Pergamon

Tetrahedron Letters, Vol. 38, No. 13, pp. 2257-2258, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00335-3

A Systematic Synthetic Approach to Phosphinophenyl-glycine and -alanine Chiral Phosphine Ligands with Amino Acid Moieties

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Abstract: *ortho*- and *para*-phosphinophenyl derivatives of glycine and alanine have been synthesised by nucleophilic phosphination of 2- and 4-fluorophenylglycine and -alanine with Ph(R)PK (R = Me, Ph). The structure of 2-diphenylphosphino-α-phenylglycine has been identified by X-ray analysis.
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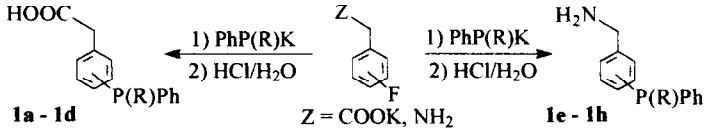
Amino acids containing functionalised aromatic substituents continue to attract attention because of their potential pharmacological utility in drugs and their use as building blocks for the design of new types of proteins with unusual properties.[1] While the syntheses of *para*-phosphonato and -phosphonatomethyl derivatives of phenylglycine[2] and phenylalanine[3] are well established, only a very few phosphinophenyl substituted amino acids have been reported very recently.[4]

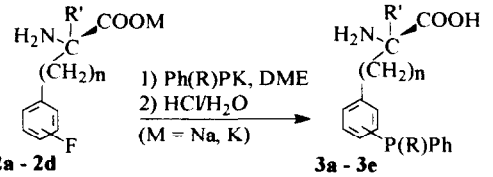
Initial studies showed, that the hitherto unknown phosphinophenyl acetic acids **1a - 1d** and phosphinobenzylamines **1e - 1h** may be obtained by nucleophilic phosphination of *ortho*- and *para*-fluorophenyl acetates or *ortho*- and *para*-fluorobenzylamine, respectively, with Ph(R)PK (R = Me, Ph) in high yields.



1a - 1d Z = COOK, NH_2 **1e - 1h**

para: **1a**, **1e** (R = Ph)
1b, **1f** (R = Me)
ortho: **1c**, **1g** (R = Ph)
1d, **1h** (R = Me)

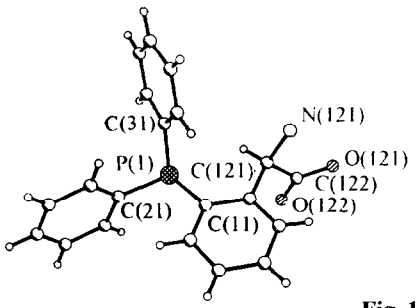
Extending this synthetic strategy to the sodium or potassium salts of 4- and 2-fluoro-α-phenylglycine and -alanine (**2a - 2d**)[5] the phosphinophenylamino acids **3a - 3e** were obtained in good yields.[6] The phenylglycine derivative **3d** with an unsymmetrically substituted phosphorus atom is formed as a 1:1 mixture of two diastereoisomers (*erythro* and *threo*, $^{31}P\{^1H\}$-NMR: δP = -38.6, -39.5 ppm)[7] which could be separated by recrystallisation from methanol.



2a - 2d **3a - 3e**

para: **2a, 3a** (R = Ph, R' = H, n = 0)
2b, 3b (R = Ph, R' = Me, n = 0)
2c, 3c (R = Ph, R' = H, n = 1)
ortho: **2d, 3d** (R = Me, R' = H, n = 0)
3e (R = Ph, R' = H, n = 0)

The betaine type structure of **3e** in the solid state was established by an X-ray structural analysis (fig. 1)[8] showing extended hydrogen bridging between the molecules.



P(1)-C(21) 1.839(4); P(1)-C(11) 1.849(4); P(1)-C(31) 1.848(4); O(121)-C(122) 1.249(4); O(122)-C(122) 1.247(4) Å
C(31)-P(1)-C(11) 104.4(2); N(121)-C(121)-C(122) 108.8(3); O(121)-C(122)-O(122) 127.7(5)°

Fig. 1. X-ray structure of **3e**·$2H_2O$

Like other related P,N-hybride donor systems[9] the *ortho*-phosphinophenyl glycines are of great potential as catalyst ligands in enantioselective syntheses due to their capability to form hemilabile P,N-chelate ring systems with a chiral backbone. Experiments are in progress.

Acknowledgement. This work was supported by the Fonds der Chemischen Industrie. Bayer AG and Hoechst AG are thanked for financial support.

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6. *Typical procedure:* (**3e**): To the solution of 3.69 g (16.5 mmol) Ph_2PK in 60 mL of 1,2-dimethoxyethane 3.0 g (15.7 mmol) of sodium 2-(2-fluorophenyl)-glycinate were added and the reaction mixture was heated at 80°C for 3 h. 10 mL of methanol were added and all volatiles were removed in vacuo (10^{-2} bar, 80°C). The residue was suspended in 100 mL of dilute aqueous HCl (pH value 4) filtered and dried in vacuo. Yield: 4.7 g (89 %). The product was recrystallised from a 3:1 mixture of water/methanol. $^{31}P\{^1H\}$-NMR: δP = -9.6 ppm; $^{13}C\{^1H\}$-NMR: δC = 137.8 (9.7), 137.4 (8.9), 134.9 (19.2), 134.6 (18.8), 129.7 (6.8), 129.6 (6.7), 130.0, 129.8, 138.4 (13.7), 142.2 (27.2), 130.1, 131.2, 128.6 (4.7), 136.1 (1.3); 57.6 (27.7, *CH*), 179.8 ppm (*COOH*); coupling constants ^nJ(PC) in Hz in parentheses.
7. $^{13}C\{^1H\}$-NMR (**3d**): δC (CH_3(P)) = 13.2 (13.9), 13.1 ppm (13.9); δC (*CH*(NH_2)(COOH) 59.8 (24.1), 59.1 ppm (26.2); coupling constants ^nJ(PC) in Hz in parentheses.
8. X-ray analysis of **3e**·$2H_2O$: $C_{20}H_{22}NO_4P$, M_w = 371.4; Siemens P4 diffractometer (MoKα radiation, λ = 0.71073 Å), graphite monochromator). Orthorhombic, space group Pbca, Z = 8, a = 9.687(2), b = 10.629(3), c = 37.856(7) Å, D_{calc} = 1.266 Mg/m^3. The structure was solved by direct methods using SHELXS-86 and refined against F^2 with SHELXL-93 to R = 0.0446 (for I > 2σ(I)) and wR2 = 0.126 for all 3463 independent reflections. Further details are available from Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen on citing the deposition number CSD 405956.
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(*Received in Germany* 6 *November* 1996; *revised* 15 *January* 1997; *accepted* 11 *February* 1997)