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ELECTROPHILIC CONDENSATION OF SILYL ETHERS OF HOMOPROPARGYL ALCOHOLS WITH ALDEHYDES -- REGIOSELECTIVE SYNTHESIS OF DIHYDROPYRANS

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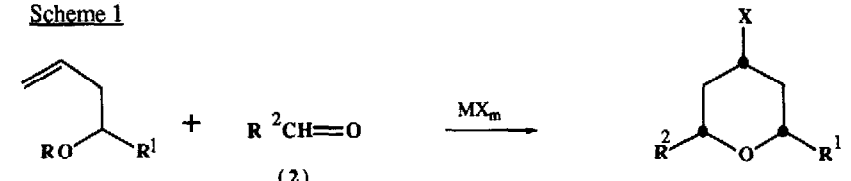
Summary : Under $TiCl_4$ conditions, the silyl ether 12c reacts with aldehydes to give regioselectively the substituted dihydropyrans 14.

Recently, several laboratories reported on the electrophilic condensation of homoallylic alcohols (**1a**) or their silyl ethers (**1b** or **c**) with carbonyl compounds (**2**) under Lewis acid conditions to give tetrahydropyrans (**3**)[1-4] according to *scheme 1*. Because of the presence of the pyran skeleton in many natural products, including

Scheme 1



1a : R = H
1b : R = Me_3Si
1c : R = $Me_2(R^3O)Si$

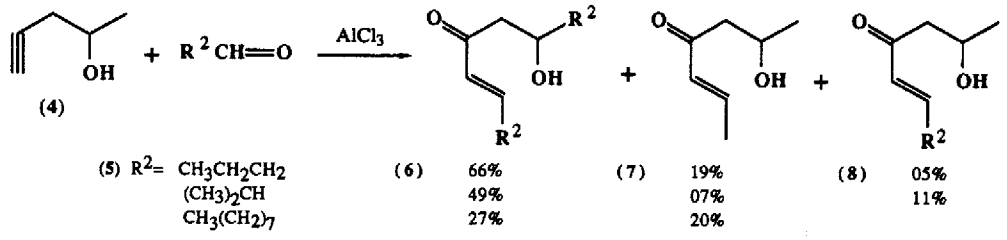
(**2**)

(**3**)

modified monosaccharides, we became interested in the condensation of the corresponding homopropargyl alcohols and their silyl ethers with carbonyl compounds under similar conditions.

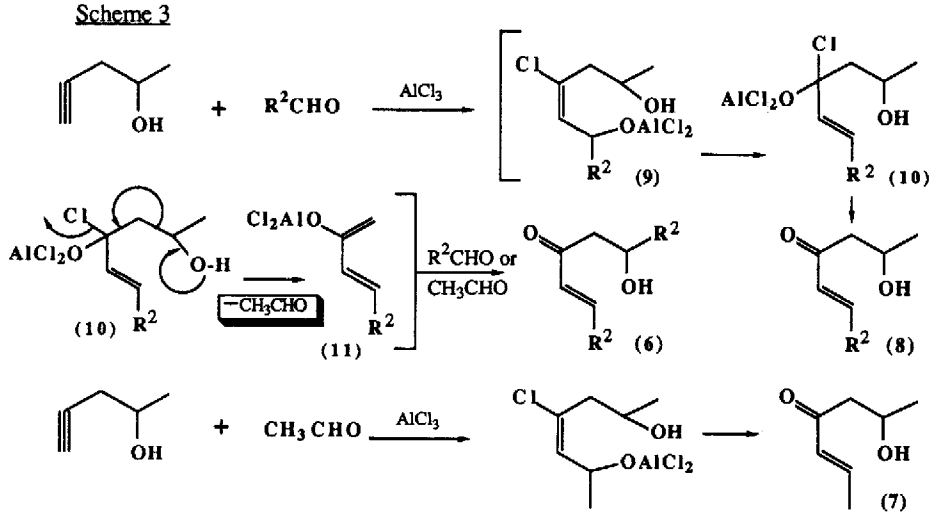
When 4-pentyn-2-ol (**4**, 0.001M) was reacted with n-butanal (**5**, 0.001M) and titanium tetrachloride (0.001M) in CH_2Cl_2 at -78° to -20° for two h, it gave a complex mixture. Using aluminium chloride as the Lewis acid in CH_2Cl_2 at -20° for 2h, the reaction gave the products **6**, **7** and **8** with no trace of any dihydropyrans. Similar products were obtained in comparable yields when 2-methylpropanal or n-nonanal was used as the aldehyde component. The structures of **6**, **7** and **8** were supported by spectroscopic evidence including IR (3100 and 1710 cm^{-1}), ^{13}C-NMR, ^1H nmr and mass spectrometry.[5] Their formation could be rationalized according to *scheme 3*. The initial product of condensation, **9**, isomerised to **10** and subsquently to **8** under the reaction conditions. A reverse aldol reaction of **10** generated **11** and acetaldehyde. Condensation of **11** with another molecule of R^2CHO gave product **6**, whereas acetaldehyde could condense with the starting homopropargyl

Scheme 2



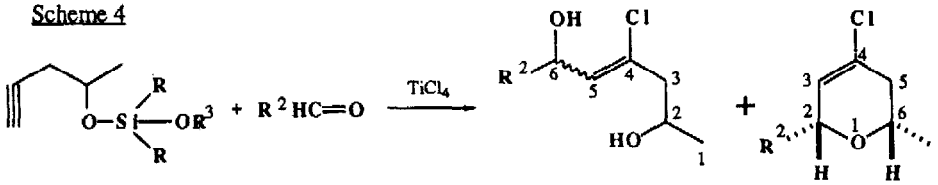
alcohol and rearranges to give **7**. These reactions may well be acid - catalysed due to the presence of proton derived from the interaction of alcohol with the Lewis acid.

Scheme 3



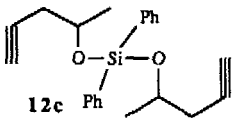
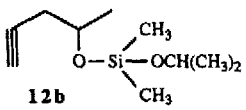
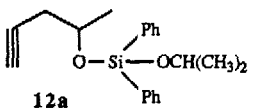
If the formation of **6**, **7** and **8** was due to presence of proton, their formation could be arrested with use of silyl ethers in place of the alcohols. The reaction of a number of silyl (i- Pr_3Si, t-$BuMe_2Si$, $PhMe_2Si$) ethers of **4** were attempted under various Lewis acid conditions. In all cases, a complex mixture of products were obtained with little dihydropyran formation. A substantial recovery of the propargyl alcohol **4** from the reaction mixtures suggested that cleavage of siloxy linkage by the Lewis acid was one of the major competing reactions. Since in the condensations of homoallylic alcohols (**1**) with carbonyl compounds according to *scheme 1*, the alkoxysilyl derivative **1c** gave good yields of the product **3**, we decided to examine the reaction of **12** with aldehydes accordingly. We were pleased to find that when **12** (R= Ph, R^3= i-Pr) was condensed with n-butanal using $TiCl_4$ as Lewis acid, the diol **13** and the dihydropyran **14** were obtained[6] in addition to recovered **4***(scheme 4)*. Evidently, the condensation of the unsymmetrical alkynes with aldehydes proceeded in a regiospecific manner as expected.[7] The stereochemistry of **13** (R^2 = n-C_3H_7) is tentatively assigned to be the Z-isomer. This is based on the following observations : (a) The reluctance of **13** to cyclize to **14** under the reaction conditions as well as on

Scheme 4



(12) (13) (14)

TABLE

Homopropargyl silyl ether	R^2CHO	Reaction Temp (time)	Yield (13)	Yield (14)
 12c	CH_3CH_2CHO	-78° (30min) -35° (1h)	7%	63%
	$CH_3CH_2CH_2CHO$	-78° (30min) -35° (1h)	8%	61%
	$CH_3(CH_2)_3CHO$	-78° (30min) -35° (1h)	9%	61%
	$CH_3(CH_2)_4CHO$	-78° (30min) -35° (1h)	10%	62%
	$CH_3(CH_2)_7CHO$	-78° (30min) -35° (1h)	13%	60%
	$C_6H_5CH_2CHO$	-78° (30min) -35° (1h)		62%
 12b	$CH_3CH_2CH_2CHO$	-78° (3h)		35%
	$(CH_3)_2CHCHO$	-78° (3h)		29%
	$CH_3(CH_2)_5CHO$	-78° (3h)		23%
	$CH_3(CH_2)_7CHO$	-23° (3h)	19%	
 12a	CH_3CH_2CHO	-78° (1h) -40° (2h)	19%	46%
	$CH_3CH_2CH_2CHO$	-78° (1h) -40° (2h)	21%	47%
	$CH_3CH_2CH_2CHO$	-78° (1h) -23° (2h)	37%	35%
	$CH_3CH_2CH_2CHO$	-78° (1h) -23° (1.5h) 0° (30min)	67%	
	$CH_3(CH_2)_7CHO$	-78° (1h) -23° (1.5h)	13%	10%
	$C_6H_5CH_2CHO$	-78° (1h) -23° (2h)		32%

treatment with MsCl / Et_3N. The mesylate of **13** could be obtained with little formation of **14**; (b) A positive nOe was obtained on the vinylic H (+12%) of **13** when the signal at 2.45 ppm (H on C-3) was irradiated. Compound **14** (R^2 = n - C_3H_7) is assigned to have the cis - stereochemistry on the observations that a positive nOe was obtained on H-6 (8%) when the signal at 4.60 ppm (H on C-2) was irriadiated. This is in agreement with MMX calculations which showed that the cis - isomer of **14** is more stable by 2.29 Kcal / mole than the trans - isomer. The cyclisation in *scheme 4* gives therefore the thermodynamically more stable stereoisomer, as in the case of tetrahydropyran synthesis according to *scheme 1*. Other aldehydes gave similar results.

To render the present reaction useful for the synthesis of dihydropyrans, the yield of **14** had to be improved. We examined further the effect of the structural variation on the silyl group on the reaction. The following silyl groups : Me_2 (O - i - Pr)Si, Me_2 (O-Bn) Si, Ph_2 (O-i-Pr) Si, Ph_2 (O-Bn)Si, Ph_2 (O-CH(COOMe)Ph)Si were compared. It seemed that the secondary isopropoxy group was superior to the primary benzyloxy group. The use of the Me_2 (O-i-Pr) Si ether (**12b**) at -78° with $TiCl_4$ gave cleanly **14** (**Table**) but the yield remained modest. By combining these observations, the reactions of **12c**, the bis-silyl ether of **4**, with aldehydes were examined[8] and found to give good isolated yields of the dihydropyrans **14**. In all cases, compound **14** was obtained as one single stereoisomer.

In conclusion, it is found that dihydropyrans can be synthesized regiospecifically and stereoselectively from the condensation of the silyl ethers of homopropargyl alcohols with aldehydes. Equally important is the observation that the substituents on the silyl group can have profound effect on the course of the reaction even though the silyl group is quite remote from the reaction site.[9] Such a substituent effect may have application in other reactions of organosilicon compounds for synthesis.

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(1) F. Perron, K. F. Albizati, *J. Org. Chem.*, **52**, 4128 (1987).

(2) L. Coppi, A. Ricci and M. Taddei, *Tetrahedron Letters*, **28**, 973 (1987).

(3) Z. Y. Wei, J.S. Li, D. Wang and T.H. Chan , *Tetrahedron Letters* , **28**, 3441 (1987).

(4) L. Coppi, A. Ricci, M. Taddei, *J. Org. Chem.*, **53**, 913 (1988).

(5) **6** (R^2 = n-C_3H_7) ^{1}H-nmr (200MHz, $CDCl_3$) : 6.76 (dt, J = 7.0,16.0Hz, 1H), 5.98 (dt, J = 1.4,16.0Hz, 1H),4.0 (m, 1H), 3.10 (d, J = 2.8Hz, 1H), 2.56 and 2.42 (ABX, J = 3.1,8.6,17.2(J_{AB})Hz, H-A&B), 2.1 (dt, J = 1.4,7.0Hz, 2H),1.38 (m, 6H), 0.84 (t, J = 7.2Hz, 3H), 0.82 (t, J = 7.2Hz, 3H); ^{13}C-NMR (75.4MHz, $CDCl_3$): 208.4, 152.5, 120.4, 71.7, 48.0,47.1, 38.5, 36.5, 18.6, 13.9, 13.7; HRMS 184.148, $C_{11}H_{20}O_2$ requires 184.146. **7** ^{1}H-nmr (200MHz, $CDCl_3$) : 6.91 (dq, J = 6.8,15.8Hz, 1H), 6.13 (dq, J = 1.8,15.8Hz, 1H), 4.3 (m, 1H), 3.35 (d, J = 3.0Hz, 1H), 2.78 and 2.62 (ABX, J = 3.1,8.6 17.2(J_{AB})Hz, H-A&B), 1.94 (dd, J = 1.8,6.8Hz, 3H),1.1 (d, J = 6.0Hz, 3H); ^{13}C-NMR (75.4MHz, $CDCl_3$) : 202.0, 148.8, 130.7, 64.7, 47.3, 34.5, 22.3,13.6; HRMS 128.086 $C_7H_{12}O_2$ reqiures 128.083. **8** (R^2 = n-C_3H_7) ^{1}H-nmr (200MHz, $CDCl_3$) : 6.92 (dt, J = 6.8, 15.9Hz, 1H), 6.11 (dt, J = 1.8, 16Hz, 1H), 4.10 (m, 1H), 2.80 and 2.60 (ABX, J = 3.0, 8.6, 17.6(J_{AB})Hz, H-A&B), 1.93 (d, J = 8.0Hz, 3H), 1.4 (m, 4H), 0.92 (t, J = 6.0Hz, 3H); ^{13}C-NMR (75.4MHz, $CDCl_3$) 201.1, 143.9, 132.3, 67.5, 45.4, 38.6, 18.7, 18.4, 14.0; HRMS 156.115 $C_8H_{16}O_2$ reqiures 156.113.

(6) **13** (R^2 = n-C_3H_7) ^{1}H-nmr (200MHz, $CDCl_3$) : 5.70 (d, J = 9.5 Hz, 1H), 4.82 (dt, J = 7.0,9.5Hz, 1H), 4.13(h, J = 6.0Hz, 1H), 2.45 (d, J = 6.0Hz, 2H), 1.6(m, 4H), 1.22 (d, J = 6.0Hz, 3H), 0.93(t, J = 7.0Hz, 3H). **14** (R^2 = n-C_3H_7) ^{1}H-nmr (200MHz, $CDCl_3$) : 5.86 (d, J = 10.4Hz, 1H), 4.60(m, 1H), 4.14 (m, 1H), 2.67 and 2.42 (ABX, J = 3.8,8.2,14.4(J_{AB})Hz, H-A&B), 1.60 (m, 4H), 1.60 (d, J = 6.2Hz, 3H), 0.92(t, J = 7.2Hz, 3H).

(7) L. E. Overman and M. J. Sharp, *J.Am.Chem.Soc.*, **110**, 612 (1988).

(8) General procedure: $TiCl_4$ (2.5ml, 0.0025M, 1M in CH_2Cl_2) was added to 10.0 ml of CH_2Cl_2 at -78°, followed by dropwise addition of n-butanal (0.26 ml, 0.003M), dissolved in 9.0 ml of CH_2Cl_2. After 15 min. bis- silyl ether of homopropargyl alcohol (**12c**, 0.522g, 0.0015M) dissolved in 10.0 ml of CH_2Cl_2 was added. After 30 min., the reaction mixture was brought to -35°, and stirred at the same temperature for further one hr. The reaction was quenched at the same temperature with buffer (pH= 7) solution and extracted with CH_2Cl_2(100 ml). Organic layer was seperated and dreid over $MgSO_4$. On evaporation of solvent, the residue was subjected to column chromatography. Elution with EtOAc: Hexane (1: 5) gave **13** (9%) and **14** (61%) .

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