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O-N, S-N AND N-N EXCHANGE REACTIONS AT OLEFINIC CARBON ATOMS: FACILE SYNTHETIC METHOD FOR β-TRIFLUOROACETYLVINYLAMINES

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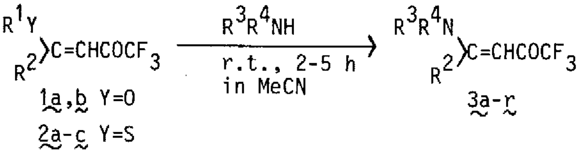
Summary: β-Trifluoroacetylvinyl ethers **1** and sulfides **2** react easily with various amines at room temperature to give β-trifluoroacetylvinylamines **3** in excellent yields. This O-N and S-N exchange reaction can be extended to N-N exchange reaction.

Recently much attention has been paid to the development of new methodologies for the syntheses of many kinds of fluorine-containing heterocycles. These compounds are now widely recognized as important materials having interesting functionalities for use in medicinal and agricultural fields of science.[1-3] The chemistry and potential utility in organic syntheses of β-acylvinylamines are now well recognized and several synthetic methods of them have been described in the literature.[4-6] However, the synthesis of β-acylvinylamines bearing trifluoromethyl group, which are expected to be a useful building block for the synthesis of fluorine-containing heterocycles, has little been reported so far.[7] During our investigations[8] on the electrophilic substitutions at olefinic carbon atoms it was found that vinyl ethers react readily with trifluoroacetic anhydride to give the corresponding β-trifluoroacetylvinyl ethers in high yields. These trifluoroacetylated vinyl ethers would be versatile intermediates for the convenient synthesis of CF_3-containing β-acylvinylamines which are hardly obtainable by other routes.[9] This situation prompted us to investigate the synthesis of the title compounds (**3**) by nucleophilic O-N exchange reaction of β-trifluoroacetylvinyl ethers (**1**) with various amines, together with the relevant S-N and N-N exchange reactions at the olefinic carbon atoms.

β-Trifluoroacetylvinyl ethers **1a**[10] and **1b**[11] were readily prepared by trifluoroacetylation of ethyl vinyl ether and acetone dimethyl acetal, respectively, in almost quantitative yields. On mixing the ethers **1a**,**b** in acetonitrile with ammonia water (28%) at room temperature, there occurred the O-N exchange reaction almost spontaneously as checked by ^{1}H-NMR spectroscopy and β-trifluoroacetylvinylamines **3a**,**k** were obtained in yields over 90% by merely evapolation of the solvent. Similarly, **1** underwent this exchange with various prim- and sec-amines and the results are listed in Table 1. Interestingly, the reaction of **1a** with a large excess of triethylamine at 80 °C gave **3i** in 35% yield, probably formed by the exchange followed by deethylation from the intermediate quarternary ammonium ion.



1a,b Y=O
2a-c Y=S
3a-r

1, 2	R^1	R^2
a	Et	H
b	Me	Me
c	Me	Ph

Table 1. O-N and S-N Exchange Reaction of 1 and 2 with Amines[a]

Substrate[b]	R^3	R^4	Product[c]	Yield[d] (%)	Substrate[b]	R^3	R^4	Product[c]	Yield[d] (%)
1a	H	H	3a	93	1b	i-Pr	H	3m	99
1a	Me	H	3b	99	1b	t-Bu	H	3n	93
1a	Et	H	3c	96	1b	$PhCH_2$	$PhCH_2$	3o	98
1a	i-Pr	H	3d	100	2a	H	H	3a	90
1a	Ph	H	3e	100	2a	Me	H	3b	67
1a	p-$MeOC_6H_4$	H	3f	93	2a	Et	Et	3i	100
1a	p-$NO_2C_6H_4$	H	3g	88	2b	H	H	3k	56
1a	Me	Me	3h	96	2b	Me	H	3l	76
1a	Et	Et	3i	100	2b	$PhCH_2$	$PhCH_2$	3o	68
1a	$-(CH_2)_4-$		3j	100	2c	H	H	3p	88
1b	H	H	3k	93	2c	Me	H	3q	100
1b	Me	H	3l	92	2c	Et	Et	3r	93

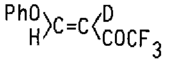
[a] Aqueous solutions of ammonia (28%), methylamine (40%), ethylamine (70%) and dimethylamine (50%) were used.

[b] 1a, trans isomer; 1b,c, either of E or Z isomer (stereochemistry is not determined yet); 2a-c, mixture of the two stereoisomers (the ratios are not fixed in all cases).

[c] 3a-g, cis isomer; 3h-j, trans isomer; 3k-n,p,q, Z isomer; 3o,r, E or Z isomer.

[d] Yield of isolated products.

Attempted reaction of vinyl ether 4 labelled with deuterium with diethylamine gave 3i-β-d without essentially any loss of the deuterium. This result suggests that elimination of phenoxide from intermediate 5 generated by Michael type attack of diethylamine upon 4 is much faster than protonolysis leading to 6.



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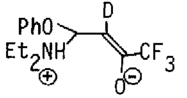

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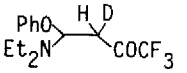

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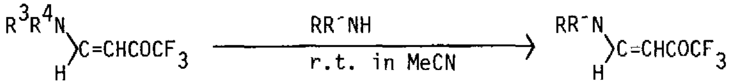
Likewise, β-trifluoroacetylvinyl sulfides 2a-c[12] underwent S-N exchange readily to give the corresponding β-acylvinylamines 3 in excellent yields and the results are shown in Table 1.[13]

This exchange reaction can be extended further to N-N exchange. Carbon-nitrogen bonds are difficult to be cleaved by nucleophiles such as amines and a little is known about nucleophilic N-N exchange reactions.[14] However, in the present system this N-N exchange occurs very readily even at room temperature. For example, β-trifluoroacetylvinylamine 3a reacts with dimethylamine at room temperature in acetonitrile as solvent to give 85% yield of dimethylamino derivative 3h within only 5 min. The amounts of reagent amines used are



$$R^3R^4N(H)C{=}CHCOCF_3 \xrightarrow[\text{r.t. in MeCN}]{RR'NH} RR'N(H)C{=}CHCOCF_3$$

3a,b,h

Table 2. N-N Exchange Reaction of 3a,b,h with Amines

Substrate	Amine[a] (RR' NH)	Molar Ratio[b]	Time (h)	Product	Yield[c] (%)
3a	$MeNH_2$	3	0.5	3b	100
3a	$i\text{-}PrNH_2$	1	0.5	3d	82
3a	$PhNH_2$	1	0.5	3e	95
3a	Me_2NH	3	5 min	3h	85
3a	Et_2NH	3	0.5	3i	100
3a	pyrrolidine	1	0.5	3j	93
3b	NH_3	4	4	-	(100)
3b	pyrrolidine	3	0.5	3j	100
3h	NH_3	6	4	-	(100)
3h	pyrrolidine	3	0.5	3j	100

[a] Aqueous solutions of ammonia (28%), methylamine (40%) and dimethylamine (50%) were used.

[b] [Amine]/[Substrate]

[c] Yield of isolated products. Values in parentheses are the recovery of substrates.

not in large excess and usually 1-3 times molar excess over the substrates is enough. Easiness of this reaction seems to depend on the relative basicities of the leaving and entering amino groups; for example, $(CH_3)_2N$ group can not be replaced by NH_2, but NH_2 can be replaced by $(CH_3)_2N$. These results are summarized in Table 2.

The stereochemistry of β-acylvinylamines 3 was confirmed by ^{1}H-NMR. The small magnitude of the coupling constant $J_{CH=CH}$ (7-8 Hz) and/or the much deshielded peak (8.7-12.4 ppm) of amino protons by hydrogen bonding between NH and C=O show the cis and Z configurations (3a-g, k-n, p, q). The large coupling constant $J_{CH=CH}$ (12 Hz) suggests the trans configuration (3h-j). The signal for β-H or α-CH_3 of 3o,r appeared as a single peak, showing presence of a single stereoisomer.

The present exchange reaction can be extended to use bifunctional nucleophiles and is applicable to the synthesis of various fluorine-containing heterocycles. Further investigations for synthetic utilization of β-acylvinylamines 3 are now in progress and the results will be published elsewhere in our forthcoming papers.

O-N, S-N and N-N Exchange Reactions; Typical Procedure: To a solution of β-acylvinyl ether 1a (1387.3 mg, 8.25 mmol) in MeCN (15 ml) was added 28% ammonia water (652.7 mg, 10.73 mmol). The mixture was stirred at room temperature for 4 h. Removal of the solvent under reduced pressure afforded 1067.2 mg (93% yield) of β-acylvinylamine 3a: bp 120 °C/9 torr (oven temperature); ^{1}H-NMR(δ,$CDCl_3$): 9.80-8.70(br,1H),7.27(dt,1H,J=7,8 Hz),7.00-6.30

(br,1H),5.40(d,1H,J=7 Hz); IR (film,cm^{-1}): ν_{NH} 3370,3210, $\nu_{C=O}$ 1660; Anal (%): Calcd. for $C_4H_4F_3NO$: C;34.54; H,2.90; F,40.98; N,10.07: Found: C,34.68; H,2.92; F,41.43; N,10.26.

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