Pergamon

Tetrahedron Letters 43 (2002) 1299–1301

TETRAHEDRON
LETTERS

Mannich-based condensation reactions as a practical route to new aminocarboxylic acid tertiary phosphines

Martin B. Smith* and Mark R. J. Elsegood

Department of Chemistry, Loughborough University, Loughborough, Leics LE11 3TU, UK

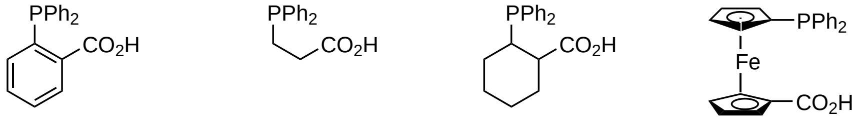
Received 12 September 2001; accepted 13 December 2001

Abstract—The facile syntheses of a range of aminocarboxylic acid tertiary phosphines are reported including the X-ray crystal structure of 2-{$Ph_2PCH_2N(H)$}-4,5-$(MeO)_2C_6H_2CO_2H$. © 2002 Published by Elsevier Science Ltd.

The synthesis of new carboxylic acid functionalised tertiary phosphines has attracted recent interest for their various uses, e.g. as precursors to phosphine amides,[1] in catalysis,[2] as *P*,*O*-hemilabile ligands and for their water-solubilising properties.[3–6] Some examples of known tertiary phosphines modified with carboxylic acid groups are illustrated in Chart 1.[1,2,7,8] To the best of our knowledge very few examples contain an additional nitrogen donor atom between both 'soft' and 'hard' donor centres.[9] In the course of our studies we have employed a phosphorus-based Mannich reaction as an extremely efficient method for generating new 'hybrid' ligands.[10] We, and others, have found this procedure reaps many advantages over more classical routes (nucleophilic substitutions using primary/secondary phosphides, palladium–catalysed P–C couplings and free-radical addition reactions) including short reaction times and no requirement for prior generation of reactive intermediates. Accordingly we describe here a facile one-step method for the synthesis of new carboxylic acid functionalised tertiary phosphines from cheap, commercially available starting materials.

Results and discussion

Using a similar procedure to that recently developed for preparing novel pyridylphosphines,[10] reaction of 1 equiv. of Ph_2PCH_2OH [readily preformed from equimolar amounts of Ph_2PH and $(CH_2O)_n$ or generated in situ] with the appropriate stoichiometry of 2-aminobenzoic acid in methanol gave the condensed ligand 2-{$Ph_2PCH_2N(H)$}$C_6H_4CO_2H$ **1a** in 88% yield.[†,‡] Furthermore, as demonstrated by the synthesis of **1b–j** (Eq. (1)), this method is extremely reliable and tolerant to a range of functional groups with no significant variation in yield. Various functional groups (F, Cl, Br, I, OH, OMe, CO_2H) substituted either in the 5- or 4-position (CO_2H) or both (OMe, **1j**) can be incorporated. The procedure also works well when the CO_2H/



I **II** **III** **IV**

Chart 1.

Keywords: amines; carboxylic acids and derivatives; Mannich reactions; phosphines.

* Corresponding author. Tel.: +44 (0)1509 222553; fax: +44 (0)1509 223925; e-mail: m.b.smith@lboro.ac.uk

[†] *Typical synthesis for* **1a**: To the solids Ph_2PCH_2OH (1.001 g, 4.63 mmol) and 2-$H_2NC_6H_4CO_2H$ (0.632 g, 4.61 mmol) was added methanol (10 ml) to afford a deep yellow solution. After stirring for 30 min, solid **1a** was filtered off in air, washed with MeOH (5 ml) and dried in vacuo. Further crops could be obtained upon allowing the filtrate to stand. Yield: 1.367 g, 88%.

[‡] All new compounds gave satisfactory microanalytical and spectroscopic results.

0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(01)02361-9

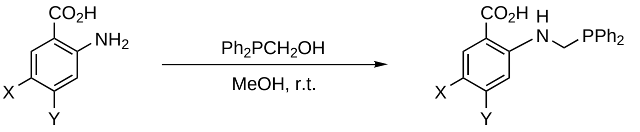
Table 1. Selected data for compounds **1**–**3**

Compound	Yield (%)	^{31}P NMR	
		δ(P) (ppm)	Solvent
1a	88	−20.0	$CDCl_3/(CH_3)_2SO$
1b	55	−19.4	$CDCl_3$
1c	76	−20.2	$CDCl_3/(CH_3)_2SO$
1d	90	−19.4	$CDCl_3/CH_3OH$
1e	81	−20.2	$CDCl_3/CH_3OH$
1f	77	−20.3	$CDCl_3/CH_3OH$
1g	66	−20.2	$CDCl_3/CH_3OH$
1h	80	−19.7	$CDCl_3/(CH_3)_2SO$
1j	94	−18.5	$CDCl_3$
2a	63	−21.5	$CDCl_3/(CH_3)_2SO$
2b	n.r.[a]	−19.8	$CDCl_3/CH_3OH$[b]
2c	96	−18.9	$CDCl_3$
3	93	−18.6	$CDCl_3$

[a] n.r. = not recorded.

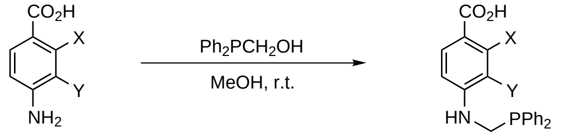
[b] In addition to small amounts of 2-(OH)-4-$\{(Ph_2PCH_2)_2N\}$-$C_6H_3CO_2H$.

NH_2 substituents are either *para* or *meta* (Eqs. (2) and (3)) to each other with the highest yield obtained for **2c**. The yields for **1**–**3** are unoptimised and in the range of 55–96% with seven examples exceeding 80% (Table 1). For **2b**, the predominant species observed was the singly substituted 2-(OH)-4-$\{Ph_2PCH_2N(H)\}C_6H_3$-CO_2H although small amounts of the bis-substituted species was also observed (NMR evidence). The $^{31}P\{^1H\}$ NMR data (Table 1) confirm single phosphorus species at δ(P) −20 ppm indicating, in all cases, substituents have negligible effect on the ^{31}P chemical shift and some 10 ppm upfield with respect to that of Ph_2PCH_2OH [δ(P) −9.9 ppm ($CDCl_3$)].[10] Attempts to prepare 2-$\{(Ph_2PCH_2)_2N\}C_6H_4$-CO_2H from 2-aminobenzoic acid and 2 equiv. of Ph_2PCH_2OH (MeOH, 31 h) gave **1a** in 64%. Compounds **1**–**3** are soluble in methanol but thus far show little evidence for solubility in water or weakly basic media.



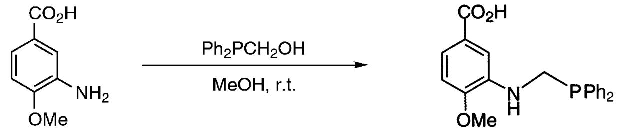
X = Y = H **1a**
X = F, Y = H **1b**
X = Cl, Y = H **1c**
X = H, Y = Cl **1d**
X = Br, Y = H **1e**
X = I, Y = H **1f**
X = OH, Y = H **1g**
X = CO$_2$H, Y = H **1h**
X = Y = OMe **1j**

(1)



X = Y = H **2a**
X = OH, Y = H **2b**
X = H, Y = OMe **2c**

(2)



3

(3)

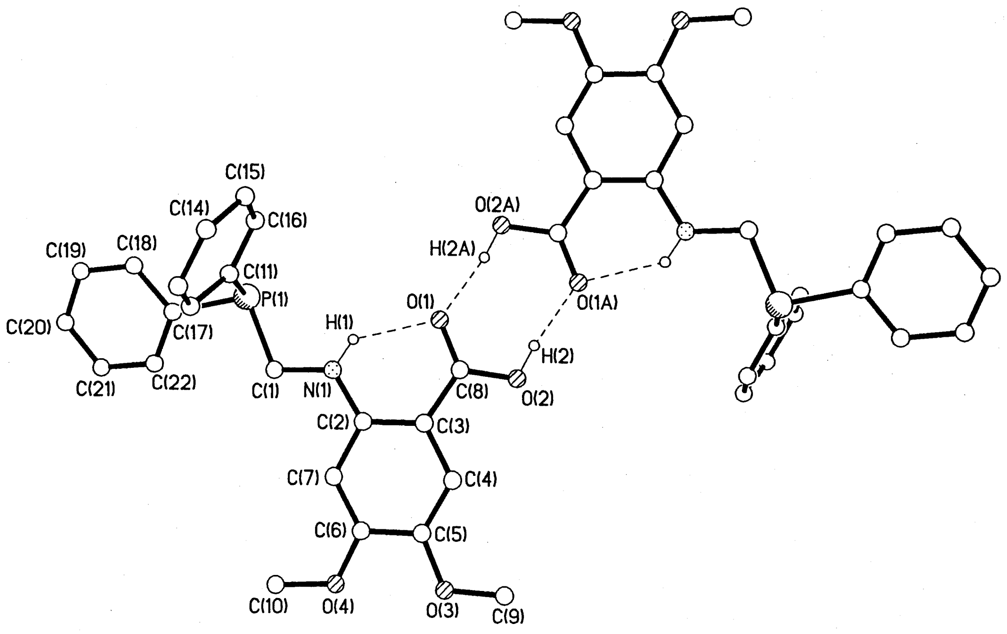


Figure 1. X-Ray structure of compound **1j** showing (i) the molecular structure (ii) the intramolecular N(1)–H(1)···O(1) H-bonded cyclisation and (iii) the intermolecular carboxylate head-to-tail H-bonding motif giving rise to dimer pairs.

An X-ray structure (Fig. 1)[§] of **1j** confirms that the overall geometry comprises *ortho*-substituted -N(H)CH_2PPh_2 and -CO_2H groups (in addition to the two methoxy groups).[¶] Hydrogen bonding is also evident and links molecules into head-to-tail dimer pairs through hydrogen bonding [O(2)···O(1A) 2.646(1), H(2)···O(1A) 1.81(3) Å; O(2)–H(2)···O(1A) 169(2)°]. There is also an intramolecular N–H···O hydrogen bond [N(1)···O(1) 2.713(2), H(1)···O(1) 2.04(2)Å; N(1)–H(1)···O(1) 137(2)°].

In conclusion, we have developed a facile procedure for the synthesis of new functionalised tertiary phosphines bearing carboxylic acid groups. This synthetic route is extremely practical with reactions generally complete within a few hours. In addition to the short reaction times this method obviates the preparation of reactive intermediates, uses cheap and commercially available starting materials, requires no purification steps nor any stringent need for performing reactions under an oxygen free atmosphere. Current efforts are directed towards understanding their co-ordination behaviour and potential utility in catalysis.

References

1. (a) Mino, T.; Kashihara, K.; Yamashita, M. *Tetrahedron: Asymmetry* **2001**, *12*, 287; (b) Lange, P.; Schier, A.; Schmidbauer, H. *Inorg. Chem.* **1996**, *35*, 637.
2. Komon, Z. J. A.; Bu, X.; Bazan, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 12379.
3. Brauer, D. J.; Schenk, S.; Robenbach, S.; Tepper, M.; Stelzer, O.; Hausler, T.; Sheldrick, W. S. *J. Organomet. Chem.* **2000**, *598*, 116.
4. Hingst, M.; Tepper, M.; Stelzer, O. *Eur. J. Inorg. Chem.* **1998**, 73.
5. Herd, O.; Hebler, A.; Hingst, M.; Tepper, M.; Stelzer, O. *J. Organomet. Chem.* **1996**, *522*, 69.
6. Heesche-Wagner, K.; Mitchell, T. N. *J. Organomet. Chem.* **1994**, *468*, 99.
7. Brauer, D. J.; Kottsieper, K. W.; Nickel, T.; Stelzer, O.; Sheldrick, W. S. *Eur. J. Inorg. Chem.* **2001**, 1251.
8. Podlaha, J.; Stepnicka, P.; Ludvik, J.; Cisarova, I. *Organometallics* **1996**, *15*, 543.
9. Karasik, A. A.; Georgier, I. O.; Sinyashin, O. G.; Hey-Hawkins, E. *Polyhedron* **2000**, *19*, 1455.
10. Durran, S. E.; Smith, M. B.; Slawin, A. M. Z.; Steed, J. W. *J. Chem. Soc., Dalton Trans.* **2000**, 2771.

[§] *Crystal data for* ***1j***: $C_{22}H_{22}NO_4P$, $M_w = 395.38$; monoclinic, space group $P2_1/c$, $a = 10.0587(8)$, $b = 19.0185(15)$, $c = 11.1660(9)$ Å, $\beta = 113.342(2)°$; $U = 1961.2(3)$ Å^3, $D_{calcd} = 1.339$ g cm^{-3}, λ(Mo Kα) = 0.71073 Å, $Z = 4$, $\mu = 0.169$ mm^{-1}, $T = 150(2)$ K, $wR_2 = 0.1153$ for all 4698 unique data, $R_1 = 0.044$ for 3473 reflections with $F^2 > 2\sigma(F^2)$. The -PPh_2 unit is disordered over two sets of positions; ratio of major:minor components 84:16(1). Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 177016. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.ac.uk].

[¶] Selected bond lengths (Å) and angles (°): P(1)–C(1) 1.8208(19), P(1)–C(11) 1.830(2), P(1)–C(17) 1.838(2), C(1)–N(1) 1.456(2), N(1)–C(2) 1.367(2), C(8)–O(1) 1.246(2), C(8)–O(2) 1.329(2). C(1)–P(1)–C(11) 100.60(10), C(1)–P(1)–C(17) 101.07(10), C(11)–P(1)–C(17) 100.84(12), P(1)–C(1)–N(1) 111.56(13).