Facile and Convenient Synthetic Methods for Bis(trifluoroacetyl)ketene *N,O*-, *N,S*- and *S,S*-Acetals and 2,2-Bis(trifluoroacetyl)vinylamines and Sulfides

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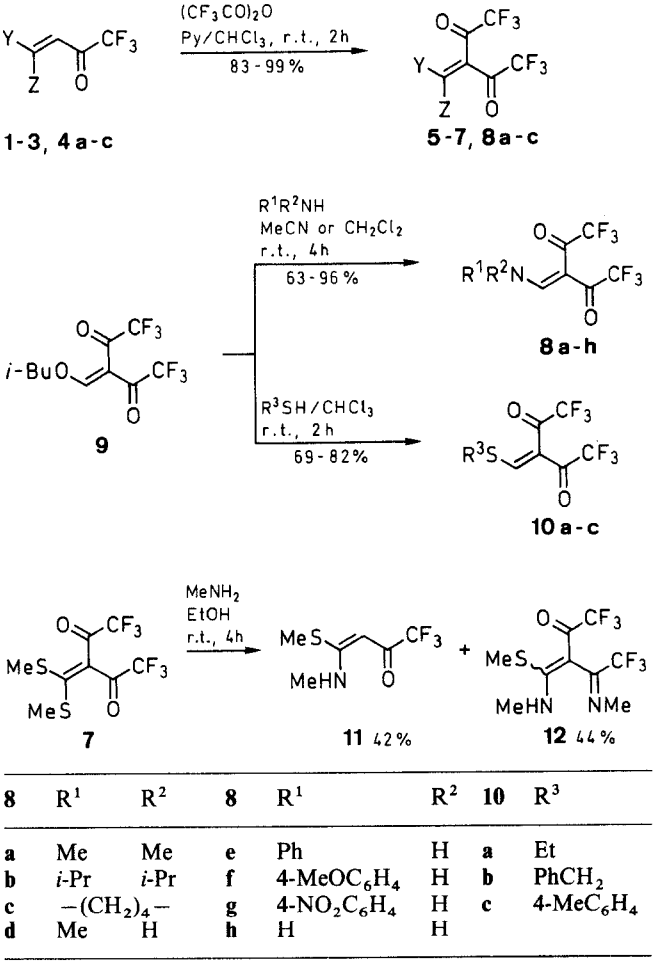
Trifluoroacetylation of (trifluoroacetyl)ketene *N,O*-, *N,S*- and *S,S*-acetals [4-dialkylamino-4-ethoxy(methylthio)-1,1,1-trifluoro-3-buten-2-one and 4,4-bis(methylthio)-1,1,1-trifluoro-3-buten-2-one] gives the corresponding 1,1,1-trifluoro-3-(trifluoroacetyl)-3-buten-2-ones. 4-Amino- and 4-alkyl(aryl)thio-1,1,1-trifluoro-3-(trifluoroacetyl)-3-buten-2-ones are obtained by O–N and O–S exchange reactions of 1,1,1-trifluoro-4-isobutoxy-3-(trifluoroacetyl)-3-buten-2-one with amines and thiols, respectively.

In the course of our extensive investigations on the electrophilic[1–5] and nucleophilic[6–9] substitutions at olefinic carbon atoms, it was found that ketene dithioacetals,[1] vinyl ethers,[2] and orthoacetates[3] react with trifluoroacetic anhydride quite easily to afford the corresponding β-trifluoroacetylated compounds in high yields, and that these acylated compounds cleanly undergo nucleopilic O–N, S–N and then even N–N exchange reactions[7,8] with various nucleophiles under mild conditions. In order to extend and generalize these works, we have tried to synthesize bis(trifluoroacetyl)ketene *N,O*-, *N,S*- and *S,S*-acetals **5–7** and 2,2-bis(trifluoroacetyl)vinylamines **8** and sulfides **10**. Recently, the development of new methodologies for the synthesis of various fluorine-containing heterocycles has received a growing interest, since many kinds of these compounds are now widely recognized as important organic materials exhibiting interesting functionalities for use in medicinal and agricultural science.[10–12] The title compounds **5–8** and **10** could serve as versatile and useful building blocks in the construction of functionalized heterocycles bearing both trifluoromethyl and trifluoroacetyl groups.

With unexpected easiness, the bistrifluoroacetylation of (trifluoroacetyl)ketene *N,O*-, *N,S*- and *S,S*-acetals **1–3**[1,8] occurred cleanly at room temperature with the use of excess trifluoroacetic anhydride in the presence of pyridine to afford bis(trifluoroacetyl)ketene *N,O*-, *N,S*- and *S,S*-acetals **5–7**, respectively, in more than 83% yield (Tables 1, 2). In the case of *S,S*-acetal **3** much longer reaction time (ca. 8 days) was required for completion of



8	R^1	R^2	8	R^1	R^2	10	R^3
a	Me	Me	e	Ph	H	a	Et
b	*i*-Pr	*i*-Pr	f	4-$MeOC_6H_4$	H	b	$PhCH_2$
c	$-(CH_2)_4-$		g	4-$NO_2C_6H_4$	H	c	4-MeC_6H_4
d	Me	H	h	H	H		

Table 1. Acylation of **1–3, 4a–c** with Trifluoroacetic Anhydride

Substrate	Product	Y	Z	Amount $(CF_3CO)_2O$	(equiv) py	Time (h)
1	**5**	Me_2N	EtO	7.0	2.0	2
2	**6**	Et_2N	MeS	4.0	2.0	17
3	**7**	MeS	MeS	7.0	2.0	192
4a	**8a**	Me_2N	H	1.5	1.5	2
4b	**8b**	*i*-Pr_2N	H	1.5	1.5	2
4c	**8c**	1-pyrrolidinyl	H	1.5	1.5	2

the reaction. In contrast, the acylation of *N,N*-dialkyl-2-(trifluoroacetyl)vinylamines **4a–c**[7] proceeded very easily to give the corresponding 2,2-bistrifluoroacetylated compounds **8a–c** in excellent yields. Alternatively, **8a–c** could be obtained by the O–N exchange reaction of 2,2-bis(trifluoroacetyl)vinyl isobutyl ether **9**[5] with appropriate secondary amines. It is worth noting that this O–N exchange method of **9** with primary amines and aqueous ammonia became the sole route to *N*-alkyl (or aryl)-substituted and *N*-unsubstituted 2,2-bis(trifluo-

Table 2. Compounds **5–8** and **10–12** Prepared

Substrate	Product	Yield[a] (%)	mp (°C) (solvent) or bp (°C)/mbar[b]	Molecular Formula[c]	IR (KBr)[d] ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS)[e] δ, J (Hz)
1	**5**	83	115–116 (hexane/benzene)	$C_{10}H_{11}F_6NO_3$ (307.2)	1668, 1640, 1594	1.44 (t, 3H, J = 7, CH_2CH_3), 3.36 (s, 6H, NCH_3), 4.45 (q, 2H, CH_2CH_3)
2	**6**	90	74–75 (benzene)	$C_{11}H_{13}F_6NO_2S$ (337.3)	1640, 1590	1.00–1.70 (m, 6H, CH_2CH_3), 2.55 (s, 3H, SCH_3), 3.60–4.10 (m, 4H, CH_2CH_3)
3	**7**[f]	99	27–30 (hexane)	$C_8H_6F_6O_2S_2$ (312.3)	1733, 1705, 1680	2.62 (s, 6H, CH_3)
4a	**8a**	87	53–54 (benzene)	$C_8H_7F_6NO_2$ (263.1)	1686, 1647, 1600	2.79 (s, 3H, CH_3), 3.47 (s, 3H, CH_3), 7.78 (s, 1H, NCH=)
9		90				
4b	**8b**	85	108–109	$C_{12}H_{15}F_6NO_2$	1710, 1640,	1.28 (d, 6H, J = 6, CH_3), 1.37 (d, 6H,
9		96	(benzene)	(319.2)	1585	J = 6, CH_3), 3.20–4.09 (m, 2H, CH), 7.66 (s, 1H, NCH=)
4c	**8c**	98	89–90 (benzene)	$C_{10}H_9F_6NO_2$	1690, 1645,	1.93–2.50 [br, 4H, NCH_2 $(CH_2)_2$],
9		91		(289.2)	1590	2.67–3.17 (br, 2H, NCH_2), 3.67–4.00 (br, 2H, NCH_2), 7.73 (s, 1H, NCH=)
9	**8d**	77	68–69 ($CHCl_3$)	$C_7H_5F_6NO_2$ (249.1)	3350, 1705, 1640, 1605	3.30 (d, 3H, J = 5, NCH_3), 7.83 (s, 1H, NCH=), 10.09–11.09 (br, 1H, NH)
9	**8e**	63	93–94 (EtOAc)	$C_{12}H_7F_6NO_2$ (311.2)	3400, 1702, 1655, 1621, 1616, 1586	7.33 (br, s, 5H_{arom}), 8.33 (d, 1H, J = 14, NCH=), 11.66–12.66 (br, 1H, NH)[g]
9	**8f**	77	105–106 ($CHCl_3$)	$C_{13}H_9F_6NO_3$ (341.2)	3300–2740, 1693, 1640, 1617, 1605, 1583	3.77 (s, 3H, OCH_3), 6.77–7.30 (m, 4H_{arom}), 8.22 (d, 1H, J = 14, NCH=), 12.00–12.83 (br, 1H, NH)
9	**8g**	96	123–124 (EtOAc)	$C_{12}H_6F_6N_2O_4$ (356.2)	3375, 1707, 1655, 1625, 1587	7.37 (d, J = 9, 2H_{arom}), 8.17 (d, J = 9, 2H_{arom}), 8.30 (d, 1H, J = 12, NCH=), 12.23 (br d, 1H, J = 12, NH)[h]
9	**8h**	82	143–144 (EtOAc)	$C_6H_3F_6NO_2$ (235.1)	3356, 3240, 1650, 1550	7.97 (d, 1H, J = 14, NCH=), 9.00–11.70 (br, 2H, NH_2)[h]
9	**10a**	82	70/1.3	$C_8H_6F_6O_2S$ (280.2)	1705, 1685, 1474[i]	1.45 (t, 3H, J = 7, CH_2CH_3), 3.00 (q, 2H, J = 7, CH_2CH_3), 8.65 (s, 1H, SCH=)
9	**10b**	78	120/1.3	$C_{13}H_8F_6O_2S$ (342.3)	1702, 1680, 1474[i]	4.10 (s, 2H, CH_2), 7.20 (s, 5H_{arom}), 8.63 (s, 1H, SCH=)
9	**10c**	69	59–60 (hexane)	$C_{13}H_8F_6O_2S$ (342.3)	1712, 1676, 1473	2.40 (s, 3H, CH_3), 7.27 (s, 4H_{arom}), 8.80 (s, 1H, SCH=)
7	**11**[8]	42	97–98 (hexane)	$C_6H_8F_3NOS$ (199.2)	3410, 1600, 1575, 1515, 1502	2.45 (s, 3H, SCH_3), 3.08 (d, 3H, J = 6, NCH_3), 5.30 (s, 1H, =CHCO), 10.80–11.80 (br, 1H, NH)
7	**12**	44	69–70 (hexane)	$C_9H_{10}F_6N_2OS$ (308.2)	3425, 1588	2.40 (s, 3H, SCH_3), 3.30–3.40 (m, 6H, NCH_3 and $=NCH_3$), 11.80–12.70 (br, 1H, NH)

[a] Yield of isolated products.
[b] Oven temperature of Kugelrohr distillation.
[c] Satisfactory microanalyses obtained (except for **7**): C ± 0.45, H ± 0.14, N ± 0.31, F ± 0.14; exception: **8a**, F – 0.45: **12**, F + 0.63; **8b, e, g**, F not analyzed.
[d] Recorded on a Hitachi Model EPI-G3 grating spectrophotometer.
[e] Measured using a JEOL PMX-60SI spectrometer.
[f] The structure of **7** was confirmed by its conversion to **11** and **12** by reaction with $MeNH_2$.
[g] In CD_3CN.
[h] In $CD_3CN/CDCl_3$.
[i] Measured as film.

roacetyl)vinylamines **8d–h**, because the acylation of *N*-alkyl (or aryl)-substituted and *N*-unsubstituted 2-(trifluoroacetyl)vinylamines occurred not at the olefinic C-atom but at the nitrogen. Likewise, 2,2-bis(trifluoroacetyl)vinyl sulfides **10a–c** were prepared in fair yields by O–S exchange reaction of **9** with appropriate thiols under mild conditions. In this case, for example, attempted trifluoroacetylation of ethyl 2-(trifluoroacetyl)vinyl sulfide failed even under forced conditions. The diacylation reaction will probably be inhibited by the presence of 2-substituent, the trifluoroacetyl group.[1]

The structure of the new compounds **5, 6, 8, 10** were supported by ^{1}H NMR, IR and microanalyses. However, purification for microanalysis of **7** was difficult. Therefore, the structural assignment was confirmed by its ^{1}H NMR and IR spectra, and further conversion of **7** into **11**[8] and **12** by reaction with methylamine in ethanol at room temperature for 4 hours.

In conclusion, facile and convenient synthetic methods for various bis(trifluoroacetyl)ketene *N,O-*, *N,S-*, *S,S-*acetals, 2,2-bis(trifluoroacetyl)vinylamines and sulfides were established. Further investigations for the synthetic utilization of these new CF_3-containing compounds are currently under way in our laboratory.

4-Dimethylamino-4-ethoxy-1,1,1-trifluoro-3-(trifluoroacetyl)-3-buten-2-one (5); Typical Procedure:

Trifluoroacetic anhydride (16.6 g, 79 mmol) was added dropwise to a stirred solution of **1** (2.39 mg, 11.3 mmol) and pyridine (1.82 g, 23 mmol) in $CHCl_3$ (40 mL) and stirring was continued at r.t. for 2 h. The mixture was washed with aq 10% Na_2CO_3 (300 mL), 2 N HCl (300 mL) and finally H_2O (300 mL), extracted with CH_2Cl_2 (300 mL), and dried (Na_2SO_4). The solvent was evaporated to give diacylketene *N,O*-acetal **5**; yield: 2.88 g (83%).

$C_{10}H_{11}F_6NO_3$	calc.	C 39.10	H 3.61	F 37.11	N 4.56
(307.2)	found	38.82	3.50	37.15	4.79

4-Dimethylamino-1,1,1-trifluoro-3-(trifluoroacetyl)-3-buten-2-one (8a) by O–N Exchange Reaction; Typical Procedure:

To a solution of **9** (2.00 g, 6.85 mmol) in CH_2Cl_2 (15 mL) was added 50% aq Me_2NH (680 mg, 7.54 mmol). The mixture was stirred at r.t. for 4 h. Removal of the solvent under reduced pressure afforded 2,2-diacylvinylamine **8a**; yield: 1.44 g (80%).

$C_8H_7F_6NO_2$	calc.	C 36.52	H 2.68	F 43.33	N 5.32
(263.1)	found	36.14	2.58	42.88	5.01

In the reactions of **9** with aq Me_2NH (50%), $MeNH_2$ (40%) and NH_3 (28%), CH_2Cl_2 was used as a solvent.

4-Ethylthio-1,1,1-trifluoro-3-(trifluoroacetyl)-3-buten-2-one (10a) by O–S Exchange Reaction; Typical Procedure:

To a stirred solution of **9** (2.00 g, 6.85 mmol) in $CHCl_3$ (3 mL) was added EtSH (0.51 mL, 6.83 mmol) and allowed to stand at r.t. for 2 h. The mixture was concentrated and the residue was distilled under reduced pressure to give pure 2,2-diacylvinyl sulfide **10a**; yield: 1.57 g (82%).

$C_8H_6F_6O_2S$	calc.	C 34.29	H 2.16	F 40.68	
(280.2)	found	34.74	2.12	40.71	

Reaction of 4,4-Bis(methylthio)-1,1,1-trifluoro-3-(trifluoroacetyl)-3-buten-2-one (7) with Methylamine:

To a stirred solution of **7** (2.00 g, 6.40 mmol) in EtOH (15 mL) was added dropwise 40% aq $MeNH_2$ (3.98 g, 51.21 mmol) and stirring was continued at r.t. for 4 h. The solvent was removed in vacuo and CH_2Cl_2 (100 mL) was added to the residue. The solution was dried (Na_2SO_4) and concentrated to afford a crude mixture of **11** and **12**, which was chromatographed on a silica gel column (5 × 15 cm; 200 mesh) using EtOAc/MeOH as eluent to give **11** [yield: 535 mg (42%); mp 97–98 °C (Lit.[8] mp 97–98 °C)] and **12** [yield: 868 mg (44%)].

$C_9H_{10}F_6N_2OS$ **(12)**	calc.	C 35.07	H 3.27	F 36.98	N 9.09
(308.2)	found	35.24	3.38	37.61	9.16

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