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Enhanced reaction rate by using N,N-dimethylformamide as a catalyst in Knoevenagel condensation

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The method of microwave-assisted synthesis of benzylidenemalononitrile and its derivatives by using N,N-dimethylformamide as the catalyst is found to be a superior alternative to the conventional method of synthesis. While the conventional methods in recent times have taken from several hours to a few minutes and produce an average yield, herein is reported the realization of a very similar reaction in comparatively much shorter time of a few seconds, producing a high yield. The products are characterized using infrared and nuclear magnetic resonance spectroscopy.

Keywords: Knoevenagel, microwave, benzylidenemalononitrile, green, solvent-free

Conventional methods of carrying out reactions are long and exhausting wherein transfer of energy to the reaction mixture is facilitated with the usage of hot plates, oil baths or a flux setup[1]. Generally, the conventional methods exploit the dependency of a reaction on convection currents and thermal conductivity of the reactants[2]. The use of microwave irradiation for synthesizing organic compounds was introduced in 1986[3,4]. The primary advantage of microwave synthesis is that it causes internal heating by direct coupling of the microwave energy with the reactants. Microwave irradiation stimulates heating by dipolar polarization and ionic conductance where the dipoles in the reaction mixture are aligned in the presence of applied electric field causing molecular friction and dielectric loss[5,6]. In early days, these reactions were carried out in domestic microwave ovens. Now, use of dedicated microwave reactors is made, designed specifically for controlled synthesis. These instruments have magnetic stirrers and software-based temperature and pressure controls for the reaction mixture. The reaction mixture is placed in a sealed container, which when exposed to microwave irradiation, rapidly heats the reaction mixture to a temperature above the boiling point of the solvent under atmospheric conditions[2]. Achieving this by the conventional method can be very tricky and time consuming. Arrhenius law guides us that the reactions where reaction mixtures need to be refluxed for hours to yield the desired product, can indeed be completed within minutes under microwave irradiation. Microwave-assisted transformations may also yield different products compared to the conventional methods, as the kinetics of the reaction, the orientation of the reactant molecules and the complex formation might be temperature-dependent. The high temperature obtained by irradiating polar materials in microwave is majorly considered as the reason behind the enhanced reaction rate and altered product distributions. This can be considered as one of the reasons why the microwave-assisted reactions give a better yield and lesser by-products[7,8]. Such reactions set a great example for green synthesis as there is no solvent used and no byproducts are produced, only the desired product is obtained[9].

Knoevenagel condensation, when accomplished using a carbamic acid ammonium salt as a catalyst, yields the desired product in about 14-24 h[16]. When triphenylphosphine is used as a catalyst, under microwave irradiation, olefins are produced in appreciable yields in 2-5 min[17].

Results and Discussions

In this paper, we are presenting the microwave-assisted synthesis of benzylidenemalononitrile and its derivatives. Benzylidenemalononitrile is known for its fluorescence based assay and its derivatives are found to exhibit bioactivities. 2-(4-chlorobenzylidene) malononitrile is used for testing the inhibition of

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microbial growth[10,11]. Hence, these fall under an important class of intermediates in pharmaceuticals and dyes[12,13]. An earlier work concerns synthesis of 2-chlorobenzalmalononitrile with chlorine in the *ortho* position[15]. In the present work, we have synthesized a different molecule with chlorine in *para* position, and certain derivatives. While it takes some fifteen hours to synthesize by conventional methods, we have accomplished synthesis in about fifteen seconds.

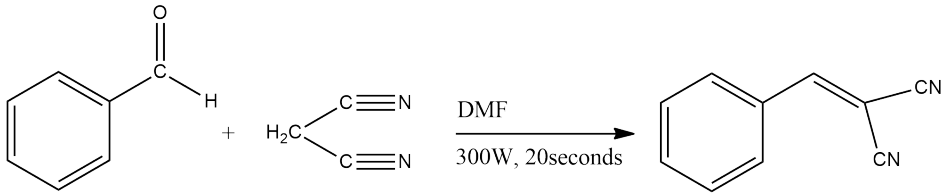
Characterization of the products has been done in terms of IR and proton NMR spectra. The reaction is based on Knoevenagel condensation, where aromatic aldehydes are made to react with compounds with active methylene group to result in an α, β – unsaturated product. The catalyst used in Knoevenagel reaction is generally a primary, secondary or a tertiary amine as the initial stage of the reaction is base-catalyzed aldol condensation with subsequent dehydration.

Microwave-assisted Knoevenagel condensation reaction is much more efficient compared to the conventional method of synthesis, as the product yield is higher, and, the reaction is solvent free. We now present the reaction schemes (Scheme I, Scheme II and Scheme III).

As is well-known, condensation of aldehydes and ketones with compounds having active methylene group in the presence of a basic catalyst to form α, β-unsaturated compounds is called Knoevenagel condensation reaction[19]. Here, N,N-dimethylformamide was used as a catalyst[20,24], the mechanism we propose is shown in Figure 1. N,N-Dimethylformamide extracts proton from the active methylene group of malononitrile to produce a carbanion. This carbanion attacks the electrophilic carbon of the aromatic aldehyde and the valency of the oxyanion is protonated by N,N-dimethylformamide, followed by removal of a water molecule, hence yielding an α, β-unsaturated compound as the product. The products were characterized using infrared and proton NMR spectroscopy. These well-known techniques reveal complementary facets of the molecules. The different normal modes of vibration are brought out by the IR spectra, as discussed below. Every proton has a different surrounding, thereby exhibiting a distinct chemical shift. In this way, the structure of the products is confirmed by proton NMR spectroscopy, more details are presented below.

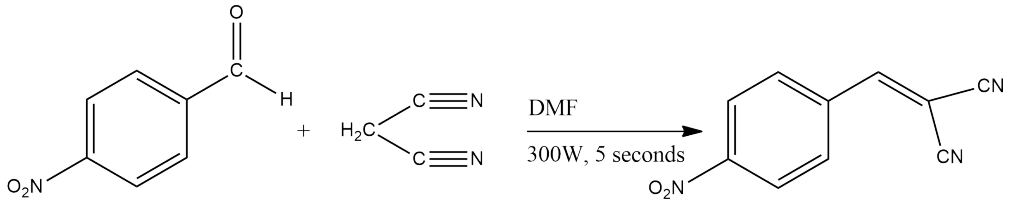
Materials and Methods

The reaction is carried out in a sealed beaker, hence the setup is not complicated, and furthermore, it is not time consuming. In this beaker, equimolar concentration of an aromatic aldehyde and



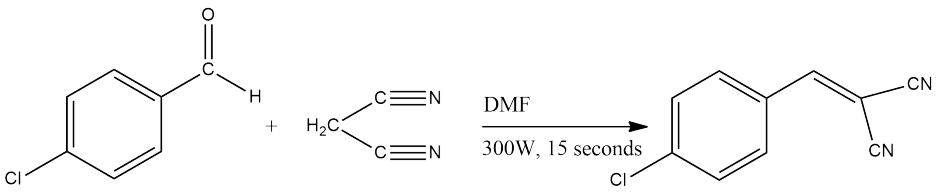
(1)

Scheme I — Synthesis of benzylidenemalononitrile



(2)

Scheme II — Synthesis of 2-(4-nitrobenzylidene)malononitrile



(3)

Scheme III — Synthesis of 2-(4-chlorobenzylidene)malononitrile

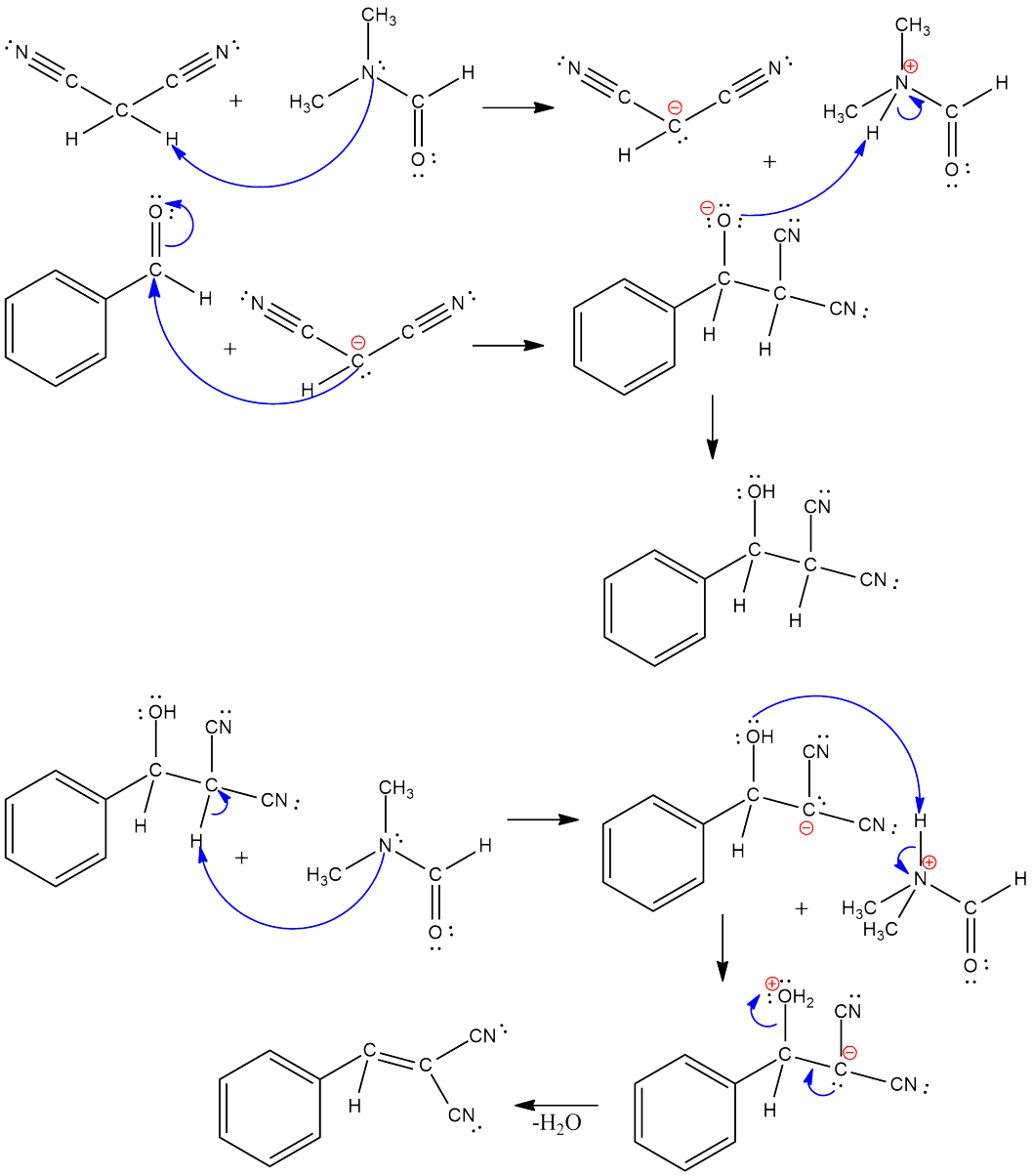


Figure 1 — Reaction mechanism of reaction of benzaldehyde with malononitrile with DM F facilitating protonation and de-protonation in its role as a catalyst

Table I — Effect of catalyst on the reaction

Catalyst	Dipole moment (Debye) [18]	Yield (%)	Time (s)
Chlorobenzene	1.5	85	300
Water	1.87	80	180
DMF	3.86	96	20

malononitrile were placed and using different catalysts (Table I), the reaction mixture was irradiated. High reactivity of the methylene compound prevents self-condensation of the aldehyde[15], hence malononitrile is preferred over ethylacetoacetate[22,23]. The intermediate unsaturated product formed during the course of the reaction with aldehydes tend to further undergo Michael reaction especially in the presence of excess of malononitrile.

Experimental Section

Synthesis of Benzylidene malononitrile

Benzaldehyde (1 g, 9.4 mmols) and malononitrile (0.524 mL) were added to a dry beaker. N,N-Dimethylformamide was introduced into the beaker and the reaction mixture was placed in the microwave chamber. With power set to 300 W, the reaction mixture was irradiated in 4 cycles for 5 seconds each.

On cooling, crystals of benzylidenemalononitrile **1** (Scheme I) were obtained which were further purified by re-crystallization in diethyl ether. The reaction of benzaldehyde and malononitrile yields benzylidene malononitrile, as shown in Scheme I. It was observed that when a catalyst with higher dipole moment was used, the reaction rate increased appreciably as shown in Table I. DMF is very viscous and non-volatile, hence it withstands the microwave radiation well, hence it is favoured[21]. IR: 3153.61, 3003.17, 2250.93, 2223.92, 1591.27, 678.94 cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.3 (s, 1H, Ar- CH=), 7.6 (m, 2H, Ar-H), 7.8 (m, 2H, Ar-H), 8.1 (s, 1H, Ar-H).

Synthesis of 2-(4-nitrobenzylidene) malononitrile

In this scheme, 4-nitrobenzaldehyde (1 g, 6.61 mmols) was made to react with malononitrile (0.37 mL), using N,N-dimethylformamide as the catalyst. The reaction between 4-nitrobenzaldehyde and malononitrile favoured completion within 5 seconds, producing crystals of 2-(4-nitrobenzylidene) malononitrile **2** (Scheme II). IR: 3116.97, 3039.81, 2231.64, 2135.20, 1581.63, 1519.91, 1344.38, 935.48 cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.3 (s, 1H, Ar-CH=), 8.1 (t, 2H, Ar-H), 8.3 (t, 2H, Ar-H).

Synthesis of 2-(4-chlorobenzylidene) malononitrile

Here, 4-chloro benzaldehyde (1 g, 7.11 mmols) was made to react with malononitrile (0.394 mL), using N,N-dimethylformamide as the catalyst. The chloro group survived the reaction as well, giving the crystals of 2-(4-chlorobenzylidene) malononitrile **3** (Scheme III). IR: 3097.68, 3034.03, 2252.86, 2227.78, 1585.49, 827.46, 775.38 cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.3 (s, 1H, ArCH=), 7.6 (m, 2H, Ar-H), 7.9 (t, 2H, Ar-H).

Conclusion

In conclusion, we have discovered N,N-dimethylformamide as a novel activation catalyst for Knoevenagel condensation of aryl aldehydes with malononitrile to achieve appreciable yields within seconds under microwave irradiation. This is appreciably more rapid than some of the other processes of synthesis known in the literature[16,17]. The detailed information of the characterization of the products is available in the Supplementary Information section.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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