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α-Phosphanyl amino acids: synthesis, structure and properties of alkyl and heterocyclic *N*-substituted diphenylphosphanylglycines

Joanna Lach [a], Normen Peulecke [a,†], Markus K. Kindermann [a], Gottfried J. Palm [b], Martin Köckerling [c], Joachim W. Heinicke [a,*]

[a] Institut für Biochemie-Anorganische Chemie, Ernst-Moritz-Arndt-Universität Greifswald, Felix-Hausdorff-Str. 4, D-17489 Greifswald, Germany
[b] Institut für Biochemie-Molekulare Strukturbiologie, Ernst-Moritz-Arndt-Universität Greifswald, Felix-Hausdorff-Str. 4, D-17489 Greifswald, Germany
[c] Institut für Chemie, Anorganische Festkörperchemie, Universität Rostock, Albert-Einstein-Str. 3a, D-18059 Rostock, Germany

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Dedicated to Professor Dr. Dr. h.c. Manfred Scheer on the occasion of his 60th birthday

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ABSTRACT

N-Alkyl and *N*-heterocyclic substituted diphenylphosphanylglycines **1a**–**j** were synthesized by a convenient one-pot, three-component reaction of diphenylphosphane, the corresponding primary amine and glyoxylic acid hydrate in diethyl ether. Phosphanylglycolates **2** and phosphoniobis(glycolates) **3** were detected as intermediates. In the case of steric hindrance or low basicity of the amine only **2** or mixtures of **2** and **1** are formed. Reactivity studies of selected phosphanylglycines showed facile decarboxylation and hydrolysis, oxidation and formation of coordination compounds with BH_3 or $W(CO)_5$. *N*-Alkyl derivatives (*tert*-butyl, *n*-hexyl, benzhydryl) with moderate steric hindrance reacted with Ni(COD)$_2$ in THF or toluene in the presence of ethylene with heating under pressure to yield highly active oligomerization catalysts, and converting the ethylene to liquid and low-molecular-weight solid ethylene oligomers (M_{NMR} 500–1250 g/mol) with high selectivity for linear α-olefins. Smaller *N*-alkyl or *N*-heterocyclic amino substituents at the phosphanyl acetic skeleton interfere with the ethylene conversion and deactivate the catalyst. The structures of the compounds were elucidated by solution NMR and single crystal XRD studies.

1. Introduction

Synthetic amino acids have found interest and applications in many fields of chemistry, biochemistry and pharmacy.[1] Introduction of a phosphanyl group into amino acids and peptides, useful particularly as coordination site for transition metals in low oxidation states, was accomplished by various strategies.[1b,2–11] Many products were utilized for a variety of transition metal catalyzed[2,3] or organocatalyzed[4] chemical transformations. Another goal was the use of water soluble phosphane derivatives as carriers for pharmaceutically interesting transition metals.[5] The known types of phosphanyl amino acids involve *a*) directly *N*-phosphanylated compounds, formed by reaction of the amino acids with $ClPPh_2$,[6] *b*) acyclic and heterocyclic *N*-phosphanylmethyl derivatives, prepared by condensation reactions of *N*–CH_2OMe substituted amino acids with secondary phosphanes[7] or of free amino acids, their salts and esters with formaldehyde and phosphanes or their addition products R_2PCH_2OH and $RP(CH_2OH)_2$,[2,8,9] and *c*) amino acids with the phosphanyl function at the α-C side group. The latter were obtained by Pd-catalyzed coupling of secondary phosphanes with *O*-triflate or *O*-mesylate derivatives of serine, proline or tyrosine[3] or alternatively by reaction of phosphides with the halogenated amino acids under appropriate conditions.[10] α-Phosphonio-*N*-acyl amino acid derivatives were reported by Mazurkiewicz et al.[1b] and the first *N*-tert-butyl and *N*-aryl derivatives of glycine with a phosphanyl substituent directly bound at the α-C atom were synthesized by us in a convenient one-pot three-component reaction.[11] Principally, the structural features of these compounds offer the potential for formation of five-membered P,COO^- or N,COO^- chelate complexes, to act as tripod P,N,COO^- ligand or as soft-hard hybrid ligand for bimetallic complexes. This prompted us to explore the scope and limits of the three-component synthesis for a wider variety of *N*-substituents and to illuminate general properties and some aspects of their reactivity. Because of the close structural relationship to diphenylphosphanylacetic acid,[12] applied as phosphanylcarboxylate nickel catalyst in the industrial ethylene oligomerization within the SHOP

* Corresponding author. Tel.: +49 3834 864318; e-mail address: heinicke@uni-greifswald.de (J.W. Heinicke).
† Current address: Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Str. 29 A, 18059 Rostock, Germany.

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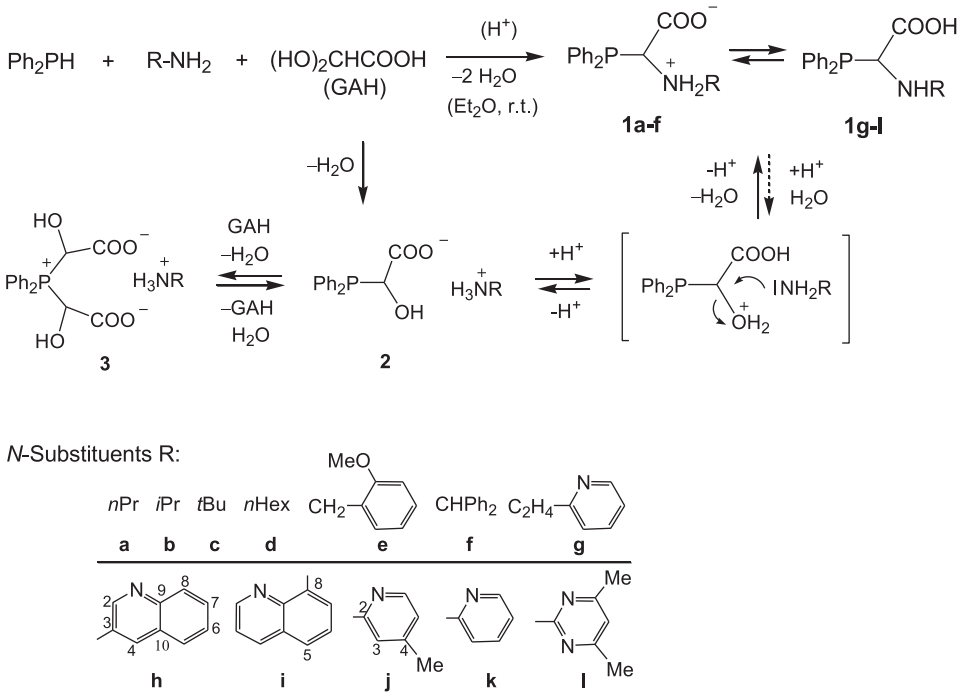
process,[13,14] ligand screening for in situ formation of nickel catalysts for ethylene oligomerization was also undertaken in this study.

2. Results and discussion

2.1. Synthesis

Three-component aminomethylations of trivalent PH-compounds with primary or secondary amines and formaldehyde are well known,[15] but knowledge about analogous reactions with other aldehydes is still sparse and restricted to arylaldehydes in THF.[16] The resulting α-phosphanyl benzylamines, preferably prepared till now by addition of R_2PH or R_2PM^I (M=Na or Li) at benzaldimines or their hydrochlorides, are rather unstable in solution but are stabilized by electron-withdrawing *p*-nitrophenyl substituents at the α-C or N atom.[17] The electron withdrawing effect of COOH suggested that phosphanylmethylamines with a COOH group at α-C also are stabilized. This inspired us to develop a convenient synthesis of aminodiphenylphosphanyl acetic acids, in the following named (diphenyl) phosphanylglycines, by three-component one-pot condensations of glyoxylic acid hydrate (GAH) with diphenylphosphane and primary amines. In addition to the recently communicated condensations with $tBuNH_2$ and some primary aryl amines,[11] a variety of linear and branched alkyl-, arylalkyl- and heterocyclic primary amines were used and found applicable in this reaction to give the corresponding phosphanyl glycines **1a**–**j**. However, **1k** and **1l** were formed only in minor amounts in addition to the corresponding phosphanylglycolates **2k** and **2l** (Scheme 1). Nitrogen atoms of *N*-heterocyclic substituents did not interfere with the reaction as long as they did not lower the reactivity of the primary amino group too strong, such as in the case of, e.g. pyrimidin-2-yl amines.

equilibrium concentrations of sparsely soluble products in solution remain low. NMR monitoring of the reaction with *tert*-butylamine revealed that the precipitate, separated after 10 min, contained considerable amounts of the *tert*-butylammonium phosphanylglycolate **2c**, whereas a sample taken from the suspension after stirring for 15 h displayed mainly the phosphanylglycine **1c**. This shows that the three-component synthesis of phosphanylglycines does not proceed via a Mannich reaction with halfaminale and immonium intermediates, as in the case of phosphanylmethylations of amines with formaldehyde,[15a] but that the OH groups of GAH are stepwise protonated and replaced with cleavage of water by the phosphane and subsequently by the amine. The second step is slower so that usually reaction times of 15–24 h were chosen, in the case of slow reactions even several days. The main reason is the presence of the COOH group that lowers the concentration of free amine, but also steric effects or low basicity of the amine diminish the reaction rate. If an excess of amine is used, as tested for with iPr_2NH (1.6 equiv), a mixture of the hydrated phosphanylglycine and its salt (**1b**·0.6$iPrNH_2$·H_2O) precipitated. If 2 equiv of glyoxylic acid were used in the three-component reaction, recently demonstrated with $tBuNH_2$ as amine component, organoammonium phosphanylbis(glycolates) **3** are formed in high yield.[11c,d] The analogous diethyl ammonium salt of **3** was formed also with diethyl amine as the NH component in good yield,[18] in this case, however, even with only 1 equiv of glyoxylic acid. This shows that phosphanylbis(glycolates) **3** may also be involved in the equilibrium reactions leading to the phosphanylglycines (Scheme 1). Disubstitution at the primary amino group, typical for many phosphanylmethylations, was never observed. The mono-phosphanylmethylations, known also for *N*-primary α-amino acids such as alanine under mild conditions,[19] may thus be attributed to the presence of the COOH group in α-position.



Scheme 1. Three-component synthesis of *N*-substituted diphenylphosphanylglycines **1a**–**l** via organoammonium diphenylphosphanylglycolates **2**, unless the latter are stabilized by bulky or electron-withdrawing substituents R.

The conversions were performed in a 1:1:1 reactant ratio at room temperature (20–24 °C), best in diethyl ether by addition of the ethereal solution of the phosphane and amine to an ethereal solution of glyoxylic acid hydrate (GAH) or reversed addition. The majority of the products precipitate in this solvent. This not only facilitates the isolation but also increases the yield, as the

The water, liberated in the condensation into the crude reaction mixtures, results in still minor equilibrium amounts of **2**. Attempts to remove this water from the suspensions by neutral drying agents $CaCl_2$ or $MgSO_4$, introduced into the reaction encapsulated in an immersed fritted glass, did not result in significant conversion of the minor residual amount of **2c** to **1c**. Alternative efforts to remove

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