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# Lewis Acid-Induced Stereoselective Ene-Cyclization of ω-Unsaturated Trifluoromethylketones

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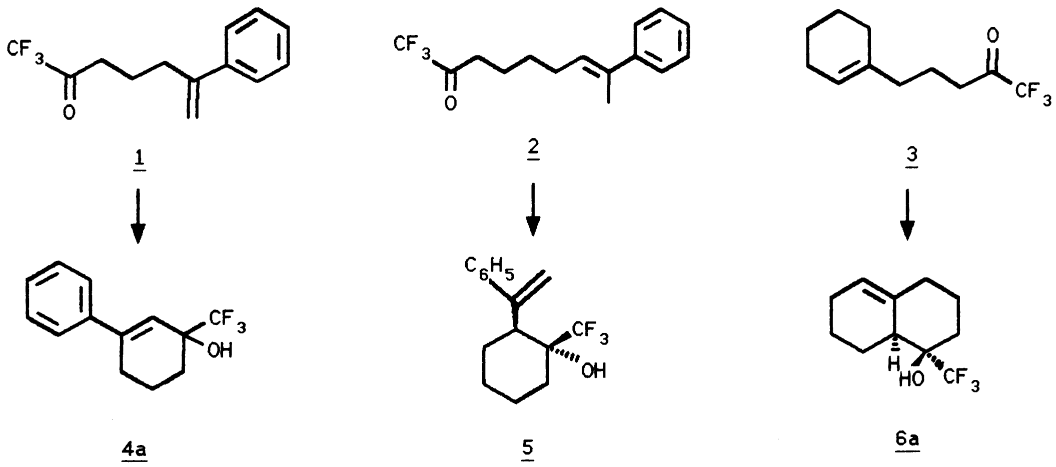
Lewis Acid-initiated ene-cyclization of ω-unsaturated trifluoromethylketones allows access to 1-trifluoromethyl cyclohexanols and their fused bicyclic derivatives

In search of new methods for obtaining alicyclic systems bearing a $CF_3$ group, we have recently reported studies of the Lewis acid promoted cycloalkylation of some ω-aryl α-trifluoromethylketones leading to 1-trifluoromethyltetralines and 1-trifluoromethylindanes.[1,2) A related strategy involving the intramolecular cyclization of ω-unsaturated carbonyl compounds is an attractive approach to prepare functionalized alicyclic compounds. These Lewis Acid-initiated ene reactions are well documented when they are performed with ω-unsaturated aldehydes.[3,4) But few examples have been reported with ω-unsaturated ketones presumably because of their lower reactivity.[5,6) However the electron deficient trifluoromethylketones are expected to be good enophiles for such Lewis Acid promoted ene cyclizations. Reported herein are the preliminary results of a study of the cyclization of the ω-unsaturated trifluoromethylketones 1, 2, and 3 with $EtAlCl_2$ and $TiCl_4$ (Table 1).

With ethylaluminium dichloride, all cyclizations occurred under mild conditions leading respectively to cycloalkanols 4a, 5, and 6a; in each case only a single regioisomeric product was obtained.

From 1, only a Prins reaction is possible. An inspection of molecular models shows that a highly strained transition state would be required in order for an ene reaction to occur. Cyclization of 1 would proceed via tertiary carbocation 7.



1 → 4a

2 → 5

3 → 6a

Table 1 . Cyclization of ketones 1, 2, and 3[a]

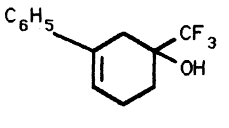
| Ketone[b] | Lewis Acid (equiv.) | T/°C (time/h) | Products (yield/%)[c] | | | |
|---|---|---|---|---|---|---|
| 1 | $EtAlCl_2$ (1.1) | 0 (4) | (4a) 68(55) | | | |
| 1 | $TiCl_4$ (1.1) | 0 (5) | (4a) 11 | (4b) 23 | (8) 31 | (9) 31(22) |
| 2 | $EtAlCl_2$ (1.1) | -78 (5) | (5) 86(75) | | | |
| 2 | $TiCl_4$ (1.1) | 0 (3) | (5) 82(70) | | | |
| 3 | $EtAlCl_2$ (1.1) | -78 (2) | (6a) 81(72) | | (11) 9(7) | |
| 3 | $Me_3Al$ (1.1) | -78 (2) | (6a) 85 | | | |
| 3 | $TiCl_4$ (1.1) | -78 (1) | (6a) 0(9) | (6b) 0(8) | (11) 85(68) | |
| 3 | $TiCl_4$(0.3) | -78 (1) | (6a) 0 | (6b) 0 | (11) 78 | |

a) General procedure: $EtAlCl_2$ and $Me_3Al$ were purchased from Aldrich as a 1 M solution in hexane. Reactions were carried out under argon. Solution of ketones in dry $CH_2Cl_2$ (0.04 M) were cooled to the desired temperature and Lewis acid was added *via* a syringe. After the indicated reaction times the reactions were quenched by the addition of saturated aqueous $NH_4Cl$ solution. Extractive work-up into ether afforded products which were then purified by $SiO_2$ chromatography.

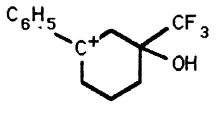
b) Ketones 1 and 3 were described in Ref. 7, ketone 2 in Ref. 8.

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

Loss of a proton might be expected to occur from both the β-sites to give a mixture of the two regioisomeric alkenes 4a and 4b, but in fact only 4a was obtained with $EtAlCl_2$. An intramolecular deprotonation by the chloroaluminium alkoxide group should explain this surprising regioselectivity. With $TiCl_4$, the reaction is not selective, both the unsaturated alcohols 4a and 4b were obtained and when staying in the medium, they turn into the dienes 8 and the trifluoromethylbiphenyl 9 .



4b



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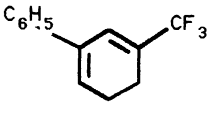
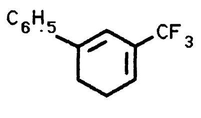
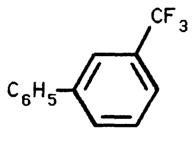


8a



8b



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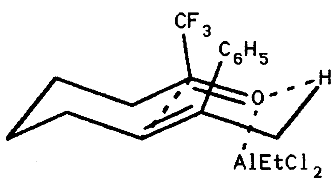
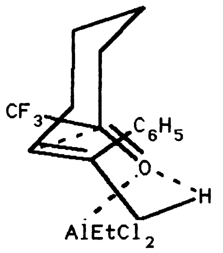
From 2 and 3, the ene and Prins processes could be invoked, but the localization of the double bond in 5 and 6a (established by NMR and mass spectra) indicates an ene reaction, since no isomerization occurs under the reaction conditions.[9)]

Furthermore, only one diastereoisomer was obtained from the *E*-enone 2. The stereochemistry of compound 5, with a ***trans*** relationship between the vicinal alkenyl and the hydroxyl group, is postulated by assuming that there is a preference for the ***trans*** chair-chair-like transition state A rather than for the *cis* transition state B.[10)] This is well consistent with the predominant formation of such a ***trans*** product in the cyclization of the 4,8-dimethyl-7-nonen-2-one.[5,11)]

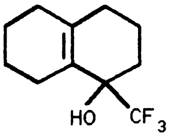


*(A)* ⟶ *Trans*

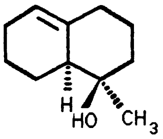


*(B)* ⟶ *Cis*

The stereochemistry of 6a, obtained from ketone 3, is the same as that of alcohol 10, resulting from cyclization of the corresponding methyl ketone[12)] and is the result of the only possible transition state in the ene reaction, as indicated by molecular models inspection. The chloride 11 was obtained very selectively from 3 and $TiCl_4$. The ***trans*** junction is inferred from its dehydrochlorination with DBU leading to the allylic alcohol 6b; the configuration of C-9 and C-1 are the same as that of 6a since in presence of $MeAl_3$, 11 leads to a mixture of 6b and the isomeric $\Delta^{4-10}$-octalin; the axial position of chlorotitanium alkoxide can favor an intramolecular transfer of chloride and explains the stereochemistry of 11.



6b



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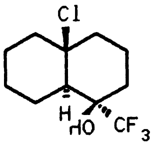

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In this way, functionalized mono and bicyclic six-membered ring compounds bearing a $CF_3$ group are available. An extension of this reaction to obtain other polycyclic compounds is now under investigation.

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## References

1) D. Bonnet-Delpon, C. Cambillau, M. Charpentier, R. Jacquot, D. Mesureur, and M. Ourevitch, J. Org. Chem., 53, 754 (1988); D. Bonnet-Delpon, M. Charpentier, and R. Jacquot, J. Org. Chem., 53, 759 (1988).
2) J.P. BÉGUÉ and C. AUBERT, Tetrahedron Lett., 29, 1011 (1988).
3) E.J. COREY and D.L. BOGER. Tetrahedron Lett., 21, 2461 (1980).
4) N.H. Andersen, S.W.Hadley, J.D. Kelly, and E.R. Bacon. J. Org. Chem., 50, 4144 (1985) and references cited herein.
5) B.B. Snider, M. Karras, R.T. Price, and D.J. Rodini, J. Org. Chem., 47, 4538 (1982).
6) A.C. Jackson, B.E. Goldman, and B.B Snider, J. Org. Chem., 49, 3988 (1984).
7) J.P. Bégué and D. Mesureur, J. Fluorine Chem., 39, 271 (1988).
8) C. Aubert, J.P. Bégué, M. Charpentier, B. Langlois, and G. Née, J. Fluorine Chem., 44, 361 (1989).
9) B.B. Snider, Acc. Chem. Res., 13, 426(1980); B.B. Snider, D.J. Rodini, M. Karras, T.C. Kirk, E.A. Deutsch, R. Cordova, and R.T. Price, Tetrahedron, 23, 3927 (1981).
10) K. Mikami, T.P Loh, and T. Nakai, Tetrahedron Lett., 29, 6305 (1988).
11) M. Karras and B.B. Snider, J. Am. Chem. Soc., 102, 7951 (1980).
12) B.B. Snider and E.A. Deutsch, J. Org. Chem., 48, 1822 (1983).

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