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Regioselective Addition of the Prenal Potassium Dienolate onto α,β-Unsaturated Aldehydes. A Short Access to Polyenaldehydes.

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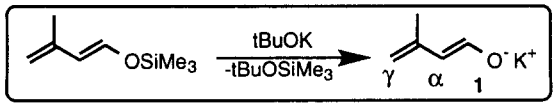
Abstract: The potassium dienolate of prenal obtained by treatment of the corresponding dienoxysilane with tBuOK was reacted with enaldehydes. In all cases a γ-specific reaction occurs. According to the reaction conditions a γ ;1,2 or a γ ;1,4 coupled product was selectively obtained with enals. The γ ;1,2 reaction provided an efficient prenylation procedure. A short two-step synthesis of retinal is described.

We have recently reported a new methodology leading to an easy access to potassium enolates by the reaction of potassium alkoxide with enoxysilanes or enol acetates of ketones, aldehydes and enaldehydes.[1] This unique preparation method of potassium enolates is of great value for producing potassium enolates which thus become as easily available as lithium enolates.

Among the multiple applications of enolates in synthetic chemistry, our attention has been focused on the prenylation reaction of α,β-unsaturated aldehydes involving the potassium dienolate of prenal. This purpose requires four conditions: -1- the dienolate of prenal must be easily generated from a readily available precursor; -2- a total γ-regiospecific reaction of the dienolate; -3- a carbon-carbon coupling reaction at the carbonyl function of the enaldehyde, namely a 1,2 addition; -4- the adduct must be easily transformed to the polyenaldehyde. We have previously surveyed the lithium dienolate of prenal and noted its propensity to undergo regioselective addition.[2] We now report the extension of the prenylation reaction to the potassium dienolate and our new findings on the regiospecific reaction of the potassium dienolate of prenal with α,β-unsaturated aldehydes that fully fulfil the four requirements mentioned above.

The potassium dienolate **1**, prepared *in-situ* by reaction of 1 equiv. of tBuOK on the starting dienoxysilane (Scheme 1), was allowed to react with diverse enaldehydes **2a-d** (Table 1).[3]

Scheme 1



† deceased on May 7th, 1997

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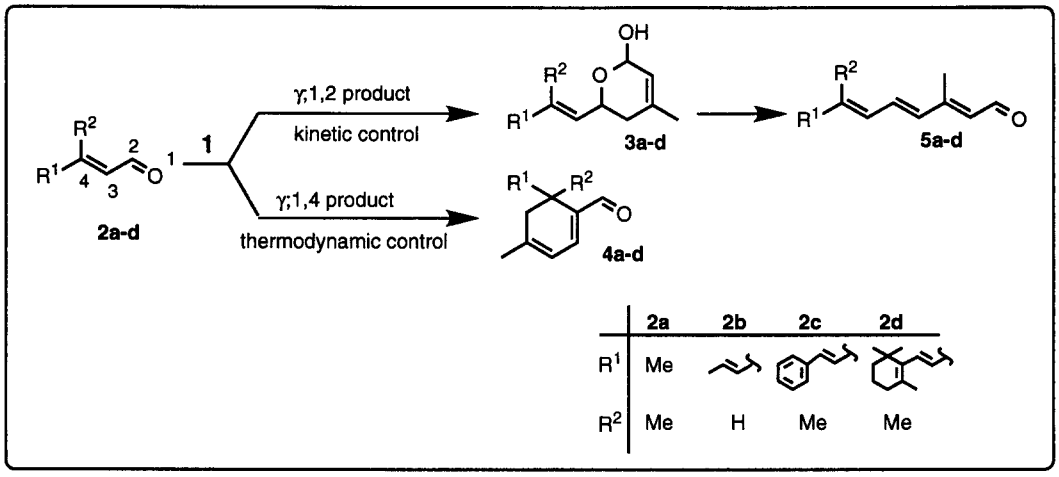
Scheme 2



In any case the α-coupling reaction occured, only the γ-coupled products were obtained.[4] The γ;1,2 addition of the dienolate **1** onto the enaldehydes **2**, followed by an intramolecular reaction of the alkoxide on the carbonyl group leads after hydrolysis, to the dihydropyrans **3**. The obtention of these compounds may or not be accompanied by the γ;1,4 addition products **4** resulting from a tandem Michael like reaction-intramolecular aldolisation followed by a dehydration (Scheme 2). Both a low temperature reaction (-78°C) and a short reaction time (<3 hours) contribute to the selective formation of the γ;1,2 coupled product. In such conditions, the ratio γ;1,2 : γ;1,4 is highly in favour of the formation of the dihydropyran **3** (Table 1, entries 1, 4, 6 and 8) whereas the increase of one or both reaction parameters raises the proportion of γ;1,4 product so far as to present only the γ;1,4 product (Table 1, entries 3 and 10). The reaction of potassium dienolate **1** with prenal **2a** was monitered by quenching small samples and analyzing their composition by ^{1}H NMR. After 5 min at -78°C, it resulted in the formation of a 90 : 10 mixture of γ;1,2 coupled product **3a** and γ;1,4 coupled product **4a** (Table 1, entry 1). Quenching the reaction after stirring for 3 hours at -78°C afforded a mixture γ;1,2:γ;1,4 = 74:26 (Table 1, entry 2). Finally, carrying out the reaction at 0°C for 3 hours gave only the γ;1,4 product. Similar feature was encountered with enaldehyde **2b**, **2c** and **2d**. Worth noting is the case of β-ionylidene acetaldehyde **2d** in which the regioselective addition of the dienolate of prenal is completely reversed, the ratio γ;1,2 : γ;1,4 switches from 100:0 to 0:100 while raising the temperature from -78°C to -10°C. Therefore, the prenylation by means of the potassium dienolate of prenal under controlled conditions (temperature and time) allowed us to get either the γ;1,2 product or the γ;1,4 product in an excellent regioselectivity. The regiochemistry can be rationalized by assuming that the potassium dienolate reacts under kinetic control affording the γ;1,2 coupled product whereas the thermodynamically more stable γ;1,4 coupled product is obtained via a retroaldol reaction upon raising the temperature (from -78°C to 0°C) and/or increasing the reaction time.

Table 1. Reaction of the Dienolate **1** with Enaldehydes.[3]

Entry	Enaldehyde	Conditions	γ;1,2 : γ;1,4 3 : 4	Yield %[a]
1	**2a**	-78°C, 5 min	90 : 10	-[b]
2	**2a**	-78°C, 3 hrs	74 : 26	53
3	**2a**	0°C, 3 hrs	0 : 100	45
4	**2b**	-78°C, 5 min	95 : 5	-[b]
5	**2b**	-78°C, 3 hrs	69 : 31	55
6	**2c**	-78°C, 3 hrs	100 : 0	66 (86)
7	**2c**	-78°C, 16 hrs	72 : 28	65
8	**2d**	-78°C, 3 hrs	100 : 0	68 (85)
9	**2d**	-40°C, 3 hrs	82 : 18	67
10	**2d**	-10°C, 3 hrs	0 : 100	59

[a] In brackets, yield based on the recovered starting aldehyde. [b] The reaction mixture was quenched right after the addition of the enaldehyde before completion of the reaction, the yield was not determined.

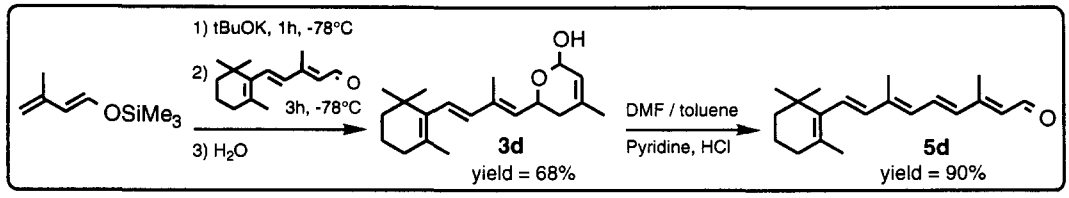
The prenylation reaction developped herein was directed to the preparation of polyene aldehydes belonging to the vitamin A series. All the so prepared dihydropyrans **3a-d** were subjected to ring-opening into polyenals **5a-d** under acidic conditions. Boric acid, p-toluenesulfonic acid or oxalic acid may serve as catalysts in a refluxing DMF / toluene mixture but the conversion is better achieved with the pyridine hydrochloride which was used to perform the reaction (Table 2).[2,5] The use of pyridine hydrochloride requires shorter reaction time to fully convert the dihydropyran into polyenal, yields are slightly improved and the stereoisomeric ratio proved to be more in favour of the all E isomer.

Table 2. Conversion of Dihydropyrans **3a-d** into Polyenals **5a-d** using pyridine hydrochloride.[6]

Dihydropyran	Polyenal	Yield (%)	Stereoisomeric ratio
3a	**5a**	76	2E,4E:2Z,4E=70:30
3b	**5b**	72	2E,4E:2Z,4E=65:35
3c	**5c**	88	4 isomers [a]
3d	**5d**	90	4 isomers [b]

[a] A 70:20:6:4 mixture of isomers was recovered. The major isomer was purified by cristallization from pentane and identified as the all E isomer. [b] Retinal **5d** was obtained as a mixture of four isomers. The all E is the major one as determined by HPLC. The stereoisomeric mixture can be easily isomerized to the all E.[7]

Particularly illustrated of our short access to polyenaldehydes is the condensation of the β-ionylidene acetaldehyde **2d** with the potassium dienolate of prenal **1** and subsequent conversion of the reaction product, dihydropyran **3d**, to retinal **5d** (scheme 3). The overall yield of this simple and efficient two-step synthesis being of 61% (76.5% based on recovered starting aldehyde **2d**)



Scheme 3

In conclusion, the potassium dienolate of prenal which is readily available by our method reacts with polyunsaturated aldehydes to yield dihydropyrans owing to an excellent kinetically regiocontrolled γ;1,2 addition. Further conversion of the dihydropyrans to elongated polyenaldehydes provides us a rapide and efficient two-step prenylation procedure.

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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. Pat. n° 93.079.65 and 93.079.66.
2. Duhamel, L.; Guillemont, J.; Poirier, J.M.; Chabardes, P. *Tetrahedron Lett.* **1991**, *32*, 4495-4498 and *Tetrahedron Lett.* **1991**, *32*, 4499-4500.
3. General procedure : The dienolate of prenal **1** was prepared by reaction of 1 equivalent of tBuOK with the corresponding dienoxysilane (1 mmol in 1 ml of THF) for 1 hour at -78°C. The aldehyde **2** (1 mmol) was then added to the potassium dienolate at -78°C or optionally at higher temperature (-40°C to 0°C). After the period of time mentioned in Table 1, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ to give after usual work-up compounds **3** and/or **4** which were purified by column chromatography on silica gel (light petroleum-diethyl ether 98:2).
4. No α-reaction product detected even in the crude reaction product.
5. Olson, G.L. Hoffmann La Roche US Patent 3,997,529 (Dec.14, 1976)
6. To a solution of 0.3 mmol of dihydropyran **3** in 1 ml of a mixture of DMF and toluene (ratio 1:4) was added at room temperature a measured quantity (0.5-3 mole%) of anhydrous pyridine hydrochloride. The reaction mixture was placed into a preheated oil bath regulated at 110°C for 5 minutes, cooled and neutralized with 1 ml of saturated sodium hydrogenocarbonate solution. The organic phase was extracted twice with 2 ml of ether. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, and solvent was removed. The crude material was chromatographed (silica gel, light petroleum-diethyl ether 98:2) to afford the polyenal **5**.
7. 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