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Obtention of 2,2-(Diethoxy) vinyl lithium and 2-Methyl-4-ethoxy butadienyl lithium by Arene-catalysed Lithiation of the corresponding Chloro Derivatives. Synthetic Applications.

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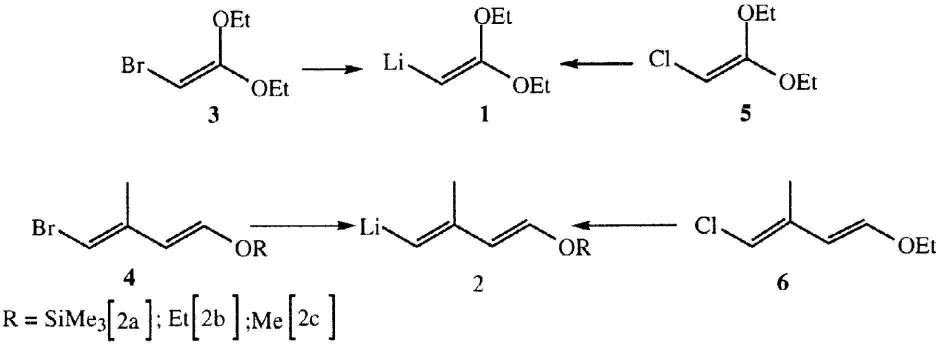
Abstract: Vinylic lithium reagents **1** and **2** could be obtained by the title procedure from their chloro precursors **5** and **6** instead of the less stable corresponding bromo derivatives **3** and **4**. Condensation with carbonyl compounds leads to interesting synthetic applications such as a two steps synthesis of retinal **13** from β-cyclocitral **10**.

Keywords: enol ethers; ketene acetals; reduction; retinoids.

We previously reported the preparation of β-lithioketene acetal **1** [1] and δ-lithio dienyl ethers **2** [2] from their bromo derivatives **3** or **4**, by bromine-lithium exchange with alkyl lithiums. The convenient procedure developped by Yus's group [3] for the reduction of numerous functionalised vinylic chlorides with powdered lithium in presence of catalytic amounts of an arene [4] prompted us to test this method for the preparation of **1** and **2** from chloro ketene acetal **5** and chloro dienyl ether **6**.



Chloro ketene acetal **5**, prepared with 92% yield by dehydrochloration of dichloro acetaldehyde dimethylacetal with *tert*- BuOK in THF at reflux [5], was further transformed into **1** by di-*tert*- butylbiphenyl (DBB)-catalysed lithiation in THF at -20°C. The latter **1** was condensed with various carbonyl compounds to yield adducts **7** which were converted either into ethylenic esters **8** or into β-hydroxy esters **9** (table 1). [6]

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It can be noted that the **yields of 8 and 9** were similar to those obtained when **1** was prepared from bromoketene acetal **3** by **bromine-lithium exchange** [1].

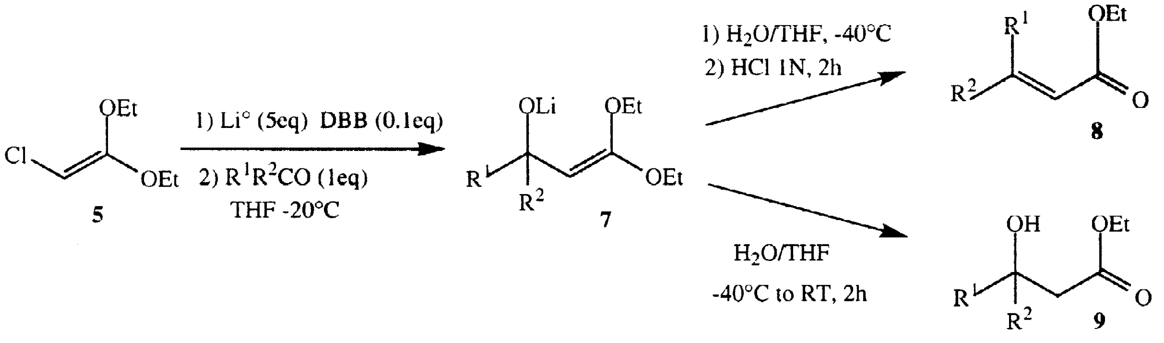
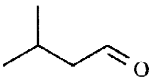
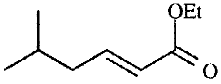
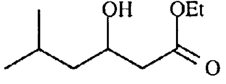
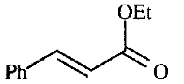
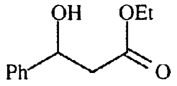
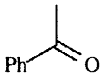
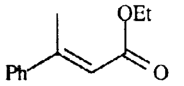
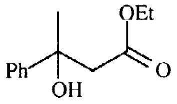
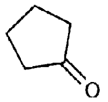
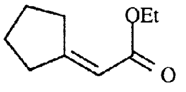
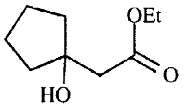
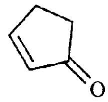
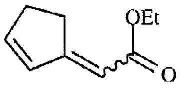
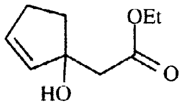
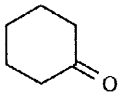
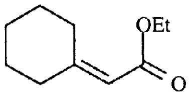
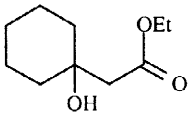
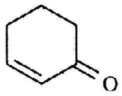
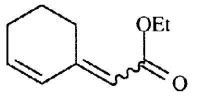
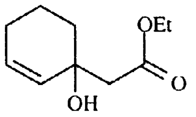
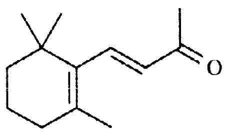
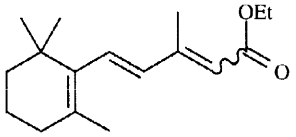
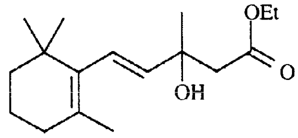


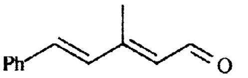
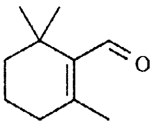
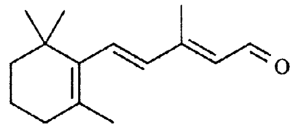
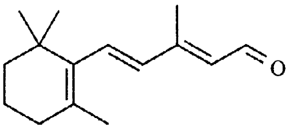
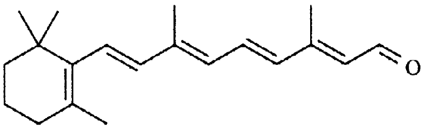
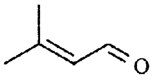
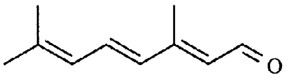
Table 1 Preparation of ethylenic esters **8** and hydroxy esters **9** by condensation with various carbonyl compounds of β-lithioketene acetal **1** obtained from chloro derivative **5**, with the « powdered Li/catalytic arene » procedure.

Entries	R^1R^2CO	Ethylenic Esters **8**	Yield %	Hydroxy Esters **9**	yield% (a)
1			59		61 (72)
2			75		73
3			79		75
4			68 (77)		(c)
5			71 (b)		(c)
6			73		75
4			75 (83)(b)		76 (73)
8			80 (84)(b)		76 (79)

a) After purification by chromatography on silicagel; in brackets, yields reported when **1** was prepared from bromoketeneacetal **3**.
b) Z-E isomers were not separated.
c) Not isolated.

These experimental conditions were also suitable for the preparation of lithio dienyl ether **2** from its chloro precursor **6** [7-9]. The reduction of chlorine was performed using 1.5 eq of powdered lithium and 0.10 eq of DBB in THF at different temperatures. The resulting lithium derivative **2** was condensed with benzaldehyde, β-cyclocitral **10**, β-ionylidene acetaldehyde **11** and prenal **12** (Table 2). The work-up involved i) H_2O/THF hydrolysis at the condensation temperature, ii) HCl 1N treatment to transform the intermediate hydroxy polyenol ether into a polyenic aldehyde. For entries 1-3, lithium derivative **2** was preformed at low temperature (-77 or -70°C) and condensed with the different carbonyl compounds at the same temperature. We could achieve a two steps synthesis of retinal **13** precursor of vitamine A, from β-cyclocitral **10** via β-ionylidene acetaldehyde **11** (entries 2 and 3) with yields of respectively 60% and 50% non optimised for each step [10]. Another procedure at higher temperature (Table 2, entry 4) was tested with prenal **12** (1 eq) and DBB (0.1 eq) which were added at 0°C to a mixture of lithium (1.5 eq) and **6** (1 eq) in THF. After 2h, the expected dehydrocitral **14** was obtained in a quantitative yield, as a crude material.

Table 2 - Condensation of aldehydes with lithium derivative **2** obtained from chloro derivative **6** by the « powdered Li/cat arene » procedure.

Entries	Carbonyl compound	Condensation product		yield % (a)
1	Ph-CHO	 Ph O	(b)	80
2	 O **10**	 O **11**	(c)	60
3	 O **11**	 O **13**	(d)	50
4	 O **12**	 O **14**		100 (e)

a) After purification by chromatography on silicagel; b) 2E,4E/2Z,4E= 90/10; c) 2E,4E/2Z,4E: 80/20; d) Four detected isomers; see note [10]; e) Crude material.

The main avantages of the DBB-catalysed lithiation for the preparation of vinylic anions **1** and **2** comparatively to the previously reported procedures [1,2] are: i) the chloro precursors **5** and **6** are more stable than their bromo analogs **3** and **4**, ii) powdered lithium is less dangerous and less expensive than organolithium reagents.

Acknowledgments: We thank Rhône Poulenc Co for a gift of chloroacetal precursor of **6**.

References and Notes

[1] Hiouni A, Duhamel L, Tetrahedron Lett. 1996;37:5507-5510.

Compound **1** was also obtained by a similar procedure: Wei HX, Schlosser M, Tetrahedron Lett. 1996;37:2771-2772.

[2] a) Duhamel L, Duhamel P, Lecouvé JP, Tetrahedron. 1987;43:4349.

b) Duhamel L, Ancel JE, Tetrahedron. 1992;48:9237-9250.

c) Le Gallic Y, Thesis, Rouen, 1992.

[3] Yus M, Chem.Soc.Rew. 1996; 152-161 and references therein.

[4] Yus M, Ramon DJ, J. Chem. Soc. Chem. Commun, 1991;398-401.

[5] **5** was obtained with 37% yield when the dehydrochloration was performed in *tert*- butanol:

Magnani A, Mc Elvain SM, J. Chem. Soc. 1938; 60:2210-2213.

[6] Di-*tert* -butyl biphenyl (DBB) (50 mg, 0.2 mmol) was added with stirring (magnetic stirrer) at RT under argon to a suspension of powdered lithium(10 mmol) in anhydrous THF (2.5 ml). The green solution was then immediately cooled to -20°C and **5** (320 mg, 2 mmol) in THF (0.5 ml) was added dropwise. Five minutes after the addition has been achieved, the carbonyl compound (1.8 mmol) in THF (0.5 ml) was added and the mixture was stirred for 2 h at -20°C; a mixture of H_2O/THF (50/50, 3 ml) was then added at -40°C.

α β-unsaturated esters **8** : immediately after warming up to 0°C, a HCl 1N (5 ml) solution was added to the above reaction mixture and the resulting mixture was further stirred for 2 h at RT.

β-Hydroxy esters **9** : after addition of a H_2O/THF (50/50, 3 ml) solution at -40°C, the mixture was stirred for 2 h at RT. The products were chromatographed on silicagel to yield **9** by petroleum ether/ Et_2O: 93/7 elution.

[7] Ferreira H, Diplôme d'Etudes Approfondies, Rouen, 1995.

[8] **6** was obtained by cracking at 120°C of the corresponding chloroacetal, which is an industrial intermediate (Rhône Poulenc Co).

a) Ancel JE, Thesis, Rouen, 1992; b) Duhamel L, Duhamel P, Ancel JE; Tetrahedron Lett, 1994;35:1209-1210.

[9] **6** was obtained as a mixture of two stereoisomers. Their configuration was determined using NOE experiments. ^1H NMR and % of each stereoisomer. C_6D_6:1E,3E (45%); 1.67 (s, 3H); 3.05 (s, 3H); 5.27 (d, 1H, J=12.8); 5.65 (s, 1H); 6.36 (d, 1H, J=12.8); 1E,3Z (55%): 1.40 (s, 3H); 3.12 (s, 3H); 5.42 (s, 1H); 6.17 (d, 1H, J=13.0); 6.55 (d, 1H, J=13.0).

[10] Synthesis of retinal **13** : DBB (35 mg, 0.13 mmol) in THF (1 ml) was added at RT to lithium (28 mg, 4 mmol) in THF (3.3 ml). The green solution was cooled to -70°C and chloro ether **6** (176 mg, 1.33 mmol) in THF (1 ml) was added in 15 minutes. About 15 minutes after the end of the addition, the green color was recovered. Then β-ionylidene acetaldehyde **11** (231 mg, 1.06 mmol) in THF (1 ml) was added in 15 minutes at -78°C. After letting stand for 5 h at this temperature, a solution of H_2O/THF (50/50, 10 ml) was added (T <-70°C). After warming to 0°C, a HCl 1N (8 ml) solution was added. The mixture was then extracted with ether 15 hours later. After work-up, retinal **13** (135 mg) was obtained by chromatography on silicagel (petroleum ether/ Et_2O : 95/5 elution) . Two main isomers were detected by ^1H NMR (60 / 40), all trans is predominant. Four isomers were detected by HPLC: all trans, 13-cis, 9-cis and 9-cis,13-cis.