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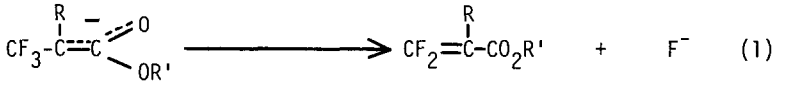
(TRIFLUOROMETHYL)KETENE SILYL ACETAL AS AN EQUIVALENT TO THE TRIFLUOROPROPIONIC ESTER ENOLATE: PREPARATION AND ALDOL-TYPE REACTIONS WITH ACETALS

Tsutomu YOKOZAWA, Takeshi NAKAI,* and Nobuo ISHIKAWA

Department of Chemical Technology, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

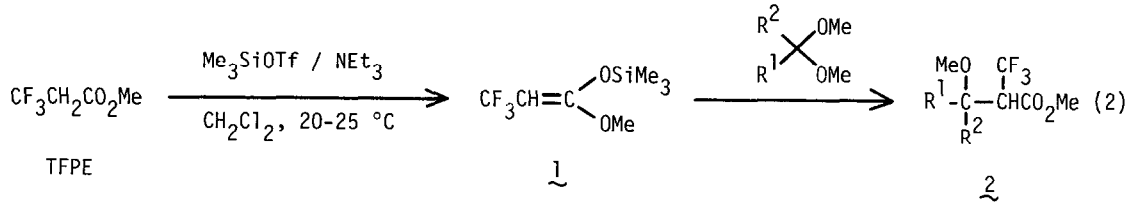
SUMMARY: The title reagent, readily prepared from methyl β,β,β-trifluoropropionate with trimethylsilyl triflate, is shown to react with a broad variety of acetals to provide the corresponding α-CF_3 β-alkoxy esters in good yields.

In view of the central role of enolate chemistry in organic synthesis, α-trifluoromethyl (CF_3)-ester enolate should serve as an extremely versatile building block for otherwise difficult preparations of a wide variety of α-CF_3 esters,[1] a class of compounds which have received much interest because of their possible biological activities.[2] However, no study has been reported on the generation and synthetic utilization of any α-CF_3-ester enolates (or the equivalents) except for our recent work on α-CF_3 malonates[3] mainly because such enolates are anticipated to undergo extremely facile defluorination prior to trapping (eq 1). In fact,



(1)

we observed complete defluorination in the reaction of methyl β,β,β-trifluoropropionate (TFPE)[4] with lithium diisopropylamide in THF at -78 °C. Herein we wish to report the successful preparation of the ketene silyl acetal (1) from TFPE and demonstrate its synthetic potential as an α-CF_3-ester enolate equivalent in the aldol-type reaction with acetals which permits ready access to a broad variety of α-CF_3 β-methoxy esters (2) (eq 2).



(2)

TFPE 1 2

First of all, we found that the transformation of TFPE into the ketene silyl acetal 1 was best carried out by using trimethylsilyl triflate/triethylamine system without an appreciable extent of defluorination.[5,6] Thus, TFPE was treated with Me_3SiOTf (1.1 equiv) and triethylamine (1.1 equiv) in dichloromethane at room temperature for 18 h to give 1 in 92% yield (^{19}F NMR assay). The E/Z ratio for 1 was found to be 1 : 4 by NMR analysis.[7] The exclusive O-silylation on TFPE is in stark contrast to the C-silylation in preference to O-silylation (9 : 1) reported for a similar reaction of methyl propionate.[8] The ketene silyl acetal 1 is thermally less stable than the non-fluorinated counterpart and gradually decomposes over 50 °C to produce methyl β,β-difluoroacrylate; however, 1 can be isolated by careful distillation under reduced pressure at lower than 50 °C.

In order to demonstrate the synthetic utility of 1 as an α-CF_3-ester enolate equivalent, we first attempted the reaction with acetals since non-fluorinated ketene silyl acetals (and silyl enol ethers) are known to react well with acetals under the catalysis of Me_3SiOTf.[5a] Thus, the ketene acetal 1, prepared *in situ* from TFPE with a little excess of Me_3SiOTf (1.2 equiv), was allowed to react with a dimethyl acetal at -78 °C for 4.5 - 9 h. Usual workup afforded the corresponding α-CF_3 β-methoxy ester (2) in good yields (Table 1).

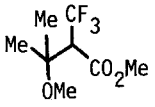
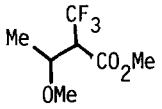
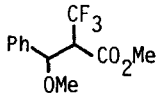
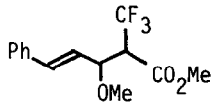
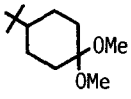
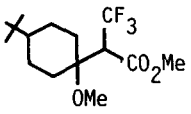
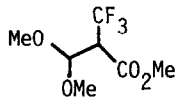
Inspection of the results in the table reveals some characteristic features of the reactivity of 1. (1) The ketene acetal 1 is quite reactive toward a broad variety of acetals including the orthoformate (entry 6). (2) The observed levels of diastereoselection are very low (entries 2-4) in analogy with the low stereoselectivities reported for similar reactions of the non-fluorinated counterpart.[5a] (3) The reaction with 4-*t*-butylcyclohexanone acetal afforded the single diastereomer (entry 5), althouh the stereochemistry has not been assigned yet.

Entry 4 deserves a special comment. Erythro-2d easily separated via column chromatography could serve as a key intermediate for synthesis of the trifluoro analogue (4) of antibiotic oudemansin (5) since the non-fluorinated counterpart (3) has been used as the key intermediate by Oishi and co-workers for their total synthesis of (±)-5.[9]

2d, X=F
3, X=H

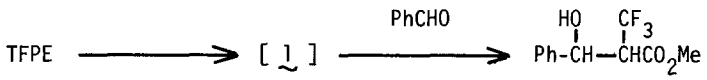
4, X=F
5, X=H (oudemansin)

Table 1. Reactions of 1 with Acetals

Entry	Acetal	Product[a]	^{19}F NMR[b] δ, ppm (J, Hz)	%yield[c] (diastereomeric ratio)[d]
1	$Me_2C(OMe)_2$		-16.1 (9.3)	74
2	$MeCH(OMe)_2$		-13.8 (7.7) -13.9 (9.8)	81 (55 : 45)
3	$PhCH(OMe)_2$		-14.1 (8.0) -14.4 (8.0)	89 (67 : 33)
4	(E)-PhCH=CHCH(OMe)$_2$		-14.0 (7.0) -14.1 (7.0)	92 (55 : 45)
5			-17.4 (9.8)	82 (100 : 0)
6	$HC(OMe)_3$		-13.4 (7.9)	76

[a] All products exhibited spectral (NMR and IR) data in accord with the assigned structures. [b] Measured in carbon tetrachloride by using trifluoroacetic acid as external standard. [c] Isolated yields based on TFPE. [d] Determined by ^{19}F NMR analysis

Finally, we found that a similar reaction of 1 with benzaldehyde instead of an acetal gave a diastereomeric mixture (60 : 40) of the α-CF_3 β-hydroxy ester 6 in 93% yield.[10] Surprisingly, however, aliphatic aldehyde did not react with 1 under similar conditions but



6

TFPE was largely recovered. Furthermore, an attempted reaction of 1 with propanal in the presence of titanium(IV) chloride resulted in a considerable extent of defluorination in contrast to the high-yild formation of the aldol adduct reported for similar reactions with non-fluorinated analogs.[11] Further efforts are in progress to expand the sythetic potential of 1.

References and Notes

1. Only a few synthetic methods have been reported for a limited number of α-CF_3 esters: (a) methyl trifluoropropionate (TFPE): N. P. Aktaev, O. G. Eremin, G. A. Sokol'skii, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1977, 1117; (b) cyclohexyl trifluoropropionate: C. Wakselman and M. Tordeux, *J. Fluorine Chem.*, 21, 99 (1982); (c) ethyl α-CF_3-hexanoate: G. W. Holland, J. L. Jernow, and P. Rosen, U. S. Pat., 1980, No. 4,187,381; (d) ethyl α-CF_3-alkanoates: S. T. Purrington, T. S. Everett, and C. L. Bumgardner, *Tetrahedron Lett.*, 25, 1329 (1984).

2. For general discussions of the biological activities of partially fluorinated compounds, see: Ciba Foundation, "Carbon-Fluorine Chemistry, Biochemistry and Biological Activities," Elsevier, Amsterdam (1972); "Biochemistry Involving Carbon-Fluorine Bonds," ed. by R. Filler American Chemical Society, Washington, D. C. (1976).

3. N. Ishikawa and T. Yokozawa, *Bull. Chem. Soc. Jpn.*, 56, 724 (1983).

4. TFPE was prepared in 70% overall yield from 1,1,3,3,3-pentafluoro-2-(trifluoromethyl)-propyl methyl ether manufactured in large quantity according to the combination of Knunyants' (ref 1a) and England's procedure: D. C. England, L. Solomon, and C. G. Krespan, *J. Fluorine Chem.*, 3, 63 (1973/74).

5. For reviews on the synthetic utility of trimethylsilyl triflate, see: (a) R. Noyori, S. Murata, and M. Suzuki, *Tetrahedron*, 37, 3899 (1981); (b) H. Emde, D. Domsch, H. Feger, U. Frick, A. Götz, H. H. Hergott, K. Hofmann, W. Kober, K. Krägeloh, T. Oesterle, W. Steppan, W. West, and G. Simchen, *Synthesis*, 1982, 1.

6. The use of Me_3SiCl in place of Me_3SiOTf did not produce 1 at all.

7. ^{19}F NMR (CCl_4, ext. CF_3COOH), δ -23.9 (d, J=7.6 Hz) for the (E)-isomer and -24.2 (d, J=7.1 Hz) for the (Z)-isomer; ^1H NMR (CCl_4, TMS), δ 0.24 and 0.32 (2s, Me-Si) and 3.61 and 3.67 (2s, Me-O), 3.90 (J=7.6 Hz) and 3.96 (J=7.1 Hz) (2q, olefinic protons).

8. H. Emde and G. Simchen, *Synthesis*, 1977, 867.

9. T. Nakata, T. Kuwabara, Y. Tani, and T. Oishi, *Tetrahedron Lett.*, 23, 1015 (1982).

10. ^{19}F NMR (CCl_4, ext. CF_3COOH), δ -14.0 (d, J=7.8 Hz) for the major isomer and -13.4 (d, J=7.8 Hz) for the minor isomer.

11. K. Saigo, M. Osaki, and T. Mukaiyama, *Chem. Lett.*, 1975, 989.

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