

Knoevenagel condensation products of Isophthalaldehyde with some active methylene compounds under thermal and microwave irradiation conditions

*¹Rasha ALSaqq, ¹Adnan Chehadeh, ¹Abdo Abd Alwahab

¹Department of Chemistry, Faculty of Sciences, Damascus University, Syria.

*Corres author: rasha7sk@hotmail.com
Tel: +965-65981432

Abstract: Six new products of Knoevenagel condensation between isophthalaldehyde and some active methylene compounds were prepared under thermal and microwave irradiation conditions. The used active methylene compounds are malononitrile, methyle cyano acetate, ethyle cyano acetate, methyl aceto acetate, acetyl acetone and dichloro methane. The obtained products were purified by recrystallization from ethanol and identified by IR, U.V, ¹H- NMR, ¹³C -NMR spectroscopy and elemental analysis.

The yield of the reaction and the related parameters (temperature, time) are controlled by the electron withdrawing ability of the functional groups in the methylene component.

Keywords: Isophthalaldehyde, Active methylene compounds, Knoevenagel condensation.

1. Introduction:

Knoevenagel condensation is a widely used reaction in organic chemistry, known for its utility in carbon-carbon double bond C=C formation^{1,2}. K.C. has found a growing interest since it was carried out, for the first time, by Emil Knoevenagel in 1894 between benzaldehyde and ethyl cyano acetate in presence of diethyl amine as a catalyst in ethanol³⁻⁵.

Knoevenagel condensation usually proceeds between aldehydes or ketones which do not contain α -hydrogens with active methylene compounds EWG-CH₂-EWG, where EWG: Electron Withdrawing Group such as NO₂, COR, CN and SO₃H, as a catalyzed, uncatalyzed or microwave enhanced reaction, in different solvents, in aqueous medium or in solvent free conditions⁶⁻¹⁰.

Knoevenagel condensation products, because of their significant properties, have found more and more increasing applications in different fields, and found employment in industrial, agricultural, medicinal and biological uses. They are important intermediates in organic synthesis and in the preparation of optical sensors, cosmetics, perfumes and pharmaceuticals¹¹⁻¹⁶.

2. Purpose of Research:

This research aims to study Knoevenagel condensation products between isophthalaldehyde and some active methylene compounds due to their importance in modern organic chemistry as well as their implementations in several pharmaceutical and industrial fields.

3. Experimental Part:

3.1. Materials:

Isophthalaldehyde (97%), malononitrile (99%), methyle cyano acetate (99%), methyle aceto acetate (99%) and acetyl acetone (> 99.5 %) from sigma Aldrich, ethyle cyano acetate (for synthesis) from RIEDEL, dichloromethane (99%) from GPR, piperidine (98%) from RECTAPUR, absolute ethanol (99.5 %) from panreac.

3.2. Used apparatus:

1. Electric heater with magnetic stirrer (AREC company) .
2. ^1H and ^{13}C nuclear magnetic resonance (NMR) Bruker DPX400.
3. IR spectrometer (Midac 300 Midac 1700).
4. UV-VIS spectrometer (U.V Perkin- Elemer $\lambda 20$) .
5. Mass spectrometer (KRATOS MS50TC).
6. Elemental analyzer (Carlo – Erba 1106).
7. Melting point apparatus (Stuart SMP30).

3.3. Synthesis:

The condensation products were synthesized according to the following procedure: a 100 ml two necks round bottom flask was connected to a reflux condenser and filled with 0.005 mole of the corresponding active methylene compound in 10 ml absolute ethanol. Five droplets of piperidine were added as a catalyst and stirred by a magnetic stirrer. Then a solution of 0.0025 mole isophthalaldehyde in 10 ml absolute ethanol was added to the stirred mixture at room temperature, heated to 50°C or refluxed, for the time given in table (1). The progress of the reaction was controlled by the use of thin layer chromatography (TLC). When the reaction was completed, the mixture was left to cool down to room temperature and a precipitated brown, white, yellow or orange compound was observed. The precipitate was filtered and washed by cold absolute ethanol and then purified by recrystallization from ethanol. The obtained precipitant is slightly soluble in water, methanol or ethanol at room temperature but is soluble in chloroform, acetone and benzene.

4. Results and Discussion:

Equation (1) shows the reaction between isophthalaldehyde and an active methylene compounds ($\text{R}_1\text{-CH}_2\text{-R}_2$) in ethanol in the presence of piperidine as a catalyst.

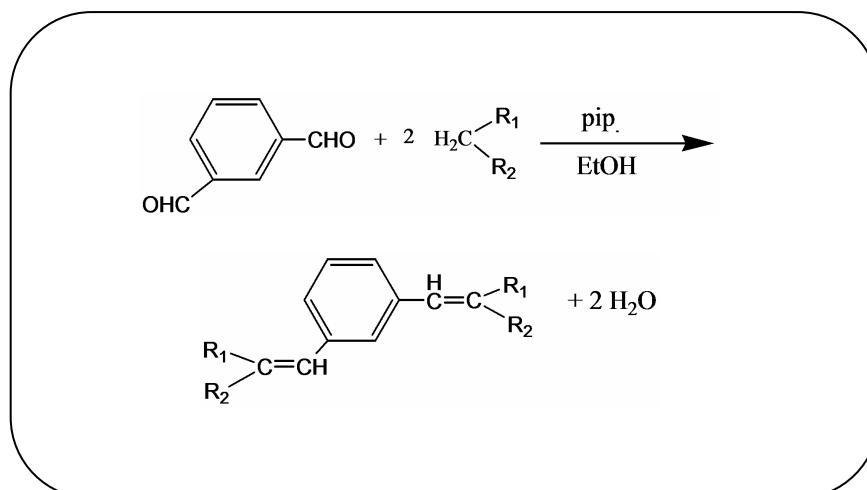


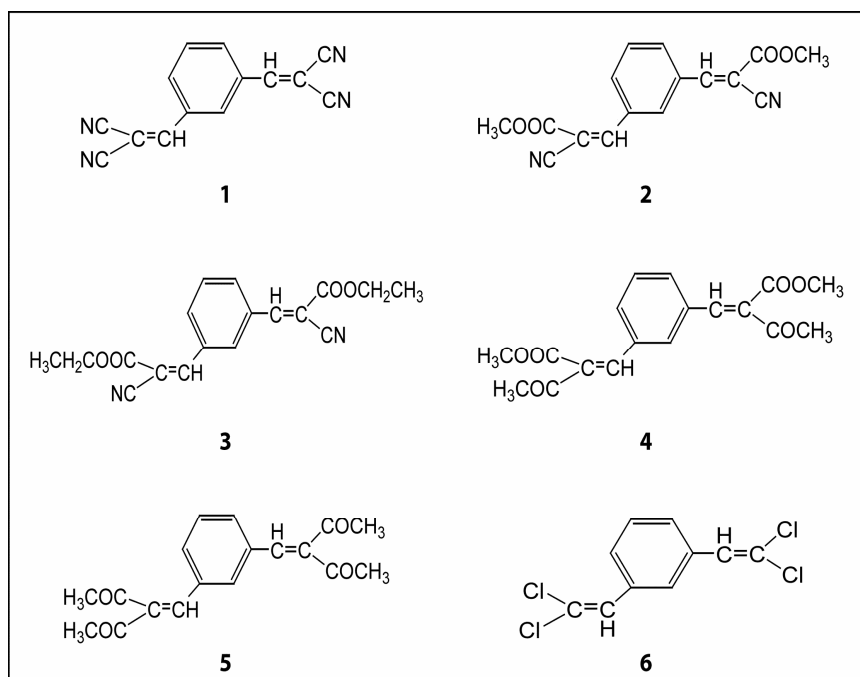
Table (1) gives a list of the performed reactions when six different active methylene compounds are used. Different reaction times, temperatures and yields were adopted depending on the easiness or the difficulty of the reaction. It is obvious from Table (1) that the reaction times under the microwave irradiation are significantly shorter than those required to get the same results in the reactions done in the traditional (thermal) means. Moreover, the yields in the case of reactions 4,5 and 6 were clearly higher under microwave irradiation. The melting points of the obtained products are also listed in Table (1).

Table1: The reaction parameters and some characterization data of the prepared compounds

| Product | R ₁ | R ₂ | T (°C) | Thermal conditions | | Microwave irradiation | | Color | M.P (°C) |
|---------|-------------------|------------------------------------|--------|--------------------|-----------|-----------------------|-----------|--------|----------|
| | | | | Time (h) | Yield (%) | Time (min) | Yield (%) | | |
| 1 | CN | CN | 50 | ½ | 91.07 | 3 | 85.71 | Brown | 147 |
| 2 | CN | COOCH ₃ | 50 | ½ | 83.33 | 3 | 76.38 | Yellow | 171 |
| 3 | CN | COOCH ₂ CH ₃ | 50 | ½ | 82.92 | 3 | 79.01 | White | 128 |
| 4 | COCH ₃ | COOCH ₃ | 80 | 4 | 30.30 | 6 | 46.06 | Orange | 210 |
| 5 | COCH ₃ | COCH ₃ | 80 | 2 | 44.29 | 4 | 65.77 | Brown | 180 |
| 6 | Cl | Cl | 80 | 6 | 26.86 | 10 | 34.32 | Yellow | 81 |

Although yield differences exist between the classical thermal and the microwave methods, there is a correlation between the thermal and the microwave methods. We mention for example reaction (1), which has a high yield in both methods. Reaction (6) has low yields in both methods.

Scheme (1) shows the structural formulas of the products obtained from reactions 1-6. This Scheme intends to facilitate interpretation of the identified IR absorption bands of the obtained products.



Scheme1: Schematic representation of the obtained compounds from reactions 1-6.

Tables 2-5 show IR, U.V., ^1H - NMR, ^{13}C -NMR spectroscopy data for the obtained products, while the APPENDEX brings the spectra. Table (6) brings the results of the elemental analysis.

Table2: Infrared data of prepared compounds (cm^{-1})

| Product | (C-H) _{Ar} | C=C | C=O | C-O | C≡N | CH ₂ | CH ₃ |
|---------|---------------------|------|------|------|------|-----------------|-----------------|
| 1 | 2924 | 1685 | - | - | 2500 | - | - |
| 2 | 2924 | 1597 | 1735 | 1275 | 2217 | - | 1365 |
| 3 | 2984 | 1602 | 1715 | 1206 | 2226 | 1419 | 1394 |
| 4 | 2940 | 1680 | 1669 | 1206 | - | - | 1387 |
| 5 | 2929 | 1604 | 1698 | - | - | - | 1358 |
| 6 | 2925 | 1693 | - | - | - | - | - |

As can be clearly seen in IR spectra of compounds **1-6**, the absorption band of the aldehyde group in the range ($2700\text{-}2800\text{ cm}^{-1}$) was disappeared and a doublet absorption can be observed in the frequency range ($1597\text{-}1735\text{ cm}^{-1}$) which is characteristic for the presence of both C=C and C=O stretching vibrations in compounds **2- 5**.

Table3: ^1H -NMR data of prepared compounds (ppm)

| Product | Ar-H | C=CH | CH ₂ | COOCH ₃ | COCH ₃ | CH ₃ |
|---------|-------------|------|-----------------|--------------------|-------------------|-----------------|
| 1 | 7.50 – 7.60 | 7.75 | - | - | - | - |
| 2 | 7.72-8.21 | 8.34 | - | 4.32 | - | - |
| 3 | 8.07-8.27 | 8.28 | 4.42 | - | - | 1.44 |
| 4 | 7.52-7.71 | 7.85 | - | 2.09 | 1.26 | - |
| 5 | 7.81-7.85 | 8.32 | - | - | 1.35 | - |
| 6 | 8.15-8.17 | 8.38 | - | - | - | - |

The absorption NMR signal for the aldehydic proton in the range (10-11) ppm has disappeared and ^1H -NMR signals in the chemical shift range (7.75-8.38) indicating formation of C=CH have appeared.

Table4: ^{13}C -NMR data of prepared compounds (ppm)

| Product | Ar-C | CH= | C= | COO | CO | COOCH ₂ | COOCH ₃ | COCH ₃ | CH ₃ | C≡N |
|---------|-------------|-------|-------|-------|-------|--------------------|--------------------|-------------------|-----------------|-------|
| 1 | 127.8-128.8 | 157.3 | 109.9 | - | - | - | - | - | - | 113.5 |
| 2 | 131.4-136.3 | 153.1 | 105.7 | 162.5 | - | - | 14.18 | - | - | 114.8 |
| 3 | 130.4-133.9 | 153.1 | 105.3 | 161.8 | - | 63.1 | - | - | 14.1 | 114.9 |
| 4 | 128.4-134.6 | 164.5 | 126.1 | 167.3 | 191.6 | - | 64.51 | 34.56 | - | - |
| 5 | 128.8-130.1 | 160.5 | 123.5 | - | 191.6 | - | - | 34.4 | - | - |
| 6 | 129.4-132.9 | 147.2 | 126.0 | - | - | - | - | - | - | - |

The absorption signal which indicated CHO group in the range (190-200) ppm disappeared in all ^{13}C -NMR spectra of the formed products and new NMR signals appeared in the range (147.2-164.5 ppm) which indicate CH= and a signal in the range (105.3-126.1) ppm indicating the existence of C= appeared.

Table 5: U.V data of prepared compounds (n.m)

| Product | 1 | 2 | 3 | 4 | 5 | 6 |
|------------------------|-----|-----|-----|-----|-----|-----|
| λ_{max} | 297 | 301 | 312 | 248 | 293 | 295 |

λ_{max} was changed in the UV-VIS spectra of all formed products relative to the raw organic reactants due to their ability to act as chromophores because of electronic conjugations in the UV-Vis range.

Table 6: Elemental Analysis of prepared compounds (%)

| Product | Calculated | | | Found | | |
|---------|------------|------|-------|-------|------|-------|
| | C | H | N | C | H | N |
| 1 | 73.04 | 2.60 | 24.34 | 73.23 | 2.82 | 23.57 |
| 2 | 64.86 | 4.05 | 9.45 | 65.17 | 4.26 | 9.40 |
| 3 | 66.66 | 4.93 | 8.64 | 66.65 | 4.88 | 8.60 |
| 4 | 65.45 | 5.45 | 0.00 | 65.92 | 5.68 | 0.00 |
| 5 | 72.48 | 6.04 | 0.00 | 71.91 | 5.83 | 0.00 |
| 6 | 45.11 | 2.25 | 0.00 | 45.92 | 2.67 | 0.00 |

Conclusions:

Six new organic products (1-6) were produced as a result of Knoevenagel condensation starting from isophthalaldehyde and some active methylene compounds. Piperidine was used as a catalyst in ethanol (a solvent) at room temperature, heating at 50 °C or reflux of the reactant mixture with yields ranging from 26.8 to 94.6 %.

The same six products (1-6) were also prepared by the simulation of microwaving with reaction times in the range (3-10)min and yields ranging from 34.3 to 93.3 %. Although the microwave technique was relatively quick, the classical “thermal” method could achieve better results, especially for those products which contain CN group. This is due to decomposition of those products at higher temperatures in the microwave technique. Those reactions which required reflux under microwave irradiation could achieve higher reaction yields with less time.

Therefore, it was deduced from this study that the microwave technique has its pros and cons. The advantages can be summarized in running the reaction in less time and effort in addition to its ability to get out better results especially for those reactions which require heating to relatively high temperatures. On the other hand, the microwave technique has the disadvantage of inability to control the reaction temperature which may lead to compound decomposition due to the high temperature. Moreover, the inability to mix the reactants well during the progress of the reaction represents also a drawback for the microwave technique because less collisions between reactants are occur.

Comparing the methylene compounds we conclude that we could obtain high reaction yields with those compounds which contain CN groups (nitrile malonate, cyano methyl acetate and cyano ethyl acetate). This is to their ability to better draw electrons when compared to keto and ester groups. The nitrile malonate was the most active reactant in this study. The cyano methyl acetate was less active due to the replacement of one CN by the ester group, which is less capable to draw electrons than the CN group. Cyano ethyl acetate falls at the

third position along reactivity because of methyl by ethyl replacement. It is well known that ethyl has higher ability to deliver electrons than methyl moiety.

For those reactants which contain keto and ester groups (acetyl acetone and methyl aceto acetate), acetyl acetone is considered to be the most reactive compound when compared to methyl aceto acetate due to the fact that acetyl acetone contains two keto groups, which are more capable to draw electrons relative to the ester group. The reaction with acetyl acetone took only two hours in the reflux condenser with a reaction yield of 44.2%.

For dichloromethane, the condensation reaction took longer time (six hours) when compared to the reactions of the cyano, keto or acetate methylene active reactants. The condensation reaction yield with dichloromethane was the less among all performed reactions in this study (26.8%). This is because of the two electron donating chlorine atoms which exist in dichloromethane and can moderately suppress the activity of this reactant toward condensation reactions.

6. Acknowledgments:

We are grateful to Department of Chemistry, Faculty of Sciences, Damascus University, Syria and Atomic Energy Commission for the support of this research.

7. Supplementary Material

IR, UV, ¹H-NMR as well as ¹³C-NMR spectra are included in the supplementary material.

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