Tetrahedron Letters,Vol.30,No.21,pp 2783-2786,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

Asymmetric synthesis of phosphinates, phosphine oxides and phosphines by Michaelis Arbuzov rearrangement of chiral oxazaphospholidine

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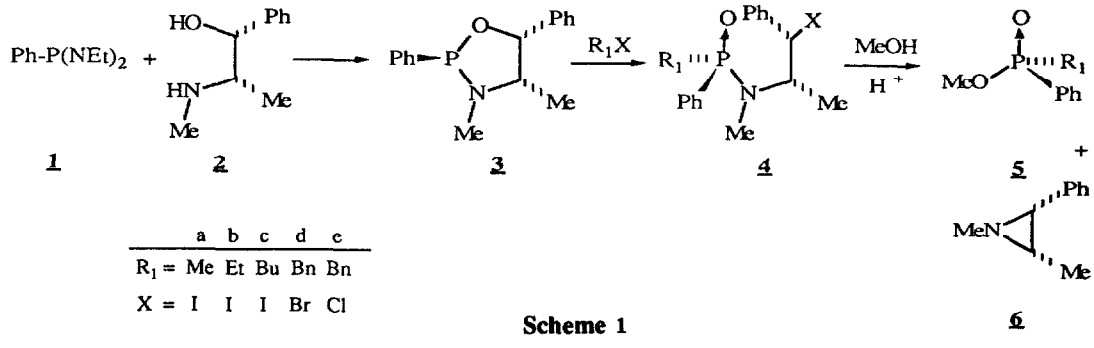
Abstract : A general approach to asymmetric synthesis of high optically active tertiary organophosphorus compounds is described. Oxazaphospholidine **3** reacts with alkyl halide to give regio and stereoselectively the corresponding phosphinamide **4**. Methyl phenyl phosphinamide **4a** is used for the preparation of methyl phenyl phosphinate **5a** with ee > 96 % . The preparation of (+) and (-) - PAMP or DIPAMP from **3** is described.

Chiral organophosphorus compounds with chirality on the phosphorus atom have been an important subject for investigation over the last twenty years due to the widespread study of these compounds for the comprehension of biochemical mechanisms (1) and in asymmetric synthesis (2).

The spectacular asymmetric syntheses with C - H and C - C bond creation described up to now, have shown the key importance of the organophosphorus ligands such as PAMP, DIPAMP, DIOP, CHIRAPHOS ... (2b).

Several asymmetric syntheses of phosphinates, phosphines or phosphine oxides have been described since the work of Mislow (3). However, chemical difficulties remain and in addition, these syntheses are often long and general applications are limited (4 - 8).

A few years ago we proposed a general method for the asymmetric synthesis of phosphinates and phosphine oxides (7,8b), using the Michaelis - Arbuzov rearrangement of chiral diheterophosphacycloalkanes (scheme 1). However this procedure approach has received little attention (8c, d) and remains to be developped.



Scheme 1

The scheme above shows that it is possible to prepare various organophosphorus compounds of known absolute configuration, from only one heterocyclic compound **3** . The method is based on two key steps :

- diastereoselectivity during the synthesis of the diheterophosphacycloalkanes **3**.
- regioselectivity of the Michaelis - Arbuzov rearrangement due to the heterocycle dissymetry at the positions 1 and 3.

Here, we present results obtained using oxazaphospholidine **1** showing the practical application for the asymmetric synthesis of optically pure (+) or (-) - PAMP and DIPAMP.

Pure oxazaphospholidine **3** was prepared from bis (diethylamino) phenylphosphine **1** and (-) - ephedrine **2** (scheme 1) (9). The absolute configuration of **3** was established according to the NMR chemical shifts and the coupling constant $^2J_{PNC}$ (11), the synthesis of the derivative oxo - 2 with known structure (12) and comparaison with similar diheterophosphacycloalkanes (13).

The reaction of **3** with an alkylhalide R_1X, give the phosphinamides **4a,e** by Michaelis Arbuzov rearrangement. The results presented in table I show that stereoselectivity depends on the steric hindrance of the R^1 group and experimental conditions. Thus, we can see that methyl is better than ethyl, butyl and benzyl groups (entries 1,2,3,5). On the other hand, when the reaction is heated in pure alkyl halide the selectivity decreases, but in similar conditions benzyl chloride gives a better result than the corresponding bromide (entries 2,4,6).

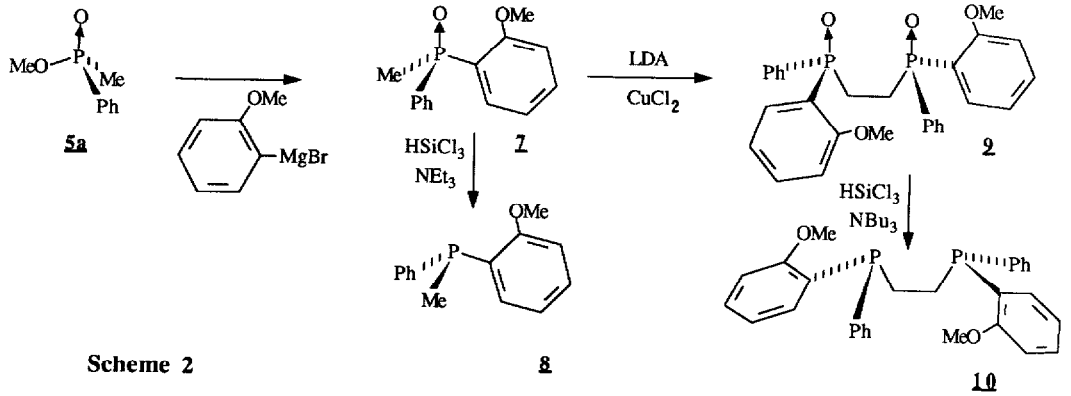
entry	R_1X	conditions	product [b]	yield %	de % [a]
1	Me I	24h / C_6H_6 / RT [c]	**4a**	85	85
2	Et I	14 mn / 80°C	**4b**	80	70
3	Pr I	24h / CH_2Cl_2 / RT	**4c**	80	80
4	$PhCH_2Br$	1h / 110°C	**4d**	80	0
5	$PhCH_2Br$	72h / C_6H_6 / RT	**4d**	90	40
6	$PhCH_2Cl$	30 mn / 100°C	**4e**	90	60

a) estimated by NMR ^1H, ^{31}P
b) spectroscopic and analytical data (14)
c) for a typical procedure see ref. (16)

Results from Arbuzov rearrangement of oxazaphospholidine **7**

TABLE I

The absolute configuration of the major isomer **4** (vide Infra), indicates a retention of the chirality at the phosphorus atom for the Michaelis Arbuzov rearrangement, similar to that observed in acyclic series (16). Diastereomeric methylphenyl phosphinamide **4a** is readily available in a satisfactory yield, by filtration from the reactive medium and recristallization in acetone or chromatography on alumina with AcOEt as eluant. Acid methanolysis of the phosphinamides **4a** (17) gives R(+)-methyl phenylphosphinate **5** with an ee more than 96% and aziridine **6**, which can be recycled into (-)-ephedrine by alcaline hydrolysis of the chloro N-acetyl derivative (18).

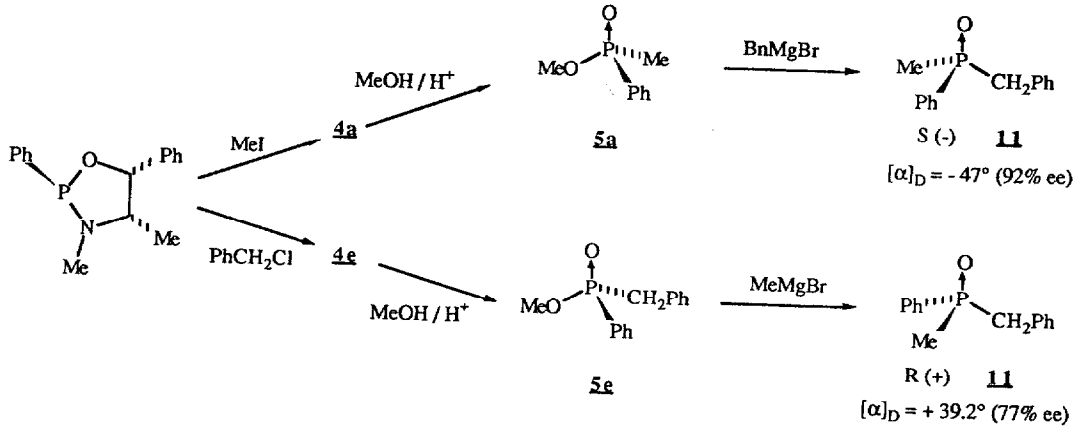


Scheme 2

The absolute configuration S of the phosphinate **5** and the stereochemistry with inversion of the chirality during the phosphinamide methanolysis (19), proves the R configuration of **4**, and the predominant retention of chirality at the phosphorus atom during a Michaelis Arbuzov rearrangement of the oxazaphospholidine **3**. The reaction of o-anisyl magnesium bromide with the phosphinate **5** gives R(+)-o-anisyl methyl phenyl phosphine oxide **7** (95 % ee), which is used for the preparation of

(+)-PAMP **8** (-)-DIPAMPO **9** and (-)- DIPAMP **10** following the procedure described by Knowles and coll. (21) (scheme 2).

Interestingly, it is possible to prepare benzyl methyl phenyl phosphine oxide **11** in the S or R configuration from the phosphinates **5a**, or **5e** which can be obtained from the same oxazaphospholidine **3** (scheme 3) (23).



Scheme 3

Similarly, S(-)-methyl phenyl phosphinate, S(-)-PAMPO, S,S(+)-DIPAMPO and S,S (+)-DIPAMP were prepared from (-)-oxazaphospholidine derived from (+)-ephedrine.

In conclusion, we have described an efficient method for the preparation of phosphine oxides with high optical purity and known absolute configuration, starting from the same oxazophospholidine derived from (-)-ephedrine. We have also prepared (+)-PAMP, (-)-PAMP, and DIPAMP using the two antipodal ephedrines showing the wide stereochemical possibilities of the procedure.

Acknowledgments : We wish to thank Professor H.B. Kagan and Drs. P. Potin, J.A. Laffitte and the ELF Aquitaine Company for their kind interest in this work.

References and notes

1) a) P.A. Frey, Tetrahedron, 1982, 38, 1541. b) K. Bruzik and M.D. Tsai, J.Am.Chem.Soc., 1984, 106, 747 and ref. therein.

2) a) J.D. Morrison, J.W. Scott, Asymmetric Synthesis, Vol 4, 1984 p.263, Academic Press. b) J.D. Morrison, Asymmetric Synthesis, Vol 5, 1985, Academic Press. c) J.W. Apsimon and T. Lee Cottier, Tetrahedron, 1986, 42, 5254.

3) a) O. Korpium, R.A. Lewis, J. Chickos and K. Mislow, J.Am.Chem.Soc.,1968, 90, 4842. b) R.A. Lewis and K. Mislow, J.Am.Chem.Soc., 1969, 91, 7009.

4) a) M. Mikolajczyk, Pure Appl.Chem., 1980, 52, 959 and ref. therein. b) K.M. Pietrusiewicz, M.Zablocka and Monkiewicz, J.Org.chem.,1984,49,1522. c) J. Neuffer and W.J. Richter, J.Organomet.Chem.,1986, 301, 289.

5) a) W. Chodkiewicz, D. Jore and W. Wodzki, Tetrahedron Lett., 1979, 12, 1069. b) W. Chodkiewicz, J.Organomet.Chem., 1984, 273, C55.

6) T. Koizumi, R. Yanada, H. Takagi, H. Hirai and E. Yoshii, Tetrahedron Lett., 1981, 22, 571.

7) a) S. Jugé, French Patents 2 518 100, 2 537 143. b) S. Jugé, Thesis Orsay 1984.

8) a) D.B. Cooper, T.D. Inch and G.L. Lewis, J.Chem.Soc., Perkin Trans I, 1974, 1043. b) S. Jugé and Y. Legras, French patents 2 562 543, 2 564 842 . c) M. Segi, Y. Nakamura, T. Nakajima and S. Suga, Chem.Lett., 1983, 913. d) T. Kato, K. Kobayashi, S. Masuda, M. Segi, T. Nakajima and S. Suga, Chem.Lett., 1987, 1915.

9) A solution of bis (diethylamino) phenyl phosphine **1** (25.2 g - 0.1 mol) and (-)-ephedrine **2** (16.5 g-0.1 mol) in 500 ml of toluene was heated at 105°C under nitrogen. After 16 h the solution was

concentrated to 250 ml and kept at room temperature, which precipitates the oxazaphospholidine 3. The concentrated filtrate gives other crops of product 3. m.p. 100°C (from toluene) 70 % yield ; $[\alpha]_D^{20}$ = + 40° (c = 2.3, C_6H_6) ; ^{31}P NMR (C_6D_6) δ = + 141.7; ^1H NMR (C_6D_6 250 MHz) δ = 0.47 (3,d,J = 7), 2.32 (3,d,J = 14), 3.02 (1,m), 5.35 (1,d,J_1 = 7, J_2 = 3), 6.9 - 7.3 (8,m), 7.45 - 7.6 (2,m) ; ^{13}C NMR (C_6D_6) δ = 13.8 (J_{PC} = 4), 30.2 (J_{PNC} = 20), 57 (J_{PNC} = 6), 86.3 (J_{POC} = 10).

10) W.J. Richter, Chem.Ber., 1984, 117, 2328.

11) J.B. Robert and H. Weichmann, J.Org.Chem., 1978, 43, 3031.

12) D.B. Cooper, C.R. Hall, J.M. Harrison and T.D. Inch, J.Chem.Soc., Perkin Trans I, 1977, 1969.

13) M.R. Marre, J.F. Brazier, R. Wolf and A. Klaebe, Phosphorus and Sulfur, 1981, 11, 87.

14) 4a : m.p = 144°C. (from acetone - diisopropylether 3 : 1); $[\alpha]_D^{20}$ = + 162° (c = 2.5, CH_3OH); ^1H - NMR ($CDCl_3$ - 250 MHz) δ = 1.1 (3,d,J = 7), 1.97 (3,d,J = 15), 2.4 (3,d,J = 11), 4.35 (1,m), 5.14 (1,d,J = 11), 7.1 - 8.2 (10,m) ; 4b : not cristallized (mixture of isomers in 85 / 15 ratio) ; ^1H - NMR ($CDCl_3$ - 90 MHz) major isomer : δ = 1.09 (3,d,J = 7), 1.13 (3,d.t,J_1 = 7,J_2 = 16), 2.1 (2,m,J = 14), 2.4 (3,d,J = 11), 4.2 (1,m), 5.11 (1,d,J = 11), 7.2 - 8.25 (10,m) ; minor isomer : δ = 2.56 (3,d,J = 11), 5.04 (1,d,J = 11) ; 4c : not cristallized (mixture of isomers in 90 / 10 ratio) ; ^1H - NMR ($CDCl_3$ - 90 MHz) major isomer : δ = 0.9 (3,t,J = 7), 1.1 (3,d,J = 7), 1.2 - 2 (6,m), 2.5 (3,d,J = 11), 5.25 (1,d,J = 11) 7.2 - 8.2 (10,m) minor isomer δ = 2.77 (3,d,J = 11), 5 (1,d,J = 11) ; 4d : mixture of isomers in 70 / 30 ratio, m.p. = 180 - 3°C (racemate from acetone) ; ^1H - NMR ($CDCl_3$ _ 90 MHz) major isomer : δ = 1.05 (3,d,J = 7), 2.48 (3,d,J = 11), 3.62 (2,m), 4.23 (1,m), 4.99 (1,d,J = 11), 7.1 - 8 (15,m) ; minor isomer : δ = 0.62 (3,d,J = 7), 2.06 (3,d,J = 9), 4.83 (1,d,J = 10) ; 4e : mixture of isomers in 80 : 20 ratio, m.p. 175°C (racemate from acetone), major isomer : m.p = 154 - 7°C, $[\alpha]_D^{20}$ = + 130° (c = 3, $CHCl_3$), ^1H NMR ($CDCl_3$ - 90 MHz) δ = 1.01 (3,d,J = 7), 2.48 (3,d,J = 10), 3.58 (2,m), 4.13 (1,m), 4.91 (1,d,J = 10), 7 - 8 (15,m) ; minor isomer : δ = 0.58 (3,d,J = 7), 2.62 (3,d,J = 9), 3.58 (2,m), 4.13 (1,m), 4.74 (1,d,J = 10).

15) Freshly purified methyl iodide (10 ml - 0.16 mol) was added under argon to a solution of oxazaphospholidine 3 (5 g - 18 mmol) in benzene (40 ml) and the mixture was stirred at room temperature for 24 h in the dark After this, approximately 4.5 g of cristallized phosphinamide 4a were isolated by filtration. The benzene filtrate was evaporated and the residue (3 g) purified by chromatography on alumina with AcOEt. The phosphinamide 4a was recristallized rapidly in a acetone / diisopropylether mixture (3 : 1) - 60 % yield of the major isomer 4a was obtained after purification.

16) a) W.G. Bentrude and J.H. Hargis, J.Am.Chem.Soc., 1970, 92, 7136. b) G.R. Van Den Berg, D.H.J.M. Platenburg and H.P. Benschop, J.Chem.Soc., Chem.Comm., 1971, 606. c) J. Omelanczuk and M. Mikolajczyk, J.Chem.Soc., Chem.Comm., 1976, 1025.

17) White cristalline phosphinamide 4a (2.1 g - 5 mmol) in 5 ml of MeOH was added to a solution of 4.2 g H_2SO_4 96 % in 400 ml MeOH. After 18 h at room temperature, the reaction was stopped with 100 ml of $NaHCO_3$ 10 % and the methanol was evaporated. The benzene extraction gave the phosphinate 5a which was purified by distillation. A 85 % yield was obtained. b.p = 115°C / 0,1 mm $[\alpha]_D$ = + 57° (c = 4, C_6H_6) litt. (19) $[\alpha]_D$ = + 58° ; ^1H - NMR ($CDCl_3$ - 90 MHz) δ = 1.65 (3,d,J = 15), 3.65 (3,d,J = 11), 7.5 - 7.8 (5,m). The ether extraction of the aqueous layer gave aziridine 6 under basic conditions. b.p. = 85°C / 155 mm, $[\alpha]_D$ = - 124° litt (20) $[\alpha]_D$ = - 127° ; ^1H - NMR ($CDCl_3$ - 90 MHz) δ = 0.92 (3,d,J = 6) 1.71 (1,q,J_1 = J_2 = 6), 2.48 (1,d,J = 6), 2.53 (3,s), 7.35 (5,s) litt. (20).

18) K. Tanaka, J.Pharm.Soc.Jap., 1950, 70, 220.

19) M.J.P. Harger, J.Chem.Soc., Perkin Trans. I, 1979, 1294.

20) S.J. Brois and G.P. Beardsley, Tetrahedron Lett., 1966, 5113.

21) B.D. Vineyard, W.S. Knowles, M.J. Sabacky, G.L. Bachman and D.J. Weinkauff, J.Am.Chem.Soc., 1977, 99, 5946.

(Received in France 16 February 1989)