



## Synthesis and antioxidant evaluation of some new pyridines

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### ARTICLE INFORMATION



DOI: 10.5155/eurjchem.6.1.84-87.1149

Received: 09 September 2014

Received in revised form: 08 October 2014

Accepted: 09 October 2014

Published online: 31 March 2015

Printed: 31 March 2015

### KEYWORDS

Pyridine  
Malononitrile  
Nicotinonitrile  
Antioxidant activity  
Aryl carboxaldehyde  
4-Methylpentan-2-one

### ABSTRACT

One-pot condensation of malononitrile (1), 4-methylpentan-2-one (2), aryl carboxaldehyde (3a-f) and ammonium acetate in ethanol afforded 2-amino-5-isopropyl-4-(4-aryl)-6-methylnicotinonitriles (4a-f). The antioxidant activity of the new synthesized compounds was evaluated and the result showed all compound exhibited weak anti-oxidant activities.

**Cite this:** *Eur. J. Chem.* 2015, 6(1), 84-87

### 1. Introduction

Multicomponent coupling reactions (MCRs) have been frequently used by synthetic chemists as a facile means to generate molecular diversity from bifunctional substrates that react sequentially in an intermolecular fashion [1,2]. Devising such types of MCRs that achieve the formation of multiple bonds in a single operation is one of the major challenges in modern organic synthesis [3,4]. As such processes avoid time consuming and costly purification processes, as well as protection-deprotection steps, they are inherently more environmentally benign and atom economic [5].

Many naturally occurring as well as synthetic compounds containing the pyridine scaffold exhibit interesting pharmacological properties [6-10]. Furthermore, pyridine is one of the most popular *N*-heteroaromatics incorporated into the structure of many pharmaceuticals. Among these, cyanopyridines with different alkyl and aryl groups were found to have antihypertensive [11], anti-inflammatory, analgesic, antipyretic properties [12,13] as well as 1KK-b inhibitor properties [14].

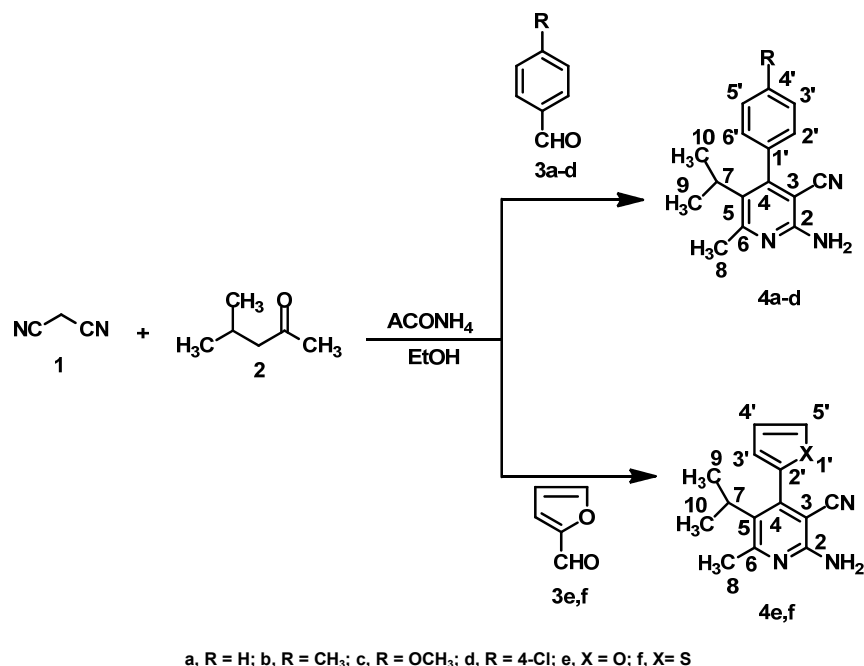
Reactive oxygen species (ROS), including free radicals, led to a decrease in the antioxidant capacity and may generate other reactive species that damage the living cell. Oxidative

stress may arise in a biological system after increasing exposure to oxidants, so the antioxidants play a major role in the protection of biological systems against threats. Different types of antioxidants such as Vitamins C and E, glutathione, lipoic acid and butylated phenols were widely used in different fields of industry and medicine to interrupt radical-chain oxidation processes that attract a high scientific interest [15-17]. We reported herein, the one pot multicomponent coupling synthesis of some 2-aminopyridines in order to evaluate their antioxidant activities.

### 2. Experimental

#### 2.1. Instrumentation

All melting points are determined on Gallenkamp electric melting point apparatus (uncorrected). Thin layer chromatography (TLC) analysis was carried out on silica gel 60F<sub>254</sub> precoated aluminum sheets. The IR spectra were recorded (KBr) on a Nicolet i55 FT-IR Spectrophotometer at the Microanalytical Unit, Faculty of Science and Arts, Ulla, Taibah University, Kingdom of Saudi Arabia. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at 600 and 150 MHz, respectively, on a JEOL Spectrophotometer using CDCl<sub>3</sub>/DMSO-*d*<sub>6</sub> as solvent and TMS



Scheme 1

as an internal reference, King Abdulaziz University, Faculty of Science, Kingdom of Saudi Arabia. The mass spectra (EI) were recorded on JEOL-JMS 600 at Assiut University, Assiut, Egypt. Elemental analyses (C, H and N) were carried out at the Micro analytical Center, Cairo University, Giza, Egypt. Biological activities were carried at Pharmacognosy Department, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt.

## 2.2. Synthesis

### 2.2.1. Synthesis of 2-amino-5-isopropyl-6-methyl-4-aryl nicotinonitriles (4a-f)

**General procedure:** A mixture of aromatic aldehyde (20 mmol), 4-methylpentan-2-one (1 g, 20 mmol), malononitrile (1.32 g, 20 mmol) and ammonium acetate (18.64 g, 160 mmol) in ethyl alcohol (30 mL) was heated under reflux for 24 h. The reaction mixture was cooled and the formed precipitate was filtered, washed with water, dried and crystallized from methanol to give compound **4a-f** (Scheme 1, Figure 1).

**2-Amino-5-isopropyl-6-methyl-4-phenylnicotinonitrile (4a):** Color: White crystals. Yield: 73%. M.p.: 178-179 °C. FT-IR (KBr,  $\nu$ , cm<sup>-1</sup>): 3426, 3316 (NH<sub>2</sub>), 2208 (CN), 1650 (C=N). <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>,  $\delta$ , ppm): 0.94 (d, 6H, *J* = 6.6 Hz, 2CH<sub>3</sub>), 2.10 (s, 1H, *J* = 6.6 Hz, CH), 2.52 (s, 3H, CH<sub>3</sub>), 5.88 (br, 2H, NH<sub>2</sub>), 7.48-7.57 (m, 5H, Ar-H). <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>,  $\delta$ , ppm): 165.3 (C<sub>6</sub>), 160.5 (C<sub>2</sub>), 153.3 (C<sub>4</sub>), 136.9 (C<sub>1'</sub>), 129.4 (C<sub>4'</sub>), 128.6 (2C, C<sub>3'</sub>, C<sub>5'</sub>), 128.1 (2C, C<sub>2'</sub>, C<sub>6'</sub>), 117.3 (C<sub>5</sub>), 113.4 (CN), 86.4 (C<sub>3</sub>), 47.5 (C<sub>7</sub>), 28.6 (C<sub>8</sub>), 22.4 (2C, C<sub>9</sub>, C<sub>10</sub>). MS (EI, *m/z* (%)): 251.39 (M<sup>+</sup>, 9.2), 236 (41.8), 210 (27.5), 209 (100), 164 (11.3), 89 (17.6), 77 (63.3), 51 (15.6). Anal. calcd. for C<sub>16</sub>H<sub>17</sub>N<sub>3</sub>: C, 76.46; H, 6.82; N, 16.72. Found: C, 76.40; H, 6.85; N, 16.67%.

**2-Amino-5-isopropyl-6-methyl-4-p-tolynicotinonitrile (4b):** Color: Yellow crystals. Yield: 74%. M.p.: 194-196 °C. FT-IR (KBr,  $\nu$ , cm<sup>-1</sup>): 3411, 3320 (NH<sub>2</sub>), 2211 (CN), 1651 (C=N). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>,  $\delta$ , ppm): 0.95 (d, 6H, *J* = 6.6 Hz, 2CH<sub>3</sub>), 2.09 (septet, 1H, *J* = 6.6 Hz, CH), 2.42 (s, 3H, CH<sub>3</sub>Ar) 2.53 (s, 3H, CH<sub>3</sub>), 5.32 (br, 2H, NH<sub>2</sub>), 7.30 (dd, 2H, *J* = 7.2 Hz, Ar-H) 7.48 (dd, 2H, *J* = 7.2 Hz, Ar-H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>,  $\delta$ , ppm): 165.4 (C<sub>6</sub>), 160.2 (C<sub>2</sub>), 154.2 (C<sub>4</sub>), 139.9 (C<sub>4'</sub>), 133.9 (C<sub>1'</sub>), 129.5

(2C, C<sub>3'</sub>, C<sub>5'</sub>), 128.1 (2C, C<sub>2'</sub>, C<sub>6'</sub>), 117.3 (C<sub>5</sub>), 114.1 (CN), 87.1 (C<sub>3</sub>), 47.8 (C<sub>7</sub>), 28.8 (C<sub>8</sub>), 22.5 (2C, C<sub>9</sub>, C<sub>10</sub>), 21.4 (CH<sub>3</sub>Ar). MS (EI, *m/z* (%)): 264.3 (M<sup>+</sup> -1, 0.1), 250 (10.8), 223 (100), 210 (2.5), 193 (4.2), 166 (5.2), 140 (16.0), 115 (30.7), 91 (28.8), 77 (13.9), 65 (32.4), 51 (24.9). Anal. calcd. for C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>: C, 76.95; H, 7.22; N, 15.84. Found: C, 76.91; H, 7.18; N, 15.78%.

**2-Amino-5-isopropyl-4-(4-methoxyphenyl)-6-methylnicotinonitrile (4c):** Color: Pale yellow crystals. Yield: 80%. M.p.: 171-173 °C. FT-IR (KBr,  $\nu$ , cm<sup>-1</sup>): 3405, 3315 (NH<sub>2</sub>), 2212 (CN), 1648 (C=N). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>,  $\delta$ , ppm): 0.95 (d, 6H, *J* = 6.6 Hz, 2CH<sub>3</sub>), 2.09 (septet, 1H, *J* = 6.6 Hz, CH), 2.51 (s, 3H, CH<sub>3</sub>), 3.87 (s, 3H, OCH<sub>3</sub>Ar), 5.28 (br, 2H, NH<sub>2</sub>), 7.01 (dd 2H, *J* = 9.0 Hz, Ar-H), 7.55 (dd 2H, *J* = 9.0 Hz, Ar-H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>,  $\delta$ , ppm): 163.3 (C<sub>6</sub>), 160.8 (C<sub>4'</sub>), 160.2 (C<sub>2</sub>), 153.8 (C<sub>4</sub>), 129.6 (2C, C<sub>2'</sub>, C<sub>6'</sub>), 129.0 (C<sub>1'</sub>) 117.6 (C<sub>5</sub>), 114.3 (2C, C<sub>3'</sub>, C<sub>5'</sub>), 113.9 (CN), 86.9 (C<sub>3</sub>), 55.4 (OCH<sub>3</sub>Ar), 47.8 (C<sub>7</sub>), 28.8 (C<sub>8</sub>), 22.5 (2C, C<sub>9</sub>, C<sub>10</sub>) 163.3 (C<sub>6</sub>), 160.8 (C<sub>4'</sub>), 160.2 (C<sub>2</sub>), 153.8 (C<sub>4</sub>), 129.6 (2C, C<sub>2'</sub>, C<sub>6'</sub>), 129.0 (C<sub>1'</sub>) 117.6 (C<sub>5</sub>), 114.3 (2C, C<sub>3'</sub>, C<sub>5'</sub>), 113.9 (CN), 86.9 (C<sub>3</sub>), 55.4 (OCH<sub>3</sub>Ar), 47.8 (C<sub>7</sub>), 28.8 (C<sub>8</sub>), 22.5 (2C, C<sub>9</sub>, C<sub>10</sub>). MS (EI, *m/z* (%)): 263 (M<sup>+</sup> -NH<sub>3</sub>, 11.7), 240 (20.1), 239 (100), 224 (9.5), 196 (10.1), 142 (10.9), 114 (22.9), 103 (17.2), 77 (23.6), 63 (41.3), 51 (32.4). Anal. calcd. for C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O: C, 72.57; H, 6.81; N, 14.94. Found: C, 72.51; H, 6.85; N, 14.90%.

**2-Amino-5-isopropyl-4-(4-chlorophenyl)-6-methylnicotinonitrile (4d):** Color: Pale yellow crystals. Yield: 70%. M.p.: 210-212 °C. FT-IR (KBr,  $\nu$ , cm<sup>-1</sup>): 3416, 3316 (NH<sub>2</sub>), 2212 (CN), 1650 (C=N). <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>,  $\delta$ , ppm): 0.94 (d, 6H, *J* = 6.6 Hz, 2CH<sub>3</sub>), 2.10 (septet, 1H, *J* = 6.6 Hz, CH), 2.51 (s, 3H, CH<sub>3</sub>), 6.17 (br, 2H, NH<sub>2</sub>), 7.48 (dd, 2H, *J* = 8.4 Hz, Ar-H), 7.53 (dd, 2H, *J* = 8.4 Hz, Ar-H). <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>,  $\delta$ , ppm): 165.4 (C<sub>6</sub>), 160.7 (C<sub>2</sub>), 152.5 (C<sub>4</sub>), 135.5 (C<sub>1'</sub>), 135.1 (C<sub>4'</sub>), 129.6 (2C, C<sub>3'</sub>, C<sub>5'</sub>) 128.7 (2C, C<sub>2'</sub>, C<sub>6'</sub>), 117.0 (C<sub>5</sub>), 112.8 (CN), 85.9 (C<sub>3</sub>), 47.4 (C<sub>7</sub>), 28.5 (C<sub>8</sub>), 22.4 (2C, C<sub>9</sub>, C<sub>10</sub>). MS (EI, *m/z* (%)): 270 (M<sup>+</sup> -CH<sub>3</sub>, 11.7), 265 (11.7), 245 (31.9), 243 (100), 191 (10.65), 196 (10.1), 164 (11.1), 140 (7.7), 127 (7.7), 113 (8.8), 77 (10.9), 63 (26.4), 51 (41.4). Anal. calcd. for C<sub>16</sub>H<sub>16</sub>ClN<sub>3</sub>: C, 67.25; H, 5.64; N, 14.70. Found: C, 67.32; H, 5.70; N, 14.65%.

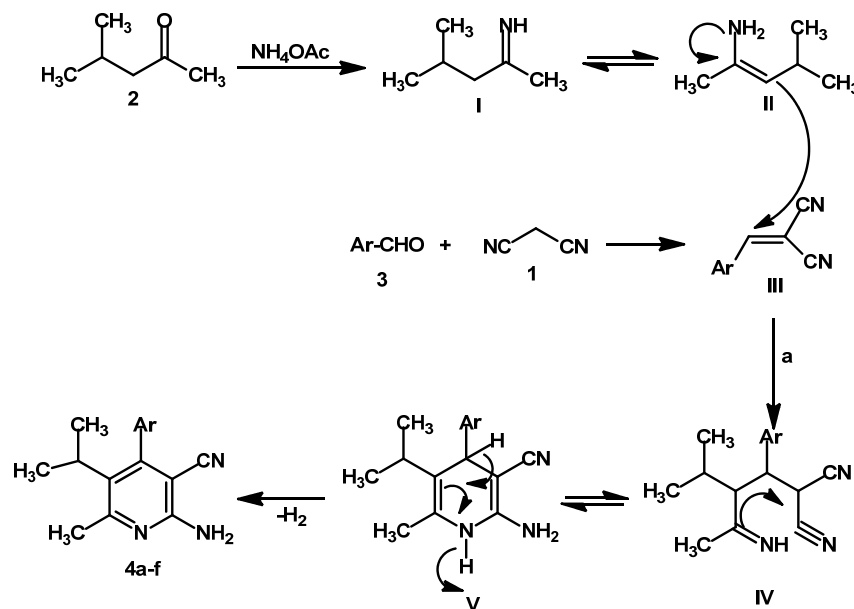


Figure 1. The possible mechanism for synthesis of 2-aminopyridines.

**2-Amino-4-(furan-2-yl)-5-isopropyl-6-methylnicotinonitrile (4e):** Color: Grey crystals. Yield: 63%. M.p.: 196-198 °C. FT-IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3425, 3319 ( $\text{NH}_2$ ), 2207 (CN), 1645 (C=N).  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 0.94 (d, 6H,  $J = 6.6$  Hz, 2CH<sub>3</sub>), 2.10 (septet, 1H,  $J = 6.6$  Hz, CH), 2.51 (s, 3H, CH<sub>3</sub>), 5.73 (br, 2H,  $\text{NH}_2$ ), 6.59 (dd, 1H,  $J = 1.8$  and 3.6 Hz, H<sub>4</sub>-furan), 7.40 (d, 1H,  $J = 3.6$  Hz, H<sub>3</sub>-furan), 7.62 (d, 1H,  $J = 3.3$  Hz, H<sub>5</sub>-furan).  $^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 165.6 (C<sub>6</sub>), 160.6 (C<sub>2</sub>), 148.7 (C<sub>4</sub>), 144.2 (C<sub>2'</sub>), 140.6 (C<sub>5</sub>), 117.7 (C<sub>5</sub>), 112.7 (CN), 112.4 (C<sub>3'</sub>), 108.6 (C<sub>4'</sub>), 81.4 (C<sub>4</sub>), 47.7 (C<sub>7</sub>), 28.6 (C<sub>8</sub>), 22.4 (2C, C<sub>9</sub>, C<sub>10</sub>). MS (EI,  $m/z$  (%)): 241 ( $\text{M}^+$ , 13.1), 226 (16.4), 200 (19.0), 199 (100), 185 (4.4), 129 (10.0), 127 (12.9), 103 (10.7), 91 (12.8), 77 (16.4), 63 (26.5), 51 (24.3). Anal. calcd. for  $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}$ : C, 69.69; H, 6.27; N, 17.14. Found: C, 69.63; H, 6.21; N, 17.10%.

**2-Amino-5-isopropyl-6-methyl-4-(thiophen-2-yl)nicotinonitrile (4f):** Color: Yellowish white crystals. Yield: 61%. M.p.: 185-187 °C. FT-IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3423, 3319 ( $\text{NH}_2$ ), 2202 (CN), 1645 (C=N).  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 0.94 (d, 6H,  $J = 6.6$  Hz, 2CH<sub>3</sub>), 2.09 (septet, 1H,  $J = 6.6$  Hz, CH), 2.48 (s, 3H, CH<sub>3</sub>), 6.09 (br, 2H,  $\text{NH}_2$ ), 7.18 (dd, 1H,  $J = 1.2$  and 4.2 Hz, H<sub>4</sub>-thiophene), 7.55 (dd, 1H,  $J = 1.2$  and 3.6 Hz, H<sub>5</sub>-thiophene), 7.77 (dd, 1H,  $J = 1.2$  and 3.6 Hz, H<sub>3</sub>-thiophene).  $^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 165.6 (C<sub>6</sub>), 160.6 (C<sub>2</sub>), 148.7 (C<sub>4</sub>), 144.2 (C<sub>2'</sub>), 140.6 (C<sub>5</sub>), 117.7 (C<sub>5</sub>), 112.7 (CN), 112.4 (C<sub>3'</sub>), 108.6 (C<sub>4'</sub>), 81.4 (C<sub>4</sub>), 47.7 (C<sub>7</sub>), 28.6 (C<sub>8</sub>), 22.4 (2C, C<sub>9</sub>, C<sub>10</sub>). MS (EI,  $m/z$  (%)): 259 ( $\text{M}^+ + 2$ , 0.3), 257 ( $\text{M}^+$ , 33.8), 242 (12.7), 215 (100), 200 (14.6), 197 (18.6), 185 (12.3), 174 (20.7), 157 (17.3), 108 (14.2), 91 (11.6), 77 (11.8), 63 (17.5). Anal. calcd. for  $\text{C}_{14}\text{H}_{15}\text{N}_3\text{S}$ : C, 65.34; H, 5.87; N, 16.33. Found: C, 65.28; H, 5.82; N, 16.27%.

## 2.2.2. ABTS Antioxidant assay [18]

Antioxidant activity determinations were evaluated from the bleaching of ABTS derived radical cations. The radical cation was derived from ABTS [2,2'-azino-bis (3-ethyl benzo thiazoline-6-sulfonic acid)] was prepared by reaction of ABTS (60  $\mu\text{L}$ ) with  $\text{MnO}_2$  (3 mL, 25 mg/mL) in 5 mL aqueous buffer solution (pH = 7). After shaking the solution for a few minutes, it was centrifuged and filtered.

The absorbance (A control) of the resulting green-blue solution (ABTS radical solution) was recorded at  $\lambda_{\text{max}} = 734$  nm. The absorbance (A test) was measured upon the addition of (20  $\mu\text{L}$  of 1 mg/mL) solution of the tested sample in spectroscopic grade MeOH:Buffer (1:1, v:v) to the ABTS solution. The decrease in the absorbance is expressed as %inhibition which calculated from the Equation (1).

$$\% \text{ Inhibition} = [A (\text{control}) - A (\text{test}) / A (\text{control})] \times 100 \quad (1)$$

Ascorbic acid (20  $\mu\text{L}$ , 2 mM) solution was used as standard antioxidant (positive control). Blank sample was run using solvent without ABTS (Table 1).

Table 1. ABTS Antioxidant activity assay of the new compounds.

Compound no	Absorbance of samples ( $\lambda$ , 734 nm)	% Inhibition
4a	0.416	16.8
4b	0.489	2.2
4c	0.420	16.0
4d	0.428	14.4
4e	0.407	18.6
4f	0.320	36.0
Control of ABTS <sup>a</sup>	0.500	0.0
Ascorbic acid	0.061	87.8

<sup>a</sup> ABTS: The method used for antioxidant activity, (% Inhibition =  $[A (\text{control}) - A (\text{test}) / A (\text{control})] \times 100$ ).

## 3. Results and discussion

### 3.1. Chemistry

Scheme 1 describes the synthesis of the target molecules. The target compounds 2-amino-5-isopropyl-4-(4-aryl)-6-methylnicotinonitrile (4a-f) were obtained with high yield and purity via one-pot condensation of malononitrile (1), 4-methylpentan-2-one (2), aryl carboxaldehyde (3a-f) and ammonium acetate in ethanol.

The structure of compounds 4a-f was established by the spectral data. Whereas, the IR spectra showed characteristic absorption bands within 3426-3315  $\text{cm}^{-1}$ , corresponding to amino groups, 2212-2202  $\text{cm}^{-1}$  due to cyano groups and 1651-1648  $\text{cm}^{-1}$  corresponding to C=N groups. Further, their  $^1\text{H}$  NMR displayed singlet signal within  $\delta$  2.52-2.48 ppm, which

corresponding to three proton of CH<sub>3</sub>, doublet signal within δ 2.10-2.09 ppm, which due to two C<sub>9,10</sub>H<sub>3</sub> groups, septets within δ 2.10-2.09 ppm due to one proton of C<sub>7</sub>H groups and broad singlet signal corresponding to two protons of amino groups. The <sup>1</sup>H NMR of compound **4b** and **4c** exhibited two singlet signals at 2.42 and 3.87 ppm corresponding to methyl and methoxy protons, respectively. Moreover the <sup>13</sup>C NMR of compounds **4a-f** displayed signals within δ 165.6-163.3, 160.7-160.2, 153.8-145.2, 117.7-117.0 and 87.1-81.4 ppm due to pyridine nucleus. Furthermore, the mass spectra of compounds **4a-f** displayed the base peaks at *m/z* 208, 222, 238, 242, 198 and 214, respectively due to M<sup>+</sup>-isopropyl moiety. The formation of compounds **4a-f** can be explained in the following possible mechanism Figure 1. There are two routes in the first one: the ketone (**2**) reacted with ammonium acetate to form the enamine derivative **II** which reacted with the arylidene derivative **III** [which formed from reaction of aldehyde **3** and malononitrile (**1**)] to form the Micheal adducts **IV**, the intermediate **IV** cyclized to dihydropyridine **V** then autoxidized to aminopyridine **4a-f**, Figure 1.

### 3.2. ABTS Antioxidant assay

The newly synthesized compounds were screened for their antioxidant activity using 2,2'-azino-bis-(3-ethylbenzothiazole-6-sulfonic acid) (ABTS) method which reported by Lissi *et al.* [18]. The antioxidant activity assay employed here is one of the several assays that depends on measuring the consumption of stable free radicals i.e. evaluate the free radical scavenging activity of the investigated component. The methodology assumes that the consumption of the stable free radical (X<sup>•</sup>) will be determined by reactions as followed:



Total antioxidant potential of resinous exudates from Heliotropium species, and a comparison of the ABTS methods.

The rate and/or the extent of the process measured in terms of the decrease in X<sup>•</sup> concentration, would be related to the ability of the added compound to trap free radicals. The decrease in color intensity of the free radical solution due to scavenging of the free radical by the antioxidant material is measured calorimetrically at a specific wavelength. The assay employs the radical cation derived from 2,2'-azino-bis-(3-ethyl benzthiazoline-6-sulfonic acid) as stable free radical to assess antioxidant potential of the investigated compounds [19,20].

The results showed that compounds **4a-f** displayed weak antioxidant activities. By comparing the results obtained of antioxidant of the compounds reported in this study to their structures, the following structure activity relationship (SARs) were postulated:

- i. Compound **4e** is more potent than compound **4a** which may be due to replacement of phenyl moiety by furan,
- ii. Compound **4e** has activity less than compound **4f** which may be attributed to replacement of furan moiety by thiophene,
- iii. Compounds **4b**, **4c** and **4d** are less potent than compound **4a** due to presence of electron donating group.

### 4. Conclusion

The objective of the present study was to synthesize and evaluate the antioxidant activity of some novel 2-amino pyridine with the hope of discovering new structure serving as antioxidant agent. The data showed clearly that all compounds displayed weak in vitro antioxidant activities using ABTS method.

### Acknowledgements

We deeply appreciate the assistance of Dr. Ahmed Abass, Pharmacognosy Department, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt for screening of the biological activities of the tested compounds.

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