

# Synthesis of novel 2-pyridyl- substituted 2,5-dihydro-2-imino- and 2-amino- furan derivatives *via* a three component condensation of alkyl isocyanides and acetylenic esters with di-(2-pyridyl) ketone or 2-pyridinecarboxaldehyde

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## Abstract

The reactive 1:1 intermediate is trapped from reaction between alkyl isocyanides and activated acetylenic esters by di-(2-pyridyl) ketone or 2-pyridinecarboxaldehyde. An effective and one-pot route is presented to synthesize novel iminolactones and 2-aminofurans.

**Keywords:** Three component condensation, alkyl isocyanides, acetylenic esters, di-(2-pyridyl) ketone, 2-pyridinecarboxaldehyde

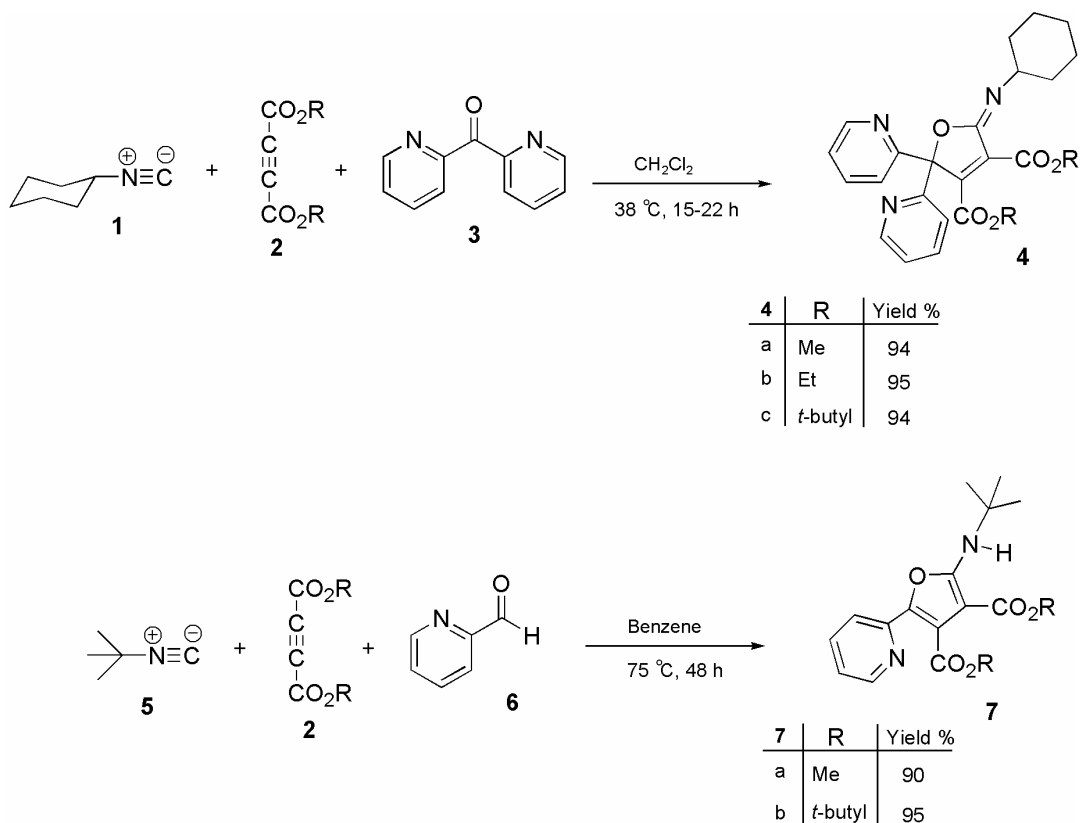
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## Introduction

Multi-component processes are at a premium for the achievement of high levels of diversity and brevity, as they allow three or more simple and flexible building blocks to be combined in practical, one-pot operations.<sup>1-3</sup> A few years ago it was reported,<sup>4</sup> that the reaction between alkyl isocyanides and 3-benzylidene-2,4-pentanedione was a convenient route to prepare densely functionalized furans. Indeed, 2-aminofurans are quite rare<sup>5</sup> and, according to the previous literature, rather difficult to prepare.<sup>6</sup>

Recently, multicomponent reactions (MCRs) have emerged as a highly valuable synthetic tool in the context of modern drug discovery. 5-Imino-2,5-dihydrofurans are potentially amenable to a number of synthetic transformation. For example, they can be easily hydrolyzed to  $\alpha,\beta$ -unsaturated  $\gamma$ -lactones, a structural motif present in a number of bioactive natural products such as chlorothricolide, kijanolide, and tetranolide.<sup>7</sup> It has been shown that alkyl or aryl isocyanides add to dialkyl acetylenedicarboxylates to generate zwitterionic species, which serve as intermediates in many different reaction.<sup>8-14</sup>

In previous works, the highly reactive 1:1 adduct, was trapped by carbonyl compounds to form 2,5-dihydro-2-imino- or 2-amino-furan derivatives in excellent yields. These reactions have been the subject of detailed investigation by a number of research groups.<sup>15-17</sup> In view of our general interest in multicomponent reactions involving zwitterionic species, we examined the reaction of alkyl isocyanides **1** or **5** and dialkyl acetylenedicarboxylates **2** with di-(2-pyridyl) ketone **3** or 2-pyridinecarboxaldehyde **6** (Scheme 1).



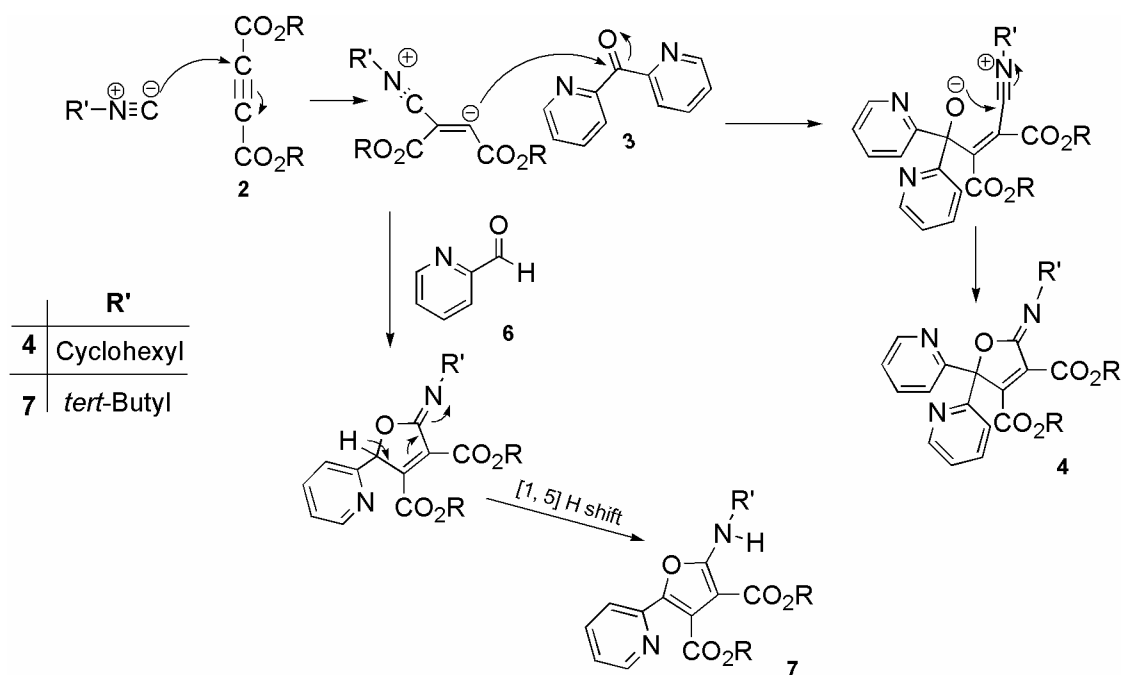
Scheme 1

## Results and Discussion

The reaction of alkyl isocyanides **1** or **5** with dialkyl acetylenedicarboxylates **2** in the presence of pyridine-containing carbonyl compounds **3** or **6** leads to the stable products **4a-c** or **7a,b** in excellent yields. A mechanistic rationale could be proposed for the formation of iminolactones or 2-aminofurans is shown (Scheme 2). The 1:1 zwitterionic intermediate which adds to the di-(2-pyridyl) ketone leading to a dipolar species, cyclization of the latter leads to the iminolactone derivatives **4a-c**, in the presence of 2-pyridinecarboxaldehyde, furan forms. This reaction, undergoes a [1,5]-hydrogen shift to yield the aminofuran derivatives **7a, b**.

It is conceivable that these multicomponent reactions will be applicable to the synthesis of heterocyclic rings with high hindrance. Products **4a-c** and **7a, b** are stable solids which structures were deduced from their IR,  $^1\text{H}$ -, and  $^{13}\text{C}$ - NMR, Mass spectral data and elemental analysis. The  $^1\text{H}$ - NMR spectrum of compound **4a** exhibited two singlet sharp lines, readily recognizable as arising from carbomethoxy groups (at  $\delta$  3.82 and 3.93) ppm. The  $^{13}\text{C}$ - NMR spectrum of **4a** showed seventeen distinct resonances in a good agreement with iminolactone structure. The characteristic signals resulting from the quaternary carbon and C=N group of iminolactone were discernible at ( $\delta$  94.73 and 155.84) ppm respectively in the  $^{13}\text{C}$ - NMR spectrum. Partial assignments of these resonances are given in the experimental data.

The  $^1\text{H}$ - NMR spectrum of compound **7a** exhibited three single sharp lines, readily recognizable as arising from *tert*-butyl ( $\delta$  1.52) and two carbomethoxy groups ( $\delta$  3.79 and 3.98) ppm and NH proton resonated at ( $\delta$  6.92) ppm supporting the IR absorption at  $3335\text{ cm}^{-1}$ . The  $^{13}\text{C}$ - NMR spectrum of **7a** showed fifteen distinct resonances in an agreement with proposed structure. Signals resulting from two ester carbonyl were discernible at ( $\delta$  164.26 and 164.91) ppm in the  $^{13}\text{C}$  NMR spectrum. The mass spectra of these compounds **7a, b** displayed molecular ion peaks at appropriate  $m/z$  values. The  $^1\text{H}$ - and  $^{13}\text{C}$ - NMR spectra of **7b** are similar to **7a** with the exception of the carboalkoxy groups.



## Scheme 2

In conclusion, we describe here, the reaction of alkyl isocyanides with activated acetylenes in the presence of pyridine-containing carbonyl compounds that leads to the one-pot and important synthesis of highly hindered and functionalized iminolactone or 2-aminofuran derivatives. The

substances can be mixed without any activation or modification in these reactions, which in the view of experimental it is an important advantages.

## Experimental Section

**General Procedures.** *tert*-Butyl- and cyclohexyl isocyanides, dialkyl acetylenedicarboxylates, di-(2-pyridyl) ketone and 2-pyridinecarboxaldehyde were purchased from Fluka and Aldrich, respectively, and used without further purification. Melting points and IR spectra were measured on an Electrothermal 9100 apparatus and a Shimadzu IR-470 spectrometer, respectively. Elemental analysis for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. The  $^1\text{H}$ - and  $^{13}\text{C}$  NMR spectra were measured with a Bruker DRX-300 AVANCE instrument with  $\text{CDCl}_3$  as solvent at 300.1 and 75.5 MHz, respectively. Mass spectra were recorded on a Shimadzu GC/MS QP 1100 EX mass spectrometer operating at an ionization potential of 70 eV.

### General experimental procedure (exemplified by 4a)

The process for the preparation of **4a** is described as an example. The solution of cyclohexyl isocyanide (0.131 g or 1.2 mmol) in 3 mL of  $\text{CH}_2\text{Cl}_2$  solvent was slowly added dropwise, to the mixture of di-(2-pyridyl) ketone (0.184 g or 1 mmol) and DMAD (0.171 g or 1.2 mmol) in 20 mL of  $\text{CH}_2\text{Cl}_2$  solvent at room temperature for 3 minutes. After the complete addition, the solution was refluxed at  $38^\circ\text{C}$  for 16 hours. Then, the solvent was removed under reduced pressure, and the solid residual washed with cold diethyl ether ( $2 \times 5$  mL) and the product (**4a**) was obtained as a brown powder.

### Dimethyl 5-(cyclohexylimino)-2,5-dihydro-2,2-di-(2-pyridyl)-3,4-furandicarboxylate (4a).

Brown powder; yield 0.41 g (94%), mp  $156\text{--}159^\circ\text{C}$ , IR (KBr) ( $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1739 and 1714 ( $2\text{C}=\text{O}$ ), 1680 ( $\text{C}=\text{N}$ ).  $^1\text{H}$ - NMR (300.1 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  1.28-2.20 (10H, m, 5  $\text{CH}_2$  of cyclohexyl), 3.53 (1H, m, NCH), 3.82 and 3.93 (6H, 2s, 2  $\text{CO}_2\text{CH}_3$ ), 7.33-8.62 (m, 8 CH).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  24.87, 25.64, 33.11 (5  $\text{CH}_2$  of cyclohexyl), 52.63 and 53.02 (2  $\text{OCH}_3$ ), 56.66 (NCH of cyclohexyl), 94.73 ( $\text{C}_{\text{quaternary}}$ ), 122.58, 123.45, 124.03, 136.70, 137.11, 146.17, 148.93 ( $\text{C}=\text{C}_{\text{iminolactone ring}}$  and  $\text{C}_{\text{arom}}$ ), 155.84 ( $\text{C}=\text{N}_{\text{imine}}$ ), 157.64 and 162.77 (2  $\text{C}=\text{O}$ ). MS ( $m/z$ , %): 435 ( $\text{M}^+$ , 2), 404 (4), 352 (1), 338 (32), 311 (44), 279 (100), 221 (15), 192 (23), 106 (13), 78 (62), 55 (53), 41 (56). Anal. Calcd for  $\text{C}_{24}\text{H}_{25}\text{N}_3\text{O}_5$  (435): C, 66.21; H, 5.75; N, 9.66%; Found: C, 65.38; H, 5.57; N, 9.81%.

### Diethyl 5-(cyclohexylimino)-2,5-dihydro-2,2-di-(2-pyridyl)-3,4-furandicarboxylate (4b).

Grey crystals; yield 0.44 g (95%), mp  $126\text{--}129^\circ\text{C}$ , IR (KBr) ( $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1741 and 1716 (2  $\text{C}=\text{O}$ ), 1677 ( $\text{C}=\text{N}$ ).  $^1\text{H}$ - NMR (300.1 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  1.14-1.81 (10H, m, 5  $\text{CH}_2$  of cyclohexyl), 1.17 (3H, t,  $J=7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 1.35 (3H, t,  $J=7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 3.72 (1H, m, NCH), 4.21 (2H, q,  $J=7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 4.37 (2H, q,  $J=7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 7.28-8.57 (m, 8 CH).  $^{13}\text{C}$ - NMR (75.5 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  13.70 and 13.99 (2  $\text{CH}_3$ ), 24.08, 24.82 and 31.02 (5  $\text{CH}_2$  of cyclohexyl), 56.49 (NCH of cyclohexyl), 62.02 and 62.28 (2  $\text{OCH}_2$ ), 91.46 ( $\text{C}_{\text{quaternary}}$ ),

122.69, 123.32, 123.89, 136.61, 137.02, 148.81, 149.08 (C=C<sub>iminolactone ring</sub> and C<sub>arom</sub>), 155.47 (C=N<sub>imine</sub>), 159.84 and 161.45 (2C=O). MS (*m/z*, %): 463 (M<sup>+</sup>, 1), 418 (6), 390 (7), 366 (37), 339 (53), 293 (100), 221 (38), 193 (44), 106 (11), 78 (49), 55 (38), 41 (35). Anal. Calcd for C<sub>26</sub>H<sub>29</sub>N<sub>3</sub>O<sub>5</sub> (463): C, 67.39; H, 6.26; N, 9.07%; Found: C, 65.24; H, 6.39; N, 8.84%.

**Di-*tert*-butyl 5-(cyclohexylimino)-2,5-dihydro-2,2-di-(2-pyridyl)-3,4-furandicarboxylate (4c).** Brown crystals; yield 0.49 g (94%), mp 154-157 °C, IR (KBr) ( $\nu_{\max}$ , cm<sup>-1</sup>): 1736 and 1712 (2 C=O), 1683 (C=N). <sup>1</sup>H-NMR (300.1 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  1.27-1.79 (10H, m, 5 CH<sub>2</sub> of cyclohexyl), 1.35 and 1.60 (18H, 2s, 2 OCM<sub>3</sub>), 3.75 (1H, m, NCH), 7.29 (2H, m, 2 CH), 7.36 (2H, t,  $J=7.8$  Hz, 2 CH), 7.75 (2H, dt,  $J_1=7.8$  Hz,  $J_2=1.0$  Hz, 2 CH), 8.56 (2H, m, 2 CH). <sup>13</sup>C-NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta_{\text{C}}$  24.55, 25.87, 33.37 (5 CH<sub>2</sub> of cyclohexyl), 27.76 and 28.08 (2 CMe<sub>3</sub>), 55.75 (NCH of cyclohexyl), 82.26 and 83.12 (2 OCM<sub>3</sub>), 94.37 (C<sub>quaternary</sub>), 122.45, 123.04, 123.83, 136.41, 136.78, 148.41, 148.47 (C=C<sub>iminolactone ring</sub> and C<sub>arom</sub>), 158.33 (C=N<sub>imine</sub>), 160.70 and 160.95 (2C=O). MS (*m/z*, %): 521 (M<sup>+</sup>+2, 14), 520 (M<sup>+</sup>+1, 37), 519 (M<sup>+</sup>, 4), 464 (2), 446 (3), 418 (4), 318 (14), 283 (57), 265 (48), 238 (25), 221 (36), 193 (39), 106 (5), 57 (100), 41 (65). Anal. Calcd for C<sub>30</sub>H<sub>37</sub>N<sub>3</sub>O<sub>5</sub> (519): C, 69.36; H, 7.13; N, 8.09%; Found: C, 66.16; H, 7.31; N, 8.26%.

#### General procedure (exemplified by 7a)

The preparation of **7a** is described as an example. To the solution of 2-pyridinecarboxaldehyde (0.107 g or 1 mmol) and DMAD (0.171 g or 1.2 mmol) in 20 mL of benzene solvent, was slowly added, dropwise, a mixture of *tert*-butyl isocyanide (0.100 g or 1.2 mmol) in 3 mL of benzene. To this mixture was allowed to stand for at room temperature for 3 min, then the reaction mixture was refluxed at 75 °C for 48 h. The solvent was removed under reduced pressure, and the solid product washed with cold diethyl ether and *n*-hexane with 1:3 ratios (2×3 mL) and the product (**7a**) was obtained as a brown powder.

**Dimethyl 2-(*tert*-butylamino)-5-(2-pyridyl)-3,4-furandicarboxylate (7a).** Brown powder; yield 0.30 g (90%), mp 83-86 °C, IR (KBr) ( $\nu_{\max}$ , cm<sup>-1</sup>): 3335 (N-H), 1738 and 1677 (2 C=O). <sup>1</sup>H-NMR (300.1 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  1.52 (9H, s, NCM<sub>3</sub>), 3.79 and 3.98 (6H, 2s, 2 OCH<sub>3</sub>), 6.92 (1H, s, NH), 7.08 (1H, dd,  $J_1=5.0$  Hz,  $J_2=0.8$  Hz, Ar-H), 7.44 (1H, d,  $J=7.9$  Hz, Ar-H), 7.68 (1H, dt,  $J_1=7.8$  Hz,  $J_2=1.7$  Hz, Ar-H), 8.52 (1H, d,  $J=4.4$  Hz, Ar-H). <sup>13</sup>C-NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta_{\text{C}}$  29.80 (NCMe<sub>3</sub>), 51.64 (NCMe<sub>3</sub>), 53.25 and 53.96 (2 OMe), 90.46, 119.35, 120.85, 121.37, 134.10, 140.81, 145.50, 150.01 and 162.51 (C=C<sub>aminofuran ring</sub> and C<sub>arom</sub>), 164.26 and 164.91 (2C=O). MS (*m/z*, %): 334 (M<sup>+</sup>+2, 2), 333 (M<sup>+</sup>+1, 7), 332 (M<sup>+</sup>, 35), 301 (3), 276 (45), 261 (4), 244 (13), 212 (62), 184 (37), 106 (33), 78 (100), 57 (91), 41 (96). Anal. Calcd for C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub> (332): C, 61.45; H, 6.02; N, 8.43%; Found: C, 63.45; H, 6.28; N, 8.31%

**Di-*tert*-butyl 2-(*tert*-butylamino)-5-(2-pyridyl)-3,4-furandicarboxylate (7b).** White powder; yield 0.40 g (95%), mp 123-125 °C, IR (KBr) ( $\nu_{\max}$ , cm<sup>-1</sup>): 3323 (N-H), 1714 and 1673 (2C=O). <sup>1</sup>H-NMR (300.1 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  1.50 (9H, s, NCM<sub>3</sub>), 1.56 and 1.64 (18H, 2s, 2 OCM<sub>3</sub>), 7.01 (1H, s, NH), 7.05 (1H, dd,  $J_1=4.8$  Hz,  $J_2=0.8$  Hz, ArH), 7.42 (1H, d,  $J=8.0$  Hz, ArH), 7.65

(1H, dt,  $J_1 = 8.0$  Hz,  $J_2 = 1.4$  Hz, ArH), 8.48 (1H, d,  $J = 4.8$  Hz, ArH).  $^{13}\text{C}$ - NMR (75.5 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  28.33 and 28.73 (2xOCMe<sub>3</sub>), 29.16 (NCMe<sub>3</sub>), 52.52 (NCMe<sub>3</sub>), 80.69 and 82.05 (2xOCMe<sub>3</sub>), 90.25, 117.35, 118.53, 120.74, 136.25, 139.11, 148.26, 148.90, 161.52 (C=C<sub>aminofuran ring</sub> and C<sub>arom</sub>), 163.70 and 164.52 (2 C=O). MS ( $m/z$ , %): 417 ( $\text{M}^+ + 1$ , 6), 416 ( $\text{M}^+$ , 17), 360 (10), 343 (2), 304 (42), 287 (6), 260 (13), 212 (9), 204 (93), 186 (54), 160 (40), 57 (100), 41 (63). Anal. Calcd for C<sub>23</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub> (416): C, 66.35; H, 7.69; N, 6.73%; Found: C, 64.30; H, 7.66; N, 6.39%.

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