Pergamon

Tetrahedron Vol. 50, No. 43, pp. 12463-12468, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00789-6

1-Substituted 1-Ethoxy Dienes Obtained by Reaction of 1,1-Diethoxybut-2-ene with Electrophiles in the Presence of the Mixed Metal Base LICKOR

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Abstract. The mixture of *sec*-butyllithium and potassium *tert*-butoxyde (LICKOR reagent) in THF at -95 °C, promotes smooth 1,4-eliminative process in 1,1-diethoxybut-2-ene (**1**) to afford conjugate (*E*)-1-ethoxybuta-1,3-diene (**2**). Moreover, when 2 equivalents of the mixed base are used for 1 equivalent of the substrate, further metallation of the derivative **2** takes place affording the corresponding α-metallated ethoxy diene (**3**). Electrophiles react with **3** to give α-substituted derivatives **4a-e**. Intermediates **4b-c** and **4e** can be converted by aqueous methanolic hydrochloric acid into the corresponding carbonyl compounds **5b-c** and **5e**. On the other hand, in mild acid (*E*)-3-*tert*-butyl-4-ethoxy-2,2-dimethylhepta-4,6-dien-3-ol (**4d**) cyclizes in a one-pot synthetic sequence to 2,2-di-*tert*-butyl-3-ethoxy-5-methyl-2,5-dihydrofuran (**5d**).

In the field of reactivity umpolung[1] many authors have shown that the use of sulfur-stabilized anions is a suited strategy for preparing acyl anions and enolate cations from carbonyl compounds that, in their usual reactivity, give acyl cation and enolate anion equivalents.[2] Lithiated vinylic[3] and allylic[4] ethers have also been prepared, and their usefulness as acyl and homoenolate anion equivalents of considerable synthetic value has been demonstrated. On the contrary, few investigations have been concerned with the design of "reversed polarity" equivalents starting from acetals.[5] In particular, it has been reported that addition and/or substitution products predominate when α,β-unsaturated acetals react with alkyllithium reagents.[6] In this paper we report the progress of our investigations on the use of α,β-unsaturated acetals as precursors of α-substituted ethoxy dienes,[7a-b] that can be successively converted to carbonyl compounds.[7d] The synthetic sequence allows acetals to be considered as masked acyl anions.

RESULTS AND DISCUSSION

(*E*)-1-Ethoxybuta-1,3-diene (**2**) can easily be prepared by a 1,4-elimination reaction, promoted by treatment of 1,1-diethoxybut-2-ene (**1**) with *sec*-butyllithium complexed with potassium *tert*-butoxide (Schlosser's base; LICKOR)[8] in THF at -95 °C.[9, 10] Moreover, when the reaction is carried out in the presence of 2 equivalents of LICKOR for 1 equivalent of substrate **1**, intermediate **2** undergoes deprotonation at the vinylic site: α-metallated 1-ethoxybut-1,3-diene (**3**)[11] is produced.[12] The metallated intermediate **3** reacts with various electrophiles affording α-substituted alkoxy dienes **4a-e**. Examples are shown in Scheme 1 and listed in Table 1.

Scheme 1

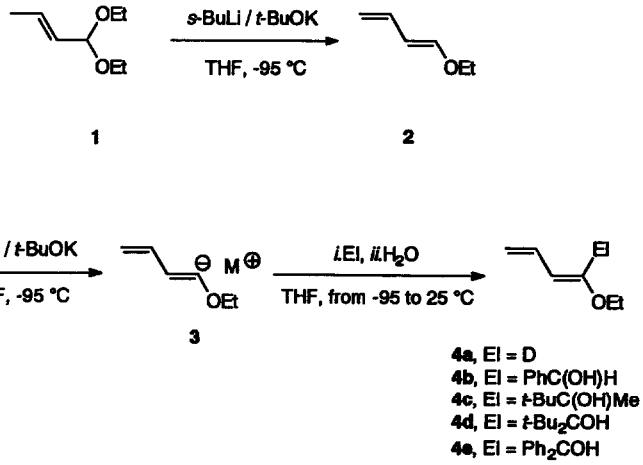


Table 1. Products Derived from 1,1-Diethoxybut-2-ene (1) and Electrophiles in the Presence of LICKOR Base[a]

Electrophile	Compound	Yield (%)[b]
D_2O[c]	**4a**	89
PhCHO	**4b**	61
t-BuCOMe	**4c**	74
t-Bu_2CO	**4d**	74
Ph_2CO	**4e**	64

[a]1,1-Diethoxybut-2-ene 5.0 mmol; THF, 10 mL; *s*-BuLi, 10.0 mmol; *t*-BuOK, 10.0 mmol; electrophile, 5.0 mmol; 3 h at T = -95 °C, then 1 h at 25 °C, unless otherwise specified. [b]Yield of pure isolated product. [c]See note 14.

Compounds **4b-c** and **4e**, like all enol ethers can be converted into carbonyl compounds by mild acidic treatment.[3, 4] Enones **5b-c** and **5e** are obtained (Scheme 2). The results are reported in Table 2. When deuterium oxide is used as an electrophile, we were unable to obtain deuteriated crotonaldehyde in satisfactory yields, by acidic work-up. After hydrolysis mainly polymeric by-products were isolated.

Scheme 2

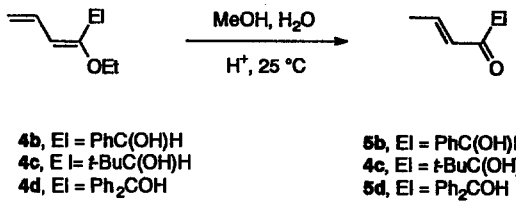


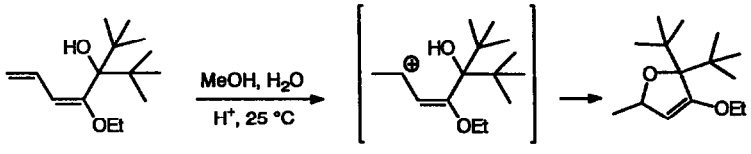
Table 2. Acid Catalysed Conversion of 1-Substituted 1-Ethoxydienes (4b-e) into Carbonyl Compounds[a]

Substrate	Compound	Yield[b] (%)
4b	**5b**	81
4c	**5d**	86
4d	**5d**[c]	75
4e	**5e**	92

[a]Substrate, (2.5 mmol); T = 25 °C; catalyst, 0.02 N HCl; solvent, MeOH : H_2O (4 : 1), 25 mL. [b]Isolated yield of products. [c] See Scheme 4.

Unlike compounds **4b-c** and **4e**, hydrolysis of intermediate **4d** proceeds according to a one-pot synthetic sequence that directly yields 2,2-di-*tert*-butyl-3-ethoxy-5-methyl-2,5-dihydrofuran (**5d**). The cyclization reaction involves an intramolecular S_N reaction that is probably promoted by the steric encumberment of the *tert*-butyl groups (Scheme 4). Unexpectedly the reaction does not proceeds to the cyclic ketone, as previously reported for substituted tetrahydro-4*H*-pyran-4-ones.[7c]

Scheme 3



4d **5d**

EXPERIMENTAL SECTION

1,1-Diethoxybut-2-ene was synthesised by reaction of the Grignard reagent of 1-bromopropene with diethyl phenyl orthoformate according to the literature method.[13] Electrophiles were commercially available reagent grade and were used without further purification. Et_2O and THF were distilled from benzophenone ketyl prior to the reaction. Flasks and all the equipment used for the generation and reactions of metallated species were flame dried under argon. *s*-BuLi (1.4 M solution in cyclohexane) was purchased from Aldrich. *t*-BuOK, obtained from Merck, was sublimed *in vacuo* (0.1 Torr) prior to the reaction. ^{1}H-NMR spectra (60 MHz) were recorded on a Hitachi Perkin-Elmer R-24B spectrometer in $CDCl_3$. ^{1}H- and ^{13}C-NMR spectra (300 MHz) were run on a Bruker-300 MHz spectrometer in $CDCl_3$. Infrared spectra were recorded with a Perkin-Elmer 599B spectrophotometer. Mass spectra were obtained on a mass selective detector HP 5970 B instrument, operating at an ionizing voltage of 70 eV connected to a HP 5890 GC, cross linked methyl silicone capillary column (25 m × 0.2 mm × 0.33 μm film thickness). TLC were performed on Merck GF 254. Products were purified by column chromatography on Merck silica gel 60 (70-230 mesh ASTM) with a cyclohexane /

diethyl ether (80/20) mixture as an eluant. Melting-point determinations were performed with an electrothermal apparatus, and are uncorrected.

Preparation of (E)-1-Ethoxybuta-1,3-diene (2).[14]

From a solution of *s*-BuLi (1.4 M solution in cyclohexane; 3.6 mL, 5.0 mmol) the solvent was stripped off under reduced pressure. Under an atmosphere of argon, precooled (-95 °C) Et_2O (10 mL), 1,1-diethoxybut-2-ene (0.72 g, 5.0 mmol) and *t*-BuOK (0.56 g, 5.0 mmol) were consecutively added with stirring at -95 °C; after a few seconds the solution turned purple and was allowed to react for 2 h, then it was quenched with aqueous THF (1 mL), and the color was discharged. The mixture was poured into water, the organic phase was separated, and the aqueous phase extracted with diethyl ether (3 × 25 mL). The combined organic phases were washed with brine (2 × 15 mL), dried (Na_2SO_4), and distilled to give crude product. Careful bulb-to-bulb (Kugelrohr) distillation gave 0.44 g (90 %) of colorless (*E*)-1-Ethoxybut-1,3-diene (**2**), bp 108-111 °C (Lit. 109-112)[15]. ^1H NMR (60 MHz, $CDCl_3$, TMS) δ 1.20 (t, J = 7 Hz, 3 H), 3.65 (q, J = 7 Hz, 2 H), 4.50 (dd, J = 10, 2 Hz, 1 H), 4.80 (dd, J = 16, 2 Hz, 1 H), 5.35 (dd, J = 13.5, 10 Hz, 1 H), 5.90 (dt, J = 16, 10 Hz, 1 H), 6.35 (d, J = 13.5 Hz, 1 H),

(E)-[1-^{2}H]-1-Ethoxybuta-1,3-diene (**4a**).[14] Colorless oil, (0.44 g, 89 %). **4a** was synthesised according to the procedure above described for **2**, in the presence of 2 equiv of LICKOR reagent for 1 equiv of **1** and by quenching the reaction with heavy water. ^1H NMR (60 MHz, $CDCl_3$, TMS) δ 1.20 (t, J = 7 Hz, 3 H), 3.65 (q, J = 7 Hz, 2 H), 4.50 (dd, J = 10, 2 Hz, 1 H), 4.80 (dd, J = 16, 2 Hz, 1 H), 5.35 (dt, J = 10, 1.5 Hz, 1 H), 5.90 (dt, J = 16, 10 Hz, 1 H).

Preparation of α-Substituted 1-Ethoxy-1,3-Dienes; General Procedure.[14]

Under an atmosphere of argon, *t*-BuOK (1.1 g, 10 mmol) was added to anhydrous THF (10.0 mL) at room temperature. The suspension was cooled to -95 °C, 1,1-diethoxybut-2-ene (0.72 g, 5.0 mmol) and *s*-BuLi (1.4 M solution in cyclohexane; 7.2 mL, 10 mmol) were consecutively added with stirring. The mixture was kept 2 h at -95 °C, then the suitable electrophile (5.0 mmol) was added and allowed to react for 2 h. After the mixture had reached 25 °C it was stirred for 1 h; then it was poured into water (50 mL), the organic layer was separated, and the aqueous phase extracted with Et_2O (3 × 25 mL). The combined organic phases were washed with brine (2 × 15 mL), dried (Na_2SO_4), and concentrated to give crude products, that were purified by column chromatography.

(E)-2-Ethoxy-1-phenylpenta-2,4-dien-1-ol (**4b**). Colorless oil, (0.62 g, 61 %), IR (cm^{-1}, neat) 3500-3300, 1635; ^1H NMR (60 MHz, $CDCl_3$, TMS) δ 1.20 (t, J = 7 Hz, 3 H), 2.90 (br s, exch., 1 H), 3.75 (q, J = 7 Hz, 2 H), 3.80 (s, 1 H), 4.80 (dd, J = 10, 2 Hz, 1 H), 5.00 (dd, J = 16, 2 Hz, 1 H), 5.30 (d, J = 10 Hz, 1 H), 6.45 (dt, J = 16, 10 Hz, 1 H), 7.10 (br s, 5 H); MS, *m/z* (relative intensity) 204 (M^+, 25), 129 (89), 105 (86), 77 (100), 41 (25). Anal. Calcd. for $C_{13}H_{16}O_2$: C 76.44; H 7.90 %. Found: C 76.58; H 7.82.

(E)-4-Ethoxy-2,2,3-trimethylhepta-4,6-dien-3-ol (**4c**). Colorless oil, (0.73 g, 74 %), IR (cm^{-1}, neat) 3500-3300, 1625; ^1H NMR (60 MHz, $CDCl_3$, TMS) δ 1.00 (s, 9 H), 1.10 (t, J = 7 Hz, 3 H), 1.30 (s, 3 H), 2.60 (br s, exch., 1 H), 3.50 (q, J = 7 Hz, 2 H), 4.60 (dd, J = 10, 2 Hz, 1 H), 4.80 (dd, J = 16, 2 Hz, 1 H),

5.10 (d, J = 10 Hz, 1 H), 6.80 (dt, J = 16, 10 Hz, 1 H); MS, *m/z* (relative intensity) 198 (M^+, 86), 183 (100), 139 (25), 57 (49), 41 (50). Anal. Calcd. for $C_{12}H_{22}O_2$: C 72.68; H 11.18 %. Found: C 73.07; H 11.16.

(E)-3-tert-Butyl-4-ethoxy-2,2-dimethylhepta-4,6-dien-3-ol (**4d**). Colorless oil, (0.89 g, 74 %), IR (cm^{-1}, neat) 3500-3300, 1625; ^1H NMR (60 MHz, $CDCl_3$, TMS) δ 1.10 (s, 18 H), 1.20 (t, J = 7 Hz, 3 H), 2.70 (br s, exch., 1 H), 3.75 (q, J = 7 Hz, 2 H), 4.70 (dd, J = 10, 2 Hz, 1 H), 4.90 (dd, J = 16, 2 Hz, 1 H), 5.15 (d, J = 10 Hz, 1 H), 6.80 (dt, J = 16, 10 Hz, 1 H); MS, *m/z* (relative intensity) 240 (M^+, 86), 183 (100), 139 (25), 57 (49), 41 (50). Anal. Calcd. for $C_{15}H_{28}O_2$: C 74.95; H 11.74 %. Found: C 75.07; H 11.87.

(E)-2-Ethoxy-1,1-diphenylpenta-2,4-dien-1-ol (**4e**). Colorless oil, (0.90 g, 64 %), IR (cm^{-1}, neat) 3500-3300, 1635; ^1H NMR (60 MHz, $CDCl_3$, TMS) δ 1.20 (t, J = 7 Hz, 3 H), 2.90 (br s, exch., 1 H), 3.75 (q, J = 7 Hz, 2 H), 4.80 (dd, J = 10, 2, 1 H), 5.00 (dd, J = 16, 2 Hz, 1 H), 5.30 (d, J = 10 Hz, 1 H), 6.80 (dt, J = 16, 10 Hz, 1 H), 7.0 (m, 10 H); MS, *m/z* (relative intensity) 280 (M^+, 19), 183 (10), 105 (100), 77 (84), 41 (7). Anal. Calcd. for $C_{19}H_{20}O_2$: C 81.40; H 7.19 %. Found: C 81.60; H 7.28.

Preparation of Carbonyl Compounds from 4a-d; General Procedure.

Intermediates **4b-e** (2.5 mmol) were stirred in 25 mL of aqueous methanolic (1 : 4) 0.02 N HCl at 25 °C for 2-6 h. The reaction was followed by TLC (Et_2O : cyclohexane, 20 : 80). After the disappearance of the spot corresponding to intermediate ethoxy diene, the solution was neutralised with 5 % aqueous $NaHCO_3$ (25 mL) and concentrated under reduced pressure. The reaction mixture was then extracted with Et_2O (2 × 50 mL), the organic phase was then washed with brine, (2 × 25 mL), dried (Na_2SO_4), filtered and concentrated to give crude products.

1-Hydroxy-1-phenylpent-3-en-2-one (**5b**). Colorless oil, (0.36 g, 81 %); IR (cm^{-1}, neat), 3500-3300, 1680, 1620; ^1H NMR (60 MHz, $CDCl_3$, TMS) δ 1.90 (dd, J = 6, 1.5 Hz, 3 H),2.95 (br s, exch., 1 H), 3.30 (s, 1 H), 6.20 (dq, J = 16, 1.5, Hz, 1 H), 6.9 (m, 6 H); MS, *m/z* (relative intensity) 176 (M^+, 19), 183 (10), 105 (100), 77 (84), 41 (7). Anal. Calcd. for $C_{11}H_{12}O_2$: C 74.98; H 6.86 %. Found: C 74.23; H 6.91.

3-Hydroxy-2,2,3-trimethylhept-5-en-4-one (**5c**). Colorless oil, (0.36 g, 86 %); IR (cm^{-1}, neat), 3450, 1680, 1620; ^1H NMR (60 MHz, $CDCl_3$, TMS) δ 0.95 (s, 9 H), 1.30 (s, 3 H), 1.80 (dd, J = 6, 1.5 Hz, 3H), 2.90 (br s, exch., 1 H), 6.20 (dq, J = 16, 1.5, Hz, 1 H), 6.90 (dq, J = 16, 6 Hz 1 H); MS, *m/z* (relative intensity) 113 ($M^+ - C_4H_9$, 45), 101 (100), 69 (49), 41 (100). Anal. Calcd. for $C_{10}H_{18}O_2$: C 70.55; H 10.66 %. Found: C 70.24; H 10.88.

2,2-Di-tert-butyl-3-ethoxy-5-methyl-2,5-dihydrofuran (**5d**). Colorless oil, (0.45 g, 75 %); IR (cm^{-1}, neat), 1650; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 1.09 (s, 9 H), 1.10 (s, 9 H), 1.25 (d, J = 6 Hz, 3 H), 1.33 (t, J = 7 Hz, 3 H), 3.72 (qd, J = 7, 2 Hz, 1 H), 3.75 (qd, J = 7, 2 Hz, 1 H), 4.48 (d, J = 2 Hz, 1 H), 4.72 (dq, J = 2, 6 Hz, 1 H); ^{13}C δ 14.54, 21.91, 28.60, 28.71, 28.91, 29.10, 29.22, 29.30, 39.03, 42.44, 64.86, 78.32, 95.18, 96.23, 159.60; MS, *m/z* (relative intensity) 183 ($M^+ - C_4H_9$, 98), 69 (51), 57 (96), 41 (100). Anal. Calcd. for $C_{15}H_{28}O_2$: C 74.95; H 11.74 %. Found: C 74.33; H 11.59.

1-Hydroxy-1,1-diphenylpent-3-en-2-one (**5e**). (mp 74-75 °C, ether / hexanes); (0.58 g, 92 %); IR (cm^{-1}, neat), 3500-3300, 1680, 1620; ^1H NMR (60 MHz, $CDCl_3$, TMS) δ 1.65 (dd, J = 6, 1.5 Hz, 3 H), 5.00 (s, exch., 1 H), 6.20 (dq, J = 6, 1.5 Hz, 1H), 7.0 (m, 11 H); MS, *m/z* (relative intensity) 252 (M^+, 2), 183 (100), 105 (69), 77 (40). Anal. Calcd. for $C_{17}H_{16}O_2$: C 80.93; H 6.39 %. Found: C 80.53; H 6.57.

Acknowledgement. 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". The authors thank Dr. M. Mella (University of Pavia) for ^1H- and ^{13}C-NMR 300 MHz spectra.

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10. Intermediate **2**, and consequently products **4a-e**, exists in an *E*-configuration. The configuration was deduced from the J_{trans} coupling constant between the α and β vinylic protons in the ^1H NMR spectrum of **2** (See Experimental Section). In our laboratory (*Z*)-1,1-diethoxybut-2-ene was synthesised (60 %), starting from *cis*-1-bromoprop-1-ene, according to the procedure reported in ref. 13. When this acetal reacts with LICKOR, under the experimental conditions set up for **1**, 1,4-elimination occurs to give (*E*)-1-ethoxybuta-1,3-diene (**2**) (90 %). In the presence of 2 equiv of LICKOR, addition to pivaldehyde (65 %) occurs.
11. The crotonyl anion equivalent was previously obtained by metallation of 1-methoxybutan-1,3-diene with *t*-BuLi in THF at -65 °C: see ref. 3a.
12. In experiments carried out in our laboratory, the reaction between (*E*)-1-ethoxybuta-1,3-diene (**2**) (1 equiv) and benzaldehyde in the presence of *s*-BuLi (1 equiv) in THF at -95 °C afforded 2-methyl-1-phenyl-1-butanol (70 %), as the only isolated product.
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14. It is advisable to strip off the cyclohexane solvent from *s*-BuLi and to use Et_2O instead of THF, just to allow a more careful distillation of **2** and **4a**. On the other hand, products **4b-e** are readily produced in THF without removing cyclohexane.
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(*Received in UK* 1 *August* 1994; *revised* 6 *September* 1994; *accepted* 9 *September* 1994)