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Regioselective reactions of *N*-monosubstituted β-aminovinyl trifluoromethyl ketones with tosyl isocyanate

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Abstract

The NH and α-CH insertion reactions of tosyl isocyanate with *N*-monosubstituted 4-amino-1,1,1-trifluorobut-3-en-2-ones have been studied. The regioselectivity of this reaction depends on the temperature, the nature of the solvent and the catalyst: high temperatures or basic catalysts direct in favour of NH insertion while low temperatures direct the process in favour of α-CH insertion.

Keywords: enaminones; insertion reactions; tosyl isocyanate; regiochemistry; ureas.

The introduction of the trifluoromethyl group into organic molecules often confers significant and useful changes in their chemical and physical properties, and therefore methods for the synthesis of trifluoromethylated compounds have received considerable interest in recent years.[1] Though direct trifluoromethylation is the most attractive and powerful tool for constructing trifluoromethylated compounds, trifluoromethyl-containing synthons are often used as accessible and convenient starting reagents.[2] Trifluoroacetyl enamines **1** are accessible trifluoromethyl-containing building blocks[3] for the synthesis of various fluorine-containing substances: dyes,[4] heterocycles,[5] drugs[3a] and for use as protective groups for amino groups in peptide synthesis.[6]

Non-fluorinated enaminones are well known to be useful and are frequently used as synthons in organic synthesis of alicyclic, aromatic and heterocyclic compounds.[7] Due to the high polarity of the C=C bond, reactions of enaminones with various electrophiles are widely used and well studied. The introduction of fluorine atoms in the acyl group of enaminones polarizes the C=C bond much more in comparison with non-fluorinated analogs. However, only a few reports are available on the reactions of fluorinated enaminones with electrophiles. Thus, *N*,*N*-dialkylaminovinyl trifluoromethyl ketones give iminium salts with $POCl_3$[4] and Tf_2O[5f] as a result of the attack on the oxygen atom of the carbonyl group, chemistry that was used for the synthesis of

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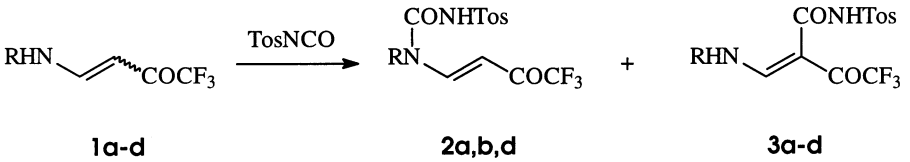
trifluoromethyl-containing dyes and quinolines. *N*,*N*-Dimethylaminovinyl trifluoromethyl ketones have also been trifluoroacetylated at the α-position to the carbonyl group by trifluoroacetic anhydride.[8] At the same time reactions of isocyanates with non-fluorinated *N*,*N*-dialkyl- and *N*-monoalkylenaminones have been used for synthesis of various heterocycles[9] and prospective drugs with hypoglycaemic activity.[10] In this letter we describe the results of our study on TosNCO insertion reactions with *N*-monosubstituted β-aminovinyl trifluoromethyl ketones **1a**–**d**.

We have found that *N*-monosubstituted β-aminovinyl trifluoromethyl ketones **1a**–**d** react with TosNCO not only at the α-carbon atom of the carbon–carbon double bond but also at the nitrogen atom and mixtures of the two products, vinylogous sulphonylureas **3a**–**d** and ureas **2a**,**b**,**d**, are obtained in high yield (Scheme 1). The separation of the reaction products was performed by crystallization.



1a-d **2a,b,d** **3a-d**

1-3	a	b	c	d
R	Me	*n*-Bu	*t*-Bu	Ph

Scheme 1.

Satisfactory analytical data (^{1}H and ^{19}F NMR spectra and elemental analyses)[11] were obtained for the compounds **2a**,**b**,**d** and **3a**–**d**. The double bond of the products **2a**,**b**,**d** has the *E*-configuration: $^3J_{HH} \sim 14$ Hz, a common feature for *N*,*N*-disubstituted enaminones.[12] The urea structure of compounds **2a**,**b**,**d** was also confirmed by disappearance in the ^{1}H NMR spectra of interactions between the NH protons and the olefinic protons at the β-position and the protons of the *N*-alkyl group (for ureas **2a**,**b**). Trifluoromethyl group signals of ureas **2a**,**b** in ^{19}F NMR spectra are slightly shifted upfield at ~1 ppm (−77.0 ppm) relative to the starting enaminones (about −76.1 ppm). On the contrary, the chemical shifts of the trifluoromethyl groups of compounds **3a**–**d** are strongly shifted downfield at ~9 ppm (−67.2 ppm), and in their ^{1}H NMR spectra two downfield signals due to NH protons are observed, one of them having a coupling interaction with the β-vinyl proton. Sometimes a weak coupling interaction ($^5J_{HF} \sim 0.5$ Hz) between the β-vinyl proton and the fluorine atoms of the CF_3 group was observed. This fact allows us to assume that the vinylogous sulphonylureas **3a**–**d** exist in the *Z*-configuration, which is stabilized by two intramolecular hydrogen bonds N–H···O=C, whereas the *E*-isomers contain only one such bond.

The regioselectivity of *N*-tosylcarbomoylation of *N*-monosubstituted β-aminovinyl trifluoromethyl ketones **1a**–**d** depends on several factors (Table 1). First of all, the increase of volume of the *N*-substituent results in difficulties for the insertion reaction at the NH group in the order Me<*n*-Bu≪*tert*-Bu, and moreover, *tert*-Bu-containing enaminone **1c** does not form urea **2c**. Increasing the solvent polarity (replacement of chloroform with acetonitrile) does not change the ratio of products **2** and **3**, but essentially accelerates the reaction rate. The reaction temperature has an influence on the ratio of products **2** and **3** as is demonstrated by the data in Table 2 using the reaction of *N*-methylenaminone **1a** with TosNCO as an example. Decreasing

the temperature results in an increase in the formation of the vinylogous sulphonylureas **3a** which becomes dominant at 0°C and at lower temperatures. However, at elevated temperatures (61°C—boiling chloroform), the reaction results in mixtures of products **2a** and **3a**.

Table 1
Yields and ratio of products **2** and **3**

1–3	R	Combined yield of **2** and **3** (%)	Ratio of **2**/**3** (conversion, %)[a]	
			$CHCl_3$	CH_3CN
a	Me	87	20/80 (97)	25/75 (100)
b	*n*-Bu	90	7/93 (94)	13/88 (100)
c	*t*-Bu	85[b]	0/100 (>99)	0/100 (100)
d	Ph	92	10/90 (100)[c]	5/95 (100)[c]

[a] The reaction time is 1 h.
[b] Yield of **3c.**
[c] The reaction time is 24 h.

Table 2
The influence of temperature on reaction enaminone **1a** with TosNCO

Entry	Temperature (°C)	Time (h)	Conversion (%)	Ratio (%)	
				2a	**3a**
1	−20	48	100	<1	>99
2	0	48	100	<2	>98
3	18	24	100	6	94
4	35	2	95	25	75
5	50	1	95	30	70
6	61	2	87	37	63

The effects of catalysts were studied. Electrophilic catalysts (such as HCl, CF_3CO_2H) did not effect the ratio of products. Nevertheless, the presence of nucleophilic catalysts (such as Py, NEt_3) caused a drastic increase in the percentage of urea **2a**. Use of an equimolar quantity of NEt_3 gave the triethylamine salt of ureas **2a**,**b**,**d** in quantitative yield. However, enaminone **1c** does not give urea **2c** even in the presence of excess NEt_3—we observed only slow formation of vinylogous sulphonylureas **3c**. Pure urea **2a** was obtained from triethylamine salts by acidic workup in modest yields due to their low stability in acid hydrolysis conditions.[6]

In summary, we have found and developed the NH and α-CH insertion reaction of TosNCO into *N*-monosubstituted fluorinated enaminones **1** which is sensitive to reaction conditions: temperature, solvents and catalysts, and affords the highly functionalized trifluoromethyl-containing sulphonylureas **2** and vinylogous sulphonylureas **3**. These fluorinated substances can be utilized as practical building blocks for effective synthesis of bioactive fluorinated compounds.

Typical procedures for the preparation of: (*Z*)-1,1,1-Trifluoro-3-tosylcarbamoyl-4-(*N*-methylamino)but-3-en-2-one (3a). Tosyl isocyanate (0.51 g, 2.6 mmol) was added dropwise to a solution of **1a** (0.44 g, 2.9 mmol) in anhydrous chloroform (5 mL) with stirring at room temperature. After 24 h the solvent was evaporated in vacuo and the residue was treated with

hexane (5×10 mL). The crude product was purified by crystallization from ethanol. The yield of **3a** is 0.72 g (72%).

(*E*)-4-(*N*-Methyl-*N*-tosylamino)-1,1,1-trifluorobut-3-en-2-one (2a). Tosyl isocyanate (0.51 g, 2.6 mmol) was added dropwise to a mixture of **1a** (0.44 g, 2.9 mmol) and Et_3N (0.44 g, 4.3 mmol) in anhydrous chloroform (5 mL) with stirring at −10°C. The reaction mixture was left for 24 h at room temperature and then washed with 5% aqueous solution of citric acid (3×20 mL). The chloroform layer was separated, dried over $MgSO_4$ and concentrated. The crude product **2a** was obtained in 50% yield and 90% purity.

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11. **2a**: mp 36–42°C; ^{1}H NMR ($CDCl_3$) δ: 2.44 (s, 3H), 3.17 (s, 3H), 5.79 (d, 1H, *J* 13.5 Hz), 7.35 (d, 2H, *J* 7.7 Hz), 7.82 (s, 1H), 7.96 (d, 2H, *J* 7.7 Hz), 8.46 (d, 1H, *J* 13.5 Hz). Anal. calcd for $C_{13}H_{13}F_3N_2O_4S$: C, 44.57; H, 3.74; N, 8.00. Found: C, 44.78; H, 3.98; N, 8.36.
3a: mp 118–120°C; ^{1}H NMR ($CDCl_3$) δ: 2.45 (s, 3H), 3.26 (d, 3H, *J* 5.3 Hz), 7.34 (d, 2H, *J* 8.0 Hz), 7.85 (d, 1H, *J* 14.2 Hz), 7.97 (d, 2H, *J* 8.0 Hz), 10.92 (br s, 1H), 11.76 (s, 1H). Anal. calcd for $C_{13}H_{13}F_3N_2O_4S$: C, 44.57; H, 3.74; N, 8.00. Found: C, 44.72; H, 3.90; N, 7.89.
3b: mp 90–91.5°C; ^{1}H NMR ($CDCl_3$) δ: 0.94 (t, 3H, *J* 7.3 Hz), 1.37 (qt, 2H, *J* 7.3 and 7.2 Hz), 1.63 (tt, 2H, *J* 7.2 and 6.7 Hz), 2.44 (s, 3H), 3.42 (dt, 2H, *J* 6.7 and 6.5 Hz), 7.33 (d, 2H, *J* 7.7 Hz), 7.84 (d, 1H, *J* 14.4 Hz), 7.96 (d, 2H, *J* 7.7 Hz), 10.93 (br s, 1H), 11.77 (s, 1H). Anal. calcd for $C_{16}H_{19}F_3N_2O_4S$: C, 48.98; H, 4.88; N, 7.14. Found: C, 49.07; H, 4.94; N, 7.05.
3c: mp 145–147°C; ^{1}H NMR ($CDCl_3$) δ: 1.38 (s, 9H), 2.44 (s, 3H), 7.34 (d, 2H, *J* 8.0 Hz), 7.97 (d, 2H, *J* 8.2 Hz), 7.98 (br d, 1H, *J* 13.8 Hz), 11.14 (br d, 1H, $J \sim 13.8$ Hz), 11.80 (s, 1H). Anal. calcd for $C_{16}H_{19}F_3N_2O_4S$: C, 48.98; H, 4.88; N, 7.14. Found: C, 49.12; H, 4.95; N, 7.02.

3d: mp 165–167°C; ^{1}H NMR ($CDCl_3$) δ: 2.45 (s, 3H), 7.35–7.55 (m, 7H), 8.01 (d, 2H, *J* 8.4 Hz), 8.52 (d, 1H, *J* 13.7 Hz), 11.70 (s, 1H), 12.56 (br d, 1H, $J \sim 13.7$ Hz). Anal. calcd for $C_{18}H_{15}F_3N_2O_4S$: C, 52.43; H, 3.67; N, 6.79. Found: C, 52.56; H, 3.78; N, 6.65.

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