Synthesis of Diethyl α-(*o*-Nitroaryl)phosphoglycines via Oxidative Nucleophilic Substitution of Hydrogen in Nitroarenes

Mieczysław Mąkosza,* Daniel Sulikowski

Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44/52, 01-224 Warsaw, Poland
Fax +48(22)6326681; E-mail: icho-s@icho.edu.pl

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Dedicated to Prof. Bernd Giese on the occasion of his 70th birthday.

Abstract: The carbanion of protected diethyl phosphoglycinate adds to nitroarenes in liquid ammonia in *ortho* position to the nitro group. Subsequent oxidation of the resulting adduct σ^H with potassium permanganate gave N-protected diethyl α-(*o*-nitroaryl)phosphoglycinates.

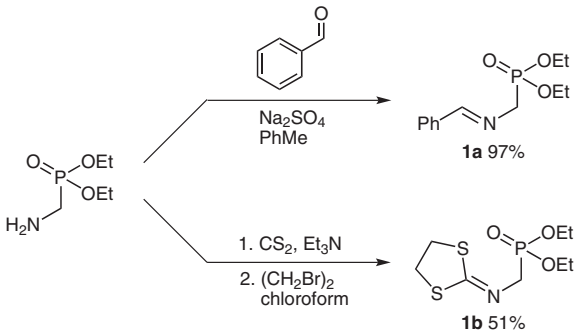
Key words: amino acids, carbanions, oxidation, arylation

α-Aminophosphonic acid analogoues of α-amino acids have found a widespread applicability.[1] For example, they are used as enzyme inhibitors[2] or for the generation of catalytic antibodies,[3] as antibacterial,[4] antiviral,[5] antifungal,[6] herbicides,[7] and antitumor agents.[8] The potential utility of α-aminophosphonic acid and their derivatives has strongly stimulated research in synthesis of these compounds.

Several approaches to construction of α-aminophosponates have been described.[9] The three-component reaction between amine, carbonyl compounds (or imine equivalents), and dialkyl phosphite – Kabachnik–Fields reaction – is one of the oldest and the most important processes.[10] This reaction has already seen a number of variants that allow to carry out the reactions also in asymmetric manner.[10c–g] An analogous route was developed by Mikołajczyk, in which imines were reacted with lithiated phosphites or its derivatives.[11]

In this communication we present a novel approach to synthesis of α-aryl-α-aminophosphonic acid using oxidative nucleophilic substitution of hydrogen in nitroarenes (ONSH). We have already shown that this reaction is of general character. On this way it is possible to introduce into electron-deficient arenes a variety of substituents such as: OH,[12] NH_2,[13] $POPh_2$, [14] and a wide range of carbon substituents.[15] Recently we have shown that ONSH in nitroarenes with carbanion of protected amino acids is an efficient way for the synthesis of amino acids containing nitroaryl substituent.[15a,b] Furthermore, we have also proven that carbanions stabilized with phosphonate group enter the ONSH reaction with nitroarenes giving nitroarylated phosphonates.[15k] On this basis we expected that similar ONSH procedure can be used to synthesis of α-aryl-α-aminophosphonic acid, particularly α-aryl-phosphoglycine derivatives. As the carbanion precursors we have chosen imino derivatives of diethyl phosphoglycinate **1a** and **1b**, prepared according to literature procedures (Scheme 1).[16]

Results of preliminary attempts of ONSH in nitrobenzene **2** with **1a** and **1b** were disappointing, thus we have tested a variety of conditions and have found that only generation of carbanion **1b**$^-$ in the presence of nitrobenzene **2** in liquid ammonia at –78 °C and subsequent oxidation with $KMnO_4$ gave desired product **2b** in 57% yield.[17]



Scheme 1 Synthesis of protected phosphoglycine esters carbanion precursors

This result indicates that, at low temperature in liquid ammonia, oxidation of σ^H adduct proceeds faster than oxidation of the sulfur in 1,3-dithiolane group.

We suppose that the negative result in the reaction of nitrobenzene **2** with **1a** might be connected with insufficient nuclepophilicity of **1a**$^-$, thus adduct σ^H is formed in a low degree. It is worth to mention that carbanions stabilized by phosphonate group exhibit much lower nucleophilicity than one could expect on the basis of their basicity. This was confirmed by quantitative measurements by Mayr.[18]

Although ONSH in nitrobenzene **2** with **1b** could give two isomeric products, the ^{1}H NMR spectrum of the reaction mixture indicated that only one isomer was formed. Analysis of the spin system of ^{1}H NMR and ^{13}C NMR spectra allowed to deduce that substitution of hydrogen in nitroarene proceeds exclusively in *ortho* position to the nitro group. So far, such behavior has been reported only for the reaction of potassium salts of carbanions in THF,[19] whereas reactions carried out in liquid ammonia give mostly product of substitution of hydrogen in *para* position to the nitro group.[15k]

Under identical conditions[17] other nitroarenes were reacted with **1b** to give the expected products (Scheme 2), the results are presented in Table 1.[20]

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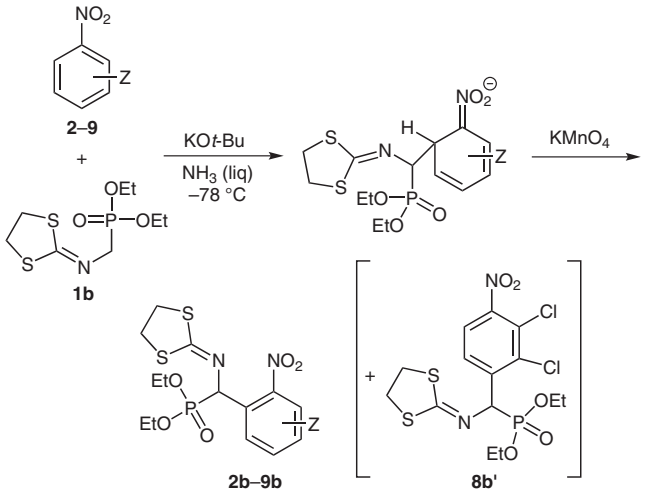
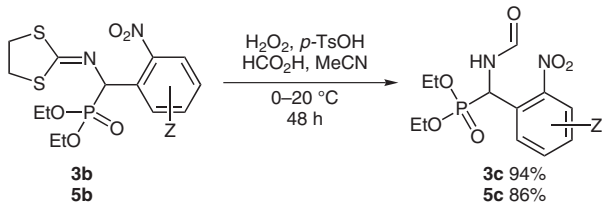


Scheme 2 ONSH in nitroarenes with carbanion of **1b**

Table 1 The results of the Reaction of Carbanion **1b**$^-$ with Nitroarenes in Liquid Ammonia

No	$ZC_6H_4NO_2$ Z		Products	Yield (%)
1	H	**2**	**2b**	57
2	4-F	**3**	**3b**	76
3	2-Cl	**4**	**4b**	23
4	3-Cl	**5**	**5b**	68
5	4-Cl	**6**	**6b**	52
6	2-MeO	**7**	**7b**	24
7	2,3-Cl_2	**8**	**8b**[a]	15
8	1-nitronaphthalene	**9**	**9b**	53

[a] Mixture of *ortho* and *para* isomers was obtained (5.7:1.0); the regioisomeric ratio was established using the ^{31}P NMR spectrum.



Scheme 3 Hydrolysis of ONSH products

All products were obtained as single *ortho* regioisomers, except the reaction of 2,3-dichloronitrobenzene **8**, where *ortho* and *para* isomer were formed in ratio 5.7:1.0. It should be stressed that even when 4-fluoronitrobenzene was used as a starting material, we did not observe formation of substitution product of fluorine in S_NAr reaction.

Products of ONSH reaction can be further deporotected to give *N*-formyl derivative in very good yield under conditions presented in Scheme 3.[21]

In summary, in this communication we have presented a new approach to the synthesis of α-(*o*-nitroaryl)phosphoglycine derivatives using the oxidative nucleophilic substitution of hyrogen in nitroarenes with carbanion of protected phosphoglycine **1b**.

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(16) (a) Oberhauser, T.; Meduna, V. *Tetrahedron* **1996**, *52*, 7691. (b) **Modified Literature Procedure**[16c]
To the solution of diethyl phosphoglycinate (4.55 g, 27.2 mmol) in $CHCl_3$ (100 mL) Et_3N (3 equiv, 81.6 mmol, 12.5 mL) was added followed by CS_2 (1.5 equiv, 40.8 mmol, 2.43 mL). The resulting mixture was stirred at r.t. for 24 h, and then ethylene bromide (1.2 equiv, 32.6 mmol, 6.07 g) was added. The solution was stirred for further 24 h at 60 °C. After cooling to r.t., the mixture was washed with H_2O, dried with anhyd Na_2SO_4, and evaporated. The residue was purified by column chromatography ($CHCl_3$–MeOH, 30:1, v/v). The N-protected phosphoglycinate was obtained as an oil, 3.73 g, 51% yield. (c) Hoppe, D.; Beckmann, L. *Liebigs Ann. Chem.* **1979**, 2066.

(17) **General Procedure**
To liquid NH_3 (15 mL) at –78 °C a solution of nitroarene (2.0 mmol) and **1b** (269 mg, 1.0 mmol) was added followed by dropwise addition of KO*t*-Bu in THF (1.05 mL, 1.00 M, 1.05 mmol) over 5 min. The reaction mixture was stirred at this temperature for 30 min and then solid $KMNO_4$ (156 mg, 1.0 mmol) was added. After 5 min reaction was quenched by addition of NH_4Cl (500 mg), and the mixture was left to evaporation of NH_3. The residue was treated with H_2O (50 mL) and EtOAc (50 mL) and filtered through a pad of Celite. The organic layer was separated, dried, and evaporated. Products were isolated by column chromatography (EtOAc–hexane).

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(20) **Selected Analytical Data**
Diethyl *N*-(1,3-Ditiholan-2-ylidene)-α-(2-nitrophenyl)-phosphoglycinate (2a)
Solidifying oil. IR (film, CH_2Cl_2): ν_{max} = 2986, 2905, 1589, 1534, 1355, 1245, 1026, 572 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.00 (m, 1 H), 7.90 (m, 1 H), 7.61 (m, 1 H), 7.41 (m, 1 H), 4.50 (s, 1 H), 5.96 (d, *J* = 18.8 Hz), 4.11–4.00 (m, 4 H), 3.64–3.40 (m, 4 H), 1.26–1.21 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6 (d, *J* = 19 Hz), 148.4 (d, *J* = 7 Hz), 132.9 (d, *J* = 4 Hz), 130.9 (d, *J* = 7 Hz), 130.7 (d, *J* = 4 Hz), 128.1 (d, *J* = 4 Hz), 124 (d, *J* = 3 Hz), 65.9 (d, *J* = 156 Hz), 63.4 (d, *J* = 15 Hz), 63.3 (d, *J* = 15 Hz), 38.1, 35.0, 16.3 (d, *J* = 10 Hz), 16.2 (d, *J* = 10 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 18.1. ESI-LRMS (+): *m/z* 391 $[M + H]^+$. Anal. Calcd for $C_{14}H_{19}N_2O_5S_2P$: C, 43.07; H, 4.91; N, 7.18; S, 16.43. Found: C, 42.85; H, 4.90; N, 7.17; S, 16.55.
Diethyl *N*-(1,3-Dithiolan-2-ylidene)-α-(1-nitro-2-naphthyl)-phosphoglycinate (9b)
Oil. IR (film, CH_2Cl_2): ν_{max} = 2983, 1581, 1528, 1254, 1049, 1020, 563 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.05–7.95 (m, 2 H), 7.90–7.85 (m, 1 H), 7.76–7.71 (m, 1 H), 7.63–7.54 (m, 2 H), 5.15 (d, *J* = 18.0 Hz), 4.20–4.00 (m, 4 H), 3.65–3.51 (m, 2 H), 3.49–3.35 (m, 2 H), 1.28 (dt, *J* = 0.4, 7.1 Hz, 3 H), 1.22 (dt, *J* = 0.4, 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7 (d, *J* = 19 Hz), 146.8 (d, *J* = 9 Hz), 133.0 (d, *J* = 2 Hz), 130.6 (d, *J* = 3 Hz), 128.4, 127.9 (d, *J* = 2 Hz), 127.4, 126.2 (d, *J* = 4 Hz), 126.0 (d, *J* = 6 Hz), 124.2 (d, *J* = 2 Hz), 121.8, 66.9 (d, *J* = 161 Hz), 63.6 (d, *J* = 8 Hz), 63.5 (d, *J* = 8 Hz), 38.2, 34.9, 16.2 (d, *J* = 6 Hz), 16.1 (d, *J* = 6 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 17.6. ESI-LRMS (+): *m/z* 463 $[M + H]^+$. Anal. Calcd for $C_{18}H_{21}N_2O_5S_2P$: C, 49.08; H, 4.91; N, 6.36; S, 14.56. Found: C, 48.62; H, 4.93; N, 6.34; S, 14.45.

(21) The hydrolysis reactions were performed according to literature procedure, see ref. 15a.
Selected Analytical Data
Diethyl α-(5-Fluoro-2-nitrophenyl)phosphoglycinate (3c)
Oil. IR (film, CH_2Cl_2): ν_{max} = 3250, 2987, 1689, 1589, 1532, 1351, 1236 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.27 (s, 1 H), 8.00 (ddd, *J* = 0.4, 5.1, 9.0 Hz, 1 H), 7.64 (dt, *J* = 2.7, 9.5 Hz, 1 H), 7.13–7.09 (m, 1 H), 5.52 (d, *J* = 21.5 Hz), 4.26–4.00 (m, 4 H), 2.95 (br s, 1 H), 1.29 (t, *J* = 7.0 Hz, 3 H), 1.17 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9 (d, *J* = 204 Hz), 160.9 (d, *J* = 7.4 Hz), 144.7 (dd, *J* = 2.3, 5.0 Hz), 137.0 (d, *J* = 6.6 Hz), 127.9 (dd, *J* = 1.6, 7.8 Hz), 116.5 (dd, *J* = 2.4, 3.5 Hz), 115.4 (dd, *J* = 2.3, 18.6 Hz), 63.6 (d, *J* = 5.5 Hz), 63.5 (d, *J* = 5.5 Hz), 47.8 (d, *J* = 118 Hz), 16.3 (d, *J* = 2.5 Hz), 16.2 (d, *J* = 2.5 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 22.0. ESI-LRMS (+): 357 $[M + Na]^+$. Anal. Calcd for $C_{12}H_{16}N_2O_6PF$: C, 43.12; H, 4.83; N, 8.38. Found: C, 43.16; H, 4.83; N, 8.30.