A Facile Synthesis of 2,4-Dialkoxy-, 2-Alkoxy-4-phenoxy-, and 2,4-Diphenoxy-6-trifluoromethyl-3,4-dihydro-2*H*-pyrans. Hetero-Diels–Alder Reactions of *trans*-β-Trifluoroacetylvinyl Ethers with Various Vinyl Ethers

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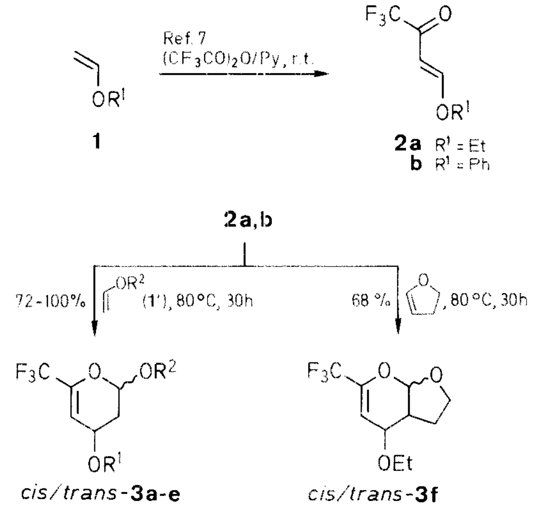
2,4-Dialkoxy-, 2-alkoxy-4-phenoxy-, and 2,4-diphenoxy-6-trifluoromethyl-3,4-dihydro-2*H*-pyrans are obtained in high yields by the hetero-Diels–Alder reaction of *trans*-β-trifluoroacetylvinyl ethers with various vinyl ethers under mild conditions.

Much attention is being paid to the biological activities of fluorine-containing heterocycles for their potential use in the medicinal and agricultural scientific field.[1,2] The formation of dihydropyran systems by thermal cycloaddition reaction of α,β-unsaturated carbonyl compounds with various olefins are known.[3-5] However, the synthesis of 3,4-dihydro-2*H*-pyrans bearing a trifluoromethyl group, which may be expected to show biological activities, has not yet been reported so far.

During our investigations[6] on electrophilic substitutions at olefinic C-atoms it was found that vinyl ethers **1** react readily with trifluoroacetic anhydride to give 2-alkoxyvinyl or 2-aryloxyvinyl trifluoromethyl ketones **2** (*trans*-β-trifluoroacetylvinyl ethers)[7] in almost quantitative yields. This trifluoroacetylvinyl system appeared to be a useful heterodiene for the simple and convenient preparation of CF_3-containing dihydropyrans which are hardly obtainable by other routes. This situation prompted us to investigate the synthesis of the title compounds **3** by the hetero-Diels-Alder reaction of *trans*-β-trifluoroacetylvinyl ethers **2** with various vinyl ethers **1′**.

The cycloaddition of heterodienes **2** with enes **1′** proceeded cleanly under mild conditions to afford 6-trifluoromethylated 3,4-dihydro-2*H*-pyrans **3** in high yields.

The reaction of *trans*-(2-ethoxyvinyl) trifluoromethyl ketone (**2a**) with ethyl, isobutyl, and 2-chloroethyl vinyl ethers **1′** was carried out without solvent in the presence of very small amounts of hydroquinone at 80 °C for 30 h to give mixtures of *cis*- and *trans*-2,4-dialkoxy-6-trifluoromethyl-3,4-dihydro-2*H*-pyrans **3a–c**[8] in 89–100% yields. Although at higher temperature (150 °C) the reaction of **2a** with ethyl vinyl ether was completed within 6 h, the yield was reduced to 69% owing to the formation of decomposed materials. Similarly, *trans*-(2-phenoxyvinyl) trifluoromethyl ketone (**2b**) reacted with ethyl and phenyl vinyl ethers **1′** to yield diastereoisomeric 2-ethoxy- and 2-phenoxy-4-phenoxy-3,4-dihydro-2*H*-pyrans (**3d** and **3e**)[8]



3	R^1	R^2
a	Et	Et
b	Et	*i*-Bu
c	Et	$ClCH_2CH_2$
d	Ph	Et
e	Ph	Ph

Table. Hetero-Diels-Alder Reaction of Heterodienes **2a**, **b** with Vinyl Ethers **1′**

Heterodiene	Product[8]	Yield (%)	mp (°C)[a] (solvent) or bp (°C)/mbar[b]	Molecular Formula[c]	IR (film)[d] $\nu_{C=C}$ (cm^{-1})	^1H-NMR ($CDCl_3$/TMS)[e] δ, *J* (Hz)
2a	**3a**	93	70/5	$C_{10}H_{15}F_3O_3$ (240.2)	1678	1.22, 1.23, 1.24 (3t, 6H, $J = 7.1$, $OCH_2C\underline{H}_3$); 1.93–2.25 (m, 2H, 3-H); 3.52–3.72 (m, 3H, 2- and 4-$OC\underline{H}_2CH_3$); 3.86–3.99 (m, 1H, 2-$OC\underline{H}_2CH_3$); 4.06–4.18 (br m, 1H, 4-H); 5.17 (dd, 1H, $J = 2.7, 6.1$, 2-H); 5.63 (d, 1H, $J = 3.4$, H-5)
2a	**3b**	100	100/4	$C_{12}H_{19}F_3O_3$ (268.3)	1686	0.91 [d, 6H, $J = 6.7$, $OCH_2CH(C\underline{H}_3)_2$]; 1.21, 1.22 (2t, 3H, $J = 6.9$, $OCH_2C\underline{H}_3$); 1.79–2.24 [m, 3H, 3-H and $OCH_2C\underline{H}(CH_3)_2$]; 3.24–3.35 [m, 1H, $OC\underline{H}_2CH(CH_3)_2$]; 3.51–3.67 [m, 3H, $OC\underline{H}_2CH_3$ and $OC\underline{H}_2CH(CH_3)_2$]; 4.07–4.24 (br m, 1H, 4-H); 5.12–5.16 (m, 1H, 2-H); 5.64 (d, 1H, $J = 2.4$, 5-H)
2a	**3c**	89	oil[12]	$C_{10}H_{14}ClF_3O_3$ (274.6)	1680	1.22 (t, 3H, $J = 7.0$, $OCH_2C\underline{H}_3$); 1.94–2.27 (m, 2H, 3-H); 3.51–3.68 (m, 4H, $OC\underline{H}_2CH_3$ and $ClC\underline{H}_2CH_2O$); 3.77–3.88 (m, 1H, $ClCH_2C\underline{H}_2O$); 4.04–4.21 (m and br, 2H, $ClCH_2C\underline{H}_2O$ and 4-H); 5.21–5.26 (m, 1H, 2-H); 5.66–5.69 (m, 1H, 5-H)
2b	**3d**	72	110/4	$C_{14}H_{15}F_3O_3$ (288.3)	1680	1.25 (t, 3H, $J = 7.1$, $OCH_2C\underline{H}_3$); 2.10–2.37 (m, 2H, 3-H); 3.55–3.74, 3.87–4.00 (2m, 1H each, $OC\underline{H}_2CH_3$); 4.88–4.96 (br m, 0.6H, 4-H); 4.99–5.10 (br m, 0.4H, 4-H); 5.26 (dd, 1H, $J = 3.1, 4.9$, 2-H); 5.71 (d, 0.4H, $J = 3.1$, 5-H); 5.76 (d, 0.6H, $J = 3.6$, 5-H); 7.01–6.90 (m, $3H_{arom}$); 7.26–7.32 (m, $2H_{arom}$)
2b	**3e**	77	120[f] (*n*-hexane)	$C_{18}H_{15}F_3O_3$ (336.3)	1686	2.36 (ddd, 1H, $J = 3.0, 6.2, 14.6$, 3-H); 2.60 (dt, 1H, $J = 3.9, 14.6$, 3-H); 4.95–5.09 (br m, 1H, 4-H); 5.87 (dd, 1H, $J = 3.0, 3.9$, 2-H); 5.89 (d, 1H, $J = 3.5$, 5-H); 6.96–7.11 (m, $6H_{arom}$); 7.27–7.35 (m, $4H_{arom}$)
2a	**3f**	68	100/2	$C_{10}H_{13}F_3O_3$ (238.2)	1685	1.23 (t, 3H, $J = 7.0$, $OCH_2C\underline{H}_3$); 1.85–2.14 (m, 2H, $OCH_2C\underline{H}_2CH$); 2.72–2.85 (br m, 1H, 3-H); 3.58, 3.59 (2q, 2H, $J = 7.0$, $OC\underline{H}_2CH_3$); 3.96–4.06, 4.17–4.25 (2m, 1H each, $OC\underline{H}_2CH_2CH$); 4.45–4.53 (br m, 1H, 4-H); 5.45 (br s, 1H, 5-H); 5.67 (d, 1H, $J = 3.9$, 2-H)

[a] Uncorrected, measured by capillary.

[b] Oven temperature of Kugelrohr distillation.

[c] Satisfactory microanalyses obtained (except for **3c**):[12] C ±0.34, H ±0.14, F ±0.41.

[d] Recorded on a Hitachi Model EPI-G3 grating spectrophotometer.

[e] Measured using a BRUKER AC 250 spectrometer at 250 MHz. Spectral data of *cis*/*trans* mixtures are listed except for **3e** for which those for the *cis*-adduct are given.

[f] *cis*-Isomer.

in 72 % and 77 % yields, respectively. The reaction of **2a** with the cyclic vinyl ether 2,3-dihydrofuran under the same conditions afforded diastereoisomers of 4-ethoxy-6-trifluoromethyl-2,3,3a,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran[8] **(3f)** in 68 % yield. These results demonstrate that this cycloaddition proceeds regioselectively to give 2,4-dialkoxydihydropyran derivatives as the sole products without formation of the 3,4-dialkoxy regioisomers; however, the reaction does not proceed stereoselectively. It is worthy of note that the present hetero-Diels–Alder reaction proceeds at much lower temperature and in higher yields in contrast to the few reported cases[9,10] of cycloaddition of vinyl ethers to β-alkoxy-α,β-unsaturated carbonyl compounds. For example, it has been reported that 3-methoxypropenal **(4)** reacted with methyl vinyl ether at 240 °C to afford, in 60 % yield, both diastereoisomers of 2,4-dimethoxy-3,4-dihydro-2*H*-pyran in an unstated ratio.[9] Another report showed that the reaction of 4-methoxy-3-buten-2-one **(5)** with isobutyl vinyl ether proceeded considerably slower even at 190–240 °C (24 h) to give a mixture of *cis* and *trans* adducts of 2-isobutoxy-4-methoxy-6-methyl-3,4-dihydro-2*H*-pyran in a ratio of 55 : 45, conversion not exceeding 45 %.[10] The observed difference in reactivities between **2** and the above-mentioned nonfluorinated compounds **4** and **5** is undoubtedly due to the presence of the powerful electron-withdrawing CF_3 group in place of H or CH_3 on the carbonyl C-atom of the α,β-unsaturated carbonyl system, by which the electron density is reduced considerably.[11] Utilization of compounds **3a–f** as synthetic intermediates for the preparation of various CF_3-containing compounds is now under investigation.

Cycloaddition of Compounds 2a, b with Vinyl Ethers 1; Typical Procedure:

A mixture of **2a** (6.39 g, 38.0 mmol), ethyl vinyl ether (8.23 g, 114.1 mmol), and hydroquinone (41.8 mg, 0.38 mmol) is heated in a sealed ampoule at 80 °C for 30 h. Removal of the excess ethyl vinyl ether and Kugelrohr distillation (oven temperature 70 °C/5 mbar) of the crude oil afford pure *2,4-diethoxy-6-trifluoromethyl-3,4-dihydro-2H-pyran* **(3a)**; yield: 8.49 g (93 %).

$C_{10}H_{15}F_3O_3$	calc.	C 50.00	H 6.29	F 23.73
(240.2)	found	49.75	6.27	23.43

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(8) It is obvious from ^1H-NMR analysis (250 MHz) of the reaction mixture that the present cycloaddition is not particularly stereoselective, if at all, although the proportions of the two diastereoisomers could not be estimated exactly except for **3d** formed in an isomer ratio of 60 : 40. In addition, extensive overlap of the signals did not allow individual assignments. Attempts to fractionate the *cis*- and *trans*-adducts by TLC were unsuccessful, owing to the very small differences of their polarities and their instability on contact with SiO_2 and alumina. Only the *cis*-isomer[13] of **3e** could be separated by recrystallization of the mixture from hexane.

(9) Eskenazi, C., Maitte, P. *C. R. Acad. Sci. Ser. C* **1974**, *279*, 233.

(10) Berti, G., Catelani, G., Colonna, F., Monti, L. *Tetrahedron* **1982**, *38*, 3067.

(11) This can be explained with the aid of MINDO/3 MO calculations for simplified models of systems such as **2**, **4**, and **5**.[14]

(12) Purification for microanalysis of **3c** was difficult; the structural assignment was confirmed by ^1H-NMR and IR spectra of the crude product which was practically pure.

(13) Structural assignment of *cis*-**3e** was accomplished by consulting: Schmidt, R.R., Maier, M. *Tetrahedron Lett.* **1982**, *23*, 1789. Apparao, S., Maier, M.E., Schmidt, R.R. *Synthesis* **1987**, 900.

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