



## Research on the reaction of furil with ammonium acetate

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### ABSTRACT

The direct reaction of furil with ammonium acetate in refluxing glacial acetic acid under the absence of appropriate aldehydes was systematically studied. The principal product with furan rings and imidazole ring 2,4,5-tri(furan-2-yl)-1H-imidazole (**I**) was obtained in moderate yield, and two new byproducts containing furan rings were successfully purified by C18 reversed phase column. All compounds were characterized by elemental analysis, MS, IR, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. The structure of **I** was further confirmed by the <sup>13</sup>C-<sup>1</sup>H COSY spectroscopy. The putative reaction mechanism *via* stable 1,2-di(furan-2-yl)ethane-1,2-diimine, furan-2-yl-(2,4,5-tri-furan-2-yl-2H-imidazol-2-yl)-methanone and intermediate **5** traced by GC-MS was proposed.

### 1. Introduction

Ammonium acetate has been extensively used in the synthesis of the N-containing heterocyclic compounds. It was mainly used to synthesize imidazole derivatives from 1,2-diketone and appropriate aldehydes [1-11]. The first is Radziszewski's classic synthesis from benzil(1,2-diphenyl-ethane-1,2-dione), benzaldehyde and ammonia in 1882 [12]. The main product 2,4,5-triphenylglyoxaline was confirmed as the structure for lophine. Subsequently, Davidson *et al.* further researched the reaction in 1937, corrected the structure of benzilimide, suggested a more rational formula for imabenzil, and offered a mechanism on the action of ammonia with benzil [13]. Until 1979, Dora *et al.* studied the condensation of furil(1,2-di(furan-2-yl)ethane-1,2-dione) with furfural in refluxing glacial acetic acid, the yield of 2,4,5-tri(furan-2-yl)-1H-imidazole obtained was only 30% [7]. However, under the absence of aldehydes, the direct reaction of furil with ammonium acetate in glacial acetic acid has rarely been studied so far.

On the one hand, because the compounds containing furan heterocycle possessed the inherent chemical properties and disadvantage, such as rich electron, lower conjugation energy, easily becoming yellow in oxygen, and so on. But they might be applied to luminescent materials under the airproofed condition [14,15]. On the other hand, furil was difficult to accomplish some reactions that were facilely performed from benzyl due to the structural characteristic of furil.

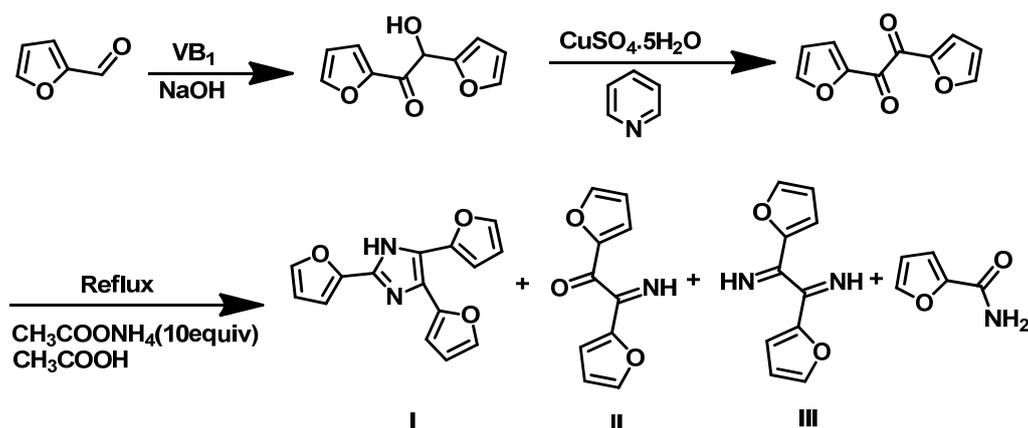
In this work, to explore the feasibility of the intended transformation of furil, we decided to systematically study the reaction of furil and ammonium acetate in glacial acetic acid. As results, the main product of 2,4,5-tri(furan-2-yl)-1H-imidazole (**I**) as well as the new and difficultly isolated byproducts of 1,2-di(furan-2-yl)-2-iminoethanone (**II**) and 1,2-di(furan-2-yl)ethane-1,2-diimine (**III**) were separated and characterized,

respectively. In addition, a familiar product named furan-2-carboxamide also existed in the products, but was not separated and characterized. Herein, furan-2-carboxamide was generated lied in the fact that furan-2-carboxylic acid subsequently reacted with ammonia and then dehydrated under the condition of reflux. In the meantime, the isolated technique of product **II** and **III** was developed. All the obtained products were characterized by elemental analysis, MS, IR, <sup>1</sup>H NMR and <sup>13</sup>C NMR spectroscopy. The structure of product **I** was further confirmed by the <sup>13</sup>C-<sup>1</sup>H COSY spectroscopy. The generating course of the products was tracked with GC-MS analyzer. The possible mechanism for the reaction of furil with ammonium acetate in refluxing glacial acetic acid was proposed.

### 2. Experimental

#### 2.1. Instrumentation

Thin layer chromatography was carried out on silica gel (GF-254) TLC plates. Column chromatography was carried out on silica gel (100-200 mesh) and C18 reversed phase column. All melting points were determined on a XT-4 melting point apparatus without correction. IR spectra were collected with a Nicolet 5PC FT-IR spectrometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were measured using a Varian Mercury-300 NMR spectrometer or a Bruker AVANCE-500 NMR spectrometer and with TMS as an internal standard. MS spectra were measured with a 4000 Q TRAP® LC/MS spectrometer. Elemental analysis was performed on a FlashEA1112 elemental analyzer. GC-MS were recorded using an Agilent 5975/6890N GC/MS spectrometer with HP-5 Capillary Column (Agilent 19091J-416) and electron impact ionization (EI).



Scheme 1

## 2.2. Materials

Ammonium acetate, glacial acetic acid, NaOH, ethyl acetate and petroleum ether were of analytical-reagent grade and were used without further purification. Furfural was distilled under vacuum distillation before use. Water was used after double distillation.

## 2.3. Synthesis

### 2.3.1. Synthesis of furin (1,2-di(furan-2-yl)-2-hydroxy ethanone)

Furin was synthesized according to the literature [16]. Vitamine B<sub>1</sub> (VB<sub>1</sub>) (0.02 mol, 6.80 g), deionized water (20 mL) and 95% alcohol (60 mL) were mixed. Adjusted pH = 9–10, distilled furfural (0.60 mol, 57.66 g) was added into the above solution. The mixed solution was heated to 65 ± 2 °C and stirred for another 3 h at pH = 8–9. The solid product generated was separated by filtration and purified by recrystallization from ethanol. The obtained product was a white needle crystal (47.58 g, 82.6% yield). M.p.: 138–139 °C. Anal. Calcd for C<sub>10</sub>H<sub>8</sub>O<sub>4</sub>: C, 62.50; H, 4.20; O, 33.30. Found: C, 62.59; H, 4.23; O, 33.37%.

### 2.3.2. Synthesis of furil

Furil was synthesized according to the literature [17]. CuSO<sub>4</sub>·5H<sub>2</sub>O (0.63 mol, 15.75 g), pyridine (0.27 mol, 21.54 g) and deionized water (10 mL) were mixed. The mixture was heated to 60–65 °C in water bath with stirring. When the mixture became a homogeneously blue solution, furin (0.03 mol, 5.76 g) was added and refluxed for 1.5 h at 98–100 °C. The product was separated by filtration. The filter cake was washed with 250 mL (5 x 50 mL) of cold deionized water, and then recrystallized from 20 mL 95% ethanol. The product obtained was a brilliant yellow needle crystal (5.16 g, 90.6% yield). M.p.: 165–166 °C. Anal. Calcd for C<sub>10</sub>H<sub>6</sub>O<sub>4</sub>: C, 63.16; H, 3.18; O, 33.66. Found: C, 63.26; H, 3.24; O, 33.72%.

### 2.3.3. The reaction of furil with ammonium acetate and the isolation of generated product

The reaction of furil with ammonium acetate was carried out according to the literature [13]. A mixture of furil (4.32 mmol, 0.82 g) and ammonium acetate (52.60 mmol, 4.05 g) in glacial acetic acid (15 mL) was refluxed. The reaction progress was monitored by thin layer chromatography (TLC) on Silufol-254 plates. After furil was completely reacted, the reaction mixture was cooled to room temperature, poured into 100 mL

of water, then neutralized with an aqueous solution of 10% NaOH to pH = 9. The mixture was extracted with ethyl acetate. The organic layer was separated, washed with water, and dried over MgSO<sub>4</sub>. The solvent was evaporated in vacuo, and the residue was purified by recrystallization after column chromatography on Chemapol (100–200 mesh) silica gel (eluent, petroleum ether:ethyl acetate = 3:1) to obtain 2,4,5-tri(furan-2-yl)-1H-imidazole (I). The further separation of the residual which were not isolated by the above method was carried out by C18 reversed phase column by using methanol and distilled water (200:85) as eluent, and then was purified by recrystallization. 1,2-Di(furan-2-yl)-2-iminoethanone (II) and 1,2-di(furan-2-yl)-ethane-1,2-diimine (III) were obtained, respectively.

**2,4,5-tri(furan-2-yl)-1H-imidazole (I):** Yield: 65.4% as yellow needle crystals. M.p.: 196–197 °C. FT-IR (KBr, ν, cm<sup>-1</sup>): 3417, 3114, 2926, 1627, 1538, 1477, 1430, 1380, 1201, 1016, 887, 748. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ, ppm): 10.48 (s, 1H, imidazole-NH), 7.42 (s, 2H, furan-5H), 7.36 (s, 1H, furan-5H), 6.92 (d, J = 3.3 Hz, 3H, furan-4H), 6.46 (dd, J = 3.0, 1.7 Hz, 2H, furan-3H), 6.41 (dd, J = 3.1, 1.6 Hz, 1H, furan-3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, δ, ppm): 147.2, 145.2, 143.1, 141.9, 139.5, 112.4, 112.1, 108.9, 108.1. MS (m/z): (M+H)<sup>+</sup> 267.3 (Calcd . 266.25). Anal. Calcd for C<sub>15</sub>H<sub>10</sub>N<sub>2</sub>O<sub>3</sub>: C, 67.67; H, 3.79; N, 10.52. Found: C, 67.53; H, 3.71; N, 10.45%.

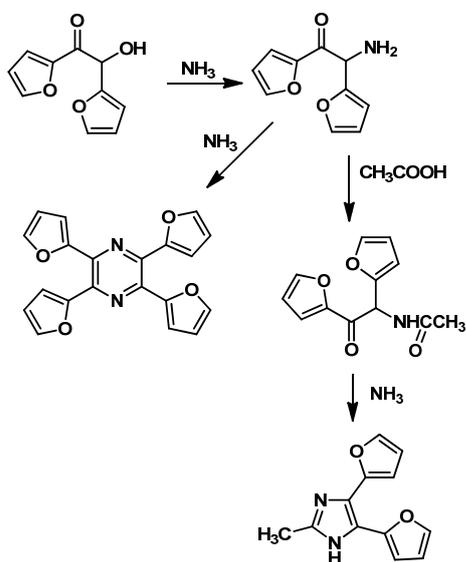
**1,2-di(furan-2-yl)-2-iminoethanone (II):** Yield: 13.5% as yellow needle crystals. M.p.: 100–101 °C. FT-IR (KBr, ν, cm<sup>-1</sup>): 3436, 3164, 3133, 2925, 1617, 1581, 1447, 1401, 1303, 1238, 1173, 1146, 1030, 959, 900, 860, 831, 722, 712. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, δ, ppm): 12.21 (s, 1H, =NH), 8.39 (d, J = 3.4 Hz, 1H, furan-5H), 8.29 (dd, J = 3.9, 1.7 Hz, 1H, furan-5H), 7.79 (s, 1H, furan-3H), 7.46–7.35 (m, 2H, furan-3H and 4H), 6.66 (dd, J = 3.6, 1.6 Hz, 1H, furan-4H), 1.55 (H<sub>2</sub>O). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, δ, ppm): 183.7, 160.6, 150.6, 141.0, 136.0, 129.8, 127.1, 126.9, 113.3. MS (m/z): (M+H)<sup>+</sup> 190.1 (Calcd. 189.16). Anal. calcd for C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>: C, 63.49; H, 3.73; N, 7.40. Found: C, 63.34; H, 3.71; N, 7.53%.

**1,2-di(furan-2-yl)ethane-1,2-diimine (III):** Yield: 2.8% as white or yellowish needle crystals. M.p.: 180–182 °C. FT-IR (KBr, ν, cm<sup>-1</sup>): 3441, 2924, 2853, 1571, 1449, 1440, 1340, 1306, 1235, 1116, 1067, 877, 799, 728. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, δ, ppm): 14.68 (s, 2H, =NH), 8.06 (dd, J = 4.6, 1.3 Hz, 2H, furan-5H), 7.44 (d, J = 1.4 Hz, 2H, furan-3H), 7.30 (dd, J = 8.4, 4.7 Hz, 2H, furan-4H), 1.55 (H<sub>2</sub>O) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, δ, ppm): 156.5, 140.3, 136.4, 126.3, 125.3. MS (m/z): (M+H)<sup>+</sup> 189.2 (Calcd. 188.18). Anal. Calcd. for C<sub>10</sub>H<sub>7</sub>N<sub>3</sub>O<sub>3</sub>: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.79; H, 4.25; N, 14.95%.

### 3. Results and discussion

In our first attempt at the reaction, it was expected that furil was treated with ammonium acetate in glacial acetic acid to obtain product **I** with the yield as high as that of the obtained 2,4,5-triphenylglyoxaline from the reaction of benzil and ammonia [13]. However, unexpected results were obtained. The yield of the product **I** was lower (65.4%), and the subordinate amount of 2,4,5-tri(furan-2-yl)-1*H*-oxazole corresponding to benzilam (2,4,5-triphenyl-1*H*-oxazole) in the literature [13] was not obtained. The compound with structure **I** and the new byproducts with structures **II** and **III** which were isolated and purified by recrystallization after C18 reversed phase column were observed, respectively, clearly resulting from the nucleophilic addition reaction of ammonia to furil. The corresponding yields for compounds **I**, **II** and **III** were 65.4%, 13.5% and 2.8%, respectively. The generating route of products was shown in Scheme 1. To explain the reaction mechanism of furil and ammonium acetate, the reaction process was tracked by GC-MS. The reaction mixture was analyzed after 40 min and the reaction end, respectively. The analytic results are shown in Table 1.

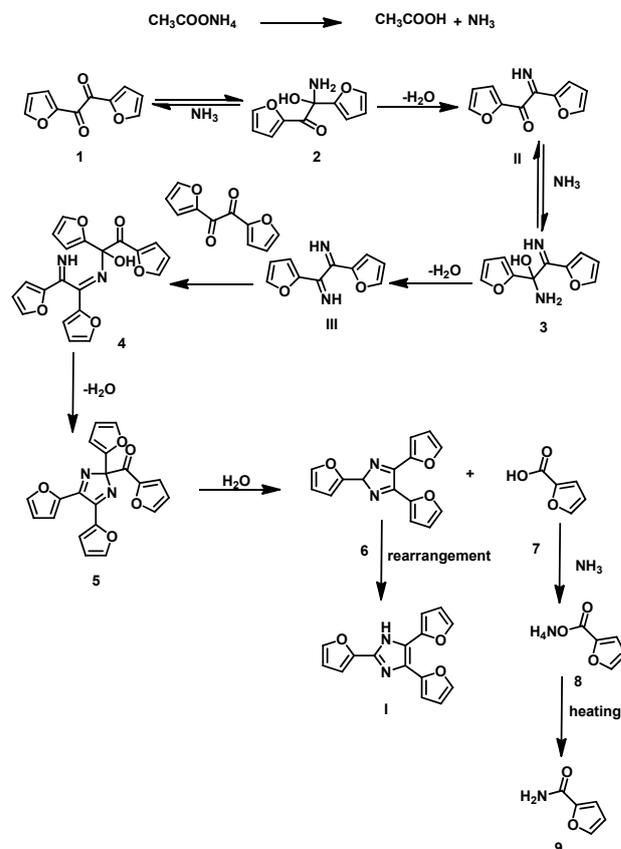
From the Table 1, compared the analytic results of 40 min to that of reaction end by GC-MS, there existed furan-2-carboxamide, furil, the product **II**, 4,5-di-furan-2-yl-2-methyl-1*H*-imidazole, the product **I**, 2,3,5,6-tetra-furan-2-yl-pyrazine and furan-2-yl-(2,4,5-tri-furan-2-yl-2*H*-imidazol-2-yl)-methanone (intermediate **5**) after 40 min (Scheme 2 and 3). While intermediate **5** disappeared, the product **II** increased and then decreased the product **III** occurred in the process of reaction and slightly increased in the reaction end. Besides, the concentration of the other compounds generated in the process of the reaction was increasing with furil gradually decreasing even being basically consumed at the reaction end. These results lied in the fact that the quick reaction rate at the beginning of the reaction made the product **III** generated entirely transforms intermediate **5**.



Scheme 2

With nucleophilic addition reaction proceeding and furil decreasing, the nucleophilic attacks of product **III** to furil became more and more difficult, which led to the product **III** increasing and the product **II** increased and then decreased. In addition, 4,5-di-furan-2-yl-2-methyl-1*H*-imidazole and 2,3,5,6-tetra-furan-2-yl-pyrazine were also produced with the reaction performing, which lied in the fact that trace furil were

remained in furil, and furil reacted with ammonia obtained the two said compounds. Their generated pathway was shown in Scheme 2. The results were in agreement with the published literature [18].



Scheme 3

Therefore, the action of ammonium acetate on furil was very complicated. When the reaction was complete by TLC, three organic products were separated. The principal final product is 2,4,5-tri(furan-2-yl)-1*H*-imidazole (**I**). All products obtained were characterized by elemental analysis, MS, IR, <sup>1</sup>H NMR and <sup>13</sup>C NMR spectroscopy. It was noteworthy that the <sup>13</sup>C NMR spectrum of product **I** was not in agreement with the expected structure. Its <sup>1</sup>H NMR spectrum showed that there were surely seven different hydrogen signals, but the two furan-5*H* in two different circumstances appeared single peak that was not split or only was slightly split, which was likely to relate with the concentration of tested product **I** and the location of furan-5*H* (Simultaneously, the <sup>1</sup>H NMR spectrum of furil was also tested, the same results of furan-5*H* hydrogen signals as that for product **I** were obtained). Furthermore, the <sup>13</sup>C NMR spectrum of product **I** showed that there were five quarterly carbons, which were not in agreement with the expected structure. In order to further confirm the structure of compound **I**, the <sup>13</sup>C-<sup>1</sup>H COSY of the compound **I** was tested. The <sup>13</sup>C-<sup>1</sup>H COSY of the compound **I** was shown in Figure 1.

The result indicated that the carbon atom nearby 142 ppm in <sup>13</sup>C NMR spectrum is not a quarterly carbon atom but furan-3C, furan-4C and furan-5C shared the same one hydrogen. Further proof of the structure for the product **I** was based on X-ray structure determination. The crystal structure of the compound **I**, belonging to monoclinic crystal system space with space group *Cc*, has been reported previously [19] (Figure 2). It was of interest to consider a putative mechanism for these reactions. The possible mechanism was shown in Scheme 3.

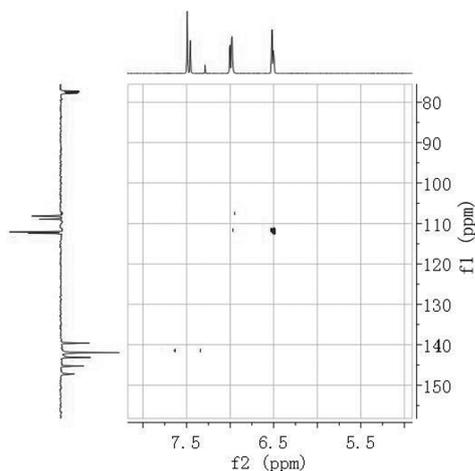


Figure 1. The  $^{13}\text{C}$ - $^1\text{H}$  COSY of the product.

Table 1. Structural formula and relative abundance of GC in the reaction course after 40 min and the reaction end.

40 min	Reaction end
 (11.823%)	 (0.562%)
 (9.595%)	 (15.574%)
 (0.890%)	 (1.267%)
 (74.321%)	 (75.566%)
 (1.522%)	 (2.361%)
 (0.333%)	 (1.003%)
 (1.143%)	 (2.164%)

<sup>a</sup> The relative abundance of GC of the product II was 19.759% between 40 min and the reaction end.

<sup>b</sup> The relative abundance of GC of the product III was 1.137% between 40 min and the reaction end.

Ammonia with a pair of electron acts as nucleophilic reagent to attack a carboxyl group of furil to form the furil-ammonia adduct **2**, which dehydrates one molecule  $\text{H}_2\text{O}$  to

form the product **II**. Similarly, ammonia subsequently attacks to a carboxyl group of the product **II** by nucleophilic addition and dehydrates  $\text{H}_2\text{O}$  to obtain the stable product **III**. Then, the nucleophilic attack of product **III** to furil affords the intermediate **4** which subsequently dehydrates  $\text{H}_2\text{O}$  between hydroxy group and the hydrogen atom of imine ( $=\text{NH}$ ) to cyclize to intermediate **5**. The intermediate **5** further reacts with  $\text{H}_2\text{O}$  in the reaction system to obtain 2,4,5-tri(furan-2-yl)-2*H*-imidazole (Intermediate **6**) which quickly rearranges to the imidazoles derivatives **I**. Currently, our experimental support for this proposed mechanism comes from the finding that the imidazole **I** and small amounts of **II** and **III** are obtained, along with intermediate **5** is traced by GC-MS. For the action of ammonia on (aryl- or alkyl-)ethane-1,2-diketone in synthesizing imidazole derivatives, both Fang *et al.* [4] and Radziszewski [12] thought that the reactions began with the conversion of aldehyde to C-pyridin-2-yl-methanediamine or C-phenyl-methanediamine, which condensed with 2,2'-pyridil or benzil to form corresponding 2*H*-imidazole and then rearranged to the product. However, seen from our result, during the formation of imidazole derivatives the furil was further attacked not by C-furan-methanediamine but by 1,2-di(furan-2-yl)ethane-1,2-diimine to obtain an intermediate **4**, which in turn dehydrated, cyclized to afford imidazole derivatives **I**. The course of forming the product **I** was confirmed by GC-MS analyses. The reaction mechanism proposed is similar to the reported mechanism where the intermediate diimine is formed in the course of ammonia attacking to 1,2-diketone by the condensation of 1,2-diketones with appropriate aldehydes [7]. Herein, Dora *et al.* thought the intermediate diimine was unstable. But our experimental results showed that the intermediate 1,2-di(furan-2-yl)ethane-1,2-diimine (**III**) was stable. The result lied in the fact that the conjugated structure was formed between furan ring and imine ( $=\text{NH}$ ).

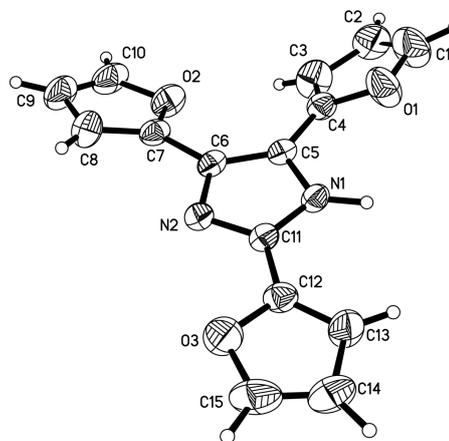


Figure 2. The crystal structure of compound I.

#### 4. Conclusion

In the action of ammonia on furil, three products named 2,4,5-tri(furan-2-yl)-1*H*-imidazole (**I**), 1,2-di(furan-2-yl)-2-iminoethanone (**II**) and 1,2-di(furan-2-yl)ethane-1,2-diimine (**III**) were isolated by column chromatography and C18 reversed phase column which was seldom used in the process of isolation. Especially a novel method for the separation of the compound containing imine group was developed. Besides, the possible reaction mechanism differentiated from the previous view was discussed, and the reaction mechanism further indicates that the forming of 1,2-di(furan-2-yl)ethane-1,2-diimine (**III**) is a key step. Further exploration of the synthesis and application of furan derivatives is currently ongoing in our laboratory.

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