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REACTIVITY OF 2-ETHOXY-5-ALKYL-3,4-DIHYDRO-2H-PYRANS TOWARDS ALUMINUM ALKYLS : A FACILE SYNTHESIS OF CYCLOBUTYLMETHANOLS

Rita Menicagli*, Corrado Malanga, Luciano Lardicci, and Laura Tinucci

Centro di Studio del CNR per le Macromolecole Stereordinate ed Otticamente Attive, Istituto di Chimica Organica della Facoltà di Scienze M.F.N. della Università di Pisa, 56100 Pisa, Italy.

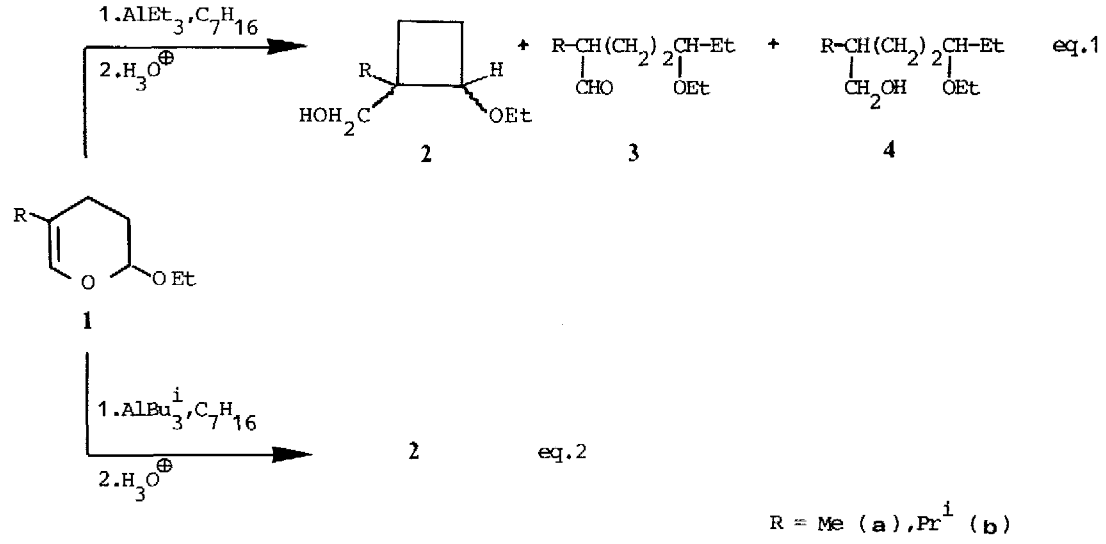
Summary: 2-Ethoxy-5-alkyl-3,4-dihydro-2H-pyrans react with $AlBu^i_3$ and through a regioselective hydride addition provide substituted cyclobutylmethanols in very good yields.

2-Ethoxy-5-alkyl-3,4-dihydro-2H-pyrans have recently been employed to prepare alkylpyridines[1], furans[2] and dihydrofurans[3] in satisfactory yields.

As part of our study in the preparation and reactivity of heterocyclic compounds we decided to undertake a general investigation about the reactivity of 2-ethoxy-5-alkyl-3,4-dihydro-2H-pyrans 1 to test their applicability in organic synthesis.

Since it has been reported[4] that 1 (R=H,Me) react with Grignarg reagents, in boiling toluene, to give cyclobutyl alkylcarbinols in 32-90% yields, it should be interesting to extend the investigation of the reactivity of 1 towards other organometallic compounds.

Scheme



We report here some results concerning the reaction of 1a,b with $AlEt_3$ and $AlBu^i_3$ (Scheme, eqs.1,2).

Reactions were carried out in a dry purified nitrogen atmosphere by adding dropwise compound 1 (24 mmol) to an ice-cooled heptane solution (25 ml) of freshly distilled aluminum alkyl (48 mmol). The mixture was stirred 5 min at 0° and then was allowed to warm to room temperature. After 30 min it was warmed, with an oil bath, to the temperature reported in the Table and, after the required reaction time (Table), the hydrolysis was accomplished with water and 10% H_2SO_4. The reaction mixture was extracted into ether, worked up as usual and analyzed by GLC. When necessary, products were separated by preparative GLC.

The structures of all the compounds recovered were established by ^{1}HNMR, IR and/or mass spectra; moreover all new products gave satisfactory elementary analyses.

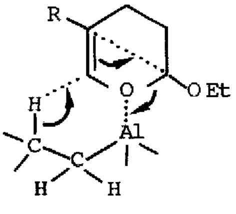
Table[a]

run	Substrate	AlR_3	Reaction time (hr)	Conversion%[b]	Product distribution%[c] 2	3	4
1	1a	R=Et	4.5[d]	96	53	20	16
2	1a		3[d]	95	42	35	9
3	1b		4.5[d]	97	23	66	11
4	1a	R=Bu^i	22[e]	≃100(>90)	≃100	-	-
5	1b		22[e]	≃100(>90)	≃100	-	-

[a] All the reactions were carried out by using an [1]/[AlR_3] = 0.5 molar ratio and they were repeated twice. Conversions and product distributions were evaluated as medium values. [b] The conversions were determined by GLC analyses and the numbers in parentheses are isolated yields. [c] Determined by GLC analysis, traces of unknown products have been disregarded. [d] At 90-95°. [e] At 60-65°.

The data reported in the Table show that $AlEt_3$ converts, in the experimental conditions adopted (runs 1,3), both 1a and 1b mainly[5] into mixtures of 2[6] and 3[7] (Scheme, eq.1).

According to what is reported[4], the formation of 2 may occur through a transfer of hydride hydrogen, from a carbon atom in the position β to the aluminum atom, to the C_6 of the pyran ring that simultaneously undergoes an intra-



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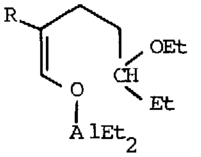

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molecular rearrangement to the aluminum alcoholate precursor of 2. On the other hand the ethyl group nucleophylic substitution on the C_2 affords the enolate 7 from which 3 arises[8].

Since compounds 2 and 3 are formed in rather different percentages when 1a or 1b are used (runs 1,3) neighbouring group participation may be supposed: in 1a the methyl group should destabilize an incipient carbanion at C_5 less than the i.propyl group present in 1b; in the latter case alkylation to the C_2 becomes the preferential pathway.

Alcohols 4[9] are always present in the reaction mixtures (Scheme,eq.1), even if 4b is formed in a smaller amount than 4a (runs 1-3); however when the reaction is stopped after 3 hr (run 2) the concentration of 4a decreases and that of 3a increases.

Such evidence suggests that 4 is formed by reduction of the aluminum enolate 7 precursor of 3.

By using $AlBu^i_3$ either 1a or 1b are quantitatively converted into the cyclobutylmethanols 2a and 2b respectively (Scheme, eq.2) and these alcohols are recovered from the reaction mixtures in very good yields (Table, runs 4,5).

The overall results clearly indicate that the behaviour of 1 towards AlR_3 also depends on the nature of the aluminum alkyl: $AlEt_3$ performs both an alkylating cleavage of the $O-C_2$ bond of the dihydropyran ring and a reductive intramolecular rearrangement through a hydride transfer to the C_6; the latter reaction becomes the only pathway when $AlBu^i_3$ is used owing to its reductive ability.

The reported one-pot conversion of ready available compounds 1[1,2] to 2, which are not easily accessible by other methods, represents a novel and efficient route to the synthesis of cyclobutyl derivatives.

Further studies are in progress to investigate the dependence of the product distribution on the $[1]/[AlR_3]$ molar ratio, and the reaction stereochemistry that might provide evidences useful to gain more insight into the reaction mechanism.

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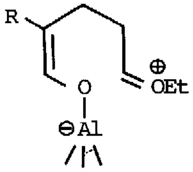
References and notes

1. D.Tatone, Tran Cong Dich, R.Nacco, and C.Botteghi, J.Org.Chem.,40,2987(1975).
2. R.Menicagli, M.L.Wis, L.Lardicci, C.Botteghi, and G.Caccia, J.Chem.Soc., Perkin Trans.I,847(1979).
3. Work in preparation.
4. (a) R.Quelet and J.D'Angelo,C.R.Acad.Sci.,Ser.C.,264,216(1967);
   (b) idem, Bull.Soc.Chim.Fr.,3390(1967).
5. When 1a is used (runs 1,2) 11-14% of a compound whose GLC retention time is very close to that of 2a has been also detected, unfortunately so far we have been unable to obtain it in a suitable chemical purity so as to determine its structure.
5. Characteristics of 2a:
   bp (uncorr.) 99°/20 mmHg; IR (film, ν cm^{-1}): 3410,1110,1020; ^{1}HNMR(100 MHz, $CDCl_3$, δ ppm/TMS): 3.80-3.66(t,1H),3.66-3.20(m,4H),3.20-2.90(broad s,1H), 2.36-1.24(m,4H),1.24-1.00(m,6H); m/e(I%): 44(100),72(78),116($M^+-C_2H_4$,20), 98(12),101(11).

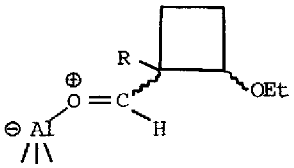
Characteristics of 2b:
bp(uncorr.) 165°/160 mmHg; IR(film, ν cm^{-1}): 3400,1110,1010; ^{1}HNMR(100 MHz, CDCl$_3$, δ ppm/TMS): 3.94-3.70(t,1H),3.44-3.20(m,4H),2.29(s,1H),2.26-1.20(m, 5H),1.20-1.02(t,3H),1.02-0.78(dd,6H); m/e(I%): 72(100),44(56),101(46),144 (M^+-C_2H_4,17),129(17).

7. Characteristics of 3a:
bp(uncorr.) 100-101°/18 mmHg; IR(film, ν cm^{-1}): 2720,1725,1105,1080; ^{1}HNMR (100 MHz, CDCl$_3$, δ ppm/TMS): 9.56(d,1H),3.52-3.42(dq,2H),3.42-2.96(m,1H), 2.60-2.15(m,2H),2.15-1.20(m,5H),1.20-0.64(m,9H); 3a 2,4-dinitrophenylhydrazone: mp(uncorr.) 65-76°;m/e(I%): 29(100),59(91),41(69),87(66),109 (23),250(19),273(16),317(12),352(M^+,9),323(9).
Characteristics of 3b:
bp(uncorr.) 110-111°/20 mmHg; IR(film, ν cm^{-1}): 2700,1720,1110,1080; ^{1}HNMR (100 MHz, CDCl$_3$, δ ppm/TMS): 9.28(dd,1H),3.40-3.10(m,2H),3.10-2.84(m,1H), 2.00-1.60(m,2H),1.60-1.14(m,6H),1.14-0.90(t,3H),0.90-0.57(m,9H); 3b 2,4-dinitrophenylhydrazone: mp(uncorr.) 57-63°; m/e(I%): 29(100),59(96),41(64), 87(57),69(40),95(16),299(11),301(10),113(9),109(8),380(M^+,7).

8. As suggested by a referee the reaction may be initiated by the formation of A, which may then either afford 7 or undergo ring closure, to give B.



A



B

In such an event, hydride transfer to give 2 occurs after the cyclization step. It is evident that the proposed reaction paths (see 6 or A and B) are quite different for what it concerns the stereochemical implications.

9. Characteristics of 4a:
IR(film, ν cm^{-1}): 3400,1105,1080,1040; ^{1}HNMR (100 MHz, CDCl$_3$, δ ppm/TMS):3.64-3.30(m,4H),3.30-3.01(m,1H),2.88-2.64(broad s,1H),1.80-1.29(m,6H),1.29-0.99 (m,4H;t,at 1.19,3H),0.99-0.74(m,6H); m/e(I%): 59(100),29(74),31(72),87(71), 41(56),43(54),57(45),99(41),55(38),81(15),145(M^+-C_2H_5,9).
Characteristics of 4b:
m/e(I%): 87(100),59(75),41(35),43(30),29(30),127(28),71(27),57(27),55(27), 31(23),69(20),173(M^+-C_2H_5,12),109(12).

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