SYNTHESIS OF *N*, *N*-DIALKYL PHOSPHORAMIDIC DICHLORIDE FROM DIALKYL AMINE AND PHOSPHORYL CHLORIDE USING BASIC ANION EXCHANGE POLYMER RESINS/BEADS

Brijesh K. Kushwaha,[1] Hemendra K. Gupta,[2] C. P. Shinde*[1]

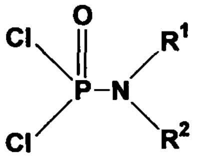
[1]*S. O. S. in Chemistry, Jiwaji University, Gwalior- 474 002, India*
[2]*Defence R & D Establishment, Jhansi Road, Gwalior-474002, India*
E-mail: cp_shinde01@rediffmail.com

Abstract- An efficient and operationally simple method is developed for the synthesis of *N, N*-dialkyl phosphoramidic dichloride from dialkyl amine and phosphoryl chloride using basic anion exchange polymer resins/beads. In the reaction, polymer resin acts as a scavenger for HCl produced as by-product and desired product is distilled under vacuum. Reaction afforded *N, N*-dialkyl phosphoramidic dichloride in 3-4 hours with excellent yields from corresponding dialkylamine and phosphoryl chloride.

Keywords- Nerve agents, phosphoramidic dichloride, solid support

Introduction- Nerve agents are extremely toxic chemical warfare agents (CWAs) that impair the conduction of nerve impulses by irreversibly reacting with the enzyme acetylcholinesterase in tissue fluid (1-2). The nerve agents are mainly of three types, namely *O*-alkyl alkylphosphonofluoridates (e.g. sarin), *O*-alkyl *N, N*-dialkyl phosphoramidocyanidates (e.g. tabun) and *O*-alkyl *S*-2-diisopropylaminoethyl alkylphosphonothiolates (e.g. VX); these have been reported to have been used in the recent past (3-8). The proliferation of CWAs is prohibited by an international treaty known as the Chemical Weapons Convention (CWC) that has been in force since April 1997 (9-10). The annex listing in the chemicals of the CWC consists of three schedules based on the toxicity, past use as CWAs, and commercial applicability of chemicals (9-11). The nerve agents sarin, tabun and VX and their analogues are placed respectively in schedules 1.A.1., 1.A.2., and 1.A.3. of the CWC (12-13).

The important synthones of nerve agents are *N, N*-dialkylphosphoramidic dihalides (Fig. 1), which are placed in the CWC as schedule 2.B.5. chemicals, respectively (9-10).



N, N-dialkylphosphoramidic Dichlorides (DAPCs)
$R^1 = CH_3, C_2H_5$, n-C_3H_7 and iso-C_3H_7
$R^2 = CH_3, C_2H_5$, n-C_3H_7 and iso-C_3H_7

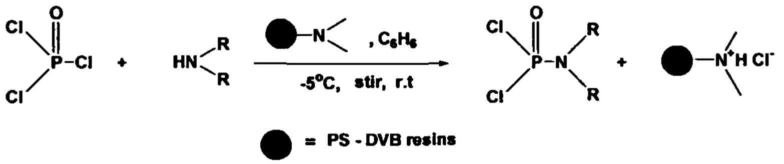
Figure 1. Synthones of nerve agents.

Since the CWC confines the alkyl groups in these dihalides to only methyl, ethyl, isopropyl and n-propyl, only those synthones that fall within the purview of the CWC were considered in this work. Since these compounds have been placed in the CWC text and are important synthones of nerve agents, they are extremely important from the synthesis viewpoint of the CWC.

Several methods (14-15) described in the literature for the preparation of *N, N*-dialkylphosphoramidic dihalides. Among these procedures, only a few can be considered as convenient laboratory methods for the synthesis of *N, N*-dialkylphosphoramidic dihalides. Most of these reported methods either use reagents or produce undesired by-products, which are difficult to remove from the moisture sensitive *N, N*-dialkylphosphoramidic dihalides, while others are time consuming, involve expensive and unstable reagents, and require harsh conditions. Prompted by these limitations of the aforesaid methods and our interest in exploring new synthetic routes of the synthesis of dialkylphosphoramidic dihalides we present herein an efficient route for their synthesis.

In recent years, the use of recyclable reagents (16-17) has received considerable interest in organic synthesis. This prompted us to explore the possibility of using the stable, nontoxic, recyclable, basic anion exchange polymer resins, *N, N*-dialkyl functionalised poly(styrene-co-divinyl benzene) beads.

The important aspect of this method is its simplicity and clean reaction condition. To a stirred and cooled (-5^{0}C) solution of an *N, N*-dialkylamine (0.1 mol) and *N, N*-dialkyl functionalised poly(styrene-co-divinyl benzene) beads (containing 0.1 mol of active base) in dry benzene, a solution of phosphorus oxychloride (0.1 mol) in dry benzene was added over a period of 1 h. The mixture was stirred at room temperature for 3-4 h in excellent yields (Scheme 1). After completion of the reaction the mixture was decanted off and solvent was removed by distillation. *N, N*-Dialkylphosphoramidic dichlorides were purified by distillation under vacuum. The yields and boiling points of the products are summarized in **Table 1**.



Scheme 1. *N, N*-Dialkylphosphoramidic dichlorides prepared from dialkylamine and phosphoryl chloride using the polystyrene divinylbenzene (PS-DVB) bound reagent.

It is interesting to note that these strongly basic anion exchange resins/beads called were recovered and reused several times after suitably treating by reported method (18) for the synthesis of different *N, N*-dialkyl phosphoramidic dichloride. Thus the added advantages of this method are simplest possible workup, room temperature reactions, and recyclability of the reagent.

Table 1. Boiling points under reduced pressure of *N, N*-dialkylphosphoramidic dichlorides

Entry	Compound	mmHg	bp(°C)
1.	*N, N*-dimethylphosphoramidic dichloride	21	90
2.	*N, N*-diethylphosphoramidic dichloride	2	76
3.	*N, N*-dipropylphosphoramidic dichloride	1	89
4	*N, N*-diisopropylphosphoramidic dichloride	1	86
5.	*N*-methyl-*N*-ethylphosphoramidic dichloride	1.5	82
6.	*N*-methyl-*N*-propylphosphoramidic dichloride	2	78
7.	*N*-methyl-*N*-isopropylphosphoramidic dichloride	1.5	88
8.	*N*-ethyl-*N*-propylphosphoramidic dichloride	1	80
9.	*N*-ethyl-*N*-isopropylphosphoramidic dichloride	1	92
10.	*N*-propyl-*N*-isopropylphosphoramidic dichloride	1	82

Conclusion- we have described an efficient reagent for the rapid and convenient synthesis of *N, N*-dialkyl phosphoramidic dichloride under mild conditions using *N, N*-dialkyl functionalised poly(styrene-co-divinyl benzene) polymeric beads as a stable, non-toxic and recyclable reagent at room temperature.

1. Trap R. The Detoxification and Natural Degradation of Chemical Warfare Agents, SIPRI Chemical and Biological Warfare Studies, vol. 3. Taylor & Francis: Philadelphia, 1985; 104.

2. Compton JAF. Military Chemical and Biological Agents: Chemical and Toxicological Properties. The Telford Press: Caldwell, NJ, 1987.

3. Tu AT. Natural and Selected Synthetic Toxins. American Chemical Society: Washington, DC, 2000; chap. 20.

4. Black RM, Clark RJ, Read RW, Reid MTJ. J. Chromatogr. A 1994; 662: 301.

5. Report S-16433, United Nations Security Council: New York, 1984.

6. Robinson JPP. SIPRI Year Book, World Armaments and Disarmament. Taylor & Francis: London, 1985; chap. 6.

7. Lundin SJ. SIPRI Year Book, World Armaments and Disarmament. Taylor &Francis: London, 1989; chap. 4.

8. Institute of Medicine. Sarin. In Gulf War and Health. National Academy of Sciences Press: Washington, DC, 2000; 135–164.

9. Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and their Destruction, Technical Secretariat of the Organisation for Prohibition of Chemical Weapons, The Hague, 1997. Available: http://www.opcw.nl.

10. Krutzsch W, Trapp R. A Commentary of CWC. Martinus Nijhoff: The Netherlands, 1994.

11. Hendrikse J. A Comprehensive Review of the Official Proficiency Test, MSc thesis, Leiden University, Gorlae Laboratories, Einsteinweg 55, The Netherlands, 2002.

12. Convention of Prohibition of the Development, Production, stockpiling and use of Chemical Warfare and on their Destruction US control and Disarmament Agency Washington, D.C. (1993).

13. Krise, J. P., Stella, V. J., Adv. Drug Delivery Rev. 19, 287, (1996).

14. Siegfried F. Manual of Military Chemistry: Chemistry of Chemical Warfare Agents, vol. 1. Deutscher Militarverlag; East Berlin, 1967; Reproduced by National Technical Information Service (NTIS), Springfield, VA, US Dept of Commerce, 237–270.

15. Barnaby F. The Problem of Chemical and Biological Warfare. Technical Aspects of Early Warning and Verification, vol. VI. Stockholm International Peace Research Institute (SIPRI), Humanities Press: New York, 1975; 192–193.

16. Gupta, H.K; Mazumder, A; Garg, P; Gutch, P. K ; Dubey, D. K; Tetrahedron letters, 2008, 49, 6704-6706.

17. Kim, D.W.; Jeong, H.J.; Lim, S.; Sohn, M.; Angew Chem. Int. Ed, 2008, 47, 8404 – 8406.

18. Organic Synthesis, Collective vol. 5. John Wiley: New York, 1973; 758.

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