Synthesis and Cycloaddition Reactions of Ethyl (*E*)-3-Aryl-2-(nonafluorobutyl)sulfonyl-2-propenoates

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Dedicated to Prof. C. W. Jefford on the occasion of his 65th birthday.

Abstract: Ethyl (nonafluorobutyl)sulfonylacetate (**2**) reacts stereoselectively with substituted benzaldehydes **3** affording (*E*)-3-aryl-2-(nonafluorobutyl)sulfonyl-2-propenoates (*E*)-**4**, which are good dienophiles. The addition to cyclopentadiene yields exclusively the *exo*-products **8**.

The (perfluorobutyl)sulfonyl group has found several interesting applications in organic synthesis especially due to its ambivalent function as an electrophile or as a nucleofuge leaving group.[2] Thus carbon-carbon multiple bonds in alkenyl and alkynyl perfluoralkylsulfones are highly activated by the electron-withdrawing effect of the perfluoralkylsulfonyl group for nucleophilic attack and cycloadditions.[2-9] For an even higher dienophilic character, it would be of interest to have two electron-withdrawing groups in the 1,1-position of the alkene.[10,11] In this regard, we report here on the stereoselective synthesis of a new type of α,β-unsaturated esters (*cis*-cinnamic esters), ethyl (*E*)-3-aryl-2-(nonafluorobutyl)sulfonyl-2-propenoates [(*E*)-**4**]. Cinnamic acids and derivatives are well recognized as useful and important building blocks in organic synthesis,[12-19] however, no stereoselective method for the preparation of 2-substituted "*cis*-cinnamic esters (acids)" exists.

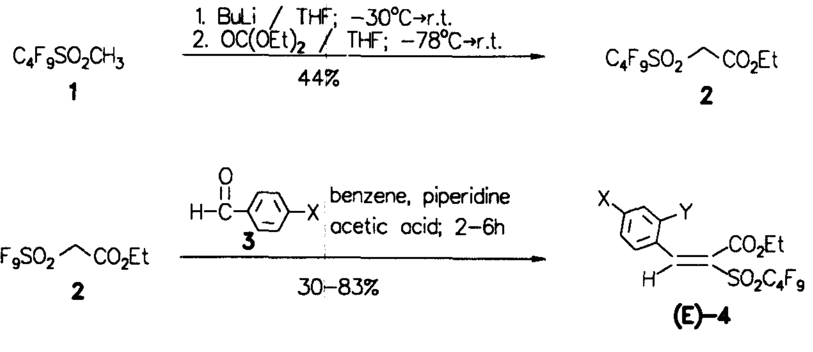
The title compounds (*E*)-**4** were synthesized by the Knoevenagel condensation of ethyl (nonafluorobutyl)sulfonylacetate [ethyl (nonaflyl)acetate] (**2**) with various aromatic aldehydes **3** (Scheme 1). The precursor **2** was prepared by the reaction of nonaflylmethane (**1**)[20,21] with butyllithium in tetrahydrofuran followed by addition of diethyl carbonate. The sulfonyl ester **2** can also be prepared by reacting nonaflyl fluoride with sodiomalonic ester.[21]

The formation of a condensation product in the reaction of *p*-dimethylaminobenzaldehyde (**3e**) with **2** in acetic anhydride has been reported in the literature.[22] However, in our hands this reaction furnished only traces of the deep yellow product (*E*)-**4e**, the main product being the recovered **2**. Under the established reaction conditions that we use[10] (catalytic amounts of piperidine and anhydrous acetic acid in benzene), the condensation between activated aldehydes **3** and sulfonyl ester **2** takes place affording only the (*E*)-isomers **4** in good yields. The products are stable crystalline solids, which were characterized by their spectral data (Table 1). The formation of only one isomer of the products **4** was recognized from their ^{1}H and ^{13}C NMR spectra. That they possess *E*-configuration was determined from the $^3J_{H,CO}$ coupling constant (~10 Hz) of the two derivatives *E*-**4d,e** in their ^{13}C NMR spectra, by selectively suppressing the disturbing coupling of the H-1' protons with the C=O group.

The esters **4** were subjected to Diels-Alder reaction with 2,3-dimethylbutadiene (**5**) and cyclopentadiene (**7**), respectively. As expected,[10,23] the donor-acceptor substituted sulfone ester **4c** does not react with the dienes **5** and **7**, but the other esters **4a,d,f** and especially **4b**, added readily to the dienes at room temperature with formation of the adducts **6** and **8**, respectively. Among the products **6a,f** and **8f** are unstable (Scheme 2) and could not be isolated. The addition of (*E*)-**4a,b,d** to cyclopentadiene takes place with complete π-facial control *syn* to the nonaflyl group, yielding only *exo*-**8a,b,d** (Scheme 2). The selectivity of this reaction is higher than the one observed in the case of the corresponding nitriles (*E*)-**9** which afforded a mixture of the *exo*/*endo* adducts (Scheme 2).[10] This fact is probably due to the higher steric demand of the COOEt in comparison with the CN-group. According to MMX force field calculations, the difference between the steric energies (E_{st}) of the *exo* and *endo* isomers is higher in the case of the esters **8** than for the corresponding nitriles **10**.

The structures of all the adducts **6** and **8** were fully confirmed by spectroscopic methods (Table 2). The configuration of *exo*-**8** was established by NOE experiments. Irradiation of H-7 proton at δ = 1.63 showed a positive NOE with the H-7' of the methylene bridge (δ = 2.42) and H-1 and H-4 (δ = 3.92 and 3.10), while no such effect was observed with the *endo*-H-3 at δ = 4.21 (Scheme 2).

In summary, we have realized the first reliable stereoselective synthesis of ethyl (*E*)-3-aryl-2-(nonafluorobutyl)sulfonyl-2-propenoates [(*E*)-**4**] which proved to be a reactive class of dienophiles for the preparation of highly substituted cyclohexene and norbornene derivatives. Further studies on the reactivity of analogous chiral esters are in progress.



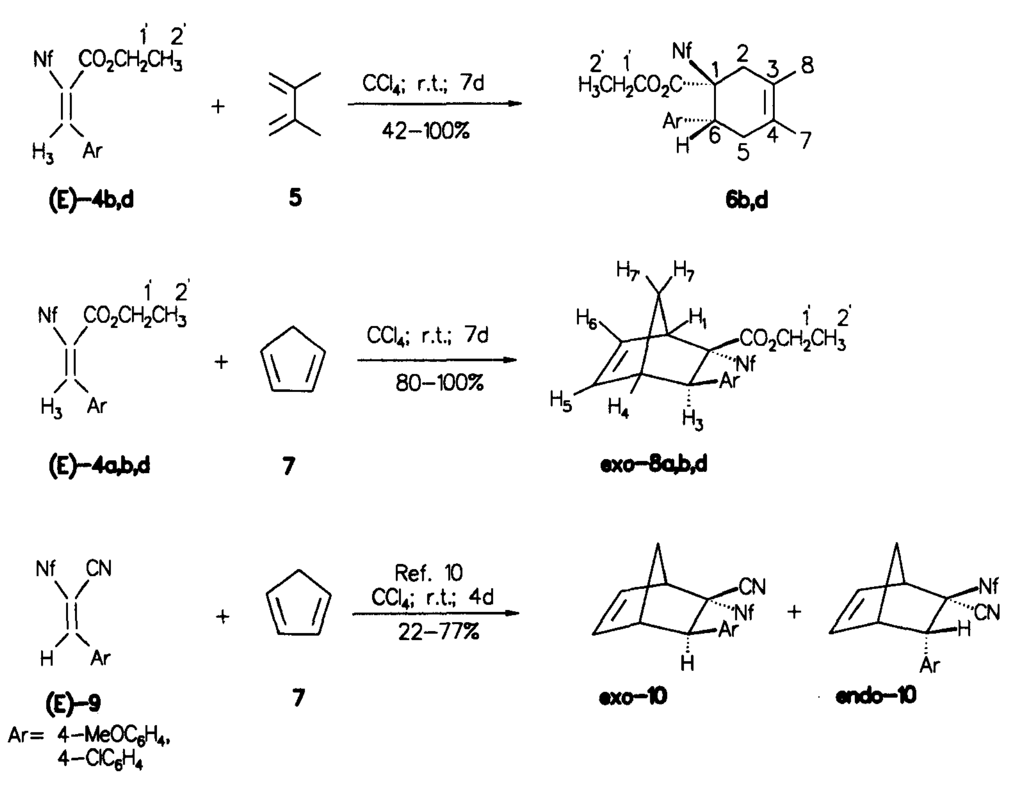
3–4	a	b	c	d	e	f
X	H	NO$_2$	OCH$_3$	Cl	N(CH$_3$)$_2$	CH$_3$
Y	H	H	H	H	H	CH$_3$

Scheme 1

Table 1. Compounds **4a-f** Prepared

Product[a]	Yield (%)	mp (°C)	IR (KBr) ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ	MS (M$^+$) *m/z* (%)
4a	50	39-41	1738,1607,1576, 1375,1352,1288, 1238-1210,1167, 1142,1117,1028, 758,725,689	7.94(s,1H,H-3),7.58-7.43(m,5H,Ar), 4.40(q,2H,*J*=7.2,H-1'),1.31(t,3H, *J*=7.1,H-2')	161.3, 153.1,133.3, 130.9, 130.5, 129.3, 128.0, 63.3, 13.6	458 (36)
4b	30	72-73	1726,1612,1595, 1535,1369,1350, 1240-1217,1163, 1140,1113,1034, 1018,866,853, 700,690	8.32(d,2H,*J*=8.9,Ar),8.03(s,1H,H-3), 7.72(d,2H,*J*=8.7,Ar),4.39(q,2H, *J*=7.2,H-1'),1.31(t,3H, *J*=7.1,H-2')	160.1,150.2,149.8,136.6 132.4,131.1,124.2,63.9 13.6	503 (12)
4c	50	50-51	1734,1610,1538, 1514,1366,1277, 1231-1182,1159, 1140,1115,1034, 860,835,723	7.84(s,1H,H-3)7.59(d,2H,*J*=8.9,Ar), 6.95(d,2H,*J*=8.9,Ar),4.40(q,2H, *J*=7.16,H-1'),3.90,(s,3H,OCH$_3$), 1.34(t,3H,*J*=7.2,H-2')	164.2,161.1,153.1,134.1 124.0,123.1,114.8,63.1, 55.6,13.7	488 (40)
4d	46	92-93	1726,1589,1367, 1352,1290,1236-1203,1163,1142, 1113,824	7.87(s,1H,H-3),7.47(m,4H,*J*=9,Ar), 4.38(q,2H,*J*=7.2,H-1'),1.31(t,3H, *J*=7.1,H-2')	160.1,151.7,139.9,132.1, 129.7,128.8,128.5,63.5, 13.6	492/494 (12/7)
4e	83	86	1711,1616,1360, 1351,1234-1200, 1157,1140,1113	7.75(s,1H,H-3),7.09(dd,4H,J=9.1, Ar),4.38(q,2H,*J*=7.1,H-1'),3.09(s,6H, N-(CH$_3$)$_2$),1.34(t,3H,*J*=7.1,H-2')	162.5,154.3,154.1,135.3 117.9,117.6,111.5,62.6, 39.9,13.8	501 (32)
4f	50	34-36	1738,1595,1373, 1352,1238,1217, 1167,1142,1115	8.21(s,1H,H-3),7.15(dd,2H,J=8.1, Ar),7.10(s,1H,Ar),4.30(q,2H, *J*=7.1,H-1'),2.39(s,3H,Ar-CH$_3$),2.35 (s,3H,Ar-CH$_3$),1.24(t,3H,H-2')	161.2,152.7,143.9,139.5 131.9,128.8,127.7,127.3, 127.2,63.1,21.5,19.7, 13.6	486 (3)

[a] Satisfactory microanalyses obtained: C ±0.36, H ±0.39. Exceptions, **4a**: C –1.19, **4d**: C –0.6.



Scheme 2

Melting points were taken using a Büchi-SMP-20 apparatus and are uncorrected. All reactions were carried out under dry conditions using freshly purified solvents and substrates. Methyl nonafluorobutyl sulfone (**1**) was prepared according to literature procedure.[10]

Ethyl (Nonafluorobutyl)sulfonylacetate 2:

To a solution of methyl nonafluorobutyl sulfone (**1**; 2 g, 6.7 mmol) in THF (50 mL) was added BuLi (4.2 mL, 6.7 mmol, 1,6 N in hexane) at -30°C. This solution was added dropwise to diethyl carbonate (2 g, 16.8 mmol) in THF (10 mL) at-30°C. The

Table 2. Compounds 6 and 8 Prepared

Product[a]	Yield (%)	IR (KBr) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ	MS (M^+) *m/z* (%)
6b	100	1744,1604,1524, 1373,13,46,1275, 1236-1180,1161, 1142,1128,1114, 1022,858,851	8.14(d,2H,*J*=8.8,Ar), 7.50(d,2H,*J*=8.8,Ar),4.17-4.04 (m,3H,H-1'/H-6),3.03-2.35 (m,4H,H-2/H-5),1.80(s,3H, H-8),1.71(s,3H,H-7),1.21 (t,3H,*J*=7.2,H-2')	164.5,147.6,146.6,130.4 124.8,123.6,121.8,79.2 63.3,42.2,36.2,33.2, 18.8,18.6,13.5	585 (0.1)
6d	42	1744,1373,1366, 1277,1234-1200, 1161,1142,1111	7.27(dd,4H,*J*=8.1,Ar), 4.05(m,3H,H-1'/H-6), 3.05-2.27(m,4H,H-2/H-5), 1.82(s,3H,H-8),1.73(s,3H, H-7),1.22(t,2H,H=7.2,H-2')	164.7,137.8,134.0,130.4, 128.8,124.7,121.7,79.3, 63.0,41.4,36.2,32.4, 18.8,18.7,13.5	575/577 (0.7/0.2)
8a	80	1740,1603,1367, 1350,1238,1161, 1142,1113,1022, 748,700	7.26-7.00(m,5H,Ar), 6.61(dd,1H,*J*=5.4/3.4,H-6), 6.47(dd,1H,*J*=5.4/3.1,H-5), 4.09(m,1H,*J*=3.4/2.0,H-1), 3.85-3.57(m,3H,H-1'/H-3), 3.05(m,1H,H-4),2.41(m,1H, *J*=9.6,H-7'),1.56(m,1H,*J*=9.6, H-7),0.68(t,3H,*J*=7.2,H-2')	164.3,138.9,138.6,129.1, 128.3,127.9,127.4,89.7, 62.5,53.9,51.7,49.1, 48.3,12.7	524 (1.2)
8b	100	1742,1601,1526, 1366,1350,1283, 1238,1161,1142, 1113,1018,868, 852	8.05(d,2H,*J*=8.9,Ar),7.25(d,2H, *J*=8.4,Ar),6.61(dd,1H,*J*=5.3/3.5, H-6),6.51(dd,1H,*J*=5.4/3.0,H-5), 4.21(m,1H,*J*=1.4,H-1),3.94-3.73 (m,3H,H-1'/H-3),3.10(m,1H,H-4) 2.42(dd,1H,*J*=9.7,H-7'),1.63(dd,1H, *J*=9.7,H-7),0.82(t,3H,*J*=7.2,H-2')	163.6,147.2,146.1,139.1, 138.8,130.1,123.0,88.8, 62.9,53.1,51.8,490, 48.2,13.0	570 (2)
8d	80	1742,1600,1364, 1350,1238,1161, 1142,1113,1016	7.20-6.96(m,4H,Ar),6.59(dd,1H, *J*=3.4/2.0,H-2),6.45(dd,1H,*J*=3.0/2.5, H-5),4.06(dd,1H,*J*=1.5,H-1),3.92-3.70 (m,3H,H-1'/H-3),3.02(dd,1H,*J*=1.0/0.6, H-4),2.39(d,1H,*J*=9.7,H-7'),1.57(m,1H, *J*=9.6,H-7),0.77(t,3H,*J*=7.1,H-2')	164.0,138.8,137.1,133.5, 130.4,128.0,119.4-110.7, 89.3,62.6,53.1,51.7 49.0,48.1,12.7	M++1 559/561 (0.2/0.1)

[a] **6d**: $C_{21}H_{20}ClF_9O_4S$ calc. C 43.08 H 3.42; found C 42.43 H 3.42. Compounds **6a**, **8a**, **b**, **d** are unstable and decompose easily hindering combustion analyses.

mixture was allowed to warm to r. t. and refluxed for 10 h to complete the reaction. The mixture was poured into ice and HCl (2 N, 20 mL) was added. The product was extracted with Et_2O and the organic layers dried (Na_2SO_4). The solvent was evaporated and the residue distilled under vacuum to give **2**; yield: 1.09 g (44%).

3-Aryl-2-(nonafluorobutyl)sulfonyl-2-propenoates 4; General Procedure:

Ethyl (nonafluorobutyl)sulfonylacetate (**2**; 1.55 g, 4.2 mmol) and the aromatic aldehyde **3** (4.2 mmol) were dissolved in benzene. Piperidine (85 mg, 1 mmol) and glacial AcOH (120 mg, 2 mmol) were added. The mixture was refluxed for 2-6 h using a water trap, until no further water separates. The solvent was evaporated and the residue was taken up in Et_2O. The Et_2O layer was washed with HCl (30 mL, 1 N), several times with water and dried (Na_2SO_4). The solvent was partly removed, replaced by hexane and cooled to -20°C. The crystals formed were recrystallized from hexane/Et_2O.

Diels–Alder Adducts 8; General Procedure:

A solution of 3-aryl-2-(nonafluorobutyl)sulfonyl-2-propenoate (*E*)-**4** (1 mmol) and the diene **5**, **7** (1.2 mmol) in CCl_4 (10 mL) was stirred at r. t. for 7 d. An additional amount of the diene (1.2 mmol) was added every 2 d. The solvent was removed and the residue recrystallized from hexane (**6d**) or purified by preparative TLC (**6b**,**8a**, **8b**, **8f**).

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