THE OPTIMIZATION OF THE DIELS-ALDER REACTIONS OF 2,5-DISUBSTITUTED FURAN DERIVATIVES WITH FUNCTIONALIZED CHAINS. SYNTHETIC APPLICATIONS

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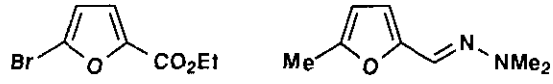
Abstract– The Diels-Alder reaction between complex 2,5-di-substituted furan derivatives and dimethyl acetylenedicarboxylate has been studied. Some synthetic applications of the cycloadducts are considered.

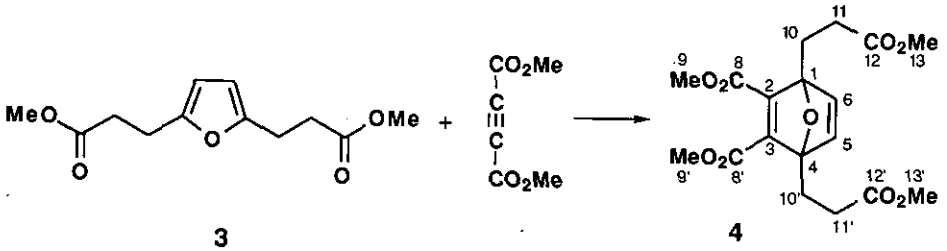
The use of furan in Diels-Alder reactions is a well documented process.[1] However, a few number of 2,5-disubstituted furan derivatives have been used as diene components[2] and, among those, only compounds (**1**) and (**2**) (Scheme 1) are differently substituted derivatives in both positions.[3] In this report we wish to account for our studies on the optimization of the Diels-Alder reaction using



1 2

Scheme 1

functionalized 2,5-disubstituted furan derivatives as diene partner and dimethyl acetylene-dicarboxylate (DMADC) as dienophile.



3 4

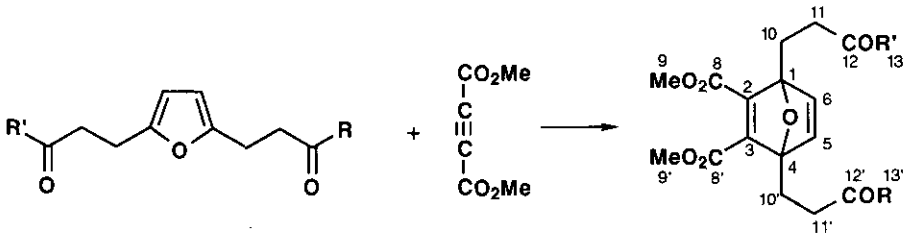
Scheme 2

Compound (**3**) was chosen as a model (Scheme 2). The results of the optimization experiments are summarized in Table 1.

Table 1. Optimization of the cycloaddition of 3 and DMADC.

Catalyst	3:DMADC:Cat.	[3] (M)	Solvent	T	Time	Yield (%)
None	1:1:0	1.0	Et_2O	room temperature	1.3 h	0
None	1:1:0	1.0	THF	Reflux	46 h	60
None	1:1:0	0.5	THF	Reflux	7 d	0
None	1.5:1:0	1.0	THF	Reflux	47 h	22
None	1:1.5:0	1.0	THF	Reflux	53 h	40
None	1:1:0	1.0	Toluene	Reflux	0.7 h	0
$BF_3.OEt_2$	1:1:1	1.0	Et_2O	room temperature	21 h	10
ZnI_2	1:1:1	1.0	Et_2O	room temperature	4 d	60
$AlCl_3$	1:1:1	1.0	THF	Reflux	36 h	55
$AlCl_3$	1:1:1	1.0	Toluene	Reflux	4.5 h	80

Extension of the optimized conditions (last essay) to the derivatives (**5**) and (**6**) allows us for the synthesis of cycloadducts (**7**) and (**8**) with 75 and 70% isolated yields respectively (Scheme 3).

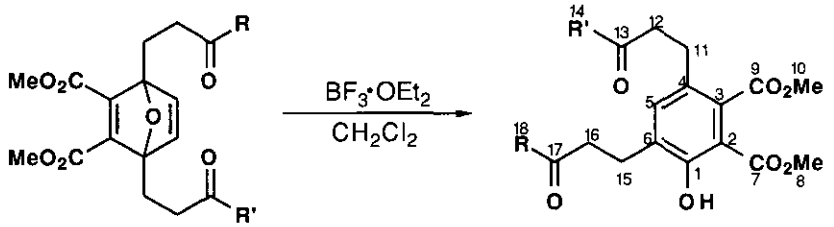


5: R=Me, R'=Me
6: R=OMe, R'=Me

7: R=Me, R'=Me
8: R=OMe, R'=Me

Scheme 3

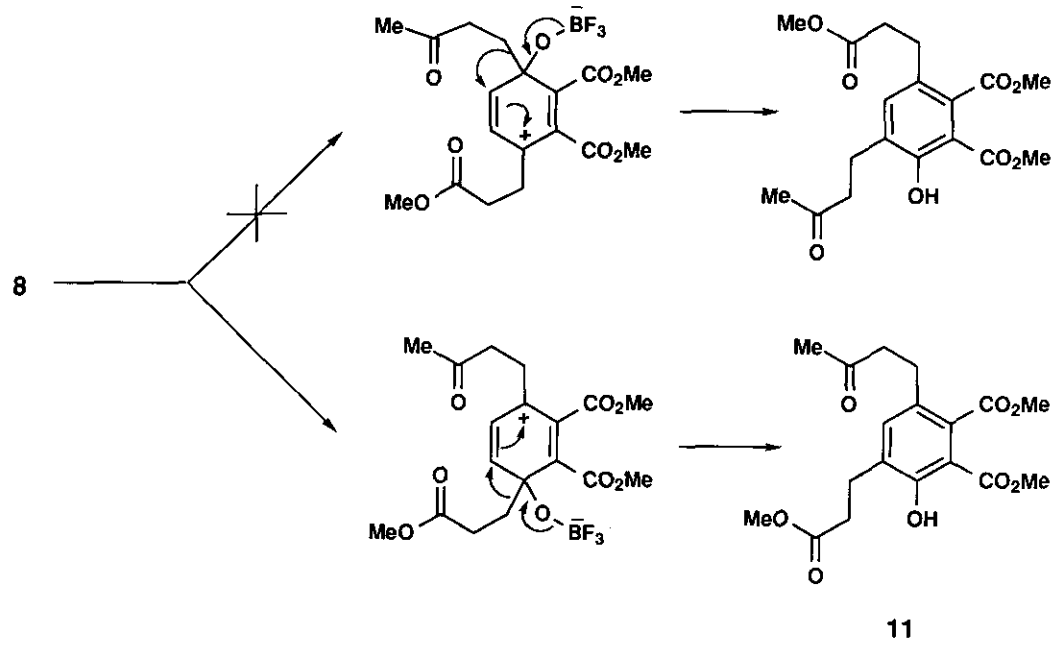
A synthetic application of the cycloadducts (**4**, **7** and **8**) involves their transformation in phenolic derivatives[5] by reaction with $BF_3.OEt_2$ in CH_2Cl_2[6] giving the "rearranged" compounds (**9-11**) in good yields (75-99%) (Scheme 4).



4 R=R'=OMe **9**
7 R=Me, R'=Me **10**
8 R=OMe, R'=Me **11**

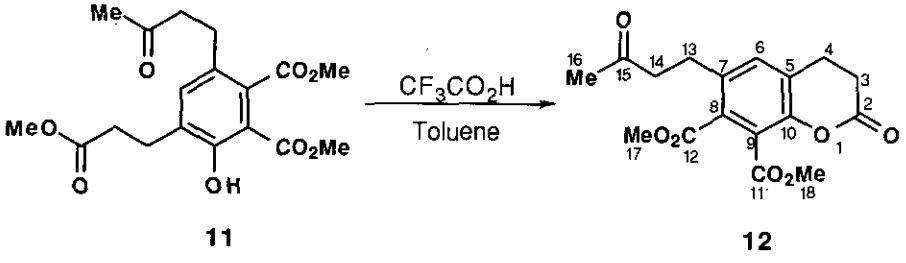
Scheme 4

According with the proposed mechanism for this transformation,[7] in the case of compound (**8**) two carbocations could be generated and hence two final products should be obtained (Scheme 5). However only the phenol (**11**) was detected and isolated (99%) from the reaction mixture. This observation constitutes an intriguing case of differential remote stabilization of a carbocationic center.[8]



Scheme 5

Confirmation of the structure of **11** was achieved by it transformation into dihydrocoumarin (**12**) (80% isolated yield) by heating with CF_3CO_2H in toluene[7] (Scheme 6).



Scheme 6

In conclusion, we have studied the hitherto not optimized Diels-Alder cycloaddition of functionalized 2,5-disubstituted furan derivatives. Some synthetic utility of the obtained cycloadducts have been considered.

EXPERIMENTAL

Ir spectra were recorded on a Perkin-Elmer 257 spectrophotometer, ν values in cm^{-1}. ^{1}H-Nmr and ^{13}C-nmr were obtained on a Varian T-300 spectrometer for $CDCl_3$ solutions and the chemical shifts are reported in δ (ppm from internal TMS). Silica gel Merk 60 (230-400 mesh) and DC-Alufolien $60F_{254}$ were used for conventional and analytical (tlc) chromatography respectively. Toluene and methylene chloride were distilled over CaH_2 before use. Dimethyl acetylenedicarboxylate, $AlCl_3$, BF_3 and trifluoroacetic acid were available through commercial sources.

Diels-Alder reaction of furan derivatives (3, 5 and 6) with dimethyl acetylenedicarboxylate (DMADC).

A solution of furan derivative[9] (1 mmol), DMADC (141 mg, 1 mmol) and $AlCl_3$ (133 mg, 1mmol) in toluene (1 ml) was warmed (reflux) by 4.5 h under argon atmosphere. After the reaction was complete, a saturated aqueous solution (1 ml) of K_2CO_3 was added. The reaction mixture was extracted with AcOEt, and the organic extracts were dried over $MgSO_4$. The drying agent was removed by filtration and the solvent was distilled to yield a pale yellow oil which was purified by column chromatography (hexane-ethyl acetate 2:1) to give the adduct (**4**, **7** or **8**).

Compound (**4**) was obtained as colorless prisms (mp 50-51°C) in 80% yield (268 mg). Ir (KBr): 1740, 1720. ^{1}H-Nmr: 6.95 (s, 2H, H5 and H6), 3.80 (s, 6H, H9 and H9'), 3.68 (s, 6H, H13 and H13'), 2.54-2.48 (m, 8H, H10, H11, H10' and H11'). ^{13}C-Nmr: 172.95 (C12 and C12'), 163.79 (C8 and C8'), 154.24 (C2 and C3), 145.88 (C5 and C6), 94.55 (C1 and C4), 52.02 (C9 and C9'), 51.40 (C13 and C13'), 29.29 (C11 and C11'), 24.10 (C10 and C10'). Anal. Calcd for $C_{18}H_{22}O_9$: C 56.54, H 5.76. Found: C 56.72, H 5.78.

Compound (**7**) was obtained as colorless prisms (mp 102-103°C) in 75% yield (263 mg). Ir (KBr): 1730, 1710. ^{1}H-Nmr: 6.93 (s, 2H, H5 and H6), 3.80 (s, 6H, H9 and H9'), 2.64-2.45 (m, 8H, H10, H11, H10' and H11'), 2.16 (s, 6H, H13 and H13'). ^{13}C-Nmr: 207.28 (C12 and C12'), 163.98 (C8 and C8'), 154.48 (C2 and C3), 146.15 (C5 and C6), 94.81 (C1 and C4), 52.22 (C9 and C9'), 38.79 (C11 and C11'), 29.85 (C13 and C13'), 22.78 (C10 and C10'). Anal. Calcd for $C_{18}H_{22}O_7$: C 61.72, H 6.28%. Found: C 61.72, H 6.32.

Compound (**8**) was obtained as a pale yellow oil in 70% yield (256 mg). Ir (film): 1740, 1720. ^{1}H-Nmr: 6.87 (s, 2H, H5 and H6), 3.72 (s, 6H, H9 and H9'), 3.61 (s, 3H, H13'), 2.55-2.36 (m, 8H, H10, H11, H10' and H11'), 2.08 (s, 3H, H13). ^{13}C-Nmr: 207.15 (C12), 173.00 (C12'), 163.93 (C8'), 163.75 (C8), 154.74 (C2), 153.89 (C3), 146.14 (C6), 145.81 (C5), 94.82 (C1), 94.53 (C4), 52.20 (C9), 52.18 (C9'), 51.57 (C13'), 38.69 (C11), 29.86 (C13), 29.48 (C11'), 24.24 (C10'), 22.73 (C10).

Transformation of cycloadducts (4, 7 and 8) into the corresponding phenolic derivatives (9, 10 and 11).

To a solution of aducts(**4**, **7** or **8**)(1 mmol) in CH_2Cl_2 (3 ml) under argon atmosphere, a solution of BF_3 (1 mmol) in ether (0.12 ml) was added. The reaction mixture was warmed under reflux by 2 h, after which it was hydrolized with water. The reaction mixture was extracted with CH_2Cl_2, and the organic extracts were dried over $MgSO_4$. The drying agent was removed by filtration and the solvent was distilled to yield a pale yellow oil which was purified by column chromatography (hexane-ethyl acetate 1:2) to give the phenolic derivatives (**9**, **10** and **11**).

Compound (**9**) was obtained as pale yellow oil in 75% yield (287 mg). Ir (film): 3150, 1740. ^{1}H-Nmr: 11.13 (s, 1H, OH), 7.26 (s, 1H, H5), 3.92 (s, 3H, H8), 3.84 (s, 3H, H10), 3.68 (s, 3H, H14), 3.66 (s, 3H, H18), 2.97 (t, 2H, J = 7.6 Hz, H15), 2.78 (t, 2H, J = 7.6 Hz, H11), 2.65 (t, 2H, J = 7.6 Hz, H16), 2.56 (t, 2H, J = 7.6 Hz, H12). ^{13}C-Nmr: 172.99 (C17), 172.63 (C13), 169.37 (C7), 168.94 (C9), 158.26 (C1), 136.62 (C5), 132.62 (C4), 130.55 (C6), 127.79 (C3), 108.61 (C2), 52.74 (C8), 52.17 (C10), 51.41 (C14), 51.34 (C18), 35.41 (C12), 32.87 (C16), 27.87 (C11), 25.46 (C15).

Compound (**10**) was obtained as colorless prisms (mp 39-40°C) in 80% yield (280 mg). Ir (KBr): 3150, 1740, 1730, 1720. ^{1}H-Nmr: 11.09 (s, 1H, OH), 7.24 (s, 1H, H5), 3.91 (s, 3H, H8), 3.87 (s, 3H, H10), 2.89-2.86 (m, 2H, H15), 2.78-2.69 (m, 2H, H16), 2.69 (s, 4H, H11 and H12), 2.13 (s, 3H, H14), 2.12 (s, 3H, H18). ^{13}C-Nmr: 207.66 (C17), 207.17 (C13), 169.45 (C7), 169.15 (C9), 158.11 (C1), 136.94 (C5), 132.29 (C4), 131.10 (C6), 128.44 (C3), 108.56 (C2), 52.77 (C8), 52.22 (C10), 45.02 (C12), 42.34 (C16), 29.73 (C14 and C18), 26.57 (C11), 24.30 (C15). Anal. Calcd for $C_{18}H_{22}O_7$: C 61.71, H 6.29. Found: C 61.68 , H 6.25.

Compound (**11**) was obtained as pale yellow oil in 99% yield (362 mg). Ir (film): 3100, 1730, 1710. ^{1}H-Nmr: 11.11 (s, 1H, OH), 7.25 (s, 1H, H5), 3.92 (s, 3H, H8), 3.88 (s, 3H, H10), 3.66 (s, 3H, H18), 2.96 (t, 2H, J = 7.5 Hz, H15), 2.70 (s, 4H, H11 and H12), 2.65 (t, 2H, J = 7.5 Hz, H16), 2.13 (s, 3H, H14). ^{13}C-Nmr: 207.17 (C13), 173.11 (C17), 169.46 (C7), 169.17 (C9), 158.21 (C1), 136.82 (C5), 132.53 (C4), 130.59 (C6), 128.45 (C3), 108.60 (C2), 52.73 (C8), 52.18 (C10), 51.34 (C18), 44.98 (C12), 32.87 (C16), 29.66 (C14), 26.52 (C11), 25.43 (C15).

Synthesis of dihydrocumarin (12)

To a solution of phenolic derivative (**11**) (366 mg, 1 mmol) in toluene (15 ml), trifluoroacetic acid (0.5 ml, 6.5 mmol) was added. The solution was warmed under reflux by 48 h, after which it was hydrolized with water (3 ml). The crude product was extracted with AcOEt and the organic extracts were dried over $MgSO_4$. The drying agent was removed by filtration and the solvent was distilled to give a pale yellow oil corresponding to dihydrocumarin (**12**), which was purified by column chromatography (hexane-ethyl acetate 1:2). Isolated yield 270 mg (80%).

Ir (film): 1790, 1740. ^{1}H-Nmr: 7.22 (s, 1H, H6), 3.83 (s, 3H, H17), 3.77 (s, 3H, H18), 2.86 (t, 2H, J = 7.2 Hz, H4), 2.71 (t, 2H, J = 7.2 Hz, H3), 2.62 (s, 4H, H13 and H14), 2.05 (s, 3H, H16). ^{13}C-Nmr: 207.35 (C15), 172.87 (C2), 166.53 (C11), 166.25 (C12), 165.32 (C10), 148.05 (C7), 136.23 (C5), 132.03 (C6), 127.32 (C8), 122.85 (C9), 52.84 (C18), 52.63 (C17), 44.63 (C16), 29.59 (C14), 28.41 (C3), 27.13 (C13), 23.83 (C4).

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