Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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To cite this article: Terry M. Balthazor & Eric L. Williams (1992) Diels-Alder Chemistry of a 2,4-Dioxygenated Furan, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 22:7, 1023-1026, DOI: 10.1080/00397919208019292

To link to this article: http://dx.doi.org/10.1080/00397919208019292

SYNTHETIC COMMUNICATIONS, 22(7), 1023-1026 (1992)

DIELS-ALDER CHEMISTRY OF A 2,4-DIOXYGENATED FURAN

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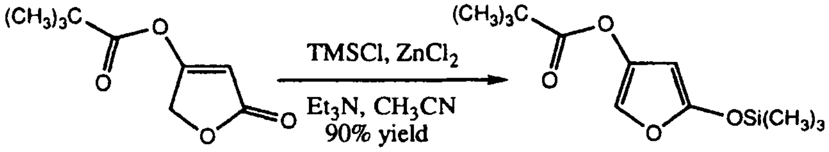
Abstract: The preparation of a 2,4-dioxygenated furan, 1, is reported. Its Diels-Alder reactivity with dienophiles is detailed.

There exist four possible regioisomers of dioxygenated furans. All the regioisomers have been reported, but only the 2,5- and 3,4-isomers have been used to any extent as Diels-Alder dienophiles.[1] The synthesis of 2-trimethylsilyloxy-4-methoxyfuran has been reported along with its reaction with maleic anhydride.[1c] No other reports of its Diels-Alder chemistry are known.

We needed a method for the production of highly oxidized aromatics. A 2,4-dioxygenated furan, with the reinforcing effect of the electron rich substituents at positions 2 and 4, could provide high regioselectivity in a Diels-Alder reaction. Since we required groups other than methoxy on our final products, we chose to look at the Diels-Alder chemistry of **1**. Furan **1** is easily prepared in two steps. Enol ester **2**, available in 88% yield by acylation of tetronic acid, is silylated utilizing Chan's procedure to give a 90% distilled yield of **1** as a colorless liquid.[1b] Furan **1** is sensitive to moisture (**1** → **2**), but brief exposure to air is not detrimental.



2 **1**

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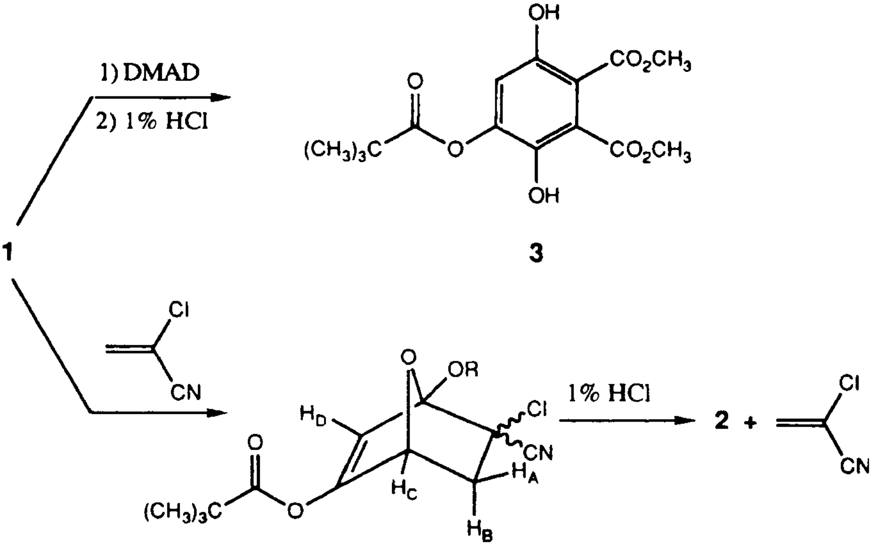
We've found the reaction of **1** with dimethylacetylenedicarboxylate (DMAD) in tetrahydrofuran for six hours at 20°C gives a Diels-Alder adduct. This is treated, in the same pot, with a 1% HCl solution to give a 70% recrystallized yield of hydroquinone **3**. Ethyl phenylpropiolate failed to react after six days.



4a, R = Si $(CH_3)_3$
4b, R = H

Reaction of **1** with olefins has been examined. Stirring one equivalent each of **1** and maleic anhydride in either chloroform or tetrahydrofuran for five days followed by workup with 1% HCl gives only the olefin and **2** as products. Likewise, ethyl acrylate, 2-chloroacrylonitrile and 1,4-naphthoquinone give only starting olefin and **2**. Closer examination of the reaction mixture by ^{1}H NMR spectroscopy, before workup, indicates cycloaddition occurred in all cases. The reaction of 2-chloroacrylonitrile is illustrative. The signals for **1** and the olefin disappear and new signals appear consistent with cycloadduct **4a** (~90% conversion after 19 h): ^{1}H NMR ($CDCl_3$) δ 2.23 (d, 1H, J_{AB} = 13 Hz, H_B), 3.17 (dd, 1H, J_{AB} = 13 Hz, J_{AC} = 5 Hz, H_A), 4.87 (d, 1H, J_{AC} = 5 Hz, H_C), 5.92 (s, 1H, H_D). These chemical shifts and coupling constants are characteristic of bicyclo[2.2.1]heptane ring systems. Although stereochemistry cannot be assigned, the spectral data suggest the regiochemistry as drawn for **4a**.

That the cycloadducts with olefins do not lead to aromatic products[2] could be explained if the retro reaction (**4a** → **1 + olefin**) is rapid, and the acidic workup preferentially hydrolyzes **1** to **2**. Two points argue against such an explanation. First, the reaction with olefins requires several hours to go to completion. Second, the cycloadduct from ethyl acrylate, formed at 20°C, was cooled to -78°C and hydrolyzed. Again only olefin and **2** are formed. An alternative explanation is that the silyl group is removed to give the protonated bicyclic system **4b**. This undergoes a rapid retro reaction promoted by relief of strain and formation of an α-β-unsaturated ester. Pelter *et. al.*[1c] did not experience the anologous retro reaction with the adduct between 2-trimethylsilyloxy-4-methoxyfuran and maleic anhydride. Apparently, the differences in electronics between having a methoxy verses an acyloxy group at the 4-position controls the outcome.

In conclusion, a 2,4-dioxygenated furan has been prepared. Reaction of **1** with olefins and acetylenes follow divergent paths.

Experimental Section

NMR spectra were recorded on a Varian EM-360 spectrometer. Chemical shifts are reported in units of ppm relative to the standard tetramethylsilane. Elemental analyses were performed by Atlantic Microlab, Inc. Melting points were obtained on a Mel-Temp capillary melting point apparatus and are uncorrected. Solvents and reagents were used as purchased.

Propanoic acid; 2,2-dimethyl-2,5-dihydro-5-oxo-3-furanyl ester (2) A mixture of 36.6 g (0.366 mol) of tetronic acid[3], 2.17 g (14.6 mmol) of 4-pyrrolidinopyridine, and 67 mL (0.384 mol) of diisopropylethylamine in 730 mL of methylene chloride was cooled in an ice bath while being stirred under nitrogen. To this mixture was added 47.3 mL (0.384 mol) of pivaloyl chloride over a 40 minute period. The reaction was stirred overnight at room temperature followed by concentration *in vacuo*. The residue was taken up into 400 mL of ether, and was washed with water. The water layer was backwashed with ether, and the combined organic phases were dried over anhydrous magnesium sulfate. Filtration and concentration *in vacuo* gave an oil which was distilled (BP 108°C, 0.3 mmHg) yielding 59.47 g (88 % yield) of **2** as a colorless oil that crystallized on standing. Recrystallization from ether-pet. ether gave 57 g (85 % yield) of colorless crystals (MP 46 - 47°C). ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 9H), 4.93 (d, 2H, J = 1.5 Hz), 6.02 (t, 1H, J = 1.5 Hz); elemental analysis: calcd. for $C_9H_{12}O_4$ - C, 58.69%; H, 6.57%; found - C, 58.65%; H, 6.62%.

Propanoic acid; 2,2-dimethyl-(2-trimethylsiloxyfuran-3-yl) ester (1) A mixture of zinc chloride (890 mg, 6.5 mmol) and triethylamine (38.6 mL, 0.277 mol) were stirred under nitrogen until a fine suspension was formed (45 min.). To this suspension was added chlorotrimethylsilane (31.0 mL, 0.244 mol) followed by a solution of **2** (30.0 g, 0.163 mol) dissolved in 86 mL of anhydrous acetonitrile. The mixture was stirred for 37 hours at room temperature followed by the addition of anhydrous ether and filtration through celite. The filtrate was concentrated *in vacuo*, diluted with hexane, and refiltered followed again by concentration. The resulting oil was distilled (BP 86 -87°C, 0.3 mmHg) to give 37.5 g (90 % yield) of furan **1** as a colorless oil. ^1H NMR ($CDCl_3$): δ 0.27 (s, 9H), 1.26 (s, 9H), 5.13 (d, 1H, J = 1 Hz), 7.07 (d, 1H, J = 1 Hz); ^{13}C NMR (25 MHz) ($CDCl_3$): δ -0.45 ($SiCH_3$), 26.92 ($C(CH_3)_3$), 38.86 ($C(CH_3)_3$), 79.75 (C-3), 120.64 (C-5), 139.30 (C-4), 153.93 (C-2), 174.87 (C=O); elemental analysis: calcd. for $C_{12}H_{20}O_4$ - C, 56.22%; H, 7.86%; found - C, 56.60%; H, 7.62%.

3,6-Dihydroxy-4[(2,2-dimethyl-1-oxopropyl)oxy]-1,2-benzenedicarboxylic acid dimethyl ester (3) A mixture of 5.55 g (21.6 mmol) of diene **1** and 2.66 mL (21.6 mmol) of dimethyl acetylenedicarboxylate were stirred together in 20 mL of tetrahydrofuran under nitrogen for 6 hours. A 1% HCl solution (5 mL) was added and the reaction was stirred for an additional 15 minutes. The reaction was diluted with 100 mL of ethyl acetate and washed with 50 mL of water followed by drying of the organic phase over anhydrous magnesium sulfate. Filtration and concentration *in vacuo* gave 7.04 g of the crude crystalline product. Recrystallized from methylene chloride - hexanes to give 4.9 g (70% yield) of **3** as white flakes (MP 178 - 178.5°C). ^1H NMR ($CDCl_3$): δ 1.32 (s, 9H), 3.88 (s, 6H), 6.47 (s,1H), 7.30 (bs, 2H); elemental analysis: calcd. for $C_{15}H_{18}O_8$ - C, 55.21%; H, 5.56%; found - C, 55.12%; H, 5.56%.

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(Received in USA 22 October, 1991)