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$LiOH.H_2O$ as a catalyst for Knoevenagel and Gewald reactions

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Commercial available lithium hydroxide monohydrate $LiOH.H_2O$ was found to be a novel 'dual activation' catalyst for tandem cross Knoevenagel condensation between malononitrile or ethylcyanoacetate and aromatic aldehydes leading to an efficient and easy synthesis of the corresponding arylidenes at room temperature in a short reaction time. In the case of salicyaldehyde the reaction lead to the formation of 3-substituted coumarins. The high efficacy, cheapness and easy availability of $LiOH.H_2O$ prompted us to investigate its validity as a basic catalyst for Gewald reaction.

Keywords: Malononitrile, Ethylcyanoacetate, Cyclohexanone, $LiOH.H_2O$, Knoevenagel reaction, Gewald reaction.

INTRODUCTION

The Knoevenagel reaction is a well-known classical reaction as a condensation between carbonyl compounds and activated methylene compounds. It may be carried out either in homogenous or heterogeneous. The usual catalysts are organic bases,[1] (primary, secondary and tertiary amines, ammonia and ammonium salts). Subsequently the uses of $TiCl_4$,[2] $AlPO_4$-Al_2O_3,[3] $ZnCl_2$,[4] KF,[5] LiCl,[6] K_3PO_4,[7] TEBA,[8] and CTMAB/H_2O,[9] *etc.* have been reported. Recently, ionic liquids such as [hmim]PF_6,[10] and $BPyAlCl_4$,[11] have been used as the green solvent. Bhagat et al.,[12] reported the use of lithium hydroxide monohydrate ($LiOH.H_2O$) which was found to be a novel 'dual activation' catalyst for a tandem cross-Aldol condensation between cyclic/acyclic ketones and aromatic/heteroaromatic/styryl/alkyl aldehydes in ethanol at room temperature in short times. Therefore, this study reports the scope of $LiOH.H_2O$-promoted Knoevenagel and Gewald reactions.

EXPERIMENTAL

General

All melting points are recorded on Gallenkamp electric melting point apparatus. The IR spectra υ (cm^{-1}) (KBr) were recorded on a Perkin Elmer Infrared Spectrophotometer Model 157. The ^1H NMR spectra were obtained on a Jeol GLM EX 500 and 270 MHz FT NMR Spectrophotometer and ^{13}C NMR spectra were obtained on a Jeol GLM EX 125 MHz using TMS as an internal reference and DMSO-d_6 as the solvent and were carried out at the National Research Center, Dokki, Giza, Egypt. Elemental analyses (C, H, and N) were carried out at the National Research Center, Dokki, Giza, Egypt.

A general procedure for the synthesis of arylidene malononitriles 3a-e, cyanoacetates 3f-j, and iminocoumarins 5a, b

Malononitrile (0.33 g, 5 mmol) or ethyl cyanoacetate (0.56 g, 5 mmol) in ethanol (15 mL) was treated with $LiOH.H_2O$ (0.11 g, 0.25 mmol, 5 mol%) under the magnetically stirred condition for 2 min at room temperature, aromatic aldehydes namely; benzaldehyde (0.53 g, 5 mmol), 4-methoxybenzaldehyde (0.68 g, 5 mmol), 4-chlorobenzaldehyde (0.70 g, 5 mmol), 4-(dimethylamino)benzaldehyde (0.75 g, 5 mmol), furfuraldehyde (0.48 g, 5 mmol) or salicyaldehyde (0.61 g, 5 mmol), was added. The reaction mixture was stirred at room temperature for 1 – 30 min (TLC). The reaction mixture was then poured into the ice-cold water, the formed precipitate was filtered, dried and crystallized from ethanol to give 3a-j and 5a, b, respectively.

2-Benzylidenemalononitrile (3a), was obtained in 89% yield, as a yellowish white powder. ^1H NMR (500 MHz, DMSO) δ 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 (125 MHz, DMSO) δ 169.1, 134.6, 131.0, 130.7, 129.8, 113.6, 112.5, 82.6; m.p. 85°C (Lit.,[13] 83°C). Anal. calcd. for $C_{10}H_6N_2$ (154.17), C, 77.91; H, 3.92; N, 18.17. Found: C, 77.83; H, 3.98; N, 18.20. FT-IR (ν, cm^{-1}) 2219 (CN), 1581 (C=C).

2-(4-Methoxybenzylidene)malononitrile (3b), was obtained in 90% yield, as yellow crystals. ^1H NMR (500 MHz, DMSO) 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=). ^{13}C NMR (125 MHz, DMSO) δ 162.0, 158.8, 132.9, 124.1, 115.4, 114.0, 113.8, 78.9, 56.1; m.p. 117-118°C (Lit.,[4] 119°C). Anal. calcd. for $C_{11}H_8N_2O$ (184.19), C, 71.73; H, 4.38; N, 15.21. Found: C, 71.66; H, 4.31; N, 15.17. FT-IR (ν, cm^{-1}) 2219 (CN), 1578 (C=C).

2-(4-Chlorobenzylidene)malononitrile (3c), was obtained in 93.5% yield, as yellowish white crystals. ^1H NMR (500 MHz, DMSO) δ 7.65 (d, 2H, J= 8.4 Hz), 7.89 (d, 2H, J= 8.4 Hz), 8.4 (s, 1H, CH=). ^{13}C NMR (125 MHz, DMSO) δ 158.8, 141.6, 132.0, 130.1, 129.0, 113.8, 112.3, 83.0; m.p. 167°C, (Lit.,[4] 167-168°C). Anal. calcd. for $C_{10}H_5ClN_2$ (188.61), C, 63.68; H, 2.67; N, 14.85. Found: C, 63.73; H, 2.70; N, 14.92. FT-IR (ν, cm^{-1}) 2221 (CN), 1583 (C=C).

2-(4-(Dimethylamino)benzylidene)malononitrile (3d), was obtained in 95% yield, as red crystals. ^1H NMR (500 MHz, DMSO) δ 3.04 (brs, 6H, $2CH_3$), 7.79 (d, 2H, J= 9.2 Hz), 7.91 (d, 2H, J= 9.15 Hz), 8.05 (s, 1H, CH=); m.p. 180°C (Lit.,[5] 179°C). Anal. calcd. for $C_{12}H_{11}N_3$ (197.24), C, 73.07; H, 5.62; N, 21.30. Found: C, 73.18; H, 5.71; N, 21.35. FT-IR (ν, cm^{-1}) 2208 (CN), 1565 (C=C).

2-(Furan-2-ylmethylene)malononitrile (3e), was obtained in 84% yield, as a pale yellow powder. ^1H NMR (500 MHz, DMSO) 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), 8.22 (s, 1H, C=CH); m.p. 70°C (Lit.,[14] 68-69°C). Anal. calcd. for $C_8H_4N_2O$ (144.13), C, 66.67; H, 2.80; N, 19.44. Found: C, 66.71; H, 2.83; N, 19.48. FT-IR (*ν*, cm^{-1}) 2221 (CN), 1583 (C=C).

(E)-Ethyl 2-cyano-3-phenylacrylate (3f), was obtained in 83% yield, as white crystals. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.41 (t, 3H, J= 8.1 Hz, OCH_2CH_3), 4.38 (q, 2H, *J*= 8.1 Hz, OCH_2CH_3), 7.37-7.53 (m, 3H), 7.99 (d, 2H, *J*= 8.4 Hz), 8.22 (s, 1H, =CH); m.p. 50°C, (Lit.,[7] 50-51°C). Anal. calcd. for $C_{12}H_{11}NO_2$ (201.22), C, 71.63; H, 5.51; N, 6.96. Found: C, 71.68; H, 5.59; N, 7.02. FT-IR (*ν*, cm^{-1}) 2234 (CN), 1727 (C=O), 1583 (C=C).

(E)-Ethyl 2-cyano-3-(4-methoxyphenyl)acrylate (3g), was obtained in 91.5% yield, as pale yellow crystals. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.39 (t, 3H, *J*= 8.1 Hz, OCH_2CH_3), 3.89 (s, 3H, OCH_3), 4.36 (q, 2H, *J*= 8.1 Hz, OCH_2CH_3), 7.00 (d, 2H, *J*= 8.1 Hz), 8.00 (d, 2H, J= 8.1 Hz), 8.17 (s, 1H, =CH); m.p. 80°C, (Lit.,[7] 79-81°C). Anal. calcd. for $C_{13}H_{13}NO_3$ (231.25), C, 67.52; H, 5.67; N, 6.06. Found: C, 67.48; H, 5.61; N, 6.13. FT-IR (*ν*, cm^{-1}) 2210 (CN), 1722 (CO), 1585 (C=C).

(E)-Ethyl 3-(4-chlorophenyl)-2-cyanoacrylate (3h), was obtained in 97% yield, as white crystals. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.40 (t, 3H, *J*= 8.1 Hz, CH_3), 4.38 (q, 2H, *J*= 8.1 Hz, CH_2), 7.48 (d, 2H, *J*= 8.8 Hz, Ar-H), 7.93 (d, 2H, *J*= 8.1 Hz, Ar-H), 8.20 (s, 1H, C=CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 153.3, 139.7, 132.3, 129.9, 129.6, 115.8, 103.0, 62.7, 14.2; m.p. 90°C, (Lit.,[7] 92-94°C). Anal. calcd. for $C_{12}H_{10}ClNO_2$ (235.67), C, 61.16; H, 4.28; N, 5.94. Found: C, 61.22; H, 4.34; N, 6.01. FT-IR (*ν*, cm^{-1}) 2223 (CN), 1722 (C=O), 1587 (C=C).

(E)-Ethyl 2-cyano-3-(4-(dimethylamino)phenyl)acrylate (3i), was obtained in 98% yield, as a yellow powder. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.37 (t, 3H, *J*= 8.1 Hz, CH_3, ester), 3.09 (s, 3H, CH_3), 3.11 (s, 3H, CH_3), 4.35 (q, 2H, *J*= 7.2 Hz, CH_2), 6.69 (d, 2H, *J*= 8.8 Hz, Ar-H), 6.69 (d, 2H, *J*= 8.1 Hz, Ar-H), 7.94 (d, 1H, *J*= 8.1 Hz, Ar-H), 8.07 (s, 1H, C=CH). ^{13}C NMR (270 MHz, $CDCl_3$) δ 184.2, 154.4, 153.4, 133.9, 119.2, 117.5, 111.3, 93.7, 61.7, 39.9, 14.2; m.p. 125°C, (Lit.,[5] 124-126°C). Anal. calcd. for $C_{14}H_{16}N_2O_2$ (244.29), C, 68.83; H, 6.60; N, 11.47. Found: C, 68.92; H, 6.65; N, 11.51. FT-IR (*ν*, cm^{-1}) 2216 (CN), 1707 (C=O), 1569 (C=C).

(E)-Ethyl 2-cyano-3-(furan-2-yl)acrylate (3j), was obtained in 86% yield, as a white powder. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.37 (t, 3H, *J*= 8.1 Hz, CH_3), 4.37 (q, 2H, *J*= 8.1 Hz, CH_2), 6.66-6.67 (m, 1H, furyl), 7.40 (d, 1H, *J*= 3.6 Hz, furyl), 7.75 (d, 1H, *J*= 1.2 Hz, furyl), 8.02 (s, 1H, C=CH); m.p. 91°C (Lit.,[15] 91-92°C). Anal. calcd. for $C_{10}H_9NO_3$ (191.18), C, 62.82; H, 4.74; N, 7.33. Found: C, 62.91; H, 4.82; N, 7.27. FT-IR (*ν*, cm^{-1}) 2221 (CN), 1718 (C=O), 1619 (C=C).

2-Imino-2H-chromene-3-carbonitrile (5a), was obtained in 84% yield, as a yellow powder. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.09-7.47 (m, 4H, Ar-H), 8.31 (s, 1H), 8.77 (s, 1H, NH); m.p. 140-141°C (Lit.,[16] 140-141°C). Anal. calcd. for $C_{10}H_6N_2O$ (170.17), C, 70.58; H, 3.55; N, 16.46. Found: C, 70.53; H, 3.60; N, 16.37. FT-IR (*ν*, cm^{-1}) 3332 (NH), 2190 (CN), 1639 (C=N), 1256 (C-O).

Ethyl 2-imino-2H-chromene-3-carboxylate (5b), was obtained in 86% yield, as a yellow powder. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.38 (t, 3H, CH_3, *J*= 8.1 Hz), 4.38 (q, 2H, CH_2, *J*= 8.1 Hz), 6.79-7.56 (m, 4H, Ar-H), 8.11 (s, 1H, NH), 8.51 (s, 1H, C4-H, coumarin); m.p. 134°C (Lit.,3 135°C), Anal. calcd. for C12H11NO3 (217.22), C, 66.35; H, 5.10; N, 6.45. Found: C, 66.50; H, 5.11; N, 6.48. FT-IR (*ν*, cm^{-1}) 3313 (NH), 1679 (CO), 1635 (C=N), 1297 (C-O).

Synthesis of 2-aminothiophenes 7a, b

General procedure

Malononitrile (1a) (0.066 g, 1 mmol) or ethyl cyanoacetate (1b) (0.113 g, 1 mmol), cyclohexanone (6) (0.098 g, 1 mmol), and sulfur (0.035 g, 1.1 mmol) catalyzed by $LiOH.H_2O$ (0.042 g, 1 mmol) in dry ethanol (6 mL) were mixed and stirred at room temperature for 4 h. The reaction mixture was poured into the ice-cold water and the formed precipitate was filtered, dried and crystallized from aqueous ethanol to give 7a, b, respectively.

2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (7a), was obtained in 84% yield, as a pale yellow powder. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.60-1.79 (m, 4H), 2.50-2.73 (m, 4H), 4.58 (br, s, 2H, NH_2); m.p. 147°C (Lit.,[17] 147-148°C). Anal. calcd. for $C_9H_{10}N_2S$ (178.25), C, 60.64; H, 5.65; N, 15.72. Found: C, 60.70; H, 5.74; N, 15.67. FT-IR (*ν*, cm^{-1}) 3328, 3205 (NH_2), 2194 (CN), 1619 (C=C).

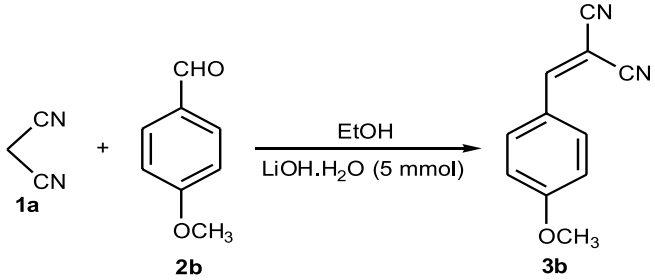
Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (7b), was obtained in 87% yield, as a pale yellow powder. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.33 (t, *J*= 8.1 Hz, 3H, CH_3), 1.67-1.76 (m, 4H), 2.5-2.7 (m, 4H), 4.24 (q, J= 8.1 Hz, 2H), 5.94 (br, s, 2H, NH2); m.p. 115°C (Lit.,[17] 116°C). Anal. calcd. for $C_{11}H_{15}NO_2S$ (225.31), C, 58.64; H, 6.71; N, 6.22. Found: C, 58.75; H, 6.68; N, 6.33. FT-IR (*ν*, cm^{-1}) 3404, 3297 (NH_2), 1646 (CO) 1276 (C-O).

RESULTS AND DISCUSSION

This work was initiated with the reaction of malononitrile (1a) with 4-anisaldehyde (2b) in the presence of $LiOH.H_2O$ in different solvents to produce 2-(4-methoxyphenyl methylene)malononitrile (Table 1).

Table 1. Solvent effect in the reaction of malononitrile (1a) with 4-anisaldehyde (2b)

Entry	Solvent	Reaction time, min	Product (yield %)
1	H_2O	1	87
2	EtOH	3	90
3	CH_2Cl_2	7	81



Scheme 1. Reaction of *p*-methoxybenzaldehyde with malononitrile promoted by $LiOH.H_2O$

The results obtained (Table 1) showed that ethanol was the best solvent. Furthermore, the influence of $LiOH.H_2O$ concentration on the same reaction was also studied. The

results (Table 2) revealed that raising the concentration of $LiOH.H_2O$ more than (5 mol %) has no marked effect on the reaction outcome.

Table 2. The effect of different concentrations of $LiOH.H_2O$ and reaction time on the (yield %) of 2-(4-methoxybenzylidene)malononitrile (3b)

Entry	Concentration of ($LiOH.H_2O$)	Time, min	Product (% yield)
4	0.025 equiv.	7	68
5	0.05 equiv.	3.0	90.0
6	0.10 equiv.	2.5	89.8
7	0.15 equiv.	2.0	89.9

Also, the influence of different bases on the yield % and reaction time on the same reaction was investigated. The results obtained (Table 3) showed that $LiOH.H_2O$ was the best choice.

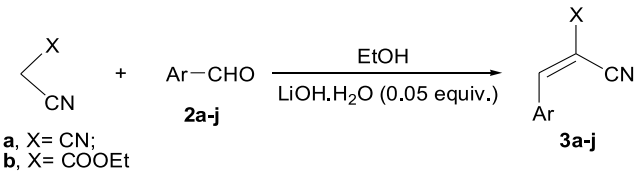
Table 3. The reaction of malononitrile (1a) with 4-anisaldehyde (2b) in the presence and absence of different bases

Entry	Base	Yield	Time
8	LiOH	90.0	3 min
9	NaOH	87.0	6 min
10	KOH	8.5	4 min
11	piperidine	84.0	5 min
12	No base	–	–
13	No base, no solvent	–	–

To establish the generality, malononitrile (1a) and ethyl cyanoacetate (1b) were treated with various aromatic aldehydes 2a – e under the catalytic influence of $LiOH.H_2O$ (0.05 equivalent, Table 4). Excellent results (83 – 98% yields) were obtained and the reactions were completed after 1 min to 11 (TLC).

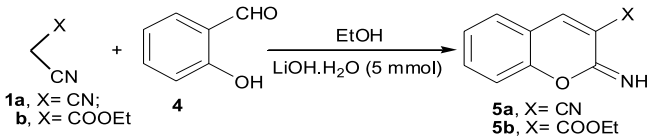
Table 4. The reaction of malononitrile (1a) with different aromatic aldehydes

Entry	Ar	X	Yield	Time
14	phenyl	CN	89	5 min
15	4-methoxyphenyl	CN	90	3 min
16	4-chlorophenyl	CN	93.5	10 min
17	4-*N,N*-dimethylaminophenyl	CN	95	2 min
18	2-furyl	CN	84	1 min
19	phenyl	COOEt	83	8 min
20	4-methoxyphenyl	COOEt	91.5	6 min
21	4-*N,N*-dimethylaminophenyl	COOEt	97	4 min
22	4-chlorophenyl	COOEt	98	11 min
23	2-furyl	COOEt	86	8 min



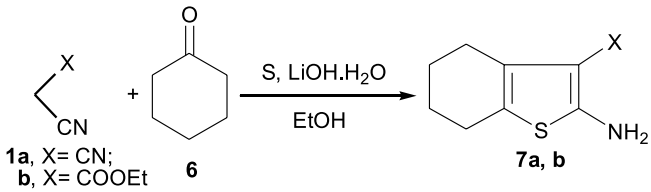
Scheme 2. Reactions of different aldehydes with malononitrile or ethylcyanoacetate promoted by $LiOH.H_2O$

This method was applied to the synthesis of coumarin derivatives 5a through the reaction of salicylaldehyde (4) with malononitrile (1a) in the presence of 0.05 equivalent of $LiOH.H_2O$ was studied. The reaction proceeded smoothly at room temperature to afford 3-cyanoiminocoumarin (5a) in 98% yield. The introduction of ethyl carboxylate to the 3-position of coumarin was achieved using ethyl cyanoacetate under identical conditions, to give 3-ethoxycarbonylcoumarin (5b) in 78% yield.



Scheme 3. Reactions of salicyaldehyde with malononitrile or ethylcyanoacetate promoted by $LiOH.H_2O$

Substituted 2-aminothiophenes are important intermediates in the synthesis of a variety of agrochemicals, dyes and pharmacologically active compounds.[18] The most convergent and well-established classical approach for the preparation of 2-aminothiophenes is Gewald's method,[17] which involves multicomponent condensation of a ketone with an activated nitrile and elemental sulfur in the presence of morpholine as a catalyst. The high efficacy, cheapness and availability of $LiOH.H_2O$ prompted us to investigate the Gewald reaction but replacing the organic base with $LiOH.H_2O$. Thus a mixture of malononitrile or ethylcyanoacetate (0.01mole), cyclohexanone (0.01 mole), elemental sulfur (0.011 mole) in the presence of $LiOH.H_2O$ (0.01 mole) in ethanol (15 mL) was stirred at room temperature for 3-4 h to produce 7a and 7b, respectively.



Scheme 4. Gewald reaction promoted by $LiOH.H_2O$

The dual role of $LiOH.H_2O$ *i.e.* generates the enolate from the malononitrile or ethylcyanoacetate and activates the aldehyde or cyclohexanone carbonyl by coordination with Li^+, is demonstrated in (Fig. 1). Proton abstraction from 1 by $LiOH.H_2O$ (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 subsequently abstracts the proton from 1a and generates the iminolate I to complete the catalytic cycle. The ol IV on dehydration results in the formation of arylidinemalononitrile V.

Also, ethylcyanoacetate undergoes a similar sequence of events are experienced by I (*e.g*, proton abstraction to form the enolate VI, condensation with aldehyde via a six-member cyclic transition state mediated through Li -coordinate VII to form the corresponding olate anion VIII, proton exchange of VIII with ethylcyanoacetate generate VI and the ol IX which on dehydration results in the formation of arylidene of ethylcyanoacetate X (Fig. 2).

Furthermore, cyclohexanone reacted with malononitrile or ethylcyanoacetate in a similar manner to form the intermediate XI, which interacts with sulfur in the presence of $LiOH.H_2O$ to form the sulphide ion XII, which then undergoes cyclization to form the imino- anion XIII. The anion XIII undergoes (1,3-H) migration to form the corresponding enamino anion XIV, followed by a proton exchange of XIV with XI to form 2-aminothiophenes 7a,

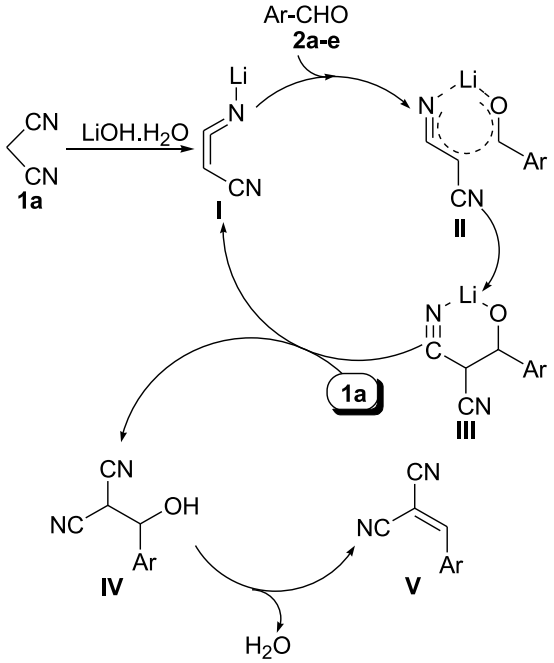


Figure 1. Dual activation role of $LiOH.H_2O$ during Knoevenagel condensation between malononitrile and aldehydes

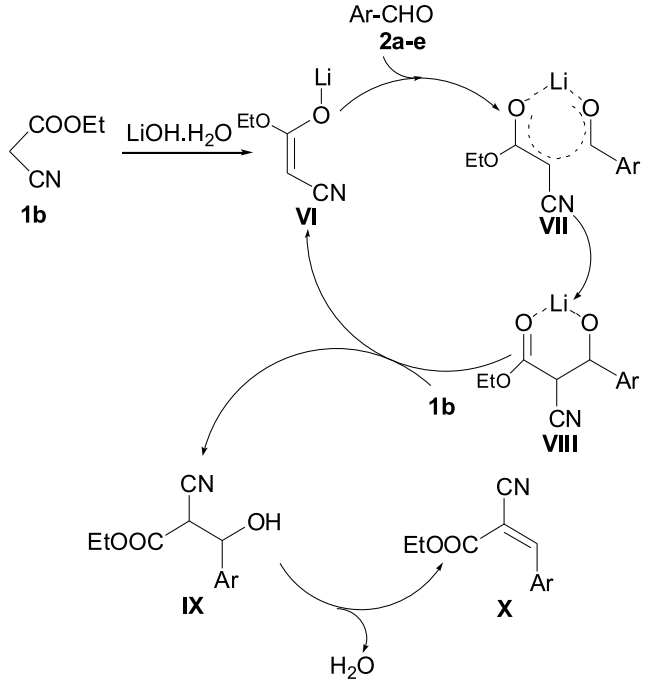


Figure 2. Dual activation role of $LiOH.H_2O$ during Knoevenagel condensation between ethyl cyanoacetate and aldehydes

b, respectively (Fig. 3). The chemical structures of the newly synthesized compounds were characterized by IR, ^1H NMR and mass spectral analysis (*c.f.* Experimental part).

CONCLUSION

In conclusion, I have discovered $LiOH.H_2O$ as a novel catalyst for Knoevenagel condensation of aryl aldehydes with malononitrle and ethylcyanoacetate. Furthermore, $LiOH.H_2O$ was used for Gewald reaction, for an easy and highly efficient synthesis of arylidene malononitrile, arylidene ethylcyanoacetate and 2-aminthiophenes. The advantages are (*i*) use of cheap and easily available catalyst, (*ii*) requirement of a small amount of the catalyst, (*iii*) short reaction times, (*iv*) high product yields and (*v*) clean product.

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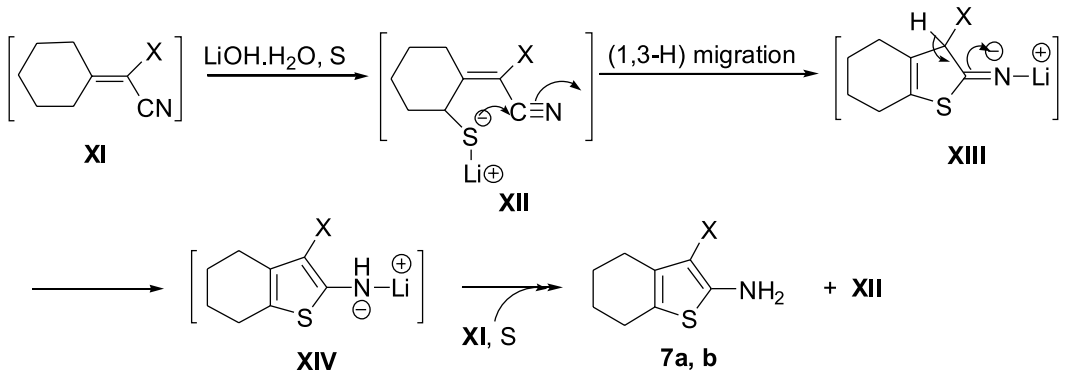

Figure 3. Activation role of $LiOH.H_2O$ during Gewald reactions of [malononitrile or ethyl cyanoacetate] with cyclohexanone and sulfur

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