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RESEARCH LETTER

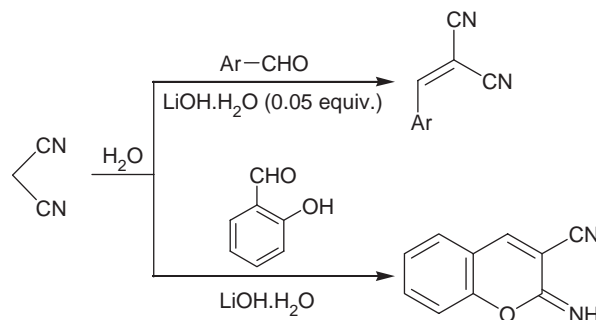
An eco-friendly procedure for the efficient synthesis of arylidenemalononitriles and 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) in aqueous media

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Commercially available lithium hydroxide monohydrate (LiOH·H₂O) was found to be a novel “dual activation” catalyst for Knoevenagel condensation between malononitrile (**1**) or 3-methyl 1-phenyl-1H-pyrazol-5-(4H)-one (**6**) with aromatic aldehydes **2a–e** leading to an efficient and easy synthesis of arylidenemalononitriles **3a–d** and 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) **7a–c** in short times. The reaction of aryl aldehydes with malononitrile afforded excellent yields after 1–6 min in aqueous media at room temperature. In case of 3-methyl-1-phenyl-1H-pyrazol-5-(4H)-one (**6**) and aromatic aldehydes afforded good yields after 60–75 min at 90°C.



Keywords: dual activation; lithium hydroxide monohydrate; Knoevenagel condensation; 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ols); arylidenemalononitrile

Introduction

The literature revealed that organic reactions under solvent-free (1), and aqueous (2), conditions have increasingly attracted chemists' interests, particularly from the view point of green chemistry (3). Generally, Knoevenagel reactions are carried out by the condensation of active methylene compounds with aldehydes in the presence of organic bases, or ammonium salts (4). Alternative protocols for Knoevenagel condensations catalyzed by Lewis acids such as TiCl₄ (5), ZnCl₂ (6), LiCl (7), and various heterogeneous solid bases sulfate-ion promoted Zirconia (8), clay (9), and layered double hydroxides (LDHs) (10), have been reported in literature. Recently, ionic liquids such as [hmim] PF₆ (11) have been proven to be an efficient catalyst for Knoevenagel condensation.

Furthermore, Bigi's group described the same reactions which could proceed efficiently in water (12). More recently, we found that aldehydes reacted with malononitrile efficiently in the absence of catalyst and solvent under microwave irradiation and thermal heating conditions (13). 4,4'-(Arylmethylene)bis(1H-pyrazol)-5-ols are applied as fungicides (14), pesticides (15), dyestuffs (16), and as the chelating and extracting reagents for different metal ions (17). The conventional chemical approach to 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) involves the successive Knoevenagel synthesis of the corresponding arylidene pyrazolones and its base-promoted Michael reaction and also one-pot tandem Knoevenagel–Michael reaction of arylaldehydes with two equivalents of 3-methyl-1-phenyl-1

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H-pyrazol-5(4*H*)-one (**6**) performed under a variety of reaction conditions (18). The first set of procedures utilizes the catalysis of the components with piperidine in ethanolic solution (19). The second set of methods involves the noncatalyzed tandem Knoevenagel–Michael reaction under neutral conditions in either ethanol (20) or benzene (21) solutions. Although it affords the corresponding (4,4-arylmethylene)*bis*(1*H*-pyrazol-5-ols) in reliable 70–90% yields, the reaction requires 3–12 h of initial reflux with a further 24 h under ambient temperature to go to completion. Finally, Wang et al. (22) reported its synthesis in water using sodium dodecyl sulphate as the surfactant catalyst over a 1-h period, but the process needs a temperature of 100°C. Further, Elinson et al. (23) utilized electro-catalytic procedure for its synthesis. However, most of the methods suffer from at least one limitation that may include moderate yields, long reaction times, harsh reaction conditions or tedious workup procedures (12). Recently, the use of LiOH·H₂O has received considerable attention as a cheap and easily available reagent in organic reactions. We have found that, it acts as a “dual activation” agent for chemoselective methyl ether (24) and methyl ester (25) formation providing an alternating method to the toxic diazo-methane protocol. Furthermore, it acts as “dual activation” catalyst for tandem cross aldol condensation between acyclic/cyclic ketones and aromatic, heteroaromatic/styryl/alkyl aldehydes (26). Herein, we report our study on the Knoevenagel condensations of aldehydes with malononitrile (**1**) or 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**6**) under aqueous conditions in the presence of LiOH·H₂O.

Result and discussion

This work was initiated with the reaction of 4-methoxybenzaldehyde with malononitrile in a variety concentration of LiOH·H₂O. Thus, malononitrile (**1**) (1 mmol) was treated with 4-methoxybenzaldehyde (**2**) (1 mmol) in the presence of LiOH·H₂O (5, 10, and 15 mmol%) in H₂O (10 mL) as shown in Table 1, we

Table 1. The reaction of 4-methoxybenzaldehyde with malononitrile in a variety concentrations of lithium hydroxide.

Entry	Concentration (mmol)	Yield	Time (min)
1	5	87	1.0
2	10	86.9	1.5
3	15	86.9	1.5

found that the reaction was accelerated by LiOH·H₂O (5 mmol) in 87% after 1 min (Figure 1).

Furthermore, the same reaction in the presence of NaOH, KOH, and piperidine under similar conditions was examined. As shown in Table 2; LiOH·H₂O produce good yield of **3b**. No Knoevenagel condensation was observed when **1** was treated with **2b** in the absence of LiOH·H₂O either in the presence or absence of solvent (Table 2) (Table 1).

The dual role of LiOH·H₂O, that is, generates the enolate from the malononitrile and activates the aldehyde carbonyl by coordination with Li⁺ is demonstrated in Figure 2. Proton abstraction from **1** by LiOH·H₂O (present in catalytic amount) generates the lithium enolate **I**. Coordination of the Li⁺ cation of **I** with the aldehyde carbonyl oxygen forms the six-membered cyclic transition state **II** and increases the electrophilicity of the aldehyde carbonyl group and makes it more susceptible to nucleophilic attack in an intramolecular fashion to form the iminolate anion **III**. The iminolate anion **III** subsequently abstracts the proton of **1** and generates the iminolate **I** to complete the catalytic cycle. The ol **IV** on dehydration results in the formation of arylidene-malononitrile **V** (Figures 2, 3) (Figure 1).

To check the generality of the catalytic system, malononitrile was treated with various aryl aldehydes under the catalytic influence of LiOH·H₂O (5 mol%, Table 3). Excellent results (76–94 yields) were obtained and the reactions were completed after 1–7 min. The reactions could be monitored visually and precipitated out in the reaction medium due to poor solubility in H₂O at room temperature. Thus, the formation of a yellow or light orange precipitate indicated completion of the reaction (Table 3; Figure 4).

The reaction of malononitrile (**1**) with salicylaldehyde (**4**) under the same condition afforded the corresponding iminocoumarin derivative **5** (Figure 5).

The synthesis of 4,4'-(arylmethylene)*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) **7a–d** involved the reaction of the electrophilic substitution reaction of

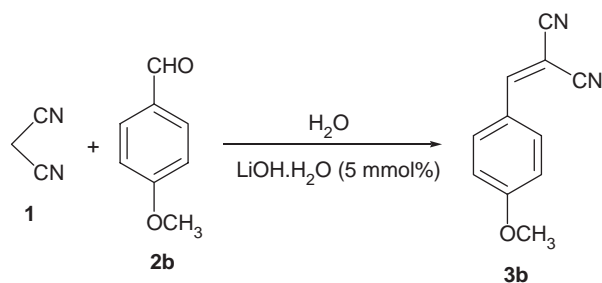


Figure 1. Synthesis of 2-(4-methoxybenzylidene)malononitrile (**3b**).

Table 2. The reaction of malononitrile (**1**) with 4-methoxybenzaldehyde (**2b**) in the presence and absence of different bases.

Entry	Base	Yield	Time (min)
4	LiOH·H ₂ O	87	1
5	NaOH	80.0	5
6	KOH	81.4	4
7	Piperidine	83.0	5
8	No base	—	—
9	No base, no solvent	—	—

3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**6**) with aryl aldehydes in water. As a test case, 4-methoxybenzaldehyde reacted with 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**6**) in water with different catalytic amounts of LiOH·H₂O and at different reaction temperatures in order to optimize the reaction conditions. Thus, 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**6**) (2 mmol) was treated with 4-methoxybenzaldehyde (**2b**) (1 mmol) in the presence of LiOH·H₂O (5, 10, and 15% mmol) in H₂O (10 mL) at room temperature and 90°C as shown in Table 1, we found that the reaction was accelerated by 10 mmol of LiOH·H₂O at 90°C. in 83.5% after 1 h (Table 4).

To show the generality and scope of this synthetic method, the electrophilic substitution reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**6**) with different aldehydes was studied in the presence of LiOH·H₂O in water, using optimized reaction conditions (Figures 3, 6; Table 5).

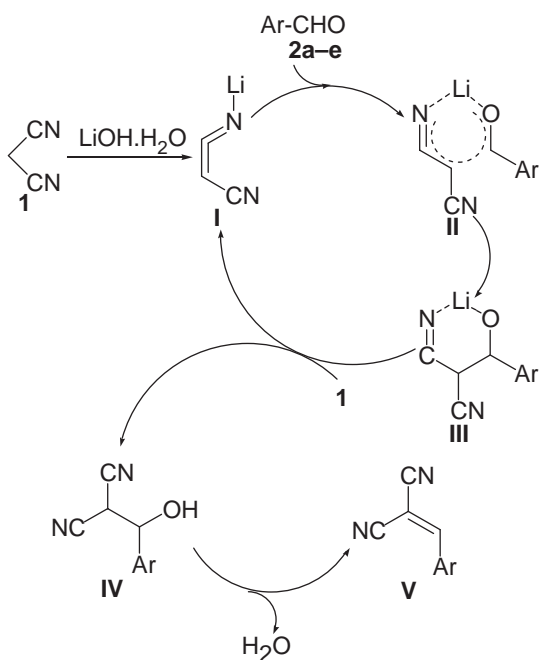


Figure 2. The dual role of LiOH·H₂O on the reaction of malononitrile with different aldehydes.

The possible mechanism for the synthesis of **7a–d** is representing in Figure 3. Proton abstraction from **6** by LiOH·H₂O (present in catalytic amount) generates the lithium enolate **VI**. Coordination of the Li⁺ cation **VI** with the aldehyde carbonyl oxygen forms the six-membered cyclic transition state **VII** and increases the electrophilicity of the aldehyde carbonyl group and makes it more susceptible to nucleophilic attack in an intramolecular fashion to form the aldolate anion **VIII**. The aldolate anion **VIII** subsequently abstracts the proton from **6** and generates the enolate **VI** to complete the catalytic cycle. The aldol **IX** on dehydration results in the formation of 4-arylidene-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one **X** which reacted with LiOH·H₂O to form the enolate **XI**, condensation with **VI** to form the corresponding *bis*-enolate anion **XII**, which subsequently abstracts proton from **6** and generate the lithium enolate **VI** to complete the catalytic cycle. The chemical structures of the newly synthesized compounds were characterized by IR (Infrared) and NMR (Nuclear Magnetic Resonance) spectral analysis (C.f. “Experimental” section).

Experimental

All melting points are recorded on Gallenkamp electric melting point apparatus and are uncorrected. The IR spectra ν (cm^{−1}) (KBr) were recorded on a Perkin Elmer Infrared Spectrophotometer Model 157. The ¹H NMR spectra were obtained on a JEOL Spectrophotometer at 500 MHz, using Tetramethylsilane (TMS) as an internal reference and DMSO-*d*₆ as solvent and were carried out in the National Research Centre, Dokki, Giza, Egypt. Elemental analyses (C, H, and N) were carried out at the Microanalytical Centre of Cairo University, Giza, Egypt.

Synthesis of 2-(substituted-methylene)malononitriles **3a–e** and 2-imino-2*H*-chromene-3-carbonitrile (**5**)

Malononitrile (**1**) (330.3 mg, 5 mmol) in water (10 mL) was treated with LiOH·H₂O (1.05 mg, 0.25 mmol) under magnetically stirred condition for 1 min at room temperature (25–30°C) followed by aromatic aldehyde namely; benzaldehyde (53.06 mg, 5 mmol), 4-methoxybenzaldehyde (68.08 mg, 5 mmol), 4-chlorobenzaldehyde (70.29 mg, 5 mmol), furfuraldehyde (48.04 mg, 5 mmol), 4-dimethylamino-benzaldehyde (74.6 mg, 5 mmol), or salicylaldehyde (61.06 mg, 5 mmol). The reaction mixture was stirred at room temperature for 1–7 min. After the completion of the reaction, a precipitate was formed and this served as indicator for monitoring the reaction visually. The

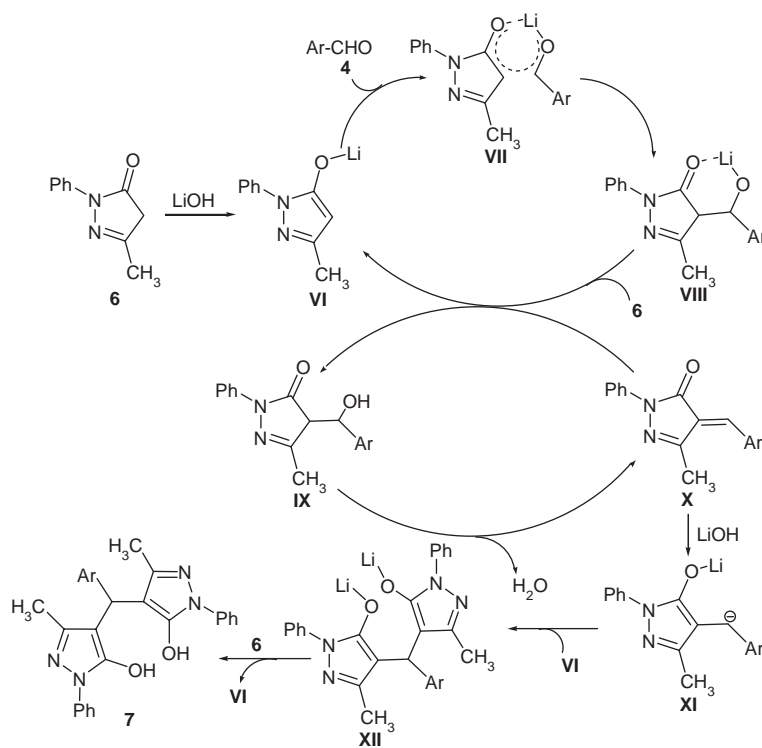


Figure 3. Dual activation role of LiOH·H₂O Knoevenagel condensation between a malononitrile and aldehydes.

formed precipitate was filtered and crystallized from ethanol to give **3a–e** and **5**, respectively.

2-Benzylidenemalononitrile (**3a**)

Yellowish white powder, mp 85°C [Lit. (27) 83°C]. IR (KBr) ν_{\max} : 2219 (CN), 1581 (C=C) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 7.58 (t, 2H, *J* = 8.45 Hz), 7.64 (t, 1H, *J* = 8.25), 7.90 (d, 2H, *J* = 8.4 Hz), 8.48 (s, 1H, CH=); ¹³C NMR (DMSO-*d*₆) δ 169.1, 134.6, 131.0, 130.7, 129.8, 113.6, 112.5, 82.6. Anal. Calc. for C₁₀H₆N₂ (154.17): C, 77.91; H, 3.92; N, 18.17. Found: C, 77.88; H, 3.87; N, 18.13.

2-(4-Methoxybenzylidene)malononitrile (**3b**)

Yellow crystals, mp 118°C [Lit. (6) 118–119°C]. IR (KBr) ν_{\max} : 2219 (CN), 1578 (C=C) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 3.82 (s, 3H), 7.14 (d, 2H, *J* = 9.28 Hz), 7.92 (d, 2H, *J* = 9.15 Hz), 8.33 (s, 1H, CH=); ¹³C

NMR (DMSO-*d*₆) δ 162.0, 158.8, 132.9, 124.1, 115.4, 114.0, 113.8, 78.9, 56.1. Anal. Calc. for C₁₁H₈N₂O (184.19): C, 71.73; H, 4.38; N, 15.21. Found: C, 71.74; H, 4.40; N, 15.24.

2-(4-Chlorobenzylidene)malononitrile (**3c**)

Yellowish white crystals, mp 167°C [Lit. (26), 165°C]. IR (KBr) ν_{\max} : 2221 (CN), 1583 (C=C) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 7.65 (d, 2H, *J* = 8.4 Hz); 7.89 (d, 2H, *J* = 8.4 Hz), 8.4 (s, 1H, CH=); ¹³C NMR (DMSO-*d*₆) δ 158.8, 141.6, 132.0, 130.1, 129.0, 113.8, 112.3, 83.0. Anal. Calc. for C₁₀H₅ClN₂ (188.61): C, 63.68; H, 2.67; N, 14.85. Found: C, 63.71; H, 2.65; N, 14.87.

2-(Furan-2-ylmethylene)malononitrile (**3d**)

Pale yellow solid, mp 70 [Lit. (28), 68–69°C]. IR (KBr) ν_{\max} : 2221 (CN), 1583 (C=C) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 6.87–6.88 (m, 1H, furyl), 7.41 (d, 1H, *J* = 3.05 Hz, furyl), 7.81 (d, 1H, *J* = 1.6 Hz, furyl),

Table 3. The reaction of malononitrile with different aldehydes with different reaction times and yield percent.

Entry	Ar	Yield	Time (min)
10	Phenyl	89	6
11	4-Methoxyphenyl	87	1
12	4-Chlorophenyl	94	3
13	2-Furyl	86	1
14	4- <i>N,N</i> -dimethylaminophenyl	92	1

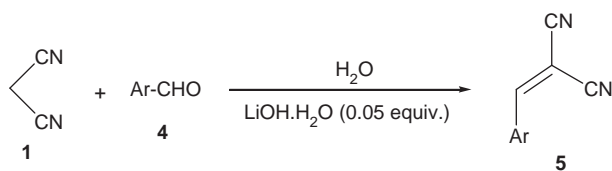


Figure 4. Synthesis of 2-(substituted-methylene)malononitriles.

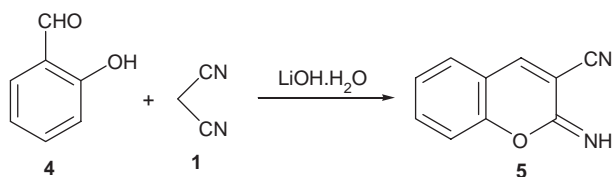


Figure 5. Synthesis of 2-imino-2H-chromene-3-carbonitrile (**5**) using $\text{LiOH} \cdot \text{H}_2\text{O}$.

8.22 (s, 1H, C=CH). Anal. Calc. for $\text{C}_8\text{H}_4\text{N}_2\text{O}$ (144.13): C, 66.67; H, 2.80; N, 19.44. Found: C, 66.71; H, 2.78; N, 19.41.

2-(4-(Dimethylamino)benzylidene)malononitrile (3e)
Red crystals, mp 179°C [Lit. (29), 180°C]. IR (KBr) ν_{max} . 2208 (CN), 1565 (C=C) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 3.04 (brs, 6H, 2CH₃), 7.79 (d, 2H, $J = 9.2$ Hz), 7.91 (d, 2H, $J = 9.15$ Hz), 8.05 (s, 1H, CH =). Anal. Calc. for $\text{C}_{12}\text{H}_{11}\text{N}_3$ (197.24): C, 73.07; H, 5.62; N, 21.30. Found: C, 73.12; H, 5.67; N, 21.35.

2-Imino-2H-chromene-3-carbonitrile (**5**)

Yellow solid, mp $140\text{--}141^\circ\text{C}$ [Lit. (30) $140\text{--}141^\circ\text{C}$]. IR (KBr) ν_{max} . 3332 (NH), 2190 (CN), 1639 (C=N), 1256 (C=O) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 7.09–7.47 (m, 4H, Ar–H), 8.31 (s, 1H, C₄–H, coumarin), 8.77 (s, 1H, NH). Anal. Calc. for $\text{C}_{10}\text{H}_6\text{N}_2\text{O}$ (170.17): C, 70.58; H, 3.55; N, 16.46. Found: C, 70.51; H, 3.63; N, 16.52.

Typical procedure for the synthesis of 4,4'-(substituted-methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) **7a–d**

To aromatic aldehydes namely; benzaldehyde (1.06 g, 10 mmol), 4-anisaldehyde (1.36 g, 10 mmol), 4-chlorobenzaldehyde (1.41 g, 10 mmol) or furfuraldehyde (0.96 g, 10 mmol) and pyrazolone **6** (3.48 g, 20 mmol) was added to a stirring solution of $\text{LiOH} \cdot \text{H}_2\text{O}$ (0.042 g, 1 mmol) in water (20 mL). The mixture was heated over a water bath at 90°C for an appropriate time (Table 5). The formed precipitate was filtered, dried, and recrystallized from ethanol to give **7a–d**.

Table 4. The reaction of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**6**) with 4-methoxybenzaldehyde (**2b**) using different concentrations of lithium hydroxide.

Entry	Conc. of $\text{LiOH} \cdot \text{H}_2\text{O}$ (mmole)	Yield at 90°C /Time, min	Yield at room temperature/Time, min
15	5%	(83.0) 60	(56.0) 120
16	10%	(83.5) 60	(57.0) 120
17	15%	(83.2) 60	(56.8) 120

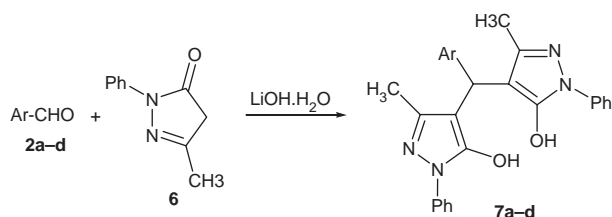


Figure 6. Synthesis of 4,4'-(substituted-methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) **7a–d**.

4,4'-(Phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**7a**)

Colorless powder, mp $170\text{--}171^\circ\text{C}$ [Lit. (31), 174°C]. IR (KBr) ν_{max} . 3030 (br, OH), 1573 (C=C) cm^{-1} ; ^1H NMR (DMSO- d_6 , 500 MHz) δ 2.27 (s, 6H, 2CH₃), 4.91 (s, 1H, CH), 7.13 (m, 1H), 7.22 (m, 6H), 7.39 (t, 4H, $J = 7.6$ Hz), 7.66 (d, 4H, $J = 7.65$ Hz), 13.9 (br, 2H, 2OH); ^{13}C NMR (DMSO- d_6) δ 12.0, 33.5, 121.3, 126.4, 126.5, 127.7, 128.7, 129.5, 137.4, 142.5, 146.7. Anal. Calc. for $\text{C}_{27}\text{H}_{24}\text{N}_4\text{O}_2$ (436.51): C, 74.29; H, 5.54; N, 12.84. Found: C, 74.32; H, 5.59; N, 12.86.

4,4'-(4-Methoxycyclohexa-2,4-dienyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**7b**)

White solid, mp 162°C [Lit. (32), $160\text{--}161^\circ\text{C}$]. IR (KBr) ν_{max} . 3035, 1578 (C=C) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.46 (s, 6H, 2CH₃), 3.85 (s, 3H, OCH₃), 4.84 (s, 1H, CH), 7.8 (d, 2H, $J = 8.55$ Hz), 7.12 (d, 2H, $J = 8.6$ Hz), 7.20 (t, 2H, $J = 7.45$ Hz), 7.39 (d, 4H, $J = 7.45$ Hz), 7.64 (d, 4H, $J = 8.0$ Hz), 13.85 (br, 2H, 2OH). Anal. Calc. for $\text{C}_{28}\text{H}_{28}\text{N}_4\text{O}_3$ (468.55): C, 71.78; H, 6.02; N, 11.96. Found: C, 71.81; H, 6.08; N, 12.03.

4,4'-(4-Chlorocyclohexa-2,4-dienyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (**7c**)

White solid, mp 207°C [Lit. (31), 208°C]. IR (KBr) ν_{max} . 3050 (O–H), 1581 (C=C) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.30 (s, 6H, 2CH₃), 4.88 (s, 1H, CH), 7.20 (d, 4H, $J = 8.55$ Hz), 7.28 (d, 2H, $J = 8.6$ Hz), 7.39 (t, 4H, $J = 8.0$ Hz), 7.66 (d, 4H, $J = 8.0$ Hz), 14.0 (br, 2H, 2OH). Anal. Calc. for $\text{C}_{27}\text{H}_{25}\text{ClN}_4\text{O}_2$

Table 5. The reaction of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**6**) with different aldehydes **2a–d** catalyzed by $\text{LiOH} \cdot \text{H}_2\text{O}$ (10 mol%) in water as solvent.

Entry	Ar	Time (min)	Yield
18	Phenyl	75	80.5
19	4-Methoxyphenyl	60	83.5
20	4-Chlorophenyl	70	86.6
21	2-Furyl	60	79.0

(472.97): C, 68.56; H, 5.33; N, 11.85. Found: C, 68.48; H, 5.29; N, 11.77.

4,4'-(Furan-2-ylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (7d)

White solid (%), mp 192°C [Lit. (33), 189–90°C]. IR (KBr) ν_{\max} : 3060, 1568 (C=C) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.24 (s, 6H, 2CH₃), 4.92 (s, 1H, CH), 6.06–6.18 (m, 1H), 6.3 (d, 1H, J = 3.1 Hz), 7.20 (t, 2H, J = 7.45 Hz), 7.40 (t, 4H, J = 8.0 Hz), 7.43 (d, 1H, J = 1.7 Hz), 7.69 (d, 4H, J = 8.0 Hz), 13.8 (br, 2H, 2OH); ^{13}C NMR (DMSO- d_6) δ 12.3, 28.5, 106.7, 111.2, 121.4, 126.0, 129.8, 142.3, 146.1, 154.9. Anal. Calc. for C₂₅H₂₂N₄O₃ (426.47): C, 70.41; H, 5.20; N, 13.14. Found: C, 70.46; H, 5.18; N, 13.20.

Conclusion

In conclusion, we have discovered LiOH·H₂O as a novel dual activation catalyst for Knoevenagel condensation of aryl aldehydes with malononitrile and 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (6), respectively, for an easy and highly efficient synthesis of arylidene malononitrile 3a–e and 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) 7a–d. The advantages are (i) use of cheap and easily available catalyst, (ii) requirement of small amount (5 or 10 mol%) of the catalyst, (iii) using of water as solvent, (iv) short reaction times, (v) high product yields, and (vi) clean product.

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