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Synthesis of 4,4'-Arylmethylene-*bis*(3-methyl-5-pyrazolones) using Diammonium Hydrogen Phosphate as an Efficient and Versatile Catalyst in Aqueous Media

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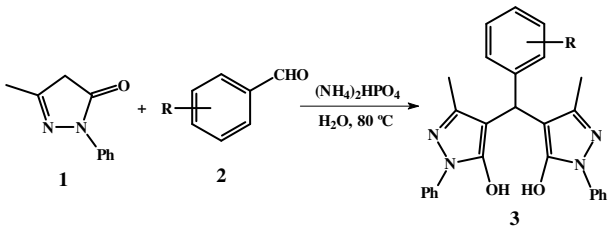
A simple and efficient synthesis of 4,4'-arylmethylene-*bis*(3-methyl-5- pyrazolones) has been accomplished by the tandem Knoevenagel-Michael reaction of arylaldehydes with two equivalents of 5-methyl-2-phenyl-2,4-dihydro-3*H*- pyrazol-3-one using diammonium hydrogen phosphate as an efficient and versatile catalyst in aqueous media.

Key Words: 4,4'-Arylmethylene-*bis*(3-methyl-5-pyrazolones), Diammonium hydrogen phosphate, 5-Methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one, Knoevenagel reaction, Michael reaction.

INTRODUCTION

4,4'-Arylmethylene-*bis*(3-methyl-5-pyrazolones) are of considerable interest as they possess a wide range of biological properties, being used as fungicides[1], pesticides[2], insecticides[2] and as the chelating and extracting reagents for different metal ions[3]. In addition, they are also useful synthetic intermediates for various pharmaceuticals and active compounds[4]. The most common methods for synthesis of 4,4'-arylmethylene-*bis*(3-methyl-5-pyrazolones) are the tandem Knoevenagel-Michael reaction of arylaldehydes with two equivalents of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one performed under a variety of reaction conditions[5]. However, most of these procedures have significant drawbacks such as long reaction time, low yields, harsh reaction conditions, tedious work-up procedures and use of environmentally toxic reagents or media. Thus, there is still need of a simple and general procedure for synthesis of 4,4'-arylmethylene-*bis*(3-methyl-5-pyrazolones) under mild conditions.

Organic reactions in water have become an important research area. Many reactions have been accomplished in aqueous medium[6]. Water has therefore become an attractive medium for many organic reactions, not only for the advantages concerning the avoidance of expensive drying reactants, catalysts and solvents, but also for some unique reactivity and selectivity. Diammonium hydrogen phosphate [$(NH_4)_2HPO_4$] is an inexpensive, non-toxic and commercially available compound that can be used in the laboratory without special precautions. There are a few reports regarding the application of $(NH_4)_2HPO_4$ in the preparation of organic compounds[7], for example, in the synthesis of pyrano[2,3-d]pyrimidinones, tetrahydrobenzo-[b]pyrans, 1,8-dioxo-octahydroxanthenes, 3,4-dihydropyrano-[c]chromenes. We now report a highly efficient procedure for the preparation of 4,4'-arylmethylene-*bis*(3-methyl-5-pyrazolones) *via* a one-pot the tandem Knoevenagel-Michael reaction using $(NH_4)_2HPO_4$ as an efficient and versatile catalyst in aqueous media (**Scheme-I**).



Scheme-I

EXPERIMENTAL

NMR spectra were determined on Bruker AV-400 spectrometer in DMSO-d_6 and were expressed in δ values relative to tetramethylsilane, coupling constants (*J*) were measured in Hz; Elemental analysis were recorded on a Vario ELIII elemental analyzer, melting points were determined on a Mel-Temp capillary tube apparatus and were uncorrected; commercially available reagents were used throughout without further purification unless otherwise stated. Commercially available reagents were used throughout without further purification unless otherwise stated.

General procedure for the preparation of 1: To a mixture of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2 mmol), aldehyde (1 mmol) and H_2O (10 mL), $(NH_4)_2HPO_4$ (0.1 mmol) was added. The mixture was stirred at 80 ºC for an appropriate time (Table-1). After completion of the reaction (TLC), the resulting solid was collected by filtration and recrystallized from ethanol.

TABLE-1
SYNTHESIS OF 4,4'-ARYLMETHYLENE-*BIS*(3-METHYL-5-PYRAZOLONES)

Entry	R	Time (h)	Product	Yield (%)
1	4-H	2	**3a**	83
2	4-NO_2	2	**3b**	90
3	4-MeO	2	**3c**	82
4	2-Cl	1	**3d**	92
5	3-NO_2	1.5	**3e**	88
6	4-$N(Me)_2$	1.5	**4**[a]	93
7	4-F	2	**3f**	87
8	2,4-Cl_2	1	**3g**	90
9	3,4-Br_2	1	**3h**	93

[a]4-(4-(Dimethylamino)benzylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one

4,4'-(Phenylmethylene)*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (3a): A white solid, m.p. 169-171 °C (lit.[5c], m.p. 172-173 °C). IR (cm^{-1}): 3064, 2917, 1599, 1582, 1499, 1455, 1419, 1317, 1287, 1158, 1025, 838, 790, 757, 693. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.78-7.70 (m, 4H), 7.45-7.42 (m, 4H), 7.30-7.17 (m, 7H), 4.95 (s, 1H), 2.32 (s, 6H). Anal. calcd. (%) for $C_{27}H_{24}N_4O_2$: C, 74.29; H, 5.54; N, 12.84. found (%): C, 74.14; H, 5.48; N, 12.91.

4,4'-((4-Nitrophenyl)methylene)*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (3b): A yellowish solid, m.p. 220-222 °C (lit.[5c], m.p. 229-231 °C). IR (cm^{-1}): 3066, 2920, 2607, 1601, 1586, 1517, 1502, 1414, 1347, 1190, 1110, 848, 757, 706, 693. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.18-8.16 (m, 2H), 7.71-7.69 (m, 4H), 7.52-7.42 (m, 6H), 7.27-7.23 (m, 2H), 5.12 (s, 1H), 2.34 (s, 6H). Anal. calcd. (%) for $C_{27}H_{23}N_5O_4$: C, 67.35; H, 4.81; N, 14.54. found (%): C, 67.09; H, 4.71; N, 14.58.

4,4'-((4-Methoxyphenyl)methylene)*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ol (3c): A white solid, m.p. 150-151 °C (lit.5c, m.p.149-150°C). IR (cm^{-1}): 3467, 2918, 2610, 1602, 1581, 1504, 1459, 1408, 1374, 1249, 1181, 1109, 1035, 912, 886, 798, 754, 692. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.91 (d, 4H, *J* = 8.2 Hz), 7.78-7.69 (m, 4H), 7.45-7.14 (m, 4H), 6.83 (d, 2H, *J* = 8.4 Hz), 4.89 (s, 1H), 3.70 (s, 3H), 2.14 (s, 6H). Anal. calcd. (%) for $C_{28}H_{26}N_4O_3$: C, 72.09; H, 5.62; N, 12.01. found (%): C, 72.15; H, 5.45; N, 11.98.

4,4'-((2-Chlorophenyl)methylene)*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (3d): A white solid, m.p. 235-236 °C (lit.[5c], m.p. 232-233 °C). IR (cm^{-1}): 3066, 2914, 2769, 1615, 1562, 1500, 1458, 1401, 1369, 1301, 1215, 1129, 1086, 1031, 900, 838, 791, 753, 691. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.89-7.81 (m, 1H), 7.69 (d, 4H, *J* = 7.6 Hz), 7.45-7.38 (m, 5H), 7.32-7.20 (m, 4H), 5.14 (s, 1H), 2.35 (s, 6H). Anal. calcd. (%) for $C_{27}H_{23}N_4O_2Cl$: C, 68.86; H, 4.92; N, 11.90. found (%): C, 69.05; H, 4.82; N, 11.85.

4,4'-((3-Nitrophenyl)methylene)*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (3e): A yellowish solid, m.p. 146-148 °C (lit.[5b], m.p.149-150 °C). IR (cm^{-1}): 3068, 2921, 1734, 1600, 1579, 1528, 1500, 1415, 1349, 903, 833, 756, 733, 693. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.09-8.07 (m, 2H), 7.75-7.58 (m, 6H), 7.46-7.42 (m, 4H), 7.27-7.23 (m, 2H), 5.14 (s, 1H), 2.35 (s, 6H). Anal. calcd. (%) for $C_{27}H_{23}N_5O_4$: C, 67.35; H, 4.81; N, 14.54. found (%): C, 67.26; H, 4.79; N, 14.43.

4,4'-((4-Fluorophenyl)methylene)*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (3f): A white solid, m.p.190-192 °C. IR (cm^{-1}): 3068, 2921, 1600, 1504, 1415, 1294, 1223, 1158, 805, 753, 692. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.70 (d, 4H, *J* = 8.0 Hz), 7.69-7.42 (m, 4H), 7.29-7.23 (m, 4H), 7.12-7.08 (m, 2H), 4.96 (s, 1H), 2.32 (s, 6H). Anal. calcd. (%) for $C_{27}H_{23}N_4O_2F$: C, 71.35; H, 5.10; N, 12.33. found (%): C, 71.38; H, 5.26; N, 12.17.

4,4'-((2,4-Dichlorophenyl)methylene)*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (3g): A white solid, m.p. 225-226 °C (lit.[5c], m.p. 229-230 °C). IR (cm^{-1}): 3068, 2925, 1600, 1506, 1412, 1291, 1103, 810, 750, 689. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.75-7.68 (m, 5H), 7.55-7.40 (m, 6H), 7.27-7.23 (m, 2H), 5.08 (s, 1H), 2.27 (s, 6H). Anal. calcd. (%) for $C_{27}H_{22}N_4O_2Cl_2$: C, 64.17; H, 4.39; N, 11.09. found (%): C, 64.09; H, 4.20; N, 11.01.

4,4'-((3,4-Dibromophenyl)methylene)*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (3h): A white solid, m.p. 230-231 °C. IR (cm^{-1}): 3068, 2917, 2605, 1601, 1578, 1499, 1411, 1292, 1191, 1029, 907, 863, 808, 751, 690. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.69 (d, 4H, *J* = 8.0 Hz), 7.55 (d, 1H, *J* = 8.4 Hz), 7.46-7.41 (m, 5H), 7.27-7.23 (m, 3H), 5.01 (s, 1H), 2.32 (s, 6H). Anal. calcd. (%) for $C_{27}H_{22}N_4O_2Br_2$: C, 54.57; H, 3.73; N, 9.43. found (%): C, 54.35; H, 3.59; N, 9.30.

4-(4-(Dimethylamino)benzylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4): A red solid, m.p. 192-193 °C (lit.[5d], m.p. 194-195 °C). IR (cm^{-1}): 1668, 1621, 1551, 1523, 1495, 1442, 1375, 1319, 1248, 1190, 1122, 1022, 995, 944, 851, 813, 766, 667. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.64 (d, 2H, *J* = 8.8 Hz), 7.96 (d, 1H, *J* = 7.6 Hz), 7.57 (s, 1H), 7.43-7.39 (m, 2H), 7.17-7.13 (m, 1H), 6.84 (d, 2H, *J* = 8.4 Hz), 3.12 (s, 6H), 2.29 (s, 6H). Anal. calcd. (%) for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. found (%): C, 74.56; H, 6.15; N, 13.55.

RESULTS AND DISCUSSION

Initially, to optimize the reaction temperature, the reaction of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**1**, 2 mmol), benzaldehyde (**2a**, 1 mmol) was studied in H_2O (10 mL) in the presence of 10 mol % $(NH_4)_2HPO_4$ at different temperatures. The results are summarized in Table-2. As shown in Table-2, the reaction at 80 °C proceeded in highest yield.

TABLE-2
TEMPERATURE OPTIMIZATION FOR THE SYNTHESIS OF 4,4'-(PHENYLMETHYLENE) *BIS*(3-METHYL-1-PHENYL-1*H*-PYRAZOL-5-OL)

Entry	Temp. (ºC)	Yield (%)
1	25	65
2	50	72
3	60	75
4	70	78
5	80	83
6	90	79
7	Reflux	80

To find the optimal solvent for this reaction, the synthesis of **3a** was carried out at 80 °C or refluxing temperature using EtOH, H_2O, CH_2Cl_2, DMF, CH_3CN as solvents, respectively. It is shown in Table-3 that the reactions with H_2O as solvent resulted in higher yield than other solvents. So H_2O was chosen as the best solvent of this reaction.

TABLE-3
SOLVENT OPTIMIZATION FOR THE SYNTHESIS OF 4,4'-(PHENYLMETHYLENE)*BIS*(3-METHYL-1-PHENYL-1*H*-PYRAZOL-5-OL)

Entry	Solvent	Temp. (ºC)	Yield (%)
1	EtOH	Reflux	62
2	H_2O	80	83
3	CH_2Cl_2,	Reflux	42
4	DMF	80	76
5	CH_3CN	80	72

To optimize the catalyst loading, 0, 5, 10, 15, 20 and 25 mol % of was tested, respectively. The results are summarized in Table-4. A 10 mol % loading of $(NH_4)_2HPO_4$ was sufficient to push the reaction forward and 5 mol % of $(NH_4)_2HPO_4$ was not enough. Higher amounts of $(NH_4)_2HPO_4$ did not lead to significant change in the reaction yields.

TABLE-4
AMOUNTS OF CATALYST OPTIMIZATION FOR THE SYNTHESIS OF 4,4'-(PHENYLMETHYLENE)*BIS*(3-METHYL-1-PHENYL-1*H*-PYRAZOL-5-OL)

Entry	$(NH_4)_2HPO_4$ (mol %)	Yield (%)
1	0	50
2	5	65
3	10	83
4	15	82
5	20	83
6	25	81

Based on the optimized reaction conditions, a range of 4,4'-arylmethylene-*bis*(3-methyl-5-pyrazolones) was synthesized by the reaction arylaldehydes with two equivalents of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one. The reaction proceeded at 80 ºC within 2 h in excellent yields after the addition of the cataylst $(NH_4)_2HPO_4$. In addition, we noticed also that arylaldehydes having an electron-withdrawing groups (entry 2, 4, 8, 9) gave high yields, whereas electron-donating group (entry 3, 6) gave lower yields. 4-(4-(dimethylamino)-benzylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one was product using 4-(dimethylamino)benzaldehyde in the reaction.

Conclusion

We have demonstrated a rapid and efficient $(NH_4)_2HPO_4$ catalyzed one-pot synthesis of 4,4'-arylmethylene-*bis*(3-methyl-5-pyrazolones) in aqueous media. The current methodology has the advantages of operational simplicity, neutral and mild reaction conditions, high to excellent yields of products, lack of toxicity and low costs.

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REFERENCES

1. D. Singh and D. Singh, *J. Indian Chem. Soc.*, **68**, 165 (1991).
2. M. Londershausen, *Pestic. Sci.*, **48**, 269 (1996).
3. (a) A.B. Uzoukwu, *Polyhedron*, **12**, 2719 (1993); (b) R.C. Maurya and R. Verma, *Indian J. Chem.*, **36A**, 596 (1997); (c) A.D. Garnovskii, A.I. Uraev and V.I. Minkin, *Arkivoc*, 29 (2004).
4. W.S. Hamama, *Synth. Commun.*, **31**, 1335 (2001).
5. (a) M.N. Elinson, A.S. Dorofeev, R.F. Nasybullin and G.I. Nikishin, *Synthesis*, 1933 (2008); (b) W. Wang, S.-X. Wang, X.-Y. Qin and J.-T. Li, *Synth. Commun.*, **35**, 1263 (2005); (c) D.-Q. Shi, J. Chen, N. Wu, Q.-Y. Zhuang and X.-S. Wang, *Chin. J. Org. Chem.*, **25**, 405 (2005); (d) Y.J. Bai, J. Lu, Z.-J. Wang, H.-Y. Gan and H.-R. Ma, *Chin. J. Org. Chem.*, **24**, 616 (2004).
6. (a) U.M. Lindstrom, *Chem. Rev.*, **102**, 2751 (2002); (b) B.N. Naidu and M.E. Sorenson, *Org. Lett.*, **7**, 1391 (2005); (c) N. Azizi, L. Torkiyan and M.R. Saidi, *Org. Lett.*, **8**, 2079 (2006); (d) L. Botella and C. Najera, *J. Org. Chem.*, **70**, 4360 (2005).
7. (a) S. Balalaie, S. Abdolmohammadi, H.R. Bijanzadeh and A.M. Amani, *Mol. Divers.*, **12**, 85 (2008); (b) S. Balalaie, M. Bararjanian, M. Sheikh-Ahmadi, S. Hekmat and P. Salehi, *Synth. Commun.*, **37**, 1097 (2007); (c) F. Darviche, S. Balalaie and F. Chadegani, *Synth. Commun.*, **37**, 1059 (2007); (d) S. Abdolmohammadi and S. Balalaie, *Tetrahedron Lett.*, **48**, 3299 (2007).