
Synthesis of Substituted Diphenyl Ethers using the Diels–Alder Reaction

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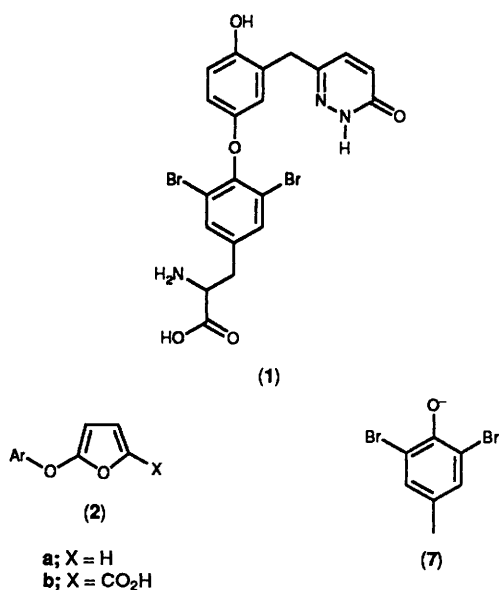
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The phenoxyfurans (**4**) and (**8**) undergo a Diels–Alder reaction with dimethyl acetylenedicarboxylate (DMAD) to give the cycloadducts (**5**) and (**9**) which can be converted into the substituted diphenyl ethers (**6**) and (**10**) respectively.

SK&F L-94901, (**1**), a selective thyromimetic showing hypocholesterolaemic activity,¹ contains a hindered diphenyl ether system, the construction of which presents considerable synthetic problems.² Diphenyl ether systems also occur in a

wide variety of natural products and the need for milder methods for their formation is well recognised.³ Herein we report a new method for the construction of diphenyl ethers related to (**1**) using a Diels–Alder reaction.



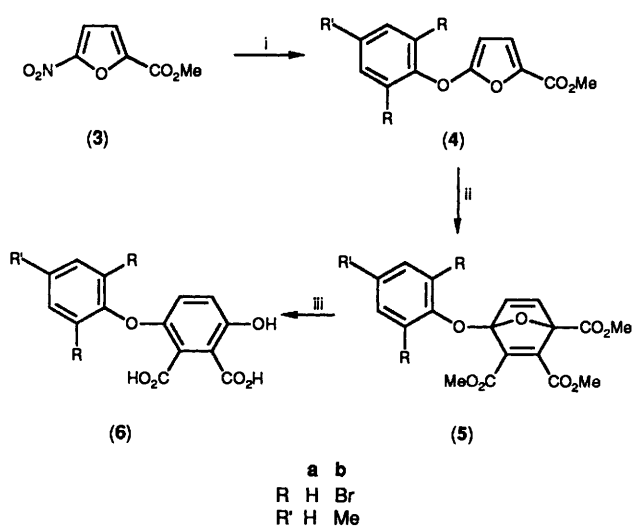
As part of a study aimed at forming the phenolic aromatic ring of (1), we became interested in the use of phenoxyfurans, for example (2), as diene components in Diels–Alder reactions. The preparation of diphenyl ethers using the phenoxyfuran (2a) has been reported,⁴ and one of the problems with the chemistry, the instability of the furan, has been overcome by its formation, *in situ* from the acid (2b).⁵

Our approach, shown in Scheme 1, is based on the idea that, upon hydrolysis, the Diels–Alder adduct (5) would undergo decarboxylation and concomitant aromatisation to give the diphenyl ether (6).⁶

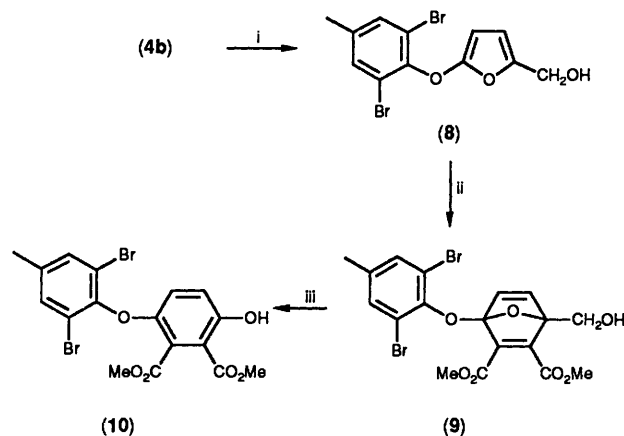
To examine this idea, the phenoxyfuran (4a) was prepared by the known displacement of the nitro group from the furan ester (3) using sodium phenoxide.⁷ We were pleased to find that reaction of (4a) with DMAD gave the cycloadduct (5)* in 75% yield and then basic hydrolysis gave the substituted diphenyl ether (6a) which was identified in its crude form by NMR spectroscopy and high resolution mass spectrometry.

For the dibromo substituted case, we needed to construct the phenyl-furan ether linkage using the weakly nucleophilic dibromophenoxy (7).⁸ However, this was readily achieved by reaction with the furan ester (3) to give the phenoxyfuran (4b) in 52% yield.⁹ Subsequent reaction with DMAD gave the cycloadduct (5b) in 41% yield which, on treatment with aqueous sodium hydroxide, gave the substituted diphenyl ether (6b) in 72% yield.

To obtain increased reactivity of the diene in Diels–Alder reactions the ester (4b) was reduced to the alcohol (8) using DIBAL (see Scheme 2). Treatment of this furan with DMAD gave the cycloadduct (9) in an increased yield of 83%. To complete the synthesis of the diphenyl ether (10), the requirement was now an elimination of formaldehyde and aromatisation. Attempts to effect this under basic conditions were unsuccessful. Of interest, however, was the isolation of a Michael adduct in 82% yield on reaction of (9) with sodium methoxide in methanol. The regiochemistry of the adduct was not established but it was shown to undergo a retro Diels–Alder reaction¹⁰ when heated to 60 °C to afford the furan alcohol (8). The required reaction pathway was effected under acidic conditions. Thus, treatment of (9) with toluene-*p*-sulphonic acid



Scheme 1. Reagents: i, Phenoxide, DMSO, 100 °C; ii, DMAD, toluene, 111 °C; iii, aq. NaOH, MeOH.



Scheme 2. Reagents: i, DIBAL, toluene, 40 °C; ii, DMAD, toluene, 111 °C; iii, toluene-*p*-sulphonic acid, benzene, room temperature.

in benzene at room temperature gave the desired product (10) in 94% yield.

In summary, a method for the construction of substituted diphenyl ethers using Diels–Alder chemistry has been developed. Ways of extending the scope of this method are currently under investigation.

Experimental

3-(2,6-Dibromo-4-methylphenoxy)-6-hydroxyphthalic Acid (6b).—To a suspension of (5b) (100 mg, 0.19 mmol) in water (1 ml) and 12M aqueous NaOH (0.3 ml) was added methanol (1 ml). The mixture was heated under reflux for 14 h, allowed to cool, and acidified with concentrated HCl. The solvents were removed under reduced pressure and the residue was extracted with chloroform. The solution was dried (Na₂SO₄) and evaporated under reduced pressure and the residue was recrystallised from ether–light petroleum to give a white solid (60 mg, 72%), m.p. 203–205 °C; ν_{\max} (Nujol) 3 600–2 400, 1 690br, 1 250, and 1 220; δ [(CD₃)₂SO] 2.33 (3 H, s, CH₃), 6.39 (1 H, d, *J* 9 Hz, 4-H), 6.83 (1 H, d, *J* 9 Hz, 5-H), and 7.62 (2 H, s, 3'- and 5'-H); *m/z* (EI) (rel. intensity) 448/446/444 (*M*⁺, 1/2/1), 430/428/426 (10/21/10), and 349/347 (100/86). [Found: (*M*-H₂O)⁺ 427.8725. C₁₅H₁₈⁷⁹Br⁸¹BrO₅ requires 427.8718].

* All new compounds gave satisfactory spectroscopic and analytical data.

Dimethyl 3-(2,6-Dibromo-4-methylphenoxy)-6-hydroxyphthalate (10).—A mixture of (9) (50 mg, 0.1 mmol) and toluene-*p*-sulphonic acid (19 mg) in benzene (2 ml) was stirred at room temperature for 4 h and then evaporated under reduced pressure. The residue was dissolved in ether, and the solution washed with water, dried (Na₂SO₄), and evaporated under reduced pressure to give a white solid which was recrystallised from ether to give white crystals (44 mg, 94%), m.p. 193–196 °C (Found: 42.95; H, 2.9. C₁₇H₁₄Br₂O₆ requires: C, 43.05; H, 3.00%; ν_{\max} (CHCl₃) 3 200, 1 740, 1 685, 1 450, and 1 330; δ (CDCl₃) 2.34 (3 H, s, CH₃), 3.95 (3 H, s, CO₂CH₃), 3.97 (3 H, s, CO₂CH₃), 6.56 (1 H, d, *J* 9.5 Hz, 4-H), 6.89 (1 H, d, *J* 9.5 Hz, 5-H), 7.40 (2 H, s, 3'- and 5'-H), and 10.63 (1 H, s, OH); *m/z* (EI) (rel. intensity) 476/474/472 (*M*⁺, 42/82/46), 444/442/440 (49/100/51), 363/361 (21/25), and 335/333 (64/100).

Acknowledgements

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