Tetrahedron Letters,Vol.26,No.8,pp 1035-1038,1985
Printed in Great Britain

0040-4039/85 $3.00 + .00

A REGIO- AND STEREOCONTROLLED ACCESS TO 2,4-DIENOLS BY AMIDE/ALCOHOLATE-PROMOTED RING-OPENING OF DIHYDRO-PYRANS

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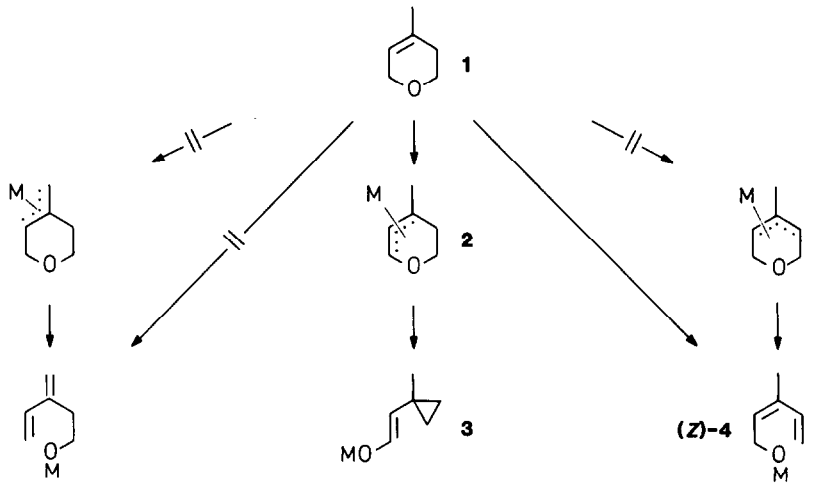
Summary: 3,6-Dihydro-2H-pyrans and other, cyclic or acyclic, homoallyl ethers undergo smooth ring-opening through β-elimination when treated with lithium diisopropylamide in the presence of catalytic amounts of potassium tert-butoxide.

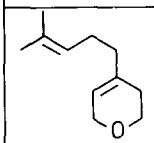
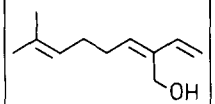
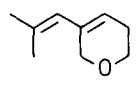
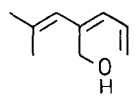
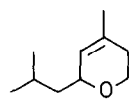
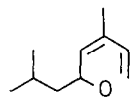
In the course of a systematic study of heteroatom effects on kinetic CH-acidities we have recognized two competing pathways for the reaction of 4-methyl-3,6-dihydro-2*H*-pyran (1) with organometallic reagents [1]. While *tert*-butyllithium or butylpotassium preferentially abstracts a proton from the allylic α-position to generate intermediate 2 (which upon warming up undergoes a Wittig rearrangement affording the cyclopropyl-enolate 3), butyllithium or *sec*-butyllithium mainly attacks the allylic β-position and promotes a concerted β-elimination leading to the dienolate 4 (M = Li). Thus, the rule-of-thumb [2], that *the more polar reagent favors the more polar transition state*, is confirmed once again.



The *cis*-3-methyl-2,4-pentadienolate (*Z*)- 4 , however, is not inert towards organometallic reagents such as *sec*-butyllithium. The rapid organolithium addition to the olefinic terminus is followed by immediate loss of dilithium oxide giving (*E*)-3,6-dimethyl-1,3-octadiene [1] as the only product [3]. As we have discovered in the meantime, lithium diisopropylamide in the presence of potassium *tert*-butoxide (roughly 10 mol%) is a far superior base to effect the

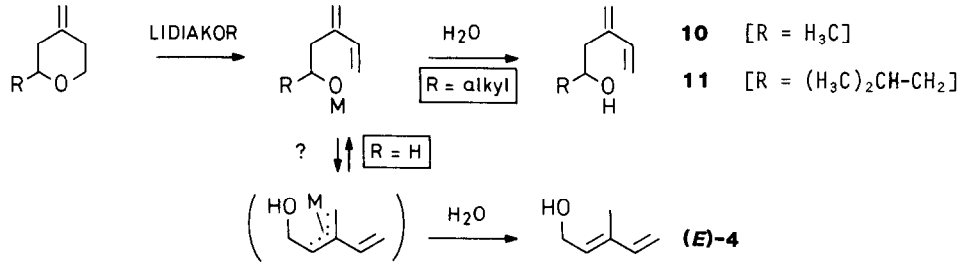
ring-opening elimination but does not interfere with the resulting 2,4-dienolate. In order to demonstrate the universality of this method, we have applied it to several other 3,6-dihydro-2*H*-pyrans (see table). As evidenced by gas chromatography, the conversion was nearly quantitative in all cases although, due to poor product stability, yields of isolated compounds 3 - 8 varied within the range of 35 - 74% (see table). The (*Z*)-configuration of the double bond, which was present from the beginning, remained always intact.

Table. 2,4-Pentadienols [4] by ring opening of dihydropyrans : yields of isolated pure products, boiling ranges and refractive indices.

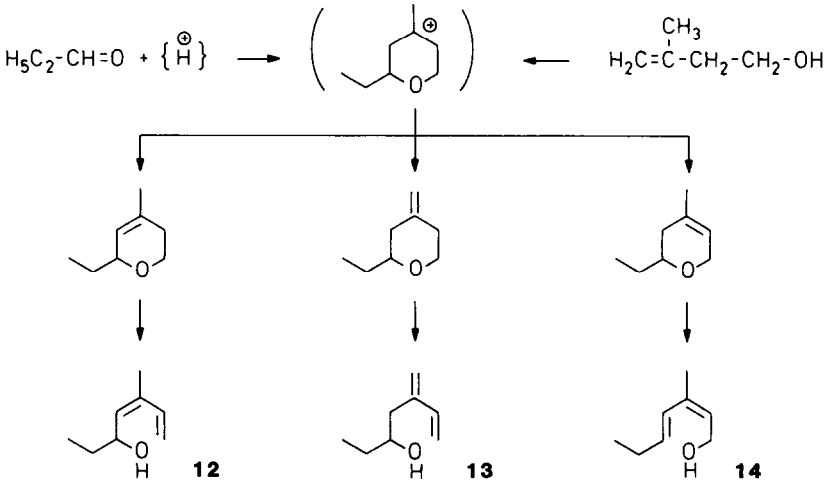
starting material	product	cpd.nr.	yield	bp[°C]/mmHg	n_D^{20}
		**5**	65%	75-80/12	1.4975
		**(*Z*)-4**	73%	44-46/1	1.4965
		**6**	35%	68-75/45	1.4881
		**7**	74 %	25-30/10^{-6}	1.5032
		**8**	47%	78-84/1	1.4935
		**9**	58%	85-88/1	1.4786

When treated with the amide/alcoholate-reagent, 4-methylene-tetrahydropyrans were found to undergo the same type of ring-opening reaction. Whenever the heterocyclic starting compound carried an alkyl substituent at the 2-position, the products had the expected structure of a β-methylene-γ,δ-unsaturated alcohol. The straight-forward preparation of 4-methylene-5-hexen-2-ol (10 , R = H_3C : 86%; bp 66 - 70°C/45 mmHg; n_D^{20} 1.4754) and 2-methyl-6-methylene-7-octen-4-ol (11 , R = $(H_3C)_2CH-CH_2$: 83%; bp 82 - 86°C/0.7 mmHg; n_D^{20} 1.4688; "ipsenol", the major pheromone component of several bark beetle species) may serve as an illustration. In the case of the

parent compound, however, total isomerization took place and (*E*)-3-methyl-2,4-pentadienol (*E*- 4 : 48%) was obtained as the only volatile product.



The Kriewitz-Prins reaction [5] allows the synthesis of a huge number of pyran derivatives. Frequently, however, a mixture of products is formed. For example the reaction between propanal and 3-methyl-3-buten-1-ol gives rise to three isomers in a 2 : 3 : 6 ratio. Due to the high selectivity of the amide/alcoholate-reagent these isomers react at substantially different rates. Competition experiments indicated relative rate constants of 9 : 3 : 1, the 6-ethyl-4-methyl-3,6-dihydro-2*H*-pyran being most, the other endo-unsaturated isomer least reactive. A satisfactory kinetic separation of the latter two isomers can be achieved after removal of the most volatile isomer, having the exocyclic double bond, by fractional distillation (bp 64 - 66°C/80 mmHg). Sequential treatment of the remaining unseparable mixture (bp 70 - 74°C/80 mmHg) by the stoichiometrically required amounts of amide/alcoholate-reagent gives (*Z*)-5-methyl-4,6-heptadien-3-ol (12) and (2*Z*,4*E*)-3-methyl-2,4-heptadien-1-ol (14) in this chronological order; the exo-double bond isomer affords 5-methylene-6-hepten-3-ol (13). The combined yield of 12 , 13 and 14 amounts to 69%.



All types of cyclic or acyclic homoallyl ethers may be submitted to amide/alcoholate-promoted elimination reactions. Thus, (*Z*)-1-methoxy-3-nonene was readily converted to (*Z*)-1,3-nonadiene (80%), 2-allyl-tetrahydropyran to (*E*)-5,7-octadien-1-ol (72%) and (*Z*)-1,4-dimethoxy-2-butene to 1-methoxy-1,3-butadiene (mixture of stereoisomers, 65%).

In general the use of equimolar rather than catalytic quantities of potassium *tert*-butoxide will give satisfactory results too, although sometimes it may cause isomerization or other undesirable side reactions. On the other hand, the yields decrease drastically when our special base-mixture is replaced by lithium diisopropylamide alone or by lithium diethylamide [6] and become negligible with the "potassium diisopropylamide" precipitate [7]. On the other hand, lithium diisopropylamide may be successfully replaced by other amides such as lithium tetramethylpiperidide and potassium tert-butoxide, for example, by potassium 1,1-dimethylpropoxide. From now on we shall designate such mixtures of lithium diorganylamides ("LIDA") and potassium alcoholates ("KOR") by the acronym "LIDAKOR".

Typical working procedure : Under vigorous stirring, 30 g (0.30 mol) diisopropylamine, 3.4 g (30 mmol) potassium *tert*-butoxide and 30 g (0.30 mol) 5,6-dihydro-4-methyl-2*H*-pyran were consecutively added to a 1 M solution of 0.30 mol butyllithium in tetrahydrofuran at -75°C. After 2 h at -50°C and addition of 200 mL water, the product was extracted with ether (3 x 50 mL; washing with 300 mL H_2O; drying with $CaSO_4$). At 44 - 46°C/1 mmHg, 21.6 g (73%) 3 were collected. The liquid remained colorless as long as protected from air.

Acknowledgement. This work was supported by the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung, Bern (grant no 2.635.0-82).

[1] E. Moret, P. Schneider, C. Margot, M. Stähle & M. Schlosser, manuscript in preparation.

[2] M. Schlosser, *Struktur und Reaktivität polarer Organometalle*, Springer Verlag, Berlin 1973 , p. 122 - 161.

[3] The corresponding (*E*)-dienol (*E*)- 4 (M. Schlosser & G. Rauchschwalbe, *J. Am. Chem. Soc.* 1978 , *100*, 3258) equally reacts with organolithium reagents, although more slowly and it leads to the *Z*-isomers of the resulting dienes.

[4] ^1H- and ^{13}C-nmr as well as mass spectra and, notably, elemental analyses corroborated the identity and purity of all new compounds.

[5] P.H. Williams, G.G. Ecke & S.A. Ballard, *J. Am. Chem. Soc.* 1950 , *72* , 5738; E. Arundale & L.A. Mikeska, *Chem. Rev.* 1952 , *51*, 505; H. Meerwein, in : *Houben/Weyl* "Methoden der organischen Chemie" (Editor : E. Müller), G. Thieme Verlag, Stuttgart 1965 , Vol. *6/3*, p. 265.

[6] J. Delaunay, *C.R. Hebd. Séances Acad. Sci., Sér. C.* 1976 , *282*, 391.

[7] L. Lochmann & J. Trekoval, *J. Organomet. Chem.* 1979 , *179*, 123. - Actually, when some time ago we prepared and examined such a precipitate, it contained substantial amounts of potassium hydride and very little diisopropylamine was recovered upon hydrolysis (J. Hartmann & M. Schlosser, 1974).

(Received in Germany 18 September 1984)