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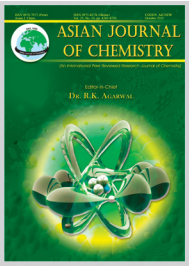

NOTE

Synthesis of ω-Phthalimidoalkylphosphonates

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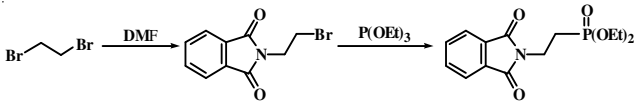
A series of carbon chain growing ω-phthalimidoalkylphosphonates was prepared from simple and easy available raw materials by two-step reaction. The yields can reach 58 %-64 %. Their structures are confirmed by ^{1}H NMR correctly.

Key Words: ω-Phthalimidoalkylphosphonates, Synthesis, New Method.

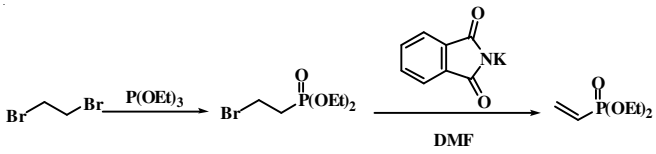
Investigations established that 2-aminoethylphosphonic acid (2-AEP) is a constituent of lipids, named as phosphonolipids by analogy with phospholipids[1]. This compound has been found in protozoa, flagellates, coelenterates, mollusks, the lower fungi and even in man[2]. Since the first isolation of 2-aminoethylphosphonic acid from several organisms and human beings, aminophosphonic acids and their peptide derivatives have been extensively studied due to their biological activities[3-5]. For example, 2-aminoethylphosphonic acid was found to be a constituent of proteins and polysaccharides, phosphonodipeptides and phosphooligopeptides often act as an inhibitor of esterases, peptidases and related enzymes and metalloenzymes. Some of them based on L- and D-1-AEP and aminomethylphosphonic acid (Alaphosphin) inhibit the growth of various types of pathogenic bacteria[6,7].

So to synthesize aminophosphonic acids which possess biological activity, several synthetic methods for aminophosphonic acid esters have been reported[8]. Aminophosphonic acids can be obtained by hydrolysis of their esters. For example, diethyl phthalimido-ethylphosphonate was synthesized by the Michaelis-Arbuzov reaction of *N*-(2-bromoethyl)phthalimide with triethyl phosphate[9,10] as shown in **Scheme-I**.



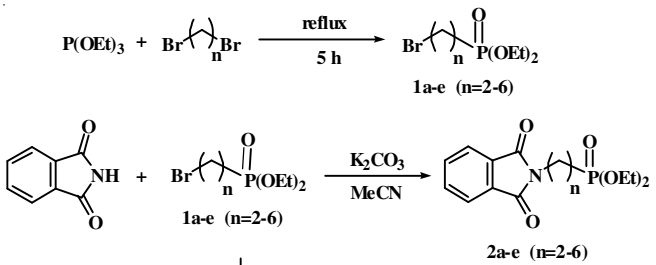
Scheme-I

When the route of synthesis was changed, potassium phthalimide reacted with 2-bromoethyphosphonate. A target product (diethyl phthalimidoethylphosphonate) has not been obtained, but hydrogen bromine elimination[2] reactions occurred as shown in **Scheme-II**.



Scheme-II

In this work, the reactants and solvent had been change a little that led to the formation of target product successfully. A series of carbon chain growing ω-phthalimidoalkylphosphonates was prepared by a similar method which gave good yields (**Scheme-III**).



	n	Yield*(%)
2a	2	64
2b	3	62
2c	4	59
2d	5	58
2e	6	60

*Isolated yields

Scheme-III

Silica gel (200-300 mesh) for column chromatography was purchased from the Qingdao Marine Chemical Factory in China and the distillation range of petroleum ether is 60-90 ºC. Phthalimide was purchased from Alfa Aesar. Other commercially available chemicals were laboratory-grade reagents from local suppliers. NMR spectra were recorded on Bruker AV-300 or Varian Mercury Plus 300 spectrometer in $CDCl_3$.

Preparation of diethyl ω-bromoalkylphosphonates 1a-e: In the dried three-necked flask (250 mL) was charged ω-alkane dibromide (n = 2-6) (237 mmol) and followed by dropwise addition of triethyl phosphate (13.11 g, 79 mmol) refluxed for 5 h with the tracking of TLC. The reaction mixture was chromatographed on a silica gel column eluted with petroleum ether (60-90 ºC)/ethyl acetate (10:1 in volume) to give diethyl ω-bromoalkylphosphonates[11] **1a-e**.

Preparation of ω-phthalimidoalkylphosphonates 2a-e: In the dried three-necked flask (250 mL) was charged anhydrous K_2CO_3 (5.5 g, 40 mmol) and phthalimide (5.88 g, 40 mmol), flushed three times with nitrogen at room temperature, added dropwise 100 mL acetonitrile solution of ω-bromoalkylphosphonates (n = 2-6) (40 mmol) then refluxed for 48 h with the tracking of TLC. The reaction mixture was concentrated under reduced pressure. After removal of the solvent, the residue was diluted with $CHCl_3$ (100 mL) and then was washed with brine (30 mL × 3), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the pale yellow liquid. The crude product was purified by silica gel column chromatography using petroleum ether (60-90 ºC)/$CHCl_3$ (4:1 in volume) to give ω-phthalimidoalkylphospho-nates[12] **2a-e**.

Conclusion

Traditional method[13] is to use potassium phthalimide and dibromo alkanes as raw materials. Then the product reacted with triethyl phosphate using DMF as solvent. Because the boil point of DMF is very high, the solvent is not easy removed from the reaction mixture. Those procedures are involved tiresome work-up and complex purification for the product and with relatively low overall yields. The solvent acetonitrile in this article has a low boil point and can be removed under reduced pressure. The cost of phthalimide as one of the reagents in this article is much cheaper than that of potassium phthalimide which is mentioned in traditional method.

In conclusion, this article described a novel and mild method for the synthesis of ω-phthalimidoalkylphosphonates. The cheapness, easy availability of the reagents, mild reaction conditions and excellent yield of the products are the advantages that make this new method a useful addition to the existing methodologies.

All the products are known and characterized by ^1H NMR. CAS Registry Number: **2a**, 62514-90-3; **2b**, 107257-50-1; **2c**, 86791-02-8; **2d**, 145119-11-5; **2e**, 86552-92-3.

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