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RESEARCH ARTICLE

Green Synthetic Methodology of (*E*)-2-cyano-3-aryl Selective Knoevenagel Adducts Under Microwave Irradiation

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Abstract: ***Background*:** The Knoevenagel condensation is an important reaction in organic chemistry because of its capacity to form new C-C bonds and its products are mainly used in organic synthesis as intermediates, due to the large number of reactions they can undergo. Based on the importance of the Knoevenagel adducts, a sustainable synthetic methodology was developed employing microwave irradiation.

***Objective*:** Develop a synthetic methodology employing microwave irradiation and green solvents to obtain Knoevenagel adducts with high yields.

***Methods*:** Knoevenagel condensation reactions were evaluated with different basic catalysts, as well as in the presence or absence of microwave irradiation. The scope of the reaction was expanded using different aldehydes, cyanoacetamide or methyl cyanoacetate. The geometry of the formed products was also evaluated.

***Results*:** After the optimization process, the reactions between aldehydes and cyanoacetamide were performed with triethylamine as catalyst, in the presence of microwave irradiation, in 35 minutes, using NaCl solution as solvent and resulted in high yields 90-99%. The reactions performed between aldehydes and methyl cyanoacetate were also performed under these conditions, but showed better yields with EtOH as solvent 70-90%. Finally, from X-ray analysis, the (*E*)-geometry of these compounds was confirmed.

***Conclusion*:** In this study we developed synthetic methodology of Knoevenagel condensation using triethylamine, green solvents and microwave irradiation. In 35 minutes, products with high yields (70-99%) were obtained and the (*E*)-geometry of the adducts was confirmed.

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1. INTRODUCTION

Acrylonitrile derivatives are unsaturated compounds that have an important role in many pathways for synthesis of biological products [1], pheromones [2], pigments [3], vitamins [4] inhibitors of prostaglandins [5] and polymers [6].

The synthesis of arylacrylonitriles occurs as a reaction between aromatic carbonyl groups (ketones and aldehydes) and arylacetonitriles [7]. In these reactions, bases such as NaOH, KOH, K_2CO_3 can be used in polar solvents, such as MeOH or EtOH [8].

The Knoevenagel condensation is an important reaction used to obtain various functionalized synthetic intermediaries, such as arylacrylonitriles [9]. Usually, the Knoevenagel reaction is carried out in the presence of organic solvents like THF, dioxane and toluene that on the industrial scale can cause significant environmental waste and pollution. The reactions can be catalyzed with different bases (piperidine, ammonia and ammonium salts) as well as Lewis acids ($TiCl_4$, $ZnCl_2$, CdI_2) [10-12].

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The Knoevenagel condensation has many applications in fine chemicals, Diels-Alder reactions and synthesis of heterocyclic compounds [13]. In accordance with these advantages, recent studies have focused on the development of green chemistry methodology, for example, use of silica functionalized with amine groups [14], solid phase resin [15], ethylenediammonium diacetate [16] and microwave irradiation [17].

In the literature, some examples of green chemistry protocols for Knoevenagel condensation under microwave irradiation have been described, such as the synthesis of phenylacrylamides [18], synthesis of pyridones [19], and Knoevenagel condensation between aromatic aldehydes and malononitrile using MgC_2O_4/SiO_2, yielding adducts, such as benzilidenemalononitrile derivatives [20].

Our group has been using low power (20 W) microwave irradiation for the synthesis of Knoevenagel adducts using water as solvent and for a short reaction time (30 min), affording 85-98% yields [21]. This study demonstrated the efficiency of microwave irradiation for this type of reaction in the presence of fibroin/$CuSO_4$. Another study showed the Knoevenagel condensation in free catalysts conditions (60 ^oC, 30 min, 20 W) obtaining yields up to 99% for benzilidenemalononitriles [22].

From this perspective, this work has developed a facile protocol to obtain the Knoevenagel adducts employing aromatic aldehydes, cyanoacetamide or methyl cyanoacetate using green solvents under microwave irradiation.

2. MATERIALS AND METHODS

2.1. General Methods

For gas chromatography–mass spectrometry, a Shimadzu GC2010 Plus gas chromatography system coupled to a mass-selective detector (Shimadzu MS2010 Plus) in electron ionization mode (70 eV), with the DB-5MS fused seed column (Agilent J&W Advances 30 m x 0.25 mm x 0.25 μm) was used. The entrainment gas helium at 65 kPa was used. FT-IR spectra were recorded on a Shimadzu IRAffinity spectrometer. The solid samples were prepared on KBr disks. The IR range analyzed was 4000-400 cm^{-1}.

NMR spectra were recorded on an Agilent Technologies 500/54 Premium Shielded or Agilent Technologies 400/54 Premium Shielded spectrometer, with CD_3OD, DMSO-d_6 or $CDCl_3$ as deuterated solvents and tetramethylsilane (TMS) as the internal standard. The chemical shifts (δ) were given in ppm and coupling constants (*J*) values were reported in Hz. The δ values were referenced to the internal standard (TMS) signal and the deuterated solvents used, *i.e.*, $CDCl_3$ (δ_H 7.26, δ_C 77.16); DMSO-d_6 (δ_H 2.50, δ_C 39.52); and CD_3OD (δ_H 4.87, 3.31, δ_C 49.00).

The microwave irradiation experiments wereperformed using a Discover System from CEM Corporation at a 2.45 GHz frequency with maximal power output of about 200 W with internal magnetic stirring. For the reactions, the power of the microwave reactor used was 55 W.

Melting points were measured on a Fisatom model 431 melting point apparatus.

The single-crystal X-ray diffraction data for the compounds **3a, 3i**, **3l and 5e** were collected at room temperature on a Rigaku XtaLAB mini diffractometer equipped with a CCD detector system using Mo radiation (λ = 0.71073Å).

2.2. Chemical Reagents

4-Bromobenzaldehyde (99%) **1a**, Methyl 4-formylbenzoate **1b**, 4-chlorobenzaldehyde (97%) **1c**, 4-fluorobenzaldehyde (98%) **1d**, 4-(dimethylamino) benzaldehyde (98%) **1e**, 4-nitrobenzaldehyde (99%) **1f**, 4-hydroxybenzaldehyde (98%) **1g**, 3,4,5-trimethoxyben-zaldehyde (98%) **1h**, *p*-anisaldehyde (98%) **1i**, furfural (99%) **1j**, syringaldehyde (98%) **1k**, 2-thiophenecarb-oxaldehyde (98%) **1l**, vanillin (99%) **1m**, isovanillin (99%) **1n**, benzaldehyde **1o** (98%) pyridine, triethylamine and cyanoacetamide (99%) **2** and methyl cyanoacetate (99%) **4**. All the reagents and solvents (hexane, ethyl acetate, methanol, THF, acetone) were purchased and were used without further purification (Aldrich, Fluka, Synth, Merck e Vertec).

The deuterated solvents, CD_3OD (99.9%), DMSO-d_6 (99.9%) and $CDCl_3$ (99.8%) were purchased from Cambridge Isotope Laboratories. The thin layer chromatography (TLC) utilized was DC-Fertigfolien ALUGRAM® XTra SIL G/UV_{254}(layer: 0.20 mm silica gel 60 with fluorescent indicator UV_{254}).

2.3. Preparation of the (*E*)-2-cyano-3-arylacrylamide Derivatives Under Microwave Irradiation

A mixture of either of the aromatic aldehydes **1a**, **1c-1n** (1.0 mmol), cyanoacetamide **2** (1.0 mmol), 5M NaOH (3 drops) in 5M NaCl (3 mL) was added in a round-bottom flask of 25 mL. In a sequence, the flask was placed into the microwave reactor for 35 min, 85 ^oC, at 55 W and stirred by internal magnetic stirring. The reaction progress was monitored by TLC in a mixture containing hexane and ethyl acetate 8:2. The TLC plates revealed sublimated iodine-impregnated on silica gel. At end of the reaction, the product was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were concentrated by vacuum until total evaporation of the solvent and the residue was purified by wash with heat hexane. These adducts **3a**, **3c-3n** were characterized by NMR, FTIR and MS analyses. The spectral data of the compounds were compared with the literature (Supplementary Material). The compounds **3a**, **3i**, **3l** were analyzed by X-ray crystallography.

This procedure was realized in similar conditions using the organic bases (pyridine 10 mol%; triethylamine 10 mol%).

2.4. Preparation of the (*E*)-2-cyano-3-arylacrylamide Derivatives Using Conventional Heating

A mixture of the aromatic aldehyde **1i** (1.0 mmol), cyanoacetamide **2** (1.0 mmol), trimethylamine (10 mol%) or 5M NaOH (3 drops) in an NaCl saturated solution (3 mL) were added in a round-bottom flask of 25 mL. After the reaction, the recipient was put in an oil bath for 240 min and stirred in magnetic plate at 85 ^oC. The reaction progress was

monitored by TLC. At end of the reaction, the product was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were concentrated by vacuum until total evaporation of the solvent and the residue was purified by wash with heat hexane.

2.5. Preparation of the (*E*)-methyl-2-cyano-3-arylacrylate Derivatives Under Microwave Irradiation

A mixture of either of the aromatic aldehydes **1a-j**, **1m**, **1o** (1.0 mmol), methyl cyanoacetate **4** (1.0 mmol), NaCl saturated solution (3 mL) or EtOH (3 mL) and triethylamine (10 mol%) were added in a round-bottom flask of 25 mL. In sequence, the flask was placed into the microwave reactor for 35 min, 85 ^{o}C when NaCl solution was used or 65 ^{o}C when EtOH was used, at 55 W and stirred by internal magnetic stirring. The reaction progress was monitored by TLC in mixture containing hexane and ethyl acetate 8:2. The TLC plates were revealed with sublimated iodine-impregnated on silica gel. At end of the reaction, the aqueous reaction was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were concentrated by vacuum until total evaporation of the solvent and the residue was purified by wash with heat hexane. These adducts **5a-j**, **5m**, **5o** were characterized by NMR, FTIR and MS analyses. The compound **5e** was analyzed by X-ray crystallography.

The spectral data of the compounds were compared with the literature (Supplementary Material).

2.6. Crystallization of Knoevenagel Adducts

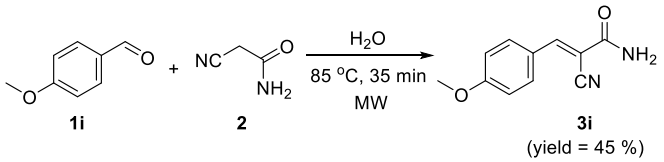
The Knoevenagel adducts **3a**, **3c-3n** and **5e** (50 mg) were added in a vial (15 mL), dissolved in 10 mL of different organic solvent (THF, acetone or methanol). In some cases, it was necessary to heat the samples in soft heating conditions (50 ^{o}C, 5 min). After this step only the Knoevenagel adducts **3a**, **3i**, **3l** and **5e** showed good quality single-crystal formation. Thus, it was only possible to perform X-ray diffraction analyzes for these three compounds.

2.7. Procedure of X-ray Analysis for Single-crystals of adducts 3a, 3i, 3l and 5e

X-ray data integration, Lorentz-polarization effects and absorption corrections were performed with CrysAlisPro [23]. Using Olex2 software [24], the structure was solved by direct methods and the model obtained was refined by full–matrix least squares on F^2 (SHELXTL–13) [25]. All hydrogen atoms were located from electron-density difference maps and were positioned geometrically and refined using the riding model [U_{iso}(H) = 1.2U_{eq} or 1.5U_{eq}]. Molecular representations were generated by Olex2 [24]. Table S1 (Supplementary Material) summarizes the selected crystallography data. The CIF files of the compounds **3a** (CCDC = 1862731)**, 3i** (CCDC = 1862730), **3l** (CCDC = 1862732) and **5e** (CCDC = 1862733) were deposited in the Cambridge Structural Data Base [26] under the codes CCDC XXXXX and XXXXX. Copies of the data can be obtained, free of charge, *via* www.ccdc.cam.ac.uk

3. RESULTS AND DISCUSSION

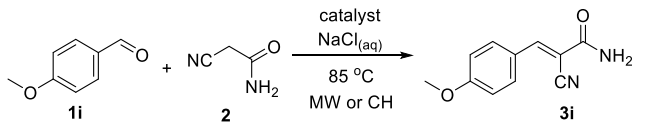
Initially, the Knoevenagel condensation reaction was realized in similar conditions to those described by Jimenez *et al.* [21]. For this reaction, 4-methoxybenzaldehyde **1i** and cyanoacetamide **2** were used in the absence of catalysts and in the presence of water as solvent under microwave (MW) irradiation (Scheme **1**). The reaction yielded 45% for the adduct **3i**. From this result, The addition of a catalyst to the system to promote a better reaction yield was evaluated. Due to the high acidity of cyanoacetamide **2** hydrogens, different basic catalysts were tested, such as NaOH, pyridine and triethylamine (TEA), along with NaCl saturated solution.



Scheme 1. Synthesis of Knoevenagel adduct (*E*)-2-cyano-3-(4-methoxyphenyl)acrylamide **3i** in the absence of catalysts assisted by MW irradiation.

The use of an electrolyte, such as NaCl, can favor the energy absorption of MW irradiation and that can be transferred more quickly, in the form of thermal energy, to the reaction.

Table 1. Knoevenagel condensation using 4-methoxybenzaldehyde 1i and cyanoacetamide 2 in the presence of NaCl saturated solution, basic catalysts under MW irradiation or conventional heating (CH).



Catalyst	Yield (%)[a] 3i	Yield (%)[b] 3i
-	46	21
NaOH (3 drops, 5M)	99	97
$(Et)_3N$ (10 mol%)	99	98
Pyridine (10 mol%)	78	70

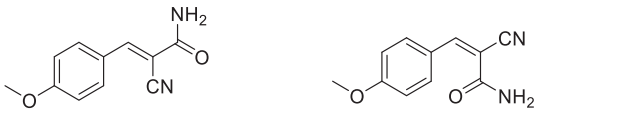
[a] MW: Microwave (55 W), 35 min; [b] CH: Conventional heating, 240 min.

By using the basic catalysts, an interesting phenomenon was observed. The yield of the reaction increased up to 99%, for adduct **3i**, in the presence of NaOH or TEA and resulted in a moderate to good yield in the presence of pyridine (78%) (Table **1**). Based on the fact that the *pKa* of the cyanoacetamide **2** in water is 8.53, the moderate yield could be explained because the pyridine has a low basic character and its conjugate acid (pyridium ion) in water has *pKa* 5.25. On the other hand, the good yields were understood because

TEA and hydroxide ion have conjugated acids with higher *pKa* values (in water) than cyanoacetamide **2.**

The reactions were developed under conventional heating conditions and required reaction times of 240 min to provide good yields (70-98%), demonstrating with this experiment the efficiency of the MW irradiation to reduce the reaction time and to provide high yields (Table **1**).

In addition, through synthetic methodology it is possible to obtain two diastereoisomers, i.e., the *E*-**3i** and *Z*-**3i** for the Knoevenagel condensation using 4-methoxybenzaldehyde **1i** and cyanoacetamide **2** (Fig. **1**).

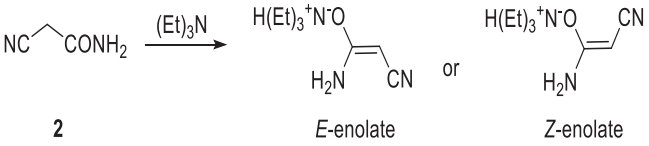


(*E*)-2-cyano-3-(4-methoxyphenyl) acrylamide **3i**

(*Z*)-2-cyano-3-(4-methoxyphenyl) acrylamide **3i**

Fig. (1). Chemical structures of the possible diastereoisomers (*E)*-**3i** and (*Z)*-**3i**.

The suggestion for the formation of *E*- and *Z*-diastereoisomers **3i** may be due to the transition state of the enolate ion formed from cyanoacetamide **2** in the presence of TEA (Fig. **2**). Thus, depending on the type of base, it may favor the formation of a preferred transition state and consequently the production of *E*- or *Z*-diastereoisomeric adduct **3i**.



2 *E*-enolate *Z*-enolate

Fig. (2). Proposal to ion enolates formation using TEA and cyanoacetamide **2** to produce (*E)*-**3i** and (*Z)*-**3i** [27].

As shown in Fig. **2**, there is the possibility of forming two transition states (ET_1 and ET_2). For the case of TEA, this determines that the formation of the *E*-isomer **3i** is the major product because there are few steric and electronic effects between the TEA, acid hydrogen and the carbonyl group of amide present in the cyanoacetamide **2** (ET_1). In addition, for this transition state it is possible to stabilize the interaction between the CN and NH_2 groups.

The transition state ET_2 for the *Z*-isomer **3i** did not exhibit the stabilizing interaction between the CN and NH_2 groups. However, this transition state has two destabilizing interactions between TEA and the CN group, and of the CN group with the amide carbonyl. Therefore, the *E*-enolate **3i** was obtained preferentially, since the interactions of destabilization are less significant in relation to the *Z*-enolate **3i** interactions (Fig. **2**).

The Knoevenagel adduct **3i** was characterized by FTIR, NMR, GC-MS techniques. For FTIR, the adduct **3i** showed one band at 2209 cm^{-1} characteristic of the cyano group and an important band at 1698 cm^{-1} characteristic of double bond of alkene.

^{1}H NMR spectrum of the adduct **3i** showed singlet signal at 8.26 ppm (s, 1H) for vinylic hydrogen, at 7.97 ppm showed double doublet signal for *ortho*-aromatic hydrogens neighbor of methoxy group. In the region at 7.0 ppm this showed a double doublet signal for *ortho*-aromatic hydrogens neighbor of vinylic group, and a singlet signal at 3.90 ppm for the methoxyl hydrogens.

In the ^{13}C NMR spectrum the signal for a carbonyl amide group was observed at 166.6 ppm, the signal *ipso*-aromatic carbon attached neighbor of vinylic group at 162.6 ppm, signal vinylic carbon at 153.5 ppm, and a signal for *ortho*-aromatic carbons neighbors of the vinylic group at 133.3 ppm. For *ortho*-aromatic carbons neighbors of the methoxy group a signal was observed at 124.2 ppm, a signal of cyano carbon at 114.7 ppm, a signal of geminal carbon attached in the cyano and amide groups at 99.3 and the signal of methoxy carbon at 55.61 ppm. By NMR analysis, it was not possible to verify the geometric formation of the possible diastereoisomers *E*-**3i** and *Z*-**3i**.

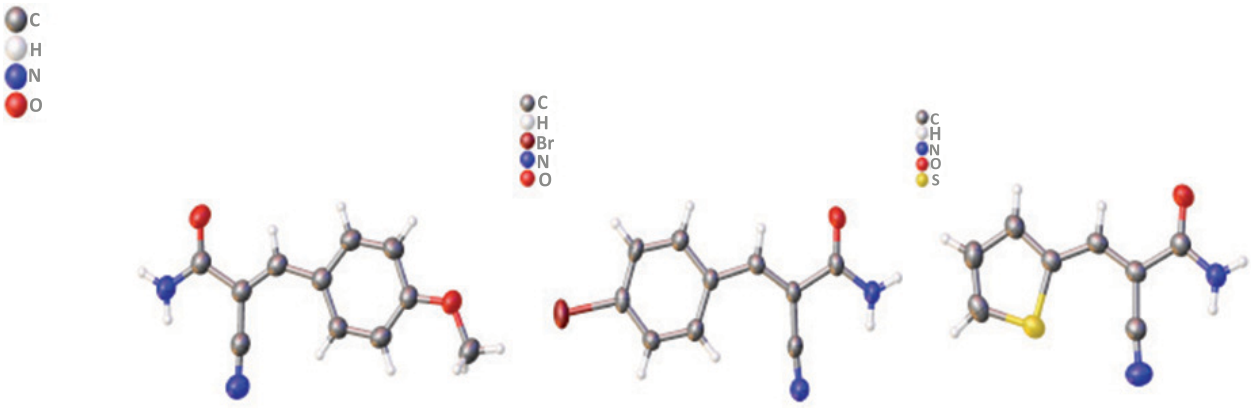


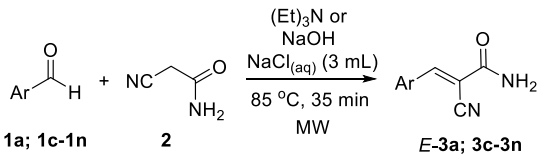
Fig. (3). Ortep type view of the asymmetric unit of the Knoevenagel adducts **3i, 3a** and **3l** obtained in reaction with $(Et)_3N$ or NaOH.

The single crystal X-ray structure of the adducts **3i**, **3a**, and **3l** were successfully elucidated and the ortep type views of its asymmetric unit (ortep diagrams) can be seen in Fig. **3**, respectively. The crystallographic analysis confirmed the geometric configuration of these adducts. In all cases, the diastereoisomer obtained had an *E*-configuration by using NaOH or TEA. It is noteworthy that, evidently for the first time in the literature, X-ray crystal structures were reported to confirm the geometry of this type of Knoevenagel adducts.

According to the proposed crystallographic models, the bond lengths of the molecules could be accurately determined. The N1-C1 bond distances of the Knoevenagel adducts have values in the 1.324-1.328 Å range in good agreement with those expected for amides groups. The C3≡N2 bond lengths (1.137–1.141 Å) are consistent with the C≡N triple bonds of the cyano group. Moreover, C1–O1 bond lengths (1.223-1.230 Å) show values characteristic of the carbonyl groups of amides.

Therefore, we have optimized the reactional conditions for Knoevenagel condensation in the preparation of adduct **3i**, and the reaction scope was expanded under the same conditions described using several aromatic aldehydes **1a** and **1c-1n** and cyanoacetamide **2** under MW irradiation (Table **2**).

Table 2. Synthesis of Knoevenagel adducts *E*-3a, 3c-3n using aromatic aldehydes 1a, 1c-1n and cyanoacetamide 2 under MW irradiation (55 W) using $NaCl_{(aq)}$.



1a; 1c-1n **2** ***E*-3a; 3c-3n**

Ar =Aromatic Group*	Yield (%)[a]	Yield (%)[b]
4-BrC_6H_4 **1a**	95	91
4-ClC_6H_4 **1c**	94	92
4-FC_6H_4 **1d**	97	94
4-$N(CH_3)_2C_6H_4$ **1e**	95	92
4-$NO_2C_6H_4$ **1f**	97	95
4-OHC_6H_4 **1g**	90	90
3,4,5-$OCH_3C_6H_2$ **1h**	96	95
Furfural **1j**	99	99
Syringaldehyde **1k**	93	93
Thiofene **1l**	95	94
Vanilin **1m**	98	96
Isovanilin **1n**	91	95

[a] $(Et)_3N$; [b] NaOH; *In all cases the major isomer showed geometric *E*-configuration.

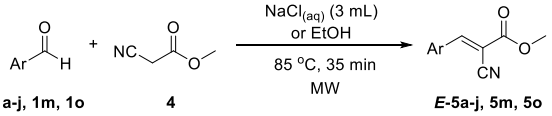
As shown in Table **2**, independently of the substituent type (electron donating or electron withdrawing group), the number of substituent groups, as well as the position of substituent group in the aromatic ring (*meta* and *para*), the Knoevenagel adducts *E*-**3a**, **3c-3n** were obtained with high yields (90-99%).

The methodology developed in this part of the work could be considered efficient when compared with some works reported in the literature. The synthesis of Knoevenagel adducts between aromatic aldehydes and cyanoacetamide, in general, needed long periods of time (2-24 h) and specific catalysts like piperidine [28], Cu [29], *N*-methyl morpholine acetate [30], 2,4,6-trichloro-1,3,5-triazine [31] are required to provide good yields (70-98%). In the cases mentioned above, single-crystal X-ray diffraction data for these adducts were not reported.

Adding up this work, considering the optimized conditions for the synthesis of *E*-2-cyano-3-arylacrylamide derivatives, a series of Knoevenagel condensations between aromatic aldehydes and methyl cyanoacetate **4**, were carried out under MW irradiation. However, it was experimentally observed that using the saturated NaCl solution as solvent resulted in moderate yields for the adducts **5a**, **5c**, **5d**, **5i**, **5j** and **5o** (46-61%).

In these cases, the low yields could be a function of the low solubility of the compounds since the reagents (aldehydes and methyl cyanoacetate) were insoluble in NaCl solution. Then, the reaction solvent was exchanged for EtOH, which resulted in significant increase for most adducts yields (70-90%), as showed in Table **3**.

Table 3. Synthesis of Knoevenagel adducts *E*-5a-j, 5m and 5o using aromatic aldehydes 1a-j, 1m and 1o and methyl cyanoacetate 4 under MW irradiation (55 W) using H_2O or EtOH as solvent.



1a-j, 1m, 1o **4** ***E*-5a-j, 5m, 5o**

Ar =Aromatic group	Yield (%)[a]	Yield (%)[b]
4-BrC_6H_4 **1a**	51	82
4-$CO_2CH_3C_6H_4$ **1b**	82	(-)
4-ClC_6H_4 **1c**	48	80
4-FC_6H_4 **1d**	54	80
4-$N(CH_3)_2C_6H_4$ **1e**	71	79
4-$NO_2C_6H_4$ **1f**	89	(-)
4-OHC_6H_4 **1g**	88	(-)
3,4,5-$OCH_3C_6H_2$ **1h**	70	(-)
4-$OCH_3C_6H_4$ **1i**	55	70
Furfural **1j**	46	90
Vanilin **1m**	88	(-)
C_6H_5 **1o**	61	89

[a] = $NaCl_{(aq)}$ as solvent; [b] = EtOH as solvent; (-) These reactions were not realized because they have already shown good yield values using $NaCl_{(aq)}$.

The X-ray crystal structure of the adduct **5e** was also successfully elucidated and the Ortep type view of the asymmetric unit of this compound can be seen in Fig. (**4**). The crystallographic analysis confirmed that the adduct had an *E*-configuration. It is noteworthy that, for the first time in the literature, a single crystal structure was reported to confirm the geometry of this type of Knoevenagel adduct.

The methodology developed in this part of the work could once again be considered highly efficient when compared with some studies reported in the literature. The orthodox Knoevenagel condensations reported between aromatic aldehydes and methyl cyanoacetate **4**, in some cases, require long periods of time (up to 24 h) [32], solvents that are aggressive to the environment like toluene [33], and specific catalysts such as ionic liquids [32] or $(NH_4)_2HPO_4$ [34], to achieve good yields. It is noteworthy that in the cases mentioned above the single-crystal X-ray structure of these adducts was not reported.

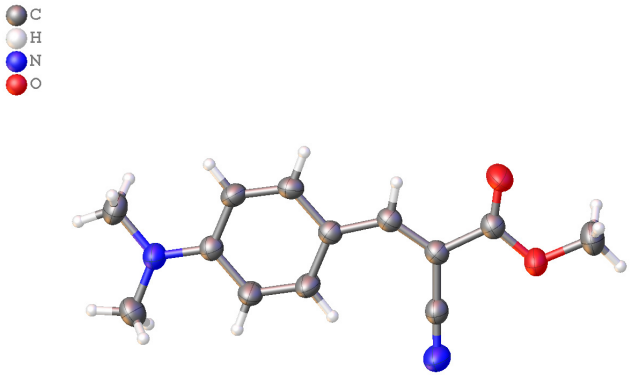


Fig. (4). Ortep type view of the asymmetric unit of the Knoevenagel adduct **5e**.

CONCLUSION

In this study, we have demonstrated that the use of low-power MW irradiation (55 W) in the synthesis by Knoevenagel condensation of *E*-2-cyano-3-aryl derivatives reduced the required reaction time from hours to minutes. Another advantage presented here was the development of a synthetic protocol that operates under green solvents conditions. Finally, this study proposes an interesting synthetic methodology to obtain Knoevenagel adducts in a short reaction time (35 min) with high yields (70-99%). Also, the single-crystal X-ray structure of the Knoevenagel adducts was determined confirming the geometric configuration for *E*-isomers.

LIST OF ABBREVIATIONS

CAPES = *in Portuguese:* Coordenação de Aperfeiçoamento de Pessoal de Nível Superior

CNPq = *in Portuguese:* Conselho Nacional de Desenvolvimento Científico e Tecnológico

FAPESP = *in Portuguese:* Fundação de Amparo à Pesquisa do Estado de São Paulo

FTIR = Fourier Transform Infrared Spectroscopy

GC-MS = Gas Chromatography – Mass Spectrometry

H = Hour/Hours

EtOH = Ethanol

Min = Minutes

MW = Microwave

NMR = Nuclear Magnetic Resonance

CH = Conventional Heating

THF = Tetrahydrofuran

TEA = Trimethylamine

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this study are available within the article and in its supplementary material.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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David Esteban Quintero Jimenez and Lucas Lima Zanin designed, performed and wrote the manuscript. Luan Farinelli Diniz and Javier Alcides Ellena: collected and analyzed the X-ray data; André Luiz Meleiro Porto*: designed and wrote the manuscript.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

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