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Novel Methods of Knoevenagel Condensation

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Abstract: **In this paper we have presented a green and novel method for the synthesis. We have carried out the synthesis of benzylidenemalononitriles by Knoevenagel condensation in solvent free environment at room temperature by using microwave and sonicator. Excellent yields were obtained in very short duration. Twelve principles of green chemistry which are universally accepted for protection of environment as well as human health from chemical pollution were used. Green synthesis provides an excellent yield with the higher purity and high atom economy. Here we have also presented the comparison of the speed of completion of reaction in microwave and sonicator and the yields obtained.**

Index Terms: **Knoevenagel Condensation, Ultrasonic method, Green Method, Atom Economy, etc.**

I. INTRODUCTION

Knoevenagel Condensation reaction is named after Knoevenagel Emil (1922). It is an important reaction for alpha C-C bond formation. Nielsen, A. T. & Houlihan W. J. (1986) have shown that Knoevenagel Condensation reaction is the modification of an Aldol Condensation Reaction. Warren, S. & Sykes, P. (1974) have discussed that it is the nucleophilic addition reaction of active hydrogen compound with carbonyl compound (Roger, C. & Neuma, Jr.) in presence of weak base (Primary, Secondary or tertiary amine) as shown by Wojcik, G. M. (2007) Benzylidenemalononitrile derivatives are generally synthesized by the Knoevenagel condensation reaction of aromatic aldehydes with active methylene compounds. Scientists have developed great interest in these compounds as they serve as valuable organic key intermediates for synthesis of drugs and various products of importance. Viel, C. & Doré, J. C. (1972) have reported antitumoral activity of these compounds. Sidhu, A., Sharma, J. R., Rai, M. (2010) have shown that products formed by reaction of malononitriles have antifungal activity. Khan, S. A. et al. (2017) have demonstrated antibacterial efficacy of these compounds. Carvalho, H. L., Amorim, A. L., Araújo, I. F., Marino, B. L. B., Jimenez, D. E. Q.; Ferreira, R. M. A., Hage-Melim, L. I. P., Souto, R. N. S, Porto, A. L. M. & Ferreira, I. M. (2018) have shown the the Larvicidal Activity of these malononitriles. Fouda, A. S., El-Ewady, Y. A., Abo-El-Enien, O. M. & Agizah, F. A. (2008) have shown use of malononitriles as corrosion inhibitors. Turpaev, K., Ermolenko, M., Cresteil, T. & Drapier, J. C. (2011) have demonstrated use of Benzylidenemalononitrile compounds as modulators of multiple signaling pathways and activators of cell resistance to oxidative stress. Maltsev, S. S., Mironov, M. A. & Bakulev, V. A. (2006) have reported use of benzylidenemalononitriles in the synthesis of cyclopentene derivatives.

Most of the Knoevenagel reactions have been carried out in presence of pyridine as solvent and piperidine as catalyst. However, pyridine being toxic, have high risk and involves tedious workup procedure. To overcome these difficulties, focus is on alternative green methods of synthesis which are more efficient. Recently, different synthetic methods have been developed using lewis acids by Wang, H., Wang, C., Yang, Y., Zhao, M. & Wang, Y. (2017). Li, G., Xiao, J. & Zhang, W. (2012) have used catalysts and carried out Knoevenagel condensation in water. De Resende Filho, J. B. M.; Pires, G. P.; De Oliveira Ferreira, J. M. G., Teotonio, E. E. S. & Vale, J. A. (2017) have carried out Knoevenagel condensation of aldehydes and ketones with malononitrile by using amine compounds-tethered Fe_3O_4-SiO_2 nanoparticles as catalyst. Lolak, N., Kuyuldar, E., Burhan, H., Goksu, H., Akocak, S., & Sen, F. (2019) have used palladium-nickel alloy nanoparticles for reaction of aldehydes with malononitrile. Almáši, M., Zeleňák, V., Opanasenko, M. & Čejka, J. A (2014) have shown use of novel nickel metal–organic framework has catalytic activity in Knoevenagel condensation.

Jimenez, D. E. Q.; Ferreira, I. M.; Yoshioka, S. A.; Fonseca, L. P. & Porto, A. L. M. (2017) have used microwave radiation for Knoevenagel condensation. Bhuiyan, M. M. H., Rahman, K. M. M., Alam, M. A. & Mahmud, M. M. (2013) have shown microwave assisted Knoevenagel Condensation.

In our present work, we are reporting environmentally friendly method for synthesis of benzylidenemalonitrile derivatives of aromatic aldehydes which is clean, efficient and gives excellent yields at room temperature. This reaction has been carried out using principles of Green Chemistry as stated by Anastas P.T. & Warner, J. C. (1998), presented by Kirchhoff, M. (2002) and recommended by United States Environmental Protection Agency (2011).

We have synthesized these compounds by Ultrasonic method reported by Novellin, Robert (1997) and Suslick Kenneth S. (ed.) (1998). Sonochemistry as explained by Hugo Miguel Santos, Carlos Lodiero & Jos-Luis Capelo-Martinez, is a branch of chemical research dealing with the chemical effects and applications of Ultrasonic waves (>20 kHz) that irradiate the liquid samples. Seyedali A. A., Ramam, A. A. A., Parthasarthy, R. & Sajjadi, B. (2016) have explained Sustainable methods. Reactions have been carried out in sonicator using ammonium acetate as catalyst. Ultrasonic energy increases the rate of reaction, by using cavitational effects and reducing reaction temperature, need of solvent and thus provides eco-friendly method. We have also synthesised these derivatives using already existing microwave synthesis techniques and compared the yields and reaction time in microwave and sonicator.

II. APPARATUS AND EXPERIMENTAL METHOD FOR NOVEL METHOD OF KNOEVENAGEL CONDENSATION

Chemicals and reagents:

Benzaldehyde, p-Chlorobenzaldehyde, p-Bromobenzaldehyde, p-Nitrobenzaldehyde, o-Nitrobenzaldehyde, Malononitrile, Ethyl acetate, n-hexane, Ammonium acetate, CDCl3, silica gel, chloroform, methanol, etc. All chemicals used were pure, of A.R. Grade and were purchased from Merck and Loba.

Apparatus:

Two 100 ml beakers, 50 ml beaker, Sonicator, Microwave oven, Glass rod, Slides, Porcelain dish, Tripod stand, Burner, Capillary tube, Thermometer, Thiele tube, etc.

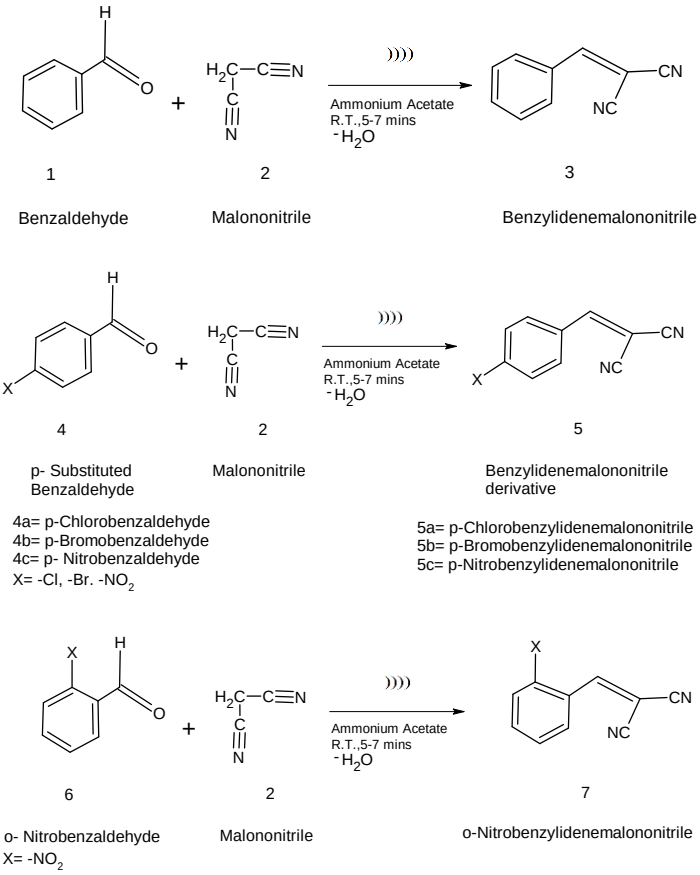
General procedure for preparation of Benzylidenemalononitrile derivatives from Benzaldehyde and substituted Benzaldehyde:

0.01M of derivative of aldehyde was mixed with 0.01M of malononitrile in 50 ml beaker. A pinch of ammonium acetate was added to the reaction with continuous stirring with glass rod. The reaction mixture was sonicated at Room Temperature for about 5-7 minutes and completion of reaction was checked with Thin Layer Chromatography (T.L.C.) technique. The amount of crude product was weighed and after that percentage yield and melting point of crude product was found out. The crude product was recrystallized by using n-hexane and ethyl acetate. The crystals obtained were filtered and dried. Percentage yield and melting point of recrystallized product were found out.

Characterization and Physical Measurements:

Melting points were recorded with thermometer via Thiele Tube Method and were uncorrected. Thin Layer Chromatography was done using mixture of silica gel and chloroform. 1H-N.M.R. peaks were recorded at 300 MHz on 1H-N.M.R spectrometer by using CDCl3 solvent. TMS was used as internal standard. Chemical shifts were reported in δ ppm and coupling constant were calculated in Hz.

III. REACTION



SPECTRAL DATA:

Compound 3: C10H6N2;

δ 7.57 (t, J=7.5 Hz, 2H), δ 7.66 (t, J=7.5 Hz, 1H), δ 7.81 (s,1H), δ 7.93 (d, J= 7.5 Hz, 2H),

Compound 5a: C10H5ClN2;

δ 7.54 (d, J= 8.4Hz, 2H), δ 7.76 (s, 1H), δ 7.88 (d, J= 8.4Hz, 2H).

Compound 5b: C10H5BrN2;

δ 7.70 (d, J= 9Hz, 2H), δ 7.74 (s, 1H), δ 7.79 (d, J= 9Hz, 2H).

Compound 5c: C10H5N3O2;

δ 7.91 (s, 1H), δ 8.10(d, J= 8.7Hz, 2H), δ 8.41(d, J= 8.7Hz, 2H).

Compound 7: C10H5N3O2;

δ 7.81-7.93 (m, 3H), δ 8.38 (d, J= 7.8 Hz, 1H), δ 8.47 (s, 1H).

Table I. Comparative Yields (in %) and Rection Time (in sec) of Benzylidenemalononitriles formed using microwave and sonicator.

U.S. Time (Sec.)	U.S. Yield (%)	M.W. Time (Sec.)	M.W. Yield (%)	M.P. °C
Substrate: **Benzaldehyde**; Product: **Benzylidenemalononitrile**				
302	93.58	56	90.78	86
Substrate: **p-Chloro-benzaldehyde**; Product: **p-Chlorobenzylidene-malononitrile**				
305	98.89	58	94.58	162
Substrate: **p-Bromo-benzaldehyde**; Product: **p-Bromobenzylidene-malononitrile**				
305	95.82	56	91.64	160
Substrate: **p-Nitro-benzaldehyde**; Product: **p-Nitrobenzylidene-malononitrile**				
305	96.73	60	93.14	151
Substrate: **o-Nitro-benzaldehyde**; Product: **o-Nitrobenzylidene-malononitrile**				
310	95.86	58	92.40	139

IV. RESULTS AND DISCUSSION

In this paper we have reported the synthesis of different Arylidene malononitrile derivatives using different aromatic aldehydes bearing different electron withdrawing groups and by using ultrasound in solvent free conditions, using principles of Green Chemistry. All the reagents used for the synthesis were of A.R. grade.

Completion of reaction was checked with Thin Layer Chromatography technique. The percentage yield and atom economy were found to be excellent via Green synthesis method for Knoevenagel condensation at room temperature. 1H-N.M.R. characterization of recrystallized products was done using $CDCl_3$ solvent. The comparison given in Table-I of green synthetic methods using microwave as well as sonicator shows that percentage yield obtained is higher when we use sonicator as compared to microwave.

CONCLUSION

Knoevenagel Condensation of aromatic aldehyde with active methylene compounds were carried out by using sonicator at room temperature simply and efficiently in presence of catalytic amount of benign ammonium acetate and high percentage yields of corresponding benzylidenemalononitriles were obtained in environmentally friendly way. Thus, we have developed greener method of Knoevenagel condensation using sonicator.

We have also shown comparison between microwave synthesis and synthesis using sonicator. Advantages of these methods are that they are very fast and excellent yields are obtained. All the materials are cheap and easily available.

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