LiCl Catalyzed Knoevenagel Condensation: Comparative Study of Conventional Method vs Microwave Irradiation

Gowravaram Sabitha,* B. V. Subba Reddy, R. Satheesh Babu, and J. S. Yadav
Organic I Division, Indian Institute of Chemical Technology, Hyderabad-500 007, India

(Received April 10, 1998; CL-980270)

LiCl catalyzes the condensation of aromatic aldehydes with active methylene compounds either in NMP or DMF at room temperature or under microwave irradiation in dry media to produce olefinic products in high yields.

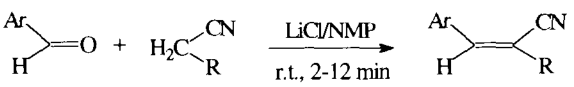
The Knoevenagel condensation is an important C-C bond forming reaction which has been studied extensively and applied in many organic syntheses.[1a,b,c] This condensation is generally catalyzed by bases,[2] Lewis acids - $ZnCl_2$,[3] $TiCl_4$/base,[4] inorganic salt CdI_2[5] and solid support catalysts like Al_2O_3 , $AlPO_4$-Al_2O_3, K10 clay, SiO_2 and Zeolites.[6] The use of LiCl/$MgCl_2$ as catalyst for this transformation has not been reported so far.

The application of LiCl in organic synthesis has received scant attention. Recently LiCl in H_2O-DMSO/DMF systems were used for the cleavage of acetals, ketals[7] and TBDMS ether group.[8] LiCl is a weak Lewis acid and the solubility of this in many organic dipolar solvents makes it an efficient source of nucleophilic chloride ion. Herein, we report that LiCl in N-methyl-2-pyrrolidone (NMP) effectively catalyzes the condensation of an aldehyde with active methylene compounds such as malononitrile, ethyl cyanoacetate and diethyl malonate. This condensation was very fast, completed within 2-12 minutes at room temperature and produced olefinic products in high yields of good purity (Scheme-1). The condensation proceeds slowly when diethyl malonate was used as an active methylene substrate. The condensation also proceeded with a catalytic amount of LiCl, when DMF was used as a solvent instead of NMP but the reaction times were little longer comparably.

The condensation was also catalyzed by $MgCl_2$,$6H_2O$, either in DMF or NMP at room temperature, but reaction was slightly slow compared with LiCl and completed in 5-20 minutes.

The reaction did not take place in the absence of LiCl/$MgCl_2$ either in NMP or DMF alone at room temperature. This clearly indicates the importance of LiCl/$MgCl_2$ for the Knoevenagel condensation.

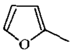
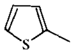
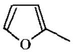
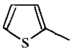
Scheme 1.



LiCl in dry media also catalyzes the condensation of aldehydes with active methylene compounds in the absence of solvent, when the reaction mixture was irradiated in microwave for 2-5 minutes (Scheme-2). While with $MgCl_2$, the condensation takes 5-8 minutes under similar conditions. It is clear from the results that LiCl effectively catalyzes this condensation either in microwave or conventionally when compared to $MgCl_2$. When the reaction was carried out in an oil bath preheated to 110°C (highest observed temperature at the end of microwave irradiation), the conversion was very poor (20-30%, 4 h); this clearly indicates the role of microwave[9a, b] in the acceleration of this reaction. All products were characterized by IR & ^1H NMR spectroscopy.

The advantages of this method are rapid reaction, mild and simple work-up and also economically viable reagent.

Table 1. Knoevenagel condensation with LiCl in NMP at room temperature

Entry	Ar	R	Reaction time min.	Yield %	M.P. °C
1	C_6H_5	CN	8	88	88
2	2-OH-C_6H_4	CN	10	86	160
3	4-Cl-C_6H_4	CN	6	88	165
4	4-N_2O-C_6H_4	CN	4	90	159
5	C_6H_5-CH=CH	CN	12	75	130
6		CN	3	92	96
7		CN	2	94	72
8	C_6H_5	COOEt	8	82	50
9	2-OH-C_6H_4	COOEt	12	80	135
10	2-Cl-C_6H_4	COOEt	12	84	93
11	4-NO_2-C_6H_4	COOEt	8	88	168
12	C_6H_5-CH=CH	COOEt	12	72	115
13		COOEt	8	88	113
14		COOEt	6	90	93

Scheme 2.

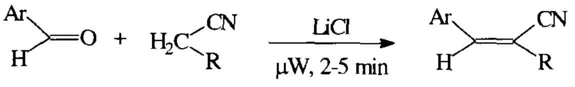
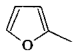
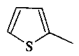
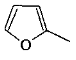
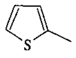


Table 2. Microwave promoted Knoevenagel condensation with LiCl in dry media

Entry	Ar	R	Irradiation time min.	Yield %	M.P. ^{0}C
1	C_6H_5	CN	3	90	88
2	2-OH-C_6H_4	CN	5	87	160
3	4-Cl-C_6H_4	CN	4	87	165
4	4-N_2O-C_6H_4	CN	2	92	159
5	C_6H_5-CH=CH	CN	5	78	130
6		CN	2	92	96
7		CN	2	94	72
8	C_6H_5	COOEt	5	80	50
9	2-OH-C_6H_4	COOEt	5	82	135
10	2-Cl-C_6H_4	COOEt	5	86	93
11	4-NO_2-C_6H_4	COOEt	4	85	168
12	C_6H_5-CH=CH	COOEt	5	86	115
13		COOEt	4	86	113
14		COOEt	4	88	93

B.V.S. thanks CSIR, New Delhi, for the award of fellowship.

References and Notes

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10 General Procedure: a) Conventional: To a mixture of aldehyde (0.01 mole) and active methylene compound (0.01 mole) in N-methyl-2-pyrrolidone, LiCl (0.001 mole) was added and stirred at room temperature for 2-12 minutes. On completion, the reaction mixture was poured into water and extracted with ethyl acetate, dried over Na_2SO_4 and concentrated in vacuo to yield olefinic products. b) Microwave irradiation: A mixture of aldehyde (0.01 mole), active methylene compound (0.01 mole) and LiCl or $MgCl_2$ (0.001 mole) was subjected to microwave irradiation in a pyrex test tube at output of about 600 Watts for a given time in table 2, then extracted with 50mL of ethyl acetate and washed with water, dried over Na_2SO_4 and concentrated in vacuo to afford pure products.

IICT Communication No. 3952.