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A rapid synthesis of highly functionalized 2-pyridones and 2-aminopyridines via a microwave-assisted multicomponent reaction

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Abstract
In the present study a novel and efficient procedure for the synthesis of 2-pyridones and 2-aminopyridines from the same enaminone has been developed. This protocol based on the new multicomponent reaction under solvent-free conditions and microwave irradiations, offers advantages in terms of higher yields, short reaction times, and mild reaction conditions.

Keywords: Enaminone, 2-Pyridones, 2-Aminopyridines, Multicomponent reaction, Solvent-free reaction, Microwave irradiations.

1. Introduction
In recent decades, heterocycles compounds have received a significant attention in pharmaceutical industry owing to their interesting biological activities [1]. They displayed broad range of therapeutic activities, including antibacterial [2], antifungal [3], and antiviral [4-7], activities. A number of methods have been reported for the synthesis of the heterocycles [8-10].
Moreover, most of the drugs belong to the class of heterocyclic compounds. Heterocyclic compounds played a vital role in the metabolism of all living cells; large numbers of them are five and six membered heterocyclic compounds having one to three heteroatoms in their nucleus [11].The compounds may be of 2-pyridones and 2-aminopyridine have shown multifarious biological activities and their synthesis has been widely investigated [12-17]. Some of these strategies require refluxing for hours in organic solvents, use of expensive catalysts and tedious work-up. With the increasing public concern over environmental degradation, the use of solvent-free methods represents very powerful green chemical technology procedures from both the economical and synthetic point of view.They have many advantages, such as reduced pollution, lower cost, and simplicity in processing which are beneficial to the industry as well as to the environment [18-23]. There is also another route to combine economic aspects with the environmental, that is, the multicomponent reaction (MCR) assisted by microwave irradiation [24-25].This process consists of two or more synthetic steps which are taken without isolation of any intermediate with several advantages like short reaction times, uniform heating, higher yields, enhanced selectivity, and associated ease of manipulation.

2. Experimental
2.1. Materials and methods
The melting points were measured using a Bank Kofler HEIZBANK apparatus standard WME 50-260°C and were uncorrected. IR spectra were obtained with solids with a Fourier transform Perkin Elmer Spectrum One

with ATR accessory. Only significant absorptions are listed. The ^{1}H NMR spectra were recorded at 400 MHz, on a Brüker AC 400 spectrometers and ^{13}C NMR spectra were recorded in the same spectrometers at 100.6 MHz. Samples were registered in $CDCl_3$ solutions using TMS as an internal standard. The chemical shifts are expressed in δ units (ppm) and quoted downfield from TMS. The multiplicities are reported as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Microwave irradiation experiments use a domestic microwave.

2.2. Synthesis

General procedure 1: Synthesis of enaminone ***1***

An equimolar mixture of ethyl 3-oxobutanoate (1 mmol) and (1 mmol) of DMFDMA was irradiated under microwave conditions for 5 min. After cooling, the reaction mixture was diluted with 30 ml of CH_2Cl_2. The organic layer obtained was washed with (3 × 20 ml) of water, (10 ml) of saturated NaCl, dried on $MgSO_4$, filtered then evaporated under vacuum. The compounds ethyl 2-((dimethylamino) methylene)-3-oxobutanoate **1** was obtained as an orange oil with 90% of the yield.

- Ethyl 2-((dimethylamino)methylene)-3-oxobutanoate ***1***:

RMN ^{1}H ($CDCl_3$)δ_H : 1,29 (3H, t, O-CH_2-CH_3); 2,30 (3H, s, CO-CH_3); 2,30 (3H , s, NCH_3); 3,06 (3H, s, NCH_3); 4,20 (2H, q, O-CH_2-CH_3); 7,60 (1H, s, HC=C-N$(Me)_2$);RMN ^{13}C ($CDCl_3$) δ_c: 14,81 (O-CH_2-CH_3); 24,25 (CO-CH_3); 39,66 (NCH_3); 43,29 (NCH_3); 62,42 (O-CH_2-CH_3); 103,61 (C=CH) ; 159,33 (C=CH); 164,86 (CO-OEt), 196,25 (CO-CH_3); IRν_{max} cm^{-1}: 1533 (C=C); 1645(C=O); 1685 (C=O).

General procedure 2: Synthesis of 2-pyridones ***I_{1-4}:***

A mixture of ethyl 2-((dimethylamino)methylene)-3-oxobutanoate **1** (1 mmol), primary amine (1 mmol) and ethyl 2-cyanoacetate (1 mmol) were irradiated under microwave conditions for 2 min. After cooling, the solid obtained was washed several times with diethyl ether to give 2-pyridone derivatives ***I_{1-4}.***

- Ethyl 1-benzyl-5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate ***I_1:***

The general procedure 2, using (0,001 mol ; 0,185 g) of enaminone**1** and (0,001 mol ; 0,105g) benzylamine, gave 91% of compound I_1as white solid, mp 198°C; RMN ^{1}H ($CDCl_3$)δ_H : 1,34 (3H, t, J_{H-H} = 7,2 Hz ,CH_2-CH_3); 2,76 (3H, s, -C=C-CH_3); 4,34 (2H, q, J_{H-H} = 7,2 Hz, CH_2-CH_3); 4,66 (2H, s, CH_2-Ph); 7,24-7,31 (5H, m, H_{arom}); 8,75 (1H, s, CH=C-CN); RMN ^{13}C ($CDCl_3$) δ_C: 13,9 (C=C-CH_3); 24,20 (OCH_2-CH_3); 44,96 (CH_2-Ph); 61,78 ((OCH_2-CH_3); 106,12 (C=C(CN)); 116,26 (CN); 128,77-134,25 (6 ×C_{arom}); 142,35 ((CO_2Et)C=C(CH_3)); 142,39 ((CO_2Et)C=C(CH_3); 163,83 (C=C(CN)); 156,92 (C=O); 167,66 (CO_2Et);IRν_{max} cm^{-1}: 1512(C=C); 1608 (C=C); 1643(C=O); 1682 (C=O); 2219 (CN).

- Ethyl 5-cyano-1,2-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxylate ***I_2:***

The general procedure 2, using (0,001 mol ; 0,185 g) of enaminone**1** and (0,001 mol ;0,075g) methylamine, gave 88% of compound **I_2**as white solid, mp 187°C; RMN ^{1}H ($CDCl_3$)δ_H : 1,38 (3H, t, J_{H-H} = 7,2 Hz ,CH_2-CH_3); 2,80 (3H, s, -C=C-CH_3), 3,89 (3H, s, NCH_3); 4,38 (2H, q, J_{H-H} = 7,2 Hz, CH_2-CH_3); 8,78 (1H, s, CH=C-CN);RMN ^{13}C ($CDCl_3$) δ_C: 13,91 (C=C-CH_3); 24,20 (OCH_2-CH_3); 34,82 (NCH_3); 61,78 ((OCH_2-CH_3); 106,12 (C=C(CN)); 115,86 (CN); 142,35 (C=C(CH_3)); 143,25 (C=C(CH_3); 164,55 (C=C(CN)); 157,98 (C=O); 167,66 (CO_2Et); IRν_{max} cm^{-1}: 1507 (C=C); 1605 (C=C); 1648 (C=O); 1680 (C=O); 2199 (CN).

- Ethyl 1-butyl-5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate ***I_3:***

The general procedure 2, using (0,001 mol ; 0,185 g) of enaminone**1**and (0,001 mol ; 0,073g) butylamine, gave 83% of compound **I_3**as white solid, mp 192°C;RMN ^{1}H ($CDCl_3$)δ_H : 0,87 (3H, t, J_{H-H} = 7,2Hz, CH_2 -CH_3); 1,31 (3H, t, J_{H-H} = 7,2Hz ,CO_2-CH_2-CH_3); 1,32 (2H, m, -N-CH_2-CH_2-CH_2 –CH_3); 1,33 (2H, m, N-CH_2-CH_2-CH_2 –CH_3); 2,61(2H, t, J_{H-H} = 7,2 Hz N-CH_2-CH_2-CH_2 –CH_3) ; 2,76 (3H, s, CO_2Et-C=C-CH_3); 4,26 (2H, q, J_{H-H} = 7,2 Hz, CO_2-CH_2-CH_3); 8,75 (1H, s, CH=C-CN).

RMN ^{13}C ($CDCl_3$)δ_C: 13,5 (-$(CH_2)_3$- CH_3); 13,8 (C=C-CH_3); 20,3 (N-CH_2-CH_2-CH_2–CH_3); 24,20 (OCH_2-CH_3); 30,6 (N-CH_2-CH_2-CH_2 –CH_3); 42,7 (N-CH_2-CH_2-CH_2 –CH_3); 62,66 ((OCH_2-CH_3); 107,12 (C=C(CN)); 115,98 (CN); 143,31 ((CO_2Et)C=C(CH_3)); 144,20 ((CO_2Et)C=C(CH_3); 165,15 (C=C(CN)); 158,18 (C=O); 168,63 (CO_2Et); IRδ_{max} cm^{-1}: 1508 (C=C); 1610 (C=C); 1645(C=C);1682 (C=O); 2222 (CN).

- Ethyl 5-cyano-1-isopropyl-2-m2thyl-6-oxo-1,6-dihydropyridine-3-carboxylate ***I_4*** :

The general procedure 2, using (0,001 mol ; 0,185 g) of enaminone 1 and (0,001 mol ;0,055g) isopropylamine, gave 79% of compound **I_4** as white solid, mp 182°C;RMN ^{1}H ($CDCl_3$)δ_H : 1,36 (3H, t, J_{H-H} = 7,2Hz ,CH_2-CH_3); 1,40 (6H, d, J_{H-H} = 7,2Hz, 2×CH_3); 2,81 (3H, s, -C=C-CH_3); 4,38 (2H, q, J_{H-H} = 7,2Hz, CH_2-CH_3); 4,48-4,68 (1H, m, CH-Me_2); 8,81 (1H, s, CH=C-CN); RMN ^{13}C ($CDCl_3$) δ_C: 13,9 (C=C-CH_3); 22,55 (2×CH_3); 24,20

(OCH_2-CH_3); 49,61 (CH-Me_2); 62,73 ((OCH_2-CH_3); 105,19 (C=C(CN)); 115,86 (CN); 143,78 ((CO_2Et)C=C(CH_3)); 142,28 ((CO_2Et)C=C(CH_3); 165,54 (C=C(CN)); 157,98 (C=O); 168,26 (CO_2Et); IR ν_{max} cm^{-1}: 1506 (C=C); 1605 (C=C); 1645 (C=O);1684 (C=O); 2222 (CN).

General procedure 3: Synthesis of 2-aminopyridines ***II*$_{1-4}$**:

A mixture of ethyl 2-((dimethylamino)methylene)-3-oxobutanoate **1**(1 mmol), primary amine (1 mmol) and malononitrile (1 mmol) were irradiated under microwave conditions for 2 min. After cooling, the solid obtained was washed several times with diethyl ether to give 2- aminopyridines derivatives ***II*$_{1-4}$**.

- Ethyl 2-(benzylamino)-3-cyano-5-methylisonicotinate ***II*$_1$** :

The general procedure 3, using (0,001 mol ; 0,185 g) of enaminone**1** and (0,001 mol ; 0,105g) benzylamine, gave 93% of compound **II$_1$**as white solid, mp 280°C;RMN ^{1}H ($CDCl_3$)δ_H :1,36 (3H, t, J_{H-H}= 7,4 Hz ,CH_2-C**H$_3$**); 2,79 (3H, s, -C=C-C**H$_3$**); 4,36 (2H, q, J_{H-H}= 7,4 Hz, C**H$_2$**-CH_3); 4,75 (2H, d, J_{H-H} = 5,20 Hz, NH-C**H$_2$**); 5,38 (1H, t, J_{H-H}= 5,20 Hz, N**H),** 7,25-7,35 (5H, m, **H**$_{arom}$);8,68 (1H, s, C**H**=N); RMN ^{13}C ($CDCl_3$) δ_C: 14,12 (C=C-**C**H_3); 24,20 (OCH_2-**C**H_3); 45,65 (**C**H_2); 61,78 ((OCH_2-CH_3);106,12 (C=**C**(CN)); 115,86 (**C**N);129,76-130,12 (6×**C**$_{arom}$);142,35 ((CO_2Et)**C**=C(CH_3)); 143,25 ((CO_2Et)C=**C**(CH_3); 154,23 (**C**=N); 164,55 (**C**=C(CN)); 167,66 (**C**O_2Et); IRν_{max} cm^{-1}: 1582C=C);1556 (C=C); 1647(C=O); 2219 (CN); 3364 (NH).

- Ethyl 3-cyano-5-methyl-2-(methylamino)isonicotinate ***II*$_2$:**

The generalprocedure 3, using (0,001 mol ; 0,185 g) of enaminone**1**and (0,001 mol ;0,075 g) methylamine, gave 89% of compound **II$_2$**as white solid, mp 214°C;RMN ^{1}H ($CDCl_3$)δ_H : 1,37 (3H, t, J_{H-H}= 7,2 Hz ,CH_2-CH_3); 2,78 (3H, s,-C=C-CH_3); 3,01 (3H, d, J_{H-H} = 4,20 Hz, NH-CH_3); 4,38 (2H, q, J_{H-H}= 7,2 Hz, CH_2-CH_3); 5,35 (1H, t, J_{H-H}= 4,20 Hz, NH),8,78 (1H, s, CH=N); RMN ^{13}C ($CDCl_3$) δ_C: 14,12 (C=C-CH_3); 24,20 (OCH_2-CH_3); 29,30 (NH-CH_3); 61,78 ((OCH_2-CH_3); 106,12 (C=C(CN)); 115,86 (CN); 142,35 (-C=C(CH_3)); 143,25 (-C=C(CH_3); 154,23 (C=N); 164,55 (C=C(CN)); 167,66 (CO_2Et); IRν_{max} cm^{-1}: 1585(C=C); 1557 (C=C); 1648(C=O); 2217 (CN); 3365 (NH).

- Ethyl 2-(butylamino)-3-cyano-5-methylisonicotinate ***II*$_3$** :

The general procedure 3, using (0,001 mol ; 0,185 g) of enaminone 1and (0,001 mol ; 0,073g) butylamine, gave 86% of compound II$_3$as white solid, mp 201°C; RMN ^{1}H ($CDCl_3$)δ_H : 0,87 (3H, t, J_{H-H} = 7,2Hz, -(CH_2)$_3$- CH_3); 1,31 (3H, t, J_{H-H}= 7,2 Hz ,CH_2-CH_3); 1,32 (2H, m, -N-CH_2-CH_2-CH_2 –CH_3); 1,33 (2H, m, N-CH_2-CH_2-CH_2 –CH_3); 2,63(2H, t, J_{H-H}= 4,30 Hz , N-CH_2-CH_2-CH_2 –CH_3) ; 2,77 (3H, s, -C=C-CH_3); 4,39 (2H, q, J_{H-H}= 7,2Hz, CH_2-CH_3); 5,37 (1H, t, J_{H-H}= 4,30 Hz, NH);8,78 (1H, s, CH=N); RMN ^{13}C ($CDCl_3$) δ_C: 13,5 (-(CH_2)$_3$- CH_3); 14,12 (C=C-CH_3); 20,3 (N-CH_2-CH_2-CH_2 –CH_3); 24,20 (OCH_2-CH_3); 30,6 (N-CH_2-CH_2-CH_2 –CH_3); 42,7 (N-CH_2-CH_2-CH_2 –CH_3); 61,78 ((OCH_2-CH_3); 106,12 (C=C(CN)); 115,86 (CN); 142,35 (-C=C(CH_3)); 143,25 (-C=C(CH_3); 154,23 (C=N); 164,55 (C=C(CN)); 167,66 (CO_2Et); IRν_{max} cm^{-1}: 1582 (C=C); 1558 (C=C); 1644 (C=O); 2219 (CN); 3364 (NH).

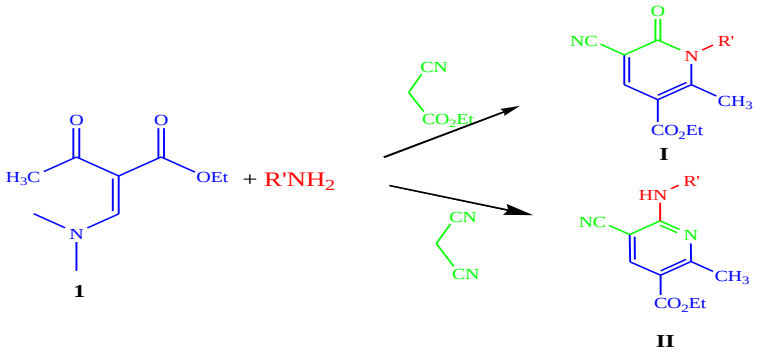
- Ethyl 3-cyano-2-(isopropylamino)-5-methylisonicotinate ***II*$_4$** :

The general procedure 3, using (0,001 mol ; 0,185 g) of enaminone **1** and (0,001 mol ; 0,055g) isopropylamine, gave 80% of compound ***II*$_4$** as white solid, mp 214°C; RMN ^{1}H ($CDCl_3$)δ_H : 1,31 (6H , d, J_{H-H}= 6,2 Hz , 2×CH_3); 1,36 (3H, t, J_{H-H}= 7,2 Hz , CH_2-CH_3); 2,77 (3H, s, -C=C-CH_3); 4,35-4,56 (1H, m, CH-Me_2);4,39 (2H, q, J_{H-H}= 7,2 Hz, CH_2-CH_3); 5,33 (1H, t, J_{H-H}= 4,0 Hz, NH), 8,76 (1H, s, CH=N); RMN ^{13}C ($CDCl_3$) δ_C: 14,12 (C=C-CH_3); 21,86 (2×CH_3); 24,20 (OCH_2-CH_3); 42,32 C(Me_2); 61,78 ((OCH_2-CH_3); 106,12 (C=C(CN)); 115,86 (CN); 142,35((CO_2Et)C=C(CH_3)); 143,25 ((CO_2Et)C=C(CH_3); 154,23 (C=N); 164,55 (C=C(CN)); 167,66 (CO_2Et); IRν_{max} cm^{-1}: 1582(C=C); 1558 (C=C); 1649(C=O); 2216 (CN); 33654 (NH).

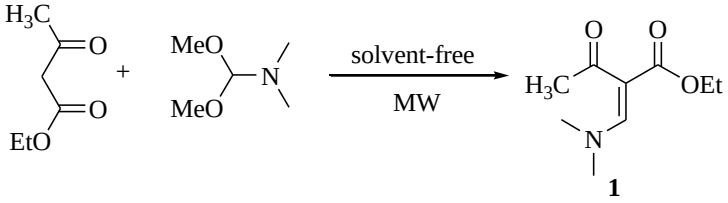
3. **Results and discussion**

As a part of systematic interest in the synthesis of nitrogen heterocyclic systems [26-29], and in continuation to our interest in the utility of enaminones as building blocks for the synthesis of novel heterocycle [30], we present in this work versatile route to synthesize a new 2-pyridones **I** and 2-aminopyridine **II** by a new multicomponent reaction (MCR) assisted with microwave irradiation and under solvent free conditions (Scheme 1).

In extension of our previous works in preparation of enaminones using the *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA), here we have synthesized the ethyl 2-((dimethylamino) methylene)-3 oxobutanoate **1** using equimolar amounts of DMFDMA with ethyl 3-oxobutanoateinabsence of solvents and under microwave irradiation (Scheme 2).The yield of this reaction is excellent 90%.



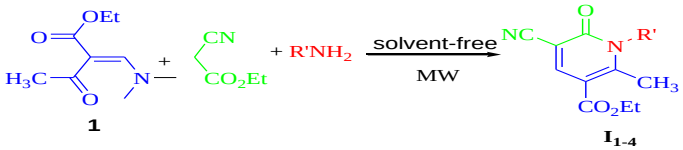
Scheme 1: MCR for the synthesis of 2-pyridones **I** and 2-aminopyridines**II**

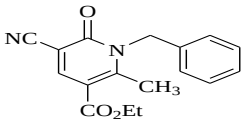
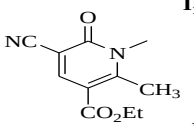
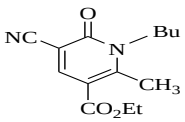
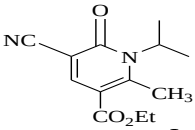


Scheme 2: Synthesis of the enaminone**1**

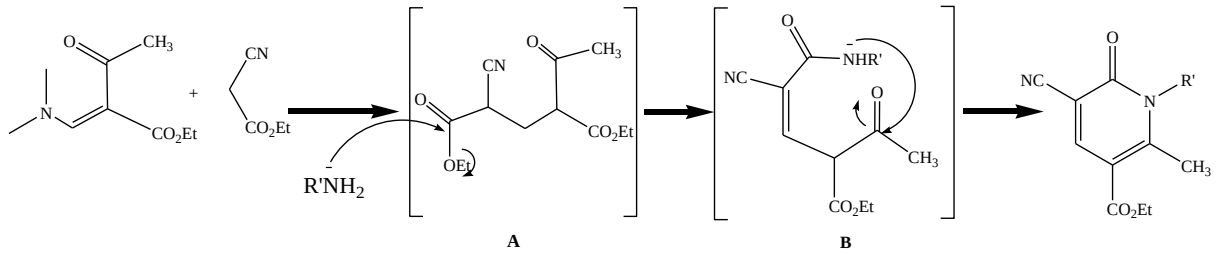
At first, and in order to optimize the reaction conditions, we have studied the synthesis of 2-pyridones **I** from multi-component condensation of enaminone**1**with ethyl 2-cyanoacetate, and benzylamine. They are frequently utilized in stoichiometric amounts and irradiate for a few minutes, we have observed that the best conditions for this reaction were solvent-free, and two minutes under microwave irradiation. Since the reaction could be carried out in this high yield (Table 1) we have used different primary amines in order to obtain a new 2-pyridones **I**. Purification of all crude mixture by diethyl ether afforded white crystalline solids, which was shown to be 2-pyridones $\mathbf{I}_{1\text{-}4}$, clearly identified by standard spectroscopic methods.

Table 1:Synthesis of 2-pyridones $\mathbf{I}_{1\text{-}4}$



R'	Product	Yield (%)
$C_6H_5CH_2$-	 $\mathbf{I}_1$	91
CH_3-	 $\mathbf{I}_2$	88
CH_3-CH_2-CH_2-CH_2-	 $\mathbf{I}_3$	83
$(CH_3)_2CH$-	 $\mathbf{I}_4$	79

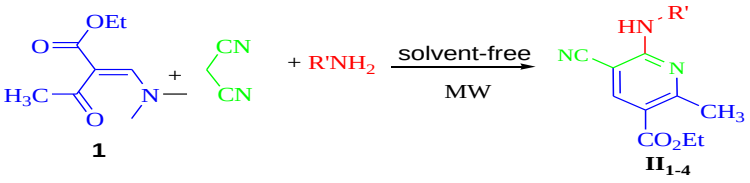
A possible mechanism for the formation of the 2-pyridones was described in (Scheme 3). First, intermediate **A** was obtained by Michael-type addition of enaminone and ethyl 2-cyanoacetate, than condensation reaction between primary amine and intermediate **A** would produce intermediate **B**. Finally, the intramolecular condensation of intermediate **B** followed by inter-cyclisation to construct the 2-pyridone structure.



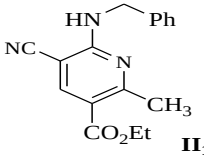
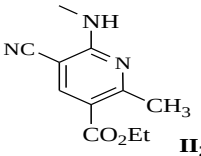
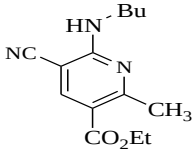
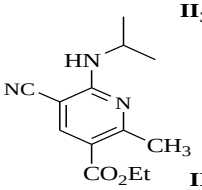
Scheme 3: Formation of 2-pyridones **II** $_{1\text{-}4}$ structures

Encouraged by this success, we have extended the preparative utility and generality of this multicomponent for the synthesis of 2-aminopyridines **II**$_{1\text{-}4}$.We have prepared this second heterocycle under the last optimized conditions and afforded the corresponding products **II** $_{1\text{-}4}$ (Table 2) in good to high yields. Similarly, the enaminone**1** also was reacted under the same conditions but in this time using the malononitrile with different primary amines and provided the desired products without any difficulties. This reaction gives a white solid for which structure has been assigned on the basis of a spectral data.

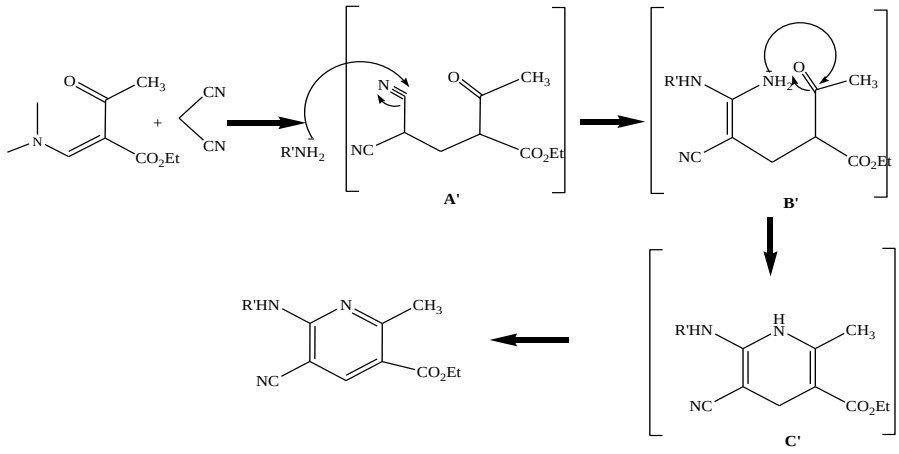
Table 2:Synthesis of 2-aminopyridines **II**$_{1\text{-}4}$



1 **II**$_{1\text{-}4}$

R'	Product	Yield (%)
$C_6H_5CH_2$-	 **II**$_1$	93
CH_3-	 **II**$_2$	89
CH_3-CH_2-CH_2-CH_2-	 **II**$_3$	86
$(CH_3)_2$CH-	 **II**$_4$	80

This new MCR reaction was a model one-pot reaction between a three compounds used here (enaminone, active methylene and primary amine), so we proposed here a reaction mechanism for our 2-aminopyridines structures **II_{1-4}**(Scheme 4)**.**



Scheme 4: Proposed reaction mechanism for the synthesis of 2-aminopyridines **II_{1-4}**

We proposed here that the enaminone react at the first with malononitrile via Miachael reaction to afford an initial intermediate **A'.** However the intermediate **B'** was obtained by a condensation reaction between primary amines and the nitrile groups of intermediate **A'**, than the product **B'** inter-cyclized to give the product **C'.** The reaction finished by an aromatization step to afford the 2-aminopyridines structure.

Conclusions

In summary, we have developed a simple and efficient methodology for the synthesis of 2-pyridones and 2-aminopyridines by a one-pot, multi-component reaction under MW irradiations. Some advantageous of this solvent-free protocol include a simple manipulation, high products yields, short reaction times, and elimination of toxicsolvents.

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