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A simple approach to the synthesis of dialkyl 5-*tert*-butylamino-[2,2′]bifuranyl-3,4-dicarboxylates

Issa Yavari,* Farough Nasiri, Loghman Moradi and Hoorieh Djahaniani

Department of Chemistry, Tarbiat Modarres University, PO Box 14115-175, Tehran, Iran

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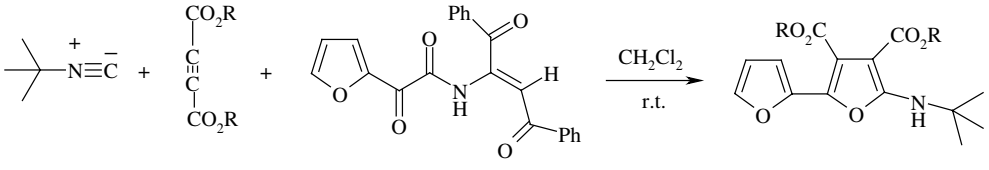
Abstract—Reaction of *tert*-butyl isocyanide with electron-deficient acetylenic esters in the presence of N^1-[(*Z*)-1-benzoyl-3-oxo-3-phenyl-1-propenyl]-2-(2-furyl)-2-oxoacetamide leads to dialkyl 5-*tert*-butylamino-[2,2′]bifuranyl-3,4-dicarboxylates in moderate yields.

The furan moiety is frequently found in natural products, such as the kallolides[1] and combranolides[2] and in important pharmaceuticals as well as in flavouring and fragrance compounds. It is often used as a building block in organic synthesis and has been the driving force for numerous synthetic efforts.[3,4] Furans can be, in principle, synthesized by either cyclization of acyclic precursors or by derivatization of furan rings.[5–7] Introduction of the substituents at the 2- or 5-positions of furan is relatively easy, while similar operations at the 3- or 4-positions is rather difficult. Thus, much attention has been paid to the synthesis of polysubstituted furans from acyclic precursors.[8–12] The usual methods for the preparation of bifurans lead to symmetrical bifurans.[13–15] We now wish to report that dialkyl acetylenedicarboxylates **1** react with N^1-[(*Z*)-1-benzoyl-3-oxo-3-phenyl-1-propenyl]-2-(2-furyl)-2-oxoacetamide[16] **2** in the presence of *tert*-butyl isocyanide, to produce highly functionalized dialkyl 5-*tert*-butylamino-[2,2′]bifuranyl-3,4-dicarboxylates **3** in moderate yields (Scheme 1).



1 **2** **3**

1,3	R	Yield of **3** (%)
a	Me	55
b	Et	50
c	^{i}Pr	56
d	^{t}Bu	58

Scheme 1.

Keywords: Three-component reaction; Bifurans; *tert*-Butyl isocyanide; Acetylenic esters.
* Corresponding author. Tel.: +92 21 8006631; fax: +98 21 8006544; e-mail: isayavar@yahoo.com

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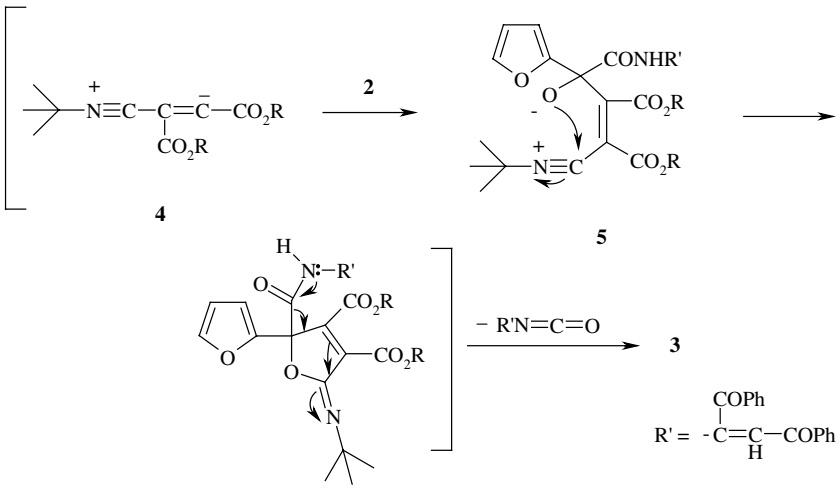

Scheme 2.

The structures of **3a**–**d** were deduced from their elemental analyses and their IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data.[16] The ^{1}H NMR spectrum of **3a** exhibited four singlets identified as *tert*-butyl (δ = 1.46 ppm), methoxy (δ = 3.76 and 3.90 ppm), and NH (δ = 6.84 ppm) protons along with multiplets for the furan ring system. The ^{13}C NMR spectrum of **3a** showed fourteen distinct resonances in agreement with the proposed structure. The mass spectra of compounds **3a**–**d** displayed molecular ion peaks at appropriate *m*/*z* values.

A plausible mechanism for the formation of the product is proposed in Scheme 2. The reaction starts with addition of the isocyanide to the electron-deficient acetylenic ester to form the zwitterionic intermediate **4**, which attacks the active carbonyl group of **2**. Then, formation of the second five-membered ring takes place via nucleophilic addition to the nitrile iminium moiety. Aromatization of the second furan ring is achieved by loss of isocyanate.

This reaction of acetylenic esters with N^1-[(*Z*)-1-benzoyl-3-oxo-3-phenyl-1-propenyl]-2-(2-furyl)-2-oxoacetamide in the presence of *tert*-butyl isocyanide provides a simple one-pot entry into the synthesis of highly functionalized dialkyl 5-*tert*-butylamino-[2,2′]bifuranyl-3,4-dicarboxylates of potential interest.

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16. *Representative experimental procedure*: Preparation of N^1-[(*Z*)-1-benzoyl-3-oxo-3-phenyl-1-propenyl]-2-(2-furyl)-2-oxoacetamide **2**. To a stirred solution of 2-(2-furyl)-2-oxoacetamide (0.28 g, 2 mmol) and dibenzoylacetylene (0.47 g, 2 mmol) in CH_2Cl_2 (10 mL) was added dropwise a mixture of triphenylphosphine (0.52 g, 2 mmol) in CH_2Cl_2 (4 mL) at 0 °C over 10 min. The reaction mixture was then allowed to warm to room temperature and stirred for 24 h. The solvent was removed under reduced pressure and the residue was triturated with ethyl acetate. The product was obtained as a white powder, yield 0.56 g (75%), mp 216–218 °C. IR (KBr): υ = 3312 (NH), 1692 and 1665 (C=O) cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 6.52–7.99 (m, 14H, vinyl H, furan–CH, and Ar–H), 13.32 (s, 1H, NH), ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 104.8 (CH, furan), 113.3 (N–C=*C*), 127.2 (CH), 128.3, 128.9, 128.9, and 129.2 (8CH), 133.6 and 134.1 (2CH), 135.0, 137.6, and 148.5 (3C), 148.9 (N−*C*=C), 150.1 (CH, furan), 158.4, 170.9, 190.2, and 191.6 (4C=O). The procedure for the preparation of dimethyl 5-*tert*-butylamino-[2,2′]bifuranyl-3,4-dicarboxylate **3a** is described as an example. To a stirred solution of N^1-[(*Z*)-1-benzoyl-3-oxo-3-phenyl-1-propenyl]-2-(2-furyl)-2-oxoacetamide (0.75 g, 2 mmol) and dimethyl acetylenedicarboxylate (0.28 g, 2 mmol) in CH_2Cl_2 (10 mL) was added dropwise a mixture of *tert*-butyl isocyanide (0.45 g, 2 mmol) in CH_2Cl_2 (4 mL) at 0 °C over 10 min. The reaction mixture was then allowed to warm to room temperature and stirred for 48 h. The solvent was removed

under reduced pressure and the residue was purified by silica gel column chromatography (Merck 230–400 mesh) using *n*-hexane–EtOAc (5:1) as eluent. The product **3a** was obtained as a light yellow powder, yield 0.35 g, (55%), mp 170–172 °C. IR (KBr): υ = 3315 (NH), 1729 and 1665 (C=O) cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.46 (s, 9H, CMe_3), 3.76 (s, 3H, OMe), 3.90 (s, 3H, OMe), 6.42 (m, 1H, CH), 6.57 (d, 1H, $^3J_{HH}$ = 3 Hz, CH), 6.84 (br s, 1H, NH), 7.41 (s, 1H, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 29.8 (C*Me*$_3$), 51.1 (*C*Me$_3$), 52.4 (OMe), 52.9 (OMe), 87.6 (N–C=*C*), 107.2 and 111.4 (2CH), 112.2 and 135.0 (2C), 142.5 (CH), 144.2 (C), 161.6 (N–*C*=C), 164.7 and 165.1 (2C=O). MS (EI, 70 eV): *m*/*z* (%) = 322 (M^+ + 1, 30), (321 (M^+, 80), 290 (15), 265 (100), 233 (90), 201 (55), 175 (25), 95 (40), 57 (35), 41 (35). Anal. Calcd for $C_{16}H_{19}NO_6$ (321.3): C, 59.81; H, 5.96; N, 4.36. Found: C, 59.8; H, 6.0; N, 4.4%. Compound **3b**: light yellow powder, yield 0.35 g, (50%), mp 143–145 °C. IR (KBr): υ = 3316 (NH), 1725 and 1664 (C=O) cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.32 (t, $^3J_{HH}$ = 7 Hz, 3H, CH_3), 1.38 (t, $^3J_{HH}$ = 7 Hz, 3H, CH_3), 1.48 (s, 9H, CMe_3), 4.25 (q, $^3J_{HH}$ = 7 Hz, 2H, OCH_2), 4.39 (q, $^3J_{HH}$ = 7 Hz, 2H, OCH_2), 6.45 (m, 1H, CH), 6.58 (d, $^3J_{HH}$ = 3 Hz, 1H, CH), 6.87 (br s, 1H, NH), 7.43 (s, 1H, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.1 (Me), 14.3 (Me), 29.8 (C*Me*$_3$), 52.8 (*C*Me$_3$), 59.7 (OCH_2), 61.4 (OCH_2), 87.7 (N–C=*C*), 106.8 and 111.3 (2CH), 112.7 and 134.6 (2C), 142.3 (CH), 144.3 (C), 161.5 (N–*C*=C), 164.3 and 164.7 (2C=O). MS (EI, 70 eV): *m*/*z* (%) = 350 (M^+ + 1, 25), 349 (M^+, 85), 293 (100), 247 (50), 219 (80), 191 (30). Anal. Calcd for $C_{18}H_{23}NO_6$ (349.4): C, 61.88; H, 6.64; N, 4.01. Found: C, 61.9; H, 6.6; N, 4.0%. Compound **3c**: light yellow crystals, yield 0.42 g, (56%), mp 86–88 °C. IR (KBr): υ = 3311 (NH), 1721 and 1659 (C=O) cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.32 (d, $^3J_{HH}$ = 7 Hz, 6 H, CH*Me*$_2$), 1.42 (d, $^3J_{HH}$ = 7 Hz, 6 H, CH*Me*$_2$), 1.48 (s, 9H, CMe_3), 5.01–5.49 (m, 2H, 2C*H*Me$_2$) 6.48 (m, 1H, CH), 6.51 (d, $^3J_{HH}$ = 3 Hz, 1H, CH), 6.90 (s, 1H, NH), 7.49 (s, 1H, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.6 (CH*Me*$_2$), 21.6 (CH*Me*$_2$), 29.7 (C*Me*$_3$), 52.8 (*C*Me$_3$), 67.3(*C*HMe$_2$), 69.2 (*C*HMe$_2$), 88.1 (N–C=*C*), 106.3 and 111.6 (2CH), 113.6 and 134.3 (2C), 142.5 (CH), 145.1 (C), 162.0 (N–*C*=C), 164.8 and 165.1 (2C=O). MS (EI, 70 eV): *m*/*z* (%) = 378 (M^+ + 1, 35), 377 (M^+, 100), 237 (50), 219 (55), 43 (20). Anal. Calcd for $C_{20}H_{27}NO_6$ (377.4): C, 63.65; H, 7.21; N, 3.71. Found: C, 63.6%; H, 7.2%; N, 3.7%. Compound **3d:** light yellow powder, yield 0.47 g, (58%), mp 94–96 °C. IR (KBr): υ = 3310 (NH), 1717 and 1658 (C=O) cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.45 (s, 9H, CMe_3), 1.54 (s, 9H, CMe_3), 1.60 (s, 9H, CMe_3), 6.44 (m, 1H, CH), 6.52 (d, 1H, $^3J_{HH}$ = 3 Hz, CH), 6.86 (s, 1H, NH), 7.41 (s, 1H, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 28.2 (C*Me*$_3$), 28.6 (C*Me*$_3$), 29.8 (C*Me*$_3$), 52.5 (N*C*Me$_3$), 80.3 (O*C*Me$_3$), 81.9 (O*C*Me$_3$), 89.0 (N–C=*C*), 106.4 and 111.2 (2CH), 114.7 and 134.1 (2C), 141.7 (CH), 144.9 (C), 161.3 (N–*C*=C), 162.8 and 164.4 (2C=O). MS (EI, 70 eV): *m*/*z* (%) = 406 (M^+ + 1, 0), 405 (M^+, 35), 237 (60), 219 (20), 57 (100). Anal. Calcd for $C_{22}H_{31}NO_6$ (405.5): C, 65.17; H, 7.71; N, 3.45. Found: C, 65.2%; H, 7.7%; N, 3.4%.