

## UNEXPECTED REGIOSELECTIVE DIELS-ALDER CYCLOADDITION REACTIONS BETWEEN 3-FLUOROBENZYNE AND 2-ALKYLFURANS

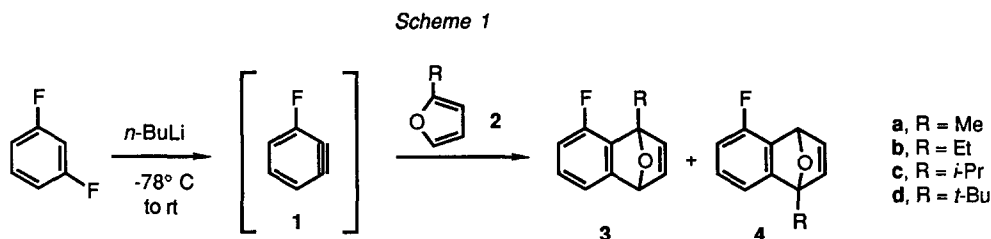
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**Summary:** The Diels-Alder reaction between 3-fluorobenzynes (1) and 2-alkylfurans (2) gives a mixture of *syn* adduct 3 and *anti* adduct 4. The *syn* cycloadduct invariably predominates and the regioselectivity increases in the order: R = Me < Et < *i*-Pr < *t*-Bu, to a maximum of 90% *syn* adduct 3d for 2-*tert*-butylfuran. These results are rationalized in terms of a concerted nonsynchronous transition state that reflects an alkyl steric effect and a polarized aryne 1.

Diels-Alder reactions of arynes and  $\pi$ -excessive heterocycles (e.g., furans, pyrroles, isobenzofurans) have been widely studied<sup>1,2</sup> since Wittig's early work with benzyne and furan.<sup>3</sup> In recent years, several examples of unanticipated regioselectivity in such cycloadditions have been reported.<sup>4</sup> In this Letter, we describe unexpected regioselectivity in Diels-Alder reactions between 3-fluorobenzynes (1) and 2-alkylfurans (2), wherein the regioselectivity, which invariably favors the *syn* cycloadduct 3, increases in the order: R = Me < Et < *i*-Pr < *t*-Bu.



In continuing our hydrogen-fluorine long-range spin-spin coupling studies in aromatic systems,<sup>5</sup> we have examined the reaction between 3-fluorobenzynes (1)<sup>6</sup> and 2-alkylfurans (2) to give the *syn* (3) and *anti* (4) naphthalen-1,4-oxides (Scheme 1). Subsequent deoxygenation provides the corresponding naphthalenes.<sup>3,4d,6b,7</sup> During this previous work,<sup>5,6b</sup> we observed that the reaction of 3-fluorobenzynes (1) and similar arynes with 2-methylfuran (2a), 2-ethylfuran (2b), and some related pyrroles consistently gives mixtures of Diels-Alder adducts in which the *syn/anti* product ratio is >1. We have extended these studies to other 2-alkylfurans and now report our results (Table).

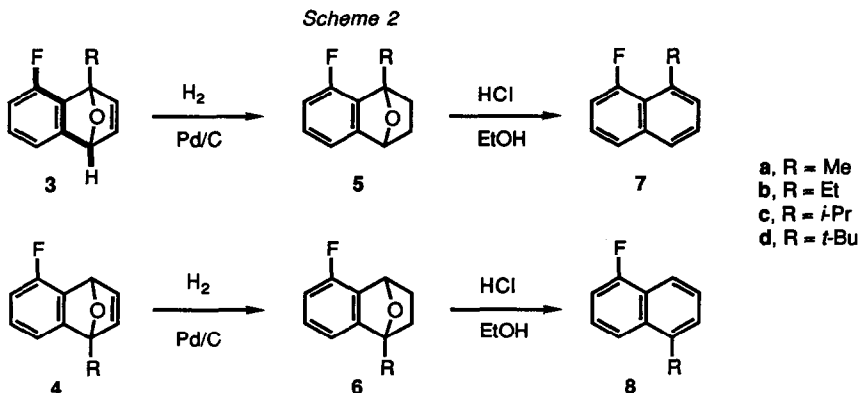
**Table.** Reaction of 3-Fluorobenzynes (1) with Alkylfurans (2 and 9).

Furan	Method <sup>a</sup>	Yield, % <sup>b</sup>	% syn (3)	% anti (4)
2a	A	61	63	37
2a	B	16	64	36
2a	C	47	64	36
2a	D	16	65	35
2b	A	71	78	22
2c	A	39	89	11
2d	A	59	90	10
9	A	55	46 (11)	54 (10)

<sup>a</sup>Method A: ref. 6; Method B: same as Method A but using 1,2-difluorobenzene; Method C: same as Method A but adding 2-lithio-1,3-difluorobenzene to a solution of 2a at 0°C; Method D: generated from 3-fluoroaniline (ref. 13).

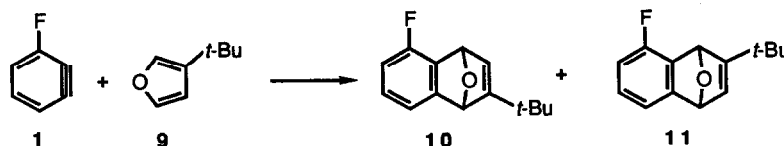
<sup>b</sup>Isolated yield of cycloadducts after flash chromatography over SiO<sub>2</sub>. The other products formed in these reactions will be discussed in a full paper.

As seen in the Table, the *syn/anti* cycloadduct ratio is invariably >1 for the reaction of 3-fluorobenzynes (1)<sup>6</sup> with 2-methyl- (2a)<sup>9</sup>, 2-ethyl- (2b)<sup>9</sup>, 2-isopropyl- (2c)<sup>10</sup>, and 2-*tert*-butylfuran (2d).<sup>11</sup> The ratio increases in the series 2 (R = Me, Et, *i*-Pr, *t*-Bu) from 1.8 for R = Me to 9.0 for R = *t*-Bu. In each case, the isomeric ratio was determined by <sup>1</sup>H NMR and/or capillary GC analysis of the crude reaction mixture, and confirmed by isolation and identification of the individual isomers.<sup>12</sup> Thus, separation of the adduct mixture by flash chromatography gives 3a–d and 4a–d (Scheme 2). The *syn* isomers 3a–d are easily characterized by virtue of long-range "zig-zag" spin-spin coupling between the fluorine and the bridgehead proton (shown for 3).<sup>6b</sup> Moreover, the *anti* isomers 4a–d display the bridgehead proton at lower field (–0.2 ppm) than the corresponding proton in the *syn* isomers. In addition, as shown in Scheme 2, we have converted most of the individual isomers (3 and 4) into their respective naphthalenes 7 and 8,<sup>12</sup> for which only the 1,8-derivatives (7a–d) exhibit the characteristic "through-space" spin-spin coupling between the alkyl group R (<sup>1</sup>H and <sup>13</sup>C) and the fluorine atom.<sup>5</sup> For example, the methyl protons appear as a doublet (<sup>5</sup>J<sub>HF</sub> = 7.5 Hz) in 7a but as a singlet in 8a. Thus, the identity of the cycloadducts 3 and 4 is secure.<sup>12</sup>

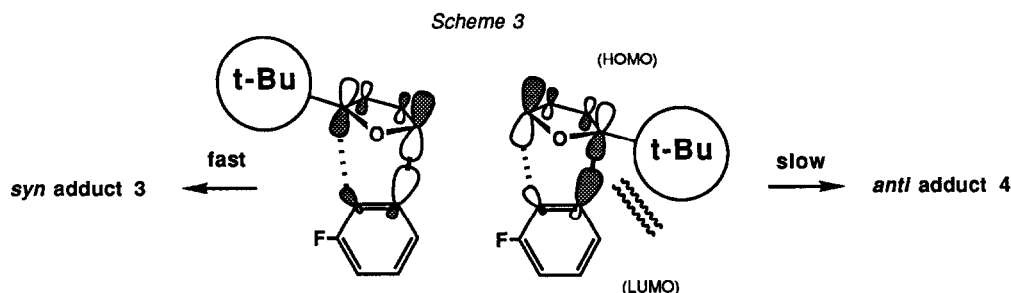


To verify the observed *syn/anti* ratios, we generated the presumed intermediate 3-fluorobenzynes (**1**) using two other methods (Table). Thus, treatment of 1,2-difluorobenzene with *n*-butyllithium in the presence of 2-methylfuran (**2a**) gives a **3a/4a** ratio of 64:36, and diazotization<sup>13</sup> of 3-fluoroaniline in the presence of **2a** affords a **3a/4a** ratio of 65:35. In both cases, the ratio is essentially unchanged from that obtained from 1,3-difluorobenzene and *n*-butyllithium (normal and inverse addition).

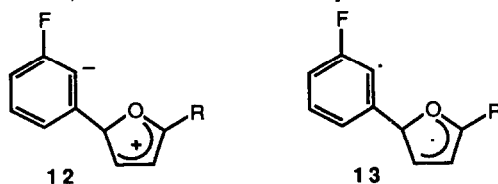
Interestingly, the cycloaddition of 3-*tert*-butylfuran (**9**)<sup>14</sup> with **1** gives a mixture of adducts<sup>12</sup> (39%) in which the *anti* isomer **10** predominates slightly over the *syn* isomer **11** (ratio = 54:46). This indicates that in the presumed absence of an appreciable steric effect, there remains a small electronic effect in the furan component.



We believe that the observed regiochemical preference for the *syn* adduct **3** is a manifestation of a concerted nonsynchronous Diels-Alder transition state<sup>15</sup> that reflects the polarization of 3-fluorobenzynes<sup>16,17</sup> (electrophilic dienophile<sup>18</sup>) coupled with the slight polarization of the 2-alkylfuran (electron-rich diene<sup>19</sup>) (cf., Scheme 3, which shows the proposed transition states between the HOMO of **2** and the LUMO of **1**). Since the electronic properties of alkyl groups are essentially uniform,<sup>20</sup> the observed trend in the *syn/anti* ratio (**3/4**) is consistent with a steric interaction between the alkyl group R and the aryl group, superimposed on the inherent electronic effect of the alkyl group in the furan. In fact, based on  $\sigma^+$  values (Me = -0.31, *t*-Bu = -0.26),<sup>20</sup> and neglecting steric effects, one would have predicted a slightly larger *syn/anti* ratio for 2-methylfuran than for 2-*tert*-butylfuran.



To be sure, it seems reasonable that a two-step (nonconcerted) mechanism involving a fluorine-stabilized zwitterionic (**12**) or biradical (**13**) intermediate would give rise to high and similar *syn/anti* ratios for all 2-alkylfurans (**2**), since steric effects are expected to be much less important in the transition states leading to **12** or **13**.<sup>21</sup> Therefore, as discussed above, we favor a concerted nonsynchronous mechanism to explain our results.



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