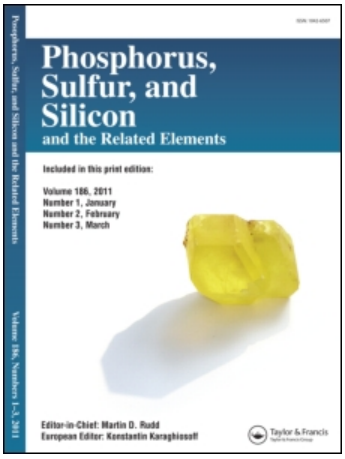

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SYNTHESIS OF SOME FUNCTIONALIZED PHOSPHINOCARBOXYLIC ACIDS

J. A. Van Doorn[a]; N. Meijboom[a]
[a] Koninklijke/Shell-Laboratorium, Amsterdam (Shell Research B.V.), AA Amsterdam, The Netherlands

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SYNTHESIS OF SOME FUNCTIONALIZED PHOSPHINOCARBOXYLIC ACIDS

J. A. VAN DOORN and N. MEIJBOOM
Koninklijke/Shell-Laboratorium, Amsterdam (Shell Research B.V.) P.O. Box 3003, 1003 AA Amsterdam, The Netherlands

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Various functionalized phosphinocarboxylic acids have been prepared by a number of complementary methods. Reactions of relatively electron-poor secondary phosphides with electron-rich halocarboxylates in liquid ammonia give high yields of phosphinocarboxylates. The substitution reaction may proceed by a classical S_N2 mechanism or by an S_N rad mechanism. Reduction of the carboxylate can be a deleterious side reaction in the preparation of phosphinoacetic acids. Several phosphinopropionic acids are prepared by the Michael addition of diphenylphosphine to unsaturated esters. A valuable method proved to be the reaction of dichlorophosphinoacetic ester with functionalized organometallic reagents.

Key words: Phosphine; carboxylic acid; ligand; functionalized; synthesis; NMR data.

INTRODUCTION

Phosphinocarboxylic acids form an important class of bidentate ligands. These molecules combine a tertiary phosphine with a soft donor atom and a carboxylate moiety with relatively hard donor atoms. Because of this bifunctional nature these chelating ligands show an interesting coordination behaviour with transition metal ions.[1–4] Moreover these ligands are of considerable economic importance. They are an indispensable component of a catalyst that oligomerizes ethene to higher olefins via the so-called SHOP process.[4]

Phosphinocarboxylic acids are relatively new compounds and papers on their synthesis continue to appear.[5] Four principal synthetic methods are available:

1. Reaction of a metal phosphide with a halocarboxylate[2,5–8]
2. Carbonation of a metallated phosphine[9–11]
3. Phosphonylation of an organometallic reagent that bears the carboxylate moiety[12–16]
4. Reaction of a secondary phosphine with unsaturated esters or halocarboxylic esters[2,17,18]

We have used these methods as a basis for our work. In particular, reactions 1 and 4 look attractive for the preparation of a variety of functionalized phosphinocarboxylic acids.

RESULTS

A. Substitution of Halocarboxylates

The nucleophilic substitution of halocarboxylates with metal phosphides has been used in the past to prepare a number of phosphinocarboxylic acids, though in variable yield.[6] We have studied the effects of the solvent and of the structure of both the phosphide and the carboxylate with a view to finding ways of increasing yield and widening the scope of the reaction.

We have used a number of solvents, polar and apolar, under various conditions to find the optimal yield for the carbon-phosphorus coupling reaction. It appears that liquid ammonia, a very polar solvent, gives by far the best yields (see Table I). In order to determine by which mechanism the nucleophilic reaction proceeds we have added azobenzene to the reaction mixture. This compound is an inhibitor for the S_N rad mechanism.[19] We have found that addition of azobenzene may have a profound effect on the yield of phosphinocarboxylate. With THF as the solvent it leads to a large decrease of the yield from the reaction between lithiumdiphenylphosphide and *t*-butyl chloroacetate. This shows that the reaction between these reactants in THF proceeds predominantly by the S_N rad mechanism.[19] By contrast, there is no effect on the reaction in liquid ammonia but this may be due to the fact that azobenzene is poorly soluble in this medium.

The electronic nature of the substituents R^1 and R^2 at the phosphorus atom has a large influence on the yield of the reaction (see Table II entries 1, 3–5).

$$R^1R^2PNa + XCR'R''COOR \rightarrow R^1R^2PCR'R''COOR$$

The phosphides in this series are sterically comparable[20] and the groups attached to them vary in electronic nature. It appears that the strongest electron-donating[20] substituents, i.e. highly nucleophilic phosphides, lead to a low yield of the desired product (also found by Issleib).[6] In Figure 1 we have given a graphical

TABLE I

Effect of solvent and conditions on the reaction of *t*-butyl chloroacetate and Ph_2PM

M	Solvent	Yield,[a] %	Temp, °C
Li	*n*-heptane	24	ca. 20
Li	do	45	−78
Li	diethyl ether	53	−78
Li	THF	50	20
Li	do	34	−78
Li	do	5[b]	−78
Na	THF	11	−78
Li	NH_3	87	−78
Na	NH_3	76	−78
Na	do	78[c]	−78

[a] Overall yield of phosphinocarboxylic acid after saponification, 100% conversion of the phosphide.
[b] 1.4 mol% of azobenzene added.
[c] 4.2 mol% of azobenzene added.

TABLE II

Yield of the reaction of R^1R^2PM and $XCR'R''COOR$

#	R^1	R^2	X	R'	R''	R	M	Yield,[a] %
1	Ph	Ph	Cl	H	H	Na	Na	87
2	Ph	2-CH_3Ph	Cl	H	H	Na	Na	65
3	3-CH_3Ph	3-CH_3Ph	Cl	H	H	Na	Na	70
4	4-CH_3Ph	4-CH_3Ph	Cl	H	H	Na	Na	66
5	Ph	*i*-Bu	Cl	H	H	Na	Na	35
6	Ph	*n*-Bu	Cl	H	H	Na	Na	56
7	Ph	Ph	Cl	H	H	*t*-Bu	Na	76
8	Ph	Ph	Cl	H	H	Ph	Na	5[b]
9	Ph	Ph	Cl	CH_3	H	Et	Na	82
10	Ph	Ph	OTs	CH_3	H	Et	Na	86
11	Ph	Ph	Cl	CH_3	CH_3	CH_3	Na	24.6
12	Ph	Ph	Cl	F	F	*n*-Bu	Na	≤1
13	Ph	Ph	Cl	Ph	H	Et	Li	0
14	Ph	Ph	F	H	H	Et	Li	66
15	Ph	Ph	Cl	H	H	*t*-Bu	Li	87
16	Ph	Ph	Br	H	H	*t*-Bu	Li	≤50

[a] Overall yield of phosphinocarboxylic acid after saponification.
[b] 44% of diphenylphosphinoacetamide.

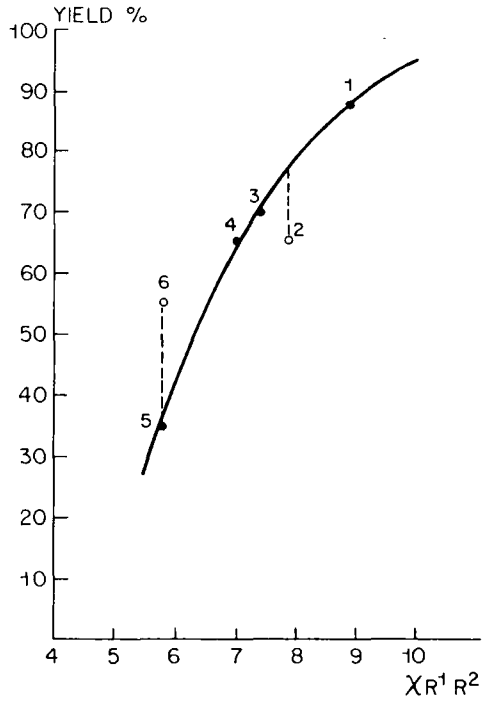


FIGURE 1 Yield as a function of electronic properties of R^1 and R^2 (see Table II for numbering).

representation of the results. In addition there is a steric effect. The yield of phosphinocarboxylic acid obtained with sodium phenyl-*o*-tolylphosphide (a relatively large phosphide) is lower than is expected from the χ value of the two substituents. By contrast the yield obtained with sodium phenyl-*n*-butylphosphide (a relatively small phosphide) is higher than is expected. We have insufficient data to give a more quantitative relation between yield and steric property of the phosphide.

The structure of the carboxylate has a profound effect on the selectivity. We have found that electron-withdrawing substituents (R′=Ph, R″=H and R′=R″=F) lead to a very low yield. No or very little phosphinocarboxylic acid was obtained from reaction between these substrates and sodium diphenylphosphide. Introduction of one methyl group leads to a small increase of the yield, whereas two methyl groups lead to a large decrease probably because of elimination of HX from the tertiary halide. The effect of the group R is relatively small but sodium carboxylates give a somewhat higher yield than the corresponding esters.[7] With R=Ph we observed the formation of phosphinoacetamide by ammonolysis.

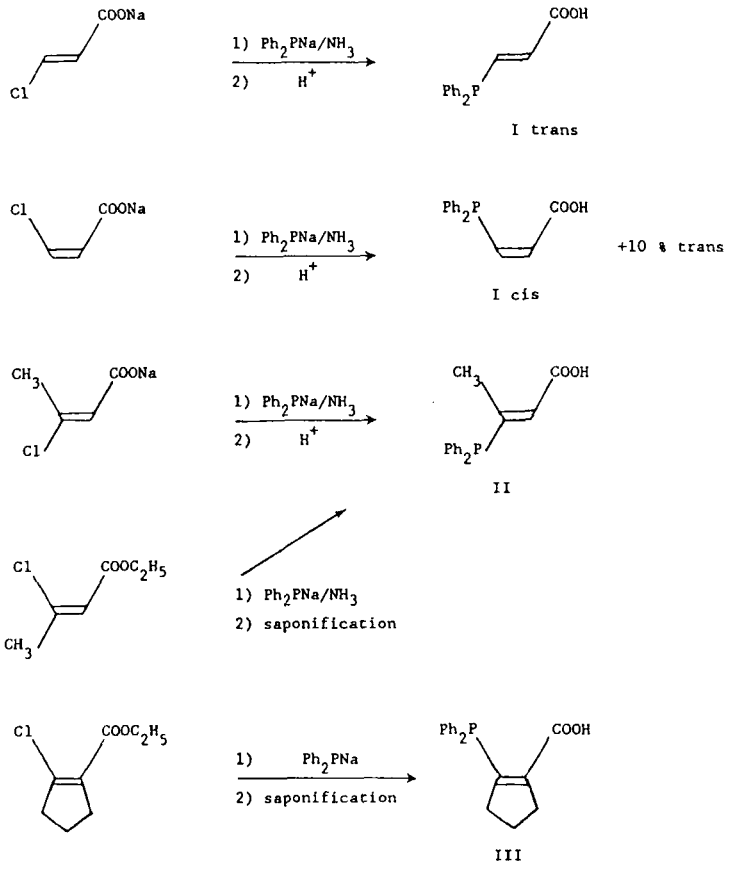
A good yield and a wide scope may be achieved by proper choice of the leaving group X. In addition to X=halogen we have tested some common leaving groups in the rection of XCH_2COOR with sodium diphenylphosphide. It appears that Cl and tosylate give the best yield of phosphinocarboxylic acid (see Table II). Thus Cl is better than both F and Br. This suggests that the reaction with the bromide occurs, at least partially, by the S_N rad mechanism.[21] Carboxylates (CH_3CH_2COO and CF_3COO) are unsuitable as a leaving group in this synthesis, no phosphinoacetic acid being obtained.

In conclusion, our efforts to optimise this reaction have not led to a broadly applicable synthesis of phosphinoacetic acids. On the other hand, no problems are encountered in the synthesis of phosphinopropionic and -butyric acids from ω-halocarboxylates. Chloroacrylates also give a good or acceptable yield of the corresponding phosphinocarboxylic acid.†

Interestingly, the reaction between sodium diphenylphosphide and sodium chloroacrylates is almost completely stereospecific. This suggests that the addition elimination mechanism observed with the reaction of chloromaleates with diphenyl(trimethylsilyl)phosphine does not occur.[23] By contrast, the corresponding esters may lead to a rearranged product (see Scheme 1 on the next page).

Unfortunately, the use of the substitution method is further limited because many interesting functionalized secondary arylphosphides cannot be readily prepared by cleavage of the corresponding triarylphosphine with alkali metal. For instance, tris-(4-dimethylaminophenyl)phosphine is not reduced and cleaved by sodium in liquid ammonia,[24] whereas tris-(4-fluorophenyl)- and tris-(4-methoxyphenyl)phosphine give no or a very low yield of the corresponding secondary phosphine,[25] respectively.

† The ^{13}C chemical shifts of these compounds were assigned on the basis of the data found for diphenylvinylphosphine and methyl crotonate. In this way we obtained a consistent set of data for the olefinic carbon atoms. However, the apparent values of ^1JPC and ^2JPC were in conflict with this interpretation. It is known that $^2JPC > {}^1JPC$ in vinylphosphines[22] but this order is reversed in our compounds. To resolve this ambiguity we have prepared the phosphinocrotonic acid. The data obtained for this compound confirm our original assignment on the basis of chemical shifts, as given in Table V.



SCHEME 1

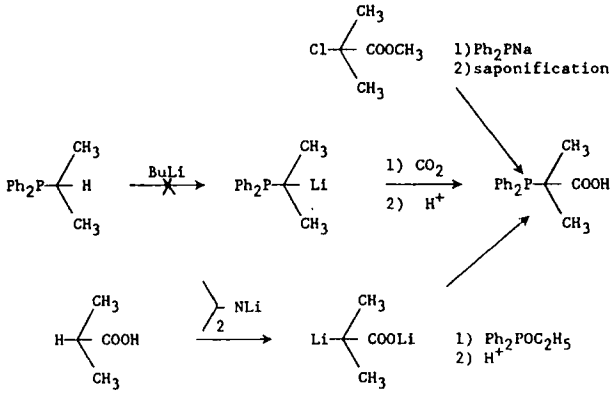
Issleib *et al.*[17] have reported a very convenient synthesis for dialkylphosphinoacetic acids by reaction of the secondary phosphine (instead of the phosphide) with the haloester. Thus complementary methods had to be sought mainly for the preparation of phosphinocarboxylic acids which bear functionalized aryl groups at the phosphorus atom.

B. Carbonation of a Metallated Phosphine

Phosphinoacetic acids can be prepared from α-lithiated phosphines and carbon dioxide.[9-10] For instance diphenylmethylphosphine is lithiated by BuLi/TMEDA in 70% yield and subsequently carbonated in 63% yield. We have found that substituents at the α-carbon have a dramatic effect on the lithiation reaction. Diphenylbenzylphosphine gives an overall yield of 62.5% of the corresponding phosphinocarboxylic acid, but from diphenylisopropylphosphine no carboxylic acid is obtained. Clearly the lithiation reaction is governed by the electron density at the α-carbon atom.

C. *Phosphonylation of an Organometallic Reagent that bears the Carboxylate Moiety*

We have prepared 2-methyl-2-diphenylphosphinopropionic acid from lithium 2-lithiopropionate and diphenylethoxyphosphine in 52% yield. The more reactive diphenylchlorophosphine does not give the target molecule. Probably, a side reaction occurs with the carboxylate oxygen atom or with the diisopropylamine which is formed in the lithiation reaction.



SCHEME 2

Indeed the methods in paragraphs B and C are complementary to the reactions we have discussed above. However, they do not lead to a simple and general route to functionalized diarylphosphinoacetic acids because the respective starting materials have either to be synthesized from Ar_2P fragments which are not readily available (vide supra) or are to be prepared from alkyldichlorophosphines. For these reasons we have tried to develop a method that gives a diversity of functionalized phosphinocarboxylic acids by a simple reaction using starting materials that are readily available.

D. *Alkylation of Chlorophosphinoacetic Ester*

Probably the best way to prepare symmetric or mixed tertiary functionalized phosphines is the reaction of a halophosphine and a suitable organometallic reagent. The method excels by its simplicity and high yields.[26] An obvious but—to the best of our knowledge—unknown extension of this method would be the reaction of an organo-metallic reagent and a halophosphinocarboxylic ester. The reaction is attractive because a great variety of symmetrically substituted functionalized phosphinoacetic acids would be obtained after saponification. Methyl dichlorophosphinoacetate itself and related compounds can be prepared in high yield by known methods.[8,12,27] Indeed coupling of this ester with Grignard or lithium reagents and subsequent saponification affords the desired phosphinoacetic acid. The procedure is simple and gives a satisfactory yield of a very pure product. We expect that the yield can be further increased using the sterically demanding *t*-butyl ester which may prevent attack at the carbonyl group.

$$Cl_2PCH_2COOCH_3 + 2ArM \rightarrow Ar_2PCH_2COOCH_3 \rightarrow Ar_2PCH_2PCOOH$$

Ar=4—FPh (72%), 3—FPh (66%), 4—CH_3OPh, 3,5-di-CH_3Ph (55%), 3,5-di-CH_3, 4—CH_3OPh (44%), 3,5-di-iPr, 4—CH_3OPh (65%), 4—CF_3Ph

The $CF_3C_6H_4$ group poses a problem. The ester is formed in good yield but a very impure acid is obtained upon saponification.

E. Addition of Diphenylphosphine to Unsaturated Esters

The base catalysed Michael addition of diphenylphosphine to various substituted acrylic esters proceeds as expected. The phosphinopropionic ester can in most cases be purified by vacuum distillation. The acid is obtained by saponification. In the Experimental Section we give a representative example.

$$Ph_2PH + R^1R^2C{=}CR^3COOCH_3 \xrightarrow[150\text{–}160°C]{KOtBu} Ph_2PR^1R^2CCHR^3COOCH_3$$

$R^1{=}R^2{=}H$,	$R^3{=}CH_3$	58%	bp ca 160°C/0.02 mm Hg
$R^1{=}R^3{=}H$,	$R^2{=}CH_3$	84	145°C/0.03
$R^1{=}R^2{=}CH_3$,	$R^3{=}H$	56†	165°C/0.25
$R^1{=}R^3{=}CH_3$,	$R^2{=}H$	82	142°C/0.02
$R^1{=}R^2{=}R^3{=}CH_3$,		low	180°C/0.05 mm Hg
$R^1{=}R^3{=}H$,	$R^2{=}Ph$	ca. 80%	

† distilled from the catalyst

MECHANISM OF NUCLEOPHILIC SUBSTITUTION OF HALOCARBOXYLATES

The nucleophilic substitution of the so-called activated halides such as haloacetic esters or salts may proceed by two mechanisms:

1. S_N2 substitution, i.e. overlap of a nucleophile with a lobe of the C-X σ^* orbital.
2. S_N rad substitution, this reaction proceeds by a radical chain mechanism and is initiated by transfer of an electron to the C–X σ^* orbital.

S_N2	$R_2P^- + XCH_2COOR$	$\rightarrow R_2PCH_2COOR + X^-$	
S_N rad	$R_2P^- + XCH_2COOR$	$\rightarrow R_2P^{\cdot} + [XCH_2COOR]^{\cdot-}$	initiation
	$[XCH_2COOR]^{\cdot-}$	$\rightarrow X^- + {}^{\cdot}CH_2COOR$	propagation
	$R_2P^- + {}^{\cdot}CH_2COOR$	$\rightarrow [R_2PCH_2COOR]^{\cdot-}$	
	$[R_2PCH_2COOR]^{\cdot-} + XCH_2COOR$	$\rightarrow R_2PCH_2COOR + [XCH_2COOR]^{\cdot-}$	
	$R_2P^- + {}^{\cdot}CH_2COOR$	$\rightarrow 1/2R_2PPR_2 + {}^-CH_2COOR$	termination

The termination reaction leads to reduction instead of substitution of the halocarboxylate. This undesired side reaction leads to low yields of the desired product and can be avoided by using conditions that promote the S_N2 substitution. Indeed we have found that the highly polar solvent liquid ammonia is the superior solvent for the preparation of diphenylphosphinoacetic esters. We believe that the reaction between sodium diphenylphosphide and t-butylchloracetate in liquid ammonia proceeds by the S_N2 mechanism. However, there are large effects from the nature of the phosphide and the carboxylate and it appears that the reaction proceeding by the S_N rad mechanism readily competes or becomes the principal reaction.

Apparently, the redox process is strongly promoted over the S_N2 reaction by electron-rich aryl-, alkyl- and dialkylphosphides, relatively large phosphides or by halocarboxylates with electron withdrawing substituents. In these cases a low yield of phosphinocarboxylic ester is obtained due to the reduction reaction of the intermediary radical that bears the carboxylate moiety. Issleib *et al.*[6] have isolated a diphosphine R_2PPR_2 (R = cyclohexyl, phenyl) from reaction mixtures. This is further evidence in support of the S_N rad mechanism.

CONCLUDING REMARKS

It is impossible to prepare a large diversity of functionalized aliphatic phosphinocarboxylic acids by one generally applicable synthetic method. The scope of the existing methods is relatively small and thus complementary methods have to be used. We have described one new method. It consists of the reaction of an organometallic reagent with a chlorophosphinoacetic ester. This reaction gives a variety of functionalized phosphinoacetic acids in good or acceptable yield.

EXPERIMENTAL

Experiments with air sensitive materials were performed in an argon atmosphere using Schlenk techniques. Solvents were dried in the usual way and freed from dioxygen by a rapid stream of argon. The ammonia was distilled from a cylinder and dried on sodium (if necessary). The NMR spectra were recorded on Varian 200 and 300 MHz and Bruker 90, 250 and 400 MHz instruments. The data are presented in Tables III and IV. Some of the NMR data are listed together with the experimental procedure used. The coupling constants with phosphorus are given in parentheses.

Starting materials which are not mentioned in the Experimental Section were prepared by standard literature methods or were obtained commercially.

Butylphenylphosphine (bp ca. 110°C/18 mm Hg, $\delta^{31}P$ −52.4, $\delta^{1}H$ PH 4.13 d 210.5 t 7, 52% yield) and isobutylphenylphosphine (bp 36/0.005, $\delta^{31}P$ −60.7, 72% yield) were obtained from reaction of butyldiphenylphosphine and isobutyldiphenylphosphine, respectively with lithium in THF. The tolylphosphines were prepared from the corresponding secondary phosphine oxides by thermal disproportionation,[28] by reduction with AlH_3 or by reductive cleavage of the corresponding tris tolylphosphine. Bromo-3,5-dimethylbenzene was prepared by a Sandmeyer reaction. Bromo-3,5-dimethyl-4-methoxybenzene was obtained by bromination of 2,6-dimethylphenol and subsequent alkylation with dimethyl sulfate in 63% overall yield. Bromination of 3,5-diisopropyl-1-methoxybenzene gave the corresponding bromo compound.

Methyl dichlorophosphinoacetate was prepared in a one-pot procedure according to the method described by Novikova.[12]

Diphenylphosphinoacetic acid. Triphenylphosphine (13.7 g, 52.3 mmol) is added in one portion to a solution of 2.4 g (104 mmol) of sodium in ca. 400 ml of liquid ammonia at −78°C. The mixture is

TABLE III

^{31}P and selected ^{1}H NMR data of phosphino(yl)acetic acids in $CDCl_3$

Structure	^{31}P	PCH[a]	Others[a]	^{31}P oxide
Ph_2PCH_2COOH	−16.5	3.15	—	30.1
$Ph_2PCH(CH_3)COOH$	0.3	3.37(3.5)	CH_3 1.32(14.5)	34.2
$Ph_2PC(CH_3)_2COOH$	18.0	—	CH_3 1.43(14)	41.1
$Ph_2PCHPhCOOH$	0.9	4.44(5)	—	31.6
Ph_2PCF_2COOH	6.2[b]	—	—	—
$(2\text{-tol})_2PCH_2COOH$	−34.9	3.06(0.5)	CH_3 2.44(1.5)	33.7
$(3\text{-tol})_2PCH_2COOH$	−16.5	3.11	CH_3 2.33	29.8
$(4\text{-tol})_2PCH_2COOH$	−18.1	3.08	CH_3 2.34	30.8
$(4\text{-}CH_3OC_6H_4)_2PCH_2COOH$	−19.2	3.01	CH_3 3.75	
$(3\text{-}FC_6H_4)_2PCH_2COOH$	−16.6	3.10	OH 11.2	28.0[c]
$(4\text{-}FC_6H_4)_2PCH_2COOH$	−18.7	3.08	OH 11.2	29.2
$(4\text{-}CF_3C_6H_4)_2PCH_2COOH$	−18.5			—
$(3,5\text{-diMeC}_6H_3)_2PCH_2COOH$	−15.5	3.09	CH_3 2.28	—
$(3,5\text{-diMe},4\text{-}CH_3OC_6H_2)PCH_2COOH$	−18.5	3.00	CH_3 2.20	—
			CH_3O 3.80	—
$(3,5\text{-diiPr},4\text{-}CH_3OC_6H_2)_2PCH_2COOH$	−15.7	2.98	CH_3 1.14	—
			CH_3O 3.65	—
(2-tol)$PhPCH_2COOH$	−25.4	3.11	CH_3 2.42(1.5)	—
i-Bu,$PhPCH_2COOH$	−28.4	2.7[d]	e	
n, $BuPhPCH_2COOH$	−28.4	2.7[d]	f	39.0

[a] JPH in parentheses.
[b] JPF = 89 Hz.
[c] JPF = 5.8 Hz.
[d] ABX spectrum.
[e] OH 10.9; 1.04(3H); 1.10(3H); 1.84(2H).
[f] CH_2 1.86; CH_2CH_2 1.4; CH_3 0.88.

stirred mechanically for 1 hour. The blue colour vanishes and the solution turns brilliantly orange. Solid ammonium chloride (1 eq.) is added to destroy the by-product sodium amide. After ca. 0.5 h 6.1 g (52.4 mmol) of sodium chloroacetate is added. Stirring is continued until the mixture turns colourless. The ammonia is allowed to evaporate overnight. Water is added to dissolve the product and subsequently the neutrals are extracted with ethyl acetate. The aqueous layer is separated off, filtered and hydrochloric acid is added until pH = 3. The product separates as an oil. Residual ethyl acetate is removed by a gentle stream of argon and the oil solidifies to white crystals. The crystals are filtered off, washed with water and dried in vacuo. Yield 11.1 g (45.5 mmol, 87%) of pure material.

^{13}C NMR ($CDCl_3$): i 136.8 (14.3), o 132.5 (20.0), m 128.5 (6.7), p 129.1, CH_2 35.2 (22.8) ^{1}J CH

TABLE IV

^{31}P and ^{1}H NMR data of diphenylphosphino(yl)propionic acids in $CDCl_3$

Structure	PCH[a]	$PCCH_3$	CHCO[a]	$C(CH_3)CO$	^{31}P	^{31}P oxide
PCH_2CH_2COOH	2.3	—	2.3	—	−16.6	34.7
$PCH(CH_3)CH_2COOH$	2.86	1.14(15)	2.2 and 2.5	—	−1.9	35.2
$PC(CH_3)_2CH_2COOH$	—	1.35(14)	2.54(7)	—	19.8	41.7
$PCH_2CH(CH_3)COOH$	2.5 and 2.6	—	2.12	1.36	−20.3	30.2
$PCH_2C(CH_3)_2COOH$	2.51(3.5)	—	—	1.29	−23.1	30.2
$PCH(CH_3)CH(CH_3)COOH$ I[b]	3.06	0.99(13)	2.60	1.26	−7.5	35.8
II[b]	?	1.07(12)	2.6	1.34	−6.4	34.4
$PCHPhCH_2COOH$					−0.6	34.9

[a] JPH in parentheses.
[b] I:II = ca. 2:1.

TABLE V

NMR data of phosphinopropenoic acids[a]

	I cis	I trans	II	III phosphine	III phosphine oxide
^{13}C CP	154.0(28.3)[157]	151.3(19.9)[157]	162.7(23.1)	158.2(30)	138.3(91.0)
ÇCO	129.3(11.5)[170]	127.3(8.4)[165]	123.3(11.3)[162]	140.8(17.9)	154.4(5.8)
CO	170.2 [13]	170.5(7.5)	170.6(8.5)	169.1(2.3)	164.4(5.3)
others	—	—	CH_3 20.0(24.4)		21.8(9.6) 38.7(13.5) 39.4(12.4)
^{1}H PCH	7.33[b] [12]	7.71(22)[c] [17]	—		
HCCO	6.38(15.5)[12]	5.48(5)[17]	5.59(7)[1.5]		
others	—	—	CH_3 2.27(12.5)[1.5]	1.8; 2.3; 2.8	
^{31}P	−12.0; oxide 26.0	−11.7; oxide 24.0	5.5; sulfide 49.7	−14.2	30.8

[a] Coupling with phosphorus in parentheses, coupling with hydrogen in square brackets.
[b] Lone pair anti.[28]
[c] Lone pair syn.[28]

133, CO 177.2 (9.2) ^2J CH 6.6. Oxide ^{13}C NMR (D_6 DMSO): i 133.3 (102), o 128.5 (12) ^1J CH 162, m 130.5 (9) ^1J CH 162, p 131.8 ^1J CH 162, CH_2 37.8 (63) ^1J CH 131, CO 167.4 (6) ^2J CH 5.

Butylphenylphosphinoacetic acid. To a solution of 2.0 g of sodium in ca. 300 ml of liquid ammonia 14.35 g (86.5 mmol) of butylphenylphosphine is added via a syringe. The mixture is stirred at −40°C until the colour of the solution turns orange yellow. After cooling to −78°C 10.1 g (86.7 mmol) of sodium chloroacetate is added in one portion. The mixture is stirred and left in the dry ice bath. The ammonia evaporates overnight. Work up as above gives 10.85 g (48.4 mmol, 56% yield) of the product, which does not crystallize.

^{13}C NMR ($CDCl_3$): i 136.4 (16.2), o 132.0 (20.1), m 128.3 (7.1), p 129.1, CH_2 34.4 (25.0), CO 176.5 (4.9), butyl group PCH_2 23.9 (12.6), CH_2CH_2 26.8 (12.9) and 27.5 (15.5), CH_3 13.5.

Cis-3-diphenylphosphinopropenoic acid. A solution of sodium diphenylphosphide and sodium amide is prepared from 2.5 g (9.5 mmol) of triphenylphosphine and 0.45 g (19.6 mmol) sodium in ca. 100 ml of liquid ammonia. To this solution 1.0 g (9.4 mmol) of cis-3-chloropropenoic acid is added in one portion at −78°C. After the orange colour has disappeared the ammonia is removed under water pump vacuum. Standard work up gives 1.9 g (7.4 mmol, 79% yield) of bright yellow crystals which contain ca. 10% of the trans isomer. The oxide of the compound is colourless. The phosphine decomposes slowly in solution on standing at room temperature.

Trans-3-diphenylphosphinopropenoic acid. This compound is prepared by the same procedure as used for the corresponding cis compound. Yield 37% of white crystals.

2-Diphenylphosphinocyclopentenecarboxylic acid. Ethyl 2-chlorocyclopentenecarboxylate is prepared from 2-ethoxycarbonyl-cyclopentanone and PCl_5.[29] According to the ^{1}H and ^{13}C NMR spectra the product is a mixture of three double bond isomers. The content of the desired isomer is ca. 35–40%. We were not able to separate the mixture by distillation and therefore we have used the mixture as such. A solution of sodium diphenylphosphide in 250 ml of liquid ammonia is prepared from 7.5 g triphenylphosphine, 1.3 g sodium and 1.5 g ammonium chloride (see above). The solution is kept at −78°C ethyl *x*-chlorocyclopentenecarboxylate (5.0 g, 28.7 mmol, in 100 ml of ether) is added. Subsequently, the cooling bath is removed and the ammonia is allowed to evaporate off overnight. Standard work up and distillation in vacuo with a free flame gives a fraction (6.7 g, b.p. 180–200°C/0.05 mm Hg) which contains the phosphinocarboxylic ester. The crude product is saponified. Standard work up gives 2.6 g (8.8 mmol, 31% on total intake) of pure carboxylic acid as off-white crystals.

Trans-3-diphenylphosphino-3-methylpropenoic acid. This compound is prepared from the corresponding sodium chloro-iso-crotonate and sodium diphenylphosphide in liquid ammonia. It is

obtained as a mixture of three phosphinocarboxylic acids in 73% yield. The content of the desired compound is ca. 85%. Exactly the same mixture of products is obtained in 80% yield from a reaction between ethyl chlorocrotonate and sodium diphenylphosphide in liquid ammonia and subsequent saponification. Recrystallisation from acetonitrile affords the pure compound as white needles.

2,2-Dimethyl,2-diphenylphosphinoacetic acid. To a solution of lithium diisopropylamide—prepared from 37.5 ml of diisopropylamine and 167.5 ml of butyllithium (1.6 M in hexane)—in 350 ml THF, 12.5 ml (134 mmol) of isobutyric acid is added in portions at 0°C. The resulting mixture is stirred at 50°C for 2 h. After cooling to 0°C 29.5 ml (135 mmol) of diphenylethoxyphosphine is added in ca. 10 min. The mixture is allowed to reach room temperature and stirred overnight. Volatiles are removed in vacuo and water is added. The water layer is extracted with ether, filtered and subsequently acidified with hydrochloric acid until pH = 3. The product separates as an oil that crystallizes on prolonged stirring while a gentle stream of argon removes residual traces of solvent. The white solid is collected by filtration, washed with water and dried in vacuo. Yield 19.1 g (70 mmol, 52%).

^{13}C NMR ($CDCl_3$): i 134.9 (18.8), o 134.4, (21.5), m 128.1 (7.3), p 129.2, PC 41.8 (26.1), CH_3 24.3 (17.7), CO 182.3.

2-Phenyl-2-diphenylphosphinoacetic acid. Diphenylbenzylphosphine is lithiated with butyllithium and TMEDA at 0°C. Then a rapid stream of carbon dioxide is led through the mixture. Standard work-up gives the title compound in 65% yield.

Bis(3,5-diisopropyl-4-methoxyphenyl)phosphinoacetic acid. A Grignard reagent is prepared from 27.2 g (100 mmol) of 1-bromo-3,5-diisopropyl-4-methoxybenzene and 2.6 g (110 mmol) of magnesium turnings in 250 ml of THF. (It is absolutely essential that the aryl bromide be free of traces of phenol. The bromide has to be filtered over basic alumina because extraction with aqueous alkali is insufficient.) At −78°C 6 ml (49 mmol) of methyl dichlorophosphinoacetate is added with mechanical stirring. The mixture is stirred overnight and subsequently a saturated aqueous solution of ammonium chloride is added to dissolve magnesium salts. The product is extracted with ether and the organic layer is washed with water. The ether is removed in vacuo and the residue is saponified (110 mmol NaOH, 100 ml ethanol and 100 ml water, 2 h reflux). Standard work up is impossible as it appears that the sodium salt does not dissolve in water and remains in the ether layer. The solvent is removed and the residue is suspended in dilute hydrochloric acid. A faintly yellow, very viscous oil is obtained. The oil is washed with water until the washings are neutral. The residue is dried in vacuo and then solidifies. Yield 14.5 g (30.7 mmol 63%) of fairly pure material.

The other phosphinoacetic acids prepared by this method (see text) can be purified by the usual method as the corresponding sodium salts dissolve well in water. Very pure material is obtained as shown by the analytical data.

Bis-(3-fluorophenyl)phosphinoacetic acid ($C_{14}H_{11}F_2O_2P$); calc.: C 60.01, H 3.96, F 13.56, P 11.05 and O 11.42%; found: C 59.95, H 4.00, F 13.56, P 11.10 and rest 11.39%.

^{13}C NMR ($CDCl_3$), *J* CF in square brackets: C_1 139.0 (17.0) [5.0], C_2 118.9 (20.7) [20.7], C_3 162.6 (8.2) [249.6], C_4 116.6 [21.2], C_5 130.3 (7.7) [7.7], C_6 128.7 (21.3) [2.7], PC 34.7 (22.9), CO 176.7 (9.4).

Bis-(3,5-dimethylphenyl)phosphinoacetic acid ($C_{18}H_{21}O_2P$); calc.: C 71.99, H 7.05, P 10.31 and O 10.65%; found: C 71.77, H 7.07, P 10.16 and rest 11.00%.

Methyl 2-methyl-3-diphenylphosphinobutanoate. A mixture of 33 ml (190 mmol) of diphenylphosphine, 21.3 g (187 mmol) of methyl 2-methyl-2-butenoate (methyl tiglate) and ca. 1 g potassium t-butoxide is heated at 150°C for 16 h. The mixture is allowed to cool to room temperature and subsequently water and methylene chloride are added. The organic layer is separated and distilled. Yield 46.2 g (154 mmol 82%), b.p. 146°C/0.02 mm Hg. According to ^{1}H and ^{31}P NMR two diastereoisomers are present.

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