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Solvent-free synthesis of functionalized 5-imino-2,5-dihydrofurans from isocyanides, activated acetylenes and alkyl cyanoformates

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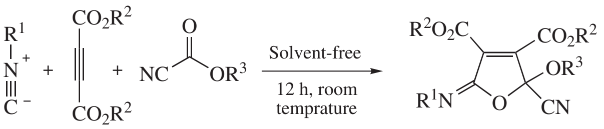
The reaction between alkyl(aryl) isocyanides, dialkyl acetylenedicarboxylates and alkyl cyanoformates under solvent-free conditions leads to dialkyl 2-cyano-5-alkyl(aryl)imino-2-alkoxy-2,5-dihydrofuran-3,4-dicarboxylates in high yields.

Reaction between isocyanides, electron-deficient acetylenes and nucleophiles was first documented by Oakes in 1969 and 1973 by the example of dialkyl acetylenedicarboxylates and 1,1,1,4,4,4-hexafluorobut-2-yne as acetylenic component and methanol as NuH.[1,2] Such an interesting transformation was nearly forgotten until Yavari in 1996 extended its application to dibenzoylmethane as NuH.[3] Later on, more publications on such a reaction were published differing mostly in the nature of NuH used.[4–12] The cyclization into furans was realized during the reaction between isocyanides, electron-deficient acetylenes and activated carbonyl compounds.[4–12]

Here, we report the results of our studies involving the trappng of zwitterions derived from isocyanides **1** and dialkyl acetylenedicarboxylates **2** by alkyl cyanoformates **3**, which constitutes a new synthesis of functionalized 2,5-dihydrofurans **4** in good yields (Scheme 1).[†]

The structures of compounds **4a–l** were deduced from their IR, ^{1}H and ^{13}C NMR spectral data. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m*/*z* values. The ^{1}H NMR spectrum of **4a** exhibited three singlet resonances identified as methoxy (δ 3.70, 3.92 and 3.96 ppm) and a multiplet for N–CH of cyclohexyl ring (δ 3.69 ppm) protons, along with multiplets for the cyclohexyl methylene protons (δ 1.27–1.79 ppm). The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 16 distinct resonances that confirm the proposed structure. Three resonances at δ 149.8, 159.4, and 161.0 ppm observed in the ^{13}C NMR spectrum of **4a**, are attributed to the imino and carbonyl groups. The ^{1}H and ^{13}C NMR spectra of **4b–l** are similar to those for **4a** except for the imino and ester moieties, which showed characteristic resonances in appropriate regions of the spectrum.



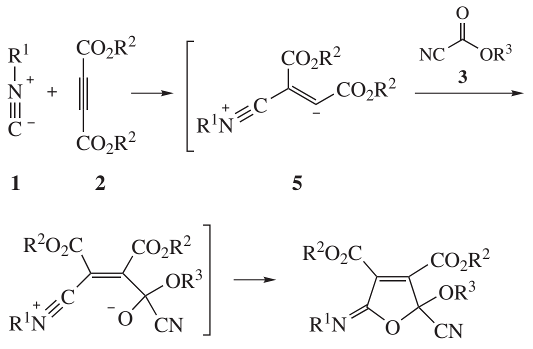
1 **2** **3** **4**

	R^1	R^2	R^3	Yield of **4**
a	Cyclohexyl	Me	Me	91%
b	Cyclohexyl	Et	Me	85%
c	1,1,3,3-Tetramethylbutyl	Me	Me	87%
d	1,1,3,3-Tetramethylbutyl	Et	Me	90%
e	2,6-Dimethylphenyl	Me	Me	85%
f	2,6-Dimethylphenyl	Et	Me	85%
g	Cyclohexyl	Me	Et	95%
h	Cyclohexyl	Et	Et	93%
i	1,1,3,3-Tetramethylbutyl	Me	Et	90%
j	1,1,3,3-Tetramethylbutyl	Et	Et	88%
k	2,6-Dimethylphenyl	Me	Et	88%
l	2,6-Dimethylphenyl	Et	Et	91%

Scheme 1

Mechanistically, it is conceivable that the reaction involves the initial formation of a 1,3-dipolar intermediate **5** between isocyanide and the acetylenic compound, which reacts with cyanoformates to produce **6** (Scheme 2). Cyclization of this zwitterionic intermediate leads to 2-cyano-5-alkyl(aryl)imino-2-alkoxy-2,5-dihydrofurans **4**.

In conclusion, a simple and efficient method for synthesis of 2-cyano-5-alkyl(aryl)imino-2-alkoxy-2,5-dihydrofurans is described. This procedure is advantageous due to one-pot and solvent-free performance.



1 **2** **5** **6** **4**

Scheme 2

[†] *Synthesis of compounds* **4** *(general procedure)*. A mixture of corresponding alkyl cyanoformate **3** (1 mmol) and dialkyl acetylenedicarboxylate **2** (1 mmol) was stirred at room temperature. Then, isocyanide **1** (1 mmol) was added slowly and the mixture was stirred at room temperature. After completion of the reaction [12 h; TLC (hexane–EtOAc, 4:1)], the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (Merck 230–400 mesh, hexane–EtOAc as an eluent) to afford compound **4**.

For **4a**: pale yellow oil, yield 0.31 g (91%). IR (KBr, ν_{max}/cm^{-1}): 2930, 2852, 2245, 1740, 1680, 1269. ^{1}H NMR (CDCl$_3$, 300 MHz), δ: 1.27–1.79 (m, 10H, 5CH$_2$), 3.69 (m, 1H, CHN), 3.70 (s, 3H, MeO), 3.92 (s, 3H, MeO), 3.96 (s, 3H, MeO). ^{13}C NMR (CDCl$_3$, 75 MHz), δ: 24.8 (CH$_2$), 24.9 (CH$_2$), 25.9 (CH$_2$), 33.5 (CH$_2$), 33.6 (CH$_2$), 53.8 (MeO), 53.9 (MeO), 55.9 (MeO), 57.9 (CHN), 99.5 (C), 112.3 (CN), 136.8 (C), 140.3 (C), 149.8, 159.4 and 161.0 (C=N and 2C=O). MS (EI, 70 eV), *m*/*z* (%): 336 (M$^+$, 100), 310 (18), 239 (65), 182 (15), 59 (15), 31 (10). Found (%): C, 57.4; H, 6.1; N, 8.5. Calc. for $C_{16}H_{20}N_2O_6$ (%): C, 57.14; H, 5.99; N, 8.33.

For characteristics of compounds **4b–l**, see Online Supplementary Materials.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2011.07.020.

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