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Mixed Metal Base LICKOR as Key Reagent in the Synthesis of Conjugate Alkadien-1-ols. A New Route to an Insect Attractant[1]

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Abstract: Tetrahydrofurfuryl alcohol has been oxidized to the corresponding aldehyde (**1**) using TPAP and NMO. Subsequent Wittig reaction afforded 2-alk-1-enyltetrahydrofurans (**2** and **3**) that can be metalated with Schlosser's reagent LICKOR. The base promotes the 1,4-eliminative ring fission, affording conjugate alkadien-1-ols (**4** and **5**) with high all *E* stereoselectivity. In the case of 2-pent-1-enyltetrahydrofuran, elimination reaction gives (4*E*,6*E*)-nona-4,6-dien-1-ol (**5**), which is structurally related to two sex pheromone components of the Caribbean fruit fly, *Anastrepha suspensa*.

In preceding papers it has been reported by Schlosser and co-workers that the mixture of lithium diisopropylamide and potassium *tert*-butoxide (LIDAKOR reagent)[2] induces a 1,2-elimination reaction in oxiranes[3] and in homoallyl ethers.[4] Data from our laboratory have shown that LICKOR reagent (butyllithium / potassium *tert*-butoxide) converts, through a 1,4-elimination reaction, α,β-unsaturated acetals into 1-alkoxy-1,3-dienes with the *E* configuration. These derivatives have been proved to be useful intermediates in the synthesis of various products, according to an *umpolung* approach,[5] and have also been used as starting material for the preparation of trienes for intramolecular Diels–Alder cycloaddition.[6] Functionalized dienes with defined configuration are moreover of widespread occurrence in natural products, or are used as key intermediates in the synthesis of important natural products.[7] In particular, some nonadienols have been identified as sex pheromone components of the Caribbean fruit fly, *Anastrepha suspensa.*[8] Nevertheless, the structure and the stereochemistry of such compounds have not yet been elucidated.

Here we report the first results that we have obtained studying the reactivity of 2-alk-1-enyltetrahydrofurans with the LICKOR super base to produce conjugate alkadienols.

RESULTS AND DISCUSSION

Our approach to the synthesis of conjugated alkadien-1-ols began with the preparation of tetrahydrofuran-2-carbaldehyde (**1**) starting from tetrahydrofurfuryl alcohol, as shown in Scheme 1. We tested three oxidation methods: Swern oxidation,[9] Corey's reagent,[10] and oxidation with tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine-*N*-oxide (NMO).[11] We found that the first two methods gave

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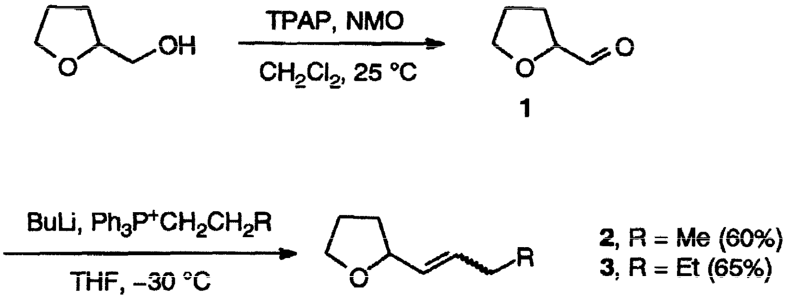
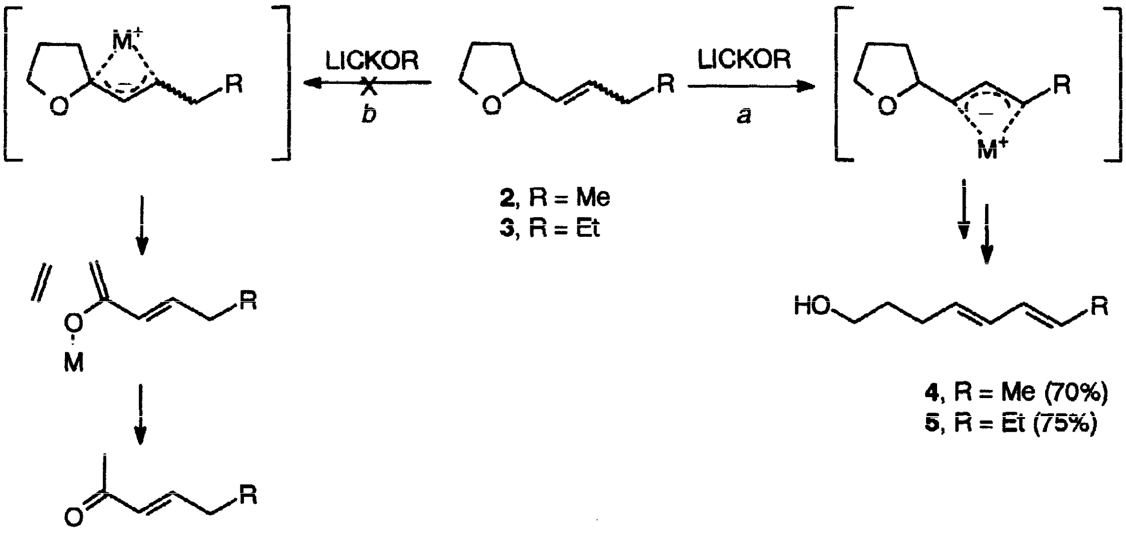
mainly the unreacted alcohol, while the oxidation reaction occurs with fairly good yield using the method described by Griffith and Ley.



Scheme 1

Tetrahydrofuran-2-carbaldehyde was transformed into the 2-alk-1-enyltetrahydrofuran (**2** and **3**) through a Wittig reaction using butyllithium as a base, according to the procedure proposed by Schlosser,[12] and the alkene was obtained with a marked selectivity.[13] The LICKOR-promoted ring opening of 2-(1-alkenyl)tetrahydrofuran gives (4*E*,6*E*)-alka-4,6-dien-1-ol as the sole product. The reaction proceeds according to the mechanism proposed in Scheme 2, path *a*.



Scheme 2

The metal-hydrogen exchange takes place at the allylic site far from the ring, and immediately promotes the 1,4-eliminative ring fission, which affords the 4*E*,6*E* conjugate dienic derivative, with high stereoselectivity.[14] No traces of the carbonyl derivative coming from metalation at the allylic carbon ring (path *b*, Scheme 2) were indeed detected in the reaction mixture. The absence of the 1,2-elimination product (path

b) can be well understood if we consider that this last derivative would be obtained through an allyl carbanion, destabilised by the presence of the oxygen substituent. Moreover, 2-pent-1-enyltetrahydrofuran (**2**) was recovered unreacted after treatment with butyllithium alone, in the absence of potassium *tert*-butoxide, under the same experimental condition set up in the present work (see Experimental Part). This datum once more stresses the high basicity and the low nucleophilicity that characterise lithium-potassium mixed bases.[15] In the literature there are relatively few articles dealing with base induced 1,4-eliminations, and usually the reactions require drastic conditions: besides LICKOR promoted 1,4-elimination in α,β-unsaturated acetals,[5] some examples are reported and discussed by Schlosser and co-workers.[16] The all *E* configuration of the elimination products is consistent with our previous results.[5] In particular, the stereochemistry of the alkadienols **4** and **5** was assigned on the basis of their ^{1}H NMR spectra, considering the patterns of the protons C4-H, C5-H, C6-H, and C7-H. These patterns display a large doublet (J= 14 Hz) that is consistent with a *trans* stereochemistry.

EXPERIMENTAL PART

Air and moisture sensitive compounds were stored and handled under an atmosphere of argon. The temperature of slush liquid nitrogen–acetone is consistently indicated as −95 °C, that of ice bath as 0 °C and "room temperature" as 25 °C. Starting materials are all commercial chemicals and were used without further purification, except potassium *tert*-butoxide, which was sublimed under vacuum (10 mm Hg) in order to eliminate traces of *tert*-butyl alcohol. Tetrahydrofuran (THF) was obtained anhydrous by distillation over sodium wire after the characteristic blue colour of *in situ* generated sodium diphenylketyl was found to persist.[17] The separation by column chromatography was performed on Merck silica gel 60 as stationary phase and light petroleum (distillation range 30–60 °C) – diethyl ether as eluent. ^{1}H NMR were recorded at 60, 300 or 400 MHz. Chemical shifts were determined using $SiMe_4$ as internal standard (60 MHz) or (300, 400 MHz) relative to the residual solvent peak ($CHCl_3$: δ_H 7.26). Coupling constants (J) are given in Hz, and coupling patterns are described by abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), p (pentuplet), m (multiplet), and br (broad). ^{13}C NMR spectra were recorded at 75.5 or 100.4 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: δ_C 77.0). A cross-linked methyl silicone capillary column [25m × 0.2 mm × 0.33 μm film thickness; oven temperature = 70 → 250 °C, 20 °C/min; flow rate (He) 5 ml/min] was used for GLC-mass spectra that were obtained at a 70 eV ionization potential.

Oxidation with tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine-N-oxide (NMO)

Solid TPAP (0.53 g, 1.5 mmol, 5 mol %) was added to a cooled (0 °C) and stirred mixture of tetrahydrofurfuryl alcohol (3.10 g, 30.0 mmol), NMO (5.28 g, 45.0 mmol) and powdered 4 Å molecular sieves (15.0 g, 500 mg/mol) in anhydrous CH_2Cl_2 (60 ml, 2 ml/mmol). On completion (1 h),[18] the mixture was filtered, the solvent was evaporated and the residue was purified by elution through a short silica gel column (6.0 g) with light petroleum–diethyl ether (50 : 50) affording 1.47 g (49.0%) of tetrahydrofuran-2-carbaldehyde (**1**), as a colourless oil. ^{1}H NMR (60 MHz): δ = 1.6–2.1 (4 H, m), 3.8–4.3 (3 H, m), 9.6 (1 H, d, J = 1.5 Hz). ν_{max}(film)/cm^{-1}: 1740 (lit.,[19] ν_{max}(CCl$_4$)/cm^{-1}:1715; lit.,[20] ν_{max}/cm^{-1}: 1732). Bp 43–46 °C/ 15 mmHg (lit.,[21] bp 43 °C/14 mmHg; lit.,[18] 75–80/2.1 mmHg).

Wittig reaction. General procedure

BuLi (1.6 M solution in hexanes, 6.3 ml, 10.0 mmol) was added dropwise to a slurry of the alkyltriphenylphosphonium salt (10 mmol) in 30 ml of anhydrous THF at –20 °C. After 30 min of vigorous stirring at that temperature the clear orange-colored solution was cooled to –75 °C and treated with tetrahydrofuran carbaldehyde (1.0 g, 10.0 mmol). After 1 h at –75 °C, the reaction mixture was left 30 min at –30 °C, and then treated with cold (T < –25 °C) pentane in order to precipitate the bulk of the triphenylphosphine oxide. The cold solution was filtered, and after evaporation of the solvent the crude reaction product was purified by column chromatography.

2-But-1-enyltetrahydrofuran (**2**): colourless oil. Purification: eluent light petroleum–Et$_2$O (90 : 10) (60 % yield); ^{1}H NMR (300 MHz): δ = 1.05 (3 H, t, J = 7.0 Hz), 1.50 (1 H, m), 1.90–2.10 (5 H, m), 3.75 (1 H, dt, J = 6.0, 8.0 Hz), 3.90 (1 H, q, J = 6.0 Hz), 4.50 (1 H, dt, J = 7.0, 7.0 Hz), 5.45 (2 H, m); ^{13}C NMR (75.3 MHz): δ = 14.1, 26.3, 30.0, 32.5, 67.0, 75.0, 130.6, 131.7; MS (EI, 70 eV): m/z (relative intensity) 125 (M$^+$–1, 1), 97 (97), 69 (18), 55 (18), 41 (65), 39 (46); ν_{max}(film)/cm^{-1}: 3015, 1655. Found C, 76.45; H, 11.08. Calc. for $C_8H_{14}O$: C, 76.14; H, 11.18.

2-Pent-1-enyltetrahydrofuran (**3**): colourless oil. Purification: eluent light petroleum–Et$_2$O (90 : 10) (65 % yield); ^{1}H NMR (400 MHz): δ = 0.89 (3 H, t, J = 7.3 Hz), 1.38 (2 H, m), 1.52 (1 H, dq, J = 11.8. 7.0 Hz), 1.90 (2 H, dt, J = 7.2, 7.7 Hz), 2.01 (1 H, m), 2.06 (2 H, m), 3.74 (1 H, dt, J = 5.9, 8.1 Hz), 3.89 (1 H, q, J = 5.9 Hz), 4.56 (1 H, dt, J = 7.0, 7.0 Hz), 5.41 (1 H, dd, J = 11.1, 7.0 Hz), 5.49 (1 H, dt, J = 11.1, 7.2 Hz); ^{13}C NMR (100.4 MHz): δ = 13.5, 22.7, 26.0, 29.5, 32.5, 67.7, 74.6, 130.6, 132.1; MS (EI, 70 eV): m/z (relative intensity) 139 (M$^+$–1, 1), 97 (100), 55 (99), 41 (71), 39 (36); ν_{max}(film)/cm^{-1}: 3013, 1658. Found C, 77.00; H, 11.45. Calc. for $C_9H_{16}O$: C, 77.09; H, 11.50.

1,4-Elimination reaction promoted by LICKOR base. General procedure

Under an inert atmosphere, BuLi (1.6 M solution in hexanes,6.3 ml, 10.0 mmol) was dropped under stirring to a cooled (–95 °C) solution of sublimed *t*-BuOK (1.12 g, 10.0 mmol) and 2-alk-1-enyltetrahydrofuran (5.0 mmol) in anhydrous THF (10 ml). After a few seconds the solution turned purple and was stirred at –95 °C for 2 h. After this time the reaction was quenched with a THF solution of H$_2$O (1 : 1, 10 ml), and the colour was discharged. The two phases were separated, and the aqueous one was extracted with

Et_2O (3 × 20 ml). The combined organic phases were washed with brine (2 × 15 ml), dried (Na_2SO_4), and concentrated to give crude alkanedienol, that was purified by column chromatography.

(4E,6E)-Octa-4,6-dien-1-ol (**4**): colourless oil. Purification: eluent light petroleum–Et_2O (70 : 30) (70 % yield); ^1H NMR (300 MHz): δ = 1.88 (3 H, d, J = 7.3 Hz), 1.90 (1 H, b s), 1.70 (2 H, p, J = 7.3 Hz), 2.18 (2 H, b q, J = 7.3 Hz), 3.65 (2 H, b t, J = 7.3 Hz), 5.60 (1 H, dt, J = 14.0, 7.3 Hz), 5.61 (1 H, dq, J = 14.0, 7.3 Hz), 6.02 (1 H, ddq, J = 14.0, 10.0, 1.2 Hz), 6.31 (1 H, ddt, J = 14.0, 10.0, 1.2 Hz); MS (EI, 70 eV): m/z (relative intensity) 126 (M^+, 24), 93 (100), 79 (93), 67 (87), 55 (49), 41 (99); ν_{max}(film)/cm^{-1}: 3350, 3015, and 1645. Found C, 76.35; H, 11.10. Calc. for $C_8H_{14}O$: C, 76.14; H, 11.18.

(4E,6E)-Nona-4,6-dien-1-ol (**5**): colourless oil. Purification: eluent light petroleum–Et_2O (70 : 30) (75 % yield); ^1H NMR (300 MHz): δ = 1.04 (3 H, t, J = 7.5 Hz), 1.62 (1 H, b s), 1.66 (2 H, p, J = 7.5 Hz), 2.08 (2 H, p, J = 7.5 Hz), 2.15 (2 H, b q, J = 7.5 Hz), 3.63 (2 H, b t, J = 7.5 Hz), 5.58 (1 H, dt, J = 14.1, 7.5 Hz), 5.61 (1 H, dt, J = 14.1, 7.5 Hz), 6.02 (1 H, ddt, J = 14.1, 10.2, 1.5 Hz), 6.31 (1 H, ddt, J = 14.1, 10.2, 1.5 Hz). ^{13}C NMR (75.3 MHz): δ = 13.5, 25.4, 28.8, 32.2, 62.2, 129.0, 130.9, 131.0, 134.3. MS (EI, 70 eV): m/z (relative intensity) 140 (M^+, 25), 93 (79), 79 (100), 77 (38), 67 (99), 55 (50), 41 (58)39 (47); ν_{max}(film)/cm^{-1}: 3345, 3015, and 1645.Found C, 77.19; H, 11.54. Calc. for $C_9H_{16}O$: C, 77.09; H, 11.50.

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13. The selectivity ($Z/E \geq 98$) has been observed using BuLi as a base, and the *Z* configuration is suggested on the basis of the coupling constant (J = 11.1 Hz) between the vinylic protons. On the contrary, with $NaNH_2$ a mixture of *Z* (80%) and *E* (20%) alkenes (by GC-MS) was obtained. In this case the two isomers have not been separated. The minor *E* isomer shows higher R_f, both by GC and TLC analyses. We have not carefully examined the configuration of compounds **2** and **3**, since the observed selectivity might be of some interest, but it is unimportant in the present case. In the following step of the synthesis the 1,4-elimination process induces the C–C double bond shift.

14. Two isomers have been detected (by GC-MS analysis) in the reaction mixture, and only the major one (≥ 98%) has been characterized as the (4*E*,6*E*) isomer (see Experimental Part). This result appears to be in contrast with what we reported in ref. 6(b), concerning the 1,4-elimination reaction carried out on 2-(but-1-enyl)-1,3-dioxane: in that case the *E,Z* isomer predominated. Experiments are in progress to account for these opposite outcomes.

15. For analogous cases proving the different reactivity of Schlosser's bases and alkyllithium reagents, compare for example the results reported by Bailey, W. F.; Zartun, D. L. *J. Chem Soc., Chem. Commun.* **1984**, 34–35 and by Mioskowski, C., Manna, S.; Falck, J. R. *Tetrahedron Lett.* **1984**, *25*, 519–522 with those of ref. 5.

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18. Longer reaction time, or insufficient cooling, causes formation of the corresponding dimeric ester as a by-product, and reduces reaction yield. For analogous cases of dimeric by-products, see ref. 10. Some preliminary tests, indicate moreover that it is important to activate molecular sieves (T = 150 °C, pressure = 10 mmHg), in order to improve the yield of the oxidation reaction.

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