Tetrahedron Letters,Vol.30,No.29,pp 3779-3780,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

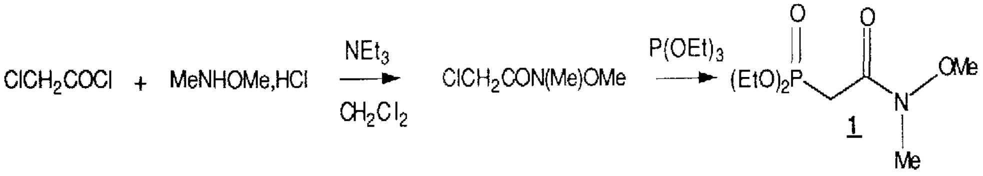
A NEW SYNTHESIS OF α,β-UNSATURATED ALDEHYDES

Jean-Marc NUZILLARD, Ahcene BOUMENDJEL, Georges MASSIOT

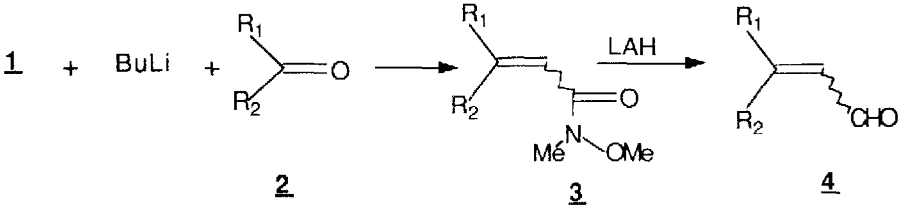
Laboratoire de Pharmacognosie, Faculté de Pharmacie, associé au C.N.R.S
51 rue Cognacq-Jay - 51096 REIMS - FRANCE

Abstract : The two carbon homologation of carbonyl compounds to α,β-unsaturated aldehydes is achieved by the Wittig-Horner reaction with N-methoxy N-methyl diethylphosphonoacetamide 1 followed by lithium aluminum hydride reduction.

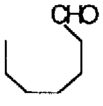
The two carbon homologation of carbonyl compounds to a α,β-unsaturated aldehydes is a useful synthetic transformation. The most commonly used routes rely on Wittig or Wittig-Horner type chemistry with reagents containing aldehyde (1), acetal (2), ester (3) or nitrile (3) fonctions ; in the last two cases further adjustement of the oxidation level is required. Oxidative transposition of readily available tertiary vinyl carbinols (4) provides an alternative route to the title compounds. The Weinreb-Nahm lithium aluminum hydride reduction of hydroxamates (5) is an excellent way of preparing aldehydes and has found elegant applications in the peptide field (6). We wish to report here on the uses and preparation of N-methoxy N-methyl diethylphosphonoacetamide 1 (7), a new reagent which combines Weinreb and Wittig-Horner chemistry and which is prepared as follows:



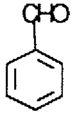
Homologation proceeds as follows (8).



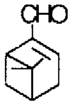
The reaction sequence has been successfully applied to saturated (2a), unsaturated (2c) and aromatic (2b) aldehydes, aliphatic (2d) and alicyclic (2e, 2f) ketones and hemiacetal (2g). The results are summarized in table 1.



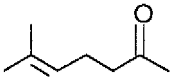
2a



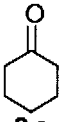
2b



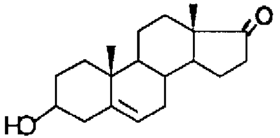
2c



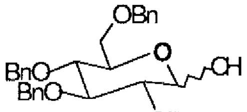
2d



2e



2f



2g

Table 1

	temperature	time	yield (3)	E/Z[a]	yield(4)
a	-78	15 min	76	95/5	95[b]
b	-78	25 min	74	95/5	84
c	-78	25 min	92	95/5	92
d	20	24 min	76	95/5	81
e	0	1 hr	82	—	90
f	65	24 hr	41	—	56
g	65	18 hr	33	35/65	65

a) from ^{1}H NMR spectra   b) nonenal/nonenol ratio is 4/1.

Aldehydes yield almost pure E products as could be expected from Wittig-Horner chemistry. A mixture of nonenal and nonenol is obtained upon $LiAlH_4$ reduction of 3a; a greater selectivity is achieved with DIBAL in THF at -78°C for 5 minutes . In the case of compound 2f an extra equivalent of deprotonated reagent 1 is used to balance the unprotected hydroxy group. Compound 3f is obtained as its rearrangement product with the double bond in the 16-17 position.

Compounds of type 3 may find various applications in organic synthesis since : 1) they behave as protected forms of highly sensitive acroleins, 2) they are convertible to ketones by addition of organolithium reagents, 3) the C=C bond is easily reduced by molecular hydrogen and, 4) acrylamides are reactive dienophiles. Introduction of Weinreb chemistry into Petersen, Knoevenagel or Reformatsky reactions promises to provide useful alternative routes for the synthesis of α,β-unsaturated carbonyl compounds.

References and notes:

1. Trippett S. ; Walker D.M. J.Chem.Soc., 2130 (1961)
2. Bestman H.J. ; Roth K; Ettlinger M. Angew. Chem. Int. Ed. 18, 687 (1979).
3. Organic Reactions ; W.S. Wadworth ; J. R .Wiley and sons , 25; 73-253 (1977).
4. Babler J.H. ; Coghlan M.J. Synth.Comm. 6, 469 (1976).
5. Nahm S. ; Weinreb S.M. Tetrahedron Lett. 22, 3815 (1981).
6. Fehrentz J.A. ; Castro B. Synthesis, 676 (1983).
7. Preparation of reagent 1 : A mixture of O,N-dimethylhydroxylamine hydrochloride (9.75 g, 100 mmol), chloroacetyl chloride (8 ml, 100 mmol), and triethylamine (28 ml, 200 mmol) in 250 ml dichloromethane is stirred for 1 h. The mixture is washed with hydrochloric acid, brine and saturated sodium hydrogenocarbonate. The organic phase is dried over Na_2SO_4 and the solvent distilled off. Triethylphosphite (13 ml, 70 mmol) is added to the residue and the mixture heated at 80°C for 24 h. Excess triethylphosphite is removed *in vacuo* and 1 is bulb to bulb distilled (90°C, 17 torr). I.R.($CHCl_3$): 3450,3000,1650,1250,1040cm^{-1}. MS (m/z): 240 (M+1),179,151,137,123.^{1}H-NMR ($CDCl_3$, 300 MHz): 4 (quintet, J=7Hz, 4H), 3.6 (s, 3H), 3 (s, 3H), 2.98 (d, J= 22 Hz, 2H), 1.2 (t, J= 6.7Hz, 6H).
8. Wittig-Horner reactions are carried out in dry THF. Amide 1 is deprotonated at -78°C by means of BuLi in THF solution (1.6 M). 1.5 equ. of the anion is used, except for run f, (2 equ.). After reaction, excess reagent 1 is removed by column chromatography. Reductions are performed by 1 equivalent 1M $LiAlH_4$ in THF solution.

(Received in France 6 March 1989)