Tetrahedron Letters,Vol.25,No.36,pp 3991-3994,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain 

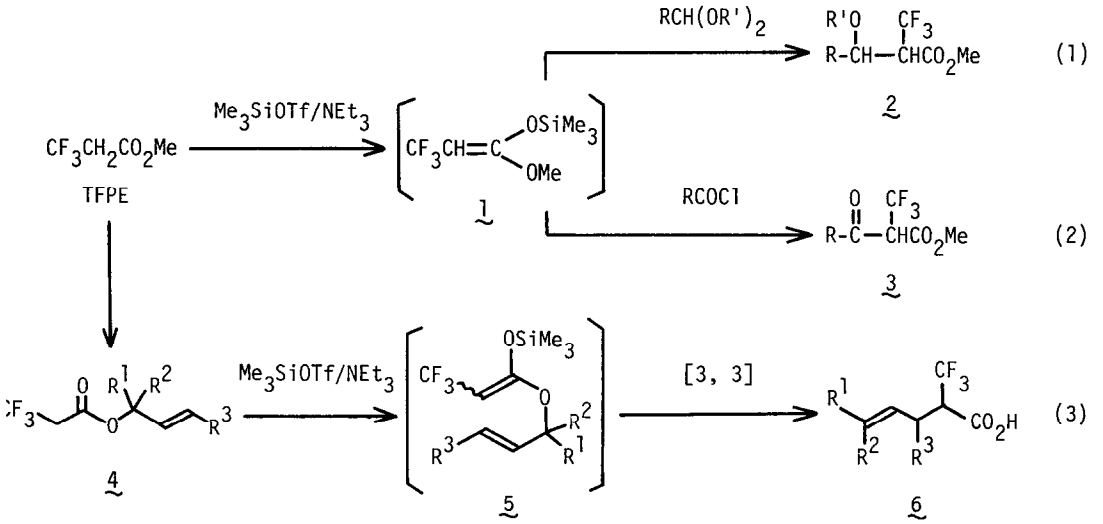
# ALPHA-ACYLATION AND -ALLYLATION OF β,β,β-TRIFLUOROPROPIONIC ESTERS VIA THE KETENE SILYL ACETALS

Tsutomu YOKOZAWA, Takeshi NAKAI,* and Nobuo ISHIKAWA

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

SUMMARY: α-Acylation of the ketene silyl acetal of methyl β,β,β-trifluoropropionate and α-allylation via the ester enolate Claisen rearrangement of the 2-alkenyl trifluoropropionates are described which provide the corresponding α-$CF_3$ β-ketoesters and α-$CF_3$ γ,δ-unsaturated acids, respectively.

In the preceding paper we reported the facile preparation of the ketene silyl acetal (1) of methyl β,β,β-trifluoropropionate (TFPE) and the *in situ* reaction with acetals (eq 1).[1] To expand further the synthetic potential of (trifluoromethyl)ketene silyl acetals as α-$CF_3$-ester enolate equivalents, our efforts have now been directed toward α-acylation and -alkylation of the trifluoropropionic esters via the ketene silyl acetals. Herein we wish to report the α-acylation of the TFPE-derived silyl acetal (1) leading to the α-$CF_3$ β-ketoesters 3 (eq 2) and also the α-allylation via the ester enolate Claisen rearrangement of the 2-alkenyl trifluoropropionates (4) providing the α-$CF_3$ γ,δ-unsaturated acids 6 (eq 3).



First, we carried out reactions of acid chlorides with the ketene silyl acetal (1) prepared in situ from TFPE as described in the preceding paper.[1] Propanoyl and pentanoyl chloride reacted at room temperture without any catalyst to afford the corresponding α-$CF_3$ β-ketoester (3) in 53% and 58% of isolated yields, respectively.[2] Surprisingly, however, neither of acetyl, benzoyl, nor N,N-dimethylcarbamoyl chloride reacted under similar conditios. After many attempts, we found that addition of zinc bromide (1.0 equiv) efficiently facilitated the reaction with acetyl chloride to give the ketoester 3 (R=$CH_3$) in 52% of isolated yield.[3,4]

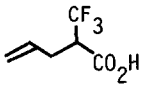
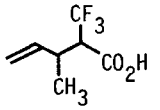
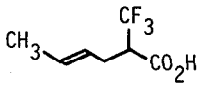
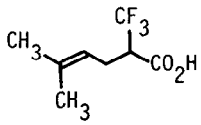
Second, we studied alkylation of 1 with various types of alkyl halides including chloromethyl ethers and allylic bromides under the catalysis of $ZnBr_2$.[5] We found that chloromethyl ethyl ether reacted with 1[6] at 20-25 °C for 6 h in the presence of $ZnBr_2$ (0.1 equiv) to give 2 (R=H, R'=Et)[7] in 85% yield.[8] However, neither of allyl nor prenyl bromide reacted under similar or enforced conditions.[9]

Third, we studied an entirely different approach to the α-allylation concerned, which relied upon the ester enolate Claisen rearrangement[10] of the 2-alkenyl trifluoropropionate (4) (eq 3). The requisite substrate 4 was readily obtained from the trifluoropropionic acid (TFPA)[11] and an allylic alcohol according to the literature procedure.[12] Thus, TFPA and an allylic alcohol were refluxed in dichloromethane for 3-6 h in the presence of N-methyl-2-chloropyridinium iodide and triethylamine to give the corresponding ester 4 in 79-94% of distilled yields.[13] The rearrangement of 4 was carried out by adding an equimolar mixture of trimethylsilyl triflate and triethylamine in dichloromethane at 20-25 °C, stirring for 2 h, and refluxing for 5-12 h. Quenching of the reaction mixture with hydrochloric acid followed by usual workup afforded the rearrangement product 6 in good yields (Table 1).

As be seen from the table, the easiness of this particular Claisen variant depends markedly upon the alkyl-substitution pattern on the allylic moiety (entry 1 vs. 2).[14] The observed stereochemistry is also worth noting. As expected, the rearrangement proceeds with a very high E selectivity (entry 3), while the diastereoselectivity is very low (entry 2) mainly because the enolization/silylation process under the present conditions leads to a mixture of the (E)- and (Z)-ketene silyl acetal 5.[15]

Finally, the general reactivity of the (trifluoromethyl)ketene silyl acetals (1 or 5)

Table 1. The Claisen Rearrangement of 4

| Entry | Substrate | Conditions | Product[a] | $^{19}$F NMR[b] δ, ppm (J, Hz) | %yield[c] (stereoisomeric ratio) |
|---|---|---|---|---|---|
| 1 | 4a ($R^1$, $R^2$, $R^3$=H) | Refl., 12 h |  | -10.4 (7.9) | 74 |
| 2 | 4b ($R^1$, $R^2$=H, $R^3$=$CH_3$) | Refl., 6 h |  | -13.8 (7.9)<br>-13.9 (7.9) | 84<br>( 72 : 28 )[d] |
| 3 | 4c ($R^1$=$CH_3$, $R^2$, $R^3$=H) | R. T., 24 h |  | -10.1 (7.9) | 100<br>( 95 : 5 )[e] |
| 4 | 4d ($R^1$, $R^2$=$CH_3$, $R^3$=H) | Refl., 5 h |  | -14.4 (7.5) | 15[f] |

[a] All products exhibited spectral (NMR and IR) data in accord with the assigned structures. [b] Measured in chloroform-d by using trifluoroacetic acid as external standard. [c] Isolated yields based on 4. [d] Refers to the diastereomeric ratio determined by $^{19}$F NMR analysis. [e] Refers to the E/Z ratio determined by $^{13}$C NMR analysis. [f] By $^{19}$F NMR assay.

relative to that of the non-fluorinated analogs should be noted on the basis of the results outlined in the present and preceding papers. Generally speaking, the reactivity of the fluorinated one is very tricky; the fluorinated one is much less reactive than the non-fluorinated one as found in the reactions with some of aldehydes, allylic bromides, and acid chloride, while the former shows essentially the same reactivity as that of the latter as observed in the reactions with acetals and the Claisen process.

In summary, the present work coupled with the preceding one convincingly demonstrates that (trifluoromethyl)ketene silyl acetals are quite useful for otherwise difficult preparations of a broad variety of α-$CF_3$ acid derivatives with different additional functionalities.

References and Notes


1. T. Yokozawa, T. Nakai, and N. Ishikawa, the preceding paper.

2. 3 (R=$C_2H_5$): IR (neat), 1730, 1760 $cm^{-1}$; $^{19}F$ NMR ($CCl_4$, ext. $CF_3COOH$(TFA)), δ -14.9 (d, J= 8.7 Hz); 3 (R=n-$C_4H_9$): IR (neat), 1735, 1765 $cm^{-1}$; $^{19}F$ NMR ($CCl_4$, ext. TFA), δ -14.1 (d, J=8.8 Hz).

3. 3 (R=$CH_3$): IR (neat), 1730, 1760 $cm^{-1}$; $^{19}F$ NMR ($CCl_4$, ext. TFA), δ -14.4 (d, J=8.8 Hz).

4. An attempted reaction with AcCl in the presence of $SnCl_4$ (1.0 equiv) led to a considerable extent of defluoronation. For the use of $SnCl_4$ in the acylation of a certain ketene silyl acetal, see: A. Wissner, *Tetrahedron Lett.*, 1978, 2749.

5. For the catalysis of $ZnBr_2$ in similar reactions of silyl dienol ethers, see: I. Fleming, J. Goldhill, and I. Paterson, *Tetrahedron Lett.*, 34, 3209 (1979).

6. This reaction was carried out after separation of 1 from the ammonium triflate via distillation; otherwise, a lower yield (40%) was obtained.

7. $^{19}F$ NMR (neat, ext. TFA), δ -11.4 (d, J=7.3 Hz).

8. A similar reaction with chloromethyl methyl thioether in the presence of $ZnBr_2$ (1.0 equiv) afforded 53% of methyl α-$CF_3$ β-(methylthio)propionate: $^{19}F$ NMR ($CCl_4$, ext. TFA), δ -10.2 (d, J=7.0 Hz).

9. This observation is in direct contrast to the high-yield allylation reported for the reaction of a certain ketene silyl acetal with prenyl bromide: I. Paterson, *Tetrahedron Lett.*, 1979, 1519.

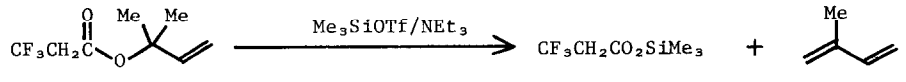
10. R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, 98, 2868 (1976).

11. Prepared in 80% yield via hydrolysis (aq. HBr) of TFPE: bp 59-60 °C/19 mmHg.

12. K. Saigo, M. Usui, K. Kikuchi, E. Shimada, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 50, 1863 (1977).

13. The boiling point and $^{19}F$ NMR data ($CCl_4$, ext. TFA) for 4 are as followes: 4a ($R^1$, $R^2$, $R^3$= H): 128 °C and δ -15.0 (t, J=10.0 Hz); 4b ($R^1$, $R^2$=H, $R^3$=$CH_3$): 87-90 °C/78 mmHg and δ -14.7 (t, J=10.1 Hz); 4c ($R^1$=$CH_3$, $R^2$, $R^3$=H): 79 °C/98 mmHg and δ -14.6 (t, J=10.1 Hz); 4d ($R^1$, $R^2$=$CH_3$, $R^3$=H): 82-87 °C/82 mmHg and δ -14.9 (t, J=10.1 Hz).

14. The very low yield observed in entry 4 probably arises from occurrence of the unusual elimination as depicted below in preference to the normal O-sillylation in analogy with a similar observation reported for the silylation of t-butyl esters with the silyl triflate. cf. H. Emde and G. Simchen, *Synthesis*, 1977, 12.




15. For a general discussion of the stereoselectivity including the diastereoselectivity in the ester enolate Claisen process, see ref 10.


(Received in Japan 18 May 1984)