1,1-Diethoxybut-2-ene as a Precursor of (2-Hydroxyethyl)-Substituted Alkoxy Dienes: Convenient Intermediates for a New Synthesis of 2-Substituted and 2,6-Disubstituted Tetrahydro-4*H*-pyran-4-ones

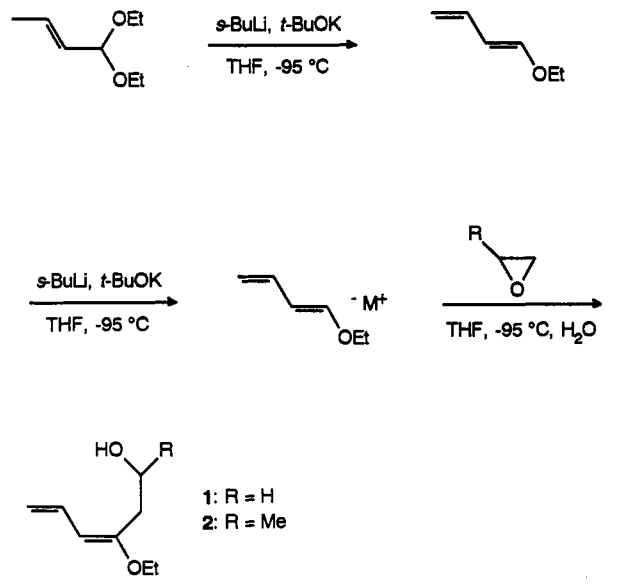
Cristina Prandi and Paolo Venturello*

Istituto di Chimica Organica dell'Università Via P. Giuria, 7-10125 Torino, Italy

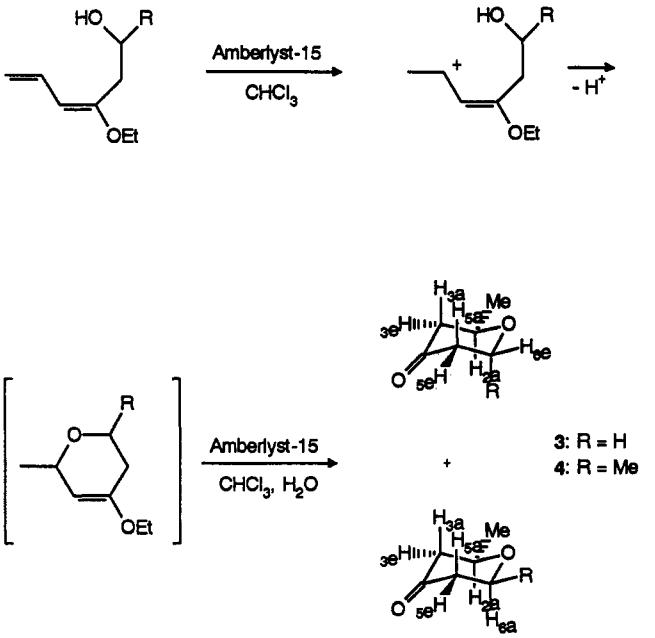
Received October 22, 1993

Substituted tetrahydro-4*H*-pyran-4-ones[1] are not commercially available; they are usually obtained by oxidation of the corresponding tetrahydropyran-4-ols. The latter are prepared by the Prin reaction, according to the procedure of Hanschke,[2] using homoallylic alcohol and aldehydes. A method for the preparation of tetrahydro-4*H*-pyran-4-one, which is an intermediate for the synthesis of 5,6-dihydro-4-methoxy-2*H*-pyran (suitable for the protection of nucleoside hydroxyl functions), has been also developed.[3] In preceding papers[4] it has been reported that in the presence of *sec*-butyllithium complexed with potassium *tert*-butoxide,[5] α,β-unsaturated acetals (derived from crotonaldehyde and 3-methyl-2-butenal) undergo a 1,4-eliminative process that affords 1-alkoxy 1,3-dienes. The reaction is promoted by proton abstraction at the γ position of the α,β-unsaturated acetal (Scheme 1). Moreover, when 2 equiv of the base are used for 1 equiv of the substrate, the produced alkoxy diene can be further metalated at the α vinylic site[6] and subsequently alkylated with different electrophiles.[4] This paper deals with aspects of the utility of the α-substituted alkoxy dienes as intermediates for a new synthesis of 2- and 2,6-disubstituted tetrahydro-4*H*-pyran-4-ones that starts from the above-described reaction sequence.

Scheme 1



Scheme 2



Results and Discussion

As shown in Scheme 1, an α-metalated alkoxy diene reacts with ethylene oxide as an electrophile to afford, after epoxide ring opening, 3-ethoxyhexa-3,5-dien-1-ol (1). The reaction with propylene oxide affords 4-ethoxyhepta-4,6-dien-2-ol (2). These enol ethers can be converted by mild acid to the corresponding carbonyl compounds.[7] In experiments directed at determining the feasibility of converting substituted alkoxy dienes into the corresponding α,β-unsaturated ketones, we have set up a one-pot synthetic sequence that directly yields 2-methyltetrahydro-4*H*-pyran-4-one (3) from 1 and 2,6-dimethyltetrahydro-4*H*-pyran-4-one (4) from 2 (Scheme 2). The results are reported in Tables 1 and 2. In a typical procedure 1,1-diethoxybut-2-ene reacts with ethylene oxide in the presence of 2 equiv of *sec*-butyllithium complexed with potassium *tert*-butoxide in dry THF at −95 °C under argon to afford 3-ethoxy-3,5-hexadien-1-ol (1) (70%).[8] Compound 1 was dissolved in chloroform and

(1) For a review, see: Heptworth, J. D. In *Comprehensive Heterocyclic Chemistry*, Vol. 3, Part B; Bulton, J. A., McKillop, A., Eds.; Pergamon Press: Oxford, 1984; pp 841–848. For other syntheses of tetrahydropyran-4-ones, see: Arentzen, R.; Yan Kui, Y. T.; Reese, C. B. *Synthesis* **1975**, 509. Owen, G. R.; Reese, C. B. *J. Chem Soc.* C **1970**, 2401. Sivakumar, R.; Satyamurthy, N.; Ramalingam, K.; O'Daniel, D. J.; Ramarajan, K.; Berlin, K. D. *J. Org. Chem.* **1979**, *44*, 1559.

(2) Hanschke, E. *Chem. Ber.* **1955**, *88*, 1053.

(3) Arentzen, R.; Yan Kui, Y. T.; Reese, C. B. *Synthesis* **1975**, 509.

(4) (a) Venturello, P. *J. Chem. Soc., Chem. Commun.* **1992**, 1032. (b) Canepa, C.; Prandi, C.; Sacchi, L.; Venturello, P. *J. Chem. Soc., Perkin Trans 1* **1993**, 1875.

(5) Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9. Schlosser, M.; Hartmann, J. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 508. Schlosser, M. *Mod. Synth. Methods* **1992**, *6*, 227.

(6) Conditions for metalation of cyclic vinyl ethers with *t*-BuLi and reaction of the resulting carbanions with electrophiles have been previously reported along with the application of this methodology to the synthesis of cyclic carbonyl compounds: Boekman, R. K., Jr.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997.

(7) Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974**, *96*, 5560. Still, W. C.; Macdonald, T. L. *Ibid.* **1974**, *96*, 5561. Baldwin, J. E.; Höfle, G. A.; Lever, O. W., Jr. *Ibid.* **1974**, *96*, 7125. Experiments are underway in our laboratory for converting the alkoxy dienes obtained from electrophiles other than ethylene and propylene oxide into α,β-unsaturated ketones.

(8) The α-substituted alkoxy dienes obtained from the reaction of α,β-unsaturated acetals with electrophiles exist in an *E*-configuration. The configuration was deduced from the coupling constant (J = 15 Hz) between the α and β protons in the ^{1}H NMR spectrum of the alkoxy diene, which was obtained by quenching the reaction with H_2O and not adding the electrophile (see ref 3b).

0022-3263/94/1959-3494$04.50/0

Table 1. Cyclization of 1,1-Diethoxybut-2-ene to 2-Substituted and 2,6-Disubstituted Tetrahydro-4*H*-pyran-4-ones via Intermediate Alkoxy Dienes[a]

epoxide	alkylation product yield[b] (%)	reaction time (h)	product yield[c] (%)
ethylene oxide	1 (70)	2	3 (60)
propylene oxide	2 (80)	2.5	4 (70)[d]

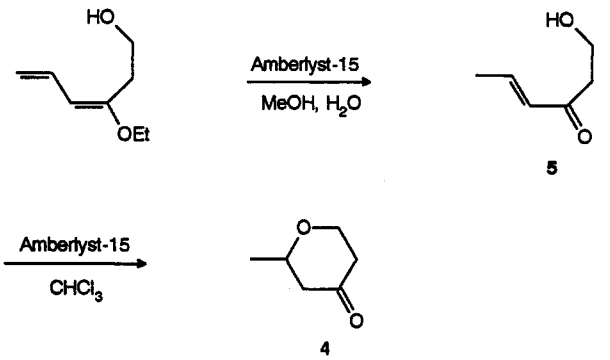
[a] T = −95 °C during the 1,4-elimination and alkylation steps; T = rt during the cyclization reaction; Amberlyst-15, 0.7 mequiv, with respect to the alkoxy diene; propylene oxide, 2.5 mmol; ethylene oxide, bubbled in excess. [b] By ^{1}H NMR analysis, on the basis of the weight of the collected product. [c] Isolated product, on the basis of the starting acetal. [d] Refers to both isomers.

Table 2. Cyclization of 1,1-Diethoxy-2-butene to 2-Substituted Tetrahydro-4*H*-pyran-4-one via Intermediate 1-Hydroxy-4-hexen-3-one[a]

hydrolysis time (min)	hydrolysis product yield[b] (%)	cyclization[c] time (h)	product yield[d] (%)
20	5 (90)	2	4 (65)

[a] Amberlyst-15, 0.7 mequiv with respect to the alkoxy diene, in aqueous metanolic (1:1) solution (50 mL); T = rt. [b] By ^{1}H NMR analysis, on the basis of the weight of the collected product. [c] For the reaction conditions see Table 1, footnote *a*. [d] Isolated product, on the basis of the starting acetal.

Scheme 3



stirred in the presence of a catalytic amount of Amberlyst-15. After 2 h at room temperature, tetrahydro-4*H*-pyran-4-one (**3**) was isolated (60%, with respect to the starting acetal).

The cyclization reaction involves an intramolecular S_N reaction that probably proceeds through the pathway shown in Scheme 2 rather than through intermediate α,β-unsaturated ketone 1-hydroxy-4-hexen-3-one (**5**) (Scheme 3). Ketone **5** is not isolable even when the reaction is quenched by filtration of the resin and neutralization before completion.[9] On the other hand, if **1** undergoes acidic treatment with Amberlyst-15 in aqueous methanolic solution, water competes as a nucleophile and the substrate follows the intermolecular hydrolysis pathway that affords α,β-unsaturated ketone **5**. Ketone **5** can be successively cyclized to tetrahydro-4*H*-pyran-4-one by treatment with a catalytic amount of Amberlyst-15 in chloroform solution (Scheme 3).

When propylene oxide is used as an electrophile, intermediate 4-ethoxyhepta-4,6-dien-2-ol (**2**) undergoes intramolecular cyclization, affording a mixture of *cis*- and *trans*-2,6-dimethyltetrahydro-4*H*-pyran-4-ones. The *cis*:*trans* ratio (70:30) was deduced by ^{1}H-NMR and GC analyses.[10] Moreover the ^{1}H NMR of the reaction mixture suggests that in the *cis* isomer the methyl groups occupy an equatorial position: H(2) and H(6) at δ 3.75 show a J = 11.5 Hz, which is typical of a vicinal coupling constant J_{anti}. Similarly, the ^{1}H NMR spectrum of 2-methyltetrahydro-4*H*-pyran-4-one suggests that the methyl substituent is in the equatorial position: H(2) at δ 3.75 shows a J_{anti} = 12 Hz.

Experimental Section

Epoxides were of commercial origin. 1,1-Diethoxybut-2-ene was prepared by reaction of the Grignard reagent of 1-bromoprop-1-ene with diethyl phenyl orthoformate according to the literature method.[11]

Alkylation Step. Under an atmosphere of argon, *t*-BuOK (0.56 g, 5.0 mmol) was added to anhydrous THF (5.0 mL) at rt. The suspension was cooled to −95 °C, and 1,1-diethoxybut-2-ene (0.36 g, 2.5 mmol) was added to it. After 15 min, *s*-BuLi (1.4 M solution in cyclohexane; 3.6 mL, 5.0 mmol) was added dropwise with stirring; after a few seconds the solution turned purple and was stirred at −95 °C for 2 h. After the addition of the appropriate epoxide (propylene oxide, 0.14 g, 2.5 mmol; ethylene oxide, bubbled in excess), the color was discharged (not completely, in the case of propylene oxide). The mixture was allowed to react for 2 h and was then quenched with aqueous THF (0.5 mL). The mixture was poured into water, the organic layer was separated, and the aqueous phase was extracted twice with diethyl ether. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated to give crude products.

Cyclization Step. Amberlyst 15 (4.6 mequiv·g^{-1}; 0.15 g) was suspended in chloroform (50 mL), and the substrate (**1**, 0.28 g, 2.0 mmol; or **2**, 0.31 g, 2.0 mmol) was added with stirring at rt. After 2 h the resin was filtered off, and the reaction mixture was treated with K_2CO_3, filtered, and concentrated under vacuum to give crude tetrahydropyranone **3** or **4**.

3: IR ($CHCl_3$) 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (d, J = 6 Hz, 3 H), 2.58 (dddd, J = 14, 7, 11.5, 1.5 Hz, 1 H), 2.20–2.45 (m, 3H), 3.68, (ddd, J = 12.0, 11.5, 3 Hz, 1 H), 3.75 (ddq, J = 12, 3, 6 Hz, 1 H), 4.30 (ddd, J = 11.5, 1.5, 7 Hz, 1H). Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.3, H, 8.6.

4 (*cis* + *trans*): IR ($CHCl_3$) 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (d, J = 6 Hz, 3H, *trans*), 1.40 (d, J = 6 Hz, 6 H, *cis* + 3 H, *trans*), 2.15–2.40 (m, 4 H, *cis* + 2 H, *trans*), 2.24 (dd, J = 14, 5 Hz, 1 H, *trans*), 2.55 (ddd, J =14, 5, 2 Hz, 1 H, *trans*), 3.75 (ddq, J = 11.5, 3, 6 Hz, 2 H, *cis* + 1 H, *trans*), 4.35 (ddq, J = 5, 5, 6 Hz, 1 H, *trans*). Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.4, H, 9.5.

Aqueous Hydrolysis. 3-Ethoxyhexa-3,5-dien-1-ol (0.23 g, 2.0 mmol) was dissolved in aqueous (1:1) methanol, Amberlyst-15 (4.6 mequiv·g^{-1}; 0.15 g) was added, and the reaction mixture was stirred at rt. After 2 h the resin was filtered out, the solution was extracted three times with diethyl ether, and the collected organic phases were dried over Na_2SO_4. After evaporation, 1-hydroxyhex-4-en-3-one (**5**) was isolated: ^{1}H NMR ($CDCl_3$) δ 1.75 (d, J = 6 Hz, 3H), 2.50 (t, J = 6 Hz, 2H), 3.30 (s, 1 H, exch), 3.50 (t, J = 6 Hz, 2H), 5.70 (d, J = 16 Hz, 1H), 6.30 (dq, J = 16, 6 Hz, 1H); MS, m/z (relative intensity) 99 (6), 96 (1), 86 (4), 69 (100). The cyclization of **5** was carried out in $CHCl_3$ solution in the presence of Amberlyst-15, according to the procedure described

(9) In this case the only detectable products (^{1}H NMR; TLC) in the reaction mixture were the unchanged starting alkoxy diene and the tetrahydro-4*H*-pyran-4-one. The absence of α,β-unsaturated ketone **5** as an intermediate (this compound is otherwise isolable in the case of acidic treatment in aqueous methanolic solution, see Scheme 3) suggests that **5** is not the precursor of cyclic ketone **3**. The absence of the cyclic enol ether in the reaction mixture is probably due to hydrolysis, which readily takes place under reaction conditions that are not anhydrous (solvent chloroform was not dried, and the reaction was carried out in an open vessel).

(10) We have deduced that the *cis* isomer predominates by considering the integration ratio between the signal at δ 3.75 (attributable to H(2) and H(6) in the *cis* isomer and to axial H (6) in the *trans* isomer) and the signal at δ 4.35 (attributable to equatorial H(2) in the *trans* form). The two isomer have not been separated. Experiments directed at reducing the diastereoisomeric mixture of ketone **4** into the corresponding alcohols prior to the chromatographic separation are underway.

(11) Barbot, F.; Poncini, L.; Randrianoelina, B.; Miginiac, P. *J. Chem. Res., Synop.* **1981**, 343.

for compounds **1** and **2**, and gives 2-methyl-tetrahydro-4*H*-pyran-4-one (65%).

Acknowledgment. This work was supported by grants from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica, from the Italian C.N.R., and from the project "Chimica Fine". We thank Prof. I. Degani (Università di Torino) for helpful discussion and criticism and Dr. M. Mella (Università di Pavia) for ^{1}H NMR spectra.

Supplementary Material Available: ^{1}H NMR and mass spectra of **3** and **4** (isomeric mixture) (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.