



Research Article

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## Microwave Assisted Synthesis of Tri Substituted Pyridine-3-Carbonitrile Derivatives Using 3-Aminobut-2-Enenitrile

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### ABSTRACT

A microwave intervened synthesis of tri substituted pyridine subsidiaries by a three-segment response of chalcones, 3-aminobut-2-enenitrile, and ammonium acetate managed 2,4,6-trisubstituted pyridine-3-carbonitrile derivatives in reasonably good yields. FTIR, NMR, HRMS and SCXRD built up the structures of all new compounds.

**Keywords:** MW mediated synthesis; 3-aminobut-2-enenitrile; Pyridine derivatives.

### INTRODUCTION

In nitrogen-containing heterocyclic compounds, pyridine and its analogues are attractive targets because of their pivotal roles in natural products, pharmaceutical compounds, agrochemicals, chiral ligands, functional materials, and synthetic intermediates. The interest in their synthesis and chemistry continues undiminished due to their wide range of applications [1,2]. Microwave-assisted organic chemistry (MAOC) is one of the high-speed techniques, which has acquired great attention over conventional method of synthesis in recent years. With no direct contact between the chemical reactants and energy source, the advantages of performing various organic reactions under microwave (MW) irradiation conditions are the high yield, significant acceleration of the rate of the chemical reactions, minimal or side reactions. Carrying out the reaction in the absence of solvent or with very small amount of solvent makes the method eco-friendly [3]. A One-pot solvent free synthesis of 2,4,6-trisubstituted pyridines by condensation of various aldehydes or ketones and ammonium acetate have been attempted under conventional and microwave heating method. In many pyridine synthetic routes, amines or ammonium salts are used as nitrogen sources [3-6]. In this study, we have synthesised poly substituted pyridine derivatives from chalcones and 3-aminobut-2-enenitrile under conventional and microwave heating method conditions.

### EXPERIMENTAL SECTION

#### Materials and Methods

The FT-IR spectra were recorded on a SPECTRUM 400 FTIR spectrophotometer.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were taken from Bruker Advance DPX-300 MHz FT-NMR spectrometer (400 MHz) in  $\text{DMSO-}d_6/\text{CDCl}_3$ . The mass

spectra were recorded using LC-Q-ToF (Xevo, G2Q-ToF MS System, Waters). Thin-layer chromatography (TLC) using Merck 60 F254 TLC plates monitored the progress of the reactions. MPHT melting point apparatus recorded melting points. Microwave assisted syntheses were carried out using a Microwave synthesizer (Anton Paars, Monowave 300). Spectrochem, Alfa-aiesr and MERK supplied the chemicals.

### General Procedure

**Synthesis of chalcones (1a-f):** To a mixture of acetophenone, (5 mmol) and substituted benzaldehyde (5 mmol) dissolved in minimum quantity of ethanol, 40% NaOH (5 ml) was added drop-wise while stirring. The stirring was continued for 3 to 4 hours at room temperature to precipitate chalcone. Thereafter the reaction mixture was poured into ice-cold water; the precipitated chalcone was filtered off, washed with cold water until the washing became neutral and recrystallized from absolute ethanol to afford pure chalcones.

**Conventional method of synthesis of pyridine derivatives (3a-f):** An equimolar mixture of chalcone (1 mmol) and 3-aminobut-2-enenitrile (1 mmol) in absolute ethanol (10 ml) was taken in a round bottom flask; ammonium acetate (1.5 mmol) was added and refluxed for 10-16 h. The reaction was monitored through TLC, after the completion of the reaction; the reaction mixture was allowed to cool. The precipitated solid product filtered and washed with ice-cold water and recrystallized from absolute ethanol.

**MW mediated synthesis of pyridine derivatives (3a-f):** To an equimolar mixture of chalcone (1 mmol) and 3-aminobut-2-enenitrile (1 mmol) in absolute ethanol (10 ml) taken in a teflon septum capped reaction vessel, ammonium acetate (1.5 mmol) was added and placed in the microwave mono mode synthesiser. The reaction mixture was subjected to microwave irradiation at 130 °C for 30 minutes, and cooled to 55 °C in the reactor. After the completion of reaction, as indicated by TLC, the reaction mixture was kept for cooling at room temperature. After cooling, ice-cold water was added to it and the resulting solid compound was filtered off, washed with water, and recrystallized from absolute ethanol. Pure pyridine derivatives were obtained in good yield.

2-Methyl-4,6-diphenylpyridine-3-carbonitrile (**3a**) was obtained by their action between 1,3-diphenylprop-2-en-1-one **1a** (1 mmol, 208 mg), and 3-aminobut-2-ene-nitrile **2** (1 mmol, 82 mg) and ammonium acetate (1.5 mmol, 115 mg) in absolute ethanol (10 ml) under MW irradiation at 130°C. A slight yellowish white powder was obtained and was recrystallized from absolute ethanol. FTIR: 2198 cm<sup>-1</sup> (ν C≡N), 3059 cm<sup>-1</sup> (ν CH, Ar); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/DMSO-*d*<sub>6</sub>) δ 2.34 ppm (s, 3H, CH<sub>3</sub>), 7.26-7.77 ppm (10 ArH), 7.61 ppm (s, 1H, C5H), <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>/DMSO-*d*<sub>6</sub>) (ppm) 22.93 (CH<sub>3</sub>), 112.97 (CN) 166.26, 167.45, 168.17, 126.10 (C, pyridine ring), 127.04, 127.41, 127.52, 127.63, 128.37, 128.58, 128.88, 129.69, 132.20, 132.32, 132.62, 132.70 (Ar, C). (M+1)=271.11.

2-Methyl-4-(4-methoxyphenyl)-6-phenylpyridine-3-carbonitrile (**3b**) was obtained by the reaction between 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one **1b**, (1 mmol, 238 mg) and 3-aminobut-2-enenitrile **2** (1 mmol, 82 mg) and ammonium acetate (1.5 mmol, 115mg) in absolute ethanol (10 ml) under MW irradiation at 130 °C as an off-white powder. FTIR: 2216 cm<sup>-1</sup> (ν C≡N), 3060 cm<sup>-1</sup> (ν CH, Ar); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.9 ppm (s, 3H, CH<sub>3</sub>), δ 3.89 ppm (s, 3H, OCH<sub>3</sub>), δ 7.06-8.07 ppm (9ArH), δ 7.66 ppm (s, 1H, C5H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) 24.42 ppm (CH<sub>3</sub>), 55.45 ppm (OCH<sub>3</sub>), 114.5 ppm (C) 105.55, 162, 161, 159, 117.61 ppm (C pyridine ring), 127.47, 128.96, 129.92, 130.24, 137.91, 153.51 (ArC); [M+1]=301.1686.

2-Methyl-4-(4-cyanophenyl)-6-phenylpyridine-3-carbonitrile (**3c**) was obtained by the reaction between 3-(4-cyanophenyl)-1-phenylprop-2-en-1-one **1c** (1 mmol, 233 mg), and 3-aminobut-2-enenitrile **2** (1 mmol, 82 mg) and ammonium acetate (1.5 mmol, 115 mg) in absolute ethanol (10 ml) under MW irradiation at 130 °C as a yellowish white powder. FTIR: 2220 cm<sup>-1</sup> (ν C≡N), 3019 cm<sup>-1</sup> (ν CH, Ar), <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.97 ppm (s, 3H, CH<sub>3</sub>), δ 7.28-8.06 ppm (9ArH), δ 7.50 ppm (s, 1H, C5H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) 31.52 ppm (CH<sub>3</sub>), 113.75, 118.55 ppm (2 CN) 174.9, 141.73, 125.20 (C, pyridine ring), 128.52, 128.71, 128.81, 129.01, 132.49, 133.49, 137.29, 139.52 (ArC). [M+1]=296.11.

2-Methyl-4-(4-nitrophenyl)-6-phenylpyridine-3-carbonitrile (**3d**) was obtained by the reaction between 3-(4-nitrophenyl)-1-phenylprop-2-en-1-one **1d** (1 mmol, 253 mg), and 3-aminobut-2-enenitrile **2** (1 mmol, 82 mg) and ammonium acetate (1.5 mmol, 115 mg) in absolute ethanol (10 ml) under MW irradiation at 130 °C as a pale yellow crystalline powder. FTIR : 2221 cm<sup>-1</sup>(ν C≡N), 3301 cm<sup>-1</sup> (ν CH, Ar); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.59 ppm (s, 3H, CH<sub>3</sub>), δ 7.19- 8.21 ppm (9ArH), δ 7.96 ppm (s, 1H, C5H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) 29.30 ppm (CH<sub>3</sub>), 116.95 (CN) 124.24, 125.83, 148.76, 152.18, 178.13 (C, pyridine ring), 128.61, 128.84, 128.91, 128.95, 133.48, 137.55, 141.60, 141.46 (Ar C); [M+1]=316.14.

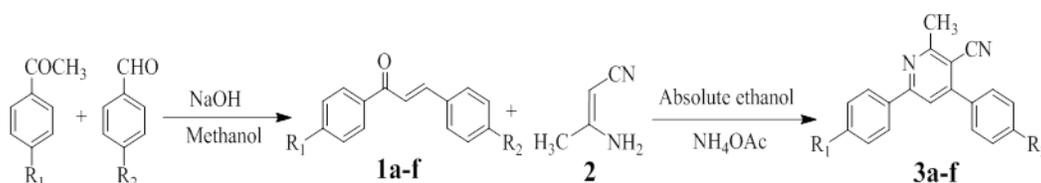
2-Methyl-4-(4-chlorophenyl)-6-phenyl pyridine-3-carbonitrile (**3e**) was obtained by the reaction between 3-(4-chlorophenyl)-1-phenylprop-2-en-1-one **1e**,(1 mmol, 243 mg), and 3-aminobut-2-enenitrile **2** (1 mmol, 82 mg) and ammonium acetate (1.5 mmol, 115 mg) in absolute ethanol (10 ml) under MW irradiation at 130 °C as an off-white powder. FTIR 2212 cm<sup>-1</sup> (ν C≡N), 3052 cm<sup>-1</sup>(ν Ar CH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.16 ppm (s, 3H, CH<sub>3</sub>), δ 7.42- 8.04 ppm ( 9ArH), δ 7.78 ppm (s, 1H, C5H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 28.09 (CH<sub>3</sub>), 115.41(CN) 107.74, 138.05, 143.33, 145.83 (C, pyridine ring),128.63, 18.73, 129.27, 129.78, 132.95, 133.40, 136.45 (ArC). [M+1]=305.08.

2-Methyl-4-(4-methylphenyl)-6-phenyl pyridine-3-carbonitrile (**3f**) was obtained by the reaction between 3-(4-methylphenyl)-1-phenylprop-2-en-1-one **1f** (1 mmol, 234 mg), and 3-aminobut-2-enenitrile **2** (1 mmol, 82 mg) and ammonium acetate (1.5 mmol, 115 mg) in absolute ethanol (10 ml) under MW irradiation at 130 °C as a slight yellowish powder. FTIR : 2211 cm<sup>-1</sup>(ν C≡N), 3047 cm<sup>-1</sup> (ν CH, Ar); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.45 ppm (s, 3H, CH<sub>3</sub>), δ 2.51 ppm (s, 3H, CH<sub>3</sub> ) δ 7.29-8.07 ppm (9ArH), δ 7.87 ppm (s, 1H, C5H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 21.72 ppm (CH<sub>3</sub>), 115.41 (CN), 109.97, 121.42, 138.56, 141.10, 145.23 (C, pyridine ring), 128.49, 128.51, 128.71, 129.63, 132.21, 132.50, 136.64 (Ar C); [M+1]=285.13.

## RESULTS AND DISCUSSION

The chalcones **1a-f** required for the synthesis of substituted pyridines were prepared by the condensation of equimolar amount of acetophenone and benzaldehyde derivatives in methanol using 40% NaOH solution as base according to Claisen-Schmidt reaction. The chalcones were obtained in 60-90% yield. The FT-IR and melting point confirmed molecular structure of the synthesized chalcones. Novel pyridine-3-carbonitriles derivatives **3a-f** were prepared by the cycloaddition of synthesised chalcones with 3-aminobut-2-enenitrile in presence of ammonium acetate under microwave irradiation at 130 oC-140 oC for 10-30 minutes in absolute ethanol and the yield was found to be 49–90%. Initially, 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one **1a**, 3-aminobut-2-enenitrile **2** ammonium acetate were adopted as simple model substrates for studying the multi-component synthesis of 2-alkyl-

4,6-diphenylpyridine-3-carbonitriles **3** under conventional heating as well as microwave irradiation at different temperatures and time. After experimentation with different reaction temperatures and time, we found that the best result is possible when the reaction mixture of 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one **1a** (1 mmol), 3-aminobut-2-enenitrile **2** (1 mmol) and ammonium acetate (1.5 mmol) is treated in absolute ethanol under microwave irradiation for 30 minutes at 130 °C. The product was precipitated by the addition of ice-cold water and was filtered, washed with cold water and recrystallized from ethanol and identified as 2-methyl-4-(4-methoxyphenyl)-6-phenylpyridine-3-carbonitrile **3b** (90% yield) (Scheme 1).



**Scheme 1.** 2-Methyl-4-(4-methoxyphenyl)-6-phenylpyridine-3-carbonitrile **3b** (90% yield)

All the compounds obtained were characterized by analytical and spectroscopic methods. The structure of the product **3b** was elucidated with the help of FT-IR,  $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$ , HRMS, and Single Crystal XRD. In the IR spectrum absorption bands around  $3060$  and  $2835\text{ cm}^{-1}$  corresponds to aromatic and aliphatic C-H stretching frequencies. The bands at  $2216\text{ cm}^{-1}$  and  $1246\text{ cm}^{-1}$  are due to the  $\text{C}\equiv\text{N}$  and  $-\text{O}-\text{CH}_3$  stretching frequencies (Figure 1). The  $^1\text{H NMR}$  spectrum of the compound **3b** contained a singlet for  $\text{CH}_3$  at  $\delta$  2.92 ppm and singlet for  $\text{OCH}_3$  at  $\delta$  3.89 ppm. The ten aromatic protons of **3b** resonated in the range of 7.05 to 8.08 ppm in  $^1\text{H-NMR}$  spectrum. The singlet at  $\delta$  7.66 ppm corresponds to C-5H in the pyridine ring (Figure 2). The characteristic  $^{13}\text{C-NMR}$  signals due to  $\text{CH}_3$  and  $\text{OCH}_3$  appeared at  $\delta$  24.34 and 55.46 ppm respectively. The cyano carbon gave a signal at  $\delta$  114.51, and the C2, C3, C4, C5, C6 atoms resonated at  $\delta$  values 161.05, 105.55, 162.82, 117.72 and 159.13 ppm respectively (Figure 3). The HRMS spectrum disclosed a molecular ion peak at  $m/z=301.1686$  corresponding to the molecular formula  $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}$  (Figure 4). The Single Crystal X-ray Diffraction (SCXRD) study revealed that the compound **3b** crystallizes in monoclinic crystal system with space group P21/c (Figure 5). All the substituted chalcones **1a-f** reacted analogously with 3-aminobut-2-enenitrile **2** and ammonium acetate under the same reaction conditions, leading to the formation of products **3a-f** in 49–90% yield as shown in Table 1.

**Table 1.** Synthesis of compounds **3 a-f**

Compound	R1	R2	Temp (°C)/Time (h)	Yield (%) conventional	Temp (°C)/Time(min)	Yield (%) MW
<b>3a</b>	H	H	Reflux/8	55	130/20	83
<b>3b</b>	H	0	Reflux/8	61	130/20	90
<b>3c</b>	H	-CN	Reflux/12	12	130/30	49
<b>3d</b>	H	0	Reflux/9	48	130/25	79
<b>3e</b>	H	-Cl	Reflux/10	58	130/20	83
<b>3f</b>	H	0	Reflux/6	70	130/15	89

It is evident from the table that the use of the microwave irradiation enhances the yield of the product considerably with dramatic reduction in the reaction time, the best result was obtained at 130 °C for a reaction time of 20 minutes.

In addition, the compounds **3a-f** were pure enough for all practical purposes even with simple water washing and recrystallization from ethanol.

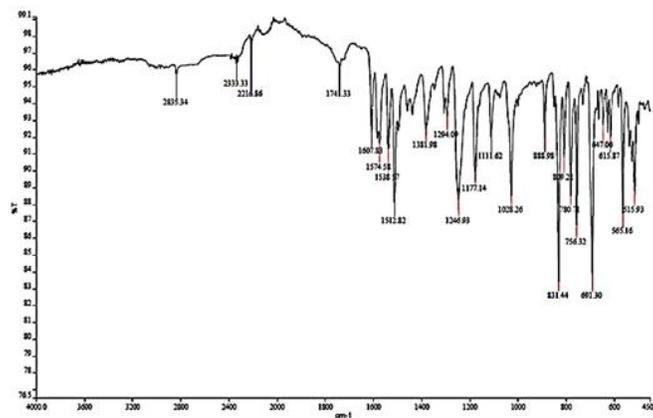


Figure 1. FTIR spectrum of 2-methyl-4-(4-methoxyphenyl)-6-phenylpyridine-3-carbonitrile

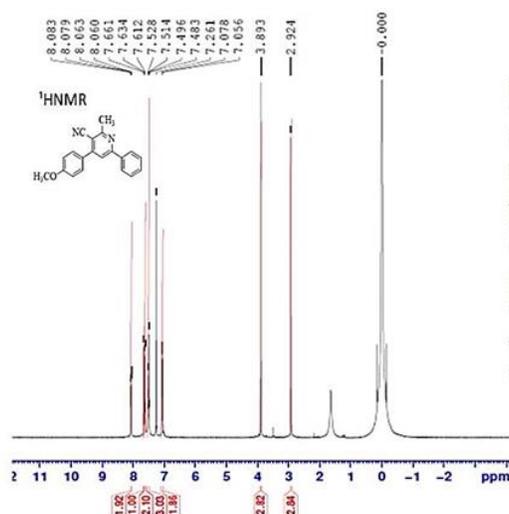


Figure 2. <sup>1</sup>H-NMR spectrum of 2-methyl-4-(4-methoxyphenyl)-6-phenylpyridine-3-carbonitrile

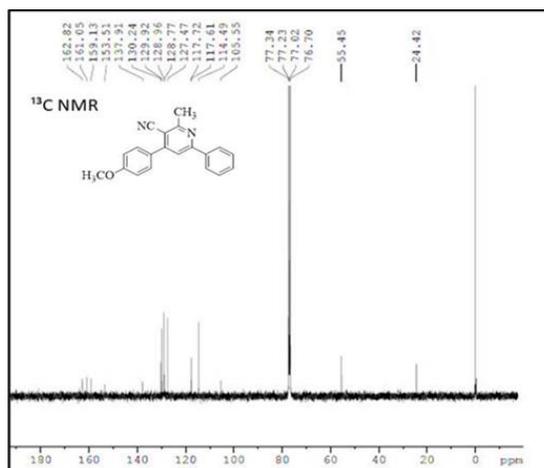


Figure 3. <sup>13</sup>C-NMR spectrum of 2-methyl-4-(4-methoxyphenyl)-6-phenylpyridine-3-carbonitrile

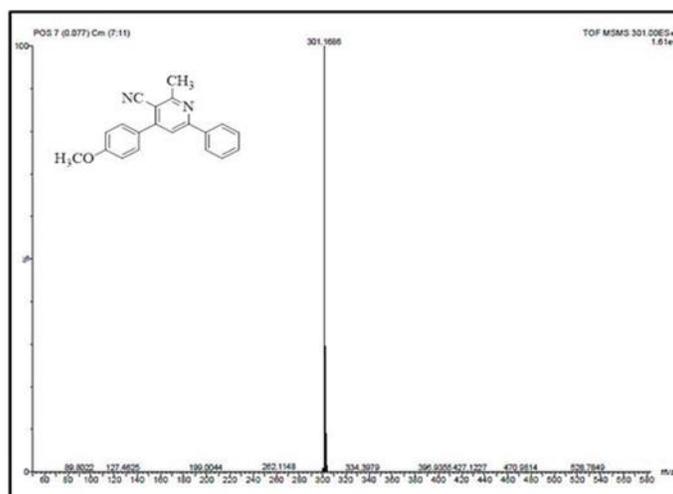


Figure 4. HRMS spectrum of 2-methyl-4-(4-methoxyphenyl)-6-phenylpyridine-3-carbonitrile

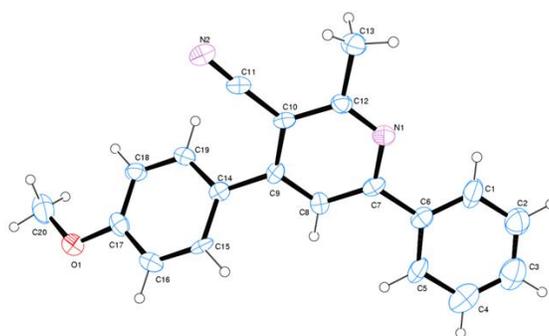


Figure 5. ORTEP view of 2-methyl-4-(4-methoxyphenyl)-6-phenylpyridine-3-carbonitrile

### CONCLUSION

In the present study, we have described a convenient, relatively low cost procedure for the synthesis of 2-methyl-4,6-diarylpyridine-3-carbonitriles under microwave irradiation in good yield, from readily available starting materials (aromatic aldehyde, acetophenone and 3-aminocrotonitrile) using very small amount of solvent with very short reaction periods. All the synthesized compounds were characterized by means of FTIR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, MS spectra and SCXRD. Further studies on the biological activities of these compounds are currently underway in our laboratory.

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