An eco-friendly procedure for the efficient synthesis of aryldinemalononitriles 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 (I) or 3-methyl-1-phenyl-1H-pyrazol-5-(4H)-one (6) with aromatic aldehydes 2a–e leading to an efficient and easy synthesis of aryldinemalononitriles 3a–d and 4,4’-(arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) 7a–e 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); aryldinemalononitrile

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 [hmm]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 aryldimepyrazolones 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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generate 2-(4-methoxybenzylidene)malononitrile \( (6) \) 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 \( 4,4\text{-arlylmethylene} \) bis[1H-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. Recently, the use of LiOH-H\(_2\)O 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 diazomethane 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-1H-pyrazol-5(4H)-one \( (6) \) under aqueous conditions in the presence of LiOH-H\(_2\)O.

**Result and discussion**

This work was initiated with the reaction of 4-methoxybenzaldehyde with malononitrile in a variety concentration of LiOH-H\(_2\)O. Thus, malononitrile \( (1) \) (1 mmol) was treated with 4-methoxybenzaldehyde \( (2) \) (1 mmol) in the presence of LiOH-H\(_2\)O (5, 10, and 15 mmol%) in H\(_2\)O (10 mL) as shown in Table 1, we found that the reaction was accelerated by LiOH-H\(_2\)O (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-H\(_2\)O produce good yield of \( 3b \). No Knoevenagel condensation was observed when \( 1 \) was treated with \( 2b \) in the absence of LiOH-H\(_2\)O either in the presence or absence of solvent (Table 2) (Table 1).

![Figure 1. Synthesis of 2-(4-methoxybenzylidene)malononitrile (3b).](image)

The dual role of LiOH-H\(_2\)O, 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-H\(_2\)O (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 \( I \) 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-H\(_2\)O (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 H\(_2\)O 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 salicyaldehyde \( (4) \) under the same condition afforded the corresponding iminocoumarin derivative \( 5 \) (Figure 5). The synthesis of 4,4’-(arylhydylene)bis[3-methyl-1-phenyl-1H-pyrazol-5-ols] \( 7a–d \) involved the reaction of the electrophilic substitution reaction of

| Entry | Concentration (mmol) | Yield | Time (min) |
|-------|----------------------|-------|------------|
| 1     | 5                    | 87    | 1.0        |
| 2     | 10                   | 86.9  | 1.5        |
| 3     | 15                   | 86.9  | 1.5        |
3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (6) with aryl aldehydes in water. As a test case, 4-methoxybenzaldehyde reacted with 3-methyl-1-phenyl-1H-pyrazol-5(4H)-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-1H-pyrazol-5(4H)-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-1H-pyrazol-5(4H)-one (6) with different aldehydes was studied in the presence of LiOH·H₂O in water, using optimized reaction conditions (Figures 3, 6; Table 5).

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-1H-pyrazol-5(4H)-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 (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-δ₆ 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-2H-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), fururaldehyde (48.04 mg, 5 mmol), 4-dimethylamino-benzaldehyde (74.6 mg, 5 mmol), or salicyaldehyde (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
formed precipitate was filtered and crystallized from ethanol to give 3a–e and 5, respectively.

**2-Benzylidemalononitrile (3a)**
Yellowish white powder, mp 85.8°C [Lit. (27) 83°C]. IR (KBr) \( \nu_{\text{max}} \) 2219 (CN), 1581 (C = C) cm\(^{-1}\); \(^1\)H NMR (DMSO-\( d_6 \)) \( \delta \) 7.58 (t, 2H, \( J = 8.45 \) Hz), 7.64 (t, 1H, \( J = 8.25 \) Hz), 7.90 (d, 2H, \( J = 8.4 \) Hz), 8.48 (s, 1H, CH); \(^{13}\)C NMR (DMSO-\( d_6 \)) \( \delta \) 169.1, 134.6, 131.0, 130.7, 129.8, 113.6, 112.5, 82.6. Anal. Calc. for C\(_{10}\)H\(_6\)N\(_2\) (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 118.8°C [Lit. (6) 118–119°C]. IR (KBr) \( \nu_{\text{max}} \) 2219 (CN), 1578 (C = C) cm\(^{-1}\); \(^1\)H NMR (DMSO-\( d_6 \)) \( \delta \) 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); \(^{13}\)C NMR (DMSO-\( d_6 \)) \( \delta \) 162.0, 158.8, 132.9, 124.1, 115.4, 114.0, 113.8, 78.9, 56.1. Anal. Calc. for C\(_{11}\)H\(_8\)N\(_2\)O (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 167.8°C [Lit. (26), 165°C]. IR (KBr) \( \nu_{\text{max}} \) 2221 (CN), 1583 (C = C) cm\(^{-1}\); \(^1\)H NMR (DMSO-\( d_6 \)) \( \delta \) 7.65 (d, 2H, \( J = 8.4 \) Hz); 7.89 (d, 2H, \( J = 8.4 \) Hz), 8.4 (s, 1H, CH); \(^{13}\)C NMR (DMSO-\( d_6 \)) \( \delta \) 158.8, 141.6, 132.0, 130.1, 129.0, 113.8, 112.3, 83.0. Anal. Calc. for C\(_{10}\)H\(_5\)ClN\(_2\) (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°C [Lit. (28), 68–69°C]. IR (KBr) \( \nu_{\text{max}} \) 2221 (CN), 1583 (C = C) cm\(^{-1}\); \(^1\)H NMR (DMSO-\( d_6 \)) \( \delta \) 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),

![Figure 3. Dual activation role of LiOH·H\(_2\)O Kno}nungevagel condensation between a malononitrile and aldehydes.](image_url)

**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-Chloro phenyl | 94        | 3          |
| 13    | 2-Furyl       | 86        | 1          |
| 14    | 4-N,N-dimethy lamino phenyl | 92 | 1 |

**Figure 4. Synthesis of 2-(substituted-methylene)malononitriles.**
2-Imino-2H-chromene-3-carbonitrile (5)

Yellow solid, mp 140–141°C [Lit. (30) 140–141°C]. IR (KBr) v_max 3332 (NH), 2190 (CN), 1639 (C=O) cm⁻¹; ¹H NMR (DMSO-d6) δ 7.09–7.47 (m, 4H, Ar-H), 7.39 (d, 4H, J = 8.6 Hz), 7.20 (t, 2H, J = 8.6 Hz). Anal. Calc. for C₁₀H₈N₂O (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-anizaldehyde (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 LiOH·H₂O (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 LiOH·H₂O (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                        |

**Table 5. The reaction of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (6) with different aldehydes 2a-d catalyzed by LiOH·H₂O (10 mol%) in water as solvent.**

| Entry | Ar         | Time (min) | Yield |
|-------|------------|------------|-------|
| 18    | Phenyl     | 75         | 80.5  |
| 19    | 4-Methoxyphenyl | 60        | 83.5  |
| 20    | 4-Chlorophenol | 70        | 86.6  |
| 21    | 2-Furyl    | 60         | 79.0  |
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) νmax. 3060, 1568 (C = C) cm⁻¹; 1H NMR (DMSO-d6) 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 = 9.0 Hz), 7.43 (d, 1H, J = 1.7 Hz), 7.69 (d, 4H, J = 8.0 Hz), 13.8 (br, 2H, 2OH); 13C NMR (DMSO-d6) 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 aryldiene 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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