

INTRAMOLECULAR CYCLOADDITIONS WITH ISOBENZOFURANS I

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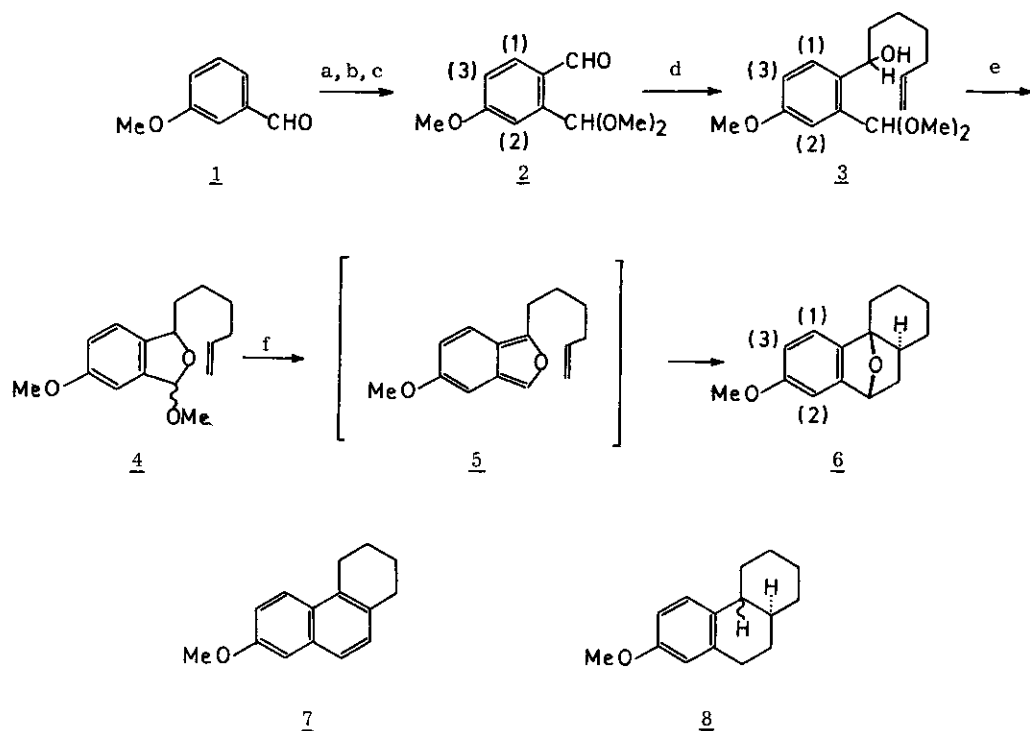
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Abstract - Intramolecular Diels-Alder reactions with isobenzofurans

(5, 12) offer an attractive route for the preparation of polycyclic systems

(6, 13).

Intramolecular Diels-Alder reactions^{1,2} are frequently encountered procedures for the preparation of complicated ring systems. Especially o-quinodimethanes generated in situ either from benzocyclobutenes^{2,3} or from silyl-substituted precursors^{2,4} have been used extensively for this purpose. In their elegant synthesis of resistomycin Rodrigo et al. have shown⁵ that isobenzofurans⁶ may offer an attractive alternative to the o-quinodimethane route. In this paper we want to describe two examples which underline the significance of their approach. - The precursor (4) of the isobenzofuran 5 was prepared as outlined in Scheme 1. 3-Methoxybenzaldehyde (1) was transformed to the acetal 2 (oil, bp 101-104°C/5·10⁻⁴ Torr; IR(film): 1684 cm⁻¹; ¹H-NMR (CDCl₃): δ = 3.40 (s, 2 OCH₃), 3.88 (s, ar-OCH₃), 5.92 (s, 1 H), 6.94 (dd, 1 H, H(3), J₁ = 8.7 Hz, J₂ = 2.7 Hz), 7.21 (d, 1 H, H(2), J = 2.7 Hz), 7.87 (d, 1 H, H(1), J = 8.7 Hz), 10.25 ppm (s, CH₂O)). The reaction of 2 with hexenylmagnesium bromide gave carbinol 3 (oil, IR(film): 3430, 2925 cm⁻¹; ¹H-NMR(CDCl₃): δ = 1.2-2.2 (m, 8 H), 2.55 (bs, OH), 3.32 (s, OCH₃), 3.35 (s, OCH₃), 3.80 (s, ar-OCH₃), 4.8-5.1 (m, 3 H, CH₂=CH-, CH₂OH), 5.50 (s, CH(OCH₃)₂), 5.55-6.05 (m, 1 H, CH₂=CH-), 6.87 (dd, 1 H, H(3), J₁ = 8.7 Hz, J₂ = 2.7 Hz), 7.09 (d, 1 H, H(2), J = 2.7 Hz), 7.41 ppm (d, 1 H, H(1), J = 8.7 Hz)) which on treatment with acetic acid in methanol (reflux) yielded a mixture of epimeric dihydrobenzo[c]furans (4, trans/cis = 1/1 to 1.4/1). The preparation and trapping of isobenzofurans from precursors of type 4 under a variety of conditions has been extensively documented^{8,11}. Treatment of the epimeric mixture 4 with acetic acid



a: Br_2 - CHCl_3 - RT, 94% (55%)⁷; b: MeOH - $\text{HC}(\text{OMe})_3$ - Dowex 50WX2⁸, 99.6%; c: $n\text{-BuLi}$ - DMF, 90%; d: hexenylmagnesium bromide⁹, 96%;
 e: MeOH - AcOH , 97%; f: AcOH - toluene, 84%

Scheme 1

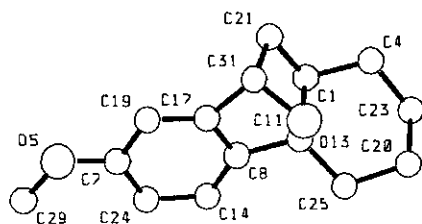
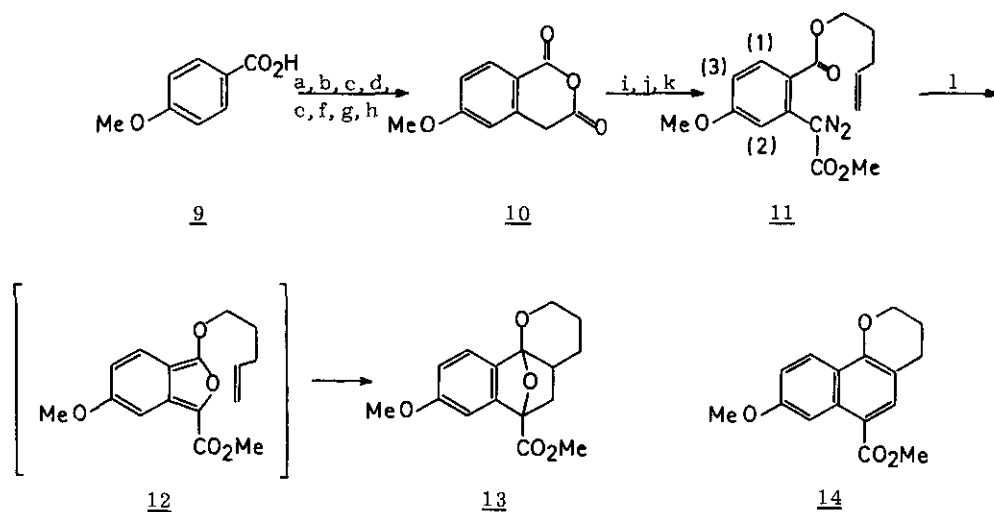


FIG. 1 : Model of compound 6 (determined by x-ray crystallography)

in refluxing toluene yielded 6 as colourless crystals with mp 64°C (IR(KBr): 1591, 1622, 2925 cm^{-1} ; $^1\text{H-NMR}(\text{acetone-}d_6)$: δ = 1.10-2.35 (m, 11 H), 3.74 (s, ar- OCH_3), 5.18 (m, 1 H, $\text{CH}=\text{O}$),

6.64 (dd, 1 H, H(3), $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz), 6.80 (d, 1 H, H(2), $J = 2.4$ Hz), 7.02 ppm (d, 1 H, H(1), $J = 8.4$ Hz)). As it seemed difficult to determine the stereochemistry of **6** unequivocally by NMR-spectroscopy even at 500 MHz¹² we undertook an x-ray analysis. The result¹³ is shown in Figure 1; as in comparable cases the *exo*-stereochemistry is favoured in the Diels-Alder reaction^{4a, 14}. - Expectedly, compound **6** showed to be sensitive against strong acids; on treatment with p-TsOH **7** was obtained (81%, mp 56-57°C). The reductive elimination of the oxygen bridge in **6** was achieved¹⁵ with Pd-C/H₂ in ethanol¹⁶; using this method methoxy-octahydrophenanthrene **8** was obtained in 88% yield (mixture of isomers, cis/trans = 9/1 (tent. assigned)).

A further approach to the generation of a reactive isobenzofuran is based on an intramolecular reaction of a diazo compound with a carbonyl group¹⁷. 6-Methoxyisochromane-1,3-dione (**10**, Scheme 2)¹⁸ was prepared from anisic acid (**9**) in 8 steps in an overall yield of 50%. The solvo-



a: SOCl₂, 97%; b: 2-amino-2-methyl-1-propanol - CH₂Cl₂, 96%; c: SOCl₂, 90%; d: n-BuLi - MeI, 92%; e: MeI - MeCN, 92%; f: 2n NaOH - MeOH, 96%; g: 4 equiv. LDA - OC(OEt)₂, 83%; h: AcCl, 89%; i: MeOH - H₂SO₄, 93%; j: N-hydroxypyridone - DCC - 4-penten-1-ol, 89%; k: TsN₃ - DBU - MeCN, 75%; l: Cu(hexafluoroacetylacetonate)₂ - dichloroethane, 90%

Scheme 2

lytic cleavage¹⁹ of the anhydride 10 with methanol yielded 2-methoxycarbonylmethyl-4-methoxybenzoic acid, mp 154°C (157-158°C)¹⁹, which was transformed to methyl 5-methoxy-2-(4-pentenoxy-carbonyl)-phenylacetate (IR(film): 1645, 1710, 1745 cm⁻¹; ¹H-NMR(CDCl₃): δ = 1.70-1.97 (m, 2 H, -CH₂-CH₂-CH₂-), 2.05 - 2.30 (m, 2 H, -CH₂-CH=CH₂), 3.68 (s, CO₂CH₃), 3.83 (s, OCH₃), 3.99 (s, 2 H, -CH₂-CO₂CH₃), 4.24 (t, 2 H, -CO₂-CH₂-CH₂-, J = 6.3 Hz), 4.90 - 5.17 (m, 2 H, -CH=CH₂), 5.62 - 6.07 (m, 1 H, -CH=CH₂), 6.73 - 6.90 (m, 2 H, ar-H), 8.02 ppm (d, 1 H, J = 9 Hz, ar-H) by employing the elegant but obviously seldom used method proposed by Paquette²⁰. The introduction of a diazo group was quite easily accomplished by the Regitz procedure²¹. In this way the diazoester 11 (mp 42 - 43°C; IR(KBr) : 1645, 1690, 1710, 2120 cm⁻¹; ¹H-NMR(CDCl₃): δ = 1.72 - 1.97 (m, 2 H, -CH₂-CH₂-CH₂-), 2.07 - 2.30 (m, 2 H, -CH₂-CH=CH₂), 3.80 (s, CO₂CH₃), 3.84 (s, OCH₃), 4.27 (t, 2 H, J = 6 Hz, -CO₂-CH₂-), 4.90 - 5.13 (m, 2 H, -CH=CH₂), 5.62 - 6.07 (m, 1 H, -CH=CH₂), 6.88 (dd, 1 H, J₁ = 9 Hz, J₂ = 3 Hz, H(3)), 7.03 (d, 1 H, J = 3 Hz, H(2)), 8.00 ppm (d, 1 H, J = 9 Hz, H(1))) was obtained from 10 in an overall yield of 62%. A number of methods have been described for the preparation of a carbene (carbenoid)²² from a precursor of type 11. Whereas dirhodiumtetraacetate²³ and copper(II)bisacetylacetonate^{19, 22a, 24} proved to be less suitable treatment of 11 with copper(II) bishexafluoroacetylacetonate²⁵ gave 13 in 90% yield. Expectedly, the ketal 13 is unstable under acidic conditions; on treatment with p-TsOH the oxa-phenanthrene derivative 14 is obtained in 77% yield.

The methods depicted in Scheme 1 and in Scheme 2 seem to be well suited for the preparation of a great variety of polycyclic systems. Work is in progress to confirm this expectation.

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