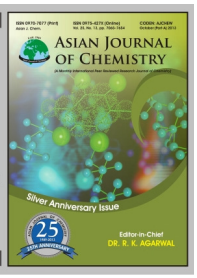
Asian Journal of Chemistry; Vol. 25, No. 13 (2013), 7290-7292

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2013.14550



# Tungstophosphoric Acid-Catalyzed Synthesis of Pyrazolones in Water

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(*Received*: 10 September 2012; *Accepted*: 24 June 2013) AJC-13693

A convenient and efficient method for the synthesis of pyrazolones *via* condensation of hydrazine derivatives with β-keto esters in water catalyzed by tungstophosphoric acid is described. It eliminates the need to dry solvents and substrates before use and the products are easily isolated with high yields.

**Key Words: Pyrazolones, Edaravone, Tungstophosphoric acid.**

## INTRODUCTION

Pyrazolones are an important class of heterocyclic compounds with a broad spectrum of biological activities such as antioxidant, inhibiting HIV-1 integrase, inhibiting TGFβR1 kinase, inhibiting SARS-coronavirus protease and antibacterial[1]. Among them, a well-known pyrazolone derivative *i.e.*, 3-methyl-1-phenyl-2-pyrazolin-5-one (edaravone), has been used in clinical as a commercial drug for brain ischemia and myocardial ischemia. Additionally, the importance of pyrazolone derivatives has also been accompanied by an increasing application in industrial preparation of herbicides[2], liquid crystals and dyes[3]. Therefore, the investigation of the synthetic chemistry of pyrazolones has continued to receive significant attention.

The traditional approach for the synthesis of pyrazolones is mainly to condense β-ketoesters with hydrazine in absolute ethanol or acetic acid. In 1987, Katrizky studied the mechanism of this reaction and it seemed to remain the standard method of pyrazolone synthesis[4]. In recent years, a number of alternative methods have been documented in the literature, including solid-phase synthesis[5], a two-step reaction of benzoyl hydrazones with silyl enolates in the presence of catalytic amounts of $Sc(OTf)_3$[6], microwave irradiation techniques[7] and ultrasound mediated synthesis[8]. In spite of their respective advantages, these methods suffered from several disadvantages such as expensive transition metal catalysts, difficult workup or product isolation. A new strategy should be explored for the synthesis of this important heterocyclic scaffold.

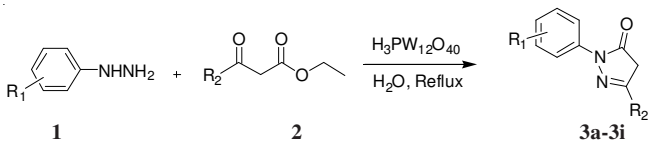
In the last decade, the use of water as a reaction solvent has continued to attract considerable interest in synthetic organic chemistry. As compared with traditional solvent, water is uniquely advantageous[9]. It is environmentally benign, non-flammable, liquid over a wide temperature range and possesses a high heat capacity making it inherently safe. Besides eliminating the need to dry solvents and substrates before use, they often bring out peculiar reactivities that are not observed under anhydrous conditions. To our best of knowledge, none has been reported to synthesize pyrazolones using water as a solvent. Tungstophosphoric acid is a kind of heteropoly acids, which has been used widely as catalysts in many reactions owing to their high acid strength, thermal stabilities and environmentally benign[10]. Herein, we report a convenient and efficient synthesis of pyrazolones in water using tungstophosphoric acid as a catalyst.

## EXPERIMENTAL

All melting points were determined on a Mel-TEMP II melting point apparatus which was uncorrected. IR spectra were recorded on a Bruker VERTEX 70 instruments. Proton magnetic resonance spectra were recorded on a Bruker AV400 instrument. The spectra were recorded in $CDCl_3$ or DMSO-$d_6$ and chemical shifts are reported in parts per million (ppm) down field from tetramethyl silane as the internal standard. Mass spectra were recorded on an Agilent 1100 LC/MSD Trap.

**General procedure:** Tungstophosphoric acid (1 % mol) was dissolved in 40 mL water and then phenylhydrazine derivative (3 mmol) was added under stirring. To the mixture was slowly added β-ketoester (3 mmol) over a period of 20 min at room temperature. The mixture was further heated under reflux for 3-6 h. The progress of the reaction was monitored by TLC. After completion of the reactions, the mixture was cooled to room temperature and solid was filtered off and washed with $H_2O$ (40 mL) and the crude products were dried. The crude products were purified by recrystallization from

ethanol or chromatograph on silica gel to give the product as a yellow powder (**Scheme-I**). The spectral data of some of the representative compounds are given below:




**1** **2** **3a-3i**

$R_1$ = H, 4-Cl, 4-F, 4-$CH_3O$, 2,4-dinitro, 3,4-dichloro. $R_2$ = $CH_3$, Ph

**Scheme-I**

**1-Phenyl-3-methyl-5-pyrazolone (3a):** $^1$H NMR ($CDCl_3$) δ: 2.21 (s, 3H), 3.47 (s, 2H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.90 (d, *J* = 7.8 Hz, 2H); IR (KBr, $cm^{-1}$) δ: 2430, 1594, 1532; ESI-MS: 175[M + H]$^+$.

**1-Phenyl-3-propyl-5-pyrazolone (3b):** $^1$H NMR ($CDCl_3$) δ:1.07 (t, *J* = 7.6 Hz, 3H), 1.67-1.77 (m, 2H), 2.50 (t, *J* = 7.5 Hz, 2H), 3.43 (s, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.91 (d, *J* = 7.7 Hz, 2H); IR (KBr, $cm^{-1}$) δ: 2928, 1593, 1541; ESI-MS: 203[M + H]$^+$.

**1,3-Diphenyl-5-pyrazolone (3c):** $^1$H NMR ($CDCl_3$) δ: 3.84 (s, 2H), 7.22 (t, *J* = 6.8 Hz, 1H), 7.48-7.41 (m, 5H), 7.78-7.74 (m, 2H), 8.18 (d, *J* = 6.8 Hz, 2H); IR (KBr, $cm^{-1}$) δ: 2965, 1705, 1593; ESI-MS: 237[M + H]$^+$.

**1-Phenyl-3-(trifluorometyl)-5-pyrazolone (3d):** $^1$H NMR ($CDCl_3$) δ: 3.71 (s, 2H), 7.52-7.36 (m, 3H), 7.66 (d, *J* = 7.8 Hz, 2H); IR (KBr, $cm^{-1}$) δ: 2720, 1758, 1599; ESI-MS: 229 [M + H]$^+$.

**1-(4-Chlorophenyl)-3-methyl-5-pyrazolone (3e):** $^1$H NMR ($CDCl_3$) δ: 2.20 (s, 3H), 3.44 (s, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.85 (d, *J* = 8.8 Hz, 2H); IR (KBr, $cm^{-1}$) δ: 2441, 1596, 1548; ESI-MS: 209 [M + H]$^+$.

**3-Phenyl-1-(4-fluorophenyl)-5-pyrazolone (3f):** $^1$H NMR ($CDCl_3$) δ: 3.88 (s, 2H), 7.13-7.16 (m, 2H), 7.49-7.51 (m, 3H), 7.78-7.80 (m, 2H), 7.96-7.99 (m, 2H); IR (KBr, $cm^{-1}$) δ: 1713, 1596, 1532; ESI-MS: 255 [M + H]$^+$.

**3-Methyl-1-(4-methoxyphenyl)-5-pyrazolone (3g):** After the reaction completed, the mixture was cooled to room temperature and solid was filtered off, which was dissolved in $Et_2O$, than washed with saturated aqueous $NaHCO_3$ and water and dried over $Na_2SO_4$. Filtration and concentration *in vacuo* and purification by silica gel flash chromatography (AcOEt/*n*-hexane = 1/1) gave a yellow solid. The solid was recrystallized from ethanol and collected by filtration to give a yellow solid.

$^1$H NMR ($CDCl_3$) δ: 2.19 (3H, s), 3.41 (2H, s), 3.81 (3H, s), 6.92 (2H, d, *J* = 8.5 Hz), 7.72 (2H, d, *J* = 8.3 Hz); IR (KBr, $cm^{-1}$) δ: 2925, 1590, 1542; ESI-MS: 205 [M + H]$^+$.

**1-(2,4-Dinitrophenyl)-3-methyl-5-pyrazolone (3h):** $^1$H NMR (DMSO-$d_6$) δ: 2.19 (s, 3H), 3.61 (s, 2H), 7.86 (d, *J* = 7.6 Hz, 1H), 8.92 (d, *J* = 3.2 Hz, H), 8.39-8.45 (m, 1H), 10.85 (br, s, 1H, OH); IR (KBr, $cm^{-1}$) δ: 2927, 1726, 1620; ESI-MS: 265 [M + H]$^+$.

**3-Phenyl-1-(3, 4-dichlorophenyl)- 5-pyrazolone (3i):** $^1$H NMR ($CDCl_3$) δ: 3.89 (s, 2H), 7.49-7.50 (m, 4H), 7.79-7.81 (m, 2H), 7.95-7.98 (m, 1H), 8.20 (m, 1H); IR (KBr, $cm^{-1}$) δ: 1709, 1624, 1547; ESI-MS: 305[M + H]$^+$.

## RESULTS AND DISCUSSION

We firstly chose the synthesis of edaravone by condensation of phenylhydrazine with ethyl acetoacetate in water as a suitable model to optimize conditions and to compare results with those from traditional method. The results are shown in Table-1. In the traditional method, after TLC indicated the completion of reaction, the solvent of ethanol was evaporated under reduced pressure and a reddish brown oil was obtained. It took a long time for the oil to solidify, the solid was filtrated and recrystallized in ethanol to give edaravone in 65 % yield. The solvent was replaced with water, after the reaction completed and the mixture was cooled to room temperature, a solid was precipitated immediately and which was dried and recrystallized in ethanol to give edaravone. The yield was related with the amount of tungstophosphoric acid, when 1 % mol of tungstophosphoric acid was used, the yield was the highest 78 %. It is obvious that the yield was much higher and workup was much easier when the reaction was carried out in water catalyzed by tungstophosphoric acid as compared with traditional approach.

TABLE-1
SYNTHESIS OF EDARAVONE UNDER DIFFERENT CONDITIONS

| Entry | Solvent | Catalyst | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | $C_2H_5OH$ | – | 4 | 65 |
| 2 | $H_2O$ | 0.5 | 5 | 70 |
| 3 | $H_2O$ | 1.0 | 3 | 78 |
| 4 | $H_2O$ | 1.5 | 3 | 72 |
| 5 | $H_2O$ | 2.0 | 3 | 62 |

In order to extend the scope of this procedure, several examples illustrating this method for the synthesis of pyrazolones were studied. The results are summarized in Table-2. The electronic and steric nature of substituents on the aromatic ring of phenylhydrazine or ethyl acetoacetate showed strongly obvious effects in the yields under this reaction conditions. The replacements of $CH_3$ of ethyl aceto-

TABLE-2
SYNTHESIS OF PYRAZOLONES **3a-3i**

| Compound | $R_1$ | $R_2$ | Time (h) | m.p. (ºC) | Yield (%) |
|---|---|---|---|---|---|
| **3a** | H | $CH_3$ | 3 | 125-127 (128-129[11a]) | 78 |
| **3b** | H | *n*-$C_3H_7$ | 4 | 109-111 (110[8]) | 74 |
| **3c** | H | Ph | 4 | 137-139 (136-138[11b]) | 68 |
| **3d** | H | $CF_3$ | 3 | 193-195 (195-196[11b]) | 81 |
| **3e** | *p*-Cl | $CH_3$ | 3 | 170-172 (173-174[11b]) | 65 |
| **3f** | *p*-F | Ph | 3 | 154-156 (158-160[1d]) | 70 |
| **3g** | *p*-$CH_3O$ | $CH_3$ | 5 | 124-126 (127-128[11b]) | 48 |
| **3h** | 2,4-Dinitro | $CH_3$ | 2 | 79-81 (81[11c]) | 92 |
| **3i** | 3,4-Dicloro | Ph | 3 | 137-139 (139-141[1d]) | 75 |

acetate with more steric Ph and *n*-$C_3H_7$ group were associated with lower yields, while phenylhydrazines with electron-donating substituent *p*-$CH_3O$ and strong electron-withdrawing nitro group resulted, respectively in a more lower and higher yield.

## Conclusion

We herein report a convenient method for the synthesis of pyrazolones *via* condensation of hydrazine derivatives with β-keto esters in water catalyzed by tungstophosphoric acid. It eliminates the need to dry solvents and substrates before use and the products are easily isolated with high yields.

## ACKNOWLEDGEMENTS

The authors thank to Department of Education of Hubei Province (Q20111112) for the financial support.

## REFERENCES

1. (a) T. Chen, R. Benmohamed and J. Kim, *J. Med. Chem*., **55**, 515 (2012); (b) V. Hadia, Y.H. Koha and T.W. Sanchez, *Bioorg. Med. Chem. Lett*., **20**, 6854 (2010); (c) K. Guckian, M.B. Carter, Edward and Y.S. Lin, *Bioorg. Med. Chem. Lett.*, **20**, 326 (2010); (d) R. Ramajayam, K.P. Tan and H.G. Liu, *Bioorg. Med. Chem*., **18**, 7849 (2010); (e) D. Castagnolo, F. Manetti and M. Radi, *Bioorg. Med. Chem*., **17**, 5716 (2009).
2. (a) H.S. Dai, H. Shi and L. Zhang, *Chin. J. Org. Chem*., **32**, 1060 (2012); (b) Y.F. Sun, Y.Q. Li, Y. Ling, H.L. Yu, S.X. Yang and X.L. Yang, *Chin. J. Org. Chem*., **31**, 1425 (2011).
3. (a) Y.L. Zhao, D.J. Zhou and G.Q. Yao, *Langmuir*, **13**, 4060 (1997); (b) K. Binnemans and G.W. Christiane, *Chem. Rev*., **102**, 2303 (2002); (c) A. Keiichi, O. Shigeru and I. Yoshio, US Patent 4833246 (1989).
4. A.R. Katrizky, P. Barczynski and D.L. Ostercamp, *J. Chem. Soc. Perkin Trans. II*, 969 (1987).
5. L.F. Tietze, H. Evers, T. Hippe, A. Steinmetz and E. Topken, *Eur. J. Org. Chem*., **9**, 1631 (2001).
6. (a) S. Kobayashi, T. Furuta, K. Sugita and H. Oyamada, *Synlett*, 1019 (1998); (b) H. Oyamada and S. Kobayashi, *Synlett*, 249 ((1998)); (c) S. Kobayashi, T. Furuta, K. Sugita, O. Okitsu and H. Oyamada, *Tetrahedron Lett*., **40**, 1341 (1999).
7. (a) M.M. Mojtahedi, M.R. Jalali, M.S. Abaee and M. Bolourtchian, *Hetrocycl. Commun*., **12**, 225 (2006); (b) M.M. Mojtahedi, M.R. Jalali and M. Bolourtchian, *Synth. Commun*., **36**, 51 (2006); (c) D.B. Thorat, R.V. Antre, R.J. Oswal, S.S. Kshirsagar and S.S. Jangam, *Asian J. Chem*., **24**, 2057 (2012).
8. M.M. Mojtahedi, M. Javadpour and M.S. Abaee, *Ultrasonics Sonochem.*, **15**, 828 (2008).
9. (a) R.N. Butler and A.G. Coyne, *Chem. Rev*., **110**, 6302 (2010); (b) A. Chanda and V.V. Fokin, *Chem. Rev*., **109**, 725 (2009); (c) C.I. Herreri´as, X. Yao, Z. Li and C.J. Li, *Chem. Rev*., **107**, 2546 (2007).
10. (a) H. Firouzabadi, N. Iranpoor, F. Nowrouzi and K. Amani, *J. Chem. Soc. Perkin Trans. I*, 2601 (2002); (b) N.S. Babu, K.M. Reddy, P.S. Sai Prasad, I. Suryanarayana and N. Lingaiah, *Tetrahedron Lett.*, **48**, 7642 (2007); (c) B. Karmakar and J. Banerji, *Tetrahedron Lett*., **51**, 3855 (2010).
11. (a) N. Hiroyoshi, W. Toshiaki and Y. Satoski, US4857542 (1989); (b) H. Nakagawa, R. Ohyama, A. Kimata, T. Suzuki and N. Miyata, *Bioorg. Med. Chem. Lett.*, **16**, 5939 (2006); (c) R. Khan, M.I. Uddin, M.S. Alam, M.M. Hossain and M.R. Islam, *Bangladesh J. Pharmacol*., **3**, 27 (2008).