Facile Synthesis of β-Trifluoroacetylketene *O,N*-, *S,N*- and *N,N*-Acetals

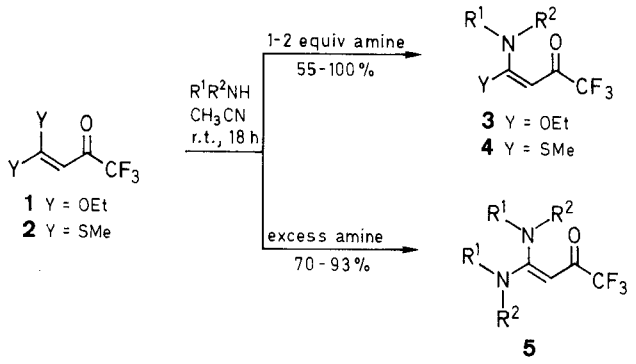
Masaru Hojo,* Ryōichi Masuda, Etsuji Okada, Hiromi Yamamoto, Katsushi Morimoto, Ken Okada
Department of Industrial Chemistry, Faculty of Engineering, Kobe University, Rokkodai, Nada, Kobe 657, Japan

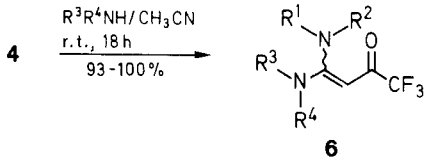
Trifluoroacetylketene *O,N*-, *S,N*- and *N,N*-acetals **3–6** are easily obtained in excellent yields by O–N and S–N exchange reactions of trifluoroacetylketene *O,O*- and *S,S*-acetals **1**, **2** with various amines.

Recently much attention has been paid to the biological activities of fluorine-containing heterocycles because of their potential utility in medicinal and agricultural scientific fields.[1,2] Trifluoroacetylketene *O,N*-, *S,N*- and *N,N*-acetals could serve as versatile building blocks in the construction of functionalized heterocycles bearing trifluoromethyl groups, which are expected to show interesting medicinal activities.[3] During our studies[4] on nucleophilic substitution at olefinic carbon atoms, it was found[5] that β-trifluoroacetylvinyl ethers and sulfides readily react with various amines to give the corresponding β-trifluoroacetylvinyl amines in high yields. These results prompted us to develop a facile synthetic method for various β-trifluoroacetylketene *O,N*-, *S,N*- and *N,N*-acetals **3–6** starting from trifluoroacetylketene *O,O*- and *S,S*-acetals **1**[6] and **2**.[7]

As anticipated the reaction of **1** and **2** with amines proceeded easily at room temperature to give *O,N*- and *S,N*-acetals **3** and **4** in excellent yields. For example trifluoroacetylketene diethylacetal **(1)**, prepared by the reaction of ethyl orthoacetate with trifluoroacetic anhydride, reacted at room temperature with 1–2 mole equivalents of aqueous ammonia (28%) in acetonitrile to afford exclusively the corresponding *O,N*-acetal **3a** in quantitative yields. Formation of any detectable amounts of trifluoroacetylketene *N,N*-acetal **5a** was not observed. Aromatic amines reacted to give the corresponding *O,N*-acetals quantitatively, though considerably less reactive

than aliphatic amines. Analogously, trifluoroacetylketene dimethylthioacetal (**2**) reacted with various amines and afforded the corresponding trifluoroacetylketene *S,N*-acetals **4** (Table 1).





By using a large excess of amine in the present exchange reaction, *O,O*-acetal **1** and *S,S*-acetal **2** could be converted into symmetrical *N,N*-acetals **5** in fair yields (Table 2). The acetals **1** and **2** are much similar in their reactivities in the reactions with ammonia and primary amines. However, in the reactions with secondary amines (e. g., diethylamine), dithioacetal **2** gave cleanly the expected *N,N*-acetal **5e** in high yield (92%), whereas acetal **1** afforded complex reaction mixtures.

Unsymmetrically substituted trifluoroacetylketene *N,N*-acetals **6** could also be prepared successfully by the selective *S–N* exchange reaction of *S,N*-acetals **4** with other differently substituted amines. However, in striking contrast to this, the reaction of *O,N*-acetals **3** with amines gave the corresponding *N,N*, instead of expected *O,N*, exchanged products preferentially.[8]

Generally aminals are very unstable species and difficult to isolate in pure state. However, the present hemiaminals **3**, **4** and aminals **5**, **6** are very stable. For example, aminal **5a** resembles formally urea and is stable in air and also towards heat. It is highly crystalline and melts sharply (Table 2).

Table 1. Synthesis of Trifluoroacetylketene *O,N*- and *S,N*-Acetals **3**, **4** from **1**, **2** and Amines[a]

Product[b]	R^1	R^2	Y	Yield[c] (%)	mp (°C)	Molecular Formula[d]	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
3a	H	H	EtO	~100	76–77	$C_6H_8F_3NO_2$ (183.1)	3250, 3108, 1662, 1608, 1550	1.40 (t, 3H, J = 7, OCH_2CH_3), 4.14 (q, 2H, J = 7, OCH_2CH_3), 5.10 (s, 1H, =CHCO), 5.50–6.60 (br, 1H, NH), 9.00–10.50 (br, 1H, NH)
3b	Me	H	EtO	93	95–96	$C_7H_{10}F_3NO_2$ (197.2)	3180, 1634, 1600, 1548	1.42 (t, 3H, J = 7, OCH_2CH_3), 2.96 (d, 3H, J = 5, NCH_3), 4.19 (q, 2H, J = 7, OCH_2CH_3), 5.10 (s, 1H, =CHCO), 9.90–10.80 (br, 1H, NH)
3c	Me	Me	EtO	~100	–[e]	$C_8H_{12}F_3NO_2$ (211.2)	1685, 1645, 1570[f]	1.35 (t, 3H, J = 7, OCH_2CH_3), 3.11 [s, 6H, $N(CH_3)_2$], 4.30 (q, 2H, J = 7, OCH_2CH_3), 4.80 (s, 1H, =CHCO)
3d	Ph	H	EtO	~100	37–38	$C_{12}H_{12}F_3NO_2$ (259.2)	3150, 1640–1610, 1580, 1535	1.43 (t, 3H, J = 7, OCH_2CH_3), 4.23 (q, 2H, J = 7, OCH_2CH_3), 5.23 (s, 1H, =CHCO), 7.24 (s, 5H_{arom}), 12.00–12.70 (br, 1H, NH)
3e	4-$CH_3C_6H_4$	H	EtO	~100	91–92	$C_{13}H_{14}F_3NO_2$ (273.3)	3140, 1642, 1603, 1577, 1540, 1512	1.45 (t, 3H, J = 7, OCH_2CH_3), 2.33 (s, 3H, $ArCH_3$), 4.30 (q, 2H, J = 7, OCH_2CH_3), 5.30 (s, 1H, =CHCO), 7.19 (s, 4H_{arom}), 12.05–12.65 (br, 1H, NH)
3f	4-$CH_3OC_6H_4$	H	EtO	~100	59–60	$C_{13}H_{14}F_3NO_3$ (289.3)	3120, 1630, 1600, 1575, 1533, 1512	1.43 (t, 3H, J = 7, OCH_2CH_3), 3.80 (s, 3H, OCH_3), 4.23 (q, 2H, OCH_2CH_3), 5.23 (s, 1H, =CHCO), 6.63–7.43 (m, 4H_{arom}), 12.00–12.66 (br, 1H, NH)
3g	4-ClC_6H_4	H	EtO	~100	94–96	$C_{12}H_{11}ClF_3NO_2$ (293.7)	3130, 1638, 1603, 1568, 1539	1.46 (t, 3H, J = 7, OCH_2CH_3), 4.27 (q, 2H, J = 7, OCH_2CH_3), 5.63 (s, 1H, =CHCO), 7.20 (s, 4H_{arom}), 12.23–12.70 (br, 1H, NH)
3h	α-naphthyl	H	EtO	~100	98–100	$C_{16}H_{14}F_3NO_2$ (309.3)	3125, 1637–1582	1.30 (t, 3H, J = 7, OCH_2CH_3), 4.17 (q, 2H, J = 7, OCH_2CH_3), 5.35 (s, 1H, =CHCO), 7.05–8.30 (m, 7H_{arom}), 12.60–12.98 (br, 1H, NH)
3i	β-naphthyl	H	EtO	~100	113–114	$C_{16}H_{14}F_3NO_2$ (309.3)	3130, 1649, 1621, 1602, 1576, 1542	1.42 (t, 3H, J = 7, OCH_2CH_3), 4.23 (q, 2H, J = 7, OCH_2CH_3), 5.28 (s, 1H, =CHCO), 7.10–7.96 (m, 7H_{arom}), 12.38–12.70 (br, 1H, NH)
4a	H	H	MeS	69	136–137	$C_5H_6F_3NOS$ (185.2)	3295, 3140, 1597, 1586, 1518	2.42 (s, 3H, SCH_3), 5.37 (s, 1H, =CHCO), 6.21–7.68 (br, 1H, NH), 9.18–11.01 (br, 1H, NH)

Table 1. (continued)

Product[b]	R^1	R^2	Y	Yield[c] (%)	mp (°C)	Molecular Formula[d]	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
4b	Me	H	MeS	65	97–98	$C_6H_8F_3NOS$ (199.2)	3140, 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)
4c	Et	Et	MeS	96	42–43	–[g]	1630, 1517	1.26 [t, 6H, J = 7, $N(CH_2\underline{CH_3})_2$], 2.54 (s, 3H, SCH_3), 3.65 [q, 4H, J = 7, $N(\underline{CH_2}CH_3)_2$], 5.38 (s, 1H, =CHCO)
4d	$PhCH_2$	H	MeS	55	87–88	$C_{12}H_{12}F_3NOS$ (275.3)	3160, 1598, 1568	2.35 (s, 3H, SCH_3), 4.45 (d, 2H, J = 5, NCH_2), 5.27 (s, 1H, =CHCO), 7.13 (s, $5H_{arom}$), 11.43–12.23 (br, 1H, NH)
4e	Ph	H	MeS	~100	55–56	$C_{11}H_{10}F_3NOS$ (261.3)	3130, 1603, 1589, 1555, 1503	2.42 (s, 3H, SCH_3), 5.53 (s, 1H, =CHCO), 7.33 (s, $5H_{arom}$), 12.41–13.30 (br, 1H, NH)
4f	α-naphthyl	H	MeS	92	106–108	$C_{15}H_{12}F_3NOS$ (311.3)	3125, 1628, 1598, 1590, 1560, 1510	2.30 (s, 3H, SCH_3), 5.59 (s, 1H, =CHCO), 7.09–7.95 (m, $7H_{arom}$), 12.80–13.30 (br, 1H, NH)

[a] Aqueous solution of ammonia (28%), methylamine (40%) or dimethylamine (50%) was used.
[b] **3a**, **b**, **d–i**, **4a**, **b**, **d–f**, *E* isomer; **3c** and **4c**, either of *E* or *Z* isomer.
[c] Yield of isolated products.
[d] Satisfactory microanalyses obtained: C ±0.28, H ±0.19, F ±0.30, N ±0.23; exception, **3d**: F −1.14.
[e] bp 220°C/13 mbar, oven temperature of Kugelrohr distillation.
[f] Measured as film.
[g] The structure of **4c** was confirmed by its conversion to **5e** via S–N exchange reaction with diethylamine.

Table 2. Synthesis of Trifluoroacetylketene *N,N*-Acetals **5**, **6** from **1**, **2**, **4** and Amines[a]

Substrate[b]	Product	R^1	R^2	R^3	R^4	Yield[c] (%)	mp (°C)	Molecular Formula[d]	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
1	**5a**	H	H	–	–	70	136–137	$C_4H_5F_3N_2O$ (154.1)	3440, 3180, 1660, 1648, 1610, 1585	4.94 (s, 1H, =CHCO), 5.96–7.63 (br, 4H, NH)[e]
1	**5b**	Me	H	–	–	92	149–150	$C_6H_9F_3N_2O$ (182.2)	3300, 1620, 1568	2.92 (d, 6H, J = 5, NCH_3), 4.96 (s, 1H, =CHCO), 5.90–6.40 (br, 1H, NH), 10.00–10.50 (br, 1H, NH)
1	**5c**	$-CH_2-$		–	–	93	210–211	$C_6H_7F_3N_2O$ (180.1)	3350, 3120, 1615, 1593, 1545	3.62 (s, 4H, NCH_2), 4.94 (s, 1H, =CHCO), 6.0–9.0 (br, 2H, NH)[e]
2	**5d**	$PhCH_2$	H	–	–	78	126–127	$C_{18}H_{17}F_3N_2O$ (334.3)	3280, 1608, 1600, 1587	4.25 (d, 4H, J = 5, NCH_2), 5.00 (s, 1H, =CHCO), 5.30–5.90 (br, 1H, NH), 7.22 (s, $10H_{arom}$), 10.40–11.25 (br, 1H, NH)
2	**5e**	Et	Et	–	–	92	54–55	$C_{12}H_{21}F_3N_2O$ (266.3)	1627, 1520	1.13 [t, 6H, J = 7, $N(CH_2\underline{CH_3})_2$], 3.28 [q, 4H, J = 7, $N(\underline{CH_2}CH_3)_2$], 4.79 (s, 1H, =CHCO)
4a	**6a**	H	H	Me	H	93	163–164	$C_5H_7F_3N_2O$ (168.1)	3400, 3290, 3150, 1660, 1630, 1520	2.81 (d, 3H, J = 5, NCH_3), 3.80–4.70 (br, 1H, NH), 4.90 (s, 1H, =CHCO), 6.00–7.30 (br, 2H, NH)
4e	**6b**	Ph	H	H	H	~100	143–144	$C_{10}H_9F_3N_2O$ (230.2)	3480, 3150, 1645, 1618, 1590, 1565	5.09 (s, 1H, =CHCO), 5.30–8.30 (br, 2H, NH), 6.94–7.41 (m, $5H_{arom}$), 8.30–11.00 (br, 1H, NH)[e]
4e	**6c**	Ph	H	Me	H	95	156–157	$C_{11}H_{11}F_3N_2O$ (244.2)	3210, 1630, 1610, 1588	2.88 (d, 3H, J = 2, NCH_3), 5.09 (s, 1H, =CHCO), 4.70–5.55 (br, 1H, NH), 7.23–7.32 (m, $5H_{arom}$), 11.55–12.35 (br, 1H, NH)

[a] Aqueous solution of ammonia (28%) or methylamine (40%) was used.
[b] Compounds **6** are either *E* or *Z* isomer.
[c] Yield of isolated products.
[d] Satisfactory microanalyses obtained: C ±0.28, H ±0.18, F ±0.22, N ±0.23; exception, **6b**: C +0.63.
[e] Solvents used; $CDCl_3$/DMSO-d_6 for **5a**: CD_3CN for **5c**: $CDCl_3/CD_3CN$ for **6b**.

The stereochemistry of acylketene *O,N*- and *S,N*-acetals **3, 4** were confirmed by ^{1}H-NMR spectra. The much deshielded peak of amino protons at $\delta = 9.0-13.3$ due to hydrogen bonding between NH and C=O indicates *E* configuration, except for **3c** and **4c**. The signal for olefinic hydrogen of **3c, 4c** and **6** appears as a single peak, respectively, showing the presence of a single stereoisomer in each case. However, their stereochemistry is not defined yet.

Melting points are uncorrected. IR-spectra were measured on a Hitachi Model EPI-G3 grating spectrophotometer.

Trifluoroacetylketene *O,N*-, *S,N*- and *N,N*-Acetals 3, 4 and 5; General Procedure:

To a solution of the ketene acetal **1** or **2** (see Tables 1 and 2, 600 mg, 2.8 mmol) in CH_3CN (9 mL) is added the appropriate amine (2.8–3.8 or 56 mmol, ammonia and volatile amines as aqueous solution). The mixture is stirred at r.t. for 18 h and the solvent is removed under reduced pressure to afford the product (Tables 1 and 2).

Unsymmetrical Trifluoroacetylketene *N,N*-Acetals 6; General Procedure:

To a stirred solution of **4** (3 mmol) in CH_3CN (15 mL) is added the appropriate amine (30 mmol, ammonia and volatile amines as aqueous solution). The mixture is stirred at r.t. for 18 h and evaporated under reduced pressure to give the product (Table 2).

Received: 1 August 1989

(1) Filler, R., in: *Organofluorine Chemicals and Their Industrial Applications*, Banks, R.E. (ed.), Ellis Horwood, London, 1979, p. 123.
(2) *Biomedicinal Aspect of Fluorine Chemistry*, Filler, R.; Kobayashi, Y. (eds.), Kodansha & Elsevier Biomedical, Tokyo, 1982, p. 1.
(3) Unpublished work.
(4) Kamitori, Y.; Hojo, M.; Masuda, R.; Fujitani, T.; Kobuchi, T.; Nishigaki, T. *Synthesis* **1986**, 340.
(5) Hojo, M.; Masuda, R.; Okada, E.; Sakaguchi, S.; Narumiya, H.; Morimoto, K. *Tetrahedron Lett.* **1989**, *30*, 6173.
(6) Hojo, M.; Masuda, R.; Okada, E. *Synthesis* **1986**, 1013.
(7) Hojo, M.; Masuda, R.; Kamitor, Y. *Tetrahedron Lett.* **1976**, 1009.
(8) Further investigations for the N–N exchange reaction of *O,N*-acetals **3** with amines are now in progress in our laboratory and will be published elsewhere in the near future.