Pergamon

Tetrahedron Letters, Vol. 35, No. 40, pp. 7383-7386, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01543-0

Efficiency of Organometallic Catalysis in a New "Ecological" Synthesis of Retinal

Hugues Bienaymé

Rhône-Poulenc Ind. CRIT-Carrières, BP 62, 69192, Saint-Fons, France

Key Words : Isoprenoid aldehydes, Vitamin A, Retinal, Palladium.

Abstract : *Isoprenoid aldehydes (such as retinal) are readily obtained from propargylic alcohols by a three step protocol involving the key palladium-catalysed transformation 1 → 2*

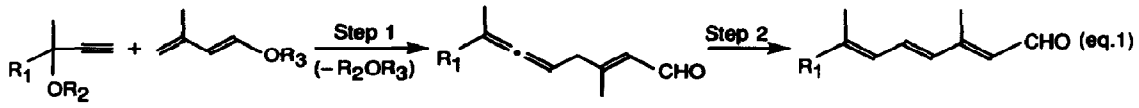
Isoprenoid aldehydes are currently a widely studied class of intermediates for terpene synthesis among which retinal (vitamin A aldehyde) is probably a cornerstone. Indeed, from this polyunsaturated aldehyde, vitamin A itself, retinoic acid, or β-carotene are conveniently prepared[1].

A unique property of retinal lies in its ability to crystallize as its "all-trans" stereoisomer-hydroquinone complex[2] : under equilibrating conditions (iodine, acids, or simply heat), a virtually quantitative yield of "all-trans" retinal is obtained from any stereoisomer mixture. Needless to say, that from an economic point of view the stereochemical issue of a retinal synthesis is of little relevance (as long as "all-trans" retinoids such as vitamin A are desired).

Several methods have already been published to prepare isoprenoid aldehydes, those based on Wittig or Wittig-like olefinitions, Julia olefination, aldol-like reactions being the most useful[3].

However, these syntheses are far from being "industrially perfect". For instance, to render a Wittig or a Julia olefination economically attractive, one needs to recycle the synthetic auxilliary (triphenylphosphine oxide, sodium phenylsulfinate), a process which is not necessarily an easy one. Aldol reactions are not hampered by such a drawback, but usually require low temperatures or special conditions to be performed.

Keeping this in mind, we reasoned that one of the shortest and most economical ways to isoprenoid aldehydes would be to perform the cationic condensation between a propargylic alcohol (or a derivative thereof) and a prenal enol ether, followed by isomerization of the resulting allenic aldehyde (eq. 1).



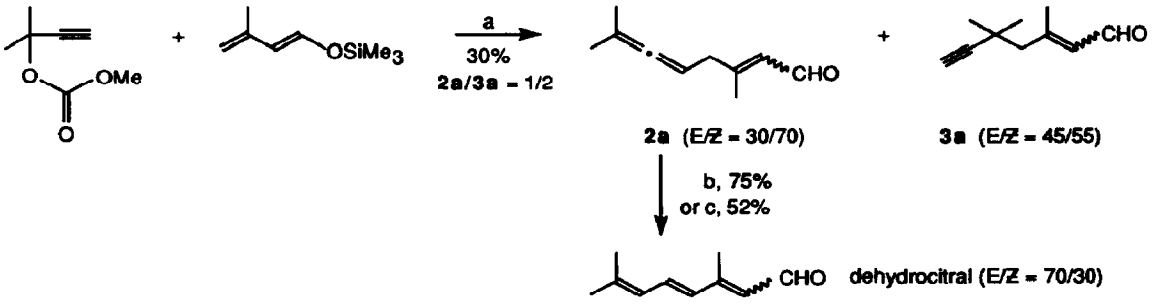
As both acetylenic carbinols and prenal are readily accessible starting materials, and in the absence of either coproduced effluents or stoechiometric reagents (if one can carry out these two steps catalytically) this transformation is likely to be the"ideal" route to retinal.

In this Letter, we will disclose our first results towards this goal.

To begin with, various protic or Lewis acids were screened in order to catalyze the first step of this process (eq. 1, step 1, $R_2 = H$; R_3 = TMS, Ac). Unfortunately no breakthrough could be made, presumably because of the excessively high acidity level (with respect to the sensitive dienol ether) associated with the generation of an allenyl cation[4]. Palladium catalysis was then selected as a possible alternative to acidic catalysis for several reasons :

- Reactive allenyl-palladium (II) species readily form upon oxydative insertion of palladium(0) complexes with activated propargylic derivatives (halides, acetates, carbonates...)[5].
- Such species essentially behave as allenic electrophiles. For instance they undergo carbonylation[6], reduction with formate anion[7] or metallic hydrides[8], Heck-type reactions[9], and cross-coupling reactions with copper, tin or zinc organometallics[10].
- Catalysis under essentially neutral conditions is possible.

The electrophilic character of allenyl-palladium (II) complexes was again experienced when methoxycarbonyl-3-methyl-butynol was allowed to react with 1-trimethylsiloxy isoprene in the presence of a catalytic amount of palladium tetrakis triphenylphosphine[11]. Thus, for the first time, the new 3,7-dimethyl-2,4,5-octatrienal **2a** was isolated (albeit in low yield and poor selectivity). Fortunately this sensitive aldehyde could be separated from its undesired regioisomer **3a** by silicagel chromatography and easily reconjugated under either basic or acidic conditions to give dehydrocitral.



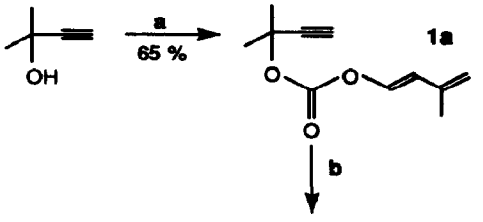
Conditions : a) $Pd(PPh_3)_4$ (0.05 eq), THF, 50°C. b) 48% HBr (0.05 eq), acetone, 0°C. c) Na_2CO_3, MeOH, R. T.

To solve the yield problem associated with this bimolecular reaction, the readily available mixed carbonate **1a** was tested[12] (table I). Under the previous conditions regioisomeric aldehydes **2a** and **3a** were obtained in a good overall yield and in the same ratio (**2a/3a** = 36/64), suggesting the intermediacy of some common organometallic species in both inter and intramolecular reactions (table I, entry 1).

As the regioisomeric outcome of this transformation was found to be rather unsatisfactory for our purposes, the ligand role was also investigated and found to be a determining factor.

On the whole, aromatic monodentate phosphines (combined with a source of palladium (0)) gave the best results, with a special mention to trisnaphthylphosphine which showed the highest regioselectivity for **2a** (table I, entry 4)[13].

Nickel tetrakistriphenylphosphine also catalyzed this reaction regioselectively, though in somewhat lower yield.



Entry	Catalyst	Yield	Selectivity (2a / 3a)
1	$Pd(PPh_3)_4$	59%	36/64
2	$Pd(dba)_2$ + 3P 	50%	45/55
3	$Pd(dba)_2$ + 3P 	70%	50/50
4	$Pd(dba)_2$ + 3P 	58%	82/18
5	$Ni(PPh_3)_4$ [c]	33%	100/0

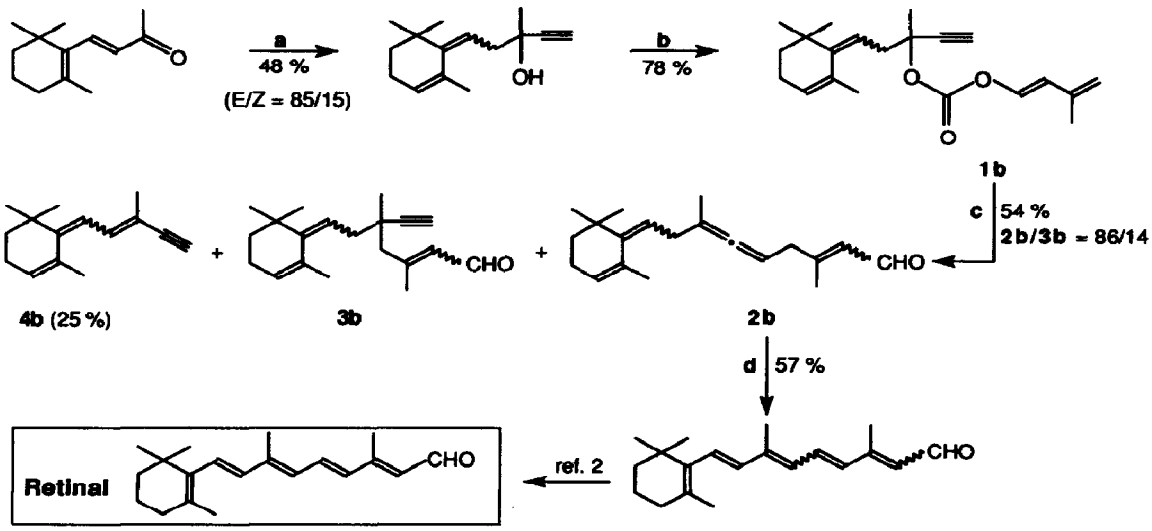
Conditions : a) BuLi (1 eq), THF-hexane, -20°C then $COCl_2$ (1eq), toluene, -20°C then trimethylsiloxyisoprene (1.2 eq), MeLi (1.1 eq), THF-ether, -40°C → R. T. b) catalyst (0.05 eq) ; THF, 50-55°C. c) catalyst (0.20 eq), THF, R. T.

Table I

This protocol was next used in the synthesis of a more valuable target : retinal. β-Ionone (the starting material for all industrial vitamin A syntheses) was smoothly deconjugated[14] and ethynylated to give ethynyl-retro-α-ionone as a mixture of E/Z stereoisomers. Formation of carbonate **1b** was then straightforward and its subsequent rearrangement with the previously "optimized" palladium catalytic system produced aldehydes **2b** and **3b** in a yield and ratio similar to those obtained for the model system. Along with these aldehydes, trieneyne **4b**, actually a β-hydride elimination product, was isolated as a major impurity.

After silica-gel chromatography, the regioisomerically correct aldehyde **2b** was completely reconjugated with a catalytic amount of hydrobromic acid in aqueous acetone.

Under these conditions, retinal was obtained as a 75/25 mixture of E/Z isomers on each trisubstituted double bond, which could be subsequently converted into the all-trans isomer by simple equilibration[2].



Conditions : a) MeONa (1.3 eq), DMSO, 15°C then acetylene, ^iPrMgCl, THF, -20°C. b) See table I. c) $Pd(dba)_2$ (0.05 eq), $P(Napht)_3$ (0.15 eq), THF, 50°C. d) 48% HBr (0.10 eq), acetone, 0°C.

In summary, the selectivity and mildness of palladium catalysis was the key to success in this new "ecological" synthesis of retinal, through the rather unusual and sensitive aldehyde **2b**. Extension of this methodology to the elaboration of other complex polyenes such as oxygenated carotenoids is currently underway in our laboratories.

Acknowledgments

We would like to thank the analytical service at CRIT. C, and Rhône-Poulenc for the permission to publish these results

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(*Received in France* 29 *July* 1994; *accepted* 9 *August* 1994)