



## UNEXPECTED EFFICIENT REACTIONS OF NITROGEN NUCLEOPHILES WITH $\alpha,\beta$ -UNSATURATED NITRILES / ESTERS

K. Suryasaraswathi<sup>a</sup>, S. Saravanan<sup>a,\*</sup> and S. Muthusubramanian<sup>b</sup>

<sup>a</sup>Center for Research and Postgraduate Studies in Chemistry,  
Ayya Nadar Janaki Ammal College (Autonomous), Sivakasi - 626 124.

<sup>b</sup>Department of Organic Chemistry, Madurai Kamaraj University, Madurai -625021

**Email:** [sivasaravanan79@gmail.com](mailto:sivasaravanan79@gmail.com)

### ABSTRACT:

$\alpha,\beta$ -Unsaturated compounds containing aldehyde, ketone, nitrile and ester functional groups are versatile precursor for the synthesis of novel organic molecules. All these compounds undergo Michael addition of carbon and other nucleophiles at  $\beta$ -carbon atom of the  $\alpha,\beta$ -unsaturated system. Different carbo- and hetero-cyclic compounds can be synthesized by varying the conditions of cyclisation of the Michael adducts. In this context, it is planned to synthesize pyrazole derivatives and diazepine derivatives by reacting  $\alpha,\beta$ -unsaturated compounds with different Nitrogen nucleophiles such as, *o*-phenylenediamine *etc.* The present investigation reports the unexpected hydrogenation of C=C in  $\alpha,\beta$ -unsaturated nitriles and the unexpected synthesis of azine derivatives from  $\alpha,\beta$ -unsaturated nitrile and hydrazinium sulphate.

**Keywords:** Knoevenagel condensation,  $\alpha,\beta$ -unsaturated nitrile, azine derivative, hydrogenation of C=C, hydrazinium sulphate, *o*-phenylenediamine

### 1. INTRODUCTION

The Knoevenagel condensation is one of the most useful Carbon-Carbon bond forming reactions in organic synthesis. It has been employed in the synthesis of fine chemicals, hetero Diels-Alder reaction and in the synthesis of

carboxylic as well as heterocyclic compounds of biological importance<sup>1-3</sup>.

Nitrogen nucleophiles such as hydrazine, *o*-Phenylenediamine are important precursor to many heterocyclic compounds like pyrazoles<sup>4-6</sup>, benzimidazoles<sup>7, 8</sup>, quinoxalines<sup>9</sup>, 1,5-

benzodiazepine<sup>10, 11</sup> etc. Hydrazine finds application in the synthesis of azine derivatives<sup>12</sup>, which have anti-bacterial, anti-fungal and anti-tumour activities<sup>13</sup>. Benzimidazoles are of significant importance in medicinal chemistry and have been recently reported to have commercial applications in veterinarian medicine, i.e., as anthelmintic agents, and in diverse human therapeutic areas, such as treatment of ulcers and as antihistaminic<sup>14</sup>. The quinoxaline derivatives have Anti-Amoebic, Anti-proliferative activity<sup>15</sup> and Antithrombotic activity<sup>16</sup>.

## 2. MATERIALS AND METHODS:

### 2.1. Preparation of ethyl 2-cyano-3-aryl-2-propenoate (2)

0.05M of substituted benzaldehyde and 5.3ml of ethylcyanoacetate and sodium ethoxide solution (0.05 mg of Na in 10ml of ethanol) were taken in RB flask. The reaction mixture was refluxed on a water bath for 2 hours. Then it was cooled for 15 minutes and poured into crush ice with continuous stirring. A white precipitate obtained was filtered and recrystallized from alcohol.

2.1.1. *Ethyl 2-cyano-3-(3-nitrophenyl)-2-propenoate (2a)*:

Yield = 95% Melting point = 140 °C

2.1.2. *Ethyl 2-cyano-3-(4-methylphenyl)-2-propenoate (2b)*:

Yield = 90% Melting point = 100-105°C

2.1.3. *Ethyl 2-cyano-3-(4-N,N-dimethylaminophenyl)-2-propenoate (2c)*:

Yield = 87% Melting point = 128°C

### 2.2. Reaction of ethyl 2-cyano-3-aryl-2-propenoate (2) with hydrazinium sulphate

0.005M of ethyl 2-cyano-3-aryl-2-propenoate (2) was dissolved in 30ml of ethanol in a 250ml round bottom flask. Then a solution of 3.2g of hydrazinium sulfate and 2.0g of anhydrous sodium acetate in 20ml of water was added into it. The reaction mixture was refluxed on a water bath for 3 hours. Then it was cooled and poured into ice. A yellow precipitate obtained was filtered and recrystallised from alcohol.

### 2.3. Preparation of 2-arylmethlenemalononitrile (4)

To a stirred solution of malononitrile (0.05M) in water (20ml), diammonium hydrogen phosphate (0.26g, 4mol%) and substitutedbenzaldehyde (0.05M) were added. Progress of the reaction was monitored by Thin – Layer Chromatography (TLC) (eluent: petroleum ether-EtOAc, 4:1). After 10 min, the solid

material obtained was filtered and recrystallised from ethanol.

2.3.1. 2-phenylmethlenemalononitrile (4d):

Yield = 95% Melting point = 90-95°C

2.3.2. 2-(4-Chlorophenylmethlene) malononitrile (4e):

Yield =98% Melting point = 160°C

2.3.3. 2-(4-Methoxyphenylmethlenemalononitrile (4f):

Yield = 90% Melting point = 122°C

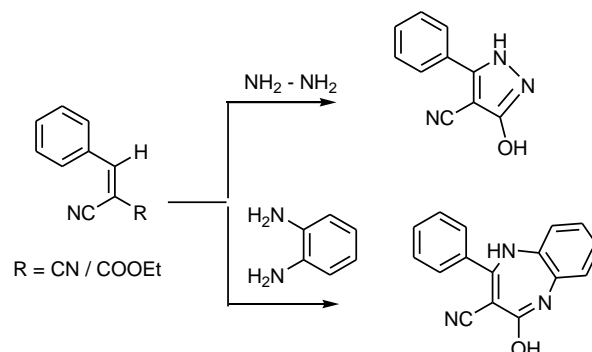
**2.4. Reaction of 2-arylmethlenemalononitrile (4) with o-Phenylenediamine:**

0.01M of 2-arylmethlenemalononitrile (4) and 1.1g (0.01M) of OPD were dissolved in 20ml of ethanol in a 250ml round bottom flask. The reaction mixture was refluxed on a water bath for 3 hours. Progress of the reaction was monitored by Thin - Layer Chromatography (TLC) (eluent: petroleum ether-EtOAc, 4:1) and cooled. Then the reaction mixture was poured into ice. A Yellow precipitate obtained was filtered and purified by the use of column chromatography (eluent: petroleum ether-EtOAc, 98:2).

**3. RESULTS AND DISCUSSION**

$\alpha,\beta$ -Unsaturated compounds containing aldehyde, ketone, nitrile and ester functional groups are versatile precursor

for the synthesis of several carbo- and hetero-cyclic compounds. They may undergo Michael addition with active methylene compounds, Aza-Michael addition with Nitrogen nucleophiles. Compounds containing more than one Nitrogen nucleophilic centre may react in more than one electrophilic centre leading to heterocyclic compounds. In this context, it is planned to synthesize pyrazole derivatives and diazepine derivatives by reacting  $\alpha,\beta$ -unsaturated compounds (derived from Knoevenagel condensation) with different Nitrogen nucleophiles such as hydrazine, o-phenylenediamine *etcas* described in **scheme 1**.



**Scheme 1:** Proposed synthesis of pyrazole and diazepine derivatives

Accordingly, the starting materials for the present investigation *viz.*, 2-cyano-3-(3-nitrophenyl)-2-propenoate (**1a**), ethyl 2-cyano-3-(4-methylphenyl)-2-propenoate (**1b**) and ethyl 2-cyano-3-(4-N,N-dimethylaminophenyl)-2-propenoate (**1c**)

were prepared by Knoevenagel condensation of substituted aromatic aldehydes with ethyl cyanoacetate. They were prepared by refluxing suitably substituted aromatic aldehydes with ethyl cyanoacetate in ethanol for 2 hrs in presence of sodium ethoxide catalyst (**Scheme 2**). The reaction was monitored by TLC. After the consumption of starting materials, the reaction mixture was poured in to the crushed ice. The product was filtered, washed with water, and then dried. The product formed was characterized by IR and NMR spectroscopic techniques. The ethanolic solution of the Knoevenagel adduct **1** was then mixed with aqueous solution of hydrazine hydrochloride and sodium acetate in 1:1 ratio and refluxed for 2-3 hours. The TLC of the reaction mixture showed only the starting material. The same result was also obtained even when the reaction was carried out in 1:2 and 1:5 ratios of the starting material and hydrazine hydrochloride. The C=N stretching vibrations in azines is found to lie in the region 1610 – 1665  $\text{cm}^{-1}$ .

Then the compound ethyl 2-cyano-3-aryl-2-propenoate (**1**) was treated with hydrazinium sulphate and anhydrous sodium acetate and refluxed for 3 hours (**Scheme 2**). In this case, it was found that no reaction took place in 1:1 and 1:2 ratios

of the compound **1** and hydrazinium sulphate. However, a yellow coloured crystalline substance (**2**) was obtained by the reacting compound **1** and hydrazinium sulphate in 1:5 molar ratio. The FT-IR and  $^1\text{H}$  NMR spectral data of the products **2 a-c** are given in **Table 1**.

The FT-IR spectrum of compounds **2a-c** showed a characteristic band around 2359  $\text{cm}^{-1}$  due to the stretching of the  $\text{CO}_2$  in the atmosphere and a band around 1600 – 1620 due to the C=N stretching vibrations. Apart from this it also showed band due to C-H stretching around 3000  $\text{cm}^{-1}$ .

**Table 1:** FT-IR and  $^1\text{H}$  NMR spectral data of **2a-2c**

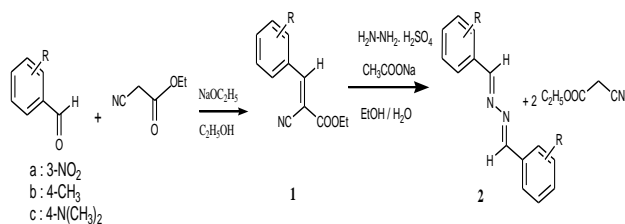
Cmpd	Yield (%)	M.Pt.	FT-IR ( $\text{cm}^{-1}$ )	
<b>2a</b>	85	195 °C {196–197 °C [17]} <sup>#</sup>	3085 2923 1623	Ar. C-H str. Ali. C-H str. C=N str.
<b>2b</b>	82	154-155°C {156 °C [18]} <sup>#</sup>	3015 2935 1620	Ar. C-H str. Ali. C-H str. C=N str.
<b>2c</b>	80	254°C {255-257°C [19]} <sup>#</sup>	2910 1600	Ali. C-H str. C=N str.

<sup>#</sup> Lit. M.Pt

	$^1\text{H}$ NMR ( $\delta$ )	$^{13}\text{C}$ NMR ( $\delta$ )
2a	7.68, t, J = 9 Hz, 2H 8.18, d, J = 9 Hz, 2H 8.35, d, J = 9Hz, 2H 8.74, s, 4 H	124.9, 128.4, 129.6, 133.8, 135.8, 148.5, 150.1
2b	2.45, s, 6 H 7.23, d, J = 9Hz, 4H 7.72, d, J = 9Hz, 4H 8.63, s, 2 H	24.5, 129.6, 129.2, 131.6, 140.5, 151.5

2c	3.05, s, 12 H 6.72, d, J = 9 Hz, 4H 7.70, d, J = 9 Hz, 4H 8.59, s, 1 H	41.9, 114.4, 124.8, 130.6, 149.5, 151.2
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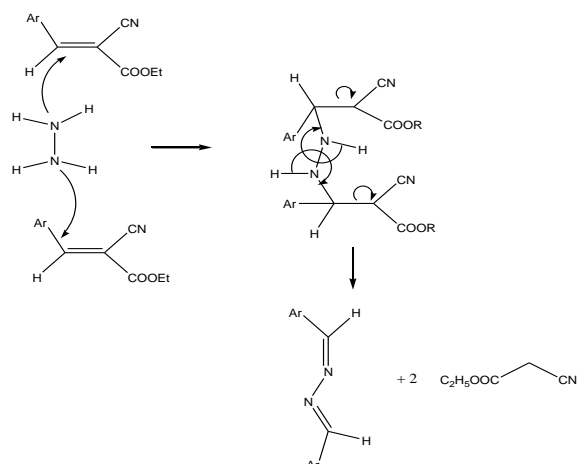
The  $^1\text{H}$  NMR spectrum of **2a-c** showed signals due to the aromatic protons and an olefinic proton. Hence, the NMR and IR spectra of **2a-c** matches well with azine derivative of general formula  $\text{ArCH}=\text{N}-\text{N}=\text{CHAr}$ . The melting point of **2a-c** also matches with the literature melting point. Therefore, the compound **2a-c** may be assigned as 1,2-bisarylidenehydrazine.



**Scheme 2:** Synthesis of 1,2-bisarylidenehydrazine

We have already reported such unexpected synthesis of azine derivatives recently<sup>20</sup>. The formation of the azine derivative may be explained on the basis of the following mechanism: 1,4-Addition would have occurred at both the ends of hydrazine to give an intermediate, which undergoes base catalysed HX elimination leading to the azine derivative. Sodium acetate is sufficiently basic in this reaction since the leaving group (carbanion) is very much stabilised by electron withdrawing

mesomeric effect of cyano and ester groups.



**Scheme 3:** Proposed mechanism for the formation of Azine derivatives

The Knoevenagel condensation of substituted aromatic aldehydes with malononitrile was carried out using diammonium hydrogen phosphate as catalyst by following a reported procedure. Accordingly, the starting materials for the present investigation were prepared by stirring suitably substituted aromatic aldehydes with malononitrile under solvent free condition in presence of diammonium hydrogen phosphate catalyst. The reaction was monitored by TLC. After the consumption of starting materials, the reaction mixture was poured in to the crushed ice. The product was filtered, washed with water, and then dried. The product formed was characterized by IR and NMR spectroscopic techniques.

The ethanolic solution of the Knoevenegal adducts **3a-c** was then refluxed with an alcoholic solution of *o*-phenylenediamine in 1:1 ratio for 2 hours. The TLC of the reaction mixture showed the formation of a new product. The product was purified by column chromatography using petroleum ether-EtOAc (98:2) as eluent. The FT-IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and Mass spectral data of the products **4a-c** are given in **Table 2**.

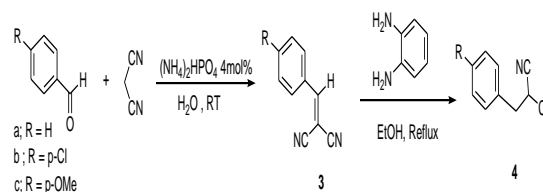
**Table 2:** FT-IR and <sup>1</sup>H NMR spectral data of **4a-c**

c	Yield (%)	M.Pt.	FT-IR (cm <sup>-1</sup> )	
<b>4a</b>	80	89-90°C {90-91°C [21]} <sup>#</sup>	3029 2914 2256	Ar. C-H str. Ali. C-H str. C≡N str.
<b>4b</b>	84	92°C {92-93°C [22]} <sup>#</sup>	302529 212259	Ar. C-H str. Ali. C-H str. C≡N str.
<b>4c</b>	78	89°C {90-91°C [23]} <sup>#</sup>	302629 16 2256	Ar. C-H str. Ali. C-H str. C≡N str.
C	<sup>1</sup> H NMR (δ)		<sup>13</sup> C NMR (δ)	
<b>4a</b>	3.27, d, J = 6Hz, 2H; 3.93, t, J = 6Hz, 1H; 7.28-7.43, m, 5H		133.5, 129.7, 129.5, 129.2, 112.7, 37.1, 25.3	
<b>4b</b>	3.24, d, J = 6Hz, 2H; 3.94, t, J = 6Hz, 1H; 7.27, d, J = 9Hz, 2H; 7.39, d, J		135.3, 131.8, 130.9, 129.9, 112.4, 36.3, 25.2	

	= 9Hz, 2H	
<b>4c</b>	3.25, d, J = 6Hz, 2H; 3.71, s, 3H; 3.89, t, J = 6Hz, 1H; 6.86, d, J = 9Hz, 2H; 7.03, d, J = 9Hz, 2H	157.9, 131.8, 128.9, 113.9, 112.4, 55.4, 38.3, 23.2

<sup>#</sup> Lit. M.Pt

The FT-IR spectrum of compounds **4a-c** showed a characteristic band around 2256 cm<sup>-1</sup> due to the stretching of the -CN stretching vibrations and a band around 2090-3050cm<sup>-1</sup> due to the aliphatic and aromatic C-H stretching vibrations. The <sup>1</sup>H NMR spectrum of the compounds **4a-c** showed signals due to -CH<sub>2</sub>-CH- protons and due to the aromatic protons. The mass spectrum of the compounds **4a-c** showed molecular ion peak and a base peak due to the benzyl (Ar-CH<sub>2</sub>) group. Hence, the NMR, mass and IR spectra of **4a-c** matches well with the compound of general formula ArCH<sub>2</sub>CH(CN)<sub>2</sub>. Therefore, the compound **4a-c** may be assigned as 2-arylmethylmalononitrile.

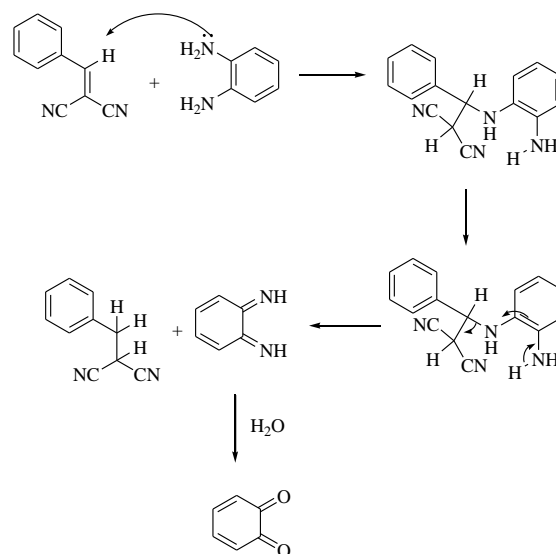


**Scheme 4:** Synthesis of 2-arylmethylmalononitrile

The reaction of *o*-phenylmethylenemalononitrile with *o*-phenylenediamine unexpectedly resulted in the hydrogenation of C=C in

$\alpha,\beta$ -unsaturated nitriles instead of the formation of diazepine derivative. Such type of hydrogenation catalyzed by *o*-phenylenediamine was not at all reported in the literature. However, conjugate reduction of activated  $\alpha,\beta$ -unsaturated nitriles with Hantzsch ester, Sodium borohydride in Methanolic Pyridine<sup>24</sup> and Ferrocenyl complex<sup>25</sup> had been reported earlier.

The hydrogenation of  $\alpha,\beta$ -unsaturated nitriles with *o*-phenylenediamine may be explained on the basis of the mechanism involving initial conjugate addition of *o*-phenylenediamine to  $\beta$ -carbon atom of the  $\alpha,\beta$ -unsaturated nitriles followed by rearrangement and removal of *o*-phenylenediamine unit as *o*-benzoquinone. The formation of *o*-benzoquinone was confirmed by recording <sup>13</sup>C NMR spectrum of the reaction mixture, which showed a signal at 189 ppm due to the C=O group.



**Scheme 5:** Proposed mechanism for the hydrogenation of  $\alpha,\beta$ -unsaturated nitriles with *o*-phenylenediamine

#### 4. CONCLUSION

In the present investigation, it is found that the compound ethyl 2-cyano-3-aryl-2-propenoate on treatment treated with hydrazinium sulphate and anhydrous sodium acetate under reflux condition unexpectedly yield an azine derivative viz., 1,2-bisarylidenehydrazine of general formula  $\text{ArCH=N-N=CHAr}$ . Similarly, the reaction of 2-phenylmethlenemalononitrile with *o*-phenylenediamine under reflux condition unexpectedly resulted in the hydrogenation of C=C in  $\alpha,\beta$ -unsaturated nitriles leading to 2-benzylmalononitrile instead of the formation of diazepine derivative. The formation of the azine

derivative and unexpected hydrogenation were explained by a plausible mechanism.

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