Prenylation Reaction Performed with Catalytically Generated Potassium Prenal Dienolate

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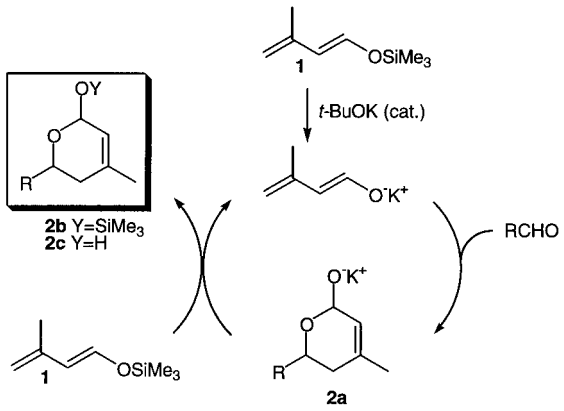
Abstract: A new prenylation method based on the reaction of catalytically generated potassium dienolate of prenal with α,β-unsaturated aldehydes is described. The reaction is highly regioselective, via a γ-1,2-addition, and provides an efficient route to retinal.

Continuing our interest in the application of alkali enolates in synthetic organic chemistry, we developed a new methodology providing an easy access to potassium enolates.[1] The regioselectivity, γ-1,2- versus γ-1,4-addition, in the addition of potassium prenal dienolate to α,β-unsaturated aldehydes was investigated,[2] and was found to be highly selective for a γ-1,2-addition. However, in some cases, the γ-1,4-addition product cannot be avoided.[2] During our investigation, we noted that catalytically generated potassium dienolate of prenal, by means of a catalytic amount of potassium *tert*-butoxide on the corresponding silyl enol ether **1**, accomplished the aldol reaction with benzaldehyde.[1] The oxygen-silicon bond, which is cleaved by *t*-BuOK is also broken by the hydroxy dihydropyran anion **2a**, that is generated *in situ*. This leads to the silyl-protected product **2b** which could be isolated or transformed into hydroxy dihydropyran **2c** during the work-up (Scheme 1).

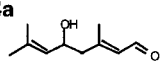
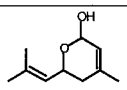
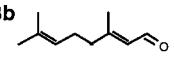
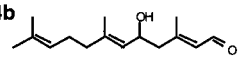
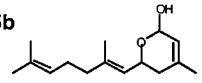
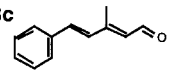
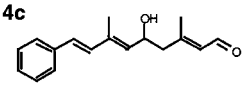
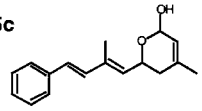
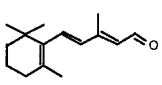
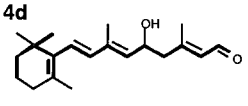
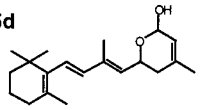
Herein, we report the outcome of the prenylation reaction of enaldehydes performed with the dienolate of prenal generated by a catalytic amount of alkali alkoxide. The significant advantage of this method is the formation of an O-silylated hydroxy dihydropyran intermediate which prevents the retroaldol reaction that causes the γ-1,4-addition.



Scheme 1

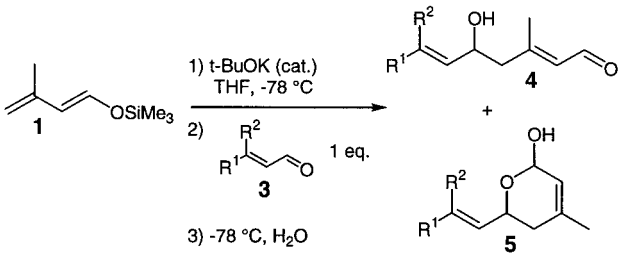
Silyl enol ether **1**[3] can be partially cleaved by 1 to 10% molar t-BuOK, to produce the equivalent amount of potassium dienolate and *t*-butoxytrimethylsilane. The addition of a polyenaldehyde to the mixture **1** / potassium dienolate produced only the hydroxy enaldehyde

Table 1. Reaction of α,β-unsaturated aldehydes with catalytically generated potassium dienolate of prenal

entry	aldehyde	conditions[a] t-BuOK(eq)	t(h)	hydroxy enaldehyde	hydroxy dihydropyran	overall yield (%)[b]
	3a 			**4a** 	**5a** 	
1	"	1	1	0	56	56[c]
2	"	0.05	1	44	33	77
3	"	0.01	1	43	33	76
	3b 			**4b** 	**5b** 	
4	"	0.05	3	38	24	62
	3c 			**4c** 	**5c** 	
5		0.05	1	21	59	80
	3d 			**4d** 	**5d** 	
6	"	0.1	3	0	55	55 (69)[d]
7	"	0.05	16	0	47	47 (68)[d]

[a] All experiments were run at -78 °C. [b] Isolated yields after flash column chromatography over silica gel. [c] In this experiment run with a stoichiometric amount of *t*-BuOK 20% of γ-1,4-coupled product was also isolated. [d] In brackets, yield based on the recovered β-ionylidene acetaldehyde **3d**

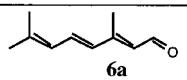
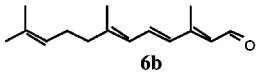
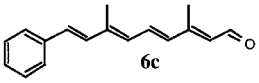
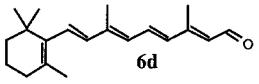
4 and the hydroxy dihydropyran **5** both resulting from the γ-1,2-coupling reaction. The hydroxy enaldehyde **4** is the primary reaction product and the 2Z isomer cyclises to form the hydroxy dihydropyran **5** (Scheme 2). The anion of the hydroxy dihydropyran **5** was the reason for the cleavage of the silyl enol ether **1** and allowed the reaction to proceed to completion.[4] Prenal **3a**, citral **3b**, 3-methyl-5-phenyl-2,4-pentadienal **3c**[5] and β-ionylidene acetaldehyde **3d** served as enaldehydes for this study (Table 1).



Scheme 2

It is essential to note that none of the γ-1,4-coupled products was detected by 200MHz ^{1}H NMR in the crude reaction mixture. Moreover, the hydroxy enaldehyde was never obtained in experiments run with a stoichiometric amount of *t*-BuOK[2] but was present when a catalytic amount of *t*-BuOK was used. As a comparison, entries 1 and 2 of table 1 show that using a catalytic amount of *t*-BuOK, to generate the dienolate, gave the γ-1,2-addition product with an improved yield. The lower yield obtained when using a stoichiometric amount of *t*-BuOK (entry 1) was due to the formation of 20% of γ-1,4-coupled product. This result clearly shows that the use of a catalytic amount of potassium alkoxide has a very positive impact on the outcome of the reaction. The reaction time to achieve the prenylation took between 1 and 3 h, with 1 to 10 % molar, at -78 °C (for a typical procedure see[6]). The stereoisomeric ratio is in favour of the 2E isomer for the hydroxy enaldehyde **4** and the cis diastereoisomer is predominant for the hydroxy dihydropyran **5**. Our methodology is of great interest in the preparation of polyene aldehydes belonging to the vitamine A series. Therefore, aldehyde **3d** served as starting material to give the hydroxy dihydropyran **5d** in 55 % yield but together with 20 % of recyclable starting aldehyde.

Table 2. Conversion of hydroxy enaldehydes **4** and hydroxy dihydropyrans **5** into polyenaldehydes **6**

starting material	method[a]	polyenaldehyde	yield[b]	2E/2Z
4a	B	 **6a**	74	38/62
5a	B		89	15/85
	A		89	70/30
4b	A	 **6b**	95	67/33
5b	B		84	58/42
	A		72	68/32
4c	B	 **6c**	81	70/30
5c	A		88	74/26
	B		83	54/46
5d	A	 **6d**	90	[c]
	B		85	

[a] Method A: Pyr, HCl; DMF/toluene (1/1) reflux, 10 min. Method B: HCl 10%/1,2-dichloroethane (1:1), 25 °C, 10 to 15 min for **5a-d**, 90 min for **4a** and 255 min for **4c**. [b] Isolated yields after flash column chromatography over silica gel. [c] Retinal **6d** was obtained as a mixture of 4 isomers: all-E, 13-cis, 9-cis and 9-cis-13-cis; HPLC surface ratio: method A 54/28/16/2, method B 46/41/13/0 (see note 9)

Access to the polyenadehydes from both the hydroxy enaldehydes and the hydroxy dihydropyrans was then studied. The reagents of choice were either pyridine hydrochloride (method A in DMF/toluene at reflux)[7] or hydrochloric acid 10% (method B in dichloroethane at r.t.)[8], due to a fast and clean reaction (Table 2). Methods A and B reported to transform hydroxy dihydropyrans into polyenadehydes led respectively to predominantly 2E and 2Z polyenadehydes **6**. Applied to hydroxy enaldehydes **4** method B led to polyenadehydes **6** via the intermediate hydroxy dihydropyrans **5** as evidenced by TLC. The 2Z polyenaldehydes that were obtained after a short reaction time slowly isomerised to the 2E isomers reaching the thermodynamic equilibrium.

In conclusion, the catalytically generated dienolate of prenal is readily available by alkoxide mediated cleavage of silyl enol ethers and it leads to only a γ-1,2-addition with enaldehydes. We believe that the short and efficient prenylation procedure we have demonstrated should prove a very efficient route to polyenaldehydes.

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References and notes

(1) Duhamel, P.; Cahard, D.; Poirier, J.M. *J. Chem. Soc. Perkin Trans.1* **1993**, 2509-2511. Cahard, D.; Desmurs, J.R.; Duhamel, L.; Duhamel, P.; Poirier, J.M. Fr. Patents 93.079.65 and 93.079.66.

(2) Cahard, D.; Poirier, J.M.; Duhamel, P. *Tetrahedron Lett*, **1998**, *39*, 7093-7096.

(3) Cazeau, P.; Duboudin, F.; Molines, F.; Laporte, O.; Dunoguès, J. *Tetrahedron* **1987**, *43*, 2089.

(4) In some experiments the O-silylated hydroxy dihydropyran was inferred in the crude reaction mixture, but due to its high propensity to hydrolyse during the work-up it was never obtained in the expected yield.

(5) **3c** was synthesised by prenylation of benzaldehyde and served as the starting aldehyde for the new prenylation reaction.

(6) Typical procedure for the formation of **5d** from **3d**: A solution of freshly sublimated potassium *tert*-butoxide (0.5 mmol) in tetrahydrofuran (2 mL) was added to a stirred solution of the silyl enol ether of prenal (5 mmol) in tetrahydrofuran (10 mL) at -78°C and the mixture was stirred for 60 min. Then β-ionylidene acetaldehyde (5 mmol) in tetrahydrofuran (5 mL) was added and stirred for 60 min at -78°C. It was then quenched with water (10 mL), extracted with Et_2O and dried over $MgSO_4$. Concentration and purification by flash chromatography on silica gel (Et_2O-light petroleum ether, 15-85) gave **5d** (833 mg, 55%) as a pale yellow oil. Compound **5d**: ^{1}H NMR ($CDCl_3$) : 0.97 (6H, s); 1.63 (3H, s); 1,74 (3H, s); 1.84 (3H, s); 1.35-2.10 (8H, m); 3.28 (OH, s); 4.84 (1H, m) ; 5.37 (1H, m) ; 5.45 (1H, m); 5.98 (1H, d, J=16.1); 6.11 (1H, d, J=16.1). ^{13}C NMR ($CDCl_3$) : 12.8, 19.1, 21.5, 22.7, 32.8, 39.4, 28.8, 34.1, 35.4, 63.7, 89.4, 120.0, 120.2, 127.1, 128.8, 129.2, 136.9, 137.3, 137.4. IR (neat): 3400, 2924, 1680. Anal. $C_{20}H_{30}O_2$ (302.4): calcd C, 79.42; H, 10.00; found: C, 79.57; H, 10.16.

(7) Olson, G.L. Hoffmann La Roche. US Patent **1976** 3,997,529.

(8) Bennani, Y.L.; Boehm, M.F. *J. Org. Chem.* **1995**, *60*, 1195-1200.

(9) HIBAR Merck Licrosorb Si 60, 5μm column, 5% ethyl acetate-hexane, 1.5 mL/min, 23 °C, λ = 366 nm. The mixture of stereoisomers of retinal can be easily isomerised to the E isomer according to Mukaiyama, T.; Ishida, T. *Chem. Lett*. **1975**, 1201-1203. Also *U.S. Patent Eastman Kodak* **1961**, 3, 013, 080; *Patent AEC* 1, 288, 972, C07c, *Patent AEC* 1, 291, 622, C07c.