A Novel Efficient Synthesis of Heteroaryl Substituted α,β-Unsaturated Trifluoromethyl Ketones

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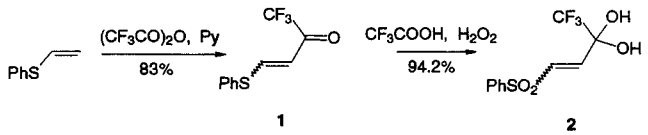
Abstract: A synthesis of a novel electrophilic reagent 1,1,1-trifluoro-4-(phenylsulfonyl)-but-3-ene-2,2-diol **2** is described. The reaction of **2** with various electron-rich heteroaromatics such as furans, pyrroles, indoles is investigated. The addition-elimination reaction proceeds under mild conditions stereospecifically and permits a novel one-step procedure for the preparation of trifluoroacetylvinyl substituted heterocycles in high yield. In all cases only *E*-isomers of unsaturated CF_3 ketones were obtained.

Introduction of fluorine into organic compounds often leads to enhanced physiological activity of products.[1,2] Heterocyclic organofluorine compounds are very promising targets from both theoretical and experimental points of view. Unsaturated ketones are of high potential importance in organic synthesis. However, unsaturated CF_3 ketones, especially ethylenic ones, are not readily accessible.[3]

1,1,1-Trifluoro-4-heteroaryl-3-buten-2-ones could be important structural units for the synthesis of fluorine containing biologically active compounds. However, now only one compound of this type, i.e. *E*-1,1,1-trifluoro-4-(1*H*-3-indolyl)-3-buten-2-one is known.[4] This is obviously due to the absence of appropriate methods of synthesis of heteroaryl substituted unsaturated CF_3 ketones.

We report here a novel procedure for the preparation of furan, pyrrole and indole derivatives of CF_3 enones based on the reaction of 1,1,1-trifluoro-4-(phenylsulfonyl)-but-3-ene-2,2-diol **2** with corresponding heteroarenes. We have prepared diol **2** for the first time according to Scheme 1.

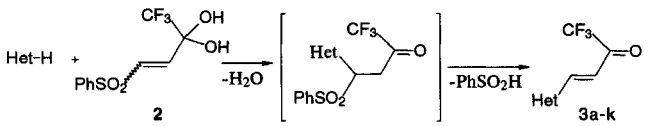


1 2

Scheme 1

1,1,1-Trifluoro-4-(phenylsulfanyl)-but-3-ene-2-one **1** was obtained as a mixture of *E*- and *Z*-isomers[5] by acylation of phenyl vinylsulfide[6] with trifluoroacetic anhydride in the presence of pyridine at 20 °C. The subsequent oxidation of **1** with peroxytrifluoroacetic acid[7] provided an efficient route to the new electrophilic reagent 1,1,1-trifluoro-4-(phenylsulfonyl)-but-3-ene-2,2-diol **2**. The reaction proceeds under very mild conditions at -20 °C to give **2** as a mixture of *E*- and *Z*-isomers[8] in excellent yield. An attempt of oxidation of sulfide **1** with peroxyacetic acid was unsuccessful. Probably this is caused by the instability of sulfone **2** under higher temperature (> 40 °C). Compound **2** exists exclusively as a diol[9] since it has two electron-withdrawing groups at the carbonyl group. It is noteworthy that analogous nonfluorinated sulfones exist only in the keto-forms.[10]

We have found that sulfone **2** easily reacts with various electron-rich heteroaromatics such as furans, pyrroles, indoles to give the corresponding unsaturated CF_3 ketones in 64-86% yield (Scheme 2).[11]



Scheme 2

The only known similar reaction of *E*-4-(phenylsulfonyl)-but-3-ene-2-one with N-methylpyrrole afforded the Michael-type adduct and double-Michael one in 4:1 ratio.[12] However, an acidic catalyst was used, whereas the reactions of **2** with heteroaromatic proceed without any catalyst. These results indicate that the trifluoroacetyl group in sulfone **2** is important for the facile formation of 1,1,1-trifluoro-4-heteroaryl-3-buten-2-ones **3** under mild conditions.

Our one-pot synthesis of **3** proceeds stereospecifically. In all cases only *E*-isomers of unsaturated ketones were obtained.[13] We believe that the reaction of **2** with heteroaromatics proceeds as an addition-elimination[12] process to form the corresponding butenones (Table 1).

In conclusion, we have prepared a new active electrophile 1,1,1-trifluoro-4-(phenylsulfonyl)-but-3-ene-2,2-diol **2**. The reaction of butendiol **2** with heteroaromatics proceeds stereospecifically at room temperature with the formation of *E*-1,1,1-trifluoro-4-heteroaryl-3-buten-2-ones in good yields.

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References and Notes

(1) Hudlicky, M.; Pavlath A.E., Eds. *Chemistry of Organic Fluorine Compounds: An Update*. ACS Monograph Series N 187, Washington, DC, **1995**.

(2) Filler, A.; Kobayashi, Y. *Biomedical Aspects of Fluorine Chemistry*. Kodansha Ltd., Tokyo, **1981**.

(3) Nenajdenko, V.G.; Sanin, A.V.; Balenkova E.S. *Molecules* **1997**, 2, 146.

(4) Gorbunova, M.G.; Gerus I.I.; Kukhar V.P. *J. Fluorine Chem.* **1993**, *65*, 25.

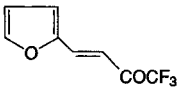
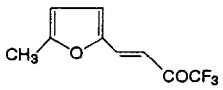
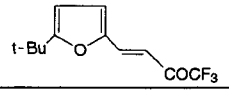
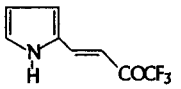
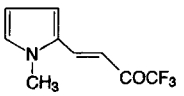
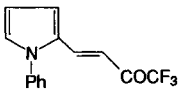
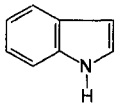
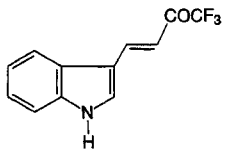
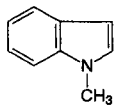
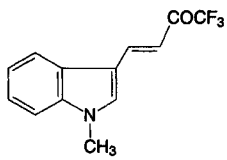
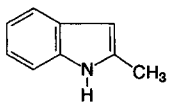
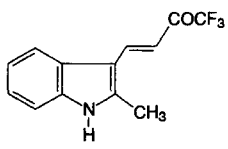
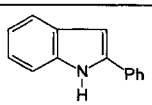
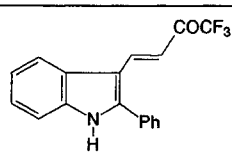
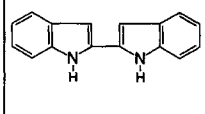
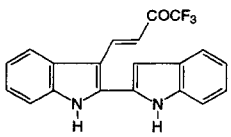
(5) 1,1,1-Trifluoro-4-(phenylsulfanyl)-but-3-ene-2-one **1** is obtained as a mixture of *Z*- and *E*- isomers in 5/7 ratio. *Z*- and *E*-stereochemistry of compound **1** was assigned from the ^1H NMR coupling constants.

(6) Hojo, M.; Masuda, R.; Kamitori Y. *Tetrahedron Lett.* **1976**, 1009.

(7) Venier, C.G.; Squires, T.G.; Chen Y.; Hussmann, G.P.; Shei, J.C.; Smith, B.F. *J. Org. Chem.* **1982**, 47, 3773.

(8) 1,1,1-Trifluoro-4-(phenylsulfonyl)-but-3-ene-2,2-diol **2** was obtained as a mixture of Z- and E-isomers in 1/3 ratio,

Table 1. Reaction of 1,1,1-trifluoro-4-(phenylsulfonyl)-but-3-ene-2,2-diol **2** with heteroaromatics.[13, 14]

HetH	Product	3	Yield,%
		**3a**	78
		**3b**	74
		**3c**	69
		**3d**	84
		**3e**	86
		**3f**	85
		**3g**	64
		**3h**	73
		**3i**	72
		**3j**	70
		**3k**	64

stereochemistry of compound **2** was assigned by use of coupling constants for protons at the double bond in the ^{1}H NMR spectra.

(9) It was proven by means of ^{1}H NMR and IR spectroscopy.

(10) Leon, F.M.; Carretero J.C. *Tetrahedron Lett.* **1991**, 5405.

(11) *General procedure for the reaction of 1,1,1-Trifluoro-4-(phenylsulfonyl)-but-3-ene-2,2-diol 2 with heteroaromatics:* A solution of 1,1,1-trifluoro-4-(phenylsulfonyl)-but-3-ene-2,2-diol **2** (5 mmol) and heteroaromatic compound (5 mmol) in dichloromethane (40 ml) was stirred at rt.[15] The organic solvents were removed *in vacuo*. The products were purified by column chromatography (silica gel, hexane).

(12) Hayakawa, K.; Yodo M.; Ohsuki S.; Kanematsu K. *J. Am. Chem. Soc.*, **1984**, 106, 6735.

(13) All compounds obtained were reliably characterised by their NMR ^{1}H, ^{13}C, IR spectra. The *trans* stereochemistry of these products was clearly indicated by the large value of coupling constant (14-16 Hz) between two olefinic protons in the ^{1}H NMR spectra.[14]

(14) Selected spectra

(E)-1,1,1-Trifluoro-4-(5-methyl-2-furyl)-3-buten-2-one 3b, oil, IR (ν, cm^{-1}): 1690 (CO) 1615 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 3H, CH_3), 6.08 (d, 1H, CH-4 or CH-3 fur., J=3.4 Hz), 6.65 (d, 1H, CH-3, J=15.4 Hz), 6.69 (d, 1H, CH-4 or CH-3 fur., J=3.4 Hz), 7.57 (d, 1H, CH-4, J=15.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 111.8 (C-3), 116.5 (CF_3, ^{1}J = 289.0 Hz), 110.4, 122.4 (C-3, C-4 fur.), 133.6 (C-4), 149.3 (C-2 fur), 158.7 (C-5 fur.), 179.4 (CO, ^{2}J = 34.6 Hz).

(E)-1,1,1-Trifluoro-4-(1-methyl-1*H*-2-pyrrolyl)-3-but-en-2-one 3e, oil, IR (ν, cm^{-1}): 1690 (CO) 1620 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.66 (s, 3H, CH_3), 6.18 (dd, 1H, CH-4 pyrr., J=2.4Hz, J=4.4Hz), 6.60 (d, 1H, CH-3, J=15.2Hz), 6.87-6.85 (m, 2H, CH-3, CH-5 pyrr.). 7.81 (d, 1H, CH-4, J=15.2Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.2 (CH_3), 109.7, 111.0 (C-3), 116.4, 116.8 (CF_3, J=289.0Hz), 129.6, 131.0 (C-4), 136.4 (pyrroles), 179.2 (CO, ^{2}J = 33.6 Hz).

(E)-1,1,1-Trifluoro-4-(2-methyl-1*H*-3-indolyl)-3-buten-2-one 3h, mp 125-130°C, IR (ν, cm^{-1}): 1685 (CO) 1620 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67 (s, 3H, CH_3), 7.00 (d, 1H, CH-3, J=15.3Hz), 7.20-7.30 (m, 2H, CH-5, CH-6 ind.), 7.43, 7.95 (m, 2H, CH-4, CH-7 ind.), 8.18 (d, 1H, CH-4, J=15.3Hz). ^{13}C NMR (100MHz, $CDCl_3$): δ 12.2 (CH_3), 108.8, 112.7 (C-3), 118.2 (CF_3, J=290.0Hz), 111.3, 121.0, 123.1, 123.9, 126.9, 137.6, 144.0 (C-4), 148.8 (indoles), 179.4 (CO, ^{2}J = 33.2 Hz).

(15) In the case of reaction with N-phenylpyrrole, 2-phenylindole and biindolyl the reaction mixture was boiled for 10 h at 40°C.