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HIGH PRESSURE INTRAMOLECULAR DIELS-ALDER REACTIONS OF THE FURAN DIENE

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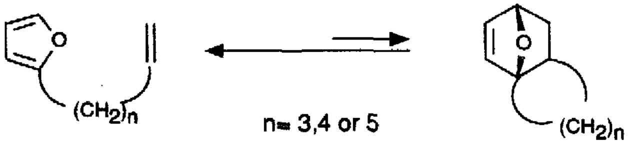
SUMMARY: A variety of substituted furans (1-6) undergo the intramolecular Diels-Alder reaction at high pressure (12.5 kbar) to provide oxatricyclo adducts (7-12) within 24 hours at room temperature.

The intramolecular Diels-Alder (IMDA) reaction is a useful synthetic tool for the formation of two or more rings simultaneously with stereo- and regio-control[1]. Unfortunately, an unfavourable equilibrium towards starting material must be alleviated in systems which incorporate a furan diene connected to a dienophile by 3,4, or 5 *carbon atoms (equation 1). To date, methods employed to alter the equilibrium ratio have involved the use of* heat[2], β-cyclodextrin[3], aqueous solutions[4], substituted side chains[5] and high pressure (14 kbar)[6a] with the most sucessful of these being the use of substituted side chains. Surprisingly, only two examples using high pressure have been reported to accelerate the IMDA reaction, and both have used furan as the diene component[6]. Since high pressure accelerates only the forward reaction in equation 1[7], and we required the oxatricyclo adducts from precursors having unsubstituted side chains, we studied the effect of high pressure on the IMDA of furan precursors 1-6 and herein report our findings.

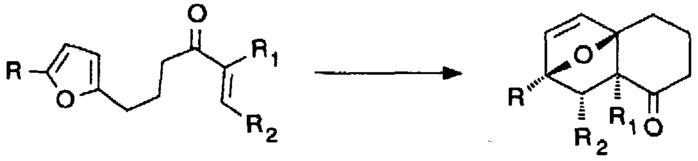


eq. 1

Precursors 1-6 (Scheme 1) were prepared as previously described[4] and subjected to the IMDA reaction under a variety of conditions (Table 1). Stirring compounds 1-6 in either Florisil®/CH_2Cl_2 or 2.0M $CaCl_2$ resulted in moderate to poor adduct:starting material ratios after 4-6 days at room temperature. Compounds 1-6, when subjected to 12.5 kbar pressure (as 0.16M solutions in CH_2Cl_2) for only 24 hours at room temperature provided adducts 7-12 in yields ranging from 43-56%; ^{1}H NMR *indicated that no starting material was present. In* contrast to the findings of Harwood *et al*[6a], adducts 7-12 did not revert to starting material at atmospheric pressure. The moderate yields may be due to a competing polymerization of the enone present in the precursors 1-6[7]. The yield of adduct 7 was increased (to 65%) upon treating compound 1 at a lower pressure of 5.2 kbar. Compound 2 did not react at 5.2 kbar pressure indicating that higher pressure is necessary as the degree of substitution on the diene (and presumably the dienophile) is increased.

Compounds 7-12 all possessed stereochemistry in which the side chain was orientated exo with respect to

SCHEME 1



1	R=R1=R2=H	7
2	R=R2=H, R1=Me	8
3	R=R1=H, R2=Me	9
4	R1=R2=H, R=Me	10
5	R2=H, R=R1=Me	11
6	R1=H, R=R2=Me	12

TABLE 1 IMDA Reactions of Furans 1-6

Conditions	Adduct : Starting Material (% Yield)[a]					
	7:1	8:2	9:3	10:4	11:5	12:6
Florisil/CH_2Cl_2[b]	9:1(71)[c,d]	7:1(65)[c,e]	N.R.[e]	N.R.[e]	N.R.[e]	N.R.[e]
2.0M $CaCl_2$[b,f]	1:1(66)[c]	1:2(68)[c]	4:1(73)[c]	2:1(78)[c]	2:1(69)[c]	1:2(61)[c]
12.5 kbar[g]	100:0(51)	100:0(55)	100:0(52)	100:0(56)	100:0(50)	100:0(43)
5.2 kbar[h]	100:0(65)	0:100(--)	----	----	----	----

a) ratio obtained by ^1H NMR; b) reactions at atmospheric pressure; c) yield based on recovered starting material; d) stirred 6 days, r.t.; e) stirred 14 days, r.t.; f) stirred 4 days, r.t.; g) 0.16M solutions in CH_2Cl_2, 1 day, r.t.; h) 0.16M solutions in CH_2Cl_2, 12h, r.t..

the oxygen bridge[8]; the corresponding endo isomers were neither detected (by ^1H NMR) nor isolated[9].

These results clearly indicate that high pressure is the method of choice for IMDA reactions involving furan precursors which contain unsubstituted side chains. The reaction times are reduced from 6 days to 1 day with the equilibrium lying entirely on the product side of equation 1.

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8) All compounds provided analytical and/or spectroscopic data consistent with their structures.
9) Harwood has reported the isolation of both the endo and exo isomers in the system where n=5 (equation 1); see reference 6a above.

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