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GENERAL METHOD FOR THE SYNTHESIS OF CHIRAL 2-OXOALKYLIDENETRIPHENYLPHOSPHORANES

Franco Buzzetti, Natale Barbugian and Carmelo A. Gandolfi*

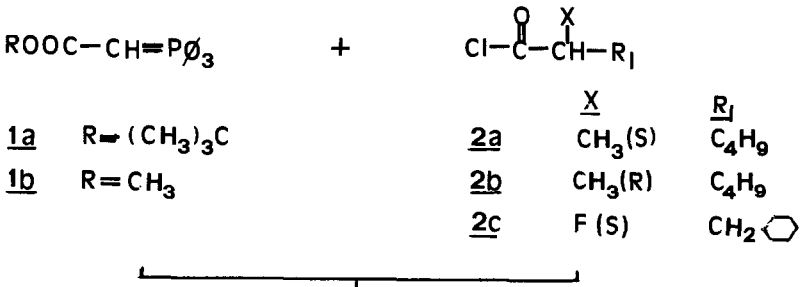
Farmitalia Carlo Erba SpA, Research and Development, Via C. Imbonati 24,
20159 Milan, Italy

Abstract: An improved method for the synthesis of chiral 3-substituted 2-oxo-alkylidene-triphenylphosphoranes and their application in the elaboration of the ω-sidechain in prostaglandins is reported.

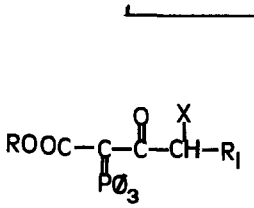
A promising synthesis for acylmethylenetriphenylphosphoranes was recently proposed by G. Doleschall[1] as an alternative to the two common routes, reaction of α-haloketones with triphenylphosphine[2] or acylation of methylenetriphenylphosphorane[3a,b]. The new approach requires very mild reaction conditions during acylation of methoxycarbonylmethylenetriphenylphosphorane[4] and in the subsequent decarbomethoxylation and should perhaps permit the synthesis of chiral 3-substituted 2-oxoalkylidenetriphenylphosphoranes without racemization of the chiral center. To our knowledge the only previous feasible method for obtaining chiral 3-substituted acylmethylenephosphoranes was the α-haloketone route which does not lend itself to large-scale use. Other methods requiring a strong base (butyl-lithium, phenyl-lithium, potassium t-butoxide) are impracticable for obvious reasons.

To our surprise the new method proved unable to solve our problem. Removal of the methoxy - carbonyl group in the 1-methoxycarbonyl-2-oxoalkylidenetriphenylphosphorane 3d (obtained from the chiral α-substituted acyl chloride by reaction with methoxycarbonylmethylenetriphenylphosphorane) proceeded with partial racemization in boiling 99.5% acetic acid in the presence (or absence) of sodium iodide. Attempts to minimize these drawbacks were unsuccessful.

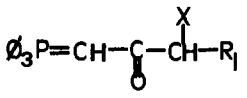
In order to check the amount of racemization, the acylmethylenephosphoranes were reacted with the aldehyde derived from the Corey-lactone and from its 11-deoxy analogue. Generally this reaction gives mixtures of 16(S)- and (16)R- α, ß-unsaturated ketones 6a and 6b when racemic phosphonates or phosphoranes are used[5].



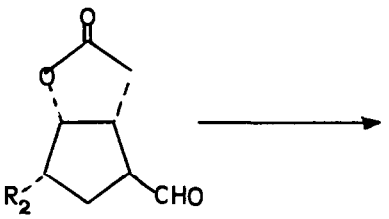
		X	R_1
2a		CH_3(S)	C_4H_9
2b		CH_3(R)	C_4H_9
2c		F (S)	CH_2



	R	R_1	X
3a	$(CH_3)_3C$	C_4H_9	CH_3(S)
3b	$(CH_3)_3C$	C_4H_9	CH_3(R)
3c	$(CH_3)_3C$	CH_2	F(S)
3d	CH_3	C_4H_9	CH_3(S)



	R_1	X
4a	C_4H_9	CH_3(S)
4b	C_4H_9	CH_3(R)
4c	CH_2	F(S)



		R_1	R_2	X
5a	R_2=H			
5b	R_2=OCO			
6a		C_4H_9	H	CH_3(S)
6b		C_4H_9	H	CH_3(R)
6c		CH_2	OCO	F (S)

The trivial substitution of a t-butyl group for the methyl group in the methoxycarbonylmethylenephosphorane permitted milder, faster cleavage conditions (p-toluenesulfonic acid in inert solvents, e.g. benzene, cyclohexane, 60-80°C) of the resulting 1-t-butoxycarbonyl-2-oxoalkylidenetriphenylphosphorane. Using this modification we noted complete retention of the chirality as confirmed by the formation of a single diastereomeric chiral α,ß-unsaturated ketone[6-7].

A solution of 10 mmol acyl chloride in 10 ml dry benzene was added at r.t. to a solution of 20 mmol t-butoxycarbonylmethylenetriphenylphosphorane in 25 ml dry benzene. After 3 h the separated phosphonium salt was filtered off and the filtrate was evaporated in vacuo. The residue was crystallized from hexane/isopropyl ether to give pure 1-t-butoxycarbonyl-2-oxoalkylidenetriphenylphosphoranes 3a, 3b and 3c in 80% yield[8].

The t-butoxycarbonyl compound (3a, 3b, 3c) (4.09 mmol) was then treated with p-toluenesulfonic acid (6.14 mmol) in boiling benzene for 3 h. After alkaline work-up and crystallization from hexane we obtained the final chiral 3-substituted 2-oxoalkylidenephosphoranes 4a-c in 80% yield and in pure form[9].

Applying the Doleschall procedure to the methylester 3d or to the butylester 3a gave in both cases the oily, partially racemized 3-substituted 2-oxoalkylidenephosphorane 4a + 4b which, after reaction with 11-deoxy-aldehyde 5a, yielded a 1:1 mixture of the diastereoisomeric α,ß-unsaturated ketones 6a and 6b. In contrast, the reaction of aldehyde 5a and 5b (1.0 mmol) with phosphoranes 4a-c (1.2 mmol), prepared according to our method, gave the pure chiral α,ß-unsaturated ketones 6a-c in a 90% yield[10-13].

Acknowledgment

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References and Notes

1. G. Doleschall, Synthesis 1981, 478.
2. M. Miyano, C.R. Dorn, J. Org. Chem., 37, 1818 (1972).
3a. H.J. Bestmann, H. Schulz, Angew. Chem., 73, 27 (1961).
3b. H.J. Bestmann, B. Arnason, Chem. Ber., 95, 1513 (1962).
4. G. Märkl, Chem. Ber. 94, 3005 (1961)
5. F. Faustini, A. Fumagalli, C.A. Gandolfi, unpublished work.
6. Satisfactory analytical data are obtained.
7. When this note was ready for publication, an article appeared in J. Org. Chem., 47, 4955 (1982) reporting a similar method for the preparation of acylmethylenephosphoranes. However under these reaction conditions, chirality is not retained.

8. 3a: m.p. 104-105°; $(\alpha)_D$ +21.6° (1% $CHCl_3$)

   3b: m.p. 104-105°; $(\alpha)_D$ -22.9°

   3c: m.p. 149-152°; $(\alpha)_D$ -65.8°

9. 4a: m.p. 85-86°; $(\alpha)_D$ +22.7° (1% $CHCl_3$)

   4b: m.p. 85.5-86.5°; $(\alpha)_D$ -23.9°

   4c: m.p. 116-118°; $(\alpha)_D$ +41.8°

10. 6a: oil; $(\alpha)_D$ +63.7° (1% MeOH); λ_{max} 227 nm (ε 14750)
    NMR ($CDCl_3$) δ 0.89 (3H, t), 1.09 (3H, d), 5.05 (1H, m), 6.28 (1H, d), 6.83 (1H, dd).

    6b: oil, $(\alpha)_D$ +32.2°

    6c: m.p. 121-122°; $(\alpha)_D$ -65.5°; F found 4.40; calc. 4.43%.

11. For 6a and 6b see also reference 5.

12. S. De Munari, G. Marazzi, F. Faustini and C.A. Gandolfi, V Int. Conf. Prostaglandins, Florence 18-21 May 1982, Abstr. 501.

13. We are grateful to Dr. A. Panzeri for an authentic sample of 6c obtained from dimethyl 3(S)-fluoro-4-cyclohexyl-2-oxo-butyl phosphonate.

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