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An efficient diastereoselective one-pot synthesis of dihydrofuro[2′,3′:2,3]indeno[2,1-*b*]furan derivatives

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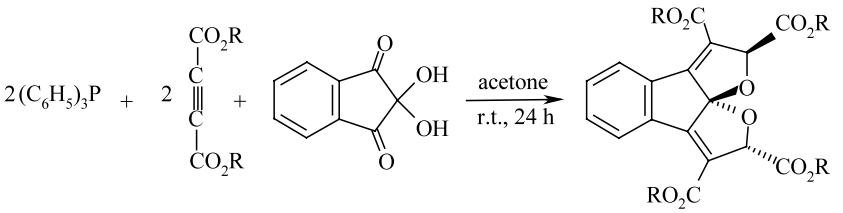
Abstract—Ninhydrin reacts smoothly with dialkyl acetylenedicarboxylates in the presence of triphenylphosphine to produce C_2-symmetric tetra-alkyl 2,5-dihydrofuro[2′,3′:2,3]indeno[2,1-*b*]furan-1,2,5,6-tetracarboxylates in excellent yields. © 2002 Published by Elsevier Science Ltd.

The development of new stereoselective reactions has been a major topic in synthetic organic chemistry, resulting in a wide variety of such reactions.[1–3] Over the years, the Wittig reaction has evolved to include many variations that constitute some of the most powerful processes for the construction of carbon–carbon bonds.[4] The importance of intramolecular Wittig reactions[5] in the synthesis of cycloalkenes and unsaturated heterocyclic compounds can hardly be overestimated.

In this letter, we wish to report that ninhydrin[6] undergoes a smooth reaction with 2 equiv. of dialkyl acetylenedicarboxylates in the presence of 2 equiv. of triphenylphosphine in dry acetone at ambient temperature to produce C_2-symmetric tetra-alkyl 2,5-dihydrofuro[2′,3′:2,3]indeno[2,1-*b*]furan-1,2,5,6-tetracarboxylates **2** in 94–97% yield (Scheme 1).

The reaction of ninhydrin with dialkyl acetylenedicarboxylates **1** in the presence of triphenylphosphine proceeded spontaneously in acetone, and was complete within a few hours. The ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of tetra-alkyl 2,5-dihydrofuro[2′,3′:2,3]indeno[2,1-*b*]furan-1,2,5,6-tetracarboxylates **2**. Any product other than **2** and triphenylphosphine oxide could not be detected by NMR spectroscopy. The structures of compounds **2a–c**



1 **2**

1, 2	R	% Yield of **2**
a	Me	97
b	Et	94
c	^{t}Bu	95

Scheme 1.

Keywords: ninhydrin; triphenylphosphine; acetylenic esters; intramolecular Wittig reaction; dihydrofuro[2′,3′:2,3]indeno[2,1-*b*]furan derivatives.
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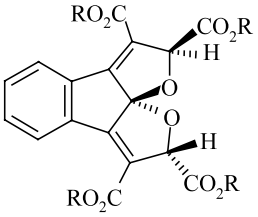
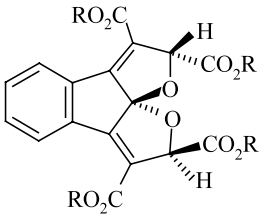
were deduced from their elemental analyses and their IR, ^{1}H and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values. Any initial fragmentation involved the loss of the ester moieties.

The ^{1}H NMR spectrum of **2a** exhibited[7] three single sharp lines readily recognized as arising from methoxy (δ 3.74 and 3.84) and methine (δ 5.90) protons along with two multiplets (δ 7.56 and 8.27) for the aromatic protons. The ^{1}H decoupled ^{13}C NMR spectrum of **2a** showed eleven distinct resonances in agreement with the C_2-symmetric structure.

The ^{1}H and ^{13}C NMR spectra of **2b** and **2c** are similar to those of **2a** except for the ester groups, which exhibited characteristic signals with appropriate chemical shifts. A noteworthy feature of the ^{1}H NMR spectrum of **2b** is the methylene absorptions for this compound, which appear as two ABX_3 systems.



2-*exo, exo*

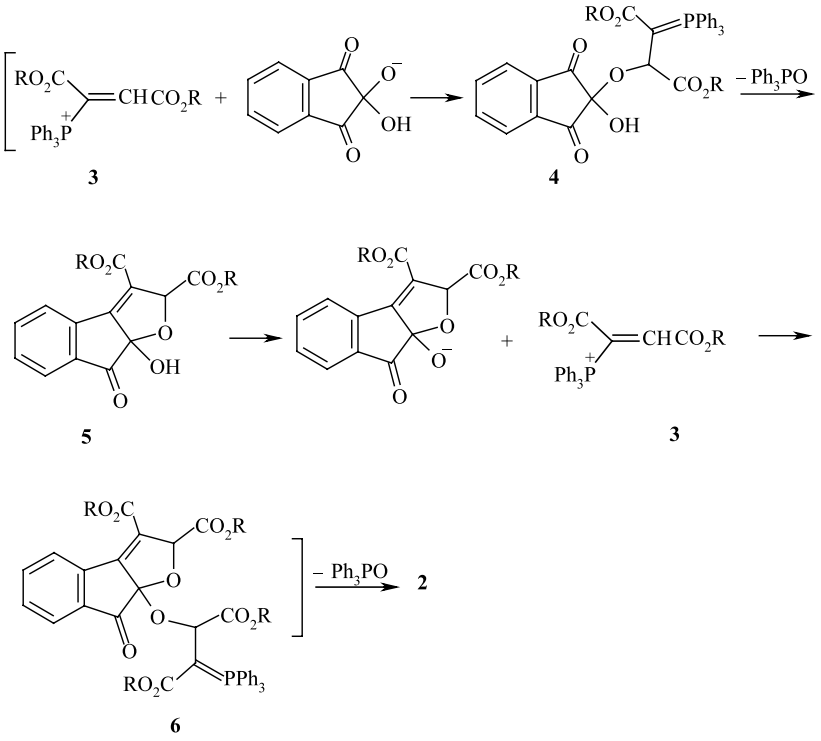


2-*endo, endo*

Two C_2-symmetric geometries, namely *exo*,*exo* and *endo*,*endo* are possible for compound **2**. The *endo*,*endo*-isomer is expected to suffer from steric crowding of the ester groups and thus, we assign the *exo*,*exo*-stereochemistry to the crystalline products **2a–c**.

On the basis of the well established chemistry of trivalent phosphorus nucleophiles,[8–11] it is reasonable to assume that compound **2** results from the initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1:1 adduct by ninhydrin. Then the positively charged ion **3** is attacked by the conjugate base of the OH-acid to form phosphorane **4**, which undergoes an intramolecular Wittig reaction to produce triphenylphosphine oxide and the dihydrofuran derivative **5**. Compound **5** undergoes the same processes under the reaction conditions employed to produce tetraalkyl 2,5-dihydrofuro[2′,3′:2,3]indeno[2,1-*b*]furan-1,2,5,6-tetracarboxylates **2** via intermediate **6** (see Scheme 2).

In summary, the present procedure carries the advantage that, not only is the reaction performed under neutral conditions, but also that the starting materials and reagents can be mixed without any activation or modification. The procedure described here provides an acceptable one-pot method for the preparation of axial symmetrical derivatives of ninhydrin.



Scheme 2.

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7. The procedure for the preparation of tetramethyl 2,5-dihydrofuro[2′,3′:2,3]indeno[2,1-*b*]furan-1,2,5,6-tetracarboxylate **2a** is described as an example. To a magnetically stirred solution of triphenylphosphine (0.524 g, 2 mmol) and ninhydrin (0.176 g, 1 mmol) in dry acetone (10 mL) was added dropwise a mixture of dimethyl acetylenedicarboxylate (0.284 g, 2 mmol) in acetone (2 mL) at −5°C for 10 min. The reaction mixture was allowed to warm to room temperature and stirred for 5 h. The solvent was removed under reduced pressure and the residual solid was purified by column chromatography (silica gel 70–230 mesh; 2:1 hexane/ethyl acetate as eluent). The product **2a** was obtained as colorless crystals, mp 160–162°C, 0.41 g, yield 97%. IR (KBr) (ν_{max}/cm^{-1}): 1725, 1627, 1630 (C=O). Anal. calcd for $C_{21}H_{18}NO_{10}$ (430.4): C, 58.61; H, 4.22. Found: C, 58.7; H, 4.3%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.74 and 3.84 (12H, 2 s, 4OCH_3), 5.90 (2H, s, 2CH), 7.56 (2H, dd, ^3J=5.8 Hz and ^4J=3.3 Hz, 2CH), 8.27 (2H, dd, ^3J=5.7 Hz and ^4J=3.3 Hz, 2CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 52.27 and 52.72 (4OCH_3), 85.62 (2CH), 126.14 (O–C–O), 127.67 (2CH), 130.91 (2C), 132.24 (2CH), 136.28 (2C), 150.15 (2C), 162.27 and 168.18 (4C=O). **2b**: colorless crystals, mp 105–107°C, 0.46 g, yield 94%. IR (KBr) (ν_{max}/cm^{-1}): 1725, 1627, 1630 (C=O). Anal. calcd for $C_{25}H_{26}NO_{10}$ (486.5): C, 61.72; H, 5.39. Found: C, 61.7; H, 5.4%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 and 1.34 (12H, 2 t, J=7.0 Hz, 4CH_3), 4.19 (4H, 2 dq, 2 ABX_3 system, ^2J=10.7 Hz and ^3J=7.0 Hz, 2OCH_2CH$_3$), 4.30 (4H, m, 2 ABX_3 system, 2OCH_2CH$_3$), 5.88 (2H, s, 2CH), 7.74 (2H, dd, ^3J=5.5 Hz and ^4J=3.0 Hz, 2CH), 8.31 (2H, dd, ^3J=5.5 Hz and ^4J=3.0 Hz, 2CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.95 and 14.18 (4CH_3), 61.50 and 61.84 (4OCH_2CH$_3$), 85.84 (2CH), 126.27 (O–C–O), 127.73 (2CH), 131.29 (2C), 132.00 (2CH), 136.41 (2C), 149.97 (2C), 161.95 and 167.85 (4C=O). **2c**: colorless crystals, mp 166–168°C, 0.57 g, yield 95%. IR (KBr) (ν_{max}/cm^{-1}): 1725, 1627, 1630 (C=O). Anal. calcd for $C_{33}H_{42}NO_{10}$ (598.7): C, 66.20; H, 7.07. Found: C, 66.2; H, 7.1%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 and 1.55 [36H, 2 s, 4C(CH_3)$_3$], 5.70 (2H, s, 2CH), 7.48 (2H, dd, ^3J=5.8 Hz and ^4J=3.2 Hz, 2CH), 8.29 (2H, dd, ^3J=5.8 Hz and ^4J=3.3 Hz, 2CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.78 and 28.19 [4C(*C*H$_3$)$_3$], 82.23 and 82.65 [4*C*(CH$_3$)$_3$], 87.11 (2CH), 127.11 (O–C–O), 127.58 and 131.18 (4CH), 132.55, 136.66 and 147.61 (6C), 161.77 and 167.08 (4C=O).
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