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# Highly Functionalized Dihydrofuran Derivatives: Synthesis by Diastereoselective Intramolecular Wittig Reaction

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ABSTRACT: *3a,8a-Dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-d]imidazole-2,8-dione* **3** *reacts with dialkyl acetylenedicarboxylates in the presence of triphenylphosphine to produce some novel interesting dihydrofuran derivatives diastereoselectively.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:277–279, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20202

## *INTRODUCTION*

Multi-substituted dihydrofurans are valuable intermediates in the syntheses of natural products [1–3] and pharmaceuticals [3–7]. Considerable attention has been focused on the development of efficient and regioselective methods for their preparation [8]. Nevertheless, to the best of our knowledge, there are no reports in the literature on the synthesis of dihydrofurans bearing an indene and an imidazole moiety. In the context of our ongoing studies on synthesis of heterocyclic compounds [9], we focused our attention on to identify and develop an efficient procedure that could afford some new interesting dihydrofurans **4**.

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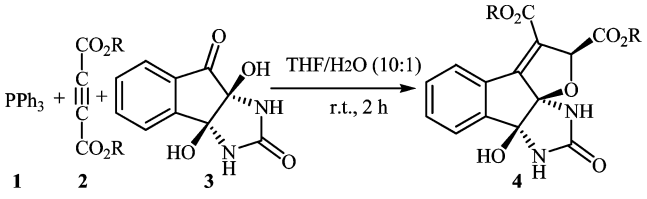
The development of simple synthetic routes for interesting heterocyclic scaffolds by the intramolecular Wittig reactions is one of the major tasks in the organic synthesis [10]. The importance of intramolecular Wittg reaction in the synthesis of cycloalkenes and unsaturated heterocyclic compounds can hardly be overestimated [11].

Herein, we wish to report an efficient diasteroselective synthetic route to some novel interesting dihydrofuran derivatives **4a–c** by a reaction of 3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione **3** and dialkyl acetylenedicarboxylates **2** in the presence of triphenylphosphine **1** in the THF/$H_2O$ (10:1) at ambient temperature in 84–94% yield (Scheme 1).

## *RESULTS AND DISCUSSIONS*

The compound **3** was formed by the reaction of ninhydrin and urea in acetone. The reaction of **3** with dialkyl acetylenedicarboxylates **2** in the presence of triphenylphosphine **1** proceeded spontaneously in THF/$H_2O$ (10:1), and was completed within 2 h. Initially, stirring the same reaction mixture in $CH_2Cl_2$ gave the corresponding products in only 10% yields. We thought a higher temperature might improve product yields. Re-examination of this reaction in refluxing $CH_2Cl_2$, however, did not enhance earlier



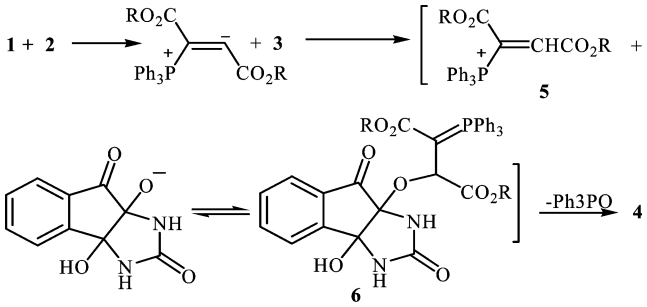

| 2,4 | R | %Yield of 4 |
|---|---|---|
| **a** | Me | 94 |
| **b** | Et | 89 |
| **c** | *t*-Bu | 84 |

SCHEME 1

results. However, solvent was found to have a pronounced effect on the reaction. With THF as a solvent, product yield was increased from less than 10% to 60% to give **4a–c**. Addition of water in THF gave the best result with 90% yield. On the basis of the well-established chemistry of trivalent phosphorus nucleophiles [12–15], it is reasonable to assume that compound **4** results from the initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1:1 adduct by **3**. Then, the positively charged ion **5** is attacked by the conjugate base of the OH-acid to form phosphorane **6**, which undergoes an intramolecular Wittig reaction to produce triphenylphosphine oxide and the dihydrofuran derivative **4** (Scheme 2).

The structures of compounds **4a–c** 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 **4a** exhibited three single sharp lines readily recognized to arise from methoxy ($\delta$ 3.7 and 3.82) and methine ($\delta$ 5.77) protons and three broad single lines related to NH-protons ($\delta$ 7.94 and 8.17) and OH-proton ($\delta$ 6.82) along with multiplets ($\delta$ 7.58–8.09) for the aromatic protons. The signal in the $^{13}$C NMR spectrum at ($\delta$ 108.16) corresponds to quaternary carbon. The $^1$H and $^{13}$C NMR spectra of **4b** and **4c** are similar to those of **4a** except for the alkoxycarbonyl groups, which exhibited characteristic signals with appropriate chemical shifts. The $^1$H NMR spectrum of **4b** exhibited two $ABX_3$ systems for two diastereotopic methylene carbons.

Two diastereomers **4a–c** and **4(a–c)′** are possible for compounds **4**. NOE experiments confirmed the formation of the **4a–c** isomers. This interesting stereochemical outcome was rationalized by considering a steric repulsion between ester group and imidazole-dione ring at the phosphorane **6′** and **4(a–c)′** isomers and thus, we assign the **4a–c** isomers to the crystalline products (Scheme 3).



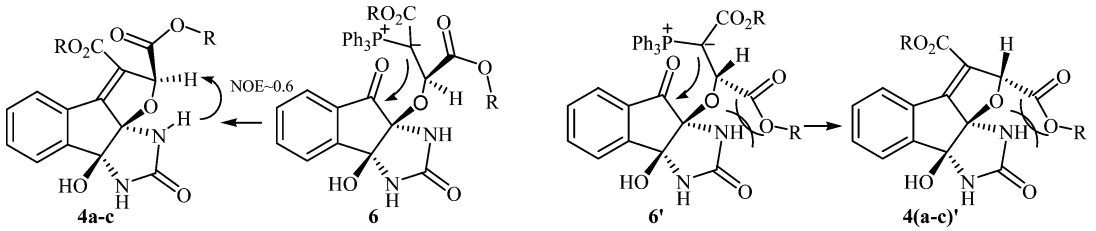
SCHEME 2

## *EXPERIMENTAL*

Melting points were measured on an Electro thermal 9100 apparatus and are uncorrected. IR spectra were measured on a Shimadzu IR-470 Spectrophotometer. $^1$H NMR, and $^{13}$C NMR spectra were determined on Bruker 500 DRX AVNCE instrument at 500 and 125 MHz, respectively. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

### *Preparation of* **3**

To a solution of ninhydrin (0.356 g, 2 mmol) in 10 mL acetone was added 0.12 g (2 mmol) of urea, and the mixture was stirred for 24 h. After completion of the reaction, dichloromethane (5 mL) was added to this mixture and the separated solid was filtered off to give a pure solid (0.41 g, yield 95%).




SCHEME 3

### *Preparation of* **4a**

To a magnetically stirred solution of triphenylphosphine (0.26 g, 1 mmol) and **3** (0.22 g, 1 mmol) in THF/$H_2O$ (10:1) was added dropwise a mixture of dimethyl acetylenedicarboxylate (0.142 g, 1 mmol) in THF (1 mL) at −5°C for 10 min. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was removed under reduced pressure, and the residual solid was recrystallized from ethanol to give **4a** as a pure white solid (0.32 g, yield 94%).

**4a:** White crystals, mp 227–229°C, IR (KBr) ($\nu_{max}$, $cm^{-1}$): 3615 (OH), 3175 (NH), 1736, 1705, 1690 (C=O). $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta_H$: 3.7 and 3.82 (6H, 2s, $2OCH_3$), 5.77 (1H, s, CH), 6.82 (1H, bs, OH), 7.58–8.09 (4H, m, ArH), 7.94 and 8.17 (2H, 2bs, 2NH); $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta_C$: 52.07 and 52.37 ($2OCH_3$), 86.72 (CH), 87.34 (HO—C—N), 108.16 (O—C—N), 119.65, 124.82, 126.54, 129.46, 129.73, 132.56, 151.21, 152.88 (arom and alkene), 157.37, 162.00, and 168.69 (3C=O). MS (*m/z*, %): 347 ($M^+ + 1$, 50), 346 ($M^+$, 20), 303 (50), 272 (80), 243 (100), 156 (60). Anal. Calcd for $C_{16}H_{14}N_2O_7$: C, 55.49; H, 4.07; N, 8.09. Found: C, 55.61; H, 4.05; N, 8.10.

**4a** and **4c** were similarly obtained using diethyl acetylenedicarboxylate (0.17, 1 mmol) and di(*t*-butyl) acetylenedicarboxylate (0.226, 1 mmol), respectively, instead of dimethyl acetylenedicarboxlate.

**4b:** White crystals, mp 210–212°C, 0.33 g, yield 89%. IR (KBr) ($\nu_{max}$, $cm^{-1}$): 3620 (OH), 3185 (NH), 1732, 1700, 1690 (C=O). $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta_H$:1.22 and 1.29 (6H, 2t, $^3J = 7.0$ Hz, $2CH_3$), 416 and 4.29 (4H, 2q, $^2J = 8.5$ Hz, $^3J = 6.5$ Hz, $2CH_2$), 5.74 (1H, s, CH), 6.79 (1H, s, OH), 7.58–8.11 (4H, m, ArH), 7.91 and 8.17 (2H, 2bs, 2NH). $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta_C$: 13.85 and 13.98 ($2CH_3$), 60.89 and 61.09 ($2CH_2$), 86.93(CH), 87.37 (HO—C—NH), 108.12 (O—C—NH), 120.05, 124.83, 126.59, 129.54, 129.65, 132.47, 151.18, 152.76 (arom and alkene), 157.4, 161.52 and 168.2 (3C=O). MS (*m/z*, %): 375 ($M^+ + 1$, 10), 374 ($M^+$, 20), 331 (45), 255 (25), 104 (90), 76 (100). Anal. Calcd for $C_{18}H_{18}N_2O_7$: C, 57.75; H, 4.85; N, 7.48. Found: C, 57.80; H, 4.80; N, 7.35.

**4c:** White crystals, mp 218–220°C, 0.36 g, yield 84%. IR (KBr) ($\nu_{max}$, $cm^{-1}$): 3545 (OH), 3165 (NH), 1732, 1694, 1690 (C=O). $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta_H$: 1.37 and 1.48 (18H, 2s, $6CH_3$), 5.5 (1H, s, CH), 6.71 (1H, bs, OH), 7.72–8.04 (4H, m, ArH), 7.82 and 8.09 (2H, 2bs, 2NH). $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta_C$: 27.92 and 28.16 ($2CH_3$), 81.72 and 82.42 ($2C_{t-Bu}$), 87.82 (CH), 88.91 (HO—C—NH), 108.62 (O—C—NH), 123.90, 125.20, 125.55, 130.53, 132.57, 137.08, 152.45, 157.18 (arom and alkene), 158.04, 160.11 and 167.77 (3C=O). MS (*m/z*, %): 431 ($M^+ + 1$, 25), 430 ($M^+$, 10), 318 (80), 273 (40), 230 (55), 177 (50), 57 (65). Anal. Calcd for $C_{22}H_{26}N_2O_7$: C, 61.39; H, 6.09; N, 6.51. Found: C, 61.45; H, 6.13; N, 6.46.

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