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Heteropolyacid Catalyzed Synthesis Of Indole Derivatives Via Fischer Indole Synthesis

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ABSTRACT

Different indole and carbazole derivatives have been synthesized via Fischer indole synthesis in the presence of catalytic amount of $H_3PW_{12}O_{40}$ in methanol

Key Words: Fischer indole synthesis, carbazole, indole, Keggin-type heteropolyacids.

1. INTRODUCTION

A wide variety of important biological activities have been featured by heterocycles containing indole nucleus. Indole frameworks have attracted a plethora of research areas due to the vast applications in material sciences[1] and pharmaceuticals.[2] Particularly, anti-inflammatory and anti-tumour activities of some indole derivatives have been proved.[3,4] Some indole derivatives act as dopamine agonists and/or selective serotonin reuptake inhibitors (SSRIs), the latter being a class of anti-depressants.[5] More than 1000 alkaloids with the indole skeleton have been reported from microorganisms[6,7] and the biogenetic importance of monoterpenoid indole alkaloids has been investigated as well.[8] Consequently, the synthesis of indole libraries has received a great deal of attention and development of one-pot approaches to carbazoles or indoles is a subject of considerable interest because of their significance in both economical and ecological points of view.

In spite of reporting various methods for the synthesis of indoles,[9] Fischer indole synthesis is probably the most widely investigated synthesis of indole and carbazole derivatives[10] and a large number of new syntheses or modifications and applications of known methods continue to be reported.[11]

In recent years, heteropolyacids (HPAs) have been used extensively as acid and redox catalysts in homogeneous and heterogeneous reactions. Heteropolyacids exhibit the very strong and efficient Brønsted acidity values, approaching the superacid region.[12] The expansion of methods using heteropolyacids (HPAs) as catalyst for synthetic processes related to fine chemicals, such as flavors and pharmaceuticals has been under attention in the last decade.[12b] Catalysts based on heteropolyacids have many advantages over liquid acid catalysts. They are not corrosive and are environmentally benign and present fewer disposal problems. Solid heteropolyacids have attracted much attention in organic synthesis owing to easy work-up procedures and reduction of cost and waste due to recycling of the catalyst.[12c]

In connection our research using heteropolyacids[12] in organic reaction and expansion of our work on one-pot multicomponent synthesis,[13] herein, we wish to report a facile protocol for the preparation of indole and carbazole derivatives in high yields from the reaction of phenylhydrazine derivatives and different carbonyl compounds in the presence of a catalytic amount of Keggin-type heteropolyacid, $H_3PW_{12}O_{40}$ as a recyclable catalyst (Schemes 1, 2 and 3).

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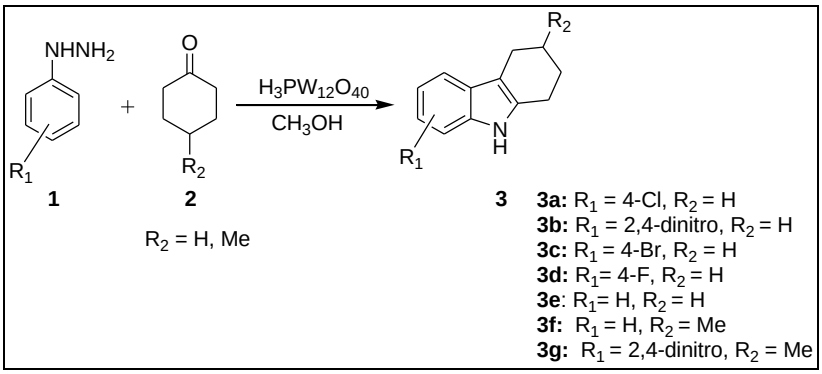
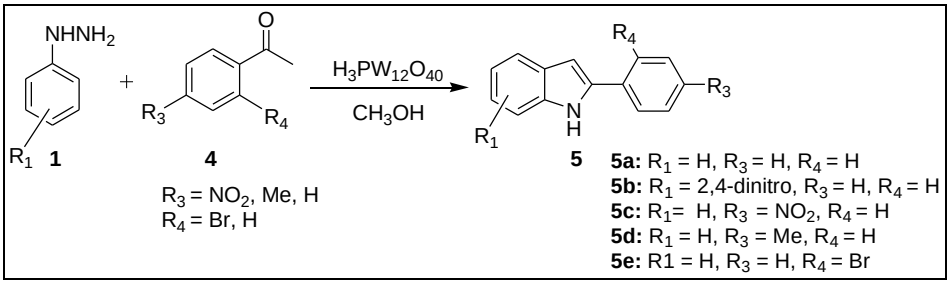
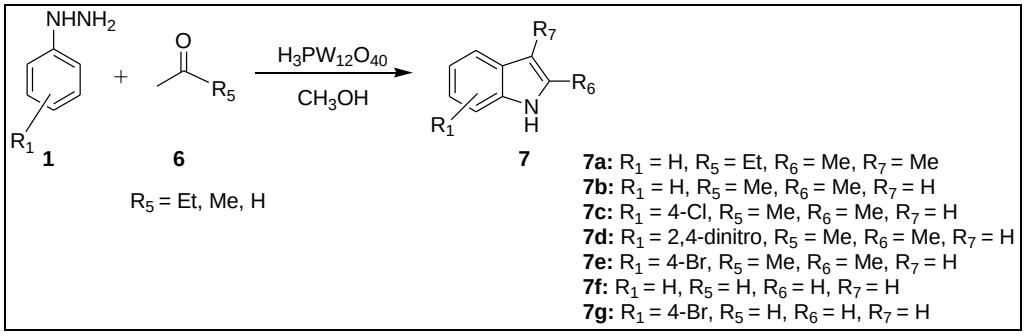


Scheme 1. Synthesis of carbazole derivatives



Scheme 2. Synthesis of indole derivatives



Scheme 3. Synthesis of indole derivatives

No report has been made so far about the use of $H_3PW_{12}O_{40}$ for synthesis of indole derivatives via Fischer indole synthesis.

2. EXPERIMENTAL

All compounds were known and their physical data were compared with those of authentic compounds and found to be identical. All the chemicals were purchased from Merck Company. Melting points were measured using Barnstead Electro thermal. GC/Mass analysis was performed using Agilent 6890 GC system Hp-5 capillary 30m×530µm×1.5µm nominal. IR spectra were recorded as KBr disc on the FT-IR Brucker Tensor 27 spectrometer. Bruker AQS-AVANCE spectrometer at 500 and 125 MHz, using TMS as an internal standard. The elemental analysis was performed with an Elemetar Analysensystem GmbH VarioEL CHNS mode.

2.1. General procedure of synthesis of indole and carbazole derivatives

A mixture of phenylhydrazine derivative (1 mmol), carbonyl compounds (1 mmol) and heteropolyacid (0.05 g) in MeOH (5 ml) was heated at reflux for appropriate time (Table 2). After completion of the reaction which was monitored by TLC, the mixture was cooled to room temperature. In the case of 3a-d, 5a-e and 7a-b, the solid product was collected by filtration, washed with water. In the case of 3e-f and 7b-g, solvent was evaporated under reduced pressure and then the product was extracted with $CHCl_3$. The organic phase was dried over anhydrous sodium sulphate and concentrated under vacuum. The products were purified by recrystallization from EtOH and H_2O. All products were known and identified by comparison of their physical and spectroscopic data with those of authentic samples.[11b,11j,15]

2.2. Reusability of the catalyst

After the end of reaction and separation of product, the solvent was evaporated under reduced pressure, washed with diethyl ether, dried at 80 °C for 1 h and re-used in another reaction. Table 3 compares the efficiency of $H_3PW_{12}O_{40}$ in synthesis of indole and carbazole and the results show that the yield of product after four runs was only slightly reduced.

1,2,3,4-Tetrahydrocarbazole (**3e**): mp 112-114 °C; IR (KBr, cm^{-1}): 3400, 1656; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.75 (m, 4H, CH_2), 2.35–2.62 (m, 4H, CH_2), 7.25–7.34 (m, 5H, ArH), 8.14 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.0, 134.3, 127.6, 121.1, 119.0, 116.7, 110.9, 109.9, 22.3, 22.9, 22.8, 20.5. MS (EI): *m/z* = 171(M^+), 143, 115, 77.

2-(4nitrophenyl)indole (5c): mp 187-190 °C; IR (KBr, cm^{-1}): 3400, 1656; ^{1}H NMR (500 MHz, $CDCl_3$): 6.79 (s, 1H, CH), 8.12 (s, 1H, NH), 7.15–8.36 (m, 8H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.0, 139.1, 137.5, 136.7, 128.0, 126.1, 124.3, 121.5, 118.7, 119.1, 108.9, 97.5. MS (EI): *m/z* = 238 (M^+), 117, 77.

2-methylindole (**7b**): mp 54-55 °C; IR (KBr, cm^{-1}): 3400, 1659; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.23 (s, 3H, CH_3), 5.93 (m, 1H, CH), 7.15–7.58 (m, 4H, ArH), 7.35 (s, 1H, NH) ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.0, 135.4, 128.9, 119.8, 119.6, 119.2, 99.7, 99.0, 12.5. MS (EI): *m/z* = 131 (M^+), 117, 77.

3. RESULT AND DISCUSSION

First, we examined the reaction using methanol as a solvent in a model reaction. In a simple experimental procedure, 1 mmol 4-bromophenylhydraziniumchloride and 1 mmol cyclohexanone in methanol were allowed to react with stirring at room temperature for 6 h in the presence of 0.05 g $H_3PW_{12}O_{40}$, to give, after workup, a 90% yield of compound **3c** (Scheme 1). The structure of **3c** was confirmed from spectroscopic data and by comparison with an authentic sample. When the model reaction was conducted under reflux condition, the reaction rate increased and shorter time was needed for completion of reaction. We also carried out the reaction in the absence of catalyst, but products were isolated in poor yields (15 –20%) and in some cases (e.g. 3b, 5b, 7a) many other by products were observed.

Table 1 Effect of varying solvent on the yield of indole and carbazole derivatives

Entry	Product	Solvent	Time (min)	Yield (%)[a]
1	3c	MeOH	30	90
2	3c	EtOH	60	85
3	3c	CH_3CN	120	40
4	3c	DMF	300	30
5	3c	CH_2Cl_2	360	5
6	3c	H_2O	360	-
7	5a	MeOH	45	70
8	5a	CH_3CN	200	35
9	5a	CH_2Cl_2	300	2
10	7f	MeOH	30	80
11	7f	CH_3CN	150	55

[a] Yields are related to isolated pure products.

Encouraged by the effect of a protic solvent and to reduce the reaction time, we studied the reaction using water as the solvent. Unfortunately, it was observed that no reaction occurred even after stirring the reaction mixture for a long time. To investigate the effect of solvent, the reactions were carried out in the presence of $H_3PW_{12}O_{40}$ in various solvents (EtOH, CH_3CN, DMF and CH_2Cl_2).

The results are shown in Table 1. From these results it is concluded that the corresponding product can be obtained in high yield in MeOH. Excellent yield of products were obtained by carrying out the reaction in MeOH and 0.05 g of catalyst under reflux condition. Higher amounts of $H_3PW_{12}O_{40}$ did not lead to significant improvement in yield of products and low amounts of $H_3PW_{12}O_{40}$ did not catalyzed some reactions (e.g. 7c, 7g) efficiently.

Table 2. Fischer indole synthesis between carbonyl compounds and phenylhydrazine derivatives catalyzed by $H_3PW_{12}O_{40}$

Entry	carbonyl compounds	phenylhydrazine derivatives	Product	Time (min)	Yield (%)[a]	Mp (°C)	
						Found	Reported
1	cyclohexanone	4-chlorophenylhydraziniumchloride	3a	30	85	145-147	147-148[15a]
2	cyclohexanone	2,4-dinitrophenylhydrazine	3b	45	80	277-279	280[11j]
3	cyclohexanone	4-bromophenylhydraziniumchloride	3c	30	90	147-149	148.5-150[15b]
4	cyclohexanone	4-fluorophenylhydraziniumchloride	3d	30	90	97-98	93-95[11i]
5	cyclohexanone	phenylhydrazine	3e	30	90	112-114	115-116[11b]
6	4-methylcyclohexanone	phenylhydrazine	3f	30	70	107-108	109-110[15c]
7	4-methylcyclohexanone	2,4-dinitrophenylhydrazine	3g	30	70	>300	>360[11j]
8	acetophenone	phenylhydrazine	5a	45	70	185-186	184-185[11b]
9	acetophenone	2,4-dinitrophenylhydrazine	5b	30	70	279-281	280-282[15d]
10	4-nitroacetophenone	phenylhydrazine	5c	30	80	187-190	188-190[11b]
11	4-methylacetophenone	phenylhydrazine	5d	30	70	211-213	210-212[11b]
12	2-bromoacetophenone	phenylhydrazine	5e	30	70	74-75	76-77[15e]
13	2-butanone	phenylhydrazine	7a	30	65	106-107	105-107[11b]
14	acetone	phenylhydrazine	7b	45	70	54-55	55-56[11b]
15	acetone	4-chlorophenylhydraziniumchloride	7c	30	80	108-110	108-111[15f]
16	acetone	2,4-dinitrophenylhydrazine	7d	30	80	159-160	160[15g]
17	acetone	4-bromophenylhydraziniumchloride	7e	30	80	102-104	104-106[15h]
18	acetaldehyde	phenylhydrazine	7f	30	70	50-51	51-52[11b]
19	acetaldehyde	4-bromophenylhydraziniumchloride	7g	30	75	89-91	91[15i]

[a]Yields are related to isolated pure products

This method not only preserves the simplicity, but also consistently gives the corresponding products in good to excellent yields. Thus, we have treated a variety of phenylhydrazine derivatives and carbonyl compounds in the presence of catalytic amount of $H_3PW_{12}O_{40}$ to form the corresponding indole and carbazole derivatives. This method has the ability to tolerate a various different phenylhydrazine derivatives, aldehydes and ketones (Table 2).

It is noteworthy to mention that the catalyst is recyclable and can be reused for several times without significant loss in activity (Table 3). At the end of the reaction, the catalyst was separated, washed with diethyl ether, dried at 80 °C for 1 h and re-used in another reaction. Even after 4 runs for the reaction, the catalytic activity of $H_3PMo_{12}O_{40}$ was almost the same as that of the freshly used catalyst.

Table 3 Reusability of catalyst in the synthesis of 2-bromo-6,7,8,9-tetrahydro-5H-carbazole (**3c**) via reaction of 4-bromophenylhydraziniumchloride and cyclohexanone

Entry	Number of recycle	Time (min)	Yield (%)[a]
1	Fresh	3	90
2	1	35	88
3	2	35	85
4	3	40	83
5	4	80	80

[a] Yields are related to isolated pure products.

In summary, an efficient and convenient approach for the synthesis of indole and carbazole derivatives using $H_3PW_{12}O_{40}$ is introduced here. The Heteropolyacid can be recovered simply and reused for several times without considerable decrease in yields of products. The protocol presents some advantages such as simple experimental, easy separation of the indoles, high product purity, short reaction time and high yields.

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