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.

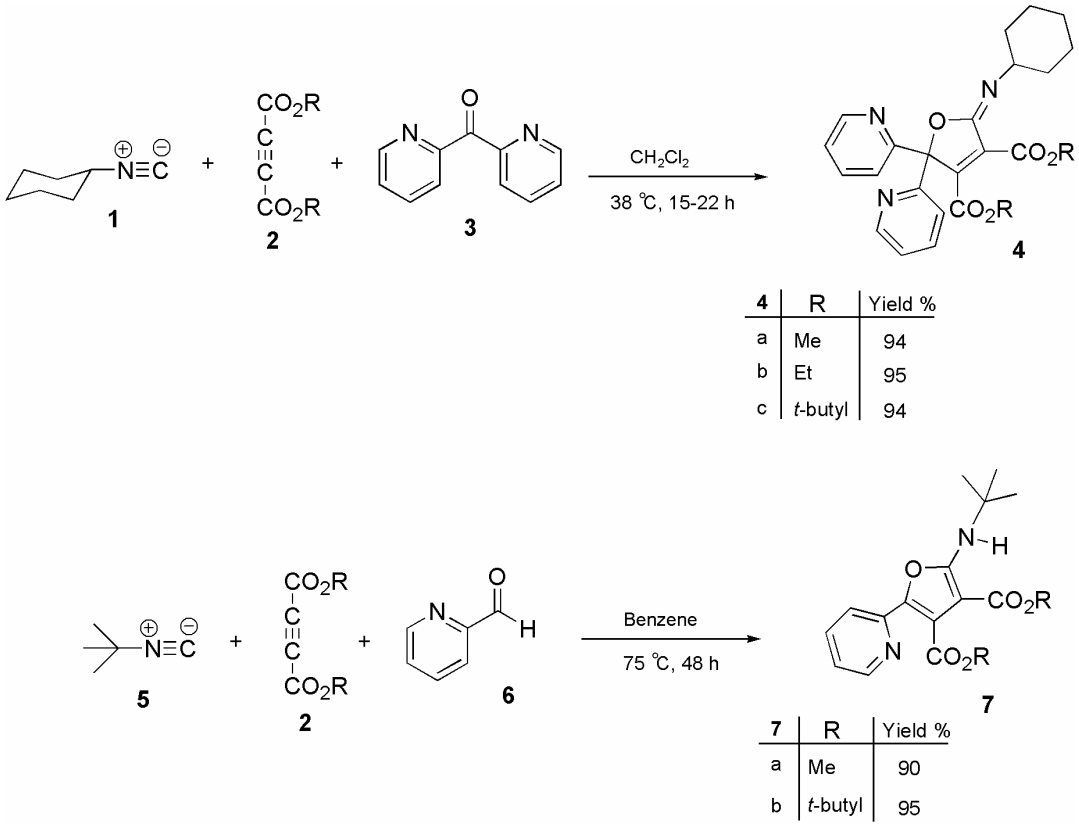
Keywords: Three component condensation, alkyl isocyanides, acetylenic esters, di-(2-pyridyl) ketone, 2-pyridinecarboxaldehyde

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.[1-3] A few years ago it was reported,[4] 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[5] and, according to the previous literature, rather difficult to prepare.[6]

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 α,β-unsaturated γ-lactones, a structural motif present in a number of bioactive natural products such as chlorothricolide, kijanolide, and tetranolide.[7] 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.[8-14]

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.[15-17] 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).



4	R	Yield %
a	Me	94
b	Et	95
c	*t*-butyl	94

7	R	Yield %
a	Me	90
b	*t*-butyl	95

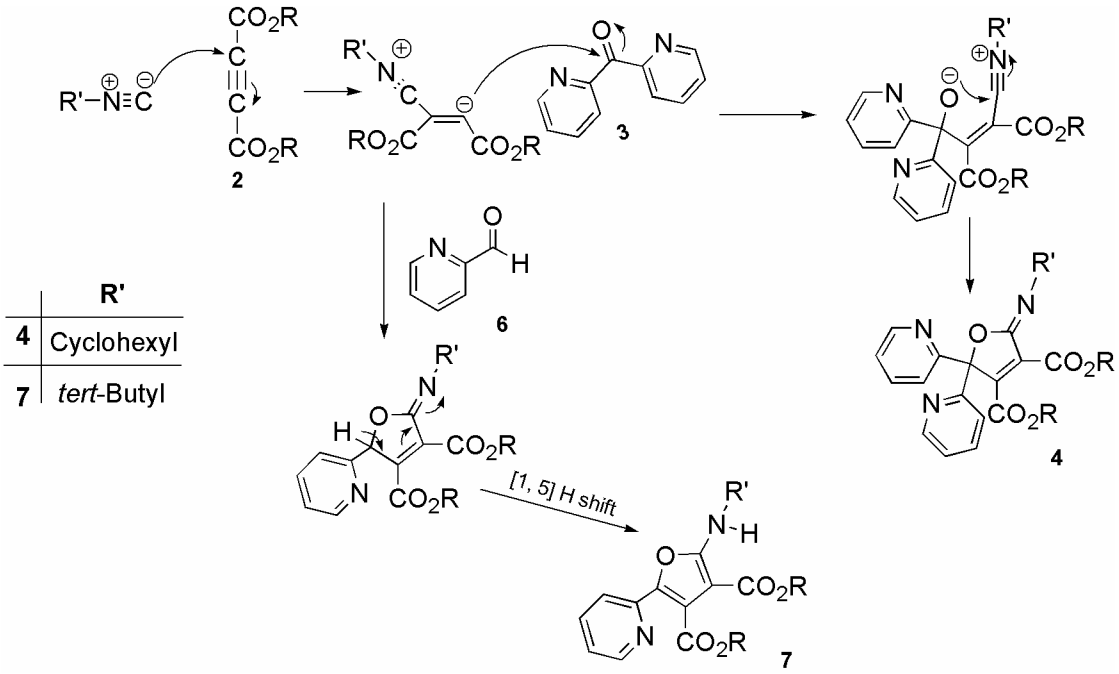
Scheme 1

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}H-, and ^{13}C- NMR, Mass spectral data and elemental analysis. The ^{1}H- NMR spectrum of compound **4a** exhibited two singlet sharp lines, readily recognizable as arising from carbomethoxy groups (at δ 3.82 and 3.93) ppm. The ^{13}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 (δ 94.73 and 155.84) ppm respectively in the ^{13}C- NMR spectrum. Partial assignments of these resonances are given in the experimental data.

The ^{1}H- NMR spectrum of compound **7a** exhibited three single sharp lines, readily recognizable as arising from *tert*-butyl (δ 1.52) and two carbomethoxy groups (δ 3.79 and 3.98) ppm and NH proton resonated at (δ 6.92) ppm supporting the IR absorption at 3335 cm^{-1}. The ^{13}C- NMR spectrum of **7a** showed fifteen distinct resonances in an agreement with proposed structure. Signals resulting from two ester carbonyl were discernible at (δ 164.26 and 164.91) ppm in the ^{13}C NMR spectrum. The mass spectra of these compounds **7a**, **b** displayed molecular ion peaks at appropriate *m/z* values. The ^{1}H- and ^{13}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}H- and ^{13}C NMR spectra were measured with a Bruker DRX–300 AVANCE instrument with $CDCl_3$ 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 CH_2Cl_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 CH_2Cl_2 solvent at room temperature for 3 minutes. After the complete addition, the solution was refluxed at 38˚C for 16 hours. Then, the solvent was removed under reduced pressure, and the solid residual washed with cold diethyl ether (2×5 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 156-159 ˚C, IR (KBr) (ν_{max}, cm^{-1}): 1739 and 1714 (2C=O), 1680 (C=N). ^{1}H- NMR (300.1 MHz, $CDCl_3$): δ_H 1.28-2.20 (10H, m, 5 CH_2 of cyclohexyl), 3.53 (1H, m, NCH), 3.82 and 3.93 (6H, 2s, 2 CO_2CH_3), 7.33-8.62 (m, 8 CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 24.87, 25.64, 33.11 (5 CH_2 of cyclohexyl), 52.63 and 53.02 (2 OCH_3), 56.66 (N*C*H of cyclohexyl), 94.73 ($C_{quaternary}$), 122.58, 123.45, 124.03, 136.70, 137.11, 146.17, 148.93 (C=$C_{iminolactone\ ring}$ and C_{arom}), 155.84 (C=N_{imine}), 157.64 and 162.77 (2 C=O). MS (*m/z*, %): 435 (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 $C_{24}H_{25}N_3O_5$ (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 126-129 ˚C, IR (KBr) (ν_{max}, cm^{-1}): 1741 and 1716 (2 C=O), 1677 (C=N). ^{1}H- NMR (300.1 MHz, $CDCl_3$): δH 1.14-1.81 (10H, m, 5 CH_2 of cyclohexyl), 1.17 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.35 (3H, t, J=7.1 Hz, OCH_2CH_3), 3.72 (1H, m, NCH), 4.21 (2H, q, J=7.1 Hz, OCH_2CH_3), 4.37 (2H, q, J=7.1 Hz, OCH_2CH_3), 7.28-8.57 (m, 8 CH). ^{13}C- NMR (75.5 MHz, $CDCl_3$): δ_C 13.70 and 13.99 (2 CH_3), 24.08, 24.82 and 31.02 (5 CH_2 of cyclohexyl), 56.49 (NCH of cyclohexyl), 62.02 and 62.28 (2 OCH_2), 91.46 ($C_{quaternary}$),

122.69, 123.32, 123.89, 136.61, 137.02, 148.81, 149.08 (C=$C_{iminolactone\ ring}$ and C_{arom}), 155.47 (C=N_{imine}), 159.84 and 161.45 (2C=O). MS (*m/z*, %): 463 (M^+, 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 $C_{26}H_{29}N_3O_5$ (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) (ν_{max}, cm^{-1}): 1736 and 1712 (2 C=O), 1683 (C=N). ^{1}H- NMR (300.1 MHz, $CDCl_3$): δ_H 1.27-1.79 (10H, m, 5 CH_2 of cyclohexyl), 1.35 and 1.60 (18H, 2s, 2 $OCMe_3$), 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). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ_C 24.55, 25.87, 33.37 (5 CH_2 of cyclohexyl), 27.76 and 28.08 (2 CMe_3), 55.75 (NCH of cyclohexyl), 82.26 and 83.12 (2 $OCMe_3$), 94.37 ($C_{quaternary}$), 122.45, 123.04, 123.83, 136.41, 136.78, 148.41, 148.47 (C=$C_{iminolactone\ ring}$ and C_{arom}), 158.33 (C=N_{imine}), 160.70 and 160.95 (2C=O). MS (*m/z*, %): 521 (M^++2, 14), 520 (M^++1, 37), 519 (M^+, 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 $C_{30}H_{37}N_3O_5$ (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^{-1}): 3335 (N-H), 1738 and 1677 (2 C=O). ^{1}H- NMR (300.1 MHz, $CDCl_3$): δ_H 1.52 (9H, s, NC*Me*$_3$), 3.79 and 3.98 (6H, 2s, 2 OCH_3), 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). ^{13}C- NMR (75.5 MHz, $CDCl_3$): δ_C 29.80 (NC*Me*$_3$), 51.64 (N*C*Me$_3$), 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=$C_{aminofuran\ ring}$ and C_{arom}), 164.26 and 164.91 (2C=O). MS (*m/z*, %): 334 (M^++2, 2), 333 (M^++1, 7), 332 (M^+, 35), 301 (3), 276 (45), 261 (4), 244 (13), 212 (62), 184 (37), 106 (33), 78 (100), 57 (91), 41 (96). Anal. Calcd for $C_{17}H_{20}N_2O_5$ (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^{-1}): 3323 (N-H), 1714 and 1673 (2C=O). ^{1}H- NMR (300.1 MHz, $CDCl_3$): δ_H 1.50 (9H, s, NC*Me*$_3$), 1.56 and 1.64 (18H, 2s, 2 OC*Me*$_3$), 7.01 (1H, s, N*H*), 7.05 (1H, dd, J_1= 4.8 Hz, J_2= 0.8 Hz, Ar*H*), 7.42 (1H, d, *J*= 8.0 Hz, Ar*H*), 7.65

(1H, dt, J_1= 8.0 Hz, J_2= 1.4 Hz, Ar*H*), 8.48 (1H, d, *J*= 4.8 Hz, Ar*H*). ^{13}C- NMR (75.5 MHz, $CDCl_3$): δ_C 28.33 and 28.73 (2xOC*Me*$_3$), 29.16 (NC*Me*$_3$), 52.52 (N*C*Me$_3$), 80.69 and 82.05 (2xO*C*Me$_3$), 90.25, 117.35, 118.53, 120.74, 136.25, 139.11, 148.26, 148.90, 161.52 (C=$C_{aminofuran\ ring}$ and C_{arom}), 163.70 and 164.52 (2 C=O). MS (*m/z*, %): 417 (M^++1, 6), 416 (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 $C_{23}H_{32}N_2O_5$ (416): C, 66.35; H, 7.69; N, 6.73%; Found: C, 64.30; H, 7.66; N, 6.39%.

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