A New Prenylation Method using the Lithium Enolate of Prenal. Reaction with Aldehydes and α,β -Unsaturated Aldehydes.

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Abstract : A γ -condensation of the enolate of prenal 1 is observed with aldehydes and α,β -unsaturated aldehydes. In this last case, a conjugate addition is obtained. Intermediate dihydropyrans 4 yield dienals 5 by hydrolysis.

The γ -regiospecific reaction of an enolate salt of unsaturated aldehydes such as crotonaldehyde or prenal is a long-standing challenge.¹⁻² In all cases¹⁻³ a self condensation of the dienolate with the starting carbonyl compound is observed. In order to overcome this problem, many processes have been proposed using ambident anions such as the anions of imines⁴⁻⁷ or dimethylhydrazones⁸⁻¹⁰ of unsaturated aldehydes. Nevertheless, there is no general procedure leading to a high regioselective reaction on the γ -site¹¹ with carbonyl compounds even with the use of HMPA.⁷ Recently, Horner-Wadworth-Emmons reagents functionalized by a dioxolane^{12,13} or an imine¹⁴ led to a γ -reaction in a multistep procedure.

In this paper,^{12,15} we report the γ -regiospecific condensation of the lithium enolate of prenal with saturated and α , β -unsaturated aldehydes. Lithium dienolate **1** was prepared from silvi dienol ether 2¹² or dienol acetate **3** by treatment with methyllithium (or n-butyllithium for silvi dienol ether **2**).



First we studied the condensation of the dienolate 1 with hard electrophiles such as PhMe2SiCl, AcCl, EtCOCl affording respectively as anticipated, the O-silylation or O-acylation products in high yields (entries 1-4, Table I). These results showed that the enolate formation is nearly quantitative and also that the dienolate 1 is stable for 4 hours at least in the reaction conditions (entries 1, 2).

With carbonyl compounds such as acetaldehyde, isobutyraldehyde or benzaldehyde (entries 5-7, Table I) dihydropyrans 4^{18} were prepared in good yields. These compounds are consistent with a γ -



addition of the dienolate 1 on the aldehydes followed by an intramolecular attack of the alkoxide on the carbonyl group leading, after hydrolysis, to compounds 4.

Entry	Electrophile	Reaction product	Yield	Yield ^a %f rom	
			2	3	
1 2 3 4	PhMe2SiCl , AcCl EtCOCl	$R = SiMe_2Ph$ " R = Ac R = EtCO	93 89b	96	
5 6 7	MeCHO iPrCH2CHO PhCHO	$R = Me \qquad 4a$ $R = iPrCH_2 \qquad 4b$ $R = Ph \qquad 4c$	74 83	74 94	
8 9		$R = Me \qquad 6a$ $R = 4 \qquad 6b$	53 61		

Table I: Reaction of Lithium Dienolate 1 with Electrophiles¹⁹

a) Yield of product purified by flash chromatography.

b) After 4 hours at -40°C.

The comparison of the results obtained for the reaction of the dienolate 1 with benzaldehyde (entry 7) shows that there is no significant difference when the dienolate 1 is prepared from either silvl enol ether 2 or from enol acetate 3 in spite of the presence, in the latter case, of lithium t-butoxide.

Dihydropyrans 4 were easily transformed into the corresponding dienals 5 in DMF / toluene in the presence of a catalytic amount of pyridinium chloride²⁰ (Table II). The overall process led to the transformation of a carbonyl compound into an elongated aldehyde 5 which is a very attractive reaction from a synthetic point of view.^{12-14,21}



The stereoselectivity (determined by ¹H NMR data) in favour of the 2E, 4E isomer is generally good (Table II).

Dihydropyrans 4	Dienals 5	Yields a	2E,4E/2Z,4Eb
4a	$R \approx Me$	5a 55	85/15
4b	$R \approx i Pr CH_2$	5 b 67	80/20
4c	R ≈ Ph	5c 70	70/30

Table II : Preparation of Dienals 5

a) yield of product purified by flash chromatography.

b) Isomer ratio was determined from the integral for the CHO proton.

With α,β -unsaturated aldehydes such as prenal or citral (entries 8,9, Table I) cyclic aldehydes 6 are obtained in fairly good yields (Table I). Such a reaction may be interpreted by a Michael addition of the dienolate 1 (regiospecific γ -attack) on the enal moiety, followed by an intramolecular aldol condensation yielding, after dehydration, aldehydes 6. Nevertheless, a Diels Alder mechanism can not be excluded in spite of the mild reaction conditions.²¹⁻²³



In conclusion, the condensation of the dienolate 1 with simple and α,β -unsaturated aldehydes occurs exclusively on the γ -position. For α,β -unsaturated aldehydes, a conjugate addition only is observed. For simple aldehydes, the overall process allows the introduction of the isoprenyl skeleton necessary for the terpene synthesis. Extension of this reaction to other polyenolates is in progress.

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- 4a IR: 3400, 1640 cm^{-1 1}H NMR: 5.5-5.0 (m,1H), 5.0-4.6 (m,2H), 3.8-3.3 (m,1H), 1.8 (s,3H), 1.4-1.0 (m,5H).¹³C NMR: 141,113.3, 96.6, 74.0, 55.6, 21.6, 18.2. 4b IR 3400, 1650 cm⁻¹. ¹H NMR: 5.6-5.2 (m,2H), 4.1-3.7 (m,2H), 2.1-1.8 (m, 5H), 1.4-1.2 (m,3H), 1.1 (d,6H). ¹³C NMR: 136.2, 120.2, 88.6, 64.15, 43.9, 35.4, 23.7, 22.55, 21.85. 4c IR: 3400, 1600 cm^{-1. 1}H NMR: 7.3 (s,5H), 5.4 (m,2H), 4.8 (m, 1H), 4.0 (d,J = 6.2Hz,1H mobile), 2.2-1.9, (m,2H), 1.8 (s,3H). ¹³C NMR: 141.7, 137.1,128.1, 127.4, 125.9, 120.1, 91.2, 63.3, 37.1, 22.7.(solvent: CCl4 and CDCl3 respectively for ¹H and ¹³C NMR).
- 19. Typical procedure: to a solution of 10 mmol of silyl enol ether 2 (or enol acetate 3) in 15 mL of THF at -20°C (or -30°C) was added a solution of methyllithium (10 mmol) in diethylether. After 30 min at -20°C, the reaction mixture was cooled to -70°C and a solution of the electrophile (10 mmol) in 2 mL of THF was added. After 15 min, the reaction mixture was allowed to warm to -20°C (entries 5-9) or to room temperature (entries 1-4) and then treated with 15 mL of a saturated aqueous solution of NaHCO₃. The reaction products were purified by flash chromatography.
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