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Synthesis of Pyrrole by 1,5,3,7-Diazadiphosphocine-1,5-Dicarboxylic Acid as Acid Catalyst

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As a part of research program related to the synthetic study of pharmacologically interesting compounds and good chelating agent for transition metal ion, we here report the synthesis of an unusual medium-sized ring heterocyclic ligand with mixed carboxylic-amino-phosphonic donating group. We have synthesized 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid (**1a**), 2-[5-(1,2-dicarboxyethyl-3,7-dihydroxy-3,7-dioxo-3[1,5,3,7]diazadiphosphocan-1-yl)-succinic acid (**1b**) and 3,7-dihydroxy-3,7-dioxoperhydro-1,3,5,7-diazadiphosphocine-1,5-di-(2-glutaric acid) (**1c**). In order to analyze reactivity of synthesized dicarboxylic acids **1a-c** as acid catalysts, we tried reactions of pyrrole formation according to acid variation. We know that the catalytic ability of synthesized dicarboxylic acids (**1a-c**) are very good at pyrrole formation reaction.

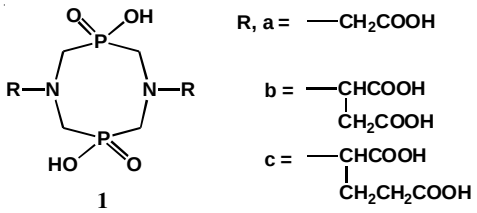
Keywords: 1,5,3,7-Diazadiphosphocine, Chelating agent, Magnetic resonance imaging, Acid catalyst.

INTRODUCTION

In last few years, great efforts have been devoted to the development of efficient ligands for transition metal ions, in order to obtain complexs whose stability, physical properties and biodistribution could make them suitable for application as contrast agent for magnetic resonance imaging (MRI)[1], diagnostic-therapeutic radiopharmaceuticals[2] or fluorecent bioassay[3].

Most of these ligands belong to the huge class of poly-aminopolycarboxylic acids as diethylenetriamine-pentaacetic acid (DTPA), 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetra-acetic acid (DOTA) and the great array of their substituted or modified derivatives[4-6]. But there is still a great effort in synthesizing new products with improved properties and for specific applications. An urgent and specific medical need is represented by the imaging of the cardiovascular system[7,8]. To perform a magnetic resonance angiography (MRA) the administered contrast agent must stay in the blood stream for a long time and three main different strategies have been proposed. It is important to synthesize new bioactive compounds and contrast agents. To the best of our knowledge, there are few reports involving the reaction of hypophosphorous (wheady) acid with formaldehyde and aromatic amines. We already reported the synthesis of1,5,3,7-diazadiphosphocine-1,5-dicarboxylic acid and their esterifications[9].

As a part of a research program related to the synthetic study of pharmacologically interesting compounds and good chelating agent for transition metal ion, we here report the synthesis of an unusual medium-sized ring heterocyclic ligand with mixed carboxylic-amino-phosphonic donating groups.



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We tried synthesis of dicarboxylic acids by treatment of various amino acids (*e.g.*, glycine, aspartic acid, glutamic acid) with paraformaldehyde and H_3PO_2. And we researched reactivity of synthesized dicarboxylic acids as acid catalysts for pyrrole synthesis.

EXPERIMENTAL

Melting points were determined on an electrothermal capillary melting point apparatus and uncorected. TLC was performed on glass plates coated with silicon oxide (silica-gel 60 F_{254}) and compounds were visualized using a UV lamp. ^1H and ^{13}C NMR spectra were obtained with Bruker AC2000 (200

MHz) and Varian Gemini (200 or 300 MHz) spectrometers. Mass spectra were measured with HP 5890 GC/MASS (70 eV, EI). The organic solvents and chemicals were obtained from commercial products and purified by the appropriate methods before use. Except where noted, all starting materials were purchased from Aldrich, Fluka, Fisher, Lancaster or TCI Chemical Companies and used as received. Known compounds prepared by modified procedures have been included in the supplemental information.

Synthesis of 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid (1a): A mixture of glycine (0.75 g, 0.01 mol), hypophosphorous acid (0.55 mL, 0.01 mol), paraformaldehyde (1.80 g, 0.02 mol) and 6 M HCl (10 mL) was stirred for 0.5 h and then the clear solution was left standing for 3 days. A white solid product (0.26 g, yield 8 %), was then collected by filteration, washed with a small amount of cold water, ethanol and dried *in vacuo*. Unreacted starting materials remained in solution.: m.p. 273-275 °C; IR (KBr, ν_{max}, cm^{-1}): 3445 (OH), 2999, 1718 (C=O), 1652; ^1H NMR (D_2O, pH 10, 200 MHz) δ: 3.87 (s, 4H), 3.50 (d, J = 9.3 Hz, 8H); ^{13}C NMR (D_2O, pH 10, 50 MHz) δ: 178.5, 59.2, 55.6; MS (MOLDI-TOF), *m/z* 331 (Anal. Calcd. for C, 26.24; H, 5.50; N, 7.65; P, 16.92 found; C, 26.50; H, 5.53; N, 7.36; P, 16.71).

Synthesis of 2-[5-(1,2-dicarboxyethyl-3,7-dihydroxy-3,7-dioxo-3[1,5,3,7]diazadiphosphocan-1-yl)-succinic acid (1b): A mixture of L-aspartic acid (1.33 g, 0.01 mol), hypophosphorous acid (0.55 mL, 0.01 mol), paraformaldehyde (1.80 g, 0.02 mol) and 6 M HCl (10 mL) was stirred for 0.5 h. And then the clear solution was left standing for 3 days. Then mixture was added ether, another separated with H_2O, dried *in vacuo*. A white solid product (0.17 g, yield 7.8 %) was then collected; m.p. 238-240 °C; IR (KBr, ν_{max}, cm^{-1}): 3445 (OH), 2999, 1718 (C=O), 1652; ^1H NMR (D_2O, pH 10, 200 MHz) δ: 4.24 (t, J = 6.9 Hz, 2H), 3.48 (d, J = 9.2 Hz, 8H), 3.34 (m, 4H); ^{13}C NMR (D_2O, pH 10, 50 MHz) δ: 174.1, 173.4, 52.1, 50.8, 48.5.

Synthesis of 3,7-dihydroxy-3,7-dioxoperhydro-1,3,5,7-diazadiphosphocine-1,5-di-(2-glutaric acid) (1c): A mixture of L-glutamic acid (1.47 g, 0.01 mol), hypophosphorous acid (0.55 mL, 0.01 mol), paraformaldehyde (1.80 g, 0.02 mol) and 6 M HCl (20 mL) was stirred for 0.5 h. Then the clear solution was left standing for 3 days. In order to precipitate solid, the clear solution in refrigerator was kept for 24 h. After filtering precipitated solid, it was washed by hexane and chloroform. A white solid product (0.32 g, yield 6.8 %) was then collected; m.p. 304-306 °C; IR (KBr, ν_{max}, cm^{-1}): 3448 (OH), 2956, 1731 (C=O), 1655; ^1H NMR (D_2O, pH 10, 200 MHz) δ: 4.27 (s, 2H), 3.50 (d, J = 9.3 Hz, 8H), 2.42 (t, J = 6.9 Hz, 4H), 2.08 (m, 4H); ^{13}C NMR (D_2O, pH 10, 50 MHz) δ: 173.0, 172.6, 170.4, 169.7, 52.3, 51.5, 48.9, 25.8.

Physical data of all the synthesized compounds **1a**-**c** are given in Table-1.

RESULTS AND DISCUSSION

As a part of research program related to the synthetic study of pharmacologically interesting compounds and good chelating agents for transition metal ions, we here report the synthesis of an unusual medium signed ring heterocyclic ligand with mixed aminophosphonic donating group. In order to synthesize 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid (**1a**), 2-[5-(1,2-dicarboxyethyl-3,7-dihydroxy-3,7-dioxo-3[1,5,3,7]diazadiphosphocan-1-yl)-succinic acid (**1b**) and 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-di-(2-glutaric acid) (**1c**), we executed the reaction of various amino acids (glycine, aspartic acid, glutamic acid) with paraformaldehyde and H_3PO_2 (Table-1).

The strongly acidic medium is required to promote the second reaction of H_3PO_2 and to avoid the side reactions of the iminium ion such as the reduction by means of formaldehyde to N-methyl derivatives. The reaction was found to be highly dependent on the experimental conditions employed. High concentrations of the reactant, heat and very long reaction times led to extensive formation of polymeric products; conversely, low acidity (pH > 1) and low reactant concentrations gave rise to complex mixtures. A clean reaction was effected dissolving glycine and H_3PO_2 in 6 M HCl to obtain a 1 M solution in both reagents and adding paraformaldehyde in slight excess

TABLE-1
PHYSICAL DATA OF PRODUCTS **1a-c**

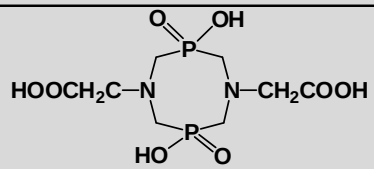
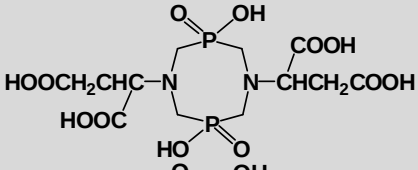
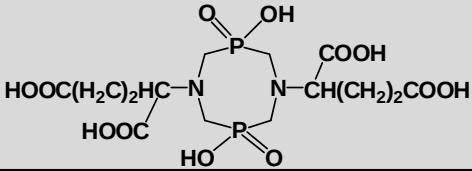
Entry	Product	Compound	m.p. (°C)	Yield[a] (%)
1		**1a**	273-274	8.0
2		**1b**	150-152	7.8
3		**1c**	304-305	6.8

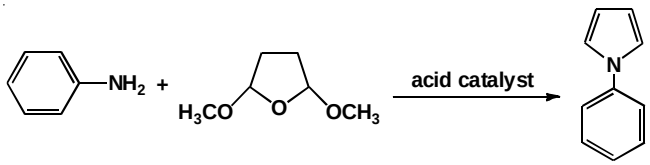
TABLE-2
YIELD OF 1-PHENYL-1*H*-PYRROLE ACCORDING TO ACID VARIATION

Entry	Acid catalyst (1 M)	pH	Reaction time (h)	Yield[a*] (%)
1	H_2O	6.80	7	0
2	HCl	0.15	7	67.2
3	H_2SO_4	0.20	7	64.0
4	CH_3COOH	1.05	7	25.6
5	Citric acid	0.51	7	25.0
6	1a	0.17	7	100
7	1b	0.15	7	100
8	1c	0.16	7	100

[*]GC yield

(3 equiv.) in one portion. Complete dissolution was achieved by stirring for 3 days. A white solid product was then collected by filtration, washed with a small amount of cold water, ethanol and dried *in vacuo*. NMR analysis of the product showed a highly symmetrical molecule, (two signals in ^{1}H NMR and three signals in the ^{13}C NMR) with a molecular weight of 330 a.m.u. characterized as 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid (**1a**). This heterocyclic ligand results from the assembly of two molecules of glycine, two molecules of H_3PO_2 and four molecules of formaldehyde. Its striking feature is that each atom of this eight-membered ring is originated from eight single different molecules, representing a formal '1+1+1+1+1+ 1+1+1 'cyclocondensation. The yield is satisfactory despite the number of elemental steps involved in the overall transformation and of the ring size, usually unfavorable for entropic reasons. In case of aspartic acid with paraformaldehyde and H_3PO_2, we could obtain 2-[5-(1,2-dicarboxyethyl-3,7-dihydroxy-3,7-dioxo-3[1,5,3,7]diazadiphosphocan-1-yl)-succinic acid (**1b**). Work-up step to get **1b** is very different and difficult than those of **1a** and **1c**. We remarked work-up step to get **1b** at the experimental section. The reaction of glutamic acid with paraformaldehyde and H_3PO_2 gave 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-di-(2-glutaric acid) (**1c**).

The relative position of the functional groups is particulary interesting in view of the possible application of carboxylic acid (**1c**) as ligand for metal ions. The N-CH_2COOH and N-CH_2-P(O)OH-CH_2-N moieties are known to chelate efficiently through formation of five-membered rings with the metal atom. Furthermore, the latter is embraced by the six donor atoms in a nearly ideal octahedral arrangement, highly advantageous for the complexation of the hexacoordinated transition metal ions. Hence we will start a preliminary investigation on the binding properties of carboxylic acid (**1c**) towards Mn^{2+} and Cd^{2+}, two paramagnetic ions of choice in the design of contrast agents for MRI, with different chemical behaviours and whose magnetic features help in the investigation of the solution structures of the corresponding adducts. In order to analyze reactivity of synthesized dicarboxyric acids (**1a-c**) as acid catalysts, we tried reactions of pyrrole formation according to acid variation.



We can easily obtain 1-phenyl-1*H*-pyrrole by treatment of aniline with 2,5-dimethoxytetrahydrofuran in acid catalyst. Reactivity comparison according to various acid catalysts are given in Table-2.

General procedure for pyrrole formation in acid catalyst: To a solution of aniline (1 mmol), 2,5-dimethoxytetrahydrofuran (1.5 mmol) and distilled water (5 mL) was added conc. HCl (1 M) 1 mL. The reaction mixture was allowed to stir at room temperature and monitored by TLC to establish completion of the reaction. The resulting solution was neutralized with 5 % sodium bicarbonate 10 mL and extracted with dichloromethane (50 mL × 2). The combined dichloromethane fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product. Purification by flashchromatography (EtOAc:hexane = 1:20, v/v) afforded the indicated compound (96 mg), in a 67.2 % yield as a brown solid (m.p. 50-51 °C). The ^{1}H and ^{13}C NMR spectra match the literature date[10].

As shown in Table-2, in case of inorganic acid like HCl, H_2SO_4 and CH_3COOH, yields of pyrrole were rather low (entry 2: 67.2 %, entry 3: 64 %, entry 3: 25.6 %). Yield of pyrrole in citric acid as an acid catalyst is 25 % (entry 5). But in case of synthesized dicarboxylic acids formed by amino acids (glycine, asparatic acid, glutamic acid), yields of pyrrole are very high (entry 6-8, GC yield, 100 %).

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