INTERNATIONAL JOURNAL FOR INNOVATIVE RESEARCH IN MULTIDISCIPLINARY FIELD ISSN: 2455-0620 Special Issue - 21, Jan – 2021
Monthly, Peer-Reviewed, Refereed, Indexed Journal with IC Value: 86.87 Impact Factor: 6.719 Publication Date: 31/01/2021

Dimethylaminopyridine catalyzed one pot synthesis of α-aminophosphonates from 2-chloroquinoline-3-carbaldehydes

Rajkumar U. Pokalwar
Departmet of Chemistry,Degloor College, Degloor, Nanded- 431717 (M.S.) India.
Email - rajupokalwar@rediffmail.com

ABSTRACT:
A simple one pot and high yielding method was developed for the synthesis of α-aminophosphonates from 2-chloroquinoline-3-carbaldehyde, aniline and triethylphosphite in the presence of Dimethylaminopyridine (DMAP) as catalyst. All the synthesized compounds were characterized by IR, ^{1}HNMR and Mass spectroscopy.
KEY WORDS: *2-chloroquinoline-3-carbaldehyde, aniline, triethylphosphite and DMAP.*

1. INTRODUCTION:

Quinoline ring systems represent a major class of heterocyclic compounds in which benzene ring is fused with pyridine heterocyclic ring system. Quinolines are known also as benzo[*b*]pyridine and 1-azanaphthalene with one nitrogen atom in one benzene ring and none in the other ring or at the ring junction. Heterocycles containing a nitrogen atom possess high and interesting medicinal and pharmaceutical properties.(1–4) Montelukast is a drug used as an antiasthma agent.(5) In addition, quinolines are the main core of many types of natural products,(6,7) drugs,(8–10) and were found in many synthetic heterocyclic compounds in order to enhance the biological and medicinal properties. Compounds incorporating quinoline ring system exhibited various biological,(11,12) and pharmaceutical activities *e.g.* anti-tuberculosis,(13) antiplasmodial,(14) antibacterial,(15,16) antihistamine,(17) antifungal,(18) antimalarial,(19,20) anti-HIV,(21) anticancer,(22) anti-infammatory,(23,24) anti-hypertensive,(25) and antioxidant activities.(26) In addition, the use of quinolines as tyro kinase PDGF-RTK inhibitor,(27) inositol 5^0-phosphatase (SH_2),(28) DNA gyrase B inhibitors as *Mycobacterium tuberculosis*,(29) and DNA topoisomerase inhibitors,(30) were reported.

Generally, α-aminophosphonates are prepared in the presence of Lewis acids or bases by the addition of phosphorous nucleophiles to the imines. Lewis acids such as $SnCl_4$, $SnCl_2$, $ZrCl_4$, $ZnCl_2$ and $MgBr_2$ have been used as catalysts for such reactions.(31-33) Recently, Lewis and Bronsted acids such as $LiClO_4$,(34) $InCl_3$,(35) lanthanide triflates,(36) $TaCl_5$-SiO_2,(37) montmorillonite clay-MW,(38) Al_2O_3- MW,(39) CF_3COOH(40) were found to be effective in the preparation of α-aminophosphonates. However, many of these procedures require expensive reagents, long reaction times and suffer from poor yields. These reactions cannot be carried out in one-step by the reaction between a carbonyl compounds, amine and dialkylphosphite.(41) 4-(Dimethylamino)pyridine (DMAP) is a catalyst of outstanding utility in a variety of group-transfer reactions, such as the acylation of alcohols and amines.(42-46) Despite the frequent use of DMAP itself and the recent development of chiral DMAP derivatives for applications in stereoselective catalysis,(47-54) the mechanisms of even the most simple DMAP-catalyzed reactions, such as the acetylation of alcohols with acetic anhydride, have not yet been studied in detail. A recent review of the mechanistic characteristics of this reaction highlighted the importance of the deprotonation step as well as the influence of the auxiliary base on the catalytic activity of DMAP.(44) Hence we were interested in the synthesis of α-aminophosphonates using DMAP as versatile catalyst, In the Search of better reaction condition for the synthesis of α-aminophosphonates using 2-chloroquinoline-3-carbaldehyde, we have developed a solvent-free reaction condition with excellent yield using DMAP catalyst at room temperature.

2. MATERIALS & METHOD:

2-Chloroquinoline-3-carbaldehydes were prepared in the laboratory by the reported procedure and were purified by column chromatography over silica gel (60–120 mesh). 3-fluoroaniline, 2-methylaniline, triethylphosphite, DMAP were procured from Lancaster. All melting points were determined in open capillaries on Kumar's melting point apparatus. 1H NMR spectra were recorded on Mercury Plus Varian in $CDCl_3$ at 400 MHz using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FTIR using KBr discs. Mass spectra were recorded on Micromass Quatrro II using electrospray Ionization technique, showing (m+1) peak as a base peak. The test for the purity of products and the progress of the reactions were accomplished by TLC on Merck silica gel plates.

EXPERIMENTAL PROCEDURE:

2a) Diethyl (3-fluorophenylamino)(2-chloroquinolin-3-yl)methylphosphonate:

To a mixture of 2-Chloroquinoline-3-carbaldehyde (0.95 g, 5 mmol), 3-fluoroaniline (0.65 g, 6 mmol) and triethylphosphite (1.66 g, 10 mmol) was added DMAP in catalytic amount. The progress of the reaction was monitored on TLC using Hexane: Ethyl acetate (8:2) as the solvent system. After the completion of the reaction, poured ice cold water in the reaction mass to get the solid product. Filtered the solid and washed with water and dried in oven at 50 ^{0}C for 8.0 h (dry wt. 1.90 g, yield 91%).

Dr. Anil Chidrawar
I/C Principal
A.V. Education Society's
Degloor College, Degloor Dist.Nanded

3. RESULTS & DISCUSSION:

In continuation of our work related to phosphorus chemistry,(55-60) we were earlier synthesized α-aminophosphonates using quinoline moiety in two steps. In the first step, imines of 2-chloroquinoline-3-carbaldehyde were synthesized from 2-chloroquinoline-3-carbaldehyde and aniline then converted to α-aminophosphonates using TMSCl and triethylphosphite in the next step. Now we were synthesized α-aminophosphonates from 2-chloroquinoline-3-carbaldehyde and aniline using triethylphosphite in the presence of DMAP as catalyst (Scheme -1, Table-1). All the compounds were synthesized using this methodology in excellent yields. All the compounds synthesized were unequivocally characterized based on analytical data.

4. ANALYSIS:

2a) Diethyl (3-fluorophenylamino)(2-chloroquinolin-3- yl)methylphosphonate:

IR (KBr): 3311 cm^{-1} (-NH); 1234 cm^{-1} (P = O); 1032 cm^{-1}(P- O - C)

1H NMR (CDCl3, δ ppm): 1.05 (t, 3H, O-CH_2-CH_3) ;1.35 (t, 3H, O-CH_2-CH_3); 3.7 (m, 1H, O-CH_2-CH_3); 3.9 (m, 1H, O-CH_2-CH_3); 4.2 (m, 2H, O-CH_2-CH_3); 5.4 (d, 1H, -NH-CH-P= O); 6.3–6.5 (m, 3H, Ph-H,C_2,C_4,C_6); 7.0 (dd, 1H, Ph-H,C_5); 7.5 (t, 1H, Quinolin-H,C_5); 7.69 (t, 1H, Quinolin-H,C_6); 7.75 (d,1H, Quinolin-H,C_7); 7.99 (d, 1H, Quinolin-H,C_8); 8.34 (d, 1H, Quinolin-H,C_4).

ES-MS: m/z 423.1 (m+1) and 425.1 (m+3).

2b) Diethyl (3-fluorophenylamino)(2-chloro6-methylquinolin-3-yl)methylphosphonate:

IR (KBr): 3305 cm^{-1} (-NH); 1230 cm^{-1} (P = O); 1022 cm^{-1}(P-O-C)

1H NMR (CDCl3, δ ppm): 1.05 (t, 3H, O-CH_2-CH_3); 1.38 (t, 3H, O-CH_2-CH_3); 2.48 (s, 3H, Quinolin-CH_3); 3.68 (m, 1H, O-CH_2-CH_3); 3.88 (m, 1H, O-CH_2-CH_3); 4.22 (m, 2H, O-CH_2-CH_3); 5.16 (s, 1H, -CH-NH-Ph); 5.35(d, 1H, -NH-CH-P=O); 6.28–6.42 (m, 3H, Ph-H,C_2,C_4,C_6); 7.02 (dd, 1H, Ph-H,C_5); 7.5 (d, 1H, Quinolin-H, C_7);7.6 (s, 1H, Quinolin-H,C_5); 7.9 (d,1H, Quinolin-H,C_8); 8.3 (d, 1H,Quinolin-H,C_4).

ES-MS: m/z 437.1 (m+1) and 439.2 (m+3).

Figures/ Tables.

Scheme-1: DMAP Facilitated Synthesis of α-Aminophosphonates

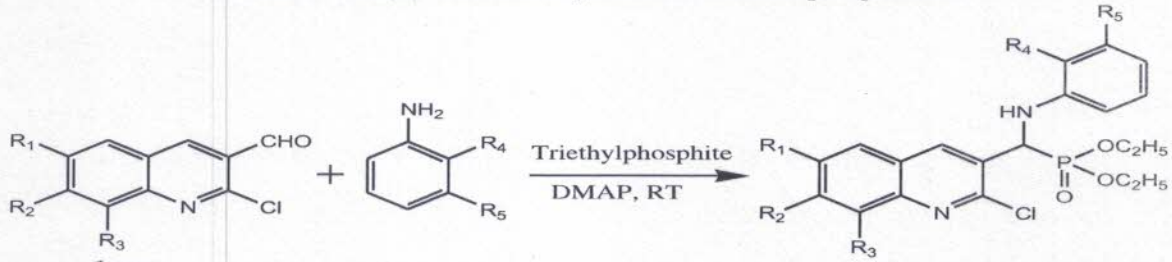

Table-1: DMAP Facilitated Synthesis of α-Aminophosphonates

Entry	R_1	R_2	R_3	R_4	R_5	Reaction Time min	Yield %	M.P. °C
2a	H	H	H	H	F	40	91	146–148
2b	CH_3	H	H	H	F	45	92	136–138
2c	H	CH_3	H	H	F	40	94	163–165
2d	H	H	CH_3	H	F	40	92	113–115
2e	OCH_3	H	H	H	F	45	91	153–155
2f	H	OCH_3	H	H	F	45	94	155–157
2g	OC_2H_5	H	H	H	F	40	92	160–162
2h	H	H	C_2H_5	H	F	40	90	159–161
2i	H	H	H	CH_3	H	45	91	139–141
2j	CH3	H	H	CH_3	H	40	92	104–106
2k	H	CH3	H	CH_3	H	45	90	143–145
2l	H	H	CH3	CH_3	H	40	92	160–162
2m	OCH3	H	H	CH_3	H	40	91	98–100
2n	H	OCH3	H	CH_3	H	45	92	126–128
2o	OC_2H_5	H	H	CH_3	H	40	91	146–148
2p	H	H	C_2H_5	CH_3	H	40	90	133–135

5. CONCLUSION:

In conclusion, a new methodology was developed for the synthesis of new α-aminophosphonate derivatives from 2-chloroquinoline-3-carbaldehydes and aniline using triethylphosphite and DMAP as catalyst. All the reactions were performed under mild reaction conditions, shorter reaction time and in quantitative yields (Table-I). The methodology developed will be of much use to combinatorial chemist.

Acknowledgement:
The authors are thankful to the IICT Hyderabad for providing mass, NMR analysis and also thankful to Degloor College, Degloor for providing laboratory facilities.

REFERENCES:

1. Nammalwar B. and Bunce R. A., *Molecules*, (2014), *19*, 204–232.
2. Mphahlele M. J. and Adeloye A. O. *Molecules*, (2013), **18**, 15769–15787.
3. Al-Shaalan N. H., *Molecules*, (2007), *12*, 1080–1091.
4. Afzal O., Bawa S., Kumar S. and Tonk R. K., *Molbank*, (2012), 748.
5. Jaware J. and Borhade S., Indo Am. *J. Pharm. Res.*, (2014), *4(5)*, 2496–2502.
6. Michael J. P., *Nat. Prod. Rep.*, (2004), 650–668.
7. Michael J. P., *Nat. Prod. Rep.*, (2003), 476–493.
8. Alhaider A. A., Abdelkader M. A. and Lien E. J., *J. Med. Chem.*, (1985), *28*, 1394–1398.
9. Campbell S. F., Hardstone J. D. and Palmer M. J., *J. Med. Chem.*, (1988), *31*, 1031–1035.
10. Wu D., *Tetrahedron*, (2003), *59*, 8649–8687.
11. Subhashini N. J. P., Amanaganti J., Boddu L. and Nagarjuna P. A., *J. Chem. Pharm. Res.*, (2013), *5(1)*, 140–147.
12. Gao W., Liu J., Jiang Y. and Li Y., Beilstein *J. Org. Chem.*, (2011), *7*, 210–217.
13. Keri R. S. and Patil S. A., Biomed. Pharmacother, (2014), *68*, 1161–1175.
14. Vandekerckhove S., Herreweghe S. V., Willems J., Danneels B. Desmet., T., de Kock C., Smith P. J., Chibale K. and D'hooghe M., Eur. *J. Med. Chem.*, (2015), *92*, 91–102.
15. Desai N. C., Kotadiya G. M. and Trivedi A. R., Bioorg. *Med. Chem. Lett.*, (2014), *24*, 3126–3130.
16. Vlahov R., Parushev J., Nickel P. and Snatzke G., *J. Pure Appl. Chem. Res.*, (1990), *7*, 1303–1306.
17. Srivastava A., Singh M. K. and Singh R. M., *Indian J. Chem.*, (2005), *45B*, 292–296.
18. Pramilla S., Garg S. P. and Nautiyal S. R., *Indian J. Heterocycl. Chem.*, (1998), *7*, 201–204.
19. Vandekerckhove S. and D'hooghe M., Bioorg. *Med. Chem.*, (2015), *23*, 5098–5119.
20. Lyon M. A., Lawrence S., William D. J. and Jackson Y. *A., J. Chem. Soc., Perkin Trans.* 1, (1999), 437–442.
21. Ahmed N., Brahmbhatt K. G., Sabde S., Mitra D., Singh I. P. and Bhutani K. K., Bioorg. *Med. Chem.*, (2010), *18*, 2872–2879.
22. Spano V., Parrino B., Carbone A., Montalbano A., Salvador, Brun P., Vedaldi D., Diana P., Cirrincione G. and Barraja P., *Eur. J. Med. Chem.*, (2015), *102*, 334–351.
23. El-Feky S. A., Abd El-Samii Z. K., Osman N. A., Lashine J., Kamel M. A. and Kh. Thabet H., *Bioorg. Chem.*, (201), *58*, 104–116.
24. Kerry M. A., Boyd G. W., Mackay S. P., Meth-cohn O. and Platt L., J. *Chem. Soc., Perkin Trans.* 1, (1999), 2315.
25. Heinz H. P., Milhahn H. C. and Eckart E., *J. Med. Chem.*, (1999), *42*, 659–668.
26. Vivekanand B., Raj K. M. and Mruthyunjaya Swamy B. H. M., *J. Mol. Struct.*, (2015), *1079*, 214–224.
27. Maguire M. P., Sheets K. R., McVety K., Spada A. P. and Zilberstein A., *J. Med. Chem.*, (1994), *37*, 2129–2137.
28. Russo C. M., Adhikari A. A., Wallach D. R., Fernandes S., Balch N., Kerr W. G. and Chisholm J. D., *Bioorg. Med. Chem. Lett.*, (2015), *25*, 5344–5348.
29. Medapi B., Renuka J., Saxena S., Sridevi J. P., Medishetti R., Kulkarni P., Yogeeswari P. and Sriram D., *Bioorg. Med. Chem.*, (2015), *23*, 2062–2078.
30. Spicer J. A., Gamage S. A., Finlay G. J. and Denny W. A., *J. Med. Chem.*, (1997), *42*, 2383–2393.
31. Kudzin Z. H., Lyzwa P., Luczak J., and Andrijewski G., *Synthesis*, (1997), 44.
32. Yadav J. S. and Reddy B. V. S., Sarita Raj K., Bhaskar Reddy K., and Prasad A. R., *Synthesis* (2001), 2277.
33. Lee S. G., Park J. H., Kang J., and Lee J. K., *Chem. Commun.*, (2001),1698.
34. Saidi M. R. and Azizi N., *Synlett*, (2002), 1347.
35. Ranu B. C., Hajra A., and Jana U., *Org. Lett.*, (1999), *1*, 1141.
36. Qian C., and Huang T., *J. Org. Chem.*, (1998), *63*, 4125.
37. Chandrasekher S., Prakash S.J., Jagadeshwar V. and Narsihmulu C., *Tetrahedron Lett.*, (2001), *42*, 5561.
38. Yadav J. S., Reddy B. V. S., and Madan C., *Synlett*, (2001), 1131.
39. Kaboudin B. and Nazari R., *Tetrahedron Lett.*, (2001), *42*, 8211.
40. Akiyama T., Sanada M., and Fuchibe K., Synlett, (2003), 1463.

41. Zon J., Pol. *J. Chem.* (1981), *55*,643.
42. Hofle G., Steglich W., *Synthesis* (1972), 619.
43. Litvinenko L. M., Kirichenko A. I., Dokl. Akad. Nauk SSSR (1967), *176*, 97.
44. a) Berry D. J., Digiovanna C. V., Metrick S. S., Murugan R., Arkivoc (2001), 201 ; b) Spivey A. C., Arseniyadis S., Angew. *Chem. (2004)*, *116*, 5552.
45. Heinrich M. R., Klisa H. S., Mayr H., Steglich W., Zipse H., Angew. *Chem.* (2003), *115*, 4975.
46. Hassner A., Krepski L. R., Alexanian V., T*etrahedro*n (1978), *34*, 2069.
47. a) Fu G. C., Acc. Chem. Res. (2004), *37*, 542–547 ; b) Dalko P. I., Moisan L., Angew. *Chem. (2004), 116*, 5248.
48. Tabanella S., Valancogne I., Jackson R. F. W., *Org. Biomol. Chem.* (2003), *1*, 4254.
49. Jeong K. S., Kim S. H., Park H. J., Chang K. J., Kim K. S., *Chem. Lett.* (2002), 1114.
50. a) Kawabata T., Yamamoto K., Momose Y., Yoshida H., Nagaoka Y., Fuji K., *Chem. Commun.* (2001), 2700; b) T. Kawabata, R. Stragies, T. Fukaya, Y. Nagaoka, H. Schedel, K. Fuji, Tetrahedron Lett. (2003), *44*, 1545.
51. Shaw S. A., Aleman P., Vedejs E., *J. Am. Chem.* Soc. (2003), *125*, 13368.
52. a) Mermerian A. H., Fu G. C., Angew. Chem. (2005), *117*, 971. b) Wilson J. E., Fu G. C., Angew. *Chem.* (2004), *116*, 6518.
53. a) Spivey A. C., Fekner T., Spey S. E., Adams H., J. Org. Chem. (1999), *64*, 9430. b) Spivey A. C., Leese D. P., Zhu F., Davey S. G., Jarvest R. L., *Tetrahedron* (2004), *60*, 4513.
54. Priem G., Pelotier B., Macdonald S. J. F., Anson M. S., Campbell I. B., *J. Org. Chem.* (2003), *68*, 3844.
55. Pokalwar R.U., Hangarge R.V., Maske P.V., Shingare M.S., *Arkivoc (2006), xi* 196.
56. Pokalwar R.U., Hangarge R.V., Madje B.R., Ware M.N., Shingare M.S., Phosphorus, Sulfur, Silicon *Relat. Elem.* (2008), *183*, 1461.
57. Pokalwar R.U., Hangarge R.V., Kategaonkar A. H., Shingare M.S., *Russian Journal of Organic Chemistry*, (2009), *45*, *3*, 430.
58. Pokalwar R.U., Sadaphal S. A., Kategaonkar A. H., Shingare M.S., *Green Chemistry letters and reviews* (2010), 1-6.
59. Pokalwar R.U., Shinde P.V., Chidrawar A. B., Shingare M. S., *Chemistry and biology interface* (2012), *2, 1,* 31.
60. Pokalwar R.U., Chidrawar A. B., *Chemistry and biology interface* (2013), *3, 5,* 339.

Dr. Anil Chidrawar
I/C Principal
A.V. Education Society's
Degloor College, Degloor Dist.Nanded