**1a**	 **2b**	 **3b**	92
3	**1a**	 **2c**	 **3c**	90
4	 **1b**	**2a**	 **3d**	90
5	**1a**	 **2d**	 **3e**	96
6	**1a**	 **2e**	 **3f**	95
7	**1a**	 **2f**	 **3g**	96
8	**1a**	 **2g**	 **3h**	92
9	 **1c**	 **2h**	 **3i**	93

10	**1a**	 **2i**	 **3j**	94
11	**1a**	 **2j**	 **3k**	93
12	**1a**	 **2k**	 **3l**	90

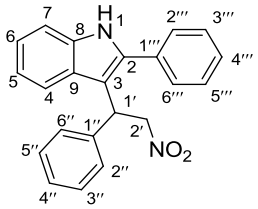
[a]All the reactions were carried out by using indole 1 (1 equivalent), β-nitrostyrene 2 (1 equivalent), PMA-SiO_2 (5 mol%) in CH_3CN at 60°C for 0.5 h; [b]Isolated yields

EXPERIMENTAL AND METHODOLOGY

General procedure for the synthesis of 3-substituted indoles (3a-l)

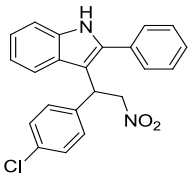
A mixture of α, β-unsaturated carbonyl or nitro compounds (2a-k) (1 equivalent), indoles (1a-c) (1 equivalent) and PMA-SiO_2 catalyst (5 mol%) in acetonitrile (5 ml) were stirred at 60°C for 0.5 h. The reaction was monitored by TLC (mobile phase 25% ethyl acetate and 75% hexane). After complete conversion, the reaction mixture was cooled to room temperature and mixture was diluted with Et_2O. The catalyst, i.e., PMA-SiO_2 was recovered by simple filtration and crude product was purified by column chromatography on silica gel using ethyl acetate/hexane to give the desired product. The filtered catalyst was reused without drying.

3-(2′-Nitro-1′-phenyl ethyl)-2-phenyl-1H-indole (3a)



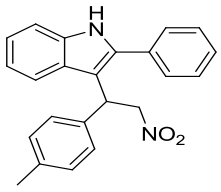
Pale yellow solid; ^{1}H-NMR (400 MHz, $CDCl_3$) (δ ppm) 5.13 (dd, 1H, J=8.4, 12.2 Hz, $–CH_2NO_2$), 5.18 (dd, 1H, J=7.6, 12.2 Hz, $–CH_2NO_2$), 5.32 (dd, 1H, J=8.4Hz, H-1′), 7.09 (t, 1H, J=7.6 Hz, H-5), 7.24 (t, 2H, J=8.4 Hz, H-6, H-4′′), 7.28 (m, 2H, J=8.4 Hz, H-2′′, H-6′′), 7.32 (d, 2H, J=7.6 Hz, H-3′′, H-5′′), 7.40 (d, 1H, J=8.4 Hz, H-4′′′), 7.42-7.47 (m, 5H, H-7, 2′′′, 3′′′, 5′′′, 6′′′), 7.50 (d, 1H, J=8.4 Hz, H-4), 8.10 (s, 1H, –NH). ^{13}C-NMR (100 MHz, $CDCl_3$) (δ ppm) 30.7 (C-1′), 86.0 (C-2′), 111.3 (C-7), 112.0 (C-3), 119.8 (C-4), 120.8 (C-6), 122.0 (C-5), 123.2 (C-2), 125.8 (C-4′′), 127.0- 128.1 (C-8, C-2′′′, C-6′′′), 128.4-128.5 (C-2′′, C-6′′), 129.0-129.3 (C-3′′, 5′′, 3′′′, 4′′′, 5′′′), 132.1 (C-1′′′), 136.1 (C-9), 136.2 (C-1′′). MS (ESI): m/z 342.

3-[1′-(4′′-Chlorophenyl)-2′-nitroethyl]-2-phenyl-1H-indole (3b)



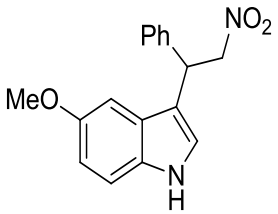
^{1}H-NMR (400 MHz, $CDCl_3$) (δ ppm) 5.09 (dd, 1H, J=8.4, 12.2 Hz, 1′-H), 5.16 (dd, 1H, J=7.6, 12.2 Hz, 2′-H_1), 5.27 (t, 1H, J=7.6 Hz, 2′-H_2), 7.03 (t, 1H, J=7.6 Hz, H-5), 7.09(m, 2H, H-2′′, H-6′′), 7.11-7.29 (m, 9H, H-6, 3′′, 5′′, 7, 2′′′, 6′′′, 3′′′, 5′′′), 8.22 (s, 1H, –NH). ^{13}C-NMR (100 MHz, $CDCl_3$) (δ ppm) 40.1(C-1′), 84.5 (C-2′), 110.9 (C-7), 111.9 (C-3), 119.0 (C-4), 119.8 (C-6), 122.6 (C-5), 125.8 (C-2), 127.7 (C-8, 2′′′, 6′′′), 128.8-129.2 (C-4′′′, 3′′, 5′′, 2′′, 6′′), 129.2 (C-3′′′, 5′′′), 132.0 (C-4′′), 133.0 (C-1′′′), 135.8 (C-9), 138.2 (C-1′′).

3-[1′-(4′′-Tolyl)-2′-nitroethyl]-2-phenyl-1H-indole (3c)



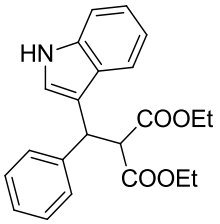
^{1}H-NMR (400 MHz, $CDCl_3$) (δ ppm): 2.32 (s, 3H, $–CH_3$), 4.82 (dd, 1H, J=8.4, 12.2 Hz, H-1′), 4.79 (dd, 1H, J=7.6, 12.2 Hz,H_1-2″), 5.20 (t, 1H, J=7.6 Hz, H_2-2″), 7.08 (m, 4H, J=8.4 Hz, H-5, 3″, 5″, 6″), 7.19 (m, 2H, J=8.4 Hz, H- 6, 2″), 7.34 (m, 1H, J=8.4 Hz, H-4‴), 7.37-7.48 (m, 5H, H-7, 2‴, 3‴, 5‴, 6‴), 7.53 (d, 1H, J=7.6 Hz, H-4), 8.46 (s, 1H,–NH). MS (ESI): m/z 356 $[M]^+$.

5-Methoxy-3-(2′-nitro-1′-phenyl ethyl)-1H-indole (3d)



^{1}H-NMR (400 MHz, $CDCl_3$): 3.75 (s, 3H, OCH_3), 4.94 (dd, J=8.1, 12.3 Hz, 1H, H-1′), 5.01 (dd, J=7.5, 12.3 Hz, 1H, H_1-2′), 5.11 (t, J=8.0 Hz, 1H, H_2-2′), 6.91 (m, J=1.5 Hz, 2H, H- 2, 6), 6.95 (m, J=2.4 Hz, 2H, H-4, 4″), 7.07 (m, J=2.4 Hz, 2H, H- 2″, 3″), 7.2-7.37 (m, 3H, H- 5″, 6″, 7), 8.10 (s, 1H, NH).

(S)-Ethyl 2-Ethoxycarbonyl-3-(3-indolyl)-3-phenyl propanoate (3l)



^{1}H-NMR (400 MHz, $CDCl_3$) δ=1.12 (t, 2 × CH_3, 6H), 3.79 (d, 1H, H-2′), 4.20 (q, 2 × OCH_2, 4H), 5.33 (d, J=11.8 Hz, 1H, H-1′), 6.70 (s,1H, NH), 7.03-7-20 (m, H-5, H-6, H-2″, H-3″, H-4″, H-5″, H-6″, J=8.1 Hz, 7H), 7.32 (d, J=7.5 Hz, 1H, H-7), 7.61 (d, J=7.9 Hz, 1H, H-5), 8.74 (s, 1H, NH); MS (ESI): m/z 366 [M+H]+.

CONCLUSION

In conclusion, PMA-SiO_2 is proved to be an inexpensive, safer, environmental friendly, reusable, efficient and versatile catalyst for the synthesis of 3-subsituted indoles through Michel addition of indoles over β-nitrostyrenes. The advantage with this catalyst lies in its easy, simple separation after the reaction which can be reused with almost the similar efficacy.

ACKNOWLEDGEMENTS

The author thanks the Faculty, Department of Chemistry, and Osmania University for the constant support and encouragement.

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