$H_3PW_{12}O_{40}$: Highly Efficient Catalysts for the Synthesis of Novel 1,3,5-Triaryl-2-Pyrazoline Derivatives

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Abstract: A series of novel 1,3,5-triaryl-2-pyrazoline derivatives has been synthesized by the reaction of chalcone and phenylhydrazine in high yields. The structures of compounds obtained were determined by IR and ^{1}H NMR spectra.

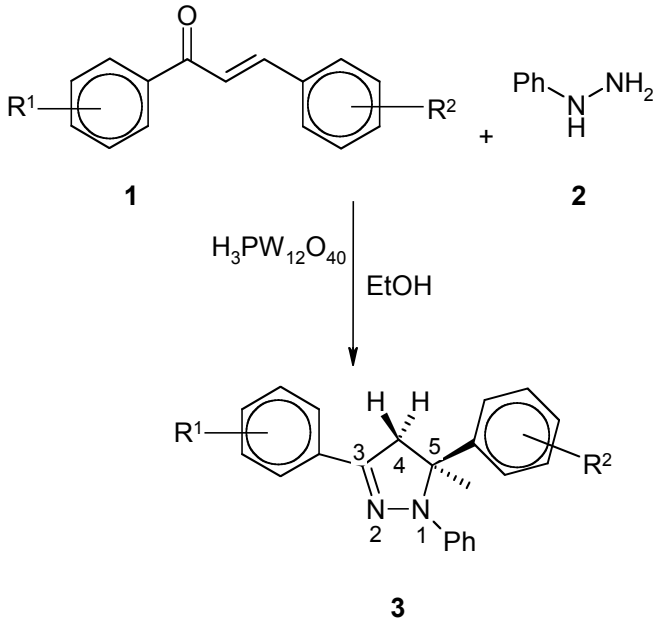
Keywords: Heteropoly acids (HPAs), polyoxometalates (POMs), 1,3,5-triaryl-2-pyrazoline, phenylhydrazine, chalcone.

INTRODUCTION

Pyrazoline derivatives are attracting increasing interest of many researchers, not only in medicinal chemistry because of their bioactivity such as antimicrobial [1, 2], antiamoebic [3, 4], antinociceptive [5], anticancer [6], antidepressant [7] and anti-inflammatory [8-12], but also in conjugated fluorescent dyes emitting blue fluorescence with high fluorescence quantum yield [13,14] and electroluminescence fields [15-17]. Recently new pyrazole derivatives were prepared as reverse transcriptase inhibitors for the treatment of HIV disorders [18]. Among the various pyrazoline isomers, 2-pyrazolines appear to be the most frequently investigated compounds. As a consequence, a large number of 2-pyrazolines have been described in the chemical literature, using different synthetic methods for their preparation. An especially popular procedure is based on the reaction of α,β-unsaturated aldehydes and ketones with hydrazines. Several catalysts have been developed for the preparation of these heterocycles, including sodium acetate-acetic acid aqueous solution under ultrasound irradiation [19], hot acetic acid solution [20] and K_2CO_3-mediated microwave irradiation [21].

In recent decades, uses of heteropoly acids (HPAs) as catalysts for fine organic synthetic processes have been developed and are important for industries related with fine chemicals [22], including flavors, pharmaceuticals and food industries [23, 24]. Solid heteropoly acids have attracted much attention in organic synthesis owing to easy work-up procedures, easy filtration, and minimization of cost and waste generation due to reuse and recycling of the catalysts [25].

In continuation of our previously reported catalytic properties of heteropoly acids, (HPAs) [26], herein, we wish to report a suitable method for the use of Keggin-type polyoxometalate (POMs), $H_3PW_{12}O_{40}$ (denoted as HTP hereafter) as heterogeneous catalyst for the synthesis of 1,3,5-triaryl-2-pyrazolines derivatives (Scheme **1**).



Scheme 1. Synthesis of 1,3-5-triaryl-2-pyrazolines.

RESULTS AND DISCUSSION

When 1 mmol of chalcone was treated with 1 mmol phenylhydrazine using 4 mol % of HTP, as catalyst for 2.5-7.5 h, 1,3,5- triaryl-2-pyrazoline was isolated in 90-98% yield. A comparative study was carried out using chalcone and phenylhydrazineas a model system with different solvents, temperature and different quantity of catalyst. Ethanol was shown to be superior to the solvents examined (Table **1**). Using 4 mol% of catalyst to chalcone shows the best result for this reaction in EtOH at 45 ^{o}C. Different stoichiometrie of the reaction were tested to find the optimized conditions. As shown in Table **1**, chalcone/ phenylhydrazine = 1:1 was determined to be the more suitable system to obtain the desired products with high yield.

On the basis of the above results, to extend the scope and generality of this method, several structurally diverse

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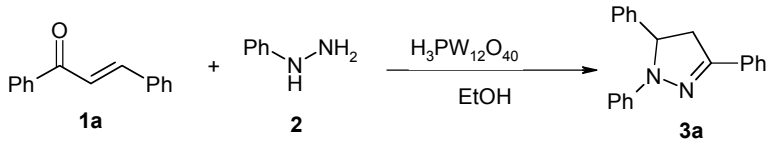
Table 1. Effect of Different Conditions in the Reaction of Chalcone with Phenylhydrazine[a]



Temperature	Yield (%)[b]								
	EtOH	MeOH	CH_3CN	CH_2Cl_2	Toluen	EtOH[c]	EtOH[d]	EtOH[e]	EtOH[f]
r.t. (25°C)	85	65	65	25	30	5	76	75	65
45 °C	98	75	86	35	45	10	86	90	85

[a]Reaction conditions: chalcone (1 mmol), phenylhydrazine (1 mmol) and catalyst (4 mol%), in solvent (5ml), after 6h. (b) Isolated Yields. (c) Without catalyst. (d) Chalcone (1 mmol), phenylhydrazine (2 mmol) was used. (e) Chalcone (1 mmol), phenylhydrazine (3 mmol) was used. (f) Catalyst (3 mol%).

Table 2. Synthesis of 1,3,5-Triaryl-2-Pyrazoline Derivatives in The Presence of HTP[a]

Entry	R_1	R_2	Time (h)	Yield (%)[b]	TON $(TON = \frac{(\%\ conv)(mol\ sub)}{mol\ catalyst})$	TOF $(TOF = \frac{TON}{time\ (h)})$	Mp(°C)	
							Found	Reported
3a	H	H	4.5	98	2.45	0.54	130-132	134-135[21]
3b	H	4-NO_2	6	92	2.30	0.38	137-139	-
3c	H	4-Me	3.5	98	2.45	0.70	128-130	128-130[19]
3d	H	4-Cl	7.5	92	2.30	0.31	135-136	133-134[20]
3e	H	3-Cl	5	92	2.30	0.46	131-133	134-136[19]
3f	H	2-Cl	5.45	90	2.25	0.41	131-133	134-135[20]
3g	H	2,4-Cl_2	6	90	2.25	0.38	127-129	-
3h	H	3-Br	5.5	92	2.30	0.42	139-141	141-143[19]
3i	H	4-MeO	2.5	98	2.45	0.98	110-112	110-112[19]
3j	4-Cl	H	5	98	2.45	0.49	143-145	143-145[19]
3k	4-Br	H	6	98	2.45	0.41	144-147	-

[a]Reaction conditions: chalcone (1 mmol), phenylhydrazine (1 mmol) and $H_3PW_{12}O_{40}$ (4 mol%), in EtOH (5 mL), at 45°C.
[b]Isolated Yield.

chalcones and phenylhydrazines were cyclized to give 1,3,5-triaryl 2-pyrazoline by HTP. The results are listed in Table **2**. It could be seen that the reactions proceeded well with all substrates, but substrates with electron-donating groups were generally more reactive than those with electron-withdrawing groups.

A reasonable pathway for the reaction of chalcone with phenylhydrazine in the presence of HTP is also presented by Scheme **2**.

EXPERIMENTAL

Material and Methods

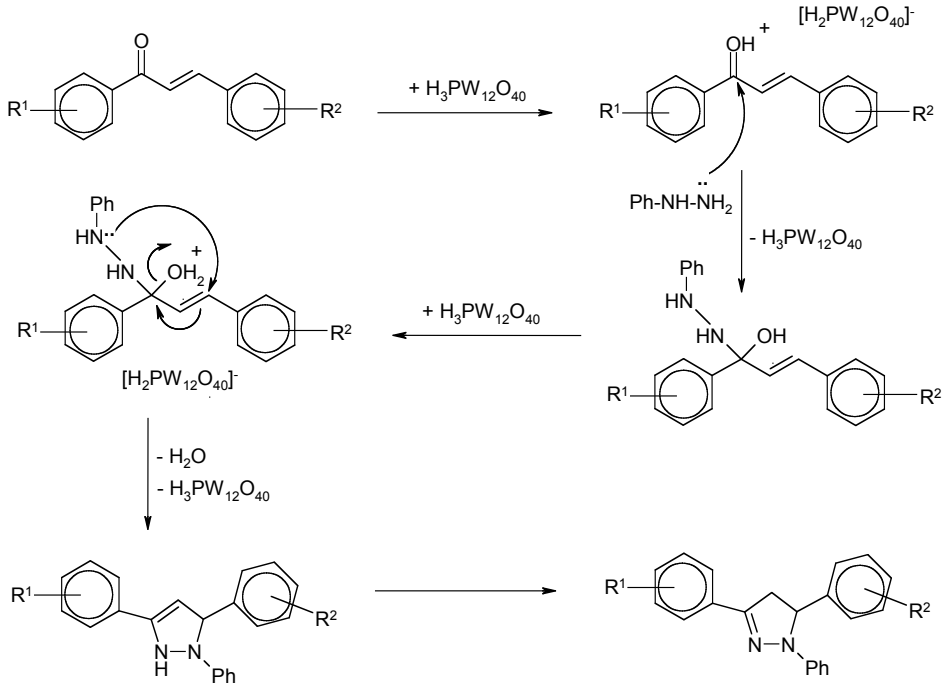
All materials were commercial reagent grade. Aldehydes, phenylhydrazine and acetophenone were obtained from Merck or Aldrich. $H_3PW_{12}O_{40}$ were purchased from Merck chemical company. FT-IR spectra were obtained as potassium bromide pellets in the range 400-4000 cm^{-1} with Nicolet *Impact 400 D*. ^1H NMR spectra were recorded with a Bruker-Avance AQS 300 MHZ. The melting points were determined using an electrothermal digital melting point apparatus and are uncorrected. Reaction courses and product mixtures were monitored by thin layer chromatography.

General Procedure for the Synthesis of Chalcone

Chalcone derivatives were synthesis and purified as described elsewhere [27].

Typical Procedure for the Synthesis of 1,3,5-Triaryl-2-Pyrazoline

The following components were added to the reaction vessels: chalcone (1 mmol), phenylhydrazine (1 mmol) and $H_3PW_{12}O_{40}$ (4 mol%) in EtOH (5 mL) at 45°C. Progress of the reaction was monitored by TLC. At the end of the reaction the mixture was washed off the vessel using EtOAc (20 ml) and then was filtered. The filtrate was dried ($MgSO_4$) and evaporated. Then, the crude product was purified on a silica gel plate or a silica gel column (20% ethyl acetate in



Scheme 2.

hexane) to provide 1,3,5-triaryl-2-pyrazoline. The products were identified by comparison of their physical data with those prepared in accordance with the literature procedures.

Some Spectroscopic Data

5-(4-Methylphenyl)-1,3-Diphenyl-2-Pyrazoline (3c)

^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H, CH_3), 3.14 (dd, J=7.1, 17.0 Hz, 1H), 3.85 (dd, J=12.1, 17.0 Hz, 1H), 5.27 (dd, J=6.9, 12 Hz, 1H) 6.77-7.75 (m, 14H) ppm. Anal. calcd. for $C_{22}H_{20}N_2$: C 84.62, H 6.41, N 8.97; found C 84.61, H 6.43, N 9.00. ^{13}C NMR: 21.68, 44.09, 64.73, 113.69, 119.47, 126.23, 128.43, 128.88, 129.34, 129.57, 130.19, 133.07, 137.67, 141.53, 145.43, 147.17. IR (KBr) ν_{max} 1117, 1499, 1593 cm^{-1}.

5-(4-Chlorophenyl)-1,3-Diphenyl-2-Pyrazoline (3d)

^{1}H- NMR ($CDCl_3$): δ 3.04 (dd, J = 7.4, 17.6 Hz, 1H), 3.77 (dd, J = 11.6, 17.6 Hz, 1H), 5.67 (dd, J = 7.4, 11.6 Hz, 1H), 6.71-7.64 (m, 14H); Anal. Calcd. for $C_{21}H_{17}ClN_2$: C, 75.78; H, 5.15; N, 8.41. Found: C, 75.69; H; 5.10; N, 8.49%. ^{13}CNMR: 43.4, 63.8, 113.4, 119.4, 125.7, 127.3, 128.5, 128.7, 128.9, 129.3, 129.9, 132.5, 133.3, 141.1, 144.6, 146.7.

5-(3-Chlorophenyl)-1,3-Diphenyl-2-Pyrazoline (3e)

^{1}H NMR ($CDCl_3$): δ3.08 (dd, J=6.8, 17.0 Hz, 1H), 3.43 (dd, J=12.2, 17.2 Hz, 1H), 5.63 (dd, J=6.9, 12.4 Hz, 1H) 6.85-7.81 (m, 14H) ppm. Anal. calcd. for $C_{21}H_{17}N_2Cl$: C 85.85, H 5.72, N 9.43; found C 85.79, H 5.70, N 9.41. ^{13}C NMR: 42.37, 61.54, 113.58, 119.60, 124.44, 127.79, 128.07, 128.92, 129.18, 129.48, 130.67, 132.53, 133.04, 135.04, 139.67, 144.84, 147.53. IR (KBr) ν_{max} 1127, 1501, 1593 cm^{-1}.

5-(2-Chlorophenyl)-1,3-Diphenyl-2-Pyrazoline (3f)

^{1}H NMR ($CDCl_3$): δ3.06 (dd, J = 4.8, 17.6 Hz, 1H), 3.96 (dd, J =11.2, 17.7 Hz, 1H), 5.64 (dd, J = 4.7, 11.0 Hz, 1H), 6.76-7.74 (m, 14H); Anal. Calcd. for $C_{21}H_{17}ClN_2$: C, 75.78; H, 5.15; N, 8.41. Found: C, 75.83; H, 5.23; N, 8.38%.^{13}C NMR (δ): 41.9, 61.5, 113.3, 119.2, 125.9, 127.5, 127.9, 128.3, 128.5, 128.8, 129.3. 129.8, 131.4, 132.2, 139.5, 144.6, 147.4.

5-(2,4-Dichlorophenyl)-1,3-Diphenyl-2-Pyrazoline (3g)

^{1}H NMR ($CDCl_3$): δ3.02 (dd, J = 6.6, 17.6 Hz, 1H), 3.97 (dd, J =12.5, 17.5 Hz, 1H), 5.59 (dd, J = 6.6, 12.2 Hz, 1H), 6.69-7.71 (m, 13H); Anal. Calcd. for $C_{21}H_{16}Cl_2N_2$: C, 68.67; H, 4.39; N, 7.62. Found: C, 68.73; H, 4.39; N, 7.71%. ^{13}CNMR (δ): 41.5, 60.9, 113.5, 119.5, 124.3, 125.6, 127.4, 127.7, 128.6, 128.5, 128.5, 129.2, 129.5, 132.1, 133.9, 137.7, 144.4, 147.5.

5-(3-Bromophenyl)-1,3-Diphenyl-2-Pyrazoline (3h)

^{1}H NMR ($CDCl_3$): δ3.08 (dd, J=7.1, 17.0 Hz, 1H), 3.35 (dd, J=12.1, 16.9 Hz, 1H), 5.68 (dd, J=6.9, 12.7 Hz, 1H) 6.80-7.75 (m, 14H) ppm. Anal. calcd. for $C_{21}H_{17}N_2Br$: C 85.85, H 5.72, N 9.43; found C 85.78, H 5.69, N 9.43. ^{13}C NMR: 42.35, 60.47, 113.35, 119.50, 124.23, 127.94, 128.05, 129.06, 129.16, 129.35, 130.59, 132.41, 133.18, 139.66, 145.25, 147.14. IR (KBr) ν_{max} 1126, 1502, 1598 cm^{-1}.

5-(4-Methoxyphenyl)-1,3-Diphenyl-2-Pyrazoline (3i)

^{1}H NMR ($CDCl_3$): δ3.12 (dd, J=7.1, 17.1 Hz, 1H), 3.82 (s, 3H, OCH_3), 3.87 (dd, J=12.1, 16.9 Hz, 1H), 5.24 (dd, J=7.2, 12 Hz, 1H) 6.75-7.85 (m, 14H) ppm. Anal. calcd. for $C_{22}H_{20}N_2O$: C 84.62, H 6.41, N 8.97; found C 84.56, H 6.40, N 8.93. ^{13}C NMR: 44.08, 55.64, 64.14, 113.72, 114.46, 119.54, 126.42, 127.91, 128.47, 128.89, 129.19, 130.56, 133.21, 135.03, 145.34, 147.17. FTIR (KBr) ν_{max} 1120, 1261, 1512, 1597 cm^{-1}.

3-(4-Chlorophenyl)-1,5-Diphenyl-2-Pyrazoline (3j)

^{1}H NMR (DMSO): δ3.15 (dd, J=7.1, 17.0 Hz, 1H), 3.87 (dd, J=12.2, 17.1 Hz, 1H), 5.33 (dd, J=7.3, 12.4 Hz, 1H)

6.83-7.67 (m, 14H) ppm. Anal. calcd. for $C_{21}H_{17}N_2Cl$: C 84.85, H 5.72, N 9.43; found C 84.81, H 5.77, N 9.47. ^{13}C NMR: 42.39, 61.31, 113.53, 117.26, 126.83, 126.94, 128.64, 129.16, 129.39, 130.55, 132.17, 132.19, 136.05, 139.61, 143.73, 147.39. IR (KBr) ν_{max} 1121, 1509, 1599 cm^{-1}.

CONCLUSIONS

In conclusion, we have developed an efficient strategy for the synthesis of 1,3,5-triaryl -2-pyrazoline using $H_3PW_{12}O_{40}$, as an eco-friendly, inexpensive and efficient catalyst. The advantages of this catalytic system is short reaction times, high product yields, non-toxicity of the catalysts, simple and clean work-up of the desired products.

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