Available online at www.sciencedirect.com

SciVerse ScienceDirect

Chinese Chemical Letters 23 (2012) 923–926

CHINESE CHEMICAL LETTERS

www.elsevier.com/locate/cclet

A facile synthesis of ω-aminoalkyl ammonium hydrogen phosphates

Wei Bo Kong, Xiao Yong Zhou, Yang Yang, Xing Yi Xie *

Department of Polymeric Biomaterials and Artificial Organs, College of Polymer Science and Engineering, Sichuan University, Chengdu 610065, China

Received 20 April 2012
Available online 4 July 2012

Abstract

A series of ω-aminoalkyl ammonium hydrogen phosphates were synthesized through a simple and efficient three-step method. The starting materials, ω-aminoalkyl alcohols (AC-*n*, with carbon number $n = 3, 4, 5, 6$), were amino-protected with 9-fluorenylmethyl chloroformate (Fmoc-Cl), followed by phosphorylation with $POCl_3$ and deprotection in piperidine/DMF. The structures of each intermediate and final product were confirmed by ^1H NMR, FTIR and mass spectrum. The yield of each step was about 77–92%, with a total yield higher than 56%. This new method was superior in low-cost raw materials, mild reaction temperatures (0–25 °C) and easy purification methods.
© 2012 Xing Yi Xie. Published by Elsevier B.V. on behalf of Chinese Chemical Society. All rights reserved.

Keywords: Amino alcohol; Phosphorus oxychloride; Synthesis; Aminoalkyl ammonium hydrogen phosphate

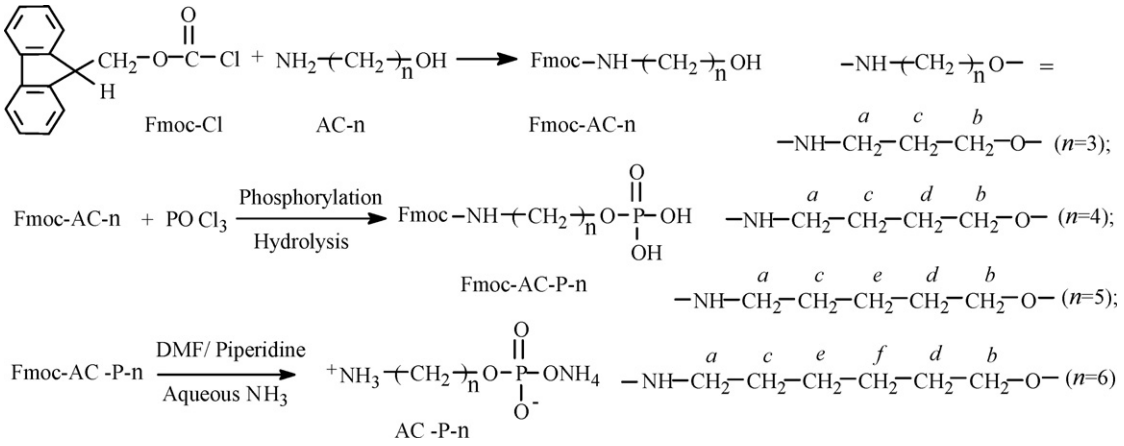
1. Introduction

ω-Aminoalkyl dihydrogen phosphates and their salts are safe and active cosmetic ingredients, promoting fibroblast proliferation and collagen biosynthesis [1]. Their phosphate groups possess unique bonding ability to metals [2] and ceramics [3], thereby functionalizing their surfaces with the amino groups for further modifications with bioactive molecules. Due to their hetero-functionality, they often serve as linkers for various bioconjugates [4,5]. In addition, they can be used as flame retardants for fibers [6] and fuel concentrates for autos [7].

Synthesis of ω-aminoalkyl dihydrogen phosphates usually involves selective phosphorylation to the hydroxyl group from corresponding α, ω-amino alcohol, rather than the amino group. Strong phosphorylation agents like phosphorus oxychloride ($POCl_3$) are generally not suitable due to reaction with the amino group [8]. Only 3-aminopropane phosphoric acid has been synthesized through that way where cyclophosphamide was formed initially, followed by acid-catalyzed breakdown the P–N bond in its six-membered ring [1]. Some milder agents such as orthophosphoric acid, pyrophosphoric acid, and polyphosphoric acid might be good choices in terms of selective phosphorylation [9,10]. However, a high reaction temperature (140–250 °C) and a long reaction time (18–40 h) in vacuum were utilized in these methods, hindering their industrialization due to high energy cost and low yield (<50%, sometimes ~20%). Another more effective agent, *i.e.*, 2-(*N*,*N*-dimethylamino)-4-nitrophenyl phosphate, has been developed to synthesize 2-aminoethyl dihydrogen phosphate in a mild condition (about 115 °C for 3 h) [8]. But the

* Corresponding author.
E-mail addresses: xiexingyi@263.net, xiexingyi@scu.edu.cn (X.Y. Xie).

1001-8417/$ – see front matter © 2012 Xing Yi Xie. Published by Elsevier B.V. on behalf of Chinese Chemical Society. All rights reserved.
http://dx.doi.org/10.1016/j.cclet.2012.06.010



Scheme 1. Synthesis route of ω-aminoalkyl ammonium hydrogen phosphates.

synthesis of the phosphorylation agent itself was very complicated, involving a purification process through ionic exchange columns.

In this study, we explored a general procedure to synthesis ω-aminoalkyl ammonium hydrogen phosphates, using low-cost $POCl_3$ as a phosphorylation agent, as shown in Scheme 1. Firstly, each α, ω-amino alcohol (AC-*n*, with carbon number $n = 3$, 4, 5, 6 hereafter) was reacted with 9-fluorenylmethyl chloroformate (Fmoc-Cl) to protect the amino group. The resulting product (Fmoc-AC-*n*) was recrystallized from an ethyl acetate/petroleum ether mixture. Secondly, each Fmoc-AC-*n* was phosphorylated with overdosed $POCl_3$ to form a dichloride phosphate which was further hydrolyzed in ice water, forming an amino-protected intermediate (Fmoc-AC-P-*n*). It was insoluble in water due to the bulky hydrophobic Fmoc group, and was separated by simple filtration. Finally, the protecting Fmoc group was removed in piperidine/DMF mixture, forming a precipitate (*i.e.*, piperidine salt of aminoalkyl dihydrogen phosphate) which was filtered and washed with ethyl acetate. The purified precipitate was dissolved in aqueous ammonia to remove piperidine by chloroform extraction. The aqueous phase was concentrated and dried to form a white salt of ω-aminoalkyl ammonium hydrogen phosphate (AC-P-*n*). All the three synthesis steps were carried out at 0–5 °C or room temperature, using traditional organic reactions and simple purification methods. The yield of each step ranged from 77% to 92%, with the total yield in 56–67% (Table 1).

The chemical structures of each intermediate and final product are confirmed by ^{1}H NMR and FTIR. The H signals at δ 7.33, 7.41, 7.70, 7.89 (hydrogen *A–D*) and at δ 4.2, 4.4 (hydrogen *E* and *F*) are characteristic for Fmoc group (Fig. 1A), showing the success of amino protection in Fmoc-AC-*n*. Accordingly, their FTIR spectra displayed four

Table 1
The yield and mass spectrum results of each intermediate and final product.

Compound	Characterization	$n = 3$	$n = 4$	$n = 5$	$n = 6$
Fmoc-AC-*n*	Yield (%)	83	83	84	82
	ESI MS				
	Calcd. M (Da)	297.14	311.15	325.17	339.18
	Found $[M+Na]^+$ (*m/z*)	320.10	334.09	348.11	362.11
Fmoc-AC-P-*n*	Yield (%)	85	77	88	85
	ESI MS				
	Calcd. M (Da)	377.10	391.12	405.13	419.15
	Found $[M-H]^-$ (*m/z*)	−376.01	−390.04	−404.01	−418.06
AC-P-*n*	Yield (%)	92	88	91	92
	ESI MS				
	Calcd. M (Da)	155.03	169.05	183.07	197.08
	Found $[M-H]^-$ (*m/z*)	−154.04	−168.03	−182.06	−196.02
Total yield (%)		65	56	67	64

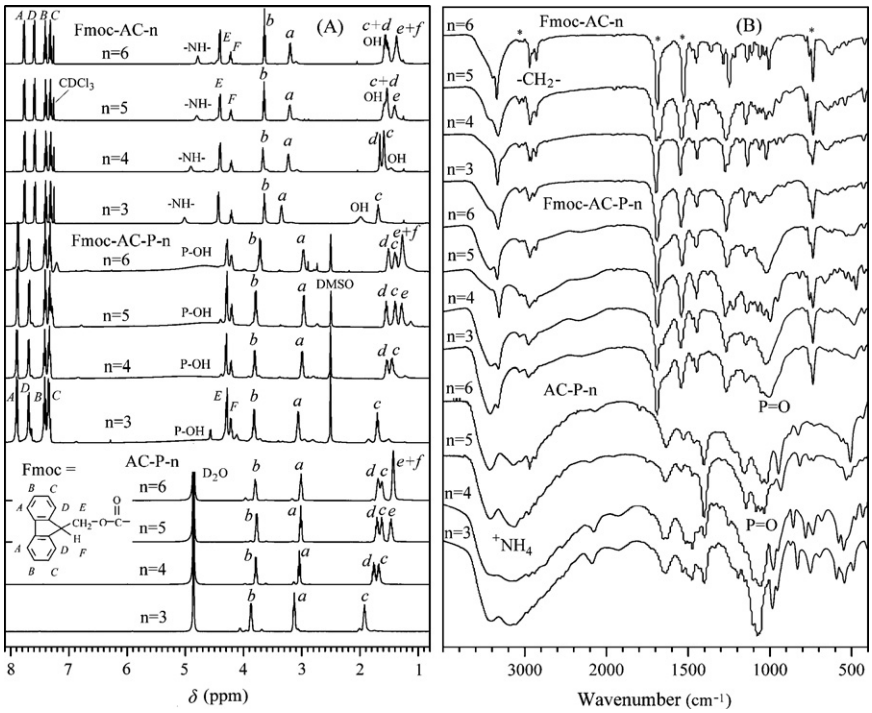


Fig. 1. ^{1}H NMR (A) and FTIR (B) spectra of each intermediate and final product.

absorptions (indicated by * in Fig. 1B) resulted from Fmoc protection, *i.e.*, aromatic C–H stretching at 3066 cm^{-1}, amide C=O stretching at 1960 cm^{-1}, C–N stretching at 1543 cm^{-1} and aromatic C–H bending at 737 cm^{-1}. After phosphorylation, the Fmoc hydrogen signals were retained, while a new broad peak appeared in δ 4.5–5.5, indicated the presence of P-OH in each Fmoc-AC-P-*n* (Fig. 1A). The FTIR spectra displayed prominent P=O vibrations at 1020 cm^{-1} (Fig. 1B), further proving the formation of phosphoric acid groups. For the final products AC-P-*n*, the H signals of Fmoc groups disappeared (Fig. 1A). Their FTIR spectra demonstrated a broad ammonium (NH_4^+) N–H stretching (2200–3600 cm^{-1}) and a phosphate P=O stretching at 1078 cm^{-1}. The mass spectra data also confirmed the structures of each intermediate and final product (Table 1).

In conclusion, we have successfully synthesized a series of ω-aminoalkyl ammonium hydrogen phosphates using amino-protection method in mild conditions, with total yields over 56%. If necessary, these products can easily be acidized to obtain the corresponding phosphoric acids. This simple and effective method might promote the scientific research about the properties and applications of ω-aminoalkyl dihydrogen phosphates and their salts.

2. Experimental

All the chemicals were of analytical grades and used as received. The ^{1}H NMR (400 MHz) and FTIR spectra were reported in Fig. 1. The yields and mass spectrum (ESI mode) data are shown in Table 1.

Synthesis of Fmoc-AC-n: Each α, ω-amino alcohol (0.025 mol) was dissolved in 25 mL THF and cooled to 0–5 °C in an ice bath. Fmoc-Cl (2.587 g, 0.01 mol) in 20 mL THF was added dropwise in 2–2.5 h, under N_2 atmosphere and magnetic stirring. Following another 7-h stirring at room temperature, the pH was adjusted to 4, using 10% HCl. The reaction mixture was extracted with 40 mL × 3 saturated NaCl solution to remove the byproduct, α, ω-amino alcohol hydrochloride. The organic phase was dried by anhydrous $NaSO_4$. The solvent was evaporated at 35 °C under reduced pressure. The residue was recrystallized from an ethyl acetate/petroleum ether (7:1, v/v) mixture, and vacuum-dried at 35 °C for 10 h to obtain the product.

Synthesis of Fmoc-AC-P-n: Each Fmoc-AC-*n* (0.01 mol) was dissolved in 20 mL THF, and dropped into 15 mL $POCl_3$ (0.16 mol) in ~1.5 h under reduced pressure. The reaction temperature was kept at ~0 °C using an ice bath. The reaction mixture was stirred for another 7 h. Thereafter it was poured into 400 mL ice water to hydrolyze the dichloride

phosphate intermediate for 3 h. The resulting precipitate was filtered, water-washed 3 times, freeze-dried for 9 h, and finally air-dried at 35 °C for 2 h. Thus the designed product was obtained.

Synthesis of AC-P-n: Each Fmoc-AC-P-*n* (0.005 mol) was dissolved in 5 mL DMF, added to 20 mL piperidine/DMF (1:4, v/v) [11], and the mixture was stirred for 30 min at 0–5 °C. The resulting white precipitate (*i.e.*, piperidine salt of ω-aminoalkyl dihydrogen phosphates) was filtered, and washed with ethyl acetate. Thereafter it was dissolved in 25 mL ammonia solution (25 wt.%) to remove piperidine by extraction with 25 mL × 4 chloroform. The aqueous phase was freeze-dried for 12 h, and then vacuum-dried at 35 °C for 10 h, to obtain the target product as a white powder. ^{13}C NMR (100 MHz, D_2O): $n = 3$, δ 63.94 (d, $J = 4.2$ Hz), 39.56, 29.78 (d, $J = 6.4$ Hz); $n = 4$, δ 65.78 (d, $J = 5.2$ Hz), 41.35, 29.20 (d, $J = 6.8$ Hz), 25.83; $n = 5$, δ 66.34 (d, $J = 4.8$ Hz), 41.55, 31.66 (d, $J = 6.4$ Hz), 28.61, 24.30; $n = 6$, δ 66.70 (d, $J = 4.7$ Hz), 41.43, 31.92 (d, $J = 6.7$ Hz), 28.77, 27.36, 26.61. ^{31}P NMR (162 MHz, 0.5 mL D_2O + 2 μL H_3PO_4): $n = 3$, δ −0.07; $n = 4$, δ −0.05; $n = 5$, δ −0.28; $n = 6$, δ −0.12. C/N molar ratio (elemental analysis), found (calcd.): $n = 3$, 1.62 (1.5); $n = 4$, 2.29 (2.0); $n = 5$, 2.43 (2.5); $n = 6$, 2.73 (3.0).

Acknowledgments

This work was sponsored by the National Science Foundation of China (No. 50973069) and the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry (No. 20101561-3-3).

References

[1] O.S. Lee, Y.H. Byon, B.S. Lee, US Patent 5,723,645 (1998).
[2] S. Gengrinovitch, PCT Int. Appl. WO 2006056984 A2 (2006).
[3] A. Bouladjine, A. Al-Kattan, P. Dufour, Langmuir 25 (2009) 12256.
[4] R. Barker, K.W. Olsen, J.H. Sharper, J. Biol. Chem. 247 (1972) 7135.
[5] L. Halby, V.A. Ryabinin, A.N. Sinyakovb, Bioorg. Med. Chem. Lett. 15 (2005) 3720.
[6] A. Mizuguchi, K. Sato, A. Sakurai, JP 47002517 B4 (1972).
[7] E.R. Morrison, US Patent 3,402,030 A (1968).
[8] Y. Taguchi, Y. Mushika, J. Org. Chem. 40 (1975) 2310.
[9] E. Cherbuliez, J. Rabinowitz, Helv. Chim. Acta 41 (1958) 1168.
[10] L.D. Li, W. Tang, W.J. Liu, Chin. J. Org. Chem. 28 (2008) 489.
[11] C.M. Zhang, J.X. Guo, L. Wang, et al. Chin. Chem. Lett. 22 (2011) 631.