AMMONIUM CHLORIDE CATALYZED KNOEVENAGEL CONDENSATION OF ALDEHYDES

Puja Nanda
Assistant Professor
Department of Chemistry,
Government College for Women Parade Ground, Jammu, India.

Abstract : Knoevenagel condensation have numerous applications in the elegant synthesis of fine chemicals.Several α,β-unsaturated alkenes have been prepared by this method using aldehydes and active methylene compounds (malonic acid, diethylmalonate, ethylcyanoacetate, methylacetoacetate and ethylacetoacetate).

***IndexTerms* – Ammonium chloride, microwaves, solvent-free, active methylene compounds.**

INTRODUCTION

Knoevenagel condensation[1] is one of the basic reactions in organic chemistry known for its synthetic utility in carbon-carbon bond formation, which is a pivotal process in organic synthesis.[2] Knoevenagel condensation have numerous applications in the elegant synthesis of fine chemicals.[3] Many of Knoevenagel products have pharmacological activity.[4] Substituted cinnamic acids posses a wide range of activities such as anti-allergic agents,[5] corrosion inhibitors,[6] in veterinary preparations,[7] in topical formulation[8] and in the synthesis of substituted styrenes.[9, 10]

The method commonly used for Knoevenagel condensation of malonic acid with carbonyl compounds is Doebner modification,[3, 11] which involves heating aromatic aldehydes and malonic acid in presence of excess of basic solvents like pyridine and piperidine to facilitate easy decarboxylation of initially generated α,β-unsaturated malonic acids which affords cinnamic acids. The condensation is classically catalyzed by bases.[12] Perron et.al[13] and Boulett et.al[14] have reported Knoevenagel condensation of ethylcyanoacetate and various aldehydes using aluminium oxide.

Knoevenagel Condensation has also been realized under microwaves. Villemin and Martin[15] used K10/$ZnCl_2$ for condensation between aldehyde and active methylene compound. Cruz et.al[16] reported silica gel catalyzed Knoevenagel condensation of ketones and malononitrile. Kumar et.al[17] have reported ammonium acetate catalyzed preparation of trans-cinnamic acids by the condensation of aromatic aldehydes with malonic acid. Mitra et.al[18] irradiated mixture of aromatic aldehyde, malonic acid, pyridine and piperadine to get cinnamic acid.

A. Loupy et.al[23] reported bentonites catalyzed condensation of malonic acid and aromatic aldehydes. Bandgar et.al[24] reported the synthesis of 3-carboxycoumarins through Knoevenagel condensation catalyzed by lithium perchlorate and lithium bromide. Kidwai et.al[25] reported the synthesis of fungicidal compounds using Knoevenagel condensation with K_2CO_3 and P_2O_5. A most recent method for Knoevenagel condensation of aromatic aldehydes and malononitrile or ethylcyanoacetate is reported by Shi et.al[26] in the heterogeneous phase using KF-montmorillonite.

S. Fioravanti et.al[27] discussed the reaction of aliphatic aldehydes with nitroalkane in presence of a catalyst like piperidine. J.S. Yadav[28] again reported Knoevenagal condensation using triphenyphosphine as catalyst. Y. Ogiwara et.al[29] used indium(II)chloride as a catalyst. B.C. Ranu et.al[30] used ionic liquid to catalyze Knoevenagal condensation. N. Mase and T, Horibe[31] used carbamic acid ammonium salt as an organocatalyst for reaction between aldehyde and active methylene group.

RESEARCH METHODOLOGY

Keeping in view the importance of Knoevenagel condensation in organic synthesis, an environmentally desirable method for Knoevenagel condensation has been developed using ammonium chloride as catalyst. The importance of this method lies in the fact that catalyst can be reused several times.

Several α,β-unsaturated alkenes have been prepared by this method using aldehydes active methylene compounds (malonic acid, diethylmalonate, ethylcyanoacetate, methylacetoacetate and ethylaceto- acetate). Experimental conditions have been carefully monitored to regulate the use of ammonium chloride, time of irradiation and power level of the oven to get maximum yields. Results are summarized in **Table 1.**

The 1mmole of aldehyde wasmixed with active methylene compound and 0.5g of ammonium chloride. This was then irradiated in a microwave oven at a power output of 700 W for the appropriate time (table 1). After irradiation, the contents were cooled to room temperature and extracted with methylene chloride (3X15mL) and the alkene was recrystallised from appropriate solvent.

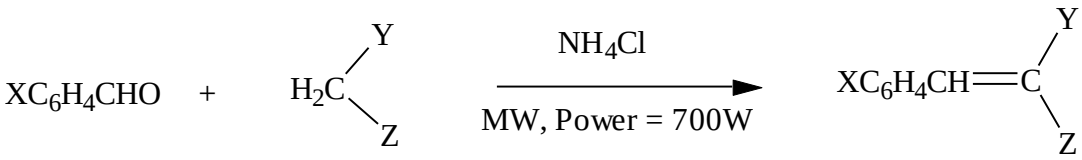

Table 1 **Knoevenagel condensation of aldehydes and active methylene compounds using ammonium acetate as catalyst. (Power = 700W)**

Entry	X	Y	Z	Reaction Temp. (^{0}C)	Time (min)	Yield (%)	mp/Lit.mp (^{0}C)
1	H	CO_2H	CO_2H	80-82	2	70	130-34/133-34[32]
2	OCH_3	CO_2H	CO_2H	48-50	11	90	169-72/170-73[32]
3	4-Cl	CO_2H	CO_2H	85-89	6	70	245-47/248-50[32]
4	4-NO_2	CO_2H	CO_2H	45-48	6	86	282-285/289[32]
5	3-NO_2	CO_2H	CO_2H	79-81	3	76	199-201/202[32]
6	3-Br	CO_2H	CO_2H	40-44	7	71	174-76/177[32]
7	2,4-DiCl	CO_2H	CO_2H	40-43	5	70	231-35/233-35[32]
8	4-OH	CO_2H	CO_2H	40-45	8	74	212(d)/214(d)[32]
9	H	CO_2Et	CO_2Et	60-64	13	77	Liq/bp164-65[33]
10	OCH_3	CO_2Et	CO_2Et	85-87	11	65	Liq/bp180[33]
11	4-NO_2	CO_2Et	CO_2Et	56-58	6	70	89-91/92-92.5[33]
12	3-NO_2	CO_2Et	CO_2Et	69-72	4	70	72-75/74.5[33]
13	H	CN	CO_2Et	81-83	9	99	47-48/49.5[33]
14	4-NMe_2	CN	CO_2Et	65-67	6	71	126-28/128[33]
15	4-Cl	CN	CO_2Et	70-72	5	75	90-92/92[33]
16	4-NO_2	CN	CO_2Et	72-74	4	70	168-70/170[33]
17	3-NO_2	CN	CO_2Et	61-64	5	70	132-34/135[33]
18	4-OH	CN	CO_2Et	77-79	6	75	170-72/172[19]
19	OCH_3	CN	CO_2Et	50-53	9	70	82-84/84[34]

The structures of the products were confirmed by ^{1}H NMR and comparison with authentic sample prepared by already reported methods.

RESULTS AND DISCUSSION

Reactions were carried out using thermo stated oil baths under the same conditions of temperature and time as for microwave-assisted method (**Table2**).

Table 2 **Comparison of results of microwave effect and oil-bath in case of benzaldehyde**

Methylene compd	Mode	Temp. (^{0}C)	Time (Min)	Yield (%)
Malonic acid	MW	80-82	2	70
	Δ	82	2	0
			40	5
Ethylcyano-	MW	81-83	9	99
acetate	Δ	82	9	64
			15	82
Diethylmalonate	MW	60-64	13	77
	Δ	64	13	37
			25	70

It has been found that significantly lower yields were obtained using oil-bath heating than using MW assisted method under identical conditions of reaction time and temperature. This observation demonstrates clearly that the effect of MW irradiation is not purely thermal.

ACKNOWLEDGMENT

Author is thankful to Prof. Rajive Gupta, ex-head, Department of Chemistry, University of Jammu for guidance. Author is also thankful to Director, IIIM, Jammu for extending library and instrumental facilities and also thankful to CSIR, New Delhi for providing SRF during the above work.

REFERENCES

[1] Knoevenagel, E. 1894. Chem. Ber. 27: 2345.
[2] Trost, B.M. 1991. Comprehensive Organic Synthesis; Pergamon Press: Oxford, vol. 2**:**p133.
[3] Jones, G. 1967. Organic Reactions. 15:204.
[4] Elliot, J.D. and Bryan, D.L. 1997. Chem. Abstr. 126:225309.
[5] Japan Pharmaceutical Reference, First Ed. 1989-90. p144.
[6] Naarding, P.C. Coleman, B. and Shepley, J.D. Shell International Research Maat Schappij B. V. EP242, 900; Chem. Abstr. 108:115917.
[7] Fatterman, G.P. and Schetelich, A.A. 1989. Exxon Chemicals Patentees, Inc. EP311, 318; Chem. Abstr. 111:P60845z.
[8] Kurisaki, H. and Ishibashi, H. (Chisso Corp.). 1991. JP0399,088; Chem. Abstr. 115:P166402a.
[9] Abbott, T. and Johnson, J. 1941. Organic Synthesis Coll. Vol. I; John Wiley & Sons: New York, p440.
[10] Galimberti, L. 1940 Bull Sci. Facultd. Chim. Ind. Bologna. 351; Chem. Abstr. 1943. 37**:**3410.
[11] Trost, B.M. 1991. Comprehensive Organic Synthesis; Pergamon Press: Oxford. Vol. 2: p341.
[12] J. March, *Advanced Organic Chemistry*, 4th Ed.,John Wiley & Sons: New York. 1999.
[13] Perron, Y.G. and Minor, W.F. 1959. J. Org. Chem. 24:1165.
[14] Boulett, F.T. and Foucar, A. 1982. Tetrahedron Lett. 47:4927.
[15] Villemin, D. and Martin, B. 1994. J. Chem. Res.(S). 146.
[16] Cruz, P. de la. Barra, E.D. Loupy, A. and Langa, F. 1996. Tetrahedron Lett. 37:1113.
[17] Kumar, H.M. S. Subbaredy, B.V. Anjaneyulu, S. and Yadav, J.S. 1998. Synth. Commun. 28:3811.
[18] Mitra, A.K. De, A. and Kavchaudhuri, N. 1999. Synth. Commun. 29:573.
[19] Mitra, A.K. De, A. and Kavchaudhuri, N. 1999. Synth. Commun. 29:2731.
[20] Dave, C.G. and Augustine, C. 2000. Ind. J. Chem. 39B:403.
[21] Pello′n, R.F. Mamposo, T. Gonz′alez, E. Caledero′n, O. and Farmace′utica, C. Q. 2000. Synth. Commun. 30:3769.
[22] Balalaie, S. and Nemati, N. 2000. Synth. Commun. 30:869.
[23] Loupy, A. Song, S.J. Sohn, S.M. Lee, Y.M. and Kon, T.W. 2001. J. Chem. Soc. Perkin Trans I. 1220.
[24] Bandgar, B.P. Uppalla, L.S. and Sadavarte, V.S. 2002. J. Chem. Res.(S). 40.
[25] Kidwai, M. Sapra, P. and Bhushan, K.R. 2002. J. Ind. Chem. Soc. 79:596.
[26] Shi, D.Q. Wang, X.S. Yao, C.S. and Mu, L. 2002. J. Chem. Res.(S). 344.
[27] Fioravanti, S. Pellacani, L. Tardella, P.A. and Vergari, M.C. 2008, Org.Lett. 10(7):1449.
[28]Yadav, J.S. Reddy, B.S.S. Basak, A.K. Visali, B. Narsaiah, A.V. and Nagaiah, K. 2004. Eur. J. Org. Chem. 2004. 546.
[29] Ogiwara, Y. Takahashi, K. Kitazawa, T. and Sakai, N. 2015. J. Org. Chem. 80:3101.
[30] Rannu, B.C. anda Jana, R. 2006. J. Org. Chem. 3767.
[31] Mase, N. and Horibe, T. 2013. Org. Lett. 15(8):1854.
[32] Aldrich Catalog Handbook of Fine Chemicals, 2002-2003.
[33] Zabicky, J. 1961. J. Org. Chem. 683.
[34] Siddiqui, R.H. and Din, S.U. 1941. J. Ind. Chem. Soc. 18:636.