Organic Chemistry

A new method for the synthesis of CF_3-containing aminovinyl ketones

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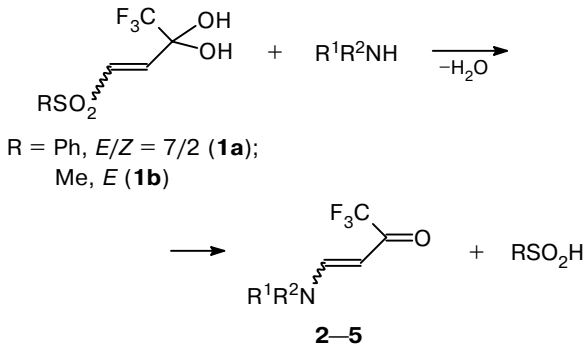
A new method for the synthesis of aminovinyl trifluoromethyl ketones was developed. The method is based on the reactions of 4-sulfonyl-1,1,1-trifluorobut-3-ene-2,2-diols with various alkyl-, aryl-, dialkyl-, and alkylarylamines. The stereochemistry of the compounds obtained was studied.

Key words: β-sulfonylvinyl(trifluoromethyl)methanediols, amines, β-trifluoroacetylvinylamines, enamines, stereochemistry, nucleophilic substitution.

Earlier, sulfones **1a** [1] and **1b** [2] were obtained for the first time by the oxidation of the corresponding easily accessible sulfides with 30% hydrogen peroxide in trifluoroacetic acid. They were found to react with various electron-enriched heteroaromatic compounds to give CF_3-containing β-hetarylalkenyl ketones.[1]

In the present paper, the reactions of easily available and stable sulfones **1a**,**b** with various amines were studied. Under mild conditions, they readily afford a variety of CF_3-containing enaminoketones **2**—**5** in virtually quantitative yields (Scheme 1).

Scheme 1



2—**5**

Results and Discussion

The reaction can involve aliphatic, aromatic, and heteroaromatic amines with a primary or secondary amino group; both pure amines and their aqueous solutions may be used, which is especially important from the preparative viewpoint. The results of the reactions of sulfones **1a**,**b** with amines are given in Table 1. The reaction course is insignificantly influenced either by the presence of the OH group in products **2d** and **3d** or by the presence of electron-withdrawing groups in the starting amines, so that both 3-aminopyridine and *p*-nitroaniline are involved in the reaction. Of particular interest is that the complete conversion of sulfone **1** is reached even with one equivalent of the amine, though

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1329—1333, August, 2001.

1066-5285/01/5008-1395 $25.00

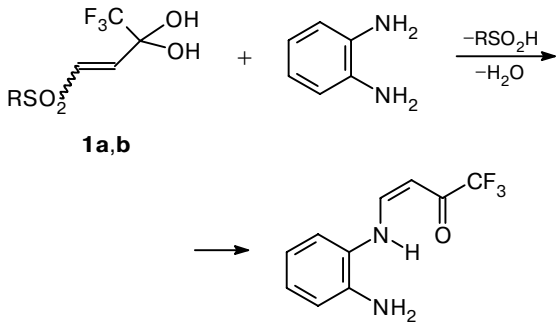
Table 1. Products in the reactions of amines with sulfones **1a**,**b**

Compound	R^1	R^2	*E*/*Z*	Yield (%)
2a	H	H	*Z*	95
2b	H	Bu^n	*Z*	96
2c	H	Allyl	*Z*	93
2d	H	$HOCH_2CH_2$	*Z*	90
2e	H	Bu^t	*Z*	96
3a	Me	Me	*E*	95
3b			*E*	92
3c	Et	Et	*E*	95
3d	$HOCH_2CH_2$	$HOCH_2CH_2$	*E*	90
3e	Pr^i	Pr^i	*E*	94
4a	H	2-NH_2Ph	*Z*	88
4b	H	3-Py	*E*	93
5a	Me	Ph	*E*	95
5b			*E*	98

the reaction produces sulfinic acid also capable of binding the starting amino compound. Apparently, this is explained by extremely high reactivity of compounds **1a**,**b**.

o-Phenylenediamine reacts with one equivalent of diol **1a** or **1b** to give unknown monosubstituted enamine **4a** in high yield, whereas its reactions with β-alkoxyvinyl trifluoromethyl ketones previously[3] afforded an addition product with both amino group involved (Scheme 2).

Scheme 2

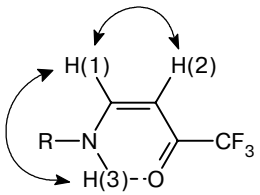


Sulfone **1a** is more reactive in this reaction than **1b**, which is probably due to the fact that the phenylsulfonyl substituent is better leaving group than the methylsulfonyl one. However, the reactions of amines with sulfone **1b** give higher yields because the resulting weak methylsulfinic acid binds the starting amine less strongly.

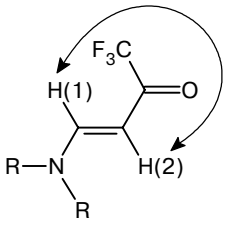
The stereochemistry of the enamines obtained depends on the structure of the starting amine, being independent of the ratio of the *E*/*Z* isomers in the starting sulfones **1a**,**b**. Thus, ammonia and primary aliphatic amines react with sulfones **1a**,**b** to give only *Z* isomers **2a**—**e** owing to the formation of intramolecular hydrogen bond,[3] while the reactions of secondary amines afford *E* isomers.[4]

The stereochemistry of enamines was determined from their ^{1}H NMR spectra. The formation of the *Z* isomer is proved by the coupling constants of the H atoms at the double bond (J = 7.0—7.8 Hz) and by a distinct splitting of the H(1) atom on the amino group H(3) atom (J = 12.9—14.1 Hz) fixed *via* an intramolecular hydrogen bond.[3] In the case of the *E* isomer, J = 12.0—12.5 Hz.

$^3J_{H,H}$ = 7.0—7.8 Hz



$^3J_{H,H}$ = 12.0—12.5 Hz



$^3J_{H,H}$ = 12.9—14.1 Hz

We studied the influence of the ring substituents in enamines **4c**—**g** on the ratio of the *E* and *Z* isomers (Table 2). The presence of electron-releasing substituents stabilizes the *Z* form owing to the formation of an intramolecular hydrogen bond which is more thermodynamically preferred than that with electron-withdrawing substituents. In solvents that are less polar than DMSO-d_6 (*e.g.*, in $CDCl_3$), the equilibrium between the *E* and *Z* isomers is completely shifted to the *Z* isomers, which is in full agreement with the literature data.[3,5]

Thus, the study of the reactions of β-sulfonylvinyl trifluoromethyl ketones with various amines showed that they proceed under mild conditions in virtually quantitative yields and allow one to develop a convenient method for the preparation of a variety of CF_3-containing enamines, which are promising reagents for the synthesis of new biologically active heterocycles. The stereochemistry of the compounds obtained was investi-

Table 2. Products in the reactions of anilines with sulfones **1a**,**b**

Aniline	Conditions*	**4**	*E*/*Z***	Yield (%)
2,4-$(MeO)_2C_6H_3NH_2$	0 °C, 15 s	**c**	1/2.5	95
4-$EtOC_6H_4NH_2$	0 °C, 15 s	**d**	2/1	95
4-$MeC_6H_4NH_2$	20 °C, 1 min	**e**	2.5/1	97
$C_6H_5NH_2$	20 °C, 1 min	**f**	2.5/1	96
4-$NO_2C_6H_4NH_2$	80 °C, 1 h	**g**	4/1	90

* MeCN.
** DMSO-d_6.

Table 3. Characteristics of synthesized aminovinyl ketones **2—5**

Compound	Found / Calculated (%) C	H	Molecular formula	IR, ν/cm^{-1}	^{1}H NMR, δ, *J*/Hz	^{13}C NMR, δ, *J*/Hz
2a*	—	—	—	—	—	179.0 (q, CO, J = 33.8); 155.7,117.1 (q, CF_3, J = 288.6); 88.8
2b*	49.23 / 49.28	6.20 / 6.16	$C_8H_{12}F_3NO$	1590 (C=C); 1655 (C=O)	10.26 (br.s, 1 H, NH); 7.10 (dd, 1 H, =CH—N, J_1 = 7.0, J_2 = 14.1); 5.32 (d, 1 H, =CH—C, J = 7.0); 3.34 (m, 2 H, CH_2—N); 1.60 (m, 2 H, CH_2); 1.40 (m, 2 H, CH_2); 0.94 (m, 3 H, Me)	178.0 (q, CO, J = 33.7); 157.9, 117.2 (q, CF_3, J = 288.5); 86.8, 49.6, 32.5, 19.5, 13.5
2c*	46.83 / 46.93	4.45 / 4.50	$C_7H_8F_3NO$	1592 (C=C); 1653 (C=O)	10.20 (br.s, 1 H, NH); 7.08 (dd, 1 H, =CH—N, J_1 = 7.1, J_2 = 13.5); 5.85 (m, 1 H, =CH); 5.38 (d, 1 H, =CH—C, J = 7.1); 5.25 (m, 2 H, $=CH_2$); 3.92 (m, 2 H, CH_2)	178.5 (q, CO, J = 34.5); 157.8, 117.3 (q, CF_3, J = 288.5); 132.7, 118.4, 87.5, 51.5
2d**	39.30 / 39.35	4.41 / 4.40	$C_6H_8F_3NO_2$	1596 (C=C); 1655 (C=O)	7.18 (dd, 1 H, =CH—N, J_1 = 7.0, J_2 = 13.2); 5.38 (d, 1 H, =CH—C, J = 7.0); 3.79 (m, 2 H, CH_2); 3.48 (m, 2 H, CH_2)	178.5 (q, CO, J = 34.6); 157.8, 117.4 (q, CF_3, J = 288.6); 84.5, 58.7, 51.3
2e*	49.10 / 49.23	6.12 / 6.20	$C_8H_{12}F_3NO$	1590 (C=C); 1655 (C=O)	10.65 (br.s, 1 H, NH); 7.25 (dd, 1 H, =CH—N, J_1 = 7.1, J_2 = 14.0); 5.36 (d, 1 H, =CH—C, J = 7.1); 1.35 (s, 9 H, 3 Me)	177.2 (q, CO, J = 32.9); 153.6, 117.3 (q, CF_3, J = 288.5); 86.7, 53.6, 29.7
3b*	45.80 / 45.94	4.79 / 4.82	$C_8H_{10}F_3NO_2$	1600 (C=C); 1670 (C=O)	7.83 (d, 1 H, =CH—N, J = 12.5); 5.48 (d, 1 H, =CH—C, J = 12.5); 3.67 (m, 4 H, 2 CH_2—O); 3.45 (m, 2 H, 2 CH_2—N); 3.22 (m, 2 H, CH_2—N)	177.6 (q, CO, J = 32.1); 155.0, 117.9 (q, CF_3, J = 291.1); 87.3, 66.7, 65.5, 53.7, 46.1
3d**	42.10 / 42.29	5.21 / 5.32	$C_8H_{12}F_3NO_3$	1610 (C=C); 1677 (C=O)	7.90 (d, 1 H, =CH—N, J = 12.3); 5.41 (d, 1 H, =CH—C, J = 12.3); 4.59 (m, 2 H, CH_2—N); 3.55 (m, 8 H, 3 CH_2 + 2 OH)	174.9 (q, CO, J = 31.1); 157.7, 117.8 (q, CF_3, J = 291.8); 86.2, 59.1, 58.7, 57.4, 51.3
3f*	53.69 / 53.80	7.11 / 7.22	$C_{10}H_{16}F_3NO$	1607 (C=C); 1677 (C=O)	7.98 (d, 1 H, =CH—N, J = 12.4); 5.45 (d, 1 H, =CH—C, J = 12.4); 3.98 (m, 1 H, CH); 3.69 (m, 1 H, CH); 1.27 (m, 12 H, 4 Me)	176.9 (q, CO, J = 32.1); 151.7, 117.9 (q, CF_3, J = 291.2); 87.1, 50.4, 49.1, 23.5, 19.5
4a*	52.06 / 52.18	3.86 / 3.94	$C_{10}H_9F_3N_2O$	1598 (C=C); 1660 (C=O)	11.78 (br.s, 1 H, NH); 7.58 (dd, 1 H, =CH—N, J_1 = 7.2, J_2 = 12.9); 7.08 (m, 2 H, CH arom.); 6.82 (m, 2 H, CH arom.); 5.68 (d, 1 H, =CH—C, J = 7.2); 3.71 (br.s, 2 H, NH_2)	179.1 (q, CO, J = 32.7); 152.1 (=CH—N); 137.7, 127.2, 126.9, 120.1, 118.0, 117.7, 117.2 (q, CF_3, J = 290.0); 90.1

(*to be continued*)

Table 3 (*continue*)

Compound	Found / Calculated (%) C	H	Molecular formula	IR, ν/cm^{-1}	^{1}H NMR, δ, *J*/Hz	^{13}C NMR, δ, *J*/Hz
4b*	49.96 50.01	3.21 3.26	$C_9H_7F_3N_2O$	1595 (C=C); 1656 (C=O)	11.65 (br.s, 1 H, NH); 8.45 (m, 2 H, CH arom.); 7.61 (dd, 1 H, =CH—N, J_1 = 7.6, J_2 = 12.9); 7.44 (m, 1 H, CH arom.); 6.31 (m, 1 H, CH arom.); 5.71 (d, 1 H, =CH—C, *J* = 7.6)	180.1 (q, CO, *J* = 33.7); 149.4, 146.7, 139.7, 135.5, 124.2, 124.2, 117.0 (q, CF_3, *J* = 288.6); 91.3
4c**	52.29 52.37	4.36 4.39	$C_{12}H_{12}F_3NO_3$	1598 (C=C); 1607 (C=C); 1660 (C=O); 1677 (C=O)	12.05 (d, 1 H, NH, *J* = 13.7, *Z*); 10.55 (br.s, 1 H, NH, *E*); 8.21 (br.d, 1 H, =CH—N, *J* = 12.0, *E*); 8.20 (dd, 1 H, =CH—N, J_1 = 7.1, J_2 = 13.7, *Z*); 7.50 (d, 1 H, CH arom., *Z*); 7.29 (d, 1 H, CH arom., *E*); 6.72 (d, 1 H, CH arom., *Z*); 6.68 (d, 1 H, CH arom., *E*); 6.59 (dd, 1 H, CH arom., Z); 6.53 (dd, 1 H, CH arom., *E*); 6.02 (d, 1 H, =CH—C, *J* = 12.0, *E*); 5.61 (d, 1 H, =CH—C, *J* = 7.1, *Z*); 3.93 (s, 3 H, Me, *Z*); 3.88 (s, 3 H, Me, *E*); 3.78 (s, 3 H, Me, *Z*); 3.76 (s, 3 H, Me, *E*)	175.6 (q, CO); 175.5 (q, CO); 156.5, 155.8, 152.2, 149.8, 132.7, 132.1, 119.5, 118.4, 117.2 (q, CF_3); 117.1 (q, CF_3); 115.4, 115.3, 90.9, 88.1, 63.3, 14.6
4d**	55.51 55.60	4.61 4.67	$C_{12}H_{12}F_3NO_2$	1595 (C=C); 1610 (C=C); 1660 (C=O); 1675 (C=O)	11.75 (d, 1 H, NH, *J* = 13.4, *Z*); 10.95 (br.s, 1 H, NH, *E*); 8.30 (br.d, 1 H, =CH—N, *J* = 12.1, *E*); 8.08 (dd, 1 H, =CH—N, J_1 = 7.3, J_2 = 13.4, *Z*); 7.38 (d, 2 H, CH arom., *Z*); 7.22 (d, 2 H, CH arom., *E*); 6.94 (d, 2 H, CH arom., Z); 7.91 (d, 2 H, CH arom., *E*); 5.80 (d, 1 H, =CH—C, *J* = 12.1, *E*); 5.54 (d, 1 H, =CH—C, *J* = 7.3, *Z*); 3.97 (m, 2 H, CH_2, *Z* and *E*); 1.30 (m, 3 H, Me, *Z* and *E*)	175.6 (q, CO); 175.5 (q, CO); 156.5, 155.8, 152.2, 149.8, 132.7, 132.1, 119.5, 118.4, 117.2 (q, CF_3); 117.1 (q, CF_3); 115.4, 115.3, 90.9, 88.1, 63.3, 14.6
4d*	—	—	$C_{12}H_{12}F_3NO_2$	—	7.53 (dd, 1 H, =CH—N, J_1 = 7.3, J_2 = 13.2); 7.04 (d, 2 H, CH arom.); 6.88 (d, 2 H, CH arom.); 5.58 (d, 1 H, =CH—C, *J* = 7.3); 3.99 (q, 2 H, CH_2); 1.39 (t, 3 H, Me)	178.6 (q, CO, *J* = 36.0); 157.1, 150.2, 131.9, 118.9, 115.6, 117.0 (q, CF_3, *J* = 290.0); 89.2, 63.8, 14.7

(*to be continued*)

Table 3 (*continue*)

Compound	Found / Calculated (%) C	H	Molecular formula	IR, ν/cm^{-1}	^{1}H NMR, δ, *J*/Hz	^{13}C NMR, δ, *J*/Hz
4e*	57.51 57.64	4.34 4.40	$C_{11}H_{10}F_3NO$	1596 (C=C); 1607 (C=C); 1662 (C=O); 1676 (C=O)	11.69 (br.d, 1 H, NH, *J* = 13.4, *Z*); 10.99 (br.d, 1 H, NH, *J* = 14.0, *E*); 8.36 (dd, 1 H, =CH—N, J_1 = 12.1, J_2 = 14.0, J_3 = 12.1, *E*); 8.17 (dd, 1 H, =CH—N, J_1 = 7.4, J_2 = 13.4, *Z*); 7.30 (m, 4 H, CH arom., *Z* and *E*); 5.81 (d, 1 H, =CH—C, *J* = 12.1, *E*); 5.57 (d, 1 H, =CH—C, *J* = 7.4, *Z*); 2.28 (s, 3 H, Me, *Z*); 2.27 (s, 3 H, Me, *E*)	170.1 (q, CO); 170.0 (q, CO); 150.8, 148.2, 135.6, 135.1, 133.6, 132.4, 128.8, 128.4, 116.5, 115.4, 117.0 (q, CF_3); 116.9 (q, CF_3); 89.9, 87.0
4f*	55.65 55.82	3.76 3.75	$C_7H_8F_3NO$	1596 (C=C); 1610 (C=C); 1658 (C=O); 1674 (C=O)	11.68 (br.s, 1 H, NH, *Z*); 10.98 (br.s, 1 H, NH, *E*); 8.40 (d, 1 H, =CH—N, *J* = 12.4, *E*); 8.23 (dd, 1 H, =CH—N, J_1 = 7.6, J_2 = 12.9, *Z*); 7.30 (m, 5 H, CH arom., *E* and *Z*); 5.87 (d, 1 H,=CH—C, *J* = 12.4, *E*); 5.61 (d, 1 H, =CH—C, *J* = 7.8, *Z*)	170.1 (q, CO); 170.0 (q, CO); 150.9, 148.6, 145.4, 145.0, 142.8, 142.6, 125.7, 125.4, 118.1, 116.8, 117.0 (q, CF_3); 116.9 (q, CF_3); 94.9, 91.0
4g**	46.02 46.16	2.60 2.71	$C_7H_8F_3NO$	1600 (C=C); 1613 (C=C); 1665 (C=O); 1679 (C=O)	11.55 (br.s, 1 H, NH, *Z*); 11.55 (br.s, 1 H, NH, *E*); 8.49 (d, 1 H, =CH—N, *J* = 12.4, *E*); 8.25 (d, 2 H, CH arom., *Z*); 8.23 (m, 1 H, =CH—N, *Z*); 8.22 (d, 2 H, CH arom., *E*); 7.71 (d, 2 H, CH arom., *Z*); 7.49 (d, 2 H, CH arom., *E*); 6.02 (d, 1 H, =CH—C, *J* = 12.4, *E*); 5.75 (d, 1 H, =CH—C, *J* = 7.8, *Z*)	170.1 (q, CO); 170.0 (q, CO); 150.9, 148.6, 145.4, 145.0, 142.8, 142.6, 125.7, 125.4, 118.1, 116.8, 117.0 (q, CF_3); 116.9 (q, CF_3); 94.9, 91.0
5a**	57.55 57.64	4.34 4.40	$C_{11}H_{10}F_3NO$	1585 (C=C); 1655 (C=O)	8.12 (d, 1 H, =CH—N, *J* = 12.4); 7.38 (m, 5 H, CH arom.); 5.78 (d, 1 H, =CH—C, *J* = 12.4); 3.42 (c, 3 H, Me)	174.7 (q, CO, *J* = 32.1); 152.0, 144.2, 130.2, 125.0, 119.7, 117.4 (q, CF_3, *J* = 290.9); 89.3, 36.3
5b*	59.63 59.75	4.09 4.18	$C_{12}H_{10}F_3NO$	1586 (C=C); 1655 (C=O)	8.41 (d, 1 H, =CH—N, *J* = 12.5); 7.17 (m, 4 H, CH arom.); 5.51 (d, 1 H, =CH—C, *J* = 12.5); 3.92 (m, 2 H, CH_2—N); 3.28 (m, 2 H, CH_2 arom.)	178.0 (q, CO, *J* = 32.0); 144.0, 142.4, 131.9, 128.3, 126.0, 125.0, 117.5 (q, CF_3, *J* = 290.8); 109.0, 91.3, 48.5, 27.5

Note. The IR and ^{1}H NMR spectra of compound **2a** correlate with the published data.[6] The spectral data for compounds **3a** and **3c** are identical to those in Refs. 6 and 7, respectively.

* $CDCl_3$.

** DMSO-d_6.

gated to find out how the electronic structure of ring substituents in amines and the polarity of the solvent influence the ratio of the resulting *E* and *Z* isomers.

Experimental

^1H and ^{13}C NMR were recorded on a Varian VXR-400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ and $(CD_3)_2SO$ with Me_4Si as the internal standard. IR spectra were recorded on a UR-20 spectrometer (Vaseline oil). TLC analysis was carried out on Silufol UV-254 plates; the spots were visualized with an acidified solution of $KMnO_4$ and in iodine vapors.

Synthesis of aminovinyl ketones 2—5 (general procedure). The corresponding amine (2 mmol) was added at ~20 °C to a solution of sulfone **1a**,**b** (1 mmol) in 5 mL of MeCN. The reaction course was monitored by TLC. β-Aminovinyl ketones were isolated by column chromatography on silica gel. The ^1H and ^{13}C NMR and IR data are given in Table 3.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 00-03-32760a).

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Received February 12, 2001;
in revised form April 10, 2001