Tetrahedron Letters,Vol.29,No.9,pp 1011-1014,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

# INTRAMOLECULAR ω-OLEFINIC-KETONE ENE-REACTION FOR THE CONSTRUCTION OF TRIFLUOROMETHYLATED FIVE-MEMBERED RING COMPOUNDS

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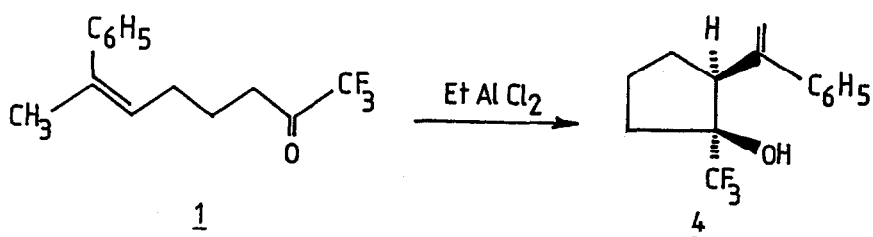
*SUMMARY : $EtAlCl_2$ and $TiCl_4$-initiated cyclizations of ω-ethylenic trifluoromethylketones and β-ketoesters provide five-membered ring compounds bearing a $CF_3$ group.*

Lewis acid induced intramolecular cyclizations from ω-ethylenic carbonyl compounds are an attractive method for the synthesis of functionalized cyclic systems. These reactions have been greatly investigated by the groups of B.B. Snider (1) and N.M. Andersen (2), especially starting from ω-ethylenic aldehydes (1,2,3) ; however, some examples have been described from activated ketones (4). Consequently, it could be expected that electron deficient trifluoromethylketones would be good enophiles for these reactions (5). So we are studying the cyclization reaction of ω-ethylenic trifluoromethylketones, as a new route to alicyclic compounds bearing a $CF_3$ group, whose access remains a difficult synthetic problem.

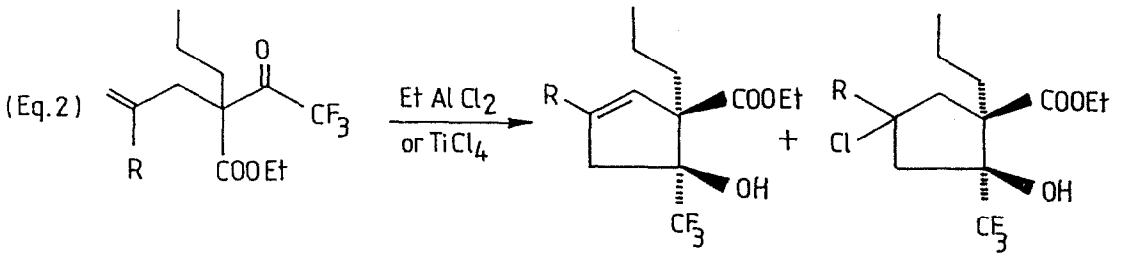
We report here preliminary results concerning cyclization catalyzed by $EtAlCl_2$ or $TiCl_4$ of ketone 1 and β-ketoesters 2 and 3. All cyclizations occurred and afforded five-membered ring carbinols (Table 1).

The $EtAlCl_2$-catalyzed cyclization of 1 provided quantitatively the trifluoromethylcyclopentanol 4 (eq.1) ; this reaction is stereospecific : only one diastereoisomer was detected by GC/MS. According to NMR data of literature (6), hydroxyl and β-styryl groups are cis.

(Eq.1)




1 4




R = $CH_3$ 2 — 5 — 8

R = H 3 — 6 — 9

Table : Cyclization of compound 1, 2, 3[a].

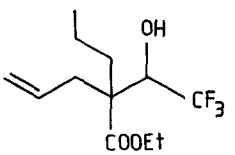
| Ketone | Catalyst (equiv.) | Conditions[b] temp °C (time h) | % product yields[c] 3 | 4 | 5 | 6 | 7[d] | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | $EtAlCl_2$ (1.1) | - 15 (7) | - | 95(100) | - | - | - | - | - |
| 2 | $EtAlCl_2$ (1.1) | 0 (3.5) | - | - | 43(54) | - | - | 30(35) | - |
| 2 | $TiCl_4$ (1.) | 0 (3.5) | - | - | 78(81) | - | - | - | - |
| 3 | $EtAlCl_2$ (1.1) | 25 (20) | (79) | - | - | - | (9) | - | (6) |
| 3 | $EtAlCl_2$ (3) | 0 (4.5) | - | - | - | - | 23(27) | - | 45(51) |
| 3 | $TiCl_4$ (1.1) | 0 (26) | (78) | - | - | (12) | - | - | (5) |
| 3 | $TiCl_4$ (3) | 0 (20) | - | - | - | 49(53) | - | - | 20(24) |

a) The preparation of ketone 1 was described (8a), the β-ketoesters 2 and 3 were prepared by alkylation of ethyltrifluoroacetylacetate (8b).

b) General procedure : the reactions were carried out under argon. The solutions of substrates in dry $CH_2Cl_2$ ($4.10^{-2}$ M) were cooled at the desired temperature and $EtAlCl_2$ (Aldrich Co, solution 1M in hexane) or $TiCl_4$ (Aldrich) was added via a syringe. After the appropriate reaction time, reactions were quenched by the addition of saturated aqueous $NH_4Cl$ solution. Extractive work-up into ether afforded the crude products purified by $SiO_2$ chromatography.

c) Isolated yields, the parenthetic values are estimated yields from GC analysis. Products were characterized by their spectral data : $^1H$, $^{19}F$, $^{13}C$ NMR, IR and MS.

d) 7 is the reduced product from ketone 3 :



The $EtAlCl_2$-catalyzed cyclization of 2 provided a mixture of cyclopenteno 5 (45 %) and chloride 8 (30 %) (eq. 2). When reaction was performed with $TiCl_4$, the yield of 5 was improved to 80 % and chloride 8 was not obtained. It was difficult to assign unambiguously the position of the double-bond ($\Delta$-3,4 or $\Delta$-4,5) of 5, nevertheless MS and $^{13}C$ NMR data support a $\Delta$-4,5 localization.

Complete reaction of 3 needed 3 equivalents of Lewis acid. Using $EtAlCl_2$, only 45 % of chloroalcohol 9 was obtained in mixture with the reduced product 7 (35 %). Using $TiCl_4$, the reaction was slower but the yield of cyclization was improved : 80 % of a mixture of the cyclopentenol 6 (54 %) and chloroalcohol 9 (25 %) (Eq 2).

Cyclizations of 2 and 3 are very stereoselective, affording only one diastereoisomer. Despite of a fully assigned configuration, IR spectral data (strong intramolecular H bonding) support a cis relationship between hydroxyl and carbethoxy groups (7).

Compared to cyclization of 3, the faster cyclizations of 1 and 2 are in agreement with the nucleophilicity of the double bond. However, it seems that cyclizations do not occur by the same process : from 1, structure of the only product 4 —i.e. position of the double bond and cis relative configuration of hydroxyl and $\beta$-styryl groups— indicates a concerted ene-process (1,9). From 2, endocyclic position of the double bond in 5 and the presence of chlorohydrin 8 indicate a non-concerted internal Prins process. Compared to corresponding cyclization of aldehydes (2), the easy cyclization of 2 is likely the result of activation of carbonyl group by the electron-withdrawing $CF_3$ group. From 3, the same non-concerted Prins process is obviously involved seeing that no allylic hydrogen is available. Concerning stereochemistry of cyclization of 2 and 3, chelation by the Lewis acid of two carbonyl groups in the starting material would provide a strict control of the transition state geometry during the cyclization, affording the only diastereoisomers 5 and 6 (7) and not the expected trans isomers resulting from a non-concerted process (2,9).

Thus, $\omega$-olefinic trifluoromethylketones are very convenient substrates to obtain trifluoromethyl five-membered carbinols. The extension of this reaction to synthesis of other alicyclic trifluoromethylcarbinols is now in progress.

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(6) The cis and trans alcohols resulting from cyclization of 3,3,6-trimethyl-5 heptenal (2), can be differentiated by their isopropenyl signals in $^1$H NMR : when hydroxyl and isopropenyl groups are in a cis relationship two vinylic protons display two distinct broad singlets, whereas the other diastereoisomer displays only on broad singlets. In as much as $^1$H NMR spectrum of cyclopentanol 4 affords two distinct broad singlets corresponding to two vinylic protons, we can conclude that hydroxyl and β-styryl groups are in a cis relationship.

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(Received in France 25 November 1987)