

N, N'-Dichloro bis(2,4,6-trichlorophenyl) urea (CC-2): an efficient reagent for synthesis of dialkyl chlorophosphates

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An efficient and simple method is described for the preparation of dialkyl chlorophosphates by the use of new positive chlorine bearing reagent namely N, N'-dichloro bis(2,4,6-trichlorophenyl) urea.

Keywords: dialkyl phosphate, dialkyl chlorophosphate, N,N'-Dichloro bis(2,4,6-trichlorophenyl) urea, CC-2

The chemistry of organophosphorus compounds is a rapidly developing area of research because of their importance in industrial, agricultural, biochemical and medicinal application.¹ One such class of compounds is known as dialkyl chlorophosphates. These chlorophosphates are used in the transformation of various functional groups.¹⁻⁷ Recently, diethyl chlorophosphate has been used as an efficient reagent in cyclisation reactions⁸ and in the regioselective ring opening of epoxides.⁹ Keeping in view the versatile synthetic applications the efficient preparation of dialkyl chlorophosphates has been examined. Numerous methods are described in literature for the preparation of dialkyl chlorophosphates from their corresponding phosphites (dialkyl phosphites/trialkyl phosphites) with various reagents such as elemental chlorine,¹⁰ phosgene,¹¹ SO₂Cl₂,¹² S₂Cl₂,¹³ SCl₂,¹⁴ CCl₄,¹⁵ CCl₃NO₂,¹⁶ PhSO₂NCl₂,¹⁷ C₂Cl₆,¹⁸ ClSCCl₃,¹⁹ CuCl₂,²⁰ perchlorofulvalene²¹ and N-chlorosuccinimide.²² Only a few can be carried out as convenient laboratory methods and most of them suffer from drawbacks. Some of the methods lack general applicability and involve the use of toxic and hazardous chemicals,¹⁰⁻¹⁵ while others are time consuming, involve expensive and unstable reagents and pose difficulty in isolation of the pure products from the moisture sensitive reaction mixture. A modified method (so called Atherton-Todd method) makes the use of carbon tetrachloride and a tertiary base to generate the dialkyl chlorophosphates *in situ*, but it still has limited scope of the formation of P–N compounds.^{3d}

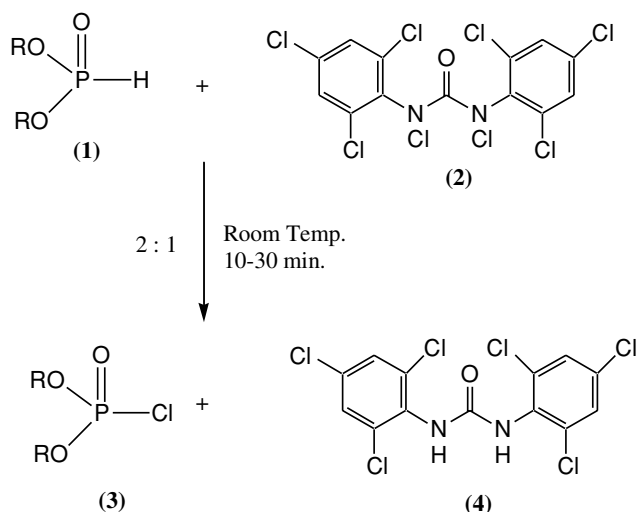
In recent years, the use of recyclable agents has received considerable interest in organic synthesis. It prompted us to explore the possibility of using stable, nontoxic and an efficient positive chlorine releasing reagent namely, N,N'-dichlorobis(2,4,6-trichlorophenyl)urea (CC-2).²³ It has been incorporated as a reactive ingredient in a formulation developed in our laboratory to decontaminate the bis-(2-chloroethyl)sulfide (sulfur mustard) chemical warfare agent.²⁴ Having established a commercially viable synthetic procedure for CC-2, we examined it as an alternative reagent

for the conversion of dialkyl phosphites to dialkyl chlorophosphates.

Herein we describe convenient, rapid, economic, method for the synthesis of dialkyl chlorophosphates from their corresponding dialkyl phosphites at room temperature. This method has allowed us to obtain rapidly quantitative yields of the products. The room temperature (20–25 °C) reaction of various dialkyl phosphites with N, N'-dichloro, bis-(2,4,6-trichlorophenyl) urea (CC-2) afforded corresponding dialkyl chlorophosphates in excellent yields.

Results and discussion

The sequence of the reaction and synthetic details for the synthesis of dialkyl chlorophosphates are depicted in Scheme 1 and Table 1 respectively.



Scheme 1

Table 1 Isolated yields of dialkyl chlorophosphate from the reaction of dialkyl phosphites and CC-2^a

| Entry | R | ³¹ P NMR ^b /ppm/min. | Time | Yield/% | B.P./°/mm/Hg | Lit. ² |
|-------|---|--|------|---------|--------------|-------------------|
| 1 | CH ₃ | 6.34 | 10 | 96 | 75–77/20 | 75–80/20–25 |
| 2 | C ₂ H ₅ | 5.04 | 10 | 97 | 92–94/20 | 93–94/10 |
| 3 | C ₃ H ₇ | 5.48 | 10 | 96 | 107–108/13 | 106–107/12 |
| 4 | <i>i</i> -C ₃ H ₇ | 3.76 | 10 | 97 | 95–96/14 | 92–94/12 |
| 5 | C ₄ H ₉ | 4.58 | 10 | 95 | 132–135/15 | 132–134/12 |
| 6 | <i>i</i> -C ₄ H ₉ | 4.16 | 10 | 95 | 122–124/12 | 122–124/12 |
| 7 | <i>sec</i> -C ₄ H ₉ | 4.71 | 10 | 94 | 85–87/1.5 | 84/0.4 |
| 8 | C ₅ H ₁₁ | 4.59 | 15 | 96 | 129–132/1 | 131–132/1 |
| 9 | <i>i</i> -C ₅ H ₁₁ | 3.58 | 15 | 95 | 131–133/1 | 122–124/1 |
| 10 | C ₆ H ₁₃ | 4.25 | 15 | 99 | Oil | Oil |
| 11 | C ₆ H ₅ CH ₂ | 4.7 | 15 | 99 | Oil | Oil |
| 12 | C ₆ H ₅ | –6.2 | 30 | 96 | 141–142/1 | 141/1 |

^aReactions were carried out at ambient temperature and the products had satisfactory IR, NMR and GC–MS data which were compared to those of authentic samples. ^bReactions were monitored by ³¹P NMR in CDCl₃ by using 400MHz NMR

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Table 1 shows the applications of the method for the preparation of diverse dialkyl chlorophosphates. We found that both alkyl and aryl phosphites reacted efficiently at room temperature to produce corresponding dialkyl chlorophosphates in excellent yields. Several experiments were also carried out to study the influence of structure of the alkyl/aryl moiety. Aliphatic dialkyl phosphites reacted a little faster as compared to aromatic phosphites (entries 1–11 vs 12 Table 1). We also examined the effect of temperature on yields and reaction time. It is interesting to note that chlorination of dialkyl phosphites with CC-2 is an exothermic reaction. However, there was no necessity to cool the reaction to avoid the formation of any side products. This is an important aspect of the reaction in comparison to earlier reported methods, which required cooling and inert atmosphere. The reaction was found to be influenced by protic solvents like alcohols which reduced the yields of desired products due to the formation of corresponding phosphates, whereas aprotic solvents like dichloro methane, CCl_4 , CH_3CN , hexane, benzene and toluene yielded the dialkyl chlorophosphates without side products. However, among these aprotic solvents, the solvents having low boiling point such as dichloromethane afforded the desired products more conveniently. The solvent could be removed without loss of dialkyl chlorophosphates. One of the unique features of this method is the isolation of the reaction products from reaction mixture. Dialkyl chlorophosphates were isolated by vacuum distillation after distilling off the solvent from the filtrate, which is obtained by filtration of the reaction mixture. The completion of the reaction was indicated by complete precipitation of the by-product (**4**) bis-(2,4,6-trichlorophenyl) urea. It was isolated from the reaction mixture by filtration, as it is practically insoluble in almost all the solvents. It could be recycled for the preparation of CC-2 as per reported method.²³

Another feature of this reaction is the requirement of half mole of CC-2 for chlorination of one mole of dialkyl phosphite, as CC-2 contains two positive chlorines. And interestingly, the transfer of both the chlorine from the N-Cl bonds to phosphorus takes place with equal efficiency, which could probably be attributed to symmetrical structure of CC-2 molecule.

Since in this reaction, the substituted protons from dialkyl phosphites were picked-up by nitrogen of CC-2, (in an exchange/displacement reaction), there was no necessity of extraneous base to scavenge the liberated protons, which is essential in the earlier reported method. We also examined the reproducibility and scale-up of the developed process by carrying out the reaction with increasing amounts of (0.01–0.2 moles) of reactants. The yield of dialkyl chlorophosphate was found to be almost comparable in each experiment (within the limit of experimental error). Filtrate contains dialkyl chlorophosphate which could either be used as such for further reactions without any purification, or could be purified as stated above.

In conclusion we have reported an efficient and convenient method for the conversion of dialkyl phosphites to dialkyl chlorophosphates using CC-2, a stable and non toxic²⁴ reagent at room temperature. The method also offers the rapid isolation of pure product by filtration. The by-product (**4**) can be recycled to prepare sym N, N'-dichloro bis (2, 4, 6-trichlorophenyl) urea adding to the economic advantage to this process.

Experimental

The boiling points are uncorrected. GC–MS data were recorded on Varian 3400 GC coupled to a TSQ 7000 mass spectrometer (Finnigan Mat) with GC Injector temperature 250 °C, Transfer line temperature 280 °C, Column (BPX5 SGE column) temperature programming

50 °C (2 min) – 10 °C/min – 280 °C (5 min), carrier gas helium at pressure of 10 psi. To obtain EI mass spectra Ion source pressure 1.5×10^{-6} torr, source temperature 150 °C, electron energy 70eV and emission current 400 μA were used as the operating conditions. To perform chemical Ionisation (CI) technique, the Ion source pressure with methane as the reagent gas 1.5×10^{-3} torr, source temperature 150 °C, electron energy 100 eV and emission current 300 μA were maintained to operate the mass spectrometer. FT-IR spectra were recorded on Nicolet FT-IR spectrometer model impact 410 on KBr disk. ^1H and ^{31}P NMR spectra were recorded on Bruker DPX Avan Ce 400 MHz FT- NMR in CDCl_3 using tetramethyl silane as an internal standard for ^1H and 85 % H_3PO_4 as an external standard for ^{31}P NMR.

General procedure

(A) *Synthesis of N,N'-dichloro bis(2,4,6-trichlorophenyl) urea (CC-2)*: Bis-(diphenyl)-urea (25 g, 0.117 mol) was dissolved in 200 ml acetic acid and 20 ml pyridine was added, it was followed by stirring at 70 °C. It was chlorinated by passing in chlorine gas for 4 h with stirring. Absorption of chlorine ceased with the complete precipitation of bis(2,4,6-trichlorophenyl)urea. The mixture was cooled to 10 °C in an ice bath, and NaOH was added to portions to bring the pH of the mixture to almost neutral. The chlorine gas was added until all the organic matter re-dissolved. The mixture was poured in to water to precipitate the CC-2, which was washed with water, filtered and re-crystallised from toluene. After the drying the yield was 56 g, m.p. 179–180 °C. The positive chlorine content of CC-2 was checked by standard iodometric titration. It was found to be 14.51% (theoretical value 14.54%).

(B) *Synthesis of Dialkyl chlorophosphates*: In a typical experimental procedure, dialkyl phosphite (0.2 moles) was added to a suspended solution of N, N'-dichlorobis(2,4,6-trichlorophenyl)urea (48.8 g, 0.1 mole) in 150 ml acetonitrile, the reaction mixture was stirred for 10–30 minutes. The progress of the reaction mixture was monitored by ^{31}P NMR by drawing a few milligrams of reaction mixture in NMR tube. After completion of the reaction a white amorphous precipitate of symmetrical bis-(2,4,6-trichlorophenyl)urea was formed which was removed by filtration. The precipitate was washed with dichloromethane (3×10 ml). The solvent was removed from the filtrate and residue was distilled under vacuum to afford the pure dialkyl chlorophosphate.

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