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AN UNUSUAL SYNTHETIC WAY TO 2-METHYL-3-ALKYL-6-ETHOXY-HEPTAN-2-OLS FROM 2-ETHOXY-5-ALKYL-3,4-DIHYDRO-2H-PYRANS

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Summary: *A simple and swift preparation of 2-methyl-3-alkyl-6-ethoxyheptan-2-ols may be accomplished in two steps starting from 2-ethoxy-5-alkyl-3,4-dihydro-2H-pyrans* via *chlorination of the heterocyclic compounds and subsequent reaction with MeMgBr.*

We recently wished to check the possibility to obtain 4-unsaturated aldehydes starting from 2-ethoxy-5-alkyl-3,4-dihydro-2H-pyrans (**1**) [R = Me (**a**), Pr^i (**b**)] with the same reaction sequence described to obtain (E)-7-methylocta-4-en-1-ol from dihydropyran.[1]

An ethereal solution of **1a** was then reacted with chlorine and the crude reaction mixture was added to an ethereal solution of MeMgBr. Repeated experiments unexpectedly showed that the chlorinated compound required three molar equivalents of the Grignard reagent to be completely reacted.[2]

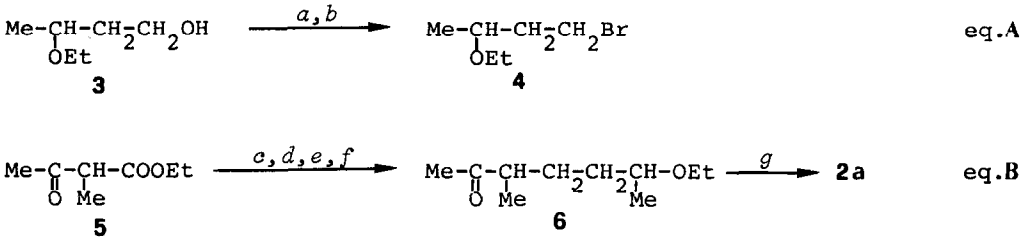
After hydrolysis, the reaction product **2a** was recovered and either elemental analysis[3] or mass spectroscopy[3] indicated that no chlorine was present in the molecule.

The overall spectral data (IR, ^1H and ^{13}C NMR)[3] suggested that the recovered compound was 2,3-dimethyl-6-ethoxyheptan-2-ol (**2a**),even if some doubt existed , owing to the complexity of the spectra.

Considering the unexpected and peculiar course of this reaction, we deemed necessary to demonstrate the structure of **2a** by its synthesis *via* a classical and un-

ambiguous reaction sequence (Scheme 1, eqs A, B).[4]

Scheme 1

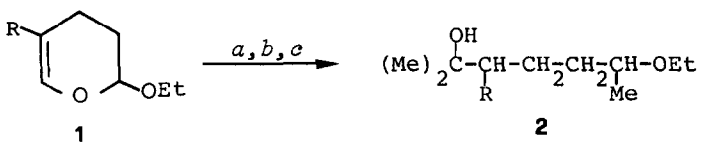


*a)TsCl,Py,0°C; b)LiBr,DMF,90°C; c)Bu^tOK,Bu^tOH; d)**4**,50-82°C; e)5% NaOH,25-50°C; f)50% H_2SO_4,40°C; g)LiMe·LiBr,Et_2O,-70+-25°C.*

The bromide **4** obtained by reaction of the tosylate of **3**[5] with LiBr in DMF,[7] was allowed to react with the enolate anion of **5**, formed from the ester by use of Bu^tOK in Bu^tOH.[9] The alkylated reaction product was saponified[10] and decarboxylated[10] to give **6** which was then methylated by means of the complex LiMe·LiBr in ether.[11]

The spectra of the obtained compound (Scheme 1) were identical with those of the product **2a** derived from **1a** by the reaction sequence depicted in Scheme 2.

Scheme 2



R = Me(**a**), Pr^i(**b**)

a)Cl_2,Et_2O; b)MeMgBr(3 molar equivalents); c)H_3O^+.

Starting from **1a**, the following experimental procedure was typical: chlorine was bubbled into an ethereal solution (30 ml) of **1a** (30 mmol), cooled at -20°C. The pale green solution was siphoned into a dropping funnel under nitrogen atmos

phere and then slowly added to an ethereal solution of 0.1 mol of MeMgBr maintained at 0°C. Upon completion of the addition, the reaction mixture was stirred for 12 hours at the same temperature and then hydrolyzed with water followed by diluted sulphuric acid. The product, recovered in ether, was distilled, and chromatographed on silica gel using pentane and then chloroform as eluent, to give chemically pure **2a** (80% yield).

To verify if such a reaction is dependent on the structure of the alkyl substituent in **1**, we reacted **1b** in the above reported reaction conditions and pure **2b**[12] was obtained in good overall yield(80-95%).

Since it is probable that the chlorination of **1** affords 2-ethoxy-5-alkyl-5,6-dichlorotetrahydropyrane (**7**)[13,14] it is hard to rationalize the formation of **2** considering that the C_2 and C_6 of **7** are respectively mono- and dialkylated and the C_5 is reduced.[15] At present we suppose that some rearrangement occurs during the reaction with MeMgBr. In a reasonable mechanistic hypothesis a possible reaction intermediate should be 5,6-epoxy-2-ethoxy-5-methylheptane.[16] This epoxide, owing to a Lewis acid catalyzed isomerization,[17] could give 3-methyl-6-ethoxy-heptan-2-one (**6**) from which **2** arises *via* Grignard reagent alkylation.

Acknowledgements: *The authors express their thanks to Mr. F. Fasanelli (^{1}HNMR) for his able assistance.*

References and notes

1. *F.W.Hougen, D.Ilse, D.A.Sutton, J.P.deVilliers,* J.Chem.Soc., *98(1953).*

2. *During the reaction only negligible amounts of methane were evolved: GLC analysis (5Å molecular sieves, room temperature) of the volatile components present in the reaction vessel.*

3. *Compound* **2a** *showed: bp (uncorr.) 71°C/1.0 mmHg; analysis, found C% 70.24, H% 12.81; m/e (I%): 73(100),58(98),45(92),43(65),55(28),84(27),56(26),42(25),41(22),69(21),130(13),127(13),47(13), 109(7),99(4),170(M^+-H_2O,0.8),173(M^+-CH_3,0.8);IR (film, ν cm^{-1}):3460,2980,2940,2880,1460,1370, 1160,1105,1080,950,910,860;^{1}HNMR (100 MHz,CCl_4, δ ppm/TMS):3.70-3.10(m,3H),2.41(s,1H),2.80-0.98 (m,5H),1.60(t,3H),1.30(d,3H),1.20(s,6H),0.88(d,3H);^{13}CNMR (65.2 MHz,$CDCl_3$, δ ppm/TMS):75.53, 75.10(2d,CH),73.24(s,C),63.44(t,CH_2),44.54,44.23(2d,CH),35.44(t,CH_2),27.49(q,CH_3),27.16(q,CH_3), 27.33,25.15(2t,CH_2),19.88,19.77(2q,CH_3),15.66(q,CH_3),14.60(q,CH_3).*

4. *All new compounds gave satisfactory microanalysis and mass spectra. The boiling points are uncorrected and the characteristics of the prepared compounds are:* **3** *: bp 105°C/90 mmHg;IR(film, ν cm^{-1}):3420,2990,2930,2885,1480,1375,1140,1100,1050;^{1}HNMR (100 MHz,CCl_4, δ ppm/TMS):3.98(s,1H), 3.80-3.15(m,5H),1.80-1.40(m,2H),1.16(t,3H),1.12(d,3H);***4** *: bp 124°C/245 mmHg;IR (film, ν cm^{-1}):*

2990, 2930, 2900, 2885, 1450, 1370, 1270, 1230, 1215, 1170, 1135, 1110, 1090, 650, 570; ^{1}HNMR (100 MHz, CCl_4, δ ppm/TMS): 3.80-3.15(m,5H), 2.10-1.60(m,2H), 1.16(t,3H), 1.12(d,3H); Ethyl 2-methyl-2-acetyl-5-ethoxyhexanoate: bp 152°C/20 mmHg; IR (film, ν cm^{-1}): 2990, 2940, 2880, 1740, 1710, 1460, 1375, 1360, 1260, 1230, 1195, 1150, 1105, 1090, 1020, 970, 860; ^{1}HNMR (100 MHz, CCl_4, δ ppm/TMS): 4.30-4.00(q,2H), 3.60-3.10(m,3H), 2.10(s,3H), 2.08-1.60(m,4H), 1.28(t,3H), 1.26(s,3H), 1.14(t,3H), 1.11(d,3H); **6** : bp 146°C/110 mmHg; IR (film, ν cm^{-1}): 2990, 2940, 2880, 1710, 1460, 1370, 1360, 1220, 1180, 1140, 1105, 1080, 960; ^{1}HNMR (100 MHz, CCl_4, δ ppm/TMS): 3.70-3.10(m,3H), 2.60-2.40(m,1H), 2.07(s,3H), 1.90-1.40 (m,4H), 1.14(t,3H), 1.10(d,3H), 1.06(d,3H).

5. The alcohol **3** was prepared starting from ethylcrotonate.[6]

6. W.E. Doering, R.W. Young, J.Am.Chem.Soc., 74, 2997(1952).

7. The reaction was performed by using the same reaction procedure described.[8]

8. R. Menicagli, O. Piccolo, L. Lardicci, M.L. Wis, Tetrahedron, 35, 1301(1979) and refs cited therein.

9. W.B. Renfrow, A. Renfrow, J.Am.Chem.Soc., 68, 1801(1946).

10. J.R. Johnson, F.D. Hager, "Organic Synthesis", Wiley, New York (1941) Coll.I, p.351.

11. P.D. Bartlett, E.B. Lefferts, J.Am.Chem.Soc., 77, 2804 (1955).

12. Characteristics of **2b**: bp 142°C/20 mmHg; mass spectra m/e (I%): 73(100), 45(84), 43(68), 69(34), 85(24), 55(24), 111(21), 139(19), 154(12), 170(6), 198(2), 184(2), 201(2), 216(M^+, 0.6); IR (film, ν cm^{-1}): 3460, 2990, 2940, 2880, 1465, 1370, 1340, 1150, 1110, 1060, 950, 920, 895, 880, 840; ^{1}HNMR (100 MHz, CCl_4, δ ppm/TMS): 3.70-3.26(m,3H), 3.26-2.90(s,1H), 2.20-1.80(m,1H), 1.70-1.30(m,5H), 1.20(t,3H), 1.18(s,6H), 1.10(d,3H), 0.96(dd,3H), 0.88(dd,3H).

13. W.A. Szarek, Advan.Carbohyd.Chem., 28, 260 (1973).

14. Since **7** is labile any attempt to determine its structure by NMR spectroscopy failed.

15. The deuteriolysis of the reaction mixture afforded only a deuterated alcoholic function in **2**. So, since any C_5-Mg bond is to be excluded, the hydrogen transfer to the C_5 must occur in a reaction intermediate.

16. Arising from reaction of **7** with two molar equivalents of MeMgBr followed by oxyrane ring formation. The possibility of occurrence of this intermediate has been suggested by a referee too. The result of deuteriolysis (see note 15) does not contrast with such a hypothesis.

17. R.E. Parker, N.S. Isaacs, Chem.Rev., 59, 737 (1959).

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