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**ORIGINAL ARTICLE**

Lithium hydroxide: A simple and an efficient catalyst for Knoevenagel condensation under solvent-free Grindstone method

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Abstract Synthesis of arylmethylidenes from araldehydes and active methylene compounds catalyzed by catalytic amount of lithium hydroxide (LiOH·H₂O) in the absence of a solvent under Grindstone method is reported. The reactions go to completion within 1–5 min and give products in excellent yields at 26 °C.

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1. Introduction

The development of cleaner technologies is a major goal in green chemistry (Metzger, 1998; Li and Chan, 1999). Among the several aspects of green chemistry, the catalytic amount of catalyst and the reduction or replacement of volatile organic solvents from the reaction medium is of at most importance

(Rajinder and Vasudevan, 2001; Pasha and Jayashankara, 2007; Pasha et al., 2006). The solid-state reaction under solvent-free condition has many advantages: reduced pollution, low cost and simplicity in process and handling, these factors are especially important in industry (Loh et al., 2000; Tanka and Toda, 2000). For the increasing environmental and economical concerns in recent years, it is now essential for chemists to search environmentally benign reactions.

Toda in the year 1987 introduced a method called Grindstone method; solids are ground together using a pestle and mortar to get the products. The method is advantageous over the existing methods as the yields of the products are high and one can avoid the use of solvents for the reaction and the method matches the green chemistry protocols (Toda et al., 1987).

On the other hand, Knoevenagel condensation has been used in many synthetic applications and continues to be an important reaction in converting carbonyl groups into alkenes (Trost, 1991). Usually gaseous ammonia, amines and their salts are used as catalysts in Knoevenagel condensation (Jones, 1967). Al₂O₃/microwave irradiation (Khalafi-Nezhad and Hashemi, 2001), [bmim] OH (Ranu and Jana, 2006), diammonium hydrogen

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phosphate (Balalaie et al., 2006), lithium bromide (Sylla et al., 2006), $Mg_6Al_2CO_3(OH)_{16} \cdot 4H_2O$ Ebitani et al., 2006, hexadecyltrimethyl ammonium bromide (Shou et al., 2006), nanocrystalline magnesium oxide (Choudary et al., 2006), MgO/ZrO_2 (Gawande and Jayaram, 2006), $CeCl_3 \cdot 7H_2O-NaI$ (Bartoli et al., 2006), imidazoles (Heravi et al., 2006), and recently silica supported ammonium acetate (Gupta et al., 2009) has been reported to bring about this reaction.

However, reported methods have limitations mainly with respect to yield, cost and availability of the reagents. Some of the systems require longer duration, stringent conditions, work at reflux temperature of the solvent, expensive catalysts and reagents and cumbersome methodologies are employed. Thus, the search for new catalysts and methods is still of practical importance.

In this paper, we are describing our work on the successful use of lithium hydroxide as a catalyst for Knoevenagel condensation of araldehydes with active methylene compounds.

2. Experimental

Araldehydes, methylene compounds and lithium hydroxide were commercial products and were used without further purification. Solvents were distilled before use. Reactions were monitored on TLC by comparison with the authentic samples prepared by standard methods. Melting points were determined on a Buchi melting point apparatus. IR, 1H NMR, and LC-mass were recorded on Nicolet 400D FT-IR spectrophotometer, 400 MHz Bruker spectrometer and Agilent LC-MSD-Trap-XCT instrument respectively.

3. General procedure for Knoevenagel condensation

A mixture of an aldehyde (1 mmol), active methylene compound (1 mmol) and lithium hydroxide (0.1 mmol) were ground together using a pestle and a mortar at 26 °C. The reaction mixture got solidified within 1–5 min. After completion of the reaction (TLC), water was added, stirred for a minute then filtered and dried. The recrystallization is not necessary. The melting point, IR, 1HNMR and LC-Mass spectral data of novel arylmethylidenes prepared by this procedure are presented below.

4. Spectroscopic and analytical data of the products

4.1. Ethyl-(E)-2-cyano-3-(4-fluorophenyl)-2-propenoate

M.p.: 98–100 °C; IR cm^{-1} : 2990, 2226, 1725, 1621, 1517; 1H NMR ($CDCl_3$) δ (ppm): 8.22 (s, 1H, $H-C=C$), 8.02–8.06 (m, 2H, Ar), 7.18–7.23 (t, 2H, $J = 8$ Hz, Ar), 4.37–4.42 (q, 2H, $J = 8$ Hz, OCH_2CH_3), 1.39–1.43 (t, 3H, $J = 16$ Hz, OCH_2CH_3); MS (m/z): 219.8 (M^+).

4.2. Ethyl-(E)-2-cyano-3-(4'-cyanophenyl)-2-propenoate

M.p.: 176–178 °C; IR cm^{-1} : 2997, 2221, 1724, 1616, 1553; 1H NMR ($CDCl_3$) δ (ppm): 8.26 (s, 1H, $H-C=C$); 8.06–8.08 (d, 2H, $J = 8$ Hz, Ar), 7.79–7.82 (d, 2H, $J = 12$ Hz, Ar), 4.39–4.45 (q, 2H, $J = 8$ Hz, OCH_2CH_3), 1.40–1.42 (t, 3H, $J = 8$ Hz, OCH_2CH_3); MS (m/z): 226.7 (M^+).

4.3. Ethyl-(E)-2-cyano-3-(2',4'-dimethoxyphenyl)-2-propenoate

M.p.: 138–140 °C; IR cm^{-1} : 2986, 2221, 1724, 1615, 1540; 1H NMR ($CDCl_3$) δ (ppm): 8.7 (s, 1H, $H-C=C$), 8.40–8.42 (d, 1H, $J = 8$ Hz, Ar), 6.59–6.62 (d, 1H, $J = 8$ Hz, Ar), 6.46 (s, 1H, Ar), 4.34–4.39 (q, 2H, $J = 8$ Hz, OCH_2CH_3), 3.90 (s, 6H, $OCH_3 \times 2$), 1.37–1.41 (t, 3H, $J = 8$ Hz, OCH_2CH_3); MS (m/z): 261.8 (M^+).

4.4. 2-(4'-Fluorophenylmethylidene) malononitrile

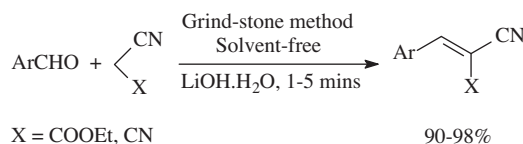
M.p.: 122–124 °C; IR cm^{-1} : 3048, 2231, 1600, 1512; 1H NMR ($CDCl_3$) δ (ppm): 1H NMR ($CDCl_3$) δ (ppm): 7.95–7.99 (m, 2H, Ar); 7.76 (s, 1H, $H-C=C$), 7.22–7.27 (m, 2H, Ar); MS (m/z): 172.6 (M^+).

4.5. 2-(2',4'-Dimethoxyphenylmethylidene) malononitrile

M.p.: 134–136 °C; IR cm^{-1} : 3090, 2231, 1605, 1569; 1H NMR ($CDCl_3$) δ (ppm): 1H NMR ($CDCl_3$) δ (ppm): 8.27–8.29 (d, 1H, $J = 8$ Hz, Ar), 8.19 (s, 1H, $H-C=C$), 6.63–6.61 (d, 1H, $J = 8$ Hz, Ar), 6.45 (s, 1H, Ar), 3.91 (s, 6H, $OCH_3 \times 2$); MS (m/z): 214.7 (M^+).

5. Results and discussion

Earlier report from our laboratory described the synthesis of bis (indolyl) methanes under Grindstone method (Pasha and Jayashankara, 2006). The same methodology has now been extended to synthesize arylmethylidenes from araldehydes and active methylene compounds using catalytic amounts of



Scheme 1

Table 1 Effect of solvents.^a

Entry	Solvent/method	Time (min)	Yield (%) ^c
1	Petroleum ether	20	ND
2	Diethyl ether	20	20
3	Carbon tetra chloride	20	40
4	Acetonitrile	20	ND
5	Hexane	20	30
6	Ethanol	10	90
7	Solvent-free	10	92
8	Solvent-free/Grindstone ^b	1	98

^a Reaction conditions: benzaldehyde (1 mmol), ethyl cyanoacetate (1 mmol), solvent (2 ml), lithium hydroxide (0.1 mmol) stirred at 26 °C.

^b Benzaldehyde (1 mmol), ethyl cyanoacetate (1 mmol) and lithium hydroxide (0.1 mmol) under Grindstone method at 26 °C.

^c Isolated yield; ND – not detected.

Table 2 Effect of catalysts.^a

Entry	Catalyst	Time (min)	Yield (%) ^b
1	ZnCO ₃	10	ND
2	CuCO ₃ ·Cu(OH) ₂ ·H ₂ O	10	ND
3	Ba(OH) ₂	10	Trace
4	2-Aminopyridine	10	80
5	TPAB	10	ND
6	LiOH·H ₂ O	1	98

^a Reaction conditions: benzaldehyde (1 mmol), ethyl cyanoacetate (1 mmol), catalyst (0.1 mmol) at 26 °C under Grindstone method.

^b Isolated yield; ND – not detected; and TPAB – tetrapropylammoniumbromide.

lithium hydroxide in the absence of a solvent under Grindstone method at 26 °C in good purity and excellent yields within 1–5 min as shown in Scheme 1.

The reaction of benzaldehyde and ethyl cyanoacetate with different catalysts and solvents was carried out at 26 °C and found that, use of lithium hydroxide under solvent-free Grindstone method gives the desired products in excellent yields (Tables 1 and 2).

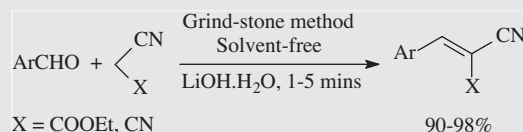
We examined several reactions and found that, the amount of the catalyst had a crucial effect on the Knoevenagel condensation. 4-Methoxybenzaldehyde (1 mmol) was treated with ethyl cyanoacetate (1 mmol) in the presence of lithium hydroxide (1 mmol) to get ethyl-(*E*)-2-cyano-3-(4-methoxyphenyl)-2-propenoate in 82% yield after grinding for 10 min. Decreasing

the amount of the catalyst to 0.5, 0.25 and 0.1 mmol results in increasing the reaction yields to 88%, 92% and 98% respectively. From this study it is clear that, use of just 0.1 mmol lithium hydroxide at 26 °C in less than 1 min under Grindstone method is sufficient to push the reaction forward. Higher amount of the catalyst did not improve the yields to a greater extent. Therefore 0.1 mmol of lithium hydroxide was chosen for further reactions.

By using 0.1 mmol of lithium hydroxide as a catalyst in a solvent-free Grindstone reaction, a systematic study was undertaken to investigate the Knoevenagel condensation of a series of araldehydes bearing electron withdrawing groups and electron donating groups with active methylene compounds. The results of this study are presented in Table 3. From this table it is clear that, excellent yields were obtained within 1–5 min.

6. Conclusion

In conclusion, we have developed a simple, efficient and solvent-free protocol for obtaining a series of arylmethylidenes from araldehydes and active methylene compounds using catalytic amounts of lithium hydroxide under Grindstone method. The advantages of the present method are: it is an environmentally benign and safe protocol that includes a simple reaction set-up not requiring specialized equipment; the reaction works at 26 °C; excellent product yields; short reaction time and elimination of solvents.

Table 3 Knoevenagel condensation catalyzed by lithium hydroxide under solvent-free Grindstone method.

Entry	Ar	X	Yield (%) ^a	M.p. (°C)	
				Found	Reported
1	C ₆ H ₅ -	COOEt	98	52	50–51
2	4-ClC ₆ H ₄ -	COOEt	98	92	89–90
3	C ₆ H ₅ CH=CH-	COOEt	96	117–118	114–115
4	4-OHC ₆ H ₄ -	COOEt	94	171	169
5	4-CH ₃ OC ₆ H ₄ -	COOEt	98	82	85
6	4-NO ₂ C ₆ H ₄ -	COOEt	96	83	85
7	3-NO ₂ C ₆ H ₄ -	COOEt	98	132	133–135
8	4-CH ₃ C ₆ H ₄ -	COOEt	94	94–96	93–94
9	4-FC ₆ H ₄ -	COOEt	98	98–100 ^b	–
10	4-CNC ₆ H ₄ -	COOEt	98	176–178 ^b	–
11	2-CH ₃ O-4-CH ₃ O-C ₆ H ₃ -	COOEt	94	138–140 ^b	–
12	C ₆ H ₅ -	CN	98	80–83	83–84
13	4-ClC ₆ H ₄ -	CN	96	162–164	161
14	C ₆ H ₅ CH=CH-	CN	94	127–129	126
15	4-OHC ₆ H ₄ -	CN	94	187	190
16	4-CH ₃ OC ₆ H ₄ -	CN	95	114	113–114
17	4-NO ₂ C ₆ H ₄ -	CN	96	160–162	161–162
18	4-FIC ₆ H ₄ -	CN	98	122–124 ^b	–
19	2-CH ₃ O-4-CH ₃ OC ₆ H ₃ -	CN	94	134–136 ^b	–

^a Isolated yield.

^b Novel compounds-characterized by IR, ¹H NMR and mass spectral analysis.

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