Synthesis of Polyfunctionalized Amino Furans with Long Conjugated Aromatic Systems Using Nucleophilic Aromatic Isocyanide

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Abstract: Polyfunctionalized amino furans with long conjugated aromatic systems have been synthesized by three component reaction of aldehydes, acetylenic esters and aromatic nucleophilic isocyanide.

Keywords: 2,6-Dimethylphenyl isocyanide, Acetylenic esters, Aldehydes, Amino furans.

Introduction

Polysubstituted furans are key structures in a lot of naturally occurring products and pharmaceutical compounds¹. Because of this importance, synthesis of such compounds attracted great attentions. The nucleophilic character of isocyanide with a formally divalent carbon atom has made it as one of the compounds with an extraordinary functional group which is very important species in the synthesis of heterocycles like furans^{2,3}. Recently, we considered the chemiluminescence properties of polyfunctionalized conjugated furans^{4,5}. In this work we have used aromatic isocyanide to synthesize new furans with longer aromatic conjugated systems. The structure shows that three aromatic rings are attached by amine and olefin groups. Therefore, we expect higher chemiluminescence activities in these compounds (Scheme1).

4	R	E	Yield, % of 4
a	$\text{Ph}-\text{C}(\text{H})=\text{C}(\text{H})-$	CO_2Me	86
b	$\text{Ph}-\text{C}(\text{H})=\text{C}(\text{H})-$	CO_2Et	80
c	$\text{Ph}-\text{C}(\text{H})=\text{C}(\text{Me})-$	CO_2Me	77
d	$\text{Ph}-\text{C}(\text{H})=\text{C}(\text{Me})-$	CO_2Et	70
e		CO_2Me	85

Scheme 1. Synthesis of compound **4**.

Experimental

Dialkyl acetylenedicarboxylates, alkylisocyanide and cinnamaldehyde were purchased from fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on a thermo scientific apparatus. ^1H and ^{13}C NMR spectra were measured with a Bruker DRX-400 Avance spectrometer at 400 and 100.6 MHz, respectively. Mass spectra were recorded on a Agilent Technology (HP) 5973 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a FT-IR Bruker (WQF-510) spectrometer.

General procedure for the preparation of compound **4**

To a magnetically stirred solution of cinnamaldehyde (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 room temperature. The mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was purified by silica gel (Merck silica gel, 230-240 mesh) column chromatography using hexane:ethyl acetate (80:20) to afford pure products.

Results and Discussion

On the basis of the extraordinary properties of isocyanide⁶⁻¹⁷, it is reasonable to assume that the reaction starts by Micheal addition of isocyanide to the acetylenic ester to form the zwitterionic intermediate **5**, which attacks the carbonyl group of the aldehyde **3**. Then, nucleophilic addition to the nitrile iminium moiety leads to the formation of the five-membered ring **6** which is aromatized to functionalized furan **4** by [1,5]-H shift (Scheme 2).

Scheme 2. Proposed mechanism for the formation of compound **4**.

Spectroscopic data

Dimethyl 2-(2,6-Dimethyl-phenylamino)-5-[(E)-2-phenyl-1-ethenyl]-3,4-furan dicarboxylate (4a)

Yellow powder, m.p. 117–119 °C, yield 86%, IR (KBr) ($\nu_{\max}$, cm^{-1}): 1662–1712 (C=O) and 3311 (NH); ^1H NMR (400 MHz, CDCl_3): δ_{H} 2.32 (6H, s, 2 CH_3), 3.89 and 3.96 (6H, 2s, 2 OCH_3), 6.67 (1H, d, $\text{CH}=\text{CH}$, $^3J_{\text{HH}}=16.4$ Hz), 7.08 (1H, d, $\text{CH}=\text{CH}$, $^3J_{\text{HH}}=16.4$ Hz), 7.19 (3H, m, Ph), 7.22 (1H, t, $^3J_{\text{HH}}=7.2$ Hz, H_{para}), 7.32 (2H, t, $^3J_{\text{HH}}=7.2$ Hz, H_{meta}), 7.40 (2H, d, $^3J_{\text{HH}}=7.2$ Hz, H_{ortho}), 8.36 (1H, s, NH); ^{13}C NMR (400 MHz, CDCl_3): δ_{C} 18.50 (2 CH_3), 51.4 and 52.1 (2 OCH_3), 87.83, 113.91, 145.93 and 160.62 (furan), 114.01 and 128.01 (C=C alkene), 126.59 (C_{ortho}), 127.23 (C_{para}), 128.51 (C_{meta}), 136.43 (C_{ipso}), 128.64 (C_{ortho}), 128.82 (C_{para}), 134.10 (C_{meta}), 135.26 (C_{ipso}), 164.04 and 165.44 (2 CO); MS: m/z (%): 59 (COOCH_3 , 7), 77 (Ph, 25), 103 ($\text{PhCH}=\text{CH}^+$, 54), 285 ($\text{M}^+ - [(\text{CH}_3)_2\text{PhNH}]$, 32), 341 ($\text{M}^+ - [2 \text{OCH}_3 + \text{H}]$, 45), 374 ($\text{M}^+ - 2 \text{CH}_3$, 78), 404 (M^+ , 100), Anal. Calcd for $\text{C}_{24}\text{H}_{23}\text{NO}_5$ (405.42): C, 71.10; H, 5.71; N, 3.45. Found: C, 71.17; H, 5.74; N, 3.47.

Diethyl 2-(2,6-Dimethyl-phenylamino)-5-[(E)-2-phenyl-1-ethenyl]-3,4-furan dicarboxylate (4b)

Yellow powder, m.p. 128–130 °C, yield 80%, IR (KBr) ($\nu_{\max}$, cm^{-1}): 1660–1710 (C=O) and 3276 (NH); ^1H NMR (400 MHz, CDCl_3): δ_{H} 1.39 (3H, t, $^3J_{\text{HH}}=7.2$ Hz, CH_3), 1.44 (3H, t, $^3J_{\text{HH}}=7.2$ Hz, CH_3), 2.32 (6H, s, 2 CH_3), 4.35 (2H, q, $^3J_{\text{HH}}=7.2$ Hz, OCH_2), 4.42 (2H, q, $^3J_{\text{HH}}=7.2$ Hz, OCH_2), 6.66 (1H, d, $\text{CH}=\text{CH}$, $^3J_{\text{HH}}=16$ Hz), 7.08 (1H, d, $\text{CH}=\text{CH}$, $^3J_{\text{HH}}=16$ Hz), 7.20 (3H, m, Ph), 7.22 (1H, t, $^3J_{\text{HH}}=7.2$ Hz, H_{para}), 7.33 (2H, t, $^3J_{\text{HH}}=7.2$ Hz, H_{meta}), 7.40 (2H, d, $^3J_{\text{HH}}=7.2$ Hz, H_{ortho}), 8.38 (1H, s, NH); ^{13}C NMR (400 MHz, CDCl_3): δ_{C} 14.36 and 14.48 (2 CH_3), 18.58 (2 CH_3Ph), 60.07 and 61.15 (2 OCH_2), 88.09, 113.93, 145.53 and 160.51 (furan), 114.55 and 128.38 (C=C alkene), 126.53 (C_{ortho}), 127.16 (C_{para}), 127.91 (C_{meta}), 136.53 (C_{ipso}), 128.50 (C_{ortho}), 128.65 (C_{para}), 134.19 (C_{meta}), 135.23 (C_{ipso}), 163.77 and 165.10 (2 CO); MS: m/z (%): 103 ($\text{PhCH}=\text{CH}^+$, 59), 265 ($\text{M}^+ - [\text{PhCH}=\text{CHfuran}]$, 91), 313 ($\text{M}^+ - [(\text{CH}_3)_2\text{PhNH}_2 + \text{H}]$, 39), 342 ($\text{M}^+ - 2 \text{CH}_3\text{CH}_2\text{OH}$, 38), 361 ($\text{M}^+ - \text{COOCH}_2\text{CH}_3$, 82), 434 (M^+ , 100), Anal. Calcd for $\text{C}_{26}\text{H}_{27}\text{NO}_5$ (433.47): C, 72.04; H, 6.27; N, 3.23. Found: C, 72.10; H, 6.31; N, 3.25.

Dimethyl 2-[(2,6-dimethylphenyl)amino]-5-[(E)-1-methyl-2-phenylvinyl]-3,4-furan dicarboxylate (4c)

Yellow powder, m.p. 125-127 °C, yield 77%, IR (KBr) ($\nu_{\max}$, cm^{-1}): 1675-1735 (C=O) and 3305 (NH); ^1H NMR (400 MHz, CDCl_3): δ_{H} 2.02(3H, s, CH_3), 2.32 (6H, s, 2 CH_3), 3.86 and 3.93 (6H, 2s, 2 OCH_3), 6.67 (1H, s, $\text{CH}=\text{CH}$), 7.15 (3H, m, Ph), 7.22 (1H, t, $^3J_{\text{HH}}=7.6$ Hz, H_{para}), 7.32 (2H, t, $^3J_{\text{HH}}=7.6$ Hz, H_{meta}), 7.34 (2H, d, $^3J_{\text{HH}}=7.6$ Hz, H_{ortho}), 8.07 (1H, s, NH); ^{13}C NMR (400 MHz, CDCl_3): δ_{C} 14.27 (CH_3), 18.49 (2 CH_3), 51.47 and 52.71 (2 OCH_3), 88.56, 113.80, 142.90 and 159.30 (furan), 124.84 and 128.14 (C=C alkene), 126.16 (C_{ortho}), 126.78 (C_{para}), 127.19 (C_{meta}), 136.91 (C_{ipso}), 128.46 (C_{ortho}), 129.23 (C_{para}), 134.10 (C_{meta}), 135.23 (C_{ipso}), 164.86 and 166.20 (2 CO); MS: m/z (%): 59 (COOCH_3 , 7), 121 ((CH_3)₂ PhNH_2 , 82), 267 ($\text{M}^+ - [2 \text{CH}_3\text{COOH} + \text{HOCH}_3]$, 25), 328 ($\text{M}^+ - [2 \text{CH}_4 + \text{COOCH}_3]$, 34), 388 ($\text{M}^+ - \text{OCH}_3$, 54), 419 (M^+ , 100), Anal. Calcd for $\text{C}_{25}\text{H}_{25}\text{NO}_5$ (419.45): C, 71.58; H, 6.00; N, 3.33. Found: C, 71.64; H, 6.04; N, 3.34.

Diethyl 2-[(2,6-dimethylphenyl)amino]-5-[(E)-1-methyl-2-phenylvinyl]-3,4-furan dicarboxylate (4d)

Yellow powder, m.p. 126-128 °C, yield 70%, IR (KBr) ($\nu_{\max}$, cm^{-1}): 1675-1739 (C=O) and 3315 (NH); ^1H NMR (400 MHz, CDCl_3): δ_{H} 1.36 (3H, t, $^3J_{\text{HH}}=7.2$ Hz, CH_3), 1.41 (3H, t, $^3J_{\text{HH}}=7.2$ Hz, CH_3), 2.04(3H, s, CH_3), 2.32 (6H, s, 2 CH_3), 4.32 (2H, q, $^3J_{\text{HH}}=7.2$ Hz, OCH_2), 4.39 (2H, q, $^3J_{\text{HH}}=7.2$ Hz, OCH_2), 6.67 (1H, s, $\text{CH}=\text{CH}$), 7.15 (3H, m, Ph), 7.23 (1H, t, $^3J_{\text{HH}}=7.6$ Hz, H_{para}), 7.31 (2H, t, $^3J_{\text{HH}}=7.6$ Hz, H_{meta}), 7.34 (2H, d, $^3J_{\text{HH}}=7.6$ Hz, H_{ortho}), 8.10 (1H, s, NH); ^{13}C NMR (400 MHz, CDCl_3): δ_{C} 14.13 and 14.30 (2 CH_3), 14.42 (CH_3), 18.51 (2 CH_3), 59.99 and 61.77 (2 OCH_2), 88.75, 114.20, 142.58 and 159.33 (furan), 124.98 and 128.13 (C=C alkene), 125.83 (C_{ortho}), 126.71 (C_{para}), 127.10 (C_{meta}), 136.99 (C_{ipso}), 128.44 (C_{ortho}), 129.23 (C_{para}), 134.20 (C_{meta}), 135.17 (C_{ipso}), 164.58 and 165.78 (2 CO); MS: m/z (%): 77 (Ph, 14), 105 ($\text{Ph}(\text{CH}_3)_2$, 25), 121 ((CH_3)₂ PhNH_2 , 100), 299 ($\text{M}^+ - 2 \text{CH}_3\text{CH}_2\text{COOH}$, 19), 373 ($\text{M}^+ - \text{CH}_3\text{CH}_2\text{COOH}$, 4), 402 ($\text{M}^+ - 3 \text{CH}_3$, 30), 447 (M^+ , 70), Anal. Calcd for $\text{C}_{27}\text{H}_{29}\text{NO}_5$ (447.50): C, 72.46; H, 6.52; N, 3.13. Found: C, 72.51; H, 6.54; N, 3.14.

Dimethyl 2-(2,6-Dimethyl-phenylamino)-5-furyl-3,4-furan dicarboxylate (4e):

Yellow powder, m.p. 140-142 °C, yield 85%, IR (KBr) ($\nu_{\max}$, cm^{-1}): 1675-1737 (C=O) and 3311 (NH); ^1H NMR (400 MHz, CDCl_3): δ_{H} 2.30 (6H, s, 2 CH_3), 3.87 and 3.95 (6H, 2s, 2 OCH_3), 6.38 (1H, dd, $^3J_{\text{HH}}=3.5$ Hz, $^4J_{\text{HH}}=1.6$ Hz, CH), 6.46 (1H, d, $^3J_{\text{HH}}=3.5$ Hz, CH) 7.15 (3H, m, Ph), 7.37 (1H, d, $^3J_{\text{HH}}=1.6$ Hz, CH) 8.12 (1H, s, NH); ^{13}C NMR (400 MHz, CDCl_3): δ_{C} 18.47 (2 CH_3), 51.48 and 52.54 (2 OCH_3), 87.76 (CN=C), 107.80 and 111.28 (2 CH), 112.32 (OC=C), 127.24 and 128.47 (Ph), 134.02 (C), 135.31 and 135.39 (Ph), 142.69 (CH), 143.76 (C), 159.99(C), 164.49 and 165.06 (2 CO); MS: m/z (%): 168 ($\text{M}^+ - \text{C}_{12}\text{H}_{12}\text{NO}$, 85), 265 ($\text{M}^+ - [\text{COOCH}_3 + 3 \text{CH}_3]$, 91), 339 ($\text{M}^+ - 2 \text{CH}_3$, 92), 369 (M^+ , 100), Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_6$ (369.35): C, 65.03; H, 5.18; N, 3.79. Found: C, 65.09; H, 5.21; N, 3.81.

Conclusion

We studied the synthesis of polyfunctionalized furans with longer conjugated aromatic systems that can show chemiluminescence activities by a three component reaction under the neutral conditions.

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