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INTRAMOLECULAR DIELS-ALDER REACTIONS OF BENZYNES
APPLICATION TO THE TOTAL SYNTHESIS OF MANSONONE E

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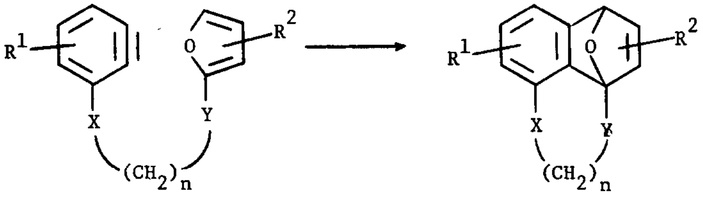
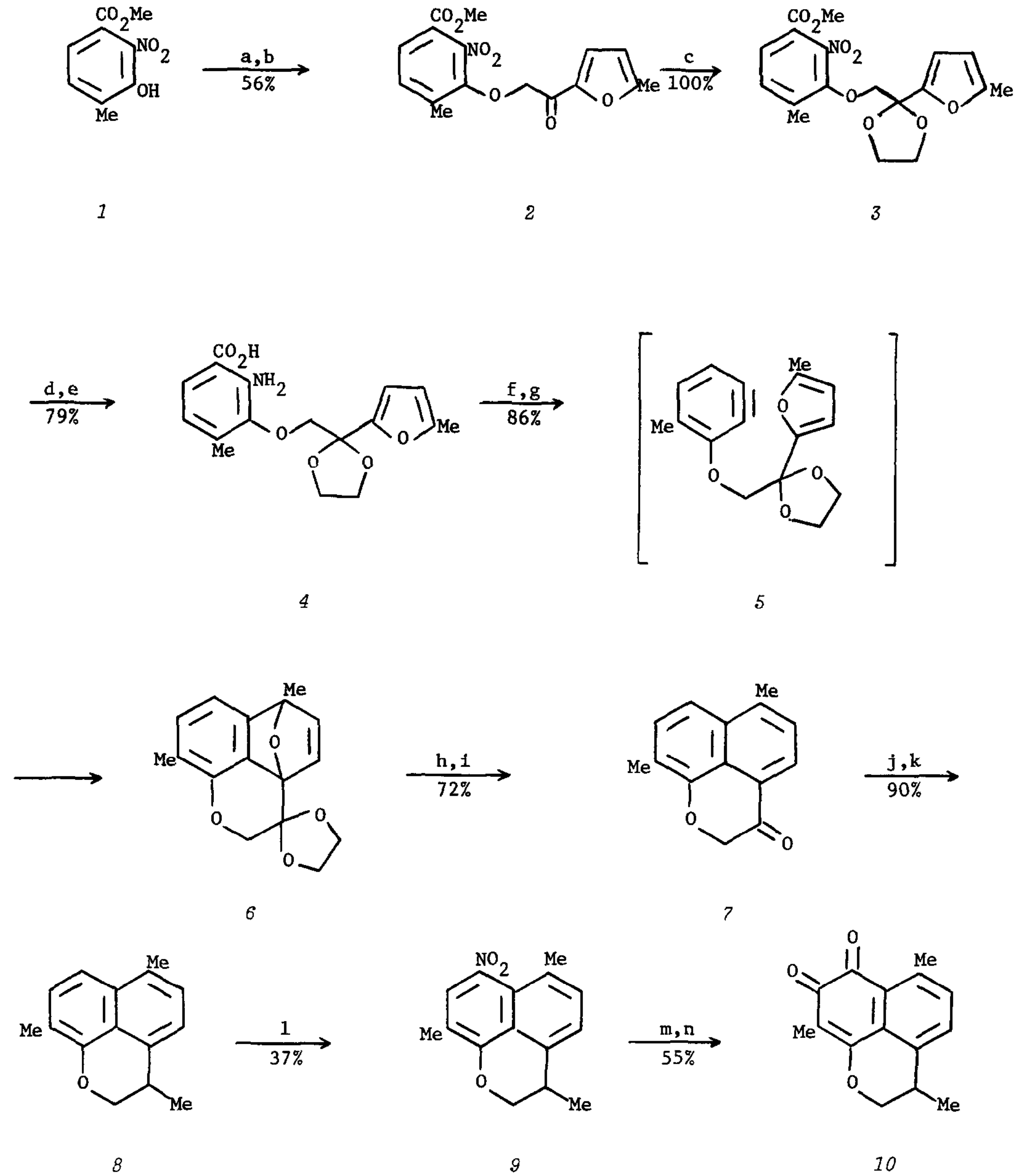
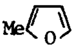
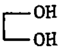
Abstract: Substituted benzynes can be trapped intramolecularly by an attached furan moiety and such a reaction has been used in the synthesis of the naturally occurring o-naphthoquinone mansonone E.

The intramolecular Diels-Alder reaction continues to enjoy considerable popularity, particularly in its application to the synthesis of natural products.[1] However, *intra*molecular Diels-Alder reactions of benzynes have, to our knowledge, not been previously reported. This is surprising in view of the fact that *inter*molecular reactions between unsymmetrical benzynes and unsymmetrical dienes exhibit little or no regioselectivity[2] and complete control of regiochemistry should be possible by linking the benzyne to the diene through a chain of suitable length. This is illustrated below for a system involving a substituted furan as the diene. The nature of the linking groups X and Y would depend on the ultimate synthetic objective, i.e. whether or not disconnection of the chain linking the benzyne and furan moieties is necessary. We now report the use of such an approach in the synthesis of mansonone E *10*, one of a series of naphthoquinones isolated from the wood of *Mansonia altissima*.[3,4]



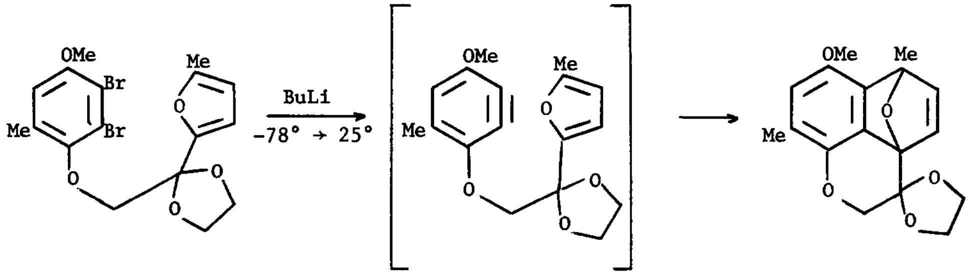
Alkylation of the phenol *1*[5] with 2-chloroacetyl-5-methylfuran[6] gave the ether *2*[7] m.p. 115.5-116°, which was converted into the acetal *3* m.p. 92.5-93.5°, and thence into the substituted anthranilic acid *4*, m.p. 153.5-154° in a standard manner. The anthranilic acid *4*



Reagents: a NaOMe, DMSO; b $COCH_2Cl$, 25°, 24h; c , p-TsOH, C_6H_6, ↑↓, 24h; d NH_2NH_2, Pd/C, EtOH, ↑↓, 10 min; e OH^-, EtOH, ↑↓, 4h; f i-$C_5H_{11}ONO$, HCl, EtOH, 0°, 30 min; g CH_2ClCH_2Cl , ↑↓, 15h; h H_2, Pd/C, MeOH; i H^+, SiO_2, CH_2Cl_2, 25°, 15h; j MeMgI; k H_2, Pd/C, HCl; l $Cu(NO_3)_2.3H_2O$, Ac_2O, 25°, 10 min; m H_2, Pd/C; n Fremy's salt.

was converted into the derived diazonium hydrochloride[8] and this was thermally decomposed in 1,2-dichloroethane in the presence of propylene oxide to give the adduct *6*, m.p. 114.5-115° in 86% yield. The key intramolecular Diels-Alder reaction of the benzyne *5* thus proceeds in a gratifying fashion. Removal of the epoxide bridge gave the naphthalene derivative *7* as bright yellow crystals, m.p. 94-5°, which on treatment with methylmagnesium iodide, followed by hydrogenolysis of the resulting benzylic alcohol, afforded *8* as an oil, b.p. (bath) 90°/.05 mm. Although *8* was readily formylated in the position peri to the methyl group, Baeyer-Villiger oxidation of the resulting aldehyde could not be effected satisfactorily. Accordingly, *8* was converted into the oily nitro derivative *9*, which was reduced to the corresponding amine and then oxidised with Fremy's salt to give (±)-mansonone E *10* as orange crystals, m.p. 146.5-148° (lit.[4] 144-146°for optically active material), identical (^{1}H n.m.r. t.l.c., u.v., i.r.) with the naturally occurring compound.

It is not essential to use anthranilic acid precursors for the benzynes in intramolecular trapping reactions. Thus we find that treatment of the o-dibromo compound *11* m.p. 117° with n-butyllithium yields the adduct *13*, m.p. 173-4° in 90% yield.



11 *12* *13*

Further work on the application of intramolecular Diels-Alder reactions of benzynes is in progress.

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References and Footnotes

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7. Satisfactory elemental analyses have been obtained for this and all other new compounds. ^{1}H n.m.r. data (90 or 80 MHz, CDCl$_3$, δ scale): *2* 2.40 (d, J 0.6 Hz, 3H, furyl Me), 2.44 (s, 3H, aryl Me), 3.88 (s, 3H, CO$_2$Me), 5.00 (s, 2H, CH$_2$), 6.23 (dq, J 3.2, 0.6 Hz, furyl H4), 7.27 (d, J 3.2 Hz, furyl H3), 7.43 and 7.73 (ABq, J_{AB} 8.5 Hz, 2H, aryl); *3* 2.30 (d, J 0.8 Hz, 3H, furyl Me), 2.39 (s, 3H, aryl Me), 3.86 (s, 3H, CO$_2$Me), 4.10 (m, 4H, acetal), 4.23 (s, 2H, CH$_2$), 5.92 (dq, J 3.0, 0.8 Hz, furyl H4), 6.36 (d, J 3.0 Hz, furyl H3), 7.33 and 7.67 (ABq, J_{AB} 8.0 Hz, 2H, aryl); *4* 2.29 (brs, 6H, 2 x Me), 4.07-4.28 (m, 6H, CH$_2$), 5.93 (dq, J 3.2, 0.8 Hz, 1H, furyl H4), 6.39 (d, J 3.2 Hz, furyl H3), 6.39 (d, J 8.0 Hz, aryl), 7.60 (d, J 8.0 Hz, aryl); *6* 1.92 (s, 3H, Me), 2.16 (s, 3H, Me), 3.91 and 4.17 (ABq, J_{AB} 12.0 Hz, 2H, CH$_2$), 4.04-4.24 (m, 4H, acetal), 6.72 (s, 2H, aryl), 6.86 and 7.06 (ABq, J_{AB} 5.2 Hz, 2H, vinyl); *7* 2.41 (s, 3H, Me), 2.70 (s, 3H, Me), 4.88 (s, 2H, CH$_2$), 7.31 (d, J 7.5 Hz, 1H, aryl), 7.36 and 7.54 (ABq, J_{AB} 8 Hz, 2H, aryl), 8.03 (d, J 7.5 Hz, 1H, aryl); *8* 1.34 (d, J 7.4 Hz, 3H, Me), 2.37 (s, 3H, Me), 2.59 (s, 3H, Me), 3.20 (6 line m, 1H, methine), 3.93-4.43 (m, J_{gem} 10.3 Hz, J_{vic} 6.3 and 4.0 Hz, 2H, CH$_2$), 7.06 and 7.14 (ABq, J_{AB} 6.9 Hz, 2H, aryl), 7.28 and 7.44 (ABq, J_{AB} 8 Hz, 2H, aryl); *9* 1.38 (d, J 6.9 Hz, 3H, Me), 2.37 (s, 3H, Me), 2.46 (s, 3H, Me), 3.22 (6 line m, 1H, methine), 4.03-4.49 (m, J_{gem} 10.3 Hz, J_{vic} 5.7 and 4.0 Hz, 2H, CH$_2$), 7.23 and 7.34 (ABq, J_{AB} 7.4 Hz, 2H, aryl), 7.63 (s, 1H, aryl); *10* 1.37 (d, J 7.1 Hz, Me), 1.94 (s, 3H, Me), 2.62 (s, 3H, Me), 3.07 (m, 1H, methine), 4.12-4.51 (m, J_{gem} 10.5 Hz, J_{vic} 5 and 4 Hz, CH$_2$), 7.24 and 7.34 (ABq, J_{AB} 8 Hz, aryl).
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