Polyhedron 77 (2014) 10–16

Contents lists available at ScienceDirect

Polyhedron

journal homepage: www.elsevier.com/locate/poly

Benzazaphospholine-2-carboxylic acids: Synthesis, structure and properties of heterocyclic phosphanyl amino acids

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ARTICLE INFO

Article history:
Received 26 January 2014
Accepted 25 March 2014
Available online 13 April 2014

Keywords:
Phosphanes
Heterocycles
Ligands
Catalysis
Ethylene

ABSTRACT

1,3-Dialkyl-1,3-benzazaphospholine-2-carboxylic acids **2a**,**b** can be conveniently prepared by metalation and alkylation of *N*-methyl- and *N*-neopentyl-*o*-phosphanylaniline in liquid ammonia and cyclocondensation of the resulting *N*,*P*-disecondary phosphanylanilines **1a**,**b** with glyoxylic acid hydrate (GAH) in ether. The primary neopentylphosphanylaniline reacts with two equivalents of GAH and forms a phosphanyl-bis(amino acid) **3** with toluidine. α-Branched *P*-substituents induce strongly preferred formation of *trans*-diastereoisomers with *R*,*R*- and *S*,*S*-configuration at P and C2, as shown by a crystal structure analysis of **2a**, whereas a *P*-neopentyl (*P*-Np) group gives rise to *trans*/*cis*-diastereoisomeric mixtures. The *trans*-configuration exhibits the P lone-pair in *cis*-position to the COOH group, suitable for formation of five-membered chelate rings, as in diphenylphosphanylacetate nickel catalysts for ethylene oligomerization. Screening of **2a**,**b**/Ni(COD)$_2$ solutions in THF by a batch procedure indeed showed formation of catalysts for conversion of ethylene to linear oligomers and waxy low-molecular weight polymers. The conversion depends strongly on the size of the *N*-alkyl group, being slow and limited for the *N*-Me catalyst **2a**/**Ni** and much faster and more complete for the *N*-Np-substituted catalysts **2b**/**Ni** and **2c**/**Ni** (*N*-Np, *P*-*t*Bu). Comparison of **2b**/**Ni** with **2c**/**Ni** shows that the more bulky P-substituent further increases the catalyst activity.

1. Introduction

Recent studies on the synthesis of bulky *tert*-butyl-substituted heterocyclic phosphane ligands by addition of *tert*-butyllithium at the P=C bond of aromatic phosphorus heterocycles have included the discovery of a convenient route to 3-*tert*-butyl-1,3-benzazaphospholine-2-carboxylic acids [1]. These possess the same P-C-COOH structural unit as diphenylphosphanylacetic acid [2], which is used in the generation of nickel catalysts for the ethylene oligomerization in the SHOProcess [3], and also form highly active catalysts for this reaction. The amino function did not interfere with the catalytic conversion. This was observed also for various acyclic alkylamino- and arylamino-diphenylphosphanyl-acetic acids (phosphanylglycines) [4], whereas more closely related heterocyclic 3-phenyl-1,3-azaphospholidine-2-carboxylic acids (3-phenyl-phosphaprolines) without benzo-annulation required activation by sodium hydride to form active catalysts with Ni(COD)$_2$ [5]. To find out whether the higher activity of the benzazaphospholine-2-carboxylate-based nickel catalysts is attributable to the bulky *P*-*tert*-butyl substituent or to electronic effects of the intrinsic *o*-aminophenyl group, a preliminary study of the synthesis of less bulky *P*-alkyl-1,3-benzazaphospholine-2-carboxylic acids and their performance as ligands in the nickel catalyzed ethylene oligomerization was carried out.

2. Results and discussion

A well established strategy was chosen for the synthesis, namely the cyclocondensation of 2-phosphanyl-substituted amines, long since known for simple aldehydes and ketones [6]. Even the reaction of *o*-phosphanylaniline with pyruvic acid was reported to give 2-methyl-1,3-benzazaphospholine-2-carboxylic acid, but information on the properties and structure of this compound, except for the detection of a P–H absorption in the range 2240–2280 cm^{-1}, is not available [6c]. We used the condensation with glyoxylic acid hydrate (GAH). This acid proved sufficiently reactive at room temperature to undergo autocatalyzed

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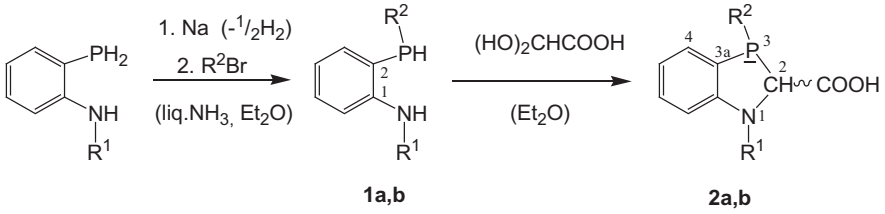
http://dx.doi.org/10.1016/j.poly.2014.03.046
0277-5387/

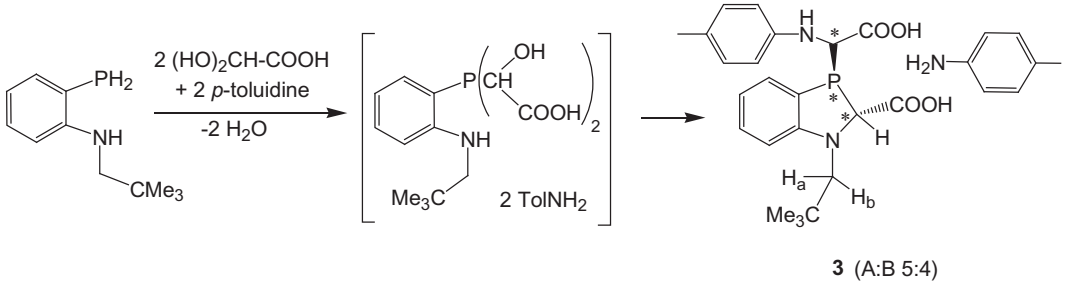
three-component one-pot condensations with secondary phosphanes and primary alkyl- or arylamines to phosphanylglycines [4] whereas aldehydes and ketones, including pyruvic and phenylglyoxyl acid, do not undergo analogous condensations. The starting phosphanes **1a**,**b** were prepared from *N*-methyl- and *N*-neopentyl-*o*-phosphanylaniline by *P*-alkylation. Attempts to achieve this via lithiation of the primary precursors with butyllithium in diethyl ether failed to give defined products, but metalation with sodium in liquid ammonia provided sufficiently reactive phosphides for preferred *P*-alkylation by isopropyl- and neopentylbromide, respectively. The reaction is regioselective but not regiospecific and also produced minor amounts of *N*-mono- and *P*-bisalkylated side products, which, because of their similar boiling points, are difficult to separate by distillation. For the subsequent cyclocondensation (Scheme 1) ethereal solutions of **1a**,**b** were added to GAH, dissolved in diethyl ether. The mixtures became turbid instantaneously, but clear again after some minutes. Small amounts of sticky precipitates were formed, identified as mixture of products and phosphine oxides. Most of the products **2a** and **2b** was still in the filtrate, and they were isolated by removal of ether as viscous oily mixtures, each consisting of two pairs of diastereoisomers. In **2a**, with a branched *P*-alkyl group and the small methyl group at nitrogen, the isomers with *trans*-configuration of the substituents in 2- and 3-position predominated (*trans:cis* ca. 9:1 by ^{1}H NMR integration) and allowed slow formation of a solid and finally crystallization, whereas **2b**, with neopentyl groups at both phosphorus and nitrogen, displayed a much lower *trans*/*cis*-isomer ratio (ca. 3:2) and remained oily. The ^{31}P NMR spectra of crude **2a** and **2b** also indicated small impurity signals (up to 10 mol%) in the region of $R_2PCH(OH)COOH$ species [7]. These are probably the primary condensation products and also formed in small equilibrium amounts by hydrolysis with traces of moisture, as demonstrated in more detail for acyclic α-phosphanyl amino acids [4]. Purification was possible by flash chromatography on silica gel using hexane/ethyl acetate (30% for **2a**, 2% for **2b**), but with a considerable loss of product by partial decomposition on reactive sites of silica gel in the column. In contrast to 1,3-benzazaphospholines without the COOH group, which were reported to be hydrolytically stable [6c], the carboxylic acid derivatives are sensitive to partial hydrolysis and attack by reactive OH species. The intrinsically Brønstedt acidic group may catalyze such reactions.

Reactions of *P*-primary *o*-phosphanylanilines with GAH are more complicated. Condensation of *N*-neopentyl-*o*-phosphanylaniline with GAH did not provide a defined product, either in a 1:1 or 1:2 M ratio. Only in the presence of *p*-toluidine (molar ratio 1:2:2) was a precipitate with defined composition obtained at room temperature (Scheme 2). According to the elemental analysis and NMR data it is a toluidinium salt (or hydrogen-bonded adduct with toluidine) of a phosphanylbis(amino acid) **3**, containing the benzazaphospholine and phosphanylglycine skeleton. Because of the rapid formation of phosphanylmono- and bis(glycolates) [7] and subsequent conversion with amines to phosphanylmono- or bis(glycines) [4] we assume primary reaction with two molecules of GAH, followed by cyclization and substitution of OH by the tolylamino group, rather than a stepwise reaction with GAH via an intermediate PH-functional benzazaphospholin-2-carboxylate.

Structural aspects. The structure elucidation of the new compounds is based on conclusive solution NMR data and for **2a** additionally on crystal structure analysis. Characteristic features of the phosphanes **1a** and **1b** are the PH doublets with one-bond P–H coupling constants of 214–217 Hz whereas the benzazaphospholine-2-carboxylic acids display typical doublets for the CH protons and carbon nuclei (Table 1). Small $^2J_{PH}$ coupling constants indicate *trans*-orientation of the P lone-pair and H-2, and therefore also *trans*-orientation of the *P*-substituent and the COOH group at C-2, which is strongly preferred in **2a** with its branched *P*-alkyl group and is the only form in the related 3-*tert*-butyl-1-neopentyl-benzazaphospholine-2-carboxylic acid (**2c**). The primary alkyl group at phosphorus in **2b**, despite the remote steric bulk of the *t*Bu-group in β-position, causes lower diastereoselectivity in the ring-closure step, with only moderate preference for *trans*- over *cis*-orientation (6:4). In compound **3** only *trans*-orientation of the *P*-substituent and 2-COOH is indicated, while the additional asymmetric carbon atom of the *P*-substituent gives rise to two pairs of diastereoisomers in a 5:4 ratio (by intensity of ^{31}P NMR signals). The $^1J_{PC}$ coupling constant is less indicative with respect to *cis*/*trans*-orientation, but proves the formation of the PCHN structural unit, and the chemical shift of this doublet allows us to distinguish



Scheme 1. Synthesis of **1a**,**b** and cyclocondensation with GAH to the heterocyclic phosphanyl amino acids **2a** (R^1 = Me, R^2 = *i*Pr) and **2b** (R^1, R^2 = neopentyl).



Scheme 2. Synthesis of the heterocyclic phosphanyl bis(amino acid) **3**.