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Multicomponent, Solvent-Free Synthesis of 1-Amidoalkyl-2-naphthols in the Presence of $H_{3+x}PMo_{12-x}V_xO_{40}$ Heteropolyacids as Recyclable and Green Catalysts

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Abstract: A rapid and efficient one-pot method for the synthesis of 1-amidoalkyl-2-naphthols has been developed in the presence of mixed-addenda vanadium(V)-substituted polyoxomolybdates including:$H_{3+x}PMo_{12-x}V_xO_{40}$ (x=1-3) heteropolyacids (HPAs) as recyclable catalysts under solvent-free conditions. In all cases heteropolyacid with x = 3 gave the highest yield under solvent-free conditions.

Keywords: Multicomponent reaction, Catalyst, Vanadium(V)-substituted Polyoxomolybdates, 1- Amidoalkyl-2-naphthols.

Introduction

The multicomponent coupling reactions[1] are emerging as a useful source for accessing small drug-like molecules with several levels of structural diversity. Multicomponent reaction (MCR) condensations involve three or more compounds reacting in a single event, but consecutively to form new products, which contains the essential parts of all the starting materials. These reactions are welcome too in terms of economic and practical considerations. The search and discovery for new MCRs on one hand[2] and the full exploitation of already known multicomponent reactions on the other hand, is therefore of considerable current interest. 1-amidoalkyl-2-naphthols and their derivatives have attracted

considerable interest in recent years due to biologically important antibacterial, natural products and potent drugs including a number of nucleoside antibiotics and HIV protease inhibitors, such as ritonavir and lipinavir[3,4].

The preparation of 1-amidoalkyl-2-naphthols can be carried out by multi-component condensation of aryl aldehydes, 2-naphthol and acetamide in the presence of Lewis or Bronsted acid catalysts such as montmorillonite K10 clay[5], $Ce(SO_4)_2$[6], iodine[7], *p*-TSA[8], sulfamic acid[9] and cation-exchange resins[10]. However, some of these catalysts suffer from the drawback of green chemistry such as prolonged reaction times, low yields, toxicity and recovery and reusability of the catalyst. Therefore, introducing clean processes and utilizing eco-friendly and green catalysts which can be simply recycled at the end of reactions, have been under permanent attention. The demand for environmentally benign procedure with heterogeneous and reusable catalysts promoted us to develop a safe alternate method for the synthesis of amidoalkyl naphthols.

Recently, we have investigated various catalytic performances of heteropolyacids in different reactions[11-18]. In seeking to develop new synthetic methods for organic compounds by using heteropolyacids, in the present work, the performance and applicability of three kinds of vanadium(V)-substituted polyoxomolybdates such as $H_4[PMo_{11}VO_{40}]$, $H_5[PMo_{10}V_2O_{40}]$ and $H_6[PMo_9V_3O_{40}]$ has been studied for synthesis of 1-amidoalkyl-2-naphthols in one-pot and solvent-free conditions. The results were compared with $H_3[PMo_{12}O_{40}]$.

Experimental

Heteropolyacid catalysts were synthesized according to the literature[19]. All of the chemicals were obtained from commercial sources. All yields were calculated from purified products. IR spectra were obtained with a Brucker 500 scientific spectrometer. ^{1}H-NMR spectra were recorded on a FT NMR 500 HZ spectrometer. Melting points were obtained on a Electro thermal type 9100 apparatus.

General procedure

In a typical reaction, a mixture of aromatic aldehyde (1.2 mmol) and 2-naphthol (1.2 mmol) and acetamide (1.7 mmol) was made with a catalytic amount of mixed-addenda vanadomolybdophosphate, (2 mol%), under solvent free conditions in oil bath at 130 ^{o}C for 12 minutes. The progress of reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to 25 ^{o}C, then the solid residue was solved in boiling EtOH and the mixture stirred for 8 minutes. The pure product was obtained by recrystallization.

Some selected spectroscopic data from (Table 2)

N-[Phenyl-(2-hydroxy-napthalen-1-yl)-methyl]-acetamide (Table 2, entry 2);^{1}H NMR (500 MHz, DMSO-d_6): δ=1.98 (s, 3H), 7.11 (m, 1H), 7.14(m, 1H), 7.16 (m, 1H), 7.19 (m, 1H), 7.20 (m, 2H), 7.21 (m, 1H), 7.23 (m, 1H), 7.33 (t, J=7.5 Hz, 1H), 7.73 (d, J=9.1 Hz, 1H), 7.78 (d, J=8.0 Hz, 1H), 7.83 (s, 1H), 8.45 (d, J=8.5 Hz, 1H),10.01 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 23.2, 40.3, 119.2, 119.4, 122.9, 123.8, 126.6, 126.8, 128.5, 126.8, 128.9, 129.1, 129.8, 132.8, 143.1, 153.7, 169.0 ppm; IR (KBr, cm $^{-1}$): 3399, 3246, 3062, 1640, 1582, 1514, 1372, 1337, 1060, 808, 742, 696, 623.

N-[(3-Nitro-phenyl)-(2-hydroxy-napthalen-1-yl)-methyl]-acetamide (Table 2, entry 3) ^{1}H NMR (500 MHz, DMSO-d_6): δ=2.01 (s, 3H), 7.17 (t, J=8.0 Hz, 1H), 7.19 (d,J=8.6 Hz, 1H), 7.24 (t, J=7.5 Hz, 1H), 7.38 (t, J=7.4 Hz,1H), 7.51 (m, 2H), 7.78 (t, J=8.6 Hz, 2H), 7.83 (br, 1H), 7.98 (m, 2H), 8.58 (d, J=8.0 Hz, 1H), 10.16 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 23.1, 48.2, 118.3, 118.9, 120.9, 121.8, 123.2, 127.3, 123.2, 128.9, 129.2, 130.1, 130.5, 132.6, 133.4, 145.9, 148.2, 153.9, 170.3 ppm; IR (KBr, cm $^{-1}$): 3373, 3088, 2598, 1645, 1524, 1350, 1232, 1158, 1063, 808, 705.

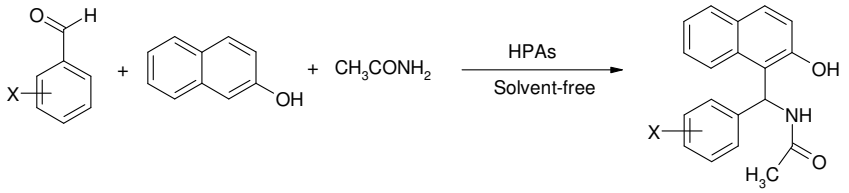
N-[(4-Nitro-phenyl)-(2-hydroxy-napthalen-1-yl)-methyl]-acetamide (Table 2, entry 4) ^{1}H NMR (500 MHz, DMSO-d_6): δ=2.02 (s, 3H), 7.19 (d, J=8.0 Hz, 1H), 7.22 (d, J=8.8 Hz, 1H), 7.28 (t, J=7.5 Hz, 1H), 7.41 (t, J=7.3 Hz, 1H), 7.52-7.58 (m, 2H), 7.81 (t, J=9.4 Hz, 2H), 7.87 (d, J=7.0 Hz, 1H), 8.03 (m, 2H), 8.60 (d, J=8.0 Hz, 1H), 10.11 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 22.5, 47.6, 117.7, 118.4, 120.3, 121.1, 122.5, 126.6, 128.3, 129.4, 129.8, 132.1, 132.7, 145.3, 147.7, 153.2, 169.5 ppm; IR (KBr, cm $^{-1}$): 3391, 3267, 2593, 1648, 1603, 1522, 1438, 1063, 825, 739, 447.

N-[(4-Chloro-phenyl)-(2-hydroxy-napthalen-1-yl)-methyl]-acetamide (Table 2, entry 6) ^{1}H NMR (500 MHz, DMSO-d_6): δ=1.96 (s, 3H), 7.05 (d, J=8.1 Hz,1H), 7.11 (d, J=8.6 Hz, 2H), 7.18 (d, J=8.6 Hz, 1H), 7.19 (m, 3H), 7.31 (t, J=7.5 Hz, 1H), 7.73 (m, 3H), 8.42 (d, J=8.6 Hz, 1H), 10.09 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 20.6, 23.1, 48.1, 118.9, 119.0, 123.0, 126.9, 128.9, 128.4, 129.1, 129.1, 130.0, 131.2, 132.7, 142.3, 153.7, 169.9 ppm; IR (KBr, cm $^{-1}$): 3392, 2962, 2700, 2613, 1637, 1577, 2523, 1490, 1436, 1374, 1331, 1278, 1243, 1171, 1091, 819, 747, 588, 499.

N-[(4-Methyl-phenyl)-(2-hydroxy-napthalen-1-yl)-methyl]-acetamide (Table 2, entry 7) ^{1}H NMR (500 MHz, DMSO-d_6): δ=1.96 (s, 3H), 2.21 (s, 3H), 7.03-7.08 (m, 5H), 7.19 (d, J=8.8 Hz, 1H), 7.24 (t, J=7.1 Hz, 1H), 7.34 (m, 1H), 7.74 (d, J=8.8 Hz, 1H), 7.78 (d, J=7.9 Hz, 1H), 7.82 (br, 1H), 8.36 (d, J=8.1 Hz, 1H), 9.91 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 20.4, 22.6, 47.6, 118.4, 118.9, 122.2, 123.1, 125.9, 126.1, 128.3, 128.4, 128.9, 132.2, 134.9, 139.4, 143.2, 152.9,168.9 ppm; IR (KBr, cm $^{-1}$): 3396, 3055, 2923, 1625, 1515, 1437, 1276, 1181, 813, 744, 482.

Results and Discussion

The synthesis of 1-amidoalkyl-2-naphthols in the presence of a catalytic amount of various heteropolyacids such as $H_6[PMo_9V_3O_{40}]$, $H_5[PMo_{10}V_2O_{40}]$, $H_4[PMo_{11}VO_{40}]$, was investigated under solvent-free conditions (scheme 1).



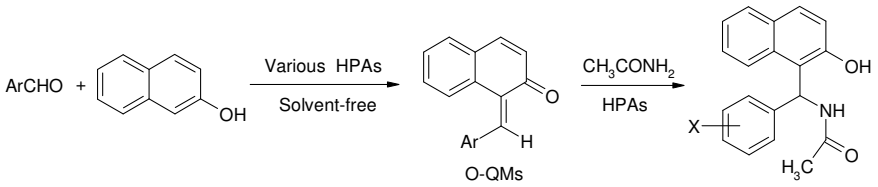
Scheme 1

To study the effect of the catalyst on this reaction, *N*-[(4-methoxy phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide, was selected as optimized and model product and the yields of the products were obtained using different heteropolyacids as catalysts. The results are shown in Table1. The suggested mechanism is shown in scheme 2.

Table 1. Effect of various heteropolyacids, (2 mol%), on the yields of *N*-[(4-methoxyphenyl)-(2-hydroxy naphthalen-1-yl)-methyl]-acetamide under solvent-free conditions at 130 ^{o}C

Entry	Heteropolyacid	Time, min	Yield, %[a]
1	$H_6[PMo_9V_3O_{40}]$	12	92
2	$H_5[PMo_{10}V_2O_{40}]$	12	87
3	$H_4[PMo_{11}VO_{40}]$	12	83
4	$H_3[PMo_{12}O_{40}]$	12	78

[a] *Yield refers to isolated products*



Scheme 2

The reaction of 2-naphthol with aromatic aldehydes in the presence of acid catalyst is known to give ortho-quinone methides (O-QMs). The same O-QMs, generated *in situ*, have been reacted with acetamide to form 1-amidoalkyl-2-naphthol derivatives. A reasonable explanation for this result can be given by considering the nucleophilic addition to O-QM intermediate favourable *via* conjugate addition on *α,β*-unsaturated carbonyl group that aromatizes ring of this intermediate. The order of efficiency of catalysts is as follows: $H_6[PMo_9V_3O_{40}] > H_5[PMo_{10}V_2O_{40}] > H_4[PMo_{11}VO_{40}] > H_3[PMo_{12}O_{40}]$. Thus, $H_6[PMo_9V_3O_{40}]$ was selected as the catalyst of choice for the synthesis of 1-amidoalkyl-2-naphthols. The results are shown in Table 2.

Table 2. Synthesis of 1-amidoalkyl-2-naphthols using catalytic amount of $H_6[PMo_9V_3O_{40}]$ (2 mol%) under solvent-free conditions at 130 °C

Entry	Aldehyde	Time, min	Yield, %[a]	mp., °C	
				Found	Reported[Ref.]
1	4-$CH_3OC_6H_4CHO$	12	92	186-187	184-186[6]
2	C_6H_5CHO	12	84	241	241-243[6]
3	3-$NO_2C_6H_4CHO$	12	87	188-189	182-184[6]
4	4- $NO_2C_6H_4CHO$	12	89	151	148-149[26]
5	4-BrC_6H_4CHO	12	90	226	228-230[9]
6	4-ClC_6H_4CHO	12	89	243-244	248-250[6]
7	4-$CH_3C_6H_4CHO$	12	84	225-226	222-223[24]

[a] *Yield refers to isolated products*

The Keggin anion with x=0, have an assembly of 12 corner-shared octahedral MoO_6 from trimetallic groups $[Mo_3O_{13}]$ around a heteroatom tetrahedron PO_4[20]. The introduction of vanadium (V) into the Keggin framework of $[PMo_{12}O_{40}]^{3-}$ is beneficial for catalysis reactions[21]. Usually positional isomers are possible and coexist when two or more vanadium atoms are incorporated into the mixed-addenda Keggin structure[22]. Studies on these isomers in catalytic reactions indicate that different isomers cause to show different reactivities[23]. With respect to the catalytic performances for these catalysts and the overall effects of all isomers, for synthesizing of them, we cannot control the reaction conditions to synthesis of positional vanadium-substituted isomers separately and hence study of their catalytic activity, is difficult. It is suggested that the presence of both Bronsted acidity and vanadium in the structure of mentioned heteropolyacids, is responsible for catalytic activity of mixed-addenda Keggins. The greater protons number may lower, the activation energy barrier and the greater vanadium atoms may provide many sites for catalytic reaction.

To optimize the temperature in the mentioned reaction, *N*-[(4-Methoxy phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide, was selected and the temperature effect was carefully investigated. The reaction was carried out in the presence of best catalyst: $H_6[PMo_9V_3O_{40}]$ heteropolyacid, under solvent-free conditions. The temperature varied from

room temperature to130 °C. The results showed that the highest yield can be obtained at 130 °C. The yields was lower when the reactions were carried out at temperatures lower than reflux temperature. We believe that increasing in the temperature for accelerating the reaction is apparently favorable.

Under optimum conditions, different amount of catalyst including 1%, 2% and 3 mol% have been studied. The results are shown in Figure 1. It is clear that the yields depend on the amount of catalyst and the optimum amount of which was 2 mol% for all derivatives. Increase in this amount has not any effect on the yield.

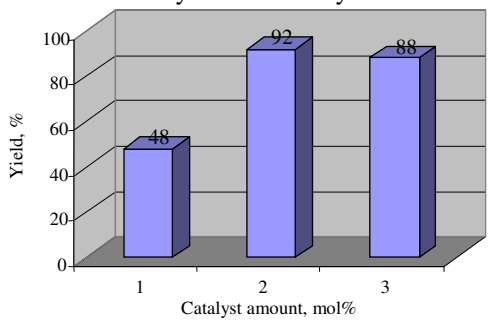


Figure 1. The result of using different amounts of $H_6[PMo_9V_3O_{40}]$ in the synthesis of *N*-[(4-methoxyphenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide under solvent-free conditions

Reusability of the catalyst

The catalyst was recovered after the reaction and reused in the reaction. Several times recoveries had only slightly decreased the catalytic activity, pointing to the stability and retention capability of this useful polyanion. At the end of the reaction, the catalyst was filtered, washed with diethyl ether, dried and reused in another reaction. The recycled catalyst was used for three reactions without observation of appreciable lost in its catalytic activities.

Conclusion

In conclusion, we have reported a new catalytic method for the synthesis of 1-amidoalkyl-2-naphthols derivatives by using vanadium(V)-substituted polyoxomolybdates as efficient, inexpensive, reusable and eco-friendly heterogeneous catalysts, *via* three-component reactions, under solvent-free conditions. The solvent-free green procedure offer advantages such as shorter reaction times, simple work up and excellent yield. Simple experimental procedure as well as high yield and selectivity, makes this method useful addition to the methodologies that require green super acid solid catalyst. Important features of this protocol are, simplicity and versatility of process engineering, decreasing reactor and plant corrosion problems and environmentally safe disposal. The catalyst can be easily recovered, regenerated and reused without loss of structure and appreciable activity, thus providing economic and environmentally friendly method for other organic reactions.

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