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Nucleophilic Substitutions at Olefinic Carbon Atoms. S-N and N-N Exchange Reactions of 4-Trifluoroacetyl- and 4,4-Bis(trifluoroacetyl)-1,3-butadienyl Sulfides and -Amines with Various Amines

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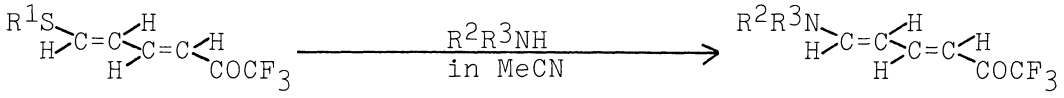
Nucleophilic substitutions at olefinic carbon atoms of 4-trifluoroacetyl- and 4,4-bis(trifluoroacetyl)-1,3-butadienyl sulfides and -amines with various amines proceed easily under mild conditions to give the corresponding S-N and N-N exchanged products.

In the course of our extensive investigations on the nucleophilic substitutions at olefinic carbon atoms, it was found that β-trifluoroacetylvinyl ethers, sulfides and -amines readily undergo O-N,[1c] O-O,[1a] S-N,[1c] and N-N[1c] exchange reactions with various amines and alcohols under mild conditions.[1] As an extension and generalization of these reactions to the vinylogous butadiene systems, we have tried nucleophilic substitutions of 4-trifluoroacetyl- and 4,4-bis(trifluoroacetyl)-1,3-butadienyl sulfides (1, 4) and -amines (2, 5a) with various amines.



1a: R^1=Et, 1b: R^1=n-Pr 2a-f

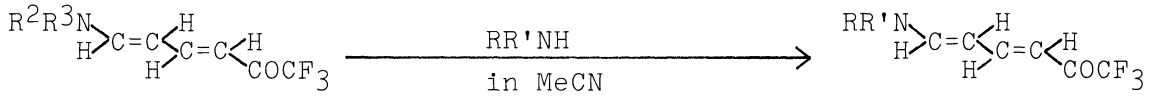
Table 1. S-N Exchange Reaction of 1 with Amines[a]

Run	Substrate	R^2	R^3	Molar ratio[b]	Temp	Time h	Product	Yield[c] %
1	1a	Et	Et	2	r.t.	2	2a	74
2	1a	$PhCH_2$	$PhCH_2$	1	reflux	4	2b	61
3	1a	Ph	Me	1	r.t.	4	2c	84
4	1a	Me	H	2	r.t.	0.5	2d	100[d]
5	1a	i-Pr	H	2	r.t.	2	2e	100[d]
6	1b	p-$MeOC_6H_4$	H	1	r.t.	4	2f	96

a) Aqueous solution of methylamine (40%) was used. b) $[R^2R^3NH]/[1]$. c) Isolated yields. d) 2d and 2e were obtained with small amounts of decomposition products.

In a typical experiment, to a stirred mixture of 4-trifluoroacetyl-1,3-butadienyl sulfide 1a[2] (420 mg, 2 mmol) in acetonitrile (3 cm^3) was added N-methylaniline (214 mg, 2 mmol) at room temperature and the solution was allowed to stand for 4 h. Evaporation and subsequent chromatography on silica gel gave a 84% yield (429 mg) of S-N exchanged product 2c: mp 92-3 °C (recrystallized from hexane/benzene); ^{1}H-NMR (δ, $CDCl_3$): 7.67 (dd, 1H, J=12, 14 Hz), 7.40-6.93 (m, 6H), 6.07 (d, 1H, J=14 Hz), 5.57 (t, 1H, J=12 Hz), 3.32 (s, 3H); IR (KBr): $\nu_{C=O}$ 1683 cm^{-1}; Anal (%): Calcd for $C_{13}H_{12}F_3NO$: C, 61.17; H, 4.74; F, 22.33; N, 5.49: Found: C, 60.96; H, 4.59; F, 22.11; N, 5.40. The results of S-N exchange reaction of 1a,b[2] with amines are summarized and shown in Table 1.

In Table 2 are shown the results for the N-N exchange. Generally fission of C-N bonds of amines by nucleophiles is a very difficult process, especially when the bonds are involved in a conjugate system. In



2g,d,f,k (2k: R^2=i-Pr, R^3=$COCH_3$)

Table 2. N-N Exchange Reaction of 2 with Amines

Run	Substrate	Amine[a] (RR'NH)	Molar ratio[b]	Temp °C	Time h	Product	Yield[c] %	Conversion[d] %
1	2g	Et_2NH	19	r.t.	4	2a	82(17)	83[85]
2	2g	Et_2NH	41	r.t.	22	2a	100(0)	100
3	2g	pyrrolidine	1	r.t.	4	2h	79(21)	79[100]
4	2g	pyrrolidine	10	r.t.	4	2h	100(0)	100
5	2g	piperidine	1	r.t.	4	2i	39(61)	39[52]
6	2g	piperidine	10	r.t.	4	2i	91(9)	91
7	2g	$EtNH_2$	20	r.t.	4	2j	86(14)	86[89]
8	2g	i-$PrNH_2$	20	r.t.	7	2e	68(32)	68[81]
9	2g	p-$MeOC_6H_4NH_2$	1	reflux	4	2f	0(100)	0[27]
10	2d	piperidine	1	r.t.	4	2i	63(34)	65
11	2f	Me_2NH	2	r.t.	1	2g	100(0)	100
12	2k	Et_2NH	2	r.t.	4	2a	86(0)	100
13	2k	i-$PrNH_2$	2	r.t.	4	2e	100(0)	100
14	2k	p-$MeOC_6H_4NH_2$	1	r.t.	4	2f	100(0)	100

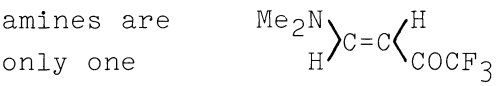
a) Aqueous solution of ethylamine (70%), methylamine (40%) and dimethylamine (50%) were used. b) [Amine]/[Substrate]. c) Yields of N-N exchanged products calculated from ^{1}H-NMR spectra of crude mixtures containing unreacted substrates. Values in parentheses are the yields of recovered substrates. d) Values in brackets are the conversions of 3 into the corresponding N-N exchanged products under the similar conditions to the case of 2g.

fact, very little is known about nucleophilic N-N exchange reaction at olefinic carbon atoms.[1c] However, in the present system most N-N exchanges occurred easily even at room temperature. For example, dimethylamino derivative (2g: R^2=R^3=Me)[3] reacts with 10-41 times molar amounts of secondary amines such as diethylamine, pyrrolidine and piperidine at room temperature for 4 h to afford the corresponding N-N exchanged products (2a,h,i) in 82-100% yields (runs 1,2,4,6 in Table 2). Pyrrolidine showed considerably enhanced reactivity compared with diethylamine and piperidine.

The results in Table 2 show that the easiness of this exchange reaction depends mostly on the relative basicities of entering and leaving amines. In order to ascertain this view, we tried the following N-N exchange reactions. Methylamine is a weaker base than dimethylamine, hence methylamino group would be a better leaving group than dimethylamino group. Expectedly, 2d reacted with an equimolar amount of piperidine to give 2i in 65% conversion (run 10), whereas the reaction of 2g with piperidine resulted in 39% conversion (run 5). The more obviously, p-methoxyphenylamino derivative (2f) underwent much easily the exchange with dimethylamine to give 2g quantitatively (run 11), in striking contrast to the reaction of 2g with p-anisidine in which there occurred no substitution at all even by heating (run 9).

Interestingly, N-isopropylacetylamino group of 2k[4] was replaced much easily at room temperature even by p-anisidine to give 2f quantitatively. These results are in good agreement with our view stated above, showing a weak base such as the amido is an excellent leaving group.

Difference in reactivity of this N-N exchange reaction between the diene system (2g) and the corresponding vinylogous ene system (3),[1c] attracted our interest. Data obtained for this comparison in the N-N exchange of 3 with various amines are shown in the last column of Table 2. With only one exception (Table 2, run 9), the conversions under the same conditions for the diene system (2g) are only 2-21% lower than those for the corresponding ene system (3) (runs 1,3,5, 7,8). It seems surprising and very interesting that in the present N-N exchange reactions at the olefinic carbon atoms the efficiency in transmitting activation effect of trifluoroacetyl group is lowered by just a little bit on changing ene system to diene system.



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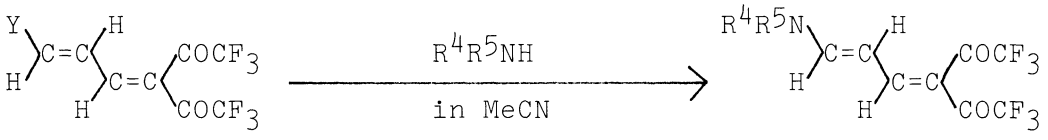
The exchange reaction is also applicable to 4,4-bistrifluoroacetyl derivatives (4[5] and 5a[3]) and the results are listed in Table 3. Expected reactions did proceed quite easily to provide the corresponding 4,4-bis(trifluoroacetyl)-1,3-butadienylamines (5b-g) in high yields. Inter-



4: Y=EtS, 5a: Y=Me_2N 5b-g

Table 3. S-N and N-N Exchange Reactions of 4 and 5a with Amines

Run	Substrate	R^4	R^5	Molar ratio[a]	Temp	Time h	Product	Yield[b] %
1	4	Et	Et	1	r.t.	0.5	5b	98
2	4	$PhCH_2$	$PhCH_2$	1	r.t.	0.5	5c	95
3	4	Ph	Me	1	r.t.	0.5	5d	94
4	4	t-Bu	H	1	r.t.	0.5	5e	84
5	5a	$-(CH_2)_4-$		2	r.t.	4	5f	100
6	5a	$-(CH_2)_5-$		10	r.t.	4	5g	94
7	5a	$PhCH_2$	$PhCH_2$	10	reflux	4	5c	91

a) $[R^4R^5NH]/[4(\text{or } 5a)]$. b) Isolated yields.

estingly, although the reaction of diacyl derivative 4 with bulky t-butylamine afforded acyclic butadienylamine 5e as was the case of monoacyl derivative 1a, the reaction of 4 (or 5a) with less bulky primary amines such as isopropylamine gave 1,2-dihydropyridines by subsequent intramolecular cyclization, in contrast to the case of 1a (or 2g).

The present reaction can be also conveniently used as an alternative and new facile method for the synthesis of various trifluoroacetylbutadienylamines (2, 5).[6]

References

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3) M. Hojo, R. Masuda, and E. Okada, Synthesis, 1990, 425.
4) M. Hojo, R. Masuda, and E. Okada, Tetrahedron Lett., 27, 353 (1986).
5) Compound 4 was prepared from 2-ethoxy-4-isobutoxy-5-trifluoroacetyl-6-trifluoromethyl-3,4-dihydro-2H-pyran (6) with sodium ethanethiolate; M. Hojo, R. Masuda, and E. Okada, submitted to Synthesis.
6) Compounds (2, 5) can be also prepared by ring-opening of 6 with secondary amines followed by deacylation with hydrochloric acid.[3] However, several other compounds (2b-f,j) were hardly obtainable by this method.

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