Communications

Lewis Acid Mediated Condensation of Alkenols and Aldehydes. A Selective Synthesis of Tetrahydropyrans and Oxepanes

Summary: A stereoselective synthesis of different oxacycles is reported starting from aldehydes and unsaturated alcohols in the presence of $AlCl_3$ or $AlBr_3$.

Sir: Acetal-initiated cyclization reactions have been recently reported for the stereoselective preparation of oxygenated heterocycles.[1]

Vinylsilanes gave different unsaturated oxacycles with a good control of the double bond stereochemistry[1b] (route 1 in Scheme I), and (2-methoxyethoxy)methyl (MEM) ethers were also employed to give 4-halotetraydropyrans with a complete control of the stereochemistry of the substituents[1a] (route 2 in Scheme I).

We and others recently reported[2] that the coupling between allylsilanes and aldehydes could be conveniently used to prepare 2,6-disubstituted 4-halotetrahydropyrans (Scheme II).

The possibility to obtain, in a single step and from simple starting materials, a heterocyclic ring so important in the field of natural products[3] prompted a more in depth study of this reaction and its mechanism, which was postulated as a cyclization of the hemiacetal formed by condensation of an intermediate homoallyl alcohol derivative with a second molecule of an aldehyde, mediated by the halogenated Lewis acid (Scheme III).

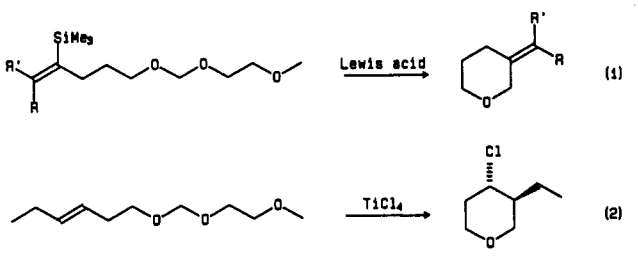
In the effort to justify this mechanism we discovered that an analogous condensation could be realized simply by mixing at 0 °C aldehydes and unsaturated alcohols in the presence of halogenated Lewis acids[4] (Scheme IV).

We report now the successful use of this reaction to prepare six- and seven-membered oxygenated rings and to synthesize (±)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**28**), a constituent of the perfume material civet, a glandular secretion of civet cat (*Viverra civetta*).[5]

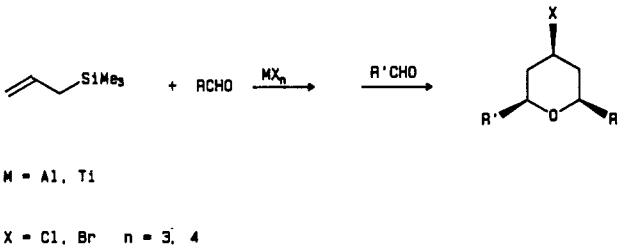
Our first studies were concerned with the preparation of 4-halotetrahydropyrans (Table I, entries 1–6).

Homoallyl alcohols **1–4** were prepared following the standard methodology that employs allylmagnesium bromide and a carbonyl compound. These were condensed[6] with different aldehydes in the presence of $AlCl_3$ and $AlBr_3$ to give the corresponding 4-chloro- and 4-bromotetrahydropyrans **12–17**.

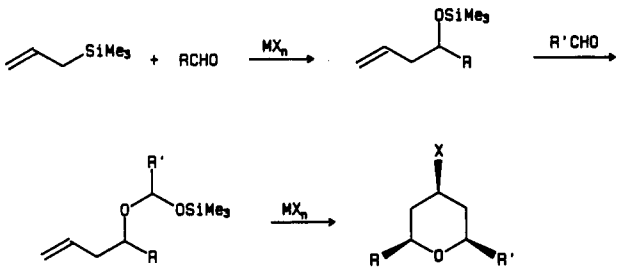
Scheme I



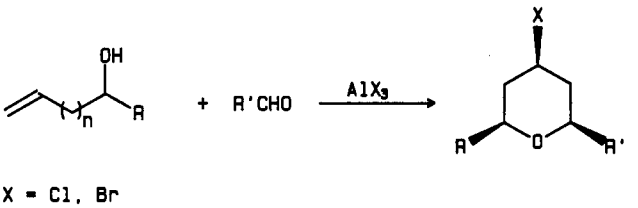
Scheme II



Scheme III



Scheme IV



As reported in Table I products **12–17** were obtained in the "all-cis" conformation[7] which is the thermodynamically favored one;[1b] this fact has been previously observed in the "allylsilane-based procedure" described in Scheme II.[2]

The conformatioms for the all-cis products are clearly 2,4,6-equatorial as indicated by the width of the ^1H NMR

(1) (a) Winstead, R. C.; Simpson, T. H.; Lock, G. A.; Schiavelli, M. D.; Thompson, D. W. *J. Org. Chem.* **1986**, *51*, 277. (b) Overman, L. E.; Castaneda, A.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 1303. (c) Nishiyama, H.; Itoh, K. *J. Org. Chem.* **1982**, *47*, 2496. (d) Cockerill, G. S.; Kocienski, P. *J. Chem. Soc., Chem. Commun.* **1983**, 705. (e) Key, I. T.; Williams, E. G. *Tetrahedron Lett.* **1983**, *24*, 5915.

(2) (a) Coppi, L.; Ricci, A.; Taddei, M. *Tetrahedron Lett.* **1987**, *28*, 973. (b) Wei, Z. Y.; Li, J. S.; Wang, D.; Chan, T. H. *Tetrahedron Lett.* **1987**, *28*, 3411.

(3) For an extensive compilation of this kind of compounds, see: Westley, J. W. Ed. *Polyether Antibiotics*; Marcel Dekker: New York, 1983; Vol. I and II.

(4) Terminal homoallylic alcohols have been reported to react in the presence of HCl or HBr to give 4-halotetrahydropyrans. Colonge, J.; Boiside, P. *Bull. Soc. Chim. Fr.* **1956**, *23*, 824.

(5) (a) Maurer, B.; Grieder, A.; Thommen, W. *Helv. Chim. Acta* **1979**, *62*, 44. (b) van Dorp, D. A.; Ward, J. P. *Experentia* **1983**, *37*, 917.

(6) For a typical cyclization reaction 5 mmol of the unsaturated alcohol and 5 mmol of the aldehyde in 10 mL of CH_2Cl_2 were added to a dispersion of 5 mmol of the Lewis acid in 2 mL of CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 3 h and then quenched with a buffer solution (pH 7.4). The product was extracted with diethyl ether and isolated by distillation or by column chromatography on silica gel.

(7) Products **12–17** showed a single peak at CLG analysis with a SE-30 25-m capillary column.

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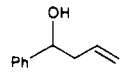
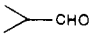
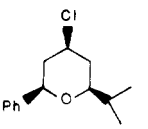
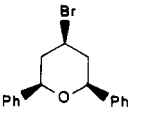
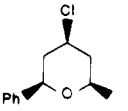
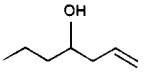
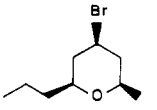
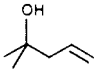
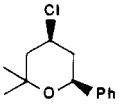
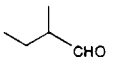
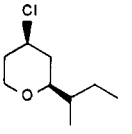
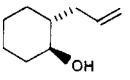
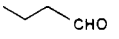
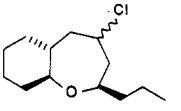
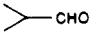
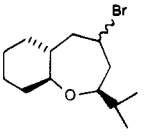
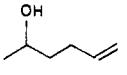
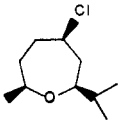
Table I. Condensation of Alkenols and Aldehydes in the Presence of AlX_3

entry	starting materials		lewis acid	product[a,b]	yield[c]
1	 1	 7	$AlCl_3$	 12	66%
2	1	PhCHO 8	$AlBr_3$	 13	55%
3	1	CH_3CHO 9	$AlCl_3$	 14	57%
4	 2	CH_3CHO 9	$AlBr_3$	 15	62%
5	 3	PhCHO 8	$AlCl_3$	 16	50%
6	 4	 10	$AlCl_3$	 17	69%
7	 5	 11	$AlCl_3$	 18	78%
8	5	 7	$AlBr_3$	 19	65%
9	 6	7	$AlCl_3$	 20	51%

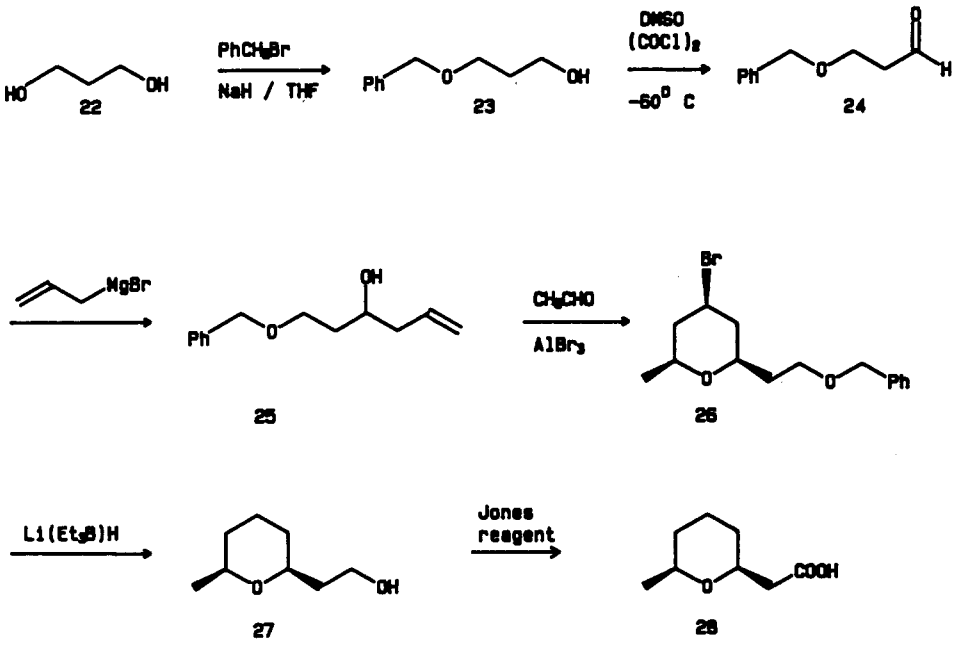
[a] All products are fully spectroscopically characterized (^1H NMR, ^{13}C NMR, MS). [b] Satisfactory analytical data (±0.4% for C, H, etc., were reported for all new compounds listed in the table (see supplementary material). [c] Yield of isolated products.

multiplets at half-height,[8] W_H, which always assumes values in the range of 12–24 Hz, meaning the existence of an axial–axial coupling. This statement is confirmed by the observation of the ^1H NMR chemical shifts of the 4-hydrogens in the range 3.9–4.2 ppm, typical for H in axial position.[9] Furthermore products **14** and **15** have the methyl ^{13}C NMR chemical shifts in the range 21–22 ppm and these δ values have been reported to be consistent with equatorial methyl disposition.[10] The formation of tetra-

(8) Gaudemer, A. In *Stereochemistry, Fundamentals and Methods*, Kagan, H. B., Ed.; Georg Thieme: Stuttgart, 1977; Vol. 1, p 96.

(9) Wigfield, D. C.; Feiner, S. *Can. J. Chem.* **1978**, *56*, 789.

Scheme V



hydrofuran derivatives was excluded on the basis of the same ^{13}C NMR analysis.

A further advantage of this procedure over the previously reported allylsilane-based one[2] is that we can prepare larger rings starting from different unsaturated alcohols as shown in entries 7–9 of Table I which report the synthesis of oxepanes **18–20**. In the case of **18–19** we obtained a mixture of two isomers characterized by the presence of the halogen in equatorial and axial position. Nevertheless treating **19** with $Li(Et_3B)H$ debromuration occurred and 2-isopropyl-1-oxabicyclo[5.4.0]undecane **21** was formed as a single isomer.

It is noteworthy that the oxepane **20** was also obtained in the all cis configuration as the former tetrahydropyran derivatives.[11]

The high flexibility of this reaction is finally demonstrated in the synthesis of (±)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**28**). The synthetic way for the preparation[12] of this product is outlined in Scheme V.

Propanediol (**22**) was protected as the monobenzyl ether and oxidized to aldehyde **24** (DMSO, $(COCl)_2$, Et_3N –60 °C, 71%).

After condensation of **24** with allylmagnesium bromide, the alcohol **25** was isolated in 75% yield and cyclized with acetaldehyde and $AlBr_3$ in benzene (70% yield).

The *all-cis*-4-bromotetrahydropyran **26** was then treated with 3 equiv of $Li(Et_3B)H$ in boiling THF for 8 h to give directly the alcohol **27**, which after oxidation with Jones reagent afforded **28**, (32% overall yield for six steps). The product shows the same spectroscopic features [^1H NMR (300 MHz), ^{13}C NMR, and MS) previously reported in the literature.[5a,12a]

Acknowledgment. We are grateful to A. Degl'Innocenti (CNR, Florence) and S. Papaleo (University, Florence) for the high-field and ^{13}C NMR spectra.

Registry No. (±)-**1**, 80735-94-0; (±)-**2**, 111321-98-3; **3**, 624-97-5; **4**, 627-27-0; (±)-**5**, 111268-65-6; (±)-**6**, 54774-27-5; **7**, 78-84-2; **8**, 100-52-7; **9**, 75-07-0; (±)-**10**, 57456-98-1; **11**, 123-72-8; (±)-**12**, 111268-66-7; **13**, 111268-67-8; (±)-**14**, 111268-68-9; (±)-**15**, 111268-69-0; (±)-**16**, 111268-70-3; **17**, 111268-71-4; (±)-**18** (isomer 1), 111268-72-5; (±)-**18** (isomer 2), 111321-99-4; (±)-**19** (isomer 1), 111268-73-6; (±)-**19** (isomer 2), 111322-00-0; (±)-**20**, 111268-74-7; (±)-**21**, 111268-75-8; **22**, 504-63-2; **23**, 4799-68-2; **24**, 19790-60-4; (±)-**25**, 111322-01-1; (±)-**26**, 111268-76-9; (±)-**27**, 82280-95-3; (±)-**28**, 82335-13-5; $AlCl_3$, 7446-70-0; $AlBr_3$, 7727-15-3.

Supplementary Material Available: Spectroscopic data for compounds **12–21**, **24**, and **26–28** (5 pages). Ordering information is given on any current masthead page.

(10) (a) Gambaro, A.; Boaretto, A.; Marton, D.; Tagliavini, G. *J. Organomet. Chem.* **1983**, *254*, 293. (b) Eliel, E. L.; Hargrave, K. D.; Pietrusiewicz, K. M.; Manoharan, J. *J. Am. Chem. Soc.* **1982**, *104*, 3635.

(11) The stereochemistry was also determined by observation of the W_H values of 24, 21, and 22 Hz, respectively, for the 7-, 4-, and 2-hydrogens.

(12) For previous synthesis of the racemic compounds, see: (a) Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496. (b) Bates, H. A.; Deng, P. N. *J. Org. Chem.* **1983**, *48*, 4479. (c) Kim, Y.; Mundy, B. P. *J. Org. Chem.* **1982**, *47*, 3556. (d) Ley, S. W.; Lygo, B.; Molines, H.; Morton, J. A. *J. Chem. Soc., Chem. Commun.* **1982**, 1251. For synthesis of the chiral product, see: (e) Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474. (f) Seebach, D.; Pohmakotr, M. *Helv. Chim. Acta* **1979**, *62*, 843. (g) Lichtenthaler, F. W.; Klinger, F. D.; Jarglis, P. *Carbohydr. Res.* **1984**, *132*, C1.

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Novel Bicyclization Methodology via Cyclialkylation of ω-Halo-1-metallo-1-alkynes Containing Aluminum and Zinc[1]

Summary: A new bicyclization methodology involving cyclization of ω-iodo-1-alkynes via metalation–carbometalation with organometals containing Al or Zn followed by acylpalladation or cyclialkylation is described.

(1) Metal-Promoted Cyclization. 17. Part 16: Negishi, E.; Zhang, Y.; Bagheri, V. *Tetrahedron Lett.* **1987**, *28*, 5793.

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