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FORMYLOLEFINATION OF CARBONYL COMPOUNDS

Wataru Nagata, Yoshio Hayase

Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka, Japan

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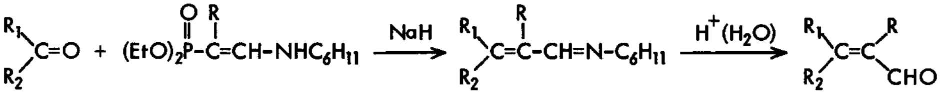
Direct conversion of ketones into α,β-unsaturated aldehydes with lengthening of two carbon atoms cannot be effected satisfactorily owing to ready self-condensation of acetaldehyde (1), although several multi-step processes (1,2) have been devised. The Wittig reagents, $Ph_3P{=}CRCHO$ (3), and a phosphonate reagent, $(C_2H_5O)_2POCH_2CH(OC_2H_5)_2$ (4,5) were reported to react with aldehydes but not ketones. A two-step process (6) involving normal aldol condensation of ketones with $LiCHRCH{=}NC_6H_{11}$, and subsequent dehydration and hydrolysis is the only simple and useful one hitherto reported. However, the process seems disadvantageous in that the dehydration step is less selective reducing often the yields of α,β-unsaturated aldehydes. We wish to describe a new and useful two-step process for formylolefination of ketones as well as aldehydes according to the following sequence (7).



1a, b, c 2a, b, c 3a, b, c

(a: R = H, b: R = CH_3, c: R = $CH_2C_6H_5$)

Diethyl β-(cyclohexylimino)ethyl phosphonate 1a (8): bp 151-152° (0.04 mm); $\lambda_{max}^{C_2H_5OH}$ 241 mμ (ε 16,300), was prepared easily by reaction of diethyl formylmethylphosphonate (9) with an equimolar amount of cyclohexylamine in methanol followed by distillation of the crude product at reduced pressure in the presence of anhydrous potassium carbonate (10). The corresponding alkyl derivatives 1b and c were prepared by treatment of the magnesium salt of 1a with methyl iodide and benzyl bromide, respectively

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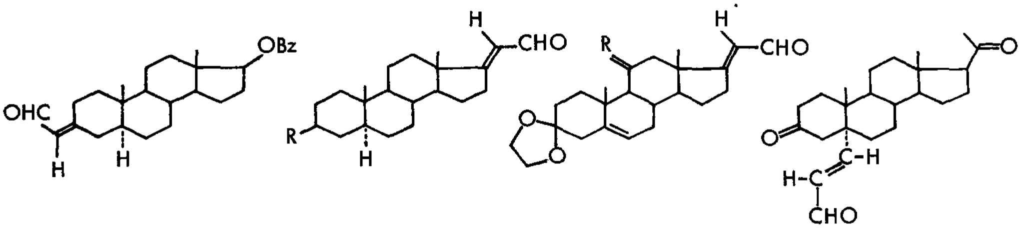
TABLE I

Conversion of $R_1R_2C{=}O$ into $R_1R_2C{=}CR{-}CHO$ (3) via α,β-Unsaturated Aldimine (2)

Substrate	Reagent	Molar ratio of reagent	Temp (°C)	Time (hr)	Hydrolysis process	Product	Yield (%)
Cyclohexanone	1a	1.2	r.t.	1.5	A	Cyclohexylidenacetaldehyde [a]	86
	1b	1.2	r.t.	4	A	2-Cyclohexylidene-propionaldehyde [b,e]	66
	1c	1.2	reflux	3	A	2-Cyclohexylidene-3-phenylpropionaldehyde (4) [b,f]	63
5α-Androstan-17β-ol-3-one 17-benzoate (5)	1a	1.2	r.t.	3.5	A	6 [g]	84
5α-Androstan-17-one (7a)	1a	3.0	r.t.	10	A	8a [h]	74
3β-Tetrahydropyranyl-oxy-5α-androstan-17-one (7b)	1a	3.0	r.t.	8	A	8b [i]	71
3-Ethylendioxyandrost-5-ene-11,17-dione (9a)	1a	3.0	r.t.	21	B	10a [j]	73
3-Ethylendioxy-11β-hydroxyandrost-5-en-17-one (9b)	1a	3.0	r.t.	19	B	10b [k]	65
Benzaldehyde	1a	1.2	0-5°	2	A	Cinnamaldehyde	77
3,20-Bisethylendioxy-5α-pregnanyl-5α-carboxaldehyde (11) [d]	1a	10	reflux	9.5	A [c]	12 [l]	83



6

8a, R = H
b, R = OH

10a, R = O
b, R = β-OH

12

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[a] Semicarbazone. [b] 2,4-Dinitrophenylhydrazone. [c] Heated with 70% acetic acid after hydrolysis with aq oxalic acid. [d] W. Nagata et al., to be published. [e] G. Saucy, R. Marbet, H. Lindlar, and O. Isler, Helv. Chim. Acta 42, 1952 (1959). [f] 2,4-Dinitrophenylhydrazone: mp 162-174°. [g] mp 157-158°. [h] mp 150-152°. [i] mp 176-180°. [j] mp 208-212°; $[\alpha]_D^{22}$ -9.8° (C_2H_5OH). See ref 11. [k] mp 224-226°. [l] mp 140-144°.

[**1b**: mp 61-64°; $\lambda_{max}^{C_2H_5OH}$ 246 mμ (ε 24,200), **1c**: mp 79-82 ; $\lambda_{max}^{C_2H_5OH}$ 246.5 mμ (ε 15,960)]. Carbanions of **1a**, **b**, and **c** were generated by adding an equimolar amount of sodium hydride in tetrahydrofuran (THF) at 0°C. The condensation was effected in most cases by treatment of a substrate with a slight excess of the reagent carbanion at room temperature for several hours. However, a higher reagent-ratio, a higher temperature, and a prolonged reaction time were needed for a poorly reactive carbonyl function. *Two-layer hydrolysis* of the resulting α,β-unsaturated aldimines **2** either with diluted (1%) oxalic acid (process A) or with an acetic acid-sodium acetate buffer solution (pH 4, process B) is recommended. Practically, the intermediates **2** were not purified and underwent hydrolysis. The results for various carbonyl compounds were summerized in TABLE I.

Cyclohexanone and benzaldehyde smoothly gave the corresponding α-enals and the homologues. Steroidal 3-ketone **5** also gave a single product **6** (11). Steroidal 17-ketones **7a**, **7b**, **9a**, and **9b**, which are known to be inert to diethyl carboethoxymethylphosphonate carbanion (5), reacted with the present carbanion giving the trans (11) enals **8a**, **8b**, **10a**, and **10b**, respectively in good yields. The sterically hindered steroidal 5α-aldehyde **11** reacted under more drastic conditions giving the corresponding trans (11) enal **12** in good yield.

Several advantages of the present process can be cited. These are: (i) the process is simple; (ii) the efficiency is high; (iii) the selectivity giving a trans formylolefin is very high. Thus, the present process is believed to provide a new and useful synthetic route to α,β-unsaturated aldehydes from carbonyl compounds, especially from ketones and poorly reactive aldehydes. It should be noted that a free hydroxy or an ester group in substrates should be protected or changed favorably in the form of an ether function such as the tetrahydropyranyl group (THP), since the former group is also attacked by the reagent (12).

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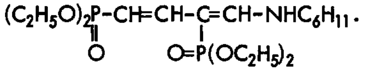
7. After completion of our work, we noticed an article of Wittig and Reiff [G. Wittig and H. Reiff, *Angew. Chem. Internat. Edit.*, **7**, 7 (1968)], in which they pointed out in connection with their aldolization reaction that some phosphorane derivatives such as $(C_6H_5)_3P{=}CH{-}CH{=}NR$ would be useful to effect formylolefination of ketones. This statement prompted us to disclose the results of our investigation which closely relates to their suggestion but arose from a quite different idea.

8. Satisfactory elemental analyses were obtained for all the compounds for which melting points or boiling points are given. All the compounds cited showed reasonable spectral data.

9. N. D. Dawson and A. Burger, *J. Am. Chem. Soc.* **74**, 5312 (1952).

10. The phosphonate **1a** is extremely sensitive to even a trace of acid and underwent self-condensation to give a crystalline mixture of geometrical isomers of



$(C_2H_5O)_2\underset{\displaystyle O}{\underset{\|}{P}}{-}CH{=}CH{-}\underset{\displaystyle O{=}P(OC_2H_5)_2}{\underset{|}{C}}{=}CH{-}NHC_6H_{11}$.

11. The trans geometry of the α-enal function in **6** (as depicted in formula), **8a** and **b**, and **10a** and **b**, was assigned on the basis of their CD curves, interpretation of which is based on a work by K. Kuriyama et al. of this laboratory (to be published). Some discrepancy in the physical constants between our sample of **10a** and that of D. Bertin et al. [*Bull. Soc. Chim. France* 1068 (1962)] was observed. However, our sample was identified by conversion into the known trans 21-hydroxy derivative and by reconversion to the parent compound **10a**.

12. However, relatively low reactivity of 17β-benzoyloxy in **5** and 11β-hydroxy in **9b** allows the selective condensation with the ketone functionality in the same molecule.