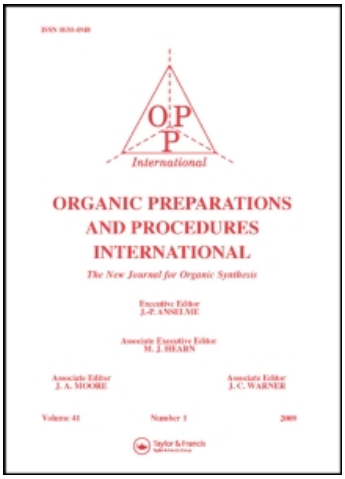

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EFFICIENT AND COST-EFFECTIVE SYNTHESIS OF DIALKYL CHLOROPHOSPHATES

P. D. Shakya[a]; D. K. Dubey[a]; Deepak Pardasani[a]; Meehir Palit[a]; A. K. Gupta[a]
[a] Defence R&D Establishment, Gwalior, INDIA

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8. The melting point of compound **2** does not agree with that of the literature.[6] The spectral data (IR, ^{1}H NMR, MS and EA) of our product support the assigned structure. Furthermore, the data of **4** synthesized from **2** are consistent with those of the literature.[3]

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EFFICIENT AND COST-EFFECTIVE SYNTHESIS OF DIALKYL CHLOROPHOSPHATES

Submitted by P. D. Shakya, D. K. Dubey, Deepak Pardasani, Meehir Palit
(06/10/05) and A. K. Gupta*

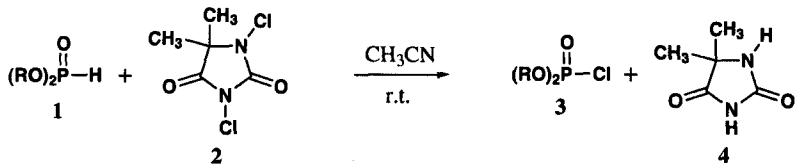
Defence R&D Establishment, Jhansi Road, Gwalior-474002, INDIA
Tel. No.: 91-751-2233488 - E-mail: arvindkumargupta2@rediffmail.com

Organophosphorus compounds have found a wide range of applications in the areas of industrial, agricultural and medicinal chemistry owing to their biological and physical properties as well as their utility as synthetic intermediates.[1] Dialkyl chlorophosphates have been used in the synthesis of phosphorus based insecticides/pesticides and have also been reported as reactive intermediates or synthons for the transformation of various functional groups such as phosphoramidates, phosphates, enolphosphates, phosphorohydrazides, pseudohalogen phosphates, and many other organophosphorus compounds.[1-9] Recently, diethyl chlorophosphate has been used as an efficient reagent in cyclization reactions[7] and regioselective ring opening of epoxides.[8] Because of their wide utility and our interest in their properties, we decided to reinvestigate their synthesis. A variety of methods have been developed for the preparation of dialkyl chlorophosphates from the reaction of the corresponding phosphites (dialkyl-H-phosphonates/trialkyl phosphites) with various reagents such as elemental chlorine,[10] phosgene,[11] SO_2Cl_2,[12] S_2Cl_2,[13] SCl_2,[14] CCl_4,[15] CCl_3NO_2,[16] $PhSO_2NCl_2$,[17] C_2Cl_6,[18] $ClSCCl_3$,[19] $CuCl_2$,[20] perchlorofulvalene,[21] and *N*-chlorosuccinimide.[22]

Among these methods, only a few could be carried out conveniently in the laboratory and most suffer from other drawbacks. Some of the methods involve the use of toxic reagents and hazardous solvents, lack general applicability and are not environmentally friendly.[10-15] The other methods require long reaction times, use of expensive and unstable reagents, and also pose difficulty in the isolation of the pure products. Thus these constitute major obstacles for scale-up methodology. A modified method (so called Atherton-Todd method) makes use of carbon tetra-

chloride and a tertiary base to generate dialkyl chlorophosphates *in situ*.[3d] Other convenient methods of preparing dialkyl chlorophosphates are the oxidative chlorination of dialkyl phosphites with chlorine or reagents which are sources of positive chlorine such as *N*-chlorosuccinimide.[22] However, this method has major drawbacks in the isolation of pure products from the crude reaction mixture and appeared troublesome due to solubility of the by-product succinimide in the reaction medium and co-distillations with desired product. In addition, this method requires equimolar amounts of reactants to give the desired products.

In recent years, the use of commercially available recyclable agents has been the focus of considerable interest. One such reagent is 1,3-dibromo-5,5-dimethylhydantoin used as an efficient agent for oxidation of thiols to disulfides.[23] This prompted us to explore the applicability of this reagent as an alternative source of chlorine gas or *N*-chlorosuccinimide (NCS) for the preparation of chlorophosphates. Therefore, we have developed a rapid, simple, safe, efficient and eco-friendly procedure for the synthesis of dialkyl chlorophosphates by using stable, commercially available 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) as an efficient reagent able to release positive chlorine. Thus the use of this reagent will serve as an alternative reagent for the rapid conversion of dialkyl phosphites to dialkyl chlorophosphates. To the best of our knowledge, this reagent has never been reported for the generation of chlorophosphates. We observed that the use of this reagent is more convenient, and efficiently afforded the dialkyl chlorophosphates from their corresponding dialkyl phosphites. This method has allowed us to obtain quantitative yields of the products in shorter reaction times at room temperature (20-25°C). The reaction scheme and yields of dialkyl chlorophosphates are depicted in the *Scheme* and *Table* respectively.



a) R = CH_3; b) R = C_2H_5; c) R = C_3H_7; d) R = *i*-C_3H_7; e) R = C_4H_9 ; f) R = *i*-C_4H_9; g) R = *sec*-C_4H_9; h) R = C_5H_{11}; i) R = *i*-C_5H_{11}; j) R = C_6H_{13}; k) R = $C_6H_5CH_2$; l) R = C_6H_5

We initially examined the reaction of equimolar amounts of diethyl phosphite (**1b**) with DCDMH (**2**) in CCl_4 at room temperature. The progress of the reaction was followed by ^{31}P NMR analysis. Surprisingly, the reaction showed complete conversion of diethyl phosphite to the diethyl chlorophosphate within 10 min. Several experiments were performed to optimize the molar ratio of the substrate and reagent. It was found that a half equivalent of reagent (**2**) was sufficient to chlorinate one equivalent of diethyl phosphite, as (**2**) provides two reactive chlorines which are transferred easily and completely transferred. The appearance of a white precipitate of by-product **4** from the homogenous reaction mixture indicates the completion of the reaction. In terms of 'atom economy', these reactions do not require the addition of extra base to scavenge

the proton. Formation of the precipitated 5,5-dimethylhydantoin (**4**) was nearly quantitative and it was readily removed by filtration from the heterogeneous reaction mixture. Concentration of the solvent provided pure diethyl chlorophosphate in 97% yield.

Table. Preparation and Properties of Compounds **3**[a] from the Reaction of Dialkyl Phosphites **1** and 1,3-Dichloro-5,5-dimethylhydantoin (**2**)

Cmpd	Yield (%)	bp. (°C/mmHg)	*lit.*[2] bp.	Time (min.)	^{31}P NMR[b] (δ)
3a	96	75-77/20	75-80/20-25	10	6.3
3b	97	92-94/20	93-94/10	10	5.04
3c	96	107-108/13	106-107/12	10	5.48
3d	97	95-96/14	92-94/12	10	2.76
3e	95	132-135/15	132-134/12	10	4.58
3f	95	122-124/12	122-124/12	10	4.16
3g	94	85-87/1.5	84/0.4	10	4.71
3h	96	129-132/1	131-132/1	15	4.59
3i	95	131-133/1	122-124/1	15	3.58
3j	99	oil[c]	not reported	15	4.25
3k	99	oil[c]	not reported	15	4.7
3l	96	141-142/1	141/1	30	-6.2

a) The products **3a-3l** had satisfactory IR, NMR and GC-MS data which were compared to those of authentic samples. b) Reactions were monitored by ^{31}P NMR, and δ values of the products from the reaction mixture were recorded after locking the signal with $CDCl_3$. c) Decompose upon attempted distillation.

With this result in hand, a series of dialkyl phosphites were treated under conditions identical to that of the model compounds to afford the corresponding chlorophosphates in essentially quantitative yields. Many factors such as the temperature, solvent, and the structure of alkyl/aryl group profoundly influenced the course of reaction. Although the reactions are exothermic no external cooling is required. Several reactions of dialkyl phosphites (**1**) with 1,3-dichloro-5,5-dimethylhydantoin (**2**) were carried out in different solvents to study the effect of the solvents on the reaction. However, there was no significant change in the yield of the products by using other aprotic solvents. Carbon tetra- chloride or acetonitrile were found to be the most suitable solvents as the by-product 5,5-dimethylhydantoin (**4**) is completely insoluble in these solvents. Thus it could be removed by simple filtration. It was also noticed that aliphatic dialkyl phosphites reacted somewhat faster than aromatic diphenyl phosphites because of the diminished steric hindrance at the phosphoryl group. The reaction with aliphatic dialkyl phosphites (C1-C4) was complete in 5-10 min. while higher dialkyl phosphites were complete within the 10-15 min; diphenyl phosphite required 30 min. for complete conversion to the corresponding chlorophosphate. At the same time, the reaction need not be performed at 0°C as

mentioned by earlier workers.[10a] Aliphatic dialkyl chlorophosphates are stable for several months, if kept below 5°C. On the other hand, diphenyl chlorophosphate is quite stable at room temperature.

The important advantages of the method are that the reactions were clean with no side-products. The work-up procedure is also very convenient due to the solubility of the reagent in the solvent and precipitation of the by-product **4** from the reaction mixture. The filtrate contains the dialkyl chlorophosphates which could either be used for further reactions without any purification or purified by vacuum distillation after distilling off the solvent. In addition, the scale-up of the process is easy, economical, and eco-friendly due to possibility of recycling the by-product and solvent. There was no significant decrease in the yield of the products at 0.01-0.2 mole levels.

In conclusion we have reported an efficient and safer method for the convenient conversion of dialkyl phosphites to dialkyl chlorophosphates utilizing a solid and commercially available reagent at room temperature. The method also offers the rapid isolation of pure product. Furthermore, this methodology represents a simplified procedure over the previously reported methods. More importantly, this procedure minimizes the involvement of toxic and environmental hazards since the use of chlorine gas is hazardous. The recycling of the solvent and the by-product 5,5-dimethylhydantoin (**4**) to regenerate 1,3,-dichloro-5,5-dimethylhydantoin adds an economic advantage to this process.

EXPERIMENTAL SECTION

The bps are uncorrected. The IR spectra were recorded on a Nicolet FT-IR spectrometer model impact 410 on KBr disk. ^{1}H and ^{31}P NMR spectra were acquired on Bruker DPX Avan Ce 400 MHz FT-NMR in $CDCl_3$ using tetramethylsilane as an internal standard for ^{1}H and 85% H_3PO_4 as an external standard for ^{31}P NMR. GC-MS data were obtained on Varian 3400 GC coupled to a TSQ 7000 mass spectrometer (Finnigan Mat). GC parameters were: the injector temperature 250°C, transfer line temperature 280°C, column temperature programming 50°C (2 min.) - @ 10°C/min - 280°C (5 min.), carrier gas helium at pressure of 10 psi. To determine the EI mass spectra, an ion source pressure 1.5 x 10^{-6} torr, a source temperature 150°C, an electron energy 70 eV and an emission current 400 mA were used as the operating conditions. To perform Chemical Ionization (CI) technique, the ion source pressure with methane as the reagent gas 1.5 x 10^{-3} torr, source temperature 150°C, electron energy 100 eV, and emission current 300 mA were maintained to operate the mass spectrometer. ***CAUTION***: Chlorophosphates are potent *acetylcholinesterase* inhibitors.

General Procedure.- 1,3-Dichloro-5,5-dimethylhydantoin (**2**, 19.7g, 0.1 mole) was placed in a 250 mL, two-necked RB flask equipped with a condenser and a drying tube. The solvent acetonitrile/CCl_4 (100 mL) was added and the reaction mixture was stirred until 1,3-dichloro-5,5-dimethylhydantoin went into solution. The dialkyl phosphite (0.2 mole) was added slowly, and the reaction mixture was stirred for 5-30 minutes, depending upon the substrate used. Completion of the reaction was heralded by the formation of a white precipitate of 5,5-dimethylhydan-

toin (**4**). When precipitation of the by-product was complete, it was removed by filtration under an inert atmosphere. The dialkyl chlorophosphate was obtained from the filtrate by vacuum distillation after removal of the solvent.

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