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Phosphites mediated decarboxylation of α-iminoacids. A straightforward route to labelled α-aminophosphates.

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Summary

This paper describes two simple procedures for the one pot synthesis of labelled α-aminophosphates using deuterated acetic acid as labelling source. The reaction of alkyl phosphites with α-iminoacids is studied in some detail.

Key Words : Deuterated α-aminophosphates, decarboxylation, phosphite, α-iminoacids.

Introduction

Aminophosphates are of great interest owing to their biological activity (1-5). These products are considered as structural analogues of the corresponding α-aminoacids but also as transition state mimics of peptide hydrolysis (6). They are known to act as antibiotic and pharmacological agents (7) as well as enzyme inhibitors (8). Despite the growing importance of these drugs, few methods have been reported for their labelling. These isotopic syntheses usually involve strong bases to generate an α-carbanion which is then quenched with D_2O (4, 9, 10). In the present article we would like to report two novel procedures for the one pot synthesis of labelled α-aminophosphates. These procedures could easily be adapted to tritium labelling.

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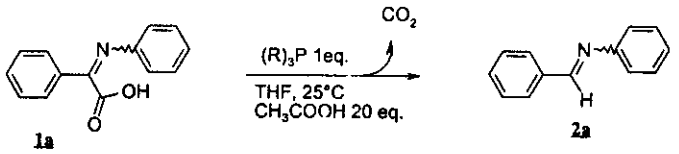
Results and discussion

In a recent publication (11), we demonstrated that tributylphosphine is an efficient catalyst for the decarboxylation of α-iminoacids. This reaction has since been extended to the synthesis of labelled N-Aryl imines (12). To further investigate the scope and limitations of this process, we studied the reaction of (N-phenylbenzimidoyl) formic acid **1a** with a range of trivalent phosphorus compounds R_3P (scheme 1, Table 1). These experiments were conducted with stoichiometric amounts of R_3P in THF in the presence of 20 eq. of acetic acid.



Scheme 1

Table 1. Reaction of trivalent phosphorus compounds with α-iminoacid **1a**.

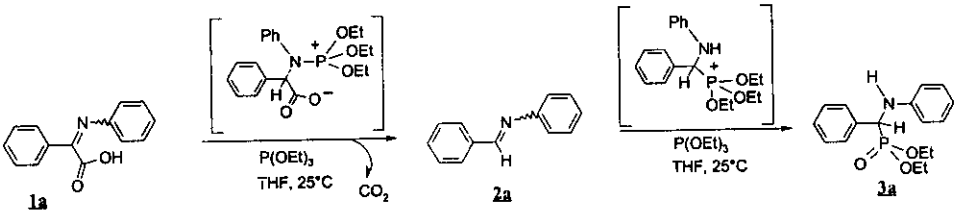
Entry	$(R)_3P$	Time	Yield of **2a**[a]
1	$(Bu)_3P$	1 min	100%
2	$(Ph)_3P$	24 h	2%
3	$(Me_2N)_3P$	5 h	95%
4	$(MeO)_3P$	3 min	98%
5	$(EtO)_3P$	3 min	97%

[a] NMR yield.

Although alkyl phosphines are the most reactive phosphorus compounds towards decarboxylation, we also found that alkyl phosphites exhibit the same reactivity (entries 4 and 5). Indeed, upon treatment with $(MeO)_3P$ or $(EtO)_3P$, imine **2a** is formed in nearly quantitative yield with simultaneous evolution of CO_2 (trapped with a saturated $Ba(OH)_2$ solution). However, when the mixture was allowed to react for an extended period of time, a slow reaction took place leading to α-aminophosphate **3a** (scheme 2). The action of alkyl phosphites on **1a** has already been reported by Sidky et al. in 1971 (13). The authors obtained 45 % of aminophosphate **3a** together with 40% of the ethyl ester of **1a** when this iminoacid was treated with $(EtO)_3P$ in

dry benzene at 25°C for 12 hours. They postulated the formation, in the first step, of a C-P bonded intermediate with no intermediacy of **2a**. A simple kinetic experiment (Table 2, entries 1 and 2) demonstrates that, under our conditions, this is not the case. Imine **2a** is the first product formed (probably *via* the same mechanism as the phosphine mediated decarboxylation (11)). Then, alkylphosphite reacts with this imine by a classical Arbuzov type reaction yielding α-aminophosphate **3a** (14).

We envisaged that the reaction of phosphites with α-iminoacids could be an easy and direct access to α-labelled α-aminophosphates using readily available deuterated or tritiated acetic acid. We therefore optimized the reaction conditions by adding nucleophiles to the reaction mixture to enhance the Arbuzov reaction (Table 2, entries 3 and 4).



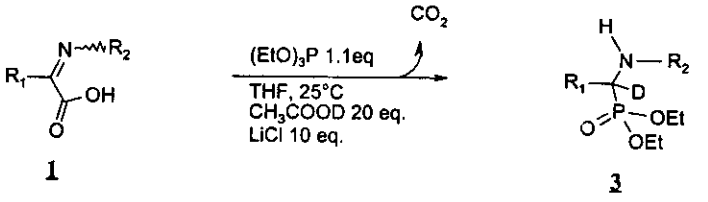
Scheme 2

Table 2. Optimization of the reaction conditions.

Entry	Conditions	Time	Yield **2a**[a]	Yield **3a**[a]
1	THF	10 min	52%	tr.
		24 h.	76%	9%
2	THF/CH_3COOH (20 eq.)	5 min.	87%	11%
		3 h.	60%	37%
		24h.	2%	95%
3	THF/ CH_3COOH (20 eq.) CH_3COONa (10 eq.)	1 h.	tr.	95%
4	THF/ CH_3COOH (20 eq.) LiCl (10 eq.)	15 min.	tr.	98%

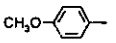
[a] NMR yields.

LiCl was found to be the most efficient nucleophile which allowed the quantitative transformation of **1a** into **3a** in only 15 min. We thus tried to extend this reaction to a family of α-iminoacids (scheme 3). Table 3 summarizes our results.



Scheme 3

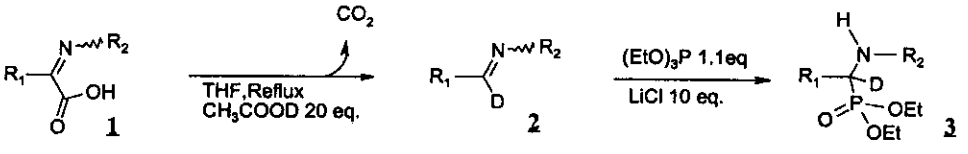
Table 3. Reaction of alkyl phosphites with α-iminoacid **1**.

3	R_1	R_2	Reaction Time	Yield[a]	Isotopic purity[b]
a			15 min.	97%	83%
b			25 min.	83%	85%
c			45 min.	87%	94%
d			48 h.	55%	70%
e			16 h.	77%	58%
f			16 h.	79%	86%

[a] Isolated yields. [b] Determined by GC

Several labelled N-Aryl α-amino phosphates were successfully obtained in satisfactory to high yields and with good isotopic purities. Attempts to increase the rate of the reaction by working at higher temperatures or higher concentrations of phosphite were unsuccessful.

During this study, we found some limitations to this procedure. N-Alkyl α-iminoacids, for example, were not phosphite-decarboxylated. However, for this class of compounds, the thermal decarboxylation (15, 16) could be an interesting alternative. N-Alkyl α-aminophosphates were thus easily obtained in a two-step sequence (Scheme 4, Table 4).



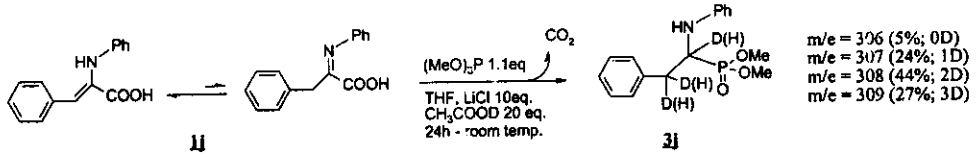
Scheme 4

Table 4. Synthesis of labelled N-Alkyl aminophosphates using thermal decarboxylation of iminoacids.

3	R_1	R_2	Decarboxylation conditions	Arbuzov conditions	Yield[a]	Isotopic purity[b]
g			Reflux 1h	25°C - 2 h.	77%	89%
h			Reflux 1h	25°C - 12 h.	58%	84%
i			Reflux 4h	25°C - 12 h.	52%	80%

[a] Isolated yields. [b] Determined by GC

We sought to take advantage of both procedures to provide labelled analogues of natural α-aminoacids such as phenylalanine (scheme 5) starting from **1j** which was predominantely in the enamine form in THF. Thermal decarboxylation attempts gave unpromising mixtures from which only trace amounts of **3j** were produced. This result could be attributed to the imine / enamine equilibrium which might inhibit decarboxylation. However, the phosphite mediated decarboxylation did provide the desired product in 15% yield (scheme 5).



1j **3j**

Scheme 5

Aminophosphate **3j** was found to be labelled at both α and β positions with satisfactory isotopic purities. This unoptimized reaction does offer the possibility of a new and straightforward route to polylabelled analogues of natural aminoacids. We are currently investigating this approach as a general synthetic method.

In conclusion, we have developed two new procedures for a simple and rapid synthesis of labelled α-aminophosphates. This methodology uses readily available labelled starting materials which could make it easily amenable to tritium labelling.

Experimental Section

α-Iminoacids were prepared from α-keto acids and the corresponding amine at room temperature in dichloromethane or under reflux in EtOH as previously described (16).

General procedure for the preparation of α-deuterated aminophosphates **3a-3f** using the phosphite mediated decarboxylation :

To a stirred mixture of α-iminoacids **1a-f** (0.5 mmol) in anhydrous THF (5 mL) was added CH_3COOD (600 µL; 20 eq.) and $P(OEt)_3$ (90 µL; 1.1 eq.). After stirring for 5 min at room temperature and under argon, LiCl (210 mg; 10 eq.) was added. The reaction was monitored by TLC. After completion, the reaction was quenched with $H_2O/NaHCO_3$ to neutrality and the product rapidly extracted with ethyl acetate. The solution was dried over magnesium sulfate, concentrated and the product purified on silica (hexane/ethyl acetate).

General procedure for the preparation of α-deuterated aminophosphates **3g-3j** using the thermal decarboxylation :

Under argon, CH_3COOD (500 µL, 20 eq.) was added to a stirred solution of **1g-i** (0.4 mmol, 1eq.) in 4 mL of anhydrous THF. The mixture was heated to reflux for the time indicated in the Table and then cooled to room temperature. LiCl (170 mg, 10 eq.) and $P(OEt_3)$ (77 µL; 1.1 eq.) were added and the solution was stirred at room temperature. The reaction was monitored by TLC. After completion, the reaction was quenched with $H_2O/NaHCO_3$ to neutrality and rapidly extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, concentrated and the product purified on silica (hexane/ethyl acetate).

• (1-Deutero-1-phenyl-1-phenylamino-methyl)-phosphonic acid diethyl ester **3a**. white solid; ^1H NMR ($CDCl_3$) δ_{ppm} = 7.44-7.48 (m, 2H), 7.25-7.34 (m, 3H), 7.09 (t, J

= 7.8 Hz, 2H), 6.68 (t, J = 7.2 Hz, 1H), 6.57 (d, J= 8.1 Hz, 2H), 4.78 (brs, 1H), 4.06-4.14 (m, 2H), 3.88-3.96 (m, 1H), 3.61-3.70 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.10 (t, J = 7.2 Hz, 3H); MS/EI : m/e = 320 (20), 321 (100).

• [1-Deutero-1-(4-methoxy-phenylamino)-1-phenyl-methyl]-phosphonic acid diethyl ester **3b**. orange oil; ^{1}H NMR ($CDCl_3$) δ_{ppm} = 7.23-7.55 (m, 5H), 6.68 (d, J = 9Hz, 2H), 6.61 (d, J = 9Hz, 2H), 4.23 (d, J = 24 Hz, residual NCHP), 4.11-4.16 (m, 2H), 3.56-3.94 (m, 2H), 3.68 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.02 (t, J = 7.2 Hz, 3H); MS/EI : m/e = 350 (15), 351 (100).

• [1-Deutero-1-(4-dimethylamino-phenylamino)-1-phenyl-methyl]-phosphonic acid diethyl ester **3c**. brown solid; ^{1}H NMR ($CDCl_3$) δ_{ppm} = 7.23-7.48 (m, 5H), 6.61 (d, J = 12 Hz, 2H), 6.56 (d, J = 12Hz, 2H), 4.69 (d, J = 24 Hz, residual NCHP), 4.46 (s, 1H), 4.07-4.16 (m, 2H), 3.64-3.98 (m, 2H), 2.76 (s, 6H), 1.27 (t, J = 7 Hz, 3H), 1.10 (t, J = 7 Hz, 3H); MS/EI : m/e = 363 (6.7), 364 (100).

•{1-Deutero-1-phenyl-1-[N"-(1- phenyl-methanoyl)-hydrazino]-methyl}-phosphonic acid diethyl ester **3d**. white solid; ^{1}H NMR ($CDCl_3$) δ_{ppm} = 8.25 (brs, 1H), 7.62 (d, J = 9 Hz, 2H), 7.43-7.49 (m, 3H), 7.35-7.42 (m, 5H), 5.52 (brs, 1H), 4.59 (d, J = 24 Hz, residual NCHP), 3.95-4.10 (m, 4H), 1.23 (m, 6H); MS/EI : m/e = 363 (39), 364 (100).

• (1-Deutero-(E)-1-phenylamino-3-*p*-tolyl-allyl)-phosphonic acid diethyl ester **3e**. white solid; ^{1}H NMR ($CDCl_3$) δ_{ppm} = 7.23 (d, J = 6 Hz, 2H), 7.07-7.18 (m, 4H), 6.62-6.76 (m, 4H), 6.18 (dd, J = 5.1 and 5.9 Hz, 1H), 4.46 (dd, J = 24 and 6 Hz, residual NCHP) 4.09-4.20 (m, 4H), 2.30 (s, 3H), 1.25-1.31 (m, 6H); MS/EI : m/e = 360 (63), 361 (100).

• [1-Deutero-1-(4-hydroxy-phenylamino)-1-thiophen-2-yl-methyl]-phosphonic acid diethyl ester **3f**. orange oil; ^{1}H NMR ($CDCl_3$) δ_{ppm} = 7.16 (d, J = 6 Hz, 1H), 7.08 (m,

1H), 6.91 (m, 1H), 6.66 (d, J = 6.6 Hz, 2H), 6.51 (d, J = 6 Hz, 2H), 5.44 (d, J = 24 Hz, residual NCHP), 4.01-4.16 (m, 4H), 1.24 (t, J= 7.2 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H); MS/EI : m/e = 342 (17), 343 (100).

• (1-Benzylamino-1-deutero-1-phenyl-methyl)-phosphonic acid diethyl ester **3g**. white solid; ^{1}H NMR ($CDCl_3$) δ_{ppm} = 7.22-7.43 (m, 10H), 3.89-4.15 (m, 4H), 3.80 (d, J = 13.5 Hz, 1H), 3.52 (d, J = 13.5 Hz, 1H), 2.73 (brs, 1H), 1.25 (t, J = 7.2 Hz, 3H), 1.10 (t, J = 7.2 Hz, 3H); MS/EI : m/e = 334 (12), 335 (100).

• (1-Butylamino-1-deutero-1-phenyl-methyl)-phosphonic acid diethyl ester **3h**. colorless oil; ^{1}H NMR ($CDCl_3$) δ_{ppm} = 7.25-7.40 (m, 5H), 3.78-4.08 (m, 4H), 2.40-2.52 (m, 2H), 1.90 (brs, 1H), 1.31-1.43 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H), 1.11 (t, J = 7.2 Hz, 3H), 0.83 (t, J = 7.2 Hz, 3H); MS/EI : m/e = 300 (20), 301 (100).

• (1-Benzylamino-1-deutero-1-thiophen-2-yl-methyl)-phosphonic acid diethyl ester **3j**. colorless oil; ^{1}H NMR ($CDCl_3$) δ_{ppm} = 7.23-7.30 (m, 6H), 7.06 (m, 1H), 7.00 (m, 1H), 4.29 (d, J = 30 Hz, residual NCHP), 4.01 (m, 4H), 3.92 (d, J = 13.2 Hz, 1H), 3.63 (d, J = 13.2 Hz, 1H), 2.03 (s, 1H), 1.25 (t, J = 7.2 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H); MS/EI : m/e = 340 (26), 341 (100).

Acknowledgments

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