A NOVEL METHOD FOR THE SYNTHESIS OF 1(2H)- PHTHALAZINONE DERIVATIVES USING HETEROPOLYACIDS AS HETEROGENEOUS AND RECYCLABLE CATALYSTS

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Abstract: A simple and efficient synthesis of 1(2H)- phthalazinone derivatives was achieved via a reaction of phthalaldehydic acid and various phenyl hydrazines in $CHCl_3$ in the presence of a catalytic amount of different heteropolyacids (HPAs) in very good yields.

1. Introduction

Nitrogen-containing heterocyclic compounds are widespread in nature, and their applications to biologically active pharmaceuticals, agrochemicals, and functional materials are becoming more and more important (1-5). The development of new efficient methods to synthesize N-heterocycles with structural diversity is one major interest of modern synthetic organic chemists (6-8). Among a large variety of nitrogen-containing heterocyclic compounds, 1(2H)- phthalazinones have received considerable attention because of their pharmacological properties and clinical applications (9-11). Phthalazinone derivatives were reported to posses antidiabatic (12), antiallergic (13), anticonvulsant (14-16), cardiotonic (17) and vasorelaxant (18,19) anti-inflammatory (20,21) activities. They are also useful intermediates for the synthesis of inhibitors of the VEGF (vascular endothelial growth factor) sreceptor tyrosine kinases for the treatment of cancer (22). In view of the emerging importance of 1(2H)- phthalazinones, still there is a need to introduce new methods for the synthesis of these compounds using more efficient, convenient and green conditions and in the presence of more safe precursors.The problems associated with the handling and disposal of the inorganic acids, and their environmental and potential hazards have raised our interest in the development of alternative procedures using solid acid catalysts.(23-30) Heteropoly compounds are economically and environmentally attractive catalysts both in academic and industrial chemistry. They are effective catalysts for various reactions and have high capability in practical uses, because their redox and acidic can be controlled at the atomic/molecular levels by changing the constituent elements as per the needs of the chemical processes.(31)

In connection with our recent interested aimed at the development of efficient protocols for the preparation of biological active heterocycles [32-35], we herein report the synthesis of 1(2H)- phthalazinone derivatives in the presence of a catalytic amount of different types of HPAs including, $H_{14}[NaP_5W_{30}O_{110}]$, $H_6[PMo_9V_3O_{40}]$, $H_5[PMo_{10}V_2O_{40}]$ and $H_6[P_2W_{18}O_{62}]$ (Scheme 1) in good yields.

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2. Experimental

2.1. Chemical and apparatus

All the chemicals were obtained from Merck Company and used as received. $H_{14}[NaP_5W_{30}O_{110}]$ was prepared according to earlier works [24,26,28,36,37]. $H_6[PMo_9V_3O_{40}]$, $H_5[PMo_{10}V_2O_{40}]$ and $H_6[P_2W_{18}O_{62}]$ were prepared according to the literatures [38]. The integrity of the synthesized heteropolyacids has been proven by comparing of spectral data with those reported in literature [39–42].All products are known compounds and were characterized by mp, IR, ^{1}HNMR and GC/MS. Melting points were measured by using the capillary tube method with an electrothermal 9200 apparatus. ^{1}HNMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network Mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. All products were characterized by spectra and physical data.

2.2. Typical procedure for Preparation of 2-phenyl-2H-phthalazin-1-one (3a)

To a mixture of phthalaldehydic acid (1mmol, 15g) and phenylhydrazine (1mmole, 1ml) in $CHCl_3$ (5ml) and $H_{14}[NaP_5W_{30}O_{110}]$ (9×10^{-3} mmol) was added and refluxing was continued for 1h. The progress of the reaction was monitored by TLC (petroleum ether:ethylacetate. 3:1). After completion of the reaction, the catalyst was filtered. The mixture was then washed with 5% $NaHCO_3$ (5mL) and the product was extracted into diethyl ether (2×5mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was obtained. The resulting solid product was recrystallized from ethanol to give the pure product. Mp 198°c; IR (KBr): 1620 (C=N), 1670 (C=O) cm^{-1}; 1H NMR (CDCl3, 300 MHz): 7.5-8.4 (m, 9H, Ar-H), 8.8 (s, 1H), MS: m/z 222 [M+].

2.3. Reusability of the catalyst

Next, we investigated the reusability and recycling of heteropolyacids. At the end of the reaction, the catalyst could be recovered by a simple filtration. The recycled catalyst could be washed with methanol and subjected to a second run of the reaction process. To assure that catalysts were not dissolved in methanol, the catalysts were weighted after filtration and before using and reusing for the next reaction. The results show that these catalysts are not soluble in methanol. In Table 1, the comparison of efficiency of $H_{14}[NaP_5W_{30}O_{110}]$ in synthesis of 3a after five times is reported. As it is shown in Table1 the first and second reaction using recovered $H_{14}[NaP_5W_{30}O_{110}]$ afforded similar yield to those obtained in the first run. In the third, fourth and fifth runs, the yield were gradually decreased.

3. Results and Discussion

1(2H)- phthalazinone were obtained by phthalaldehydic acid and various phenyl hydrazines in $CHCl_3$ by using $H_{14}[NaP_5W_{30}O_{110}]$ (scheme1) in good yields (table2). The reactions proceeded efficiently at mild conditions and completed within 1-2h, in contrast to conventional methods that require long reaction times. This method not only affords the products in good yields but also avoids the problems associated with catalyst cost, handling, safety and pollution. This catalysts can act as eco-friendly for

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a variety of organic transformations, non-volatile, non-explosive, easy to handle and thermally robust. Phenyl hydrazine required shorter reaction time due to the electron withdrawing groups (Table-2, entries 2-7). Moreover, the steric hindrance seems to have significant effects on the reaction times and yields (Table-2, entries 3, 4, 7).In a systematic study and aimed work, we have also been studied the effects of the catalyst, temperature and solvent in this article.

3.1. Effect of the catalyst type

Initially, we compared the catalytic performance of Preyssler, $H_{14}[NaP_5W_{30}O_{110}]$ with Keggin, $H_5[PMo_{10}V_2O_{40}]$, $H_6[PMo_9V_3O_{40}]$ and Wells–Dawson, $H_6[P_2W_{18}O_{62}]$ in the synthesis of 1(2H)- phthalazinone derivatives. The results are shown in Table 3. The yield of product decreases in the following order:

$H_{14}[NaP_5W_{30}O_{110}] > H_6[P_2W_{18}O_{62}] > H_5[PMo_{10}V_2O_{40}] > H_6[PMo_9V_3O_{40}]$

As could be seen Preyssler type of heteropolyacid, $H_{14}[NaP_5W_{30}O_{110}]$, is more effective than the other heteropoly anions and in the presence of this catalyst the highest yields of products are obtained. The interesting feature of this polyanion compared the other heteropolyacids is its hydrolytic stability (pH 0–12), which is very important in catalytic processes. In addition this polyanion is more stable than the Keggin catalysts under thermal conditions, which makes high temperature for the reactions possible. A significant interpretation for observed different activities of tested heteropoly anions is very difficult. Their properties can be varied by their constitutive elements as heteroatom, polyatom, and counter-cation. However, because one of the important factors that affect the oxidation capacity and activity of poly anions which is the energy gap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied orbital (LUMO), it is suggested that the energy and composition of the LUMOs have significant effects on the redox properties and activity of the studied poly anions as catalyst. The highest activity for $H_{14}[NaP_5W_{30}O_{110}]$ is attributed to the energy and composition of the LUMO, strong acidic property, and higher acidic protons. The larger number of protons may low the activation barrier and the large anion can provide many sites on the oval-shaped molecule that are likely to render the catalyst effective.

The reaction was studied with various moles of Preyssler catalyst from 2×10^{-3} mmol to 9×10^{-3} mmol. In all cases, with 9×10^{-3} mmol catalyst (Table 4, entry2) the maximum yields of 1(2H)- phthalazinones was obtained within 1-2h. The progress of the reaction was followed by TLC and GC and the results indicate that the yields were affected by changing the catalyst moles. The reactions proceeded well with 9×10^{-3} mmol catalyst and use of an increased amount of catalyst does not make much difference.

3.2. Effect of temperature

The effect of temperature was studied by carrying out the reactions at different temperatures [room temperature, 25°C, 50 °C and under refluxing temperature (61°C)]. As it shown in Tables 2 by raising the reaction temperature from ambient temperature (25 °C) to refluxing temperature (61°C) the yield of reactions increased. From these results, it was decided that refluxing temperature would be the best

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temperature for all reactions. The reaction proceeds very cleanly under reflux condition and free of side products.

3.3. Effect of the solvent

The synthesis of 1(2H)- phthalazinone derivatives at reflux temperature was carried out using various common solvents such as CCl_4, CH_2Cl_2, $CHCl_3$ and THF. The results are shown in Table 5. With using all of the catalysts the highest yield of products was obtained with $CHCl_3$ as solvent. In addition, the time required for completion of the reaction was found to be less in $CHCl_3$. Because of large negative charge of polyoxoanions, all of the HOMOs and LUMOs of them have very high energy levels. These highly charged heteropolyanions do not exist in the gas phase and that the external field generated by the solvent is crucial to stabilize them. With regard to the heteropolyanions which are reducible easily and is required in catalytic reactions, the energy of the LUMO must be sufficiently low to accept the electrons in catalytic reactions. The solvent molecules can place these molecular orbitals at the appropriate level. As shown in Table 5, the solvent effects change in parallel to the charges of the anions. The greater negative charge lead to the greater solvent effects and finally the higher yields. It is suggested that the solvent effects are dominated by the interactions of the polarized polyanions with the solvent, to place the molecular orbitals at the appropriate level and or to lower the activation energy. Apparently this effect is higher for $CHCl_3$.

4. Conclusion

In conclusion we have achieved an efficient process for the synthesis of biologically interesting functionalized 1(2H)- phthalazinone derivatives starting from readily available and inexpensive reagents. This method offers some advantages in terms of simplicity of performance, easy work-up, use of inexpensive, available and easy to handle catalyst and high yields of products and relatively short reaction times.

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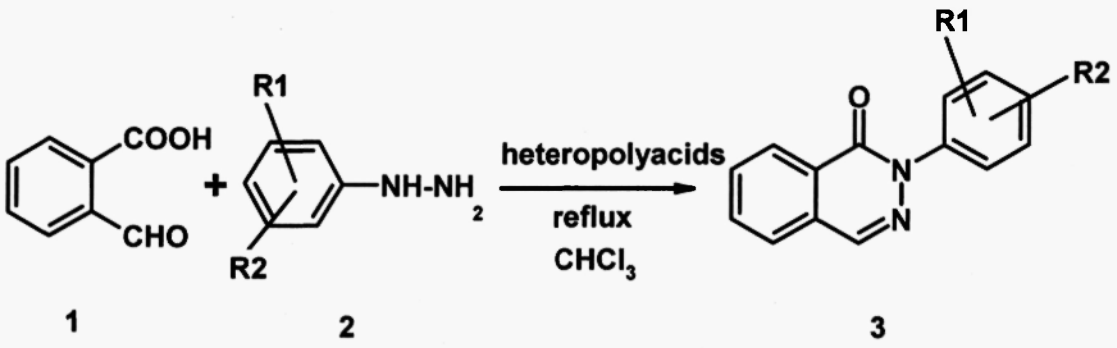

Scheme 1

Table 1: Reuse of the $H_{14}[NaP_5W_{30}O_{110}]$ for synthesis of 3a

Entry	Time(h)	Yield (%)[a]
1	1	95
2	1	94
3	1.20	90
4	1.30	88
5	2	85

[a]Yields were analyzed by GC

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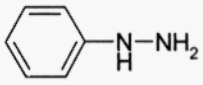
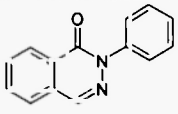
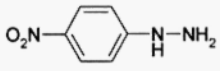
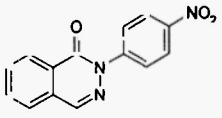
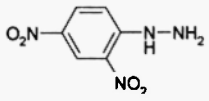
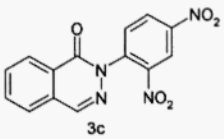
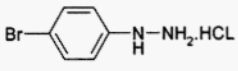
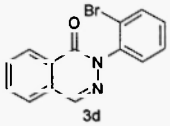
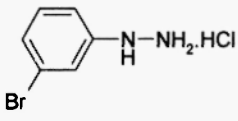
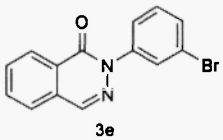
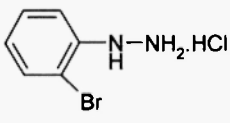
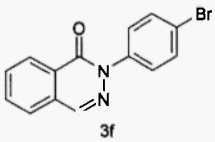
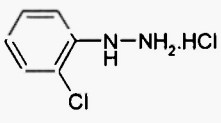
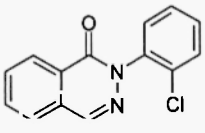
Table2:Synthesis of 1(2H)- phthalazinone derivatives catalyzed by $H_{14}[NaP_5W_{30}O_{110}]$

Entry	Substrate	Product	Time(h)	Yield(%)[a]		
				25°C	40°C	61°C
1		 3a	1	55	85	95
2		 3b	1.5	45	75	87
3		 3c	2	40	70	80
4		 3d	2	45	72	81
5		 3e	1.5	50	79	88
6		 3f	1.5	50	77	89
7		 3g	2	43	70	80

[a]Yields were analyzed by GC

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Table 3 : Synthesis of 1(2H)- phthalazinones using various heteropolyacids under refluxing condition

Entry	Catalyst	Product	Yield(%)[a]
1	$H_{14}[NaP_5W_{30}O_{110}]$	3a	95
	$H_6[P_2W_{18}O_{62}]$	3a	92
	$H_5[PMo_{10}V_2O_{40}]$	3a	90
	$H_6[PMo_9V_3O_{40}]$	3a	88
2	$H_{14}[NaP_5W_{30}O_{110}]$	3b	87
	$H_6[P_2W_{18}O_{62}]$	3b	83
	$H_5[PMo_{10}V_2O_{40}]$	3b	80
	$H_6[PMo_9V_3O_{40}]$	3b	80
3	$H_{14}[NaP_5W_{30}O_{110}]$	3c	80
	$H_6[P_2W_{18}O_{62}]$	3c	76
	$H_5[PMo_{10}V_2O_{40}]$	3c	75
	$H_6[PMo_9V_3O_{40}]$	3c	73
4	$H_{14}[NaP_5W_{30}O_{110}]$	3d	81
	$H_6[P_2W_{18}O_{62}]$	3d	76
	$H_5[PMo_{10}V_2O_{40}]$	3d	73
	$H_6[PMo_9V_3O_{40}]$	3d	70
5	$H_{14}[NaP_5W_{30}O_{110}]$	3e	88
	$H_6[P_2W_{18}O_{62}]$	3e	82
	$H_5[PMo_{10}V_2O_{40}]$	3e	80
	$H_6[PMo_9V_3O_{40}]$	3e	79
6	$H_{14}[NaP_5W_{30}O_{110}]$	3f	89
	$H_6[P_2W_{18}O_{62}]$	3f	84
	$H_5[PMo_{10}V_2O_{40}]$	3f	81
	$H_6[PMo_9V_3O_{40}]$	3f	80
7	$H_{14}[NaP_5W_{30}O_{110}]$	3g	80
	$H_6[P_2W_{18}O_{62}]$	3g	76
	$H_5[PMo_{10}V_2O_{40}]$	3g	73
	$H_6[PMo_9V_3O_{40}]$	3g	72

[a]Yields were analyzed by GC

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Table4:Yields of 1(2H)- phthalazinones in the presence of different moles of Peryssler catalyst

Entry	mmoles of $H_{14}[NaP_5W_{30}O_{110}]$	Yields(%)[a]						
		3a	3b	3c	3d	3e	3f	3g
1	12×10^{-3}	95	88	81	81	88	90	80
2	9×10^{-3}	95	87	80	81	88	89	80
3	7×10^{-3}	90	80	72	70	73	76	77
4	5×10^{-3}	84	72	68	65	66	70	69
5	2×10^{-3}	65	60	61	60	60	60	62

[a]Yields were analyzed by GC

Table 5:Synthesis of 3a in the presence of different solvents

Entry	Solvent	Catalyst	Temperature(°C)	Time(h)	Yield(%)[a]
1	THF	$H_{14}[NaP_5W_{30}O_{110}]$	Reflux	1	93
	THF	$H_6[P_2W_{18}O_{62}]$	Reflux	1.5	90
	THF	$H_5[PMo_{10}V_2O_{40}]$	Reflux	1.5	87
	THF	$H_6[PMo_9V_3O_{40}]$	Reflux	1.5	85
2	$CHCl_3$	$H_{14}[NaP_5W_{30}O_{110}]$	Reflux	1	95
	$CHCl_3$	$H_6[P_2W_{18}O_{62}]$	Reflux	1.5	92
	$CHCl_3$	$H_5[PMo_{10}V_2O_{40}]$	Reflux	1.5	90
	$CHCl_3$	$H_6[PMo_9V_3O_{40}]$	Reflux	1.5	88
3	CH_2Cl_2	$H_{14}[NaP_5W_{30}O_{110}]$	Reflux	2	90
	CH_2Cl_2	$H_6[P_2W_{18}O_{62}]$	Reflux	2.5	88
	CH_2Cl_2	$H_5[PMo_{10}V_2O_{40}]$	Reflux	2.5	85
	CH_2Cl_2	$H_6[PMo_9V_3O_{40}]$	Reflux	2.5	85
4	CCl_4	$H_{14}[NaP_5W_{30}O_{110}]$	Reflux	2	90
	CCl_4	$H_6[P_2W_{18}O_{62}]$	Reflux	2.5	87
	CCl_4	$H_5[PMo_{10}V_2O_{40}]$	Reflux	2.5	86
	CCl_4	$H_6[PMo_9V_3O_{40}]$	Reflux	2.5	83

[a]Yields were analyzed by GC

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