Asian Journal of Chemistry; Vol. 23, No. 7 (2011), 2871-2873

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

# Synthesis and Characterization of α-Aminophosphonic Acids Containing Adenine

DU-LIN KONG[1,2], MING-SHU WU[1,2*], CHANG-RI HAN[1,2], JING-YA MA[1,2] and DE-HUI WAN[1,2]

[1]Key Laboratory of Tropical Medicinal Plant Chemistry of Ministry of Education, Hainan Normal University, Haikou 571158, Hainan Province, P.R. China
[2]College of Chemistry and Chemical Engineering, Hainan Normal University, Haikou 571158, Hainan Province, P.R. China

*Corresponding author: Fax: +86 898 65889422; Tel: +86 898 65889422; E-mail: 173548977@qq.com; wumingshu@126.com

(*Received*: 8 July 2010; *Accepted*: 4 March 2011) AJC-9689

Seven novel α-aminophosphonic acids containing adenine **2** were synthesized by the three component condensation reactions of adenine with triphenyl phosphite and aldehydes **1** in presence of acetic acid and xylene. The product structures were characterized by IR and NMR spectral data and elemental analyses.

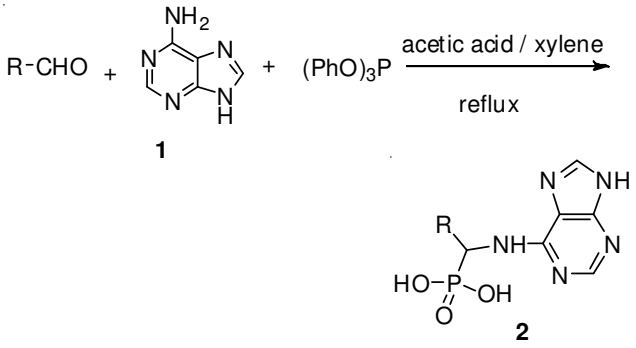
**Key Words: α-Aminophosphonates, Adenine, Mannich-type reaction.**

## INTRODUCTION

The chemistry of α-aminophosphonic acids and their derivatives have received much attention because of their unique structural features and diverse potential biological and industrial importance. Their potential as herbicides[1], insecticides[2], fungicides[3], peptidomimetics[4], enzyme inhibitors[5] and antiviral agents[6] as well as their role for antibody generation[7] is well documented. Adenine, which exists in the nucleic acid of the organism as the base, has drawn great attention of biochemists and organic synthetic chemists in recent years because of its remarkable biological activities. Especially in the respects of antivirus and restraint of cancer cells[8-13], adenine and adenine derivatives are great practical significance as raw material for medicine and agricultural chemicals. They are found in a variety of biologically active molecules[14-16], adenine derivatives have obvious effect and alluring prospect of clinical application.

To the best of our knowledge, only a few examples of α-aminophosphonates of N-heterocycles were reported. Several workers have described that pyridine[17], tetrazole[18], pyrazole[19] and thiazole[20] were introduced into α-aminophosphonates by Mannich-type reaction. But to the best of our knowledge, there have been no report on the synthesis of α-aminophosphonates bearing the adenine.

In view of the above observations and our interest in the organic phosphorus chemistry and biologically active compound, herein we wish to report a convenient and facile one-pot synthesis of adenine-containing α-aminophosphonates derivatives **2** based on the three component condensation reactions of adenine with triphenyl phosphite and aldehydes **1** in the presence of acetic acid and xylene (**Scheme-I**).




**Scheme-I**

## EXPERIMENTAL

All melting points were determined on a Yanaco apparatus and they are uncorrected. NMR spectra were measured on a Brucker 400 NMR instrument in $D_2O$ + NaOH and chemical shifts are expressed as units, TMS being used as an internal standard for $^1H$ NMR, $^{13}C$ NMR and 85 % $H_3PO_4$ was used as an external standard for $^{31}P$ NMR spectroscopy. IR spectra were determined as KBr pellets on Avatar360 FT-IR spectrophotometer. Elemental analysis was carried out with a Yanaco Chncorder MT-3 analyzer.

**General procedure for the synthesis of the product (2a-g):** The mixture of adenine (2 mmol), aldehyde **1** (2 mmol) and triphenyl phosphite (2 mmol) in acetic acid (2 mL) and xylene (6 mL) was heated under reflux for 8-18 h. After

completion of the reaction, as indicated by TLC, a white precipitate was formed, collected by filtration and recrystallized from a mixture of DMSO to give pure products **2**.

**(9*H*-Purin-6-ylamino)(phenyl)methylphosphonic acid (2a):** White powder; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3433, 3238, 3016, 2899, 2631, 2536, 1643, 1613, 1408, 1130, 1075, 939; $^1H$ NMR (400 MHz, $D_2O$ + NaOH): δ 7.95(1H, s, H-2), 7.73 (1H, s, H-8), 7.45 (2H, d, $J_{HH}$ = 8 Hz, ArH), 7.25 (2H, t, $J_{HH}$ = 7.6 Hz, ArH), 7.16 (1H, t, $J_{HH}$ = 7.2 Hz, ArH), 5.13 (1H, d, $J_{PH}$ = 20.4 Hz, CHP); $^{13}C$ NMR (100 MHz, $D_2O$ + NaOH): δ 152.6, 152.1, 150.9, 141.2, 140.6, 127.4, 126.5, 126.4, 115.3, 55.3 (d, $J_{PC}$ = 124 Hz); $^{31}P$ NMR: δ 14.35. Anal. calcd. (%) for $C_{12}H_{12}N_5O_3P$: C, 47.22; H, 3.96; N, 22.94. Found (%): C, 47.08; H, 3.87; N, 22.98.

**(9*H*-Purin-6-ylamino)(4-methoxyphenyl)methyl phosphonic acid (2b):** White powder; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3429, 3238, 3012, 2926, 2632, 2537, 1647, 1613, 1517, 1142, 1074, 943; $^1H$ NMR (400 MHz, $D_2O$ + NaOH): δ 7.89(1H, s, H-2), 7.84 (1H, s, H-8), 7.33 (2H, d, $J_{HH}$ = 7.2 Hz, ArH), 6.80 (2H, d, $J_{HH}$ = 8.4 Hz, ArH), 5.01 (1H, d, $J_{PH}$ = 20 Hz, CHP), 3.66 (1H, s, $C_6H_5OCH_3$); $^{13}C$ NMR (100 MHz, $D_2O$ + NaOH): δ 158.3, 157.3, 153.6, 152.1, 149.9, 134.3, 128.5, 120.5, 113.6, 54.9 (d, $J_{PC}$ = 127 Hz), 23.4; $^{31}P$ NMR: δ 14.65. Anal. calcd. (%) for $C_{13}H_{14}N_5O_4P$: C, 46.57; H, 4.21; N, 20.89. Found (%): C, 46.41; H, 4.15; N, 20.98.

**(9*H*-Purin-6-ylamino)(*p*-tolyl)methylphosphonic acid (2c):** White powder; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3233, 3014, 2894, 2629, 2536, 1643, 1612, 1142, 1074, 945; $^1H$ NMR (400 MHz, $D_2O$ + NaOH): δ 7.89 (1H, s, H-2), 7.85 (1H, s, H-8), 7.29 (2H, d, $J_{HH}$ = 6.8 Hz, ArH), 7.03(2H, d, $J_{HH}$ = 8 Hz, ArH), 5.03 (1H, d, $J_{PH}$ = 20.4 Hz, CHP), 2.16 (1H, s, $CH_3$); $^{13}C$ NMR (100 MHz, $D_2O$ + NaOH): δ 153.6, 151.5, 150.1, 138.4, 136.1, 133, 128.6, 127.3, 120.2, 55.2 (d, $J_{PC}$ = 130 Hz), 20.1; $^{31}P$ NMR: δ 14.58; anal. calcd. (%) for $C_{13}H_{14}N_5O_3P$: C, 48.91; H, 4.42; N, 21.94. Found (%): C, 49.07; H, 4.36; N, 22.02.

**(9*H*-Purin-6-ylamino)methylphosphonic acid (2d):** White powder; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3439, 2531, 1662, 1601, 1169, 1131, 1050, 877, 845, 514, 472; $^1H$ NMR (400 MHz, $D_2O$ + NaOH): δ 7.72(1H, s, H-2), 7.59 (1H, s, H-8), 3.42 (2H, d, $J_{PH}$ = 12.4 Hz, $CH_2P$); $^{13}C$ NMR (100 MHz, $D_2O$ + NaOH): δ 151.6, 151.3, 150.8, 140.6, 113.4, 39.1 (d, $J_{PC}$ = 137 Hz); $^{31}P$ NMR: 14.57. Anal. calcd. (%) for $C_6H_8N_5O_3P$: C, 31.45; H, 3.52; N, 30.56. Found (%): C, 31.62; H, 3.42; N, 30.64.

**1-(9*H*-Purin-6-ylamino)-3-methylbutylphosphonic acid (2e):** White powder; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3431, 3237, 3017, 2930, 2633, 2529, 1660, 1617, 1129, 1072, 945; $^1H$ NMR (400 MHz, $D_2O$ + NaOH): δ 7.93 (1H, s, H-2), 7.78 (1H, s, H-8), 4.18-4.35 (1H, m, $J_{PH}$ = 17 Hz, CHP), 1.53-1.65 (2H, m, $CH_2$), 1.34-1.44 (1H, m, $(CH_3)_2CH$), 0.69 (6H, d, $J_{HH}$ = 15.2 Hz, $(CH_3)_2CH$); $^{13}C$ NMR (100 MHz, $D_2O$ + NaOH): δ 153.8, 152.9, 151.1, 145.2, 117.8, 48.5 (d, $J_{PC}$ = 138 Hz), 40.9, 23.1, 21.1; $^{31}P$ NMR: 18.28; anal. calcd. (%) for $C_{10}H_{16}N_5O_3P$: C, 42.11; H, 5.65; N, 24.55. Found (%): C, 42.03; H, 5.59; N, 24.57.

**1-(9*H*-Purin-6-ylamino)butylphosphonic acid (2f):** White powder; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3438, 3275, 3138, 3102, 2777, 1687, 1623, 1256, 1046, 877, 612; $^1H$ NMR (400 MHz, $D_2O$ + NaOH): δ 8.11(1H, s, H-2), 7.91 (1H, s, H-8), 4.23-4.38 (1H, m, $J_{PH}$ = 15 Hz, CHP), 1.48-1.61 (2H, m, $CH_2$), 1.26-1.46 (2H, m, $CH_3CH_2$), 0.88 (3H, t, $J_{HH}$ = 3.7 Hz, $CH_3$); $^{13}C$ NMR (100 MHz, $D_2O$ + NaOH): δ 154.5, 152.9, 150.1, 138.5, 119.8, 50.3 (d, $J_{PC}$ = 148 Hz), 34.7, 19.6, 13.7; $^{31}P$ NMR: 17.21. Anal. calcd. (%) for $C_9H_{14}N_5O_3P$: C, 39.86; H, 5.20; N, 25.82. Found (%): C, 39.69; H, 5.33; N, 25.75.

**(E)-1-(9*H*-Purin-6-ylamino)-3-phenylallyphosphonic acid (2g):** White powder; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3430, 3243, 3014, 2924, 2631, 2526, 1658, 1608, 1135, 1071, 935; $^1H$ NMR (400 MHz, $D_2O$ + NaOH): δ 8.02 (1H, s, H-2), 7.89 (1H, s, H-8), 7.32 (2H, d, $J_{HH}$ = 7.6 Hz, ArH), 7.23 (2H, t, $J_{HH}$ = 14 Hz, ArH), 7.13 (1H, t, $J_{HH}$ = 4.8 Hz, ArH), 6.59 (1H, dt, $J_{HH}$ = 16 Hz, $C_6H_5CH$), 6.38 (1H, dd, $J_{HH}$ = 2.4 Hz, $C_6H_5CHCH$), 4.82 (1H, d, $J_{PH}$ = 24 Hz, CHP); $^{13}C$ NMR (100 MHz, $D_2O$ + NaOH): δ 153.8, 151.4, 150.1, 137.6, 129.6, 128.9, 127.2, 126.3, 125.4, 122.4, 119.8, 53.7 (d, $J_{PC}$ = 133 Hz); $^{31}P$ NMR: 14.24. Anal. calcd. (%) for $C_{14}H_{14}N_5O_3P$: C, 50.76; H, 4.26; N, 21.14. Found (%): C, 50.65; H, 4.21; N, 21.18.

## RESULTS AND DISCUSSION

It is noted that after the condensation reactions of adenine with triphenyl phosphite and different substituents on aldehyde, such as 4-$MeOC_6H_4$, Ph, $(CH_3)_2CHCH_2$, 4-$MeC_6H_4$, in the acetic acid and xylene under reflux for 8-18 h, a white precipitate was formed, then collected by filtration and recrystallized from dimethyl sulfoxide. The products **2** were obtained in moderate yields. The experimental results are summarized in Table-1. However, aldehyde carrying electron-withdrawing substituents did not occur at all. In addition, the reaction was performed using adenine, trimethyl phosphite and aldehydes **1**. The products **2** were obtained under the same conditions.

TABLE-1
SYNTHESIS OF THE PRODUCT (**2a-g**)

| Entry | R | Time (h) | Product | Yields (%) | m.p. (ºC) |
|---|---|---|---|---|---|
| 1 | Ph | 17 | **2a** | 50 | >300 |
| 2 | 4-$MeOC_6H_4$ | 17 | **2b** | 55 | >300 |
| 3 | 4-$MeC_6H_4$ | 17 | **2c** | 55 | >300 |
| 4 | H | 8 | **2d** | 51 | >300 |
| 5 | $(CH_3)_2CHCH_2$ | 8 | **2e** | 52 | >300 |
| 6 | $CH_3CH_2CH_2$ | 18 | **2f** | 48 | >300 |
| 7 | $C_6H_5CHCH$ | 17 | **2g** | 54 | >300 |

All the compounds **2** exhibited characteristic IR absorptions, indicating the existence of the NH (3400-3200 $cm^{-1}$), P=O (1300-1100 $cm^{-1}$) and O-H (3300-2500 $cm^{-1}$) groups. The $^{31}P$ NMR spectra of products **2** exhibited only one signal in the range of δ 14.21-18.28 depending on the elements present at phosphorus. In the $^1H$ NMR spectra of product **2**, the signal of CHP proton appears as doublet and multiple peak (δ = 3.42-5.13, $J_{PH}$ = 15-24 Hz) because of its coupling with phosphorus. The adenine proton (H-2, H-8) showed respectively a singlet at δ 7.72-8.11. In the $^{13}C$ NMR spectra of compounds **2**, the C-P carbon resonated as a doublet at δ 39.1-55.3 (d, $J_{PC}$ = 130-148 Hz) due to coupling with phosphorus. However, the

sign of ester groups weren't appeared by the IR, NMR spectral data, which was suggested that the products **2** may be made acid hydrolysis from α-aminophosphonates under the acetic acid and xylene reaction conditions.

## Conclusion

A convenient and facile one-pot synthesis of α-aminophosphonic acids containing adenine *via* the three component condensation reaction is described with the advantages of mild conditions, simple operation and moderate yields. The product structures were characterized by IR and NMR spectral data and elemental analyses.

## ACKNOWLEDGEMENTS

This work was financially supported by the Education Department of Hainan Province (hjkj200738).

## REFERENCES

1. I.A. Natchev, *Liebigs Ann. Chem*., 861 (1988).
2. J. Emsley and D. Hall, The Chemistry of Phosphorus, Harper and Row, London, p. 494 (1976).
3. L. Maier and H. Spörri, *Phosphorus, Sulfur, Silicon Rel. Elem*., **61**, 69 (1991).
4. P. Kafarski and B. Lejczak, *Phosphorus, Sulfur, Silicon Rel. Elem*., **63**, 1993 (1991).
5. (a) M.C. Allen, W. Fuhrer, B. Tuck, R. Wade and J.M. Wood, *J. Med. Chem*., **32**, 1652 (1989); (b) E.W. Logusch, D.M. Walker, J.F. McDonald, G.C. Leo and J.E. Franz, *J. Org. Chem*., **53**, 4069 (1988); (c) P.P. Giannousis and P.A. Bartlett, *J. Med. Chem*., **30**, 1603 (1987).
6. J. Huang and R. Chen, *Heteroatom Chem*., **11**, 480 (2000).
7. (a) R. Hirschmann, A.B. Smith III, C.M. Taylor and S.J. Benkovic, *Science*, **265**, 234 (1994); (b) A.B. Smith III, C.M. Taylor, S.J. Benkovic and R. Hirschmann, *Tetrahedron Lett*., **35**, 6853 (1994).
8. C. Ballatre and E. De Clercq, *Bioorg. Med. Chem. Lett*., **11**, 1053 (2001).
9. L. Jeffery, J.H. Kim and D.F. Wiemer, *Tetrahedron*, **56**, 5077 (2000).
10. H.P. Guan, Y.L. Qiu, M.B. Ksebati, E.R. Kern and J. Zemlicka, *Tetrahedron*, **58**, 6047 (2002).
11. O.H. Ko and J.H. Hong, *Tetrahedon Lett*., **43**, 6399 (2002).
12. R.S. Shatila and K.H. Bouhadir, *Tetrahedon Lett*., **47**, 1767 (2006).
13. E. Ichikawa, S. Yamamura and K. Kato, *Tetrahedon Lett*., **40**, 7385 (1999).
14. E. De Clercq, *J. Clin. Virol*., **22**, 73 (2001).
15. M. Bayes, X. Rabasseda and J.R. Prous, *Methods Find. Exp. Clin. Pharmacol*., **25**, 53 (2003).
16. Z. Suo and K.A. Johnson, *J. Biol. Chem*., **273**, 27250 (1998).
17. Z.G. Li and R.Q. Huang, *Chin. J. Synth. Chem*., **8**, 130 (2000).
18. Y.G. Wang and B.X. Lu, *J. Org. Chem*., **22**, 862 (2002).
19. W.X. Long and K.S. Zhang, *Chem. J. Chin. Univ*., **17**, 1247 (1996).
20. S.M. Lu and R.Y. Chen, *Heteroatom Chem*., **11**, 317 (2000).