Preliminary Note

Intramolecular Diels–Alder reactions of furan derivatives: Steric and electronic effects of trifluoromethyl groups

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Abstract

Intramolecular Diels–Alder reactions of furan derivatives each containing a trifluoromethyl group in the dienophilic part or the tethering chain of the dienophile to the furan ring showed a notable electronic effect of the trifluoromethyl group on the stereoselectivity The electronic effect of the trifluoromethyl group was confirmed by results of a comparison with other substituents (phenyl, methyl and isopropyl)

Lewis acid-catalyzed Diels–Alder and ene reactions of the chiral ester obtained from 2-trifluoromethylpropenoic acid and D-pantolactone were recently shown to proceed efficiently to afford the trifluoromethylated quaternary or tertiary carbon with excellent diastereoselectivity [1, 2]. Through Diels–Alder reactions of a 2-trifluoromethylpropenoic acid ester, the biochemically significant molecules, trifluororetinal [1] and an angularly trifluoromethylated steroid [3], have been prepared. In connection with the intermolecular Diels–Alder reactions of a 2-trifluoromethylpropenoic acid ester reported by us [1], it is considered significant to examine intramolecular Diels–Alder reactions of 2-trifluoromethylpropenoic acid derivatives. It is also pertinent to study substituent effects between the electron-withdrawing trifluoromethyl group at the dienophile and substituents at the tethering chain of the dienophile to the diene. Structural effects on intramolecular Diels–Alder reactions of furan derivatives have been extensively studied [4] and the tethering chain of the dienophile to furan has been shown to be particularly important [5]. In this note, we describe an electronic effect of a trifluoromethyl group which affects the stereoselectivity in intramolecular Diels–Alder

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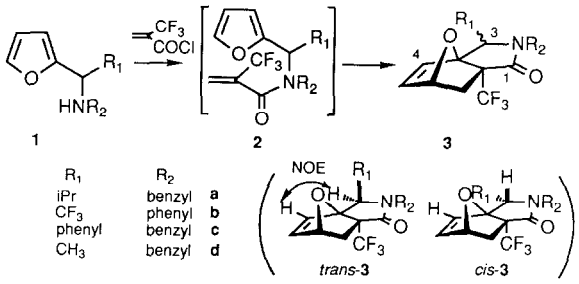


Scheme 1.

reactions of the amides **2**. Intermediates **2** were generated by reactions of 2-trifluoromethylpropenoyl chloride with the furfurylamine derivatives **1**.

Reactions of the furfurylamine derivatives **1** with 2-trifluoromethylpropenoyl chloride at 0 °C gave the intramolecular Diels–Alder adducts **3** directly, in good yields, as a mixture of diastereoisomers (Scheme 1, Table 1). No amide intermediate **2** could be isolated except for **2b** ($R_1 = CF_3$; R_2 = phenyl) obtained in 94% yield. Amide **2b** was readily cyclized to give **3b** by heating at 60 °C. Since the intermolecular Diels–Alder reaction of a 2-trifluoromethylpropenoic acid ester with furan gave no products [6], it is probable that the cyclized products **3** listed in Table 1 were obtained through formation of the amide **2** and subsequent intramolecular Diels–Alder reaction. The stereochemistry of products **3** was confirmed in the following way. (i) The obvious preference for the *endo*-orientation of the trifluoromethyl group rather than *exo*-orientation is clear from inspection of a space-filling molecular model and reported examples [4]. (ii) The closer proximity of the 3-H and 4-H protons in *trans*-**3** than in *cis*-**3** was confirmed by 2-D NOESY spectral studies. That is, *trans*-**3** showed a clear NOE correlation between the 3-H and 4-H protons, but no correlation could be detected in *cis*-**3**. (iii) Finally, assignment of the stereochemistry was confirmed by X-ray analysis of the *trans*-**3a** (R_1 = iPr). Compound **3b** substituted at the tethering chain with a trifluoromethyl group, which has a comparable size to that of an isopropyl group [7], showed a lower selectivity (*trans*/*cis* = 3/1) than the isopropyl compound **3a** (*trans*/*cis* = 7/1). This lowering of selectivity in **3b** is considered to be due to the electronic effect of the trifluoromethyl group on the tethering chain (*vide infra*). To confirm the effect of the trifluoromethyl group, intramolecular Diels–Alder reactions of compound **4**, possessing a methyl group at the dienophile instead of a trifluoromethyl group, were carried out (Scheme 2, Table 2).

It is clear that stronger conditions were required for **4** than for **2** to complete the reaction, and a longer reaction period did not alter the ratio of the products. It is worth noting that intramolecular Diels–Alder reaction of **4** in which the substituent on the tethering chain was a trifluoromethyl or phenyl group (entries 2 and 3 in Table 2), gave *cis*-**5** as

TABLE 1

Intramolecular Diels–Alder reactions of **2**[a]

Entry	Product	Yield (%)[b]	Ratio (*trans*/*cis*)[c, d]
1	**3a**[e]	77	7/1
2	**3b**	quant	3/1[f]
3	**3c**	98	3/1
4	**3d**	94	1 3/1

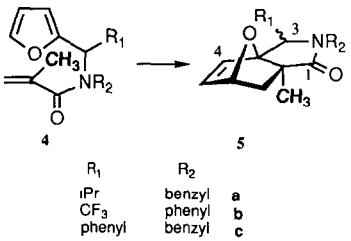
[a]All reactions were carried out by treating **1** with trifluoromethylpropenoyl chloride (1 eq) in the presence of Et_3N (1 eq) at 0 °C in CH_2Cl_2

[b]Isolated yields

[c]Determined by ^{19}F NMR and ^1H NMR

[d]Heating a toluene solution of *cis*- or *trans*-**3a**, **d** in a sealed tube at 140 °C until thermodynamic equilibration was attained (10 to 20 h, by ^{19}F NMR), gave 3/1 to 4/1 ratios (*trans*/*cis*) of **3** In the case of **3b**, heating a toluene solution in a sealed tube at 140 °C led to extensive decomposition of the product.

[e]*trans*-**3a** ^1H NMR ($CDCl_3$) δ 0 98 (3H, d, $J = 7$ Hz), 1.00 (3H, d, $J = 7$ Hz) 1 68 (1H, d, $J = 2$ 2 Hz), 2 23 (1H, m), 2 53 (1H, dd, $J = 4$ 6 and 12 3 Hz), 3.91 (1H, d, $J = 15$ 2 Hz), 3 93 (1H, d, $J = 4$ 9 Hz), 5 09 (1H, dd, $J = 4$ 6 Hz), 5 37 (1H, d, $J = 15.2$ Hz), 6 35 (1H, dd, $J = 1$ 7 and 5 8 Hz), 6 4 (1H, dd, $J = 1$ 7 and 5 8 Hz), 7 2–7 4 (5H, m) ^{19}F NMR ($CDCl_3$) ppm −2.96 (s) (a higher field than the external benzotrifluoride signal was assigned as negative) X-ray crystal data of *trans*-**3a** $C_{19}H_2NO_2F_3O_2$, M = 351 4, monoclinic, $P2_1/C$, $\beta = 111$ 34 (6°), $a = 16$ 084 (10) Å, $b = 9$ 060 (6) Å, $c = 11$ 974 (7) Å, $V = 1723$ Å^3, $D_x =$ 1 354 g cm^{-3}, $Z = 4$, μ for Cu $K_\alpha = 9$ 0 cm^{-1} The structure was solved by direct methods and refined by a block-diagonal least squares method to $R = 0$ 05 for 2662 observed reflections within the 2θ range of 6° to 140°



Scheme 2.

TABLE 2

Intramolecular Diels–Alder reactions of **4** in toluene[a]

Entry	Product	Temp. (°C)	Time (h)	Yield (%)[b]	Ratio (*trans*/*cis*)[c]
1	**5a**	140	3	97	2/1
2	**5b**	150	12	75	1/5
3	**5c**	120	12	29	1/3

[a]Reactions were continued until the disappearance of **4** as shown by TLC

[b]Isolated yield

[c]Determined by ^1H NMR

the preferred isomer. This did not occur in the case of the isopropyl compound **5a** (entry 1). The structure of **5** was determined in the same way as that of **3**. Based on data from intramolecular Diels–Alder reactions of **2** and **4**, the reactivity of **2** and *trans*/*cis*-ratios of the products **3** and **5** appear to be affected mainly by the electronic but not the steric effect of the trifluoromethyl group. The higher reactivity of **2** than that of **4** can be ascribed to the lowering of the electron density of the dienophile by the electron-withdrawing effect of the trifluoromethyl group. Although electronic and steric repulsion between two trifluoromethyl groups in the reaction of **2b** should give the *trans*-isomer in a much higher ratio than the isopropyl compound **2a**, unfavorable interaction due to electronic repulsion between the trifluoromethyl group on the tethering chain and the lone-pair electrons of the furan oxygen in the transition state decreases the *trans*-selectivity (Fig. 1). This electronic effect, which is not exerted by the isopropyl compound **2a**, diminished the *trans*-selectivity of the product but the preferable pathway to *trans*-**3** was never altered. That is, in the intramolecular Diels–Alder reactions of **2**, sterically repulsive interaction between the trifluoromethyl group on the dienophile and the R_1 group on the tethering chain remains predominant in controlling the stereoselectivity. In the reactions of compound **4** (Table 2), the electronic effect of the trifluoromethyl group on the tethering chain becomes predominant for preferable formation of *cis*-**5**. That is, the electronic repulsion between the substituent on the tethering chain (R_1 = Ph, CF_3) and the lone-pair electrons of oxygen or carbonyl π-electrons overrides the steric effect between the methyl group on the dienophile and the substituent on the tethering chain in the transition state (Fig. 1). A similar

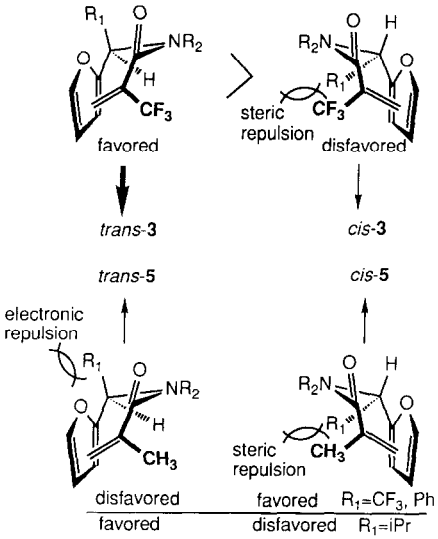


Fig. 1. Favored and disfavored transition states of compounds **2** and **4**.

electronic effect of the trifluoromethyl group has also been observed in the enantioselective reduction of trifluoromethyl alkynyl ketone with the binaphthol-mediated lithium aluminum hydride reagent [8].

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