Short communication

A Facile One-Pot Synthesis of Amino Furans Using Trans-Cinnamaldehyde in the Presence of Nucleophilic Isocyanides

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Received: 07-05-2007

Abstract

The 1 : 1 reactive intermediate generated by the addition of alkyl isocyanide to dialkyl acetylenedicarboxylates was trapped by *trans*-cinnamaldehyde to yield polyfunctionalized furan rings.

Keywords: *Tert*-butylisocyanide, dialkyl acetylenedicarboxylate, *trans*-cinnamaldehyde

1. Introduction

The development of reactions to produce heterocyclic compounds is of vital importance in organic synthesis, especially the heterocycles which can be found in naturally occurring products. A number of heterocyclic compounds such as furan, and pyran rings are found in natural systems. Furan rings, one example of five-membered heterocycles, are found in a lot of naturally occurring products.[1] The furan ring is not only present as key structural unit in naturally occurring products, but is also important in the pharmaceutical chemistry.[2–4] Therefore, there has been interest in the synthesis of polyfunctionalized furans, and some of the useful synthetic methods for furans have been reported, by many synthetic chemists.[5–12] The Paal–Knorr method,[13] the Feist–Benary method,[14] etc. are the most important methods for furan ring construction. Here, we wish to describe in detail the preparation of polyfunctionalized furan ring by reaction of alkyl isocyanides **1** with dialkyl acetylenedicarboxylate **2** in the presence of trans-cinnamaldehyde **3**.

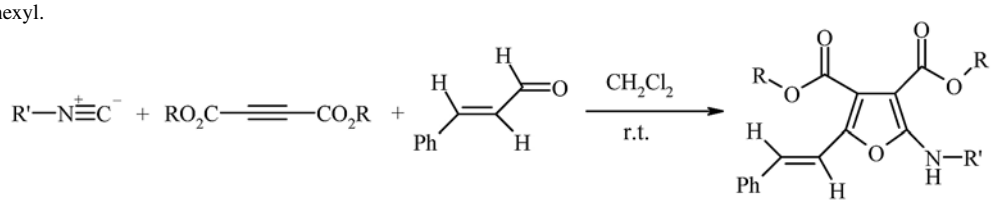
This three component reaction produces highly functionalized furans **4** in fairly good yields (Scheme 1).

2. Results and Discussion

On the basis of the well established chemistry of isocyanide,[15–17] it is reasonable to assume that compound **4** results from the initial addition of the isocyanides to the acetylenic ester to form the zwitterionic intermediate **5**, which attacks the carbonyl group of the trans-cinnamaldehyde **3**. Then, nucleophilic addition to the nitrile iminium moiety leads to the formation of the five-membered ring **6** which is aromatized to heterocyclic compound **4** by [1,5]-H shift (Scheme 2).

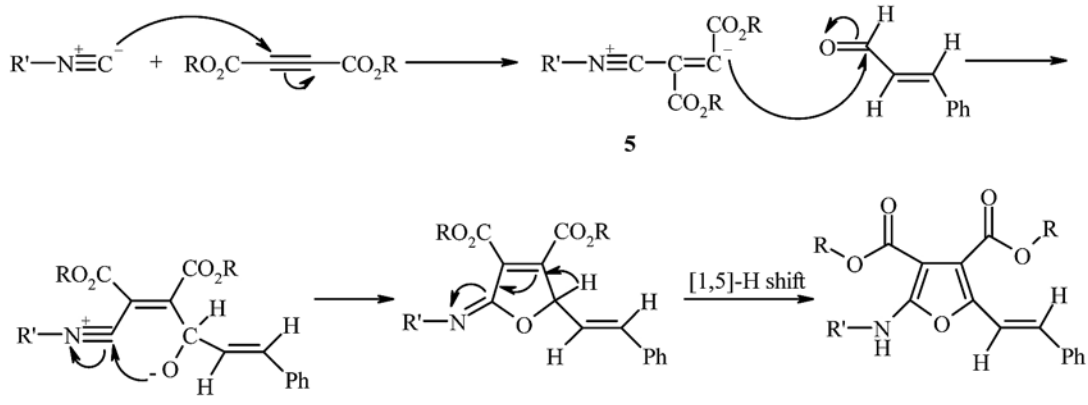
4	R	R´	yield of **4** (%)
a	Me	*t*-Bu	65
b	Et	*t*-Bu	60
c	*t*-Bu	*t*-Bu	68
d	Me	Cya	58
e	Et	Cy	72
f	*t*-Bu	Cy	68

[a] Cy: cyclohexyl.



1 **2** **3** **4**

Scheme 1



Scheme 2

The structure of **4a–f** were deduced from their ^{1}H and ^{13}C NMR and IR spectra and their mass spectrometric data. The ^{1}H NMR spectrum of **4a** exhibited a sharp signal for tert-butyl (δ = 1.5 ppm), two singlets for two methoxy groups (3.78 and 3.91 ppm), and a singlet for NH group (7.08 ppm) and two doublets for vinyl protons at about 6.88 and 7.07 ppm ($^3J_{HH}$ = 16 Hz) showing E-geometry. The ^{13}C NMR spectrum of **4a** exhibited sixteen sharp lines in agreement with the proposed structure. The ^{1}H and ^{13}C NMR spectra of **4b** and **4c** are similar to that of **4a**, except for the signals of alkoxy groups. The mass spectrum of **4a** exhibited molecular ion peak at m/z 357($M^{+\cdot}$, 4%). Initial fragmentations involved loss or complete loss of the side chains of the furan system.

The ^{1}H NMR spectrum of **4d** displayed a quintet for the cyclohexyl CH proton (δ = 3.5 ppm), and methylene groups (1.72–1.74 and 1.76–1.77 and 2.02–2.03 ppm), methoxy (3.87 and 3.75 ppm), and NH proton (6.85 ppm), and vinyl protons (7.08 and 7.22 ppm). The ^{13}C NMR spectrum of **4d** exhibited eighteen sharp lines in agreement with the proposed structure. This spectrum indicated four signals for cyclohexyl (δ = 24.3, 25.2, 33.42 and 51.03 ppm), two methoxy groups (51.5 and 51.9 ppm) and carbonyl groups (164.17 and 165.3 ppm). Partial assignment of these resonances for **4a–f** is given in the experimental section. The structural assignments of **4a–f** were supported by their IR spectra which have a strong absorption band at about 3320 cm^{-1} for NH groups and 1650–1730 cm^{-1} for COO groups.

3. Conclusion

We have found a simple and efficient method for the preparation of some functionalized amino furans of potential interest. The one-pot nature of the present procedure makes it an acceptable alternative to previous multistep approaches.

The present method carries some advantages including mild and neutral reaction conditions without any activation or modification.

4. Experimental

Dialkyl acetylenedicarboxylates, alkylisocyanides and trans-cinnamaldehyde were obtained from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electerothermal 9100 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-500 Avance spectrometer at 500 and 125.8 MHz, respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. Elemental analysis were performed using a Heraeus CHN-O-Rapid analyzer.

General procedure for preparation of dialkyl 2-(tert-butylamino)-5-[(E)-2-phe- nyl-1-ethenyl]-3,4-furandicarboxylate (exemplified by 4a)

To a magnetically stirred solution of trans-cinnamaldehyde (0.264 g, 2 mmol) and dialkyl acetylenedicarboxylate (2 mmol) in CH_2Cl_2 (10 mL), dropwise, 2 mmol of alkyl isocyanide in CH_2Cl_2 (4 mL) was added at –10 °C over 10 min. The mixture was allowed to stir at room temperature for 2 days. The solvent was removed under reduced pressure and the residue was purified by silica gel (Merck silica gel, 230–400 mesh) column chromatography using hexane:ethyl acetate (80:20) as eluent. The solvent was removed under reduced pressure, the products **4a**–**f** were obtained as yellow powders or viscous oil (**4d**).

Dimethyl 2-(tert-butylamino)-5-[(E)-2-phenyl-1-ethenyl]-3,4-furandicarboxyl- ate (4a).

Yellow powder, m.p. 74–75 °C, yield 65%, IR (KBr) (ν_{max}, cm^{-1}): 1699–1657 (COO) and 3315 (NH); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.50 (9H, s, CMe_3), 3.78 and 3.91 (6H, 2s, 2 × OCH_3), 6.88 (1H, d, $^3J_{HH}$ = 16 Hz, –CH=), 7.07 (1H, dd, $^3J_{HH}$ = 16 Hz and $^4J_{HH}$ = 0.87 Hz, –CH=), 7.08 (1H, s, NH), 7.23 (1H, t, $^3J_{HH}$ = 7.5 Hz, H_{para}), 7.32 (2H, t, $^3J_{HH}$ = 7.5 Hz, H_{meta}), 7.45 (2H, d, $^3J_{HH}$ = 7.5 Hz, H_{ortho}); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 29.8

(NHCMe$_3$), 51.1 and 52.0 (2 × OCH$_3$), 52.8 (NCMe$_3$), 87.6, 114.1, 145.5 and 162.3 (furan), 114.2 and 128.0 (–C=), 126.5 (C$_{ortho}$), 127.9 (C$_{para}$), 128.7 (C$_{meta}$), 136.6 (C$_{ipso}$), 164.2 and 165.4 (2COO); MS: m/z (%): 357 (M$^{+\cdot}$, 4), 301 (M$^{+\cdot}$– C$_4$H$_8$, 8), 269 [M$^{+\cdot}$– (HNC$_4$H$_9$ + CH$_3$ + H), 19], 237 [M$^{+\cdot}$ – (2CO$_2$CH$_3$ + 2H), 16], 181 [M$^{+\cdot}$– (PhCH=CH + HNC$_4$H$_9$ + H), 37], 131 [M$^{+\cdot}$ –(Ph + C$_4$H$_9$ + CO$_2$Me + OMe + 2H), 100], 103 (PhCH=CH$^+$, 100), 77 (Ph, 100), 57 (C$_4$H$_9$, 100). Anal. Calcd for C$_{20}$H$_{23}$NO$_5$ (357.4): C, 67.21; H, 6.48; N, 3.92. Found: C, 67.10; H, 6.41; N, 3.91.

Diethyl 2-(tert-butylamino)-5-[(E)-2-phenyl-1-ethenyl]-3,4-furandicarboxylate (4b).

Yellow powder, m.p. 84–86 °C, yield 60%, IR (KBr) (ν_{max}, cm^{-1}): 1669–1712 (COO) and 3333 (NH); ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 1.29 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH$_3$), 1.37 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH$_3$), 1.48 (9H, s, CMe$_3$), 4.22 (2H, q, $^3J_{HH}$ = 7.1 Hz, OCH$_2$), 4.34 (2H, q, $^3J_{HH}$ = 7.1 Hz, OCH$_2$), 6.87 (1H, d, $^3J_{HH}$ = 16.1 Hz, –CH=), 7.07 (1H, d, $^3J_{HH}$ = 16.1 Hz, –CH=), 7.07 (1H, s, NH), 7.22 (1H, t, $^3J_{HH}$ = 7.5 Hz, H$_{para}$), 7.31 (2H, t, $^3J_{HH}$ = 7.5 Hz, H$_{meta}$), 7.44 (2H, d, $^3J_{HH}$ = 7.5 Hz, H$_{ortho}$); ^{13}C NMR (125.8 MHz, CDCl$_3$): δ_C 14.3 (CH$_3$), 14.4 (CH$_3$), 29.8 (CMe$_3$), 52.8 (NCMe$_3$), 59.6 (OCH$_2$), 60.9 (OCH$_2$), 87.9, 114.7, 145.1 and 162.2 (furan), 114.2 and 127.7 (–C=), 126.5 (C$_{ortho}$), 127.5 (C$_{para}$), 128.6 (C$_{meta}$), 136.7 (C$_{ipso}$), 163.9 and 165.0 (2 × COO); MS: m/z (%): 385 (M$^{+\cdot}$, 41), 329 (M$^{+\cdot}$ – C$_4$H$_8$, 59), 283 [M$^{+\cdot}$– (CO$_2$Et + Et), 44], 255 [M$^{+\cdot}$– (2C$_2$H$_5$ + NHC$_4$H$_9$), 43], 238 [M$^{+\cdot}$– (PhCH=CH + OC$_2$H$_5$ + H), 100], 131 [M$^{+\cdot}$– (Ph + C$_4$H$_9$ + CO$_2$Et + OEt + 2H), 100], 103 (PhCH=CH$^+$, 100), 77 (Ph$^+$, 100), 57 (C$_4$H$_9^+$, 100). Anal. Calcd for C$_{22}$H$_{27}$NO$_5$ (385.45): C, 68.55; H, 7.06; N, 3.63. Found: C, 68.40; H, 6.92; N, 3.61.

Di(tert-butyl)-2-(tert-butylamino)-5-[(E)-2-phenyl-1-ethenyl]-3,4-furandicarboxylate (4c).

Yellow powder, m.p. 124–126 °C, yield 68%, IR (KBr) (ν_{max}, cm^{-1}): 1657–1699 (COO) and 3322 (NH); ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 1.46 (9H, s, NHCMe$_3$), 1.51 (9H, s, OCMe$_3$), 1.61 (9H, s, OCMe$_3$), 6.92 (1H, s, NH), 6.81 (1H, d, $^3J_{HH}$ = 16 Hz, –CH=), 7.05 (1H, d, $^3J_{HH}$ = 16 Hz, –CH=), 7.22 (1H, t, $^3J_{HH}$ = 7.5 Hz, H$_{para}$), 7.32 (2H, t, $^3J_{HH}$ = 7.5 Hz, H$_{meta}$), 7.41 (2H, d, $^3J_{HH}$ = 7.5 Hz, H$_{ortho}$); ^{13}C NMR (125.8 MHz, CDCl$_3$): δ_C 28.4 (NCMe$_3$), 28.5 (OCMe$_3$), 29.8 (OCMe$_3$), 52.6 (NHCMe$_3$), 80.1 (OCMe$_3$), 81.4 (OCMe$_3$), 90.0, 116.9, 144.1 and 161.8 (furan), 114.4 and 127.5 (–C=), 126.2 (C$_{ortho}$), 126.5 (C$_{para}$), 128.7 (C$_{meta}$), 137.1 (C$_{ipso}$), 162.3 and 164.4 (2 × COO); MS: m/z (%): 441 (M$^{+\cdot}$, 7), 329 (M$^{+\cdot}$–2C$_4$H$_8$, 100), 273 (M$^{+\cdot}$– 3C$_4$H$_8$, 100), 255 [M$^{+\cdot}$– (2C$_4$H$_9$ + NHC$_4$H$_9$), 37], 238 [M$^{+\cdot}$– (C$_4$H$_9$ + OC$_4$H$_9$ + NHC$_4$H$_9$ + H), 30], 166 [M$^{+\cdot}$– (2CO$_2$ C$_4$H$_9$ + NHC$_4$H$_9$ + H), 26], 131[M$^{+\cdot}$– Ph + C$_4$H$_9$ + CO$_2$C$_4$H$_9$ + OC$_4$H$_9$ + 2H), 100], 103 (PhCH=CH$^+$, 33), 77 (Ph$^+$, 21), 57 (C$_4$H$_9^+$, 100). Anal. Calcd for C$_{26}$H$_{35}$NO$_5$ (441.56): C, 70.72; H, 7.99; N, 3.17. Found: C, 70.61; H, 7.86; N, 3.09.

Dimethyl 2-(cyclohexylamino)-5-[(E)-2-phenyl-1-ethenyl]-3,4-furandicarboxy- late (4d).

Viscous oil, yield 58%, IR (KBr) (ν_{max}, cm^{-1}): 1671–1727 (COO) and 3350 (NH); ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 1.72–1.74 (4H, m, Cy), 1.76–1.77 (2H, m, Cy), 2.02–2.03 (4H, m, Cy), 3.50 (1H, q, $^3J_{HH}$ = 3.5 Hz, Cy), 3.75 and 3.87 (6H, 2s, 2 × OCH$_3$), 6.85 (1H, s, NH), 7.08 (1H, d, $^3J_{HH}$ = 16 Hz, –CH=), 7.22 (1H, q, $^3J_{HH}$ = 16 Hz, –CH=), 7.25 (1H, t, $^3J_{HH}$ = 7.5 Hz, H$_{para}$), 7.32 (2H, t, $^3J_{HH}$ = 7.5 Hz, H$_{meta}$), 7.44 (2H, d, $^3J_{HH}$ = 7.5 Hz, H$_{ortho}$); ^{13}C NMR (125.8 MHz, CDCl$_3$): δ_C 24.3, 25.2, 33.4 and 51.0 (Cy), 51.5 and 51.9 (2 × OCH$_3$), 86.8, 114.4, 145.2 and 161.9 (furan), 114.2 and 127.9 (–C=), 126.5 (C$_{ortho}$), 127.8 (C$_{para}$), 128.6 (C$_{meta}$), 136.7 (C$_{ipso}$), 164.1 and 165.3 (2 × COO); MS: m/z (%): 383 (M$^{+\cdot}$, 3), 279 [M$^{+\cdot}$ – PhCH=CH$^+$ + H), 8], 237 [M$^{+\cdot}$– (2CO$_2$Me + 2H), 2), 167 [M$^{+\cdot}$– (2CO$_2$Me + NHC$_6$H$_{11}$), 82], 149 [M$^{+\cdot}$ – (PhCH=CH$^+$, + NHC$_4$H$_9$ + CO$_2$Me), 100], 103 (PhCH=CH$^+$, 37), 77 (Ph$^+$, 95), 72 (NC$_4$H$_9^+$, 67). Anal. Calcd for C$_{22}$H$_{25}$NO$_5$ (383.43): C, 68.91; H, 6.57; N, 3.65. Found: C, 68.80; H, 6.49; N, 3.60.

Diethyl 2-(cyclohexylamino)-5-[(E)-2-phenyl-1-ethenyl]-3,4-furandicarboxylate (4e).

Yellow powder, m.p. 66–68 °C, yield 72%, IR (KBr) (ν_{max}, cm^{-1}): 1669–1704 (COO) and 3311 (NH); ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 1.30 and 1.37 (6H, 2t, $^3J_{HH}$ = 7 Hz and $^3J_{HH}$ = 7.5 Hz, 2 × CH$_3$), 1.61–1.63 (4H, m, Cy), 1.76–1.78 (2H, m, Cy), 2.02–2.03 (4H, m, Cy), 3.73 (1H, q, $^3J_{HH}$ = 3.5 Hz, Cy), 4.22 and 4.33 (4H, 2q, $^3J_{HH}$ = 7 Hz and $^3J_{HH}$ = 7.5 Hz, 2 × OCH$_2$), 6.87 (1H, s, NH), 6.85 (1H, d, $^3J_{HH}$ = 16 Hz, –CH=), 7.07 (1H, d, $^3J_{HH}$ = 16 Hz, –CH=), 7.22 (1H, t, $^3J_{HH}$ = 7.5 Hz, H$_{para}$), 7.31 (2H, t, $^3J_{HH}$ = 7.5 Hz, H$_{meta}$), 7.44 (2H, d, $^3J_{HH}$ = 7.5 Hz, H$_{ortho}$); ^{13}C NMR (125.8 MHz, CDCl$_3$): δ_C 14.3 and 14.4 (2 × CH$_3$), 24.5, 25.4, 33.4 and 51.4 (Cy), 59.6 and 60.9 (2 × OCH$_2$) 87.0, 115.0, 144.8 and 161.9 (furan), 114.2 and 127.7 (–C=), 126.4 (C$_{ortho}$), 127.4 (C$_{para}$), 128.7 (C$_{meta}$), 136.8 (C$_{ipso}$), 163.8 and 164.9 (2 × COO); MS: m/z (%): 411 (M$^{+\cdot}$, 21), 366 (M$^{+\cdot}$ – C$_2$H$_5$, 3), 329 [M$^{+\cdot}$– (C$_6$H$_{11}$ + H), 2), 255 [M$^{+\cdot}$ – (2C$_2$H$_5$ + NHC$_6$H$_{11}$), 11], 238 [M$^{+\cdot}$ +1 – (NHC$_6$H$_{11}$ + OEt + Et + H), 24], 210 [M$^{+\cdot}$ – (PhCH=CH$^+$ + NHC$_6$H$_{11}$), 10], 131[M$^{+\cdot}$ –(Ph + C$_6$H$_{11}$ + CO$_2$Et + OEt + 2H), 100], 103 (PhCH=CH$^+$, 57), 83 (C$_6$H$_{11}^+$, 33), 77 (Ph$^+$, 59). Anal. Calcd for C$_{24}$H$_{29}$NO$_5$ (411.49): C, 70.05; H, 7.10; N, 3.40. Found: C, 69.92; H, 6.98; N, 3.25.

Di(tert-butyl)-2-(cyclohexylamino)-5-[(E)-2-phenyl-1-ethenyl]-3,4-furandicarb-oxylate (4f).

Yellow powder, m.p. 93–95 °C, yield 68%, IR (KBr) (ν_{max}, cm^{-1}): 1664–1713 (COO) and 3329 (NH); ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 1.55 and 1.75 (18H, 2s, 2 × CMe$_3$), 1.43–1.46 (4H, m, Cy), 1.52–1.55 (2H, m, Cy), 2.02–2.03 (4H, m, Cy), 3.10 (1H, q, $^3J_{HH}$ = 3.5 Hz, Cy), 6.98 (1H, s, NH), 6.82 (1H, d, $^3J_{HH}$ = 16 Hz, –CH=), 7.20 (1H, d, $^3J_{HH}$ = 16 Hz, –CH=), 7.21 (1H, t, $^3J_{HH}$ = 7.5 Hz, H$_{para}$), 7.32

(2H, t, $^3J_{HH}$ = 7.5 Hz, H_{meta}), 7.45 (2H, d, $^3J_{HH}$ = 7.5 Hz, H_{ortho}); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 24.4 and 24.4 (2 × CMe_3), 27.9, 28.4, 33.5 and 51.4 (Cy), 56.2 and 58.5 (2 × $OCMe_3$), 80.1, 115.1, 143.8 and 161.5 (furan), 114.4 and 127.5 (–C=), 126.2 (C_{ortho}), 126.8 (C_{para}), 128.7 (C_{meta}), 137.1 (C_{ipso}), 164.1 and 164.3 (2 × COO); MS: m/z (%): 467 ($M^{+\cdot}$, 3), 355 ($M^{+\cdot} - 2C_4H_8$, 70), 255 [$M^{+\cdot} - (2C_4H_9 + NHC_6H_{11})$, 9), 238 [$M^{+\cdot} - (C_4H_9 + HOC_4H_9 + NHC_6H_{11})$, 26], 167 [$M^{+\cdot} - (2CO_2C_4H_9 + NHC_6H_{11})$, 73], 149 [$M^{+\cdot} - (Ph + C_6H_{11} + CO_2C_4H_9 + C_4H_9)$, 100], 131[$M^{+\cdot} - (Ph + C_6H_{11} + CO_2C_4H_9 + OC_4H_9 + 2H)$, 100], 103 ($PhCH{=}CH^+$, 38), 83 ($C_6H_{11}^+$, 100), 77 ($Ph^+$, 16.2). Anal. Calcd for $C_{28}H_{37}NO_5$ (467.59): C, 71.92; H, 7.97; N, 2.99. Found: C, 71.80; H, 7.90; N, 2.94.

5. References

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Povzetek

Reaktivni intermediat, ki nastane pri adiciji alkil izocianida na dialkil acetilendikarboksilate (v razmerju 1:1) je bil uspešno cikliziran s *trans*-cimetaldehidom pri čemer so nastali polifunkcionalizirani derivati furana.