Tetrahedron Letters,Vol.29,No.27,pp 3291-3294,1988	0040-4039/88 $3.00 + .00
Printed in Great Britain	Pergamon Press plc

FLUORINE-CONTAINING ORGANOZINC REAGENTS. V.[1]
THE REFORMATSKII-CLAISEN REACTION OF CHLORODIFLUOROACETIC ACID DERIVATIVES

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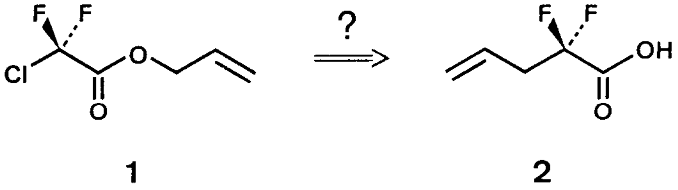
Summary: Silicon induced Reformatskii-Claisen reaction of allyl chlorodifluoroacetate (1) affords 2,2-difluoro-4-pentenoic acid (2) in good yields. Starting from inexpensive chlorodifluoroacetic acid, a variety of useful fluorine-containing synthetic building blocks can be obtained under the same reaction conditions.

Fluorinated ketones have been successfully employed as enzyme inhibitors in modern bioorganic chemistry.[2] Therefore, the synthesis of selectively fluorinated molecules which have fluorine substituents adjacent to a carbonyl group became a major target in fluoroorganic chemistry.[3] In particular, the search for versatile synthetic building blocks from easily accessible fluorinated precursors seems to be an attractive approach to solve the inherent synthetic problem.

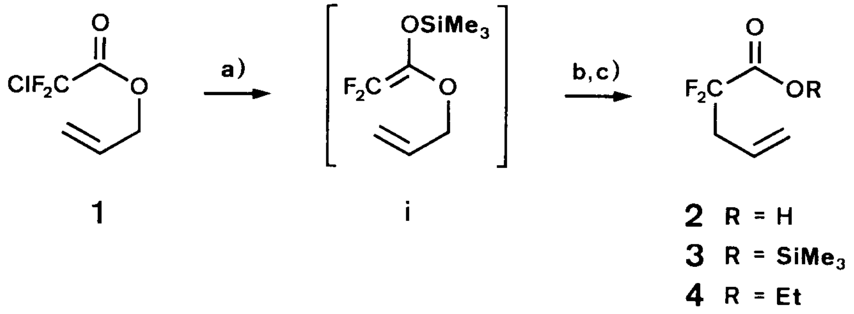
Starting from highly reactive tetrafluoroethylene, Normant et al. have described the synthesis of 2,2-difluoro-4-pentenoic acid (2) in 1974.[4] Very recently, this acid became the starting material for an elegant approach to α-amino ketones, which after incorporation into some selected peptide sequences should act as tailor-made protease inhibitors.[5]

As part of our ongoing search for new synthetic applications of inexpensive chlorodifluoroacetic acid derivatives in fluoroorganic chemistry, we became interested to know whether allyl chlorodifluoroacetate (1) can undergo the Reformatskii-Claisen reaction,[6] and yielding 2,2-difluoro-4-pentenoic acid (2). Under the originally reported reaction conditions, this particular type of reaction seemed to be restricted to trichloroacetyl esters of allylic alcohols and thus providing only the corresponding dichloro acids.[6]



Here we like to report on the experimental details for various chlorodifluoroacetic acid derivatives to undergo a silicon induced Reformatskii-Claisen reaction. When a mixture of 160 g (0.94 mol) of allyl chlorodifluoroacetate (1),[7] 151 g (1.39 mol) of chlorotrimethylsilane, and

Scheme 1



a) $Zn/ClSiMe_3/CH_3CN$; 100°; 20 h. 1 → 3 (95%)
b) SiO_2 cont. 1 mol-equiv. H_2O; rt.; 12 h. 1 → 2 (78%)
c) EtOH ($-H_2O$); $CHCl_3$; rfl.; 12 h. 1 → 4 (60%)

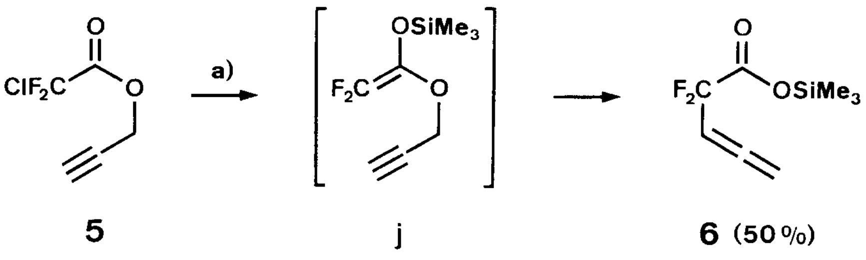
70 g (1.07 g-atom) of freshly activated zinc dust[8] was heated for 20 h in 700 ml of dry acetonitrile at 100°, 100 g (78%) of 2,2-difluoro-4-pentenoic acid (2)[9] could be isolated after hydrolysis of the trimethylsilyl pentenoate 3[10] by adding 300 g of wet silica gel, filtration, and concentration in vacuo. To avoid decomposition on storage, the crude acid was esterified with ethanol under Fischer conditions yielding 93 g of colourless ethyl 2,2-difluoro-4-pentenoate (4)[11] in 60% overall yield (Scheme 1).

It is noteworthy that according to a competition experiment under the forementioned reaction conditions, the Reformatskii-Claisen reaction of chlorodifluoroacetate 1 was four times faster than the rearrangement of the corresponding trichloroacetate (cf. ref. 6). Furthermore, no reaction took place in the absence of chlorotrimethylsilane, indicating the ketene acetal i to be an apparent reaction intermediate.

In analogy to what is reported in Scheme 1, a variety of alkyl substituted allyl chlorodifluoroacetates also underwent the Reformatskii-Claisen reaction (See Table).

Finally, this method is also applicable to acetylenic esters as was shown by the conversion of 5[12] into the allenic ester 6[13] (Scheme 2).

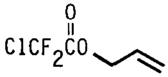
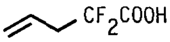
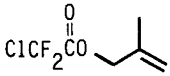
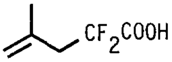
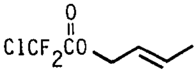
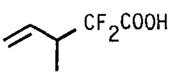
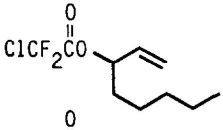
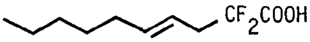
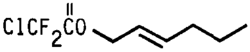
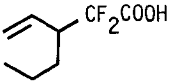
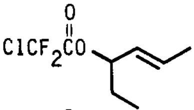
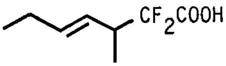
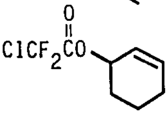
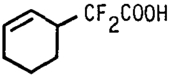
Scheme 2



a) $Zn/ClSiMe_3/CH_3CN$; 80°; 24 h.

In summary the Reformatskii-Claisen reaction of chlorodifluoroacetic acid derivatives provides an attractive alternative to the earlier described methods of effecting the synthesis of 2,2-difluoro-4-pentenoic acid derivatives.

Table. Reformatskii-Claisen Reaction of Chlorodifluoroacetic Acid Derivatives[a)]

Entry	Starting material	Product[b)]	Yield[c)]
1			78%
2			44%
3			47%
4			33%
5			54%
6			26%
7			5%

[a)] All reactions were carried out under the conditions reported in Scheme 1.

[b)] All products gave ^{1}H-NMR and IR spectra that were fully consistent with the indicated structures.

[c)] Isolated yields referring to non-optimized reaction conditions.

Acknowledgments: We like to thank Miss J. Schaub and Mr. K. Ohnemus for their skillful assistance in the laboratory, and we are grateful to our colleagues in the Physical Department for performing spectral analyses.

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4. J.F. Normant, O. Reboul, R. Sauvêtre, H. Deshayes, D. Masure, J. Villieras, Bull. Soc. Chim. Fr. 1974, 2072.
5. M. Kolb, B. Neises, Tetrahedron Lett. 27, 4437 (1986).
6. J.E. Baldwin, J.A. Walker, J. Chem. Soc., Chem. Commun. 1973, 117.
7. Allyl chlorodifluoroacetate (1): colourless oil; bp: 98-103°/760 Torr. IR (neat): 1780s, 1370m, 1305s, 1285 (sh), 1170s, 1125s, 980s. ^{1}H-NMR (250 MHz, $CDCl_3$): 5.95 (m, =CH); 5.52-5.35 (m, $=CH_2$); 4.84 (d, J = 5 Hz, CH_2).
8. L.F. Fieser, M. Fieser, 'Reagents for Organic Synthesis', J. Wiley & Sons, New York, 1967, p. 1276.
9. 2,2-Difluoro-4-pentenoic acid (2):[4] colourless oil; bp: 73°/11 Torr. IR (neat): 1760s, 1650m. ^{1}H-NMR (60 MHz, $CDCl_3$): 9.20 (s (br.), OH); 5.95-5.05 (m, 3 olef. H); 2.65 (dt, J = 6/16 Hz, CH_2).
10. Trimethylsilyl 2,2-difluoro-4-pentenoate (3). ^{1}H-NMR (60 MHz, CD_3CN): 6.10-5.00 (m, 3 olef. H); 2.75 (dt, J = 6/16 Hz, CH_2); 0.27 (s, $Si(CH_3)_3$).
11. Ethyl 2,2-difluoro-4-pentenoate (4): colourless oil; bp: 43-45°/11 Torr. IR (neat): 2980m, 1780s, 1645w, 1430m, 1375m, 1340s, 1295s, 1230s, 1195s, 1150s, 1080s, 1045s, 1000m, 930m. ^{1}H-NMR (60 MHz, $CDCl_3$): 6.10-5.00 (m, 3 olef. H); 4.30 (q, J = 7 Hz, OCH_2); 2.80 (dt, J = 6/16 Hz, CH_2); 1.30 (t, J = 7 Hz, CH_3).
12. 2-Propynyl chlorodifluoroacetate (5): colourless oil; bp: 117-119°/760 Torr. ^{1}H-NMR (250 MHz, $CDCl_3$): 4.92 (d, J = 2.5 Hz, CH_2); 2.64 (t, J = 2.5 Hz, CH).
13. Trimethylsilyl 2,2-difluoro-3,4-pentadienoate (6): colourless oil; bp: 41-44°/0.1 Torr. ^{1}H-NMR (250 MHz, $CDCl_3$): 5.51 (m, ==CH); 5.17 (m, $==CH_2$); 0.35 (s, $Si(CH_3)_3$).

(Received in Germany 11 March 1988)