# **Radical Addition to Substituted Furans: Diels-Alder Like products Versus Fragmentation Reactions**

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**Abstract:** The intramolecular addition of alkenyl radicals to furans has been further investigated. The reaction can lead to Diels-Alder like adducts or products derived from a radical cyclisation / fragmentation / electrocyclisation cascade.

Cascade reactions are now well established in the armoury of the synthetic chemist and in our continued search for the ideal synthesis we have recently developed methods for the construction of polycyclic structures using palladium and radical cascade sequences.<sup>1</sup> We now report further on our findings on the addition of alkenyl radicals to furans, in view of a recent publication by Pattenden *et al.*<sup>2</sup> We discovered that alkenyl radicals (2) add to furans and that the resulting intermediate radicals (3) can fragment to give the cyclopentenes (4).<sup>3</sup> (Scheme 1)



Scheme 1

If the TBSO group in (3) is replaced with PhS, a further reaction sequence is possible which will allow construction of fused ring systems in one synthetic operation. (Scheme 2)



Scheme 2

In order to evaluate this exciting possibility we synthesised the radical precursor (8). (Scheme 3)



Reagents : i. n-BuLi, then 4-pentyn-1-al, THF, -78°C (62%). ii. DHP / pTSA / THF, (82%). iii. n-BuLi, (CH<sub>2</sub>O)n, THF, -78°C, (90%). iv. LiAlH<sub>4</sub> / NaOMe then I<sub>2</sub>, THF, (70%). v. PhSSPh, Bu<sub>3</sub>P, THF, (89%). Scheme 3

Metallation of (5) with n-butyllithium followed by the addition of 4pentynal gave the alcohol (6) in 62% isolated yield. Protection of (6) as its dihydropyranyl ether followed by metallation with n-butyllithium and reaction of the resulting anion with paraformaldehyde gave the substituted propargylic alcohol (7) in 90% yield. Reduction of the alcohol (7) with lithium aluminium hydride in the presence of sodium methoxide gave an intermediate which upon quenching with iodine<sup>4</sup> and further reaction with diphenyl disulfide in the presence of tri-nbutylphosphine gave the key iodofuran (8),<sup>5</sup> (89%).

The iodofuran (8) was treated with tri-n-butyltin hydride in boiling toluene in the presence of a catalytic amount of AIBN, resulting in a one pot conversion of (8) into the aromatic ketone (9). (Scheme 4).



 $Reagents: i. \ Bu_3SnH \ / \ AIBN \ / \ PhMe, \ Reflux, \ 21 \ hr, \ 51\%.$  Scheme 4

With this interesting result in hand, we investigated the use of a heteroatom linker, in order to construct heterocyclic rings by cyclisation/fragmentation sequences. (Scheme 5)



### Scheme 5

In contrast to the reactions observed in the all carbon series, furyl ethers were found to undergo Diels-Alder like reactions under radical conditions. (Scheme 6)



c) R=C<sub>5</sub>H<sub>11</sub>

Reagents : i. NaH, 2,3-dibromopropene. ii. TTMSS, AIBN, PhMe, 85°C.

## Scheme 6

The alkenyl bromides (11) were prepared using Williamson's ether synthesis<sup>6</sup> and each ether (12) in turn was treated with tris-trimethylsilyl silane in hot toluene containing a catalytic quantity of AIBN. Analysis of the reaction products showed that (13) and (14) were formed but that the dihydrofurans (10) were not present. (Table 1)

Table 1

Substrate	Conditions	Product	Ratio	Yield
12a	TTMSS(1.1eq)	13a : 14a	1:4	16%
12b	TTMSS(1.1eq)	13b : 14b	1:5	19%
12c	TTMSS(1.1eq)	13c : 14c	1:6	26%

When the reaction was conducted in the presence of tri-n-butyltin hydride a multicomponent mixture was formed and only traces of (13) and (14) were observed.





The Diels-Alder pathway appears to be favoured over fragmentation in the ether series due possibly to the increased strain encountered in forming dihydrofuran (10); the intermediate radical (15) is also highly stabilised being both tertiary and  $\beta$  to two oxygen atoms.

#### **Experimental Procedure**

Preparation of 1-tetrahydropyranyloxy-6-heptanoyl-2,3-dihydroindene (9). To a refluxing solution of 2-[(1-tetrahydropyranyloxy-4-iodo-6thiophenyl)-4-hexenyl]-5-n-pentylfuran (8) (0.3 g, 0.52 mmol) and AIBN (26 mg, 0.15 mmol) in toluene (43 ml) was added a solution of tri-n-butyltin hydride (0.35 ml, 1.3 mmol) and AIBN (26 mg, 0.15 mmol) in toluene (19 ml) over a period of 18 hr. with the aid of syringe pump. The reaction was heated at reflux for additional 3 hr, allowed to cool and concentrated under reduced pressure. The resultant liquid was diluted with ethyl acetate (30 ml) and potassium fluoride (1.35 g) followed by water (1.25 ml) was added and the mixture was stirred for 3 hr. Potassium carbonate was then added to the mixture and the solids filtered off. The resultant solution was concentrated *in vacuo* and the residue chromatographed on silica (gradient elution petroleum ether (40-60) then 5:1 petroleum ether (40-60) : diethyl ether, Rf: 0.29) to afford the title compound in (0.083 g, 51%) as a mixture of inseparable diastereoisomers.

ϑmax(cm<sup>-1</sup>): 2937, 2871, 1684, 1132.

δH(CDCl<sub>3</sub>, 300 MHz): 7.78 (d., *J* 7.29 Hz, 1H); 7.20 (m., 2H); 5.12 (m., 1H); 4.83 (t., *J* 6.82 Hz, 1H); 3.94 (m., 2H); 3.42 (m., 2H); 2.88 (t., *J* 7.35 Hz, 2H); 2.32 (m., 2H); 2.12 (m., 2H); 1.80 & 1.35 (m., 6H); 1.28 & 1.11 (m., 4H); 0.78 (m., 3H) ppm.

δC(CDCl<sub>3</sub>, 75.5 MHz): 201.9, 151, 145.2, 137.3, 130, 126.8, 126.4, 100.2, 81.9, 64.3, 40.1, 35.9, 33, 31.8, 26.9, 25.6, 24.2, 23.9, 21.2, 15.4 ppm.

MS: 316, 260, 232, 215, 158, 129, 115, 85.

High resolution Mass Spectrum: calc. 316.2038; found 316.2023

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