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A Useful One-Step Synthesis of β-Trihaloacetylvinyl Ethers and Trihaloacetylketene Acetals

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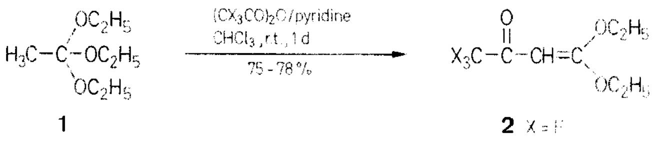
Trifluoro- and trichloroacetylation of ethyl orthoacetate and some methyl ketone acetals affords the corresponding acylketene acetals and α-substituted β-acylvinyl ethers, respectively, in high yields.

We have earlier reported that β-trifluoro- and β-trichloroacetylation of vinyl sulfides[1], ketene dithioacetals[1], vinyl ethers[2], *N*-vinylsulfonamides[2], and *N*-vinylpyrrolidone[2] proceed quite easily to give the corresponding β-acylvinyl compounds in high yields. Further, the reaction of trithioorthoacetates with these trihaloacetylating reagents gave acylketene dithioacetals in high yields under mild conditions[3].

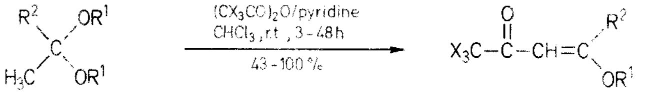
As an extension of this work we tried the trifluoro- and trichloroacetylation of ethyl orthoacetate (**1**) and some methyl ketone acetals (**4**). As anticipated, these reactions proceed quite easily at room temperature to afford the corresponding acylketene acetals (**2**,**3**) and α-substituted β-acylvinyl ethers (**5**,**6**) in high yields.

It has been reported[4] that the reaction of triethyl orthocarboxylates with acetic anhydride give 1,1-diethoxyalkyl acetates, not acetylketene acetals. In contrast, trihaloacetic anhydrides (2 molecular equivalents) react cleanly with ethyl orthoacetate (**1**) in the presence of pyridine at room temperature to give acylketene acetals (**2**, **3**) in high yields. Interestingly, the analogous reaction with trithioorthoacetates is inhibited upon addition of small amounts of pyridine[3]. However, in the present case, the trihaloacetylation of compound **1** proceeds satisfactorily in the presence of pyridine, by the addition of which the formation of resinous material can be completely avoided.



1

2 X = F
3 X = Cl



4a,b

5a,b/6a,b

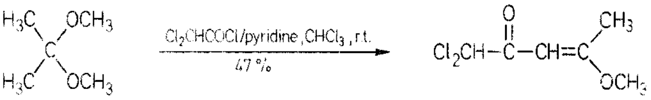
4	R^1	R^2
a	C_2H_5	C_6H_5
b	CH_3	CH_3

	R^1	R^2	X
5a	C_2H_5	C_6H_5	F
5b	CH_3	CH_3	F
6a	C_2H_5	C_6H_5	Cl
6b	CH_3	CH_3	Cl

The formation of compounds **2** and **3** presumably proceeds via ketene diethyl acetal as intermediate which is acylated by the trihaloacetic anhydride. This assumption led us extend the reaction to methyl ketone acetals. In fact, acetals **4a**, **b** reacted cleanly with trihaloacetic anhydrides in the presence of pyridine at room temperature to give the α-substituted β-acylvinyl alkyl ethers **5** or **6** (2-alkoxy-1-alkenyl trihalomethyl ketones) in high yields[5].

Compounds **2**, **3**, **5**, **6** can also be obtained by acylation of ketene diethyl acetal or α-substituted alkyl vinyl ethers[6]. However, both of these starting materials are less readily available than our starting materials **1** and **4** so that our method described here is more convenient.

Under the conditions used by us, acetone dimethyl acetal (**4b**) reacts with dichloroacetyl chloride to give the expected vinyl ether **7** (5,5-dichloro-2-methoxy-2-penten-4-one) in moderate yield, whereas the analogous reaction with chloroacetyl chloride gives only tarry material.

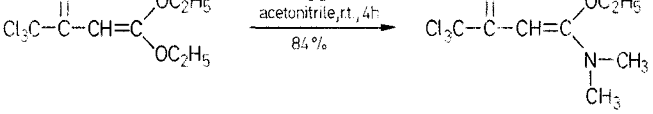


4b

7

The attempted reaction of triethyl orthoacetate (**1**) with dichloroacetyl chloride leads only to the formation of ethyl dichloroacetate.

Compound **3** reacts with dimethylamine to give the trichloroacetylketene *O*,*N*-acetal **8** and compounds **5** and **6** can be utilized for the preparation of the β-acylenamines **9**, **10** (2-amino-1-alkenyl trihalomethyl ketones) via their reaction with primary or secondary amines.



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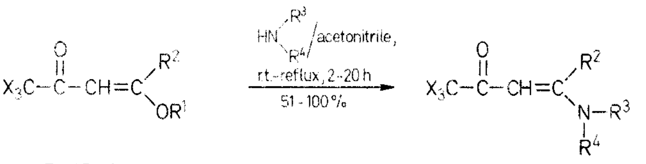
8



5a/6a,b

9a/10a,b

	R^2	R^3	R^4	X
9a	C_6H_5	C_2H_5	C_2H_5	F
10a	C_6H_5	C_6H_5	H	Cl
10b	CH_3	C_6H_5	H	Cl

The reaction of compounds **2**, **3**, **5**, **6** with bifunctional nucleophiles such as hydrazines, hydroxylamine, urea, guanidine, etc. to give heterocyclic compounds is under investigation[6].

Table. Syntheses of Trihaloacetylketene Acetals **2**, **3**, **8**, β-Trihaloacetylvinyl Ethers **5**, **6**, **7**, and β-Trihaloacetylenamines **9**, **10**

Product	Reaction Time [h]	Yield [%]	b.p. [°C][a]/torr or m.p. [°C]	Molecular Formula	IR (film) $\nu_{C=O}$ [cm^{-1}]	^{1}H-NMR (CDCl$_3$) δ [ppm]
2	24	75	b.p. 117–118/14	$C_8H_{11}F_3O_3$[b] (212.2)	1683	4.90 (s, 1H); 4.55–3.90 (m, 4H); 1.88–1.10 (m, 6H)
3	24	78	oil	$C_8H_{11}Cl_3O_3$ (261.5)	1690	5.27 (s, 1H); 4.58–3.98 (m, 4H); 1.78–1.26 (m, 6H)
5a[c]	3	100	b.p. 170/7	$C_{12}H_{11}F_3O_2$ (244.2)	1705	7.41 (s, 5H); 5.78 (s, 1H); 4.15 (q, 2H, J = 7.2 Hz); 1.45 (t, 3H, J = 7.2 Hz)
6a[d]	3	87	b.p. 250/9	$C_{12}H_{11}Cl_3O_2$ (293.6)	1690	7.37 (s, 5H); 6.11 (s, 1H); 4.09 (q, 2H, J = 7.2 Hz); 1.39 (t, 3H, J = 7.2 Hz)
5b	4	94	b.p. 68/20	$C_6H_7F_3O_2$[b] (168.1)	1700	5.69 (s, 1H); 3.80 (s, 3H); 2.41 (s, 3H)
6b[e]	48	43	b.p. 101/9	$C_6H_7Cl_3O_2$ (217.5)	1700	5.95 (s, 1H); 3.77 (s, 3H); 2.36 (s, 3H)
7	2	47	b.p. 80/9	$C_6H_8Cl_2O_2$ (183.0)	1670	5.77 (s, 1H); 5.73 (s. 1H); 3.73 (s, 3H); 2.33 (s, 3H)
8	4	84	b.p. 230/10	$C_8H_{12}Cl_3NO_2$[b] (260.5)	1650	5.20 (s, 1H); 4.26 (q, 2H, J = 7.2 Hz); 3.05 (s, 6H); 1.38 (t, 3H, J = 7.2 Hz)
9a	2	100	m.p. 93–94	$C_{14}H_{16}F_3NO$[b] (271.3)	1655	7.70–7.00 (m, 5H); 5.43 (s, 1H); 3.80–2.80 (br., 4H); 1.80–0.80 (br., 6H)
10a	16[f]	51	m.p. 120–121	$C_{16}H_{12}Cl_3NO$[b] (340.6)	1600	12.01 (br., 1H); 7.17–6.50 (m, 10H); 5.93 (s, 1H)
10b	20	95	m.p. 91–92	$C_{11}H_{10}Cl_3NO$[b] (278.6)	1620	12.50–11.80 (br., 1H); 7.23 (d, 5H); 5.85 (s, 1H); 2.15 (s, 3H)

[a] Oven temperature.

[b] Satisfactory microanalyses: C ±0.23, H ±0.14, F ±0.23.

[c] The structure of **5a** was confirmed by conversion of **5a** into **9a** by reaction with diethylamine in acetonitrile at room temperature (2 h)[6].

[d] Obtained by reaction of **4a** with trichloroacetyl chloride in place of the anhydride. The structure of **6a** was confirmed by conversion of **6a** into **10a** by reaction with aniline in boiling acetonitrile (16 h)[6].

[e] The structure of **6b** was confirmed by conversion of **6b** into **10b** by reaction with aniline in acetonitrile at room temperature (20 h)[6].

[f] In boiling acetonitrile.

Trifluoroacetylketene Diethyl Acetal (2); Typical Procedure:

To a stirred solution of ethyl orthoacetate (**1**; 4.878 g, 30.07 mmol) and pyridine (5.442 g, 68.79 mmol) in chloroform (30 ml) is added dropwise, with cooling, trifluoroacetic anhydride (12.823 g, 61.05 mmol) and the mixture is stirred at room temperature for 1 day. It is then washed quickly with ice-cold aqueous 10% sodium carbonate (50 ml), and finally with water (2 × 50 ml), and is dried with sodium sulfate. The solvent and pyridine is removed in vacuo to give product **2** as an oil; yield: 4.76 g (74%). The product is essentially pure according to ^{1}H-NMR analysis. Distillation under reduced pressure affords the pure product **2**; b.p. 111 °C/12 torr.

1-Ethoxy-4,4,4-trifluoro-1-phenyl-1-buten-3-one (β-Acylvinyl Ether 5a); Typical Procedure:

To an ice-cold stirred mixture of acetophenone diethyl acetal (**4a**, prepared from acetophenone and triethyl orthoformate; 4.00 g, 20.6 mmol), pyridine (3.259 g, 41.2 mmol), and chloroform (5 ml) is added dropwise a solution of trifluoroacetic anhydride (8.436 g, 41.2 mmol) in chloroform (5 ml) and the mixture is stirred for 3 h at room temperature. Then, ice water (20 ml) is added and the mixture is extracted with dichloromethane (50 ml). The dichloromethane extract is washed with 2 normal hydrochloric acid (20 ml), aqueous 10% sodium carbonate (30 ml), and water (2 × 30 ml), and is dried with sodium sulfate. The solvent is evaporated to give the practically pure (^{1}H-NMR) product **5a**; yield: 5.02 g (~100%). The pure product **5a** is obtained by distillation under reduced pressure; b.p. 170 °C/7 torr.

Trichloroacetylketene *O*-Ethyl-*N*,*N*-dimethyl *O*,*N*-Acetal (4,4,4-Trichloro-1-ethoxy-1-dimethylamino-3-oxo-1-butene, 8); Typical Procedure:

To a stirred solution of trichloroacetylketene diethyl acetal (**3**; 300 mg, 1.41 mmol) in acetonitrile (5 ml) is added dropwise aqueous 40% dimethylamine solution (635.7 mg, 5.65 mmol) and stirring is continued for 4 h at room temperature. The solvent is then removed in vacuum and dichloromethane (10 ml) is added to the residue. This solution is washed with water (2 × 20 ml), dried with sodium sulfate, and evaporated to give the practically pure product **8** as an oil; yield: 312.5 mg (84%); b.p. 230 °C/10 torr.

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[4] Post, H.W., Erickson, E.R. *J. Org. Chem.* **1937**, *2*, 260.

[5] In connection with the present investigation it should be mentioned that the reaction of a few 3,3-dialkoxysteroids (acetals of steroidal 3-ketones) with acetic anhydride in the presence of boron trifluoride gave the corresponding 2-acetylated enol ethers together with other products: Youssefyeh, R.D. *J. Am. Chem. Soc.* **1963**, *85*, 3901.
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[6] Hojo, M., Masuda, R., unpublished results.