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2-Substituted (*E*)-2-(2-Lithioethenyl)-1,3-dioxolanes: New Diastereoisomeric Pure β-Acylvinyl Anion Equivalents

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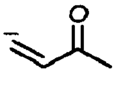
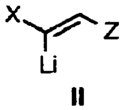
***Abstract*:** The reaction of (*E*)-chloroketals **1** with lithium powder and a catalytic amount of DTBB (4 mol %) in THF at -90°C followed by treatment with different electrophiles [H_2O, D_2O, Bu^tCHO, PhCHO, Me_2CO,$\overline{(CH_2)_4C}O$, PhCOMe] at -90 to -60°C affords, after hydrolysis with water, the expected functionalised protected (*E*)-α,β-unsaturated ketones **3**. The deprotection of products **3** is easily achieved with silica gel/aqueous oxalic acid (cat.) to yield (*E*)-functionalised alkenones **5**.

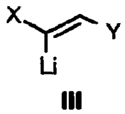
β-Acylvinyl anion equivalents of the type **I** are important intermediates in synthetic organic chemistry because of their ability to transfer the α,β-unsaturated acyl functionality to electrophilic reagents[1]. Lithium intermediates **II** of this type, which can also be consider as sp^2-hybridised[2] homoenolate equivalents[1] and d^3-reagents[3], are prepared in general by deprotonation of the corresponding activated precursors and contain usually the carboxylic acid derivatives functionality[4]. However, the corresponding carbonyl derivatives of the type **III**, prepared by deprotonation, have been far less studied[5]; in fact, to the best of our knowledge, only the naked lithium intermediate **IV**, prepared by bromine-lithium exchange, has been described[5b]. Moreover, the preparation of the lithiated species **IV** presents problems because, together with the mentioned process (debromolithiation), a deprotonation takes place in some extension yielding also an anion of the type **III** [X=Br, Y=C(OR)$_2$] as a by-intermediate[5b]. In this paper we describe the direct and stereoselective preparation of intermediates of type **IV** derived from α,β-unsaturated ketones by a chlorine-lithium exchange process catalysed by 4,4'-di-*tert*-butylbiphenyl (DTBB)[6,7] and their stereoselective reaction with electrophiles.



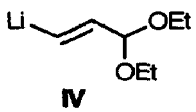
I



II



III

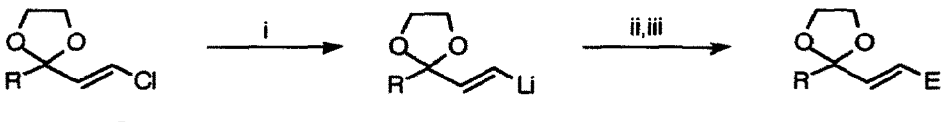


IV

[X=R,RO,RS,R_2N,Cl,Br,Ts
Z=CO_2Li,CO_2R,CONLiR,$CONR_2$,CN]

[X=Br,ArSO,R_2N,Ts
Y=PhCO,CR(OR)$_2$]

The reaction of (*E*)-chloroketals **1** with an excess of lithium powder (1:16 molar ratio) and a catalytic amount of DTBB (1:0.08 molar ratio; 4 mol %) in THF at -90°C led to the formation of the corresponding intermediates **2**, which suffered a S_E reaction with different electrophiles [H_2O, D_2O, Bu^{t}CHO, PhCHO, Me_2CO, $\overline{(CH_2)_4C}O$, and PhCOMe] at temperatures ranging between -90 and -60°C yielding, after hydrolysis with water, the expected products **3** bearing *E*-geometry [>95% *E* from 300 MHz ^1H NMR ($J_{CH=CH}$=15.4-17.2 Hz) and GLC], so a retention in both the lithiation and the S_E steps took place[8] (Scheme 1 and Table 1).



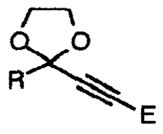
1a : R=Pr^n
1b : R=Pr^i

2a,b

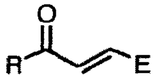
3ag-bg

Scheme 1. *Reagents and conditions*: i, Li powder, DTBB cat. (4 mol %), THF, -90°C, 1.5 h; ii, E^+=H_2O, D_2O, Bu^{t}CHO, PhCHO, Me_2CO, $\overline{(CH_2)_4C}O$, PhCOMe, -90 to -60°C; iii, H_2O, -60 to 20°C.

The temperature should be kept at -90°C in order to avoid by-processes; thus, for instance , working at -78°C compounds **4af** and **4be** were isolated in 14 and 13% yield, respectively, in the reaction of intermediates **2a** and **2b** with cyclopentanone and acetone, respectively (compare to Table 1, entries 6 and 12, respectively). The formation of these by-products can be explained by a dehydrochlorination of the starting material **1** and further lithiation of the corresponding alkyne prior to the last condensation with the electrophile.



4af : X=Pr^n, E=$\overline{(CH_2)_4C}$OH
4be : X=Pr^i, E=Me_2COH



5ac : R=Pr^n, E=Bu^{t}CHOH
5ad : R=Pr^n, E=PhCHOH
5ae : R=Pr^n, E=Me_2COH
5af : R=Pr^n, E=$\overline{(CH_2)_4C}$OH
5ag : R=Pr^n, E=PhC(OH)Me
5bg : R=Pr^i, E=PhC(OH)Me

Starting materials **1** were prepared by careful ketalisation of the corresponding unsaturated chloroketones [obtained by Friedel-Crafts type addition of the corresponding acyl chloride to acetylene promoted by aluminum chloride ($J_{CH=CH}$=13.3 Hz)][9] with 1,2-bis(trimethylsilyloxy)ethane under trimethylsilyl triflate catalysis[10].

Finally, compounds **3** can be easily deprotected under controlled conditions (silica gel, CH_2Cl_2, 10% aqueous solution of oxalic acid cat.)[11]. Thus compounds **5ac-ag** and **5bg** were obtained in almost quantitative isolated yield (>95%), the corresponding *E*-geometry and diastereoisomeric purity (>95%) being unambiguously determined by 300 MHz ^1H NMR ($J_{CH=CH}$=15.6-15.9 Hz)[12].

Table 1. Preparation of Compounds **3**

			Product 3^a				
Entry	Starting material	Electrophile E^+	No.	R	E	Yield (%)^b	R_f^c
1	**1a**	H_2O	**3aa**	Pr^n	H	90	0.93
2	**1a**	D_2O	**3ab**	Pr^n	D	88	0.93^d
3	**1a**	Bu^tCHO	**3ac**	Pr^n	Bu^tCHOH	55	0.53
4	**1a**	PhCHO	**3ad**	Pr^n	PhCHOH	52	0.64
5	**1a**	Me_2CO	**3ae**	Pr^n	Me_2COH	65	0.23
6	**1a**	$\overline{(CH_2)_4C}O$	**3af**	Pr^n	$\overline{(CH_2)_4C}OH$	52	0.36
7	**1a**	PhCOMe	**3ag**	Pr^n	PhC(OH)Me	53	0.45
8	**1b**	H_2O	**3ba**	Pr^i	H	90	0.86
9	**1b**	D_2O	**3bb**	Pr^i	D	67	0.86^d
10	**1b**	Bu^tCHO	**3bc**	Pr^i	Bu^tCHOH	53	0.45
11	**1b**	PhCHO	**3bd**	Pr^i	PhCHOH	43	0.60
12	**1b**	Me_2CO	**3be**	Pr^i	Me_2COH	63	0.44
13	**1b**	$\overline{(CH_2)_4C}O$	**3bf**	Pr^i	$\overline{(CH_2)_4C}OH$	62	0.57
14	**1b**	PhCOMe	**3bg**	Pr^i	PhC(OH)Me	55	0.56

[a] All products **3** were >95% pure and >95% *E* (GLC and 300MHz ^1H NMR) and were fully characterised by spectroscopic means (IR, ^1H and ^{13}C NMR, and mass spectrometry). [b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting chloroketal **1**. [c] Silica gel, hexane/ethyl acetate: 2/1. [d] >90% deuterium (mass spectrometry).

From the results described in this paper we conclude that this methodology represents an adequate and direct way for preparing lithiated β-acylvinyl anion intermediates in a stereoselective manner from easily available precursors; the reaction of these species with electrophiles is a convenient route for the preparation of both protected and unprotected functionalised α,β-unsaturated ketones, **3** and **5**, respectively.

In a *typical procedure* to a blue suspension of lithium powder (150 mg, 21 mmol) and DTBB (30 mg, 0.11 mmol) in THF (10 ml) was added the corresponding chloroketal **1** (1.3 mmol) at -90°C (bath temperature) and the reaction mixture was stirred for 1.5 h at the same temperature (disappearance of the starting material by GLC). Then, the corresponding electrophile (2.0 mmol) was added and the mixture was stirred 30 min allowing the temperature to rise to -60°C. Then it was hydrolysed with water (5 ml) and extracted with ethyl acetate. The organic layer was dried with Na_2SO_4 and evaporated (15 Torr) giving a residue, which was finally purified by column chromatography (silica gel, hexane/ethyl acetate) to yield pure compounds **3**.

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