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Breathing air as oxidant: Optimization of 2-chloro-2-oxo-1,3,2-dioxaphospholane synthesis as a precursor for phosphoryl choline derivatives and cyclic phosphate monomers

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ABSTRACT

Phosphoryl choline derivatives are important compounds for drug development. Also other phosphoesters have received increased demand in recent years. Many of such compounds rely 2-chloro-2-oxo-1,3,2-dioxaphospholane (COP) as an intermediate. COP is available in a two-step reaction from the cyclic adduct of phosphorus chloride and ethylene glycol after oxidation. Although commercially available, in-house synthesis of COP is often required due to pricing, purity, and delivery issues. Air is a convenient and economical oxidizing agent, yet not used for synthesis of COP. While slow consumption of the P(III)-precursor 2-chloro-1,3,2-dioxaphospholane with molecular oxygen from a gas bottle, high amounts of unreacted oxygen are lavished and even may cause an explosion. Oxygen from air is a reasonable and safer alternative. Additionally, catalytic amounts of cobalt(II)chloride increase the reaction kinetics remarkably. The results presented allow a controlled and fast access to a variety of phosphoesters by optimized reaction conditions of COP and its derivatives.

1. Introduction

2-Chloro-2-oxo-1,3,2-dioxaphospholane (COP) (also known as ethylene chlorophosphate or ethylene phosphochloridate) is an essential precursor and a key building block for mainly two purposes: the synthesis of (i) phosphorylcholine (PC) derivatives, a polar zwitterion naturally present in phospholipids of cell membranes, which are used in diverse drug delivery applications. A popular synthetic representative is the monomer 2-methacryloyloxyethyl phosphorylcholine (MPC), which produces the water-soluble and biocompatible polymer PMPC, mimicking the phospholipids.[1–5] Also the synthesis of small molecule PC's for different polymers has been reported.[6–9] However also the preparation of (ii) cyclic phosphate monomers for the ring-opening polymerization to produce poly(phosphoester)s (PPEs)[10–19] is a valuable reaction pathway of COP (Scheme 1). Synthetic PPEs are inspired by desoxyribose nucleic acid (DNA) and a versatile class of polymers ranging from hydrophobic to water-soluble materials. They find currently an increased attention as potential materials for biomedical applications[13,20,21] or as flame retardant additives.[22]

The most common route for the synthesis of COP refers to protocols from Scully et al.[23] and Edmundson[24] from the 1950's and 1960's. Nowadays, COP is still synthesized via this route in a two-step reaction: (i) esterification of phosphorus trichloride with ethylene glycol generates 2-chloro-1,3,2-dioxaphospholane (CP) (**1a**), which is (ii) oxidized by molecular oxygen in refluxing organic solvent to prepare 2-chloro-2-oxo-1,3,2-dioxaphospholane (**1**) (Scheme 2). For the oxidation reaction slight modifications are reported, substituting the reaction solvent benzene using toluene[5,25] or dichloromethane[26] instead. Also the reaction times from 8 h to 4d[24, 27] and temperatures from room temperature[5,26] to reflux[24,27] vary. However, moderate yields from 37 to 83%[5,27] are reported so far, often lacking high purity of the product. Additionally, molecular oxygen from a gas bottle in large excess is used in all cases as reagent and bubbled through the reaction, showing only poor and slow consumption with unreacted oxygen being released in large amounts (note: in a well-ventilated fume hood this should be unproblematic, however flying sparks need to be prevented). Several attempts in our group conducting the oxidation in a closed system were sparsely satisfying and can cause unwelcome overpressure in the system due to reflux conditions.[10] In our search for alternative

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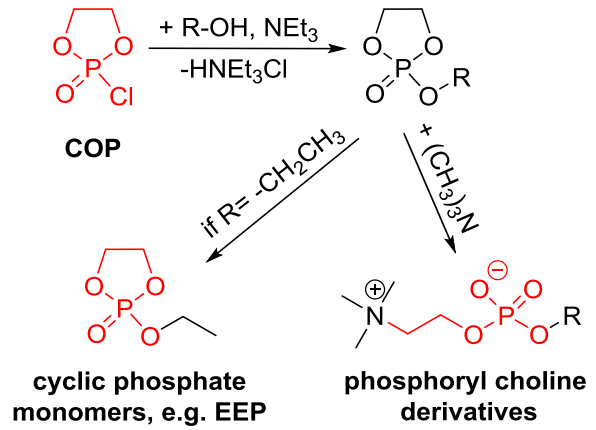
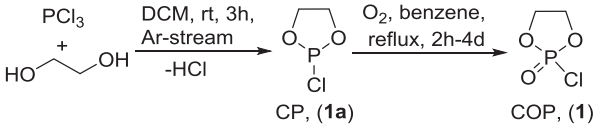


Scheme 1. Application examples for 2-chloro-2-oxo-1,3,2-dioxaphospholane (COP) as precursor.



Scheme 2. Typical reaction protocol for the preparation of COP.

routes, reported literature protocols include the use of dinitrogen tetroxide (N_2O_4)[28] or ozone (O_3)[29] as oxidants, also resulting in poor yields in the case of N_2O_4 and challenging handling of reactant. Also phosphorus oxychloride, ethylene glycol and catalytic amounts of copper(I)chloride (CuCl) were reported to produce COP in a one-step reaction, but several attempts of this protocol in our group did not produce COP in reasonable yields or purity.[30]

There is a high demand in COP. Although commercially available, price, delivery time and purity of the commercial product are often unsatisfactory. Therefore an efficient, inexpensive and safer in-house preparation is indispensable. Herein, we present a facilitated synthesis protocol using the oxygen from air as oxidant, instead of molecular oxygen from a gas bottle. Still used in excess, large amounts of wasted unreacted molecular oxygen can be avoided. Additionally, cobalt(II)chloride has been found to be an efficient catalyst that accelerates the reaction from days to several hours, resulting in COP with a very high purity and overall acceptable yields of 70%.

2. Experimental section

2.1. Materials

All reagents were used without further purification, unless otherwise stated. Solvents, dry solvents (over molecular sieves) and deuterated solvents were purchased from Acros Organics, Sigma-Aldrich, Deutero GmbH (Germany) or Fluka. Ethylene glycol was purchased from Sigma-Aldrich, dried prior to use with NaH, distilled and stored over molecular sieves. PCl_3 was purchased from Acros Organics. Cobalt(II)chloride hexahydrate was purchased from Sigma Aldrich, and dried at reduced pressure at ~500 °C directly prior to use.

2.2. Methods

For nuclear magnetic resonance (NMR) analysis ^1H, ^{13}C and ^{31}P NMR spectra were recorded either on a Bruker AVANCE III 300 spectrometer operating with 300 MHz, 75 MHz and 121 MHz or a Bruker AVANCE III 700 spectrometer operating with 700 MHz, 176 MHz and 283 MHz. All spectra were measured either in DMSO-d_6 or $CDCl_3$. ^1H and ^{13}C spectra were calibrated against the solvent signal, ^{31}P spectra used as conducted. Spectra were analyzed using MestReNova 8 from Mestrelab Research S.L. for 1D spectra All ^{13}C and ^{31}P NMR spectra are ^1H-decoupled.

2.3. Synthesis

2.3.1. 2-Chloro-1,3,2-dioxaphospholane (CP, 1a)

A flame-dried 500 mL three-neck flask, equipped with a dropping funnel and a reflux condenser, was charged with phosphorus trichloride (137.3 g, 1.000 mol) in dry dichloromethane (150.0 mL). Ethylene glycol (62.07 g, 1.000 mol) was added drop-wise to the stirred solution, while argon was bubbled through the solution to remove the released hydrogen chloride. The Ar-stream with released hydrogen chloride was passed through a NaOH-solution for neutralization. The reaction was continued for additional 2 h. Then, the solvent was removed and the residue purified by distillation at reduced pressure to give a fraction at 72–78°C/65–67 mbar, obtaining the clear, colorless, liquid product (84.15 g, 0.670 mol, yield: 67%). NMR data matches literature values.[31]

^1H NMR (700 MHz, $CDCl_3$): δ 4.35–4.13 (m, 4H, O-C*H*$_2$-C*H*$_2$-O). ^{13}C NMR (176 MHz, $CDCl_3$): δ 65.29. $^{31}P\{H\}$-NMR (283 MHz, $CDCl_3$): δ 167.80.

2.3.2. 2-Chloro-2-oxo-1,3,2-dioxaphospholane (COP, 1)

A flame-dried 500 mL three-neck flask, equipped with a reflux condenser, was charged with 2-chloro-1,3,2-dioxaphospholane (20.00 g, 0.160 mol) dissolved in benzene (250.0 mL) and dry $CoCl_2$ (20.50 mg, $1.590*10^{-4}$ mol) was added. A stream of dried air (passed through conc. H_2SO_4) was passed through the solution for 3 h at 80 °C and for 12h at room temperature (overnight). Subsequently, the solvent was removed *in vacuo* and the residue purified by fractionated distillation at reduced pressure to give a fraction at 66–74 °C/0.13–0.15 mbar, obtaining the clear, colorless, liquid product COP in high purity (15.82 g, 0.110 mol, yield: 70%, 99% purity). NMR data matches literature values.[26] ^1H NMR (300 MHz, $CDCl_3$): δ 4.61–4.44 (m, 4H, O-C*H*$_2$-C*H*$_2$-O), $^{13}C\{H\}$-NMR (176 MHz, $CDCl_3$): δ 66.54, $^{31}P\{H\}$-NMR (121 MHz, $CDCl_3$): δ 22.74.

2.3.3. Isolation of byproduct in entry 3

After fractionated distillation, 1.500 g of product with non-phosphorus containing byproduct was stirred in 10 mL DCM with 5.000 g silica gel for 10 min. The silica gel was removed by filtration and the solvent removed, obtaining the byproducts 1-(benzyl)-4-methylbenzene and 1-(benzyl)-2-methylbenzene (180.0 mg, $6.420*10^{-4}$ mol, yield: 12%).

Ratio 1-(benzyl)-4-methylbenzene: 1-(benzyl)-2-methylbenzene from ^1H NMR is 0.42: 0.57.

NMR data matches literature values[32,33]: *1-(benzyl)-4-methylbenzene:* ^1H NMR: δ 7.29–7.09, 3.93, 2.30. ^{13}C NMR: δ 141.5, 138.2, 135.6, 130.4, 129.3, 129.0, 128.6, 126.0, 41.7, 21.1. *1-(benzyl)-2-methylbenzene:* ^1H NMR: δ 7.35–7.11, 4.03, 2.23. ^{13}C NMR: δ 140.8, 139.4, 137.1, 130.7, 130.4, 129.2, 128.8, 126.9, 126.4, 126.3, 39.9, 20.1.

2.3.4. 1-(benzyl)-2-methylbenzene

^1H NMR (300 MHz, CD_2Cl_2): δ 7.32–7.11 (m, 8H, aromatic protons), 3.94 (s, 2H, Ar-C*H*$_2$-Ar-CH$_3$), 2.32 (s, 3H, Ar-CH$_2$-Ar-C*H*$_3$). $^{13}C\{H\}$-NMR (75 MHz, CD_2Cl_2): δ 141.19, 138.86, 136.18, 130.79, 130.41, 129.33, 128.96, 126.95, 126.50, 126.44, 39.89, 19.98.

2.3.5. 1-(benzyl)-4-methylbenzene

^1H NMR (300 MHz, CD_2Cl_2): δ 7.32–7.11 (m, 8H, aromatic

Table 1
Overview on the reaction conditions for the oxidation of 2-chloro-1,3,2-dioxaphospholane (CP) to 2-chloro-2-oxo-1,3,2-dioxaphospholane (COP).

Entry	Reactant	Catalyst	Solvent	T/°C	t/h	Conversion[a]/%	Yield COP/%	Purity[b]/%
1	O_2	–	benzene	80	96	>90	83	98
2	air	–	benzene	80/rt	96/72	98	86	97
3	air	–	toluene	111	23	98	–	93
4	air	$CoCl_2$	benzene	80/rt	3/12	97	70	99
5	air	$CoCl_2$	PC[c]	80/120/rt	3/10/14	100	8[d]	–
6	air	$CoCl_2$	EA[e]	80	13	10	5[d]	–
7	air	$CoCl_2$	ACN[f]	80	25	17	15[d]	–
8	air	$CoCl_2$	chlorobenzene	80	16	69	10[d]	–

[a] Conversion of reagent 2-chloro-1,3,2-dioxaphospholane.
[b] Determined by ^{31}P NMR.
[c] PC: propylene carbonate.
[d] Not distilled.
[e] EA: ethyl acetate.
[f] ACN: acetonitrile.

protons), 4.01 (s, 2H, Ar-C*H*$_2$-Ar-CH$_3$), 2.26 (s, 2H, Ar-CH$_2$-Ar-C*H*$_3$). $^{13}C\{H\}$-NMR (75 MHz, CD_2Cl_2): δ 142.27, 139.72, 137.20, 129.65, 129.27, 129.25, 128.90, 126.50, 42.04, 21.28. FD-MS: 182.35 (calculated for $C_{14}H_{14}$: 182.11).

3. Results and discussion

Following the protocol of Edmundson,[24] the oxidation of 2-chloro-1,3,2-dioxaphospholane (CP) with molecular oxygen from a gas bottle bubbled through the reaction in benzene under reflux shows slow consumption and requires several days (4d) for the reaction to reach full conversion to 2-chloro-2-oxo-1,3,2-dioxaphospholane (COP) (yields up to 83%, 98% purity, Table 1, **entry 1**). The major disadvantage of the set-up is the waste of unreacted molecular oxygen and the potential risk with high amounts of oxygen in the atmosphere. Previously, we reported on the conduction of the reaction in a closed system using a peristaltic pump to reuse the unreacted oxygen and to avoid wasting high amounts of oxygen.[10] However, care has to be taken that no over- or under pressure is produced in the set-up; also the organic solvent vapors are problematic for tubing and they have to be replaced regularly.

The use of oxygen from air would be a cheap, easy, and safer alternative, however has not been reported in literature before and also previous attempts in our laboratory remained unsatisfactory in terms of reaction time and product purity. Detailed optimization of this oxidation step allowed us to prepare COP by a set-up with dried air bubbled through the reaction (**entry 2**), but turned out to be very slow (similar to the one with pure oxygen): in benzene 4d at reflux temperatures and 3d at room temperature were necessary to reach almost full conversion (98%) (Fig. 1). Small amounts of ring-opened side-product were also found in the reaction mixture. After fractionated distillation, an overall yield of 86% can be reached with typically ca. 97% purity of the product.

Instead, the reaction is much faster in refluxing toluene (<1d) reaching a conversion of starting material of >98% (**entry 3,** Fig. 2). After fractionated distillation, $^{31}P\{H\}$-NMR spectroscopy shows purity of 93% of product and 7% opened ring as byproduct. However, a second, non-phosphorus-containing byproduct can be observed in ^{1}H NMR spectroscopy (Fig. S7). The second byproduct was isolated by filtration over silica gel and identified as 1-(benzyl)-4-methylbenzene and 1-(benzyl)-2-methylbenzene (Figs. S8–11), resulting from coupling of the solvent during reaction. The product COP cannot be purified from the byproduct by distillation due to very similar boiling points. However, for the purpose of COP as precursor for cyclic phosphate monomers, the byproduct disturbs neither the synthesis of the monomers nor their ring-opening polymerization.

A modified reaction in benzene with air and 0.1 mol% of anhydrous $CoCl_2$ as catalyst shows high conversions (>98%) within 15 h (3 h under reflux and 12 h at room temperature (**entry 4**)). After fractionated distillation, purity of 99% of the desired product and 1% opened ring as a byproduct (yields: 70–75%, Figs. S4–6).

Several other solvents were screened for the reaction to substitute benzene. While the reaction in the "green" solvent propylene carbonate (PC) with air and 0.1 mol% of dry $CoCl_2$ (**entry 5**) shows 21% product after 13 h at high temperature (3 h at 80 °C and 10 h at 120 °C), further 14 h at room temperature does not lead to an increase in the COP amount, but instead opening of the ring was detected in NMR kinetics (Fig. S12). Since $^{31}P\{H\}$-NMR shows 92% byproduct and only 8% COP product at that point, purification was not attempted. The reaction in ethyl acetate (**entry 6**) after 13 h at 80 °C also shows low conversion of CP, only 5% formed product COP and 5% byproduct. Two solvents suitable for radical reactions were

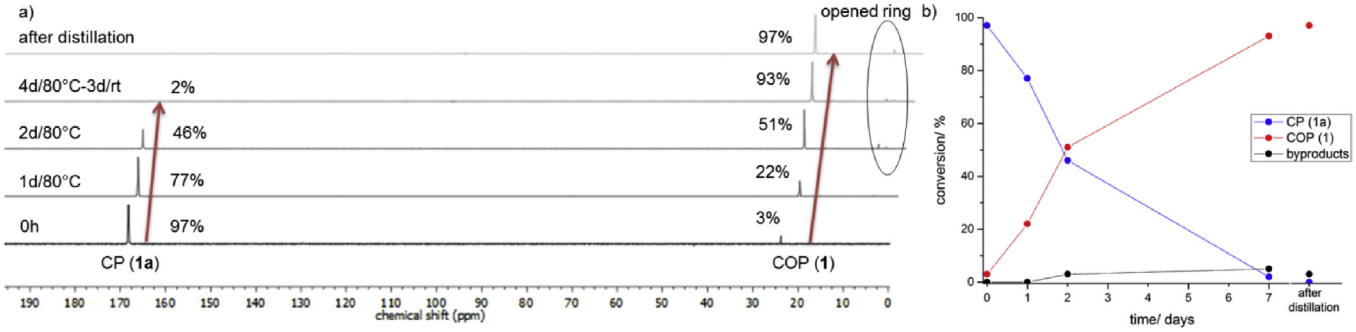


Fig. 1. a) ^{31}P NMR spectra (121 MHz, $CDCl_3$, 298 K) of the oxidation reaction of CP to COP in benzene (Table 1, **entry 2**), b) plotted conversion of reagent and formation of COP in **entry 2**, measured by ^{31}P NMR spectroscopy.

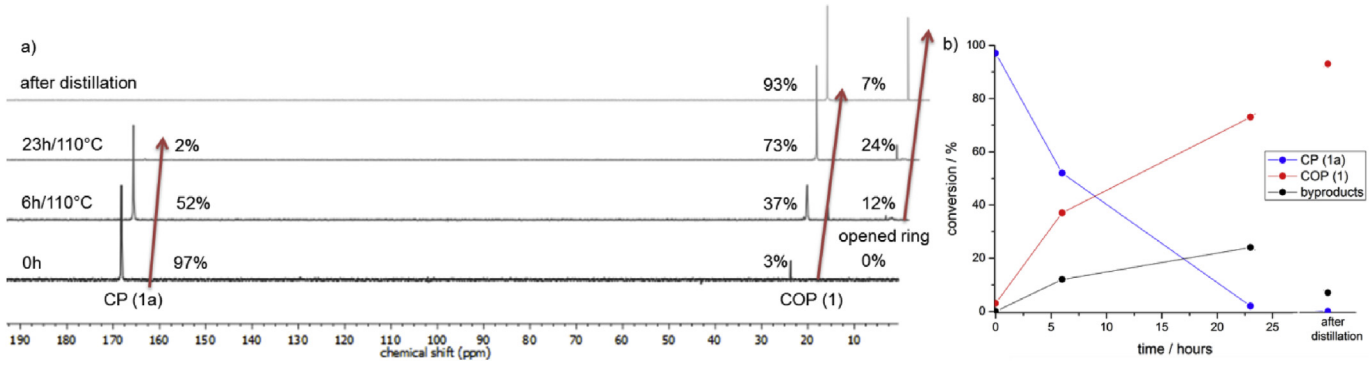


Fig. 2. a) ^{31}P NMR spectra (121 MHz, $CDCl_3$, 298 K) of the oxidation reaction of CP to COP in toluene (Table 1, **entry 3**), b) plotted conversion of reagent and formation of COP in **entry 3**, measured by ^{31}P NMR spectroscopy. Note: only phosphorus-containing byproducts are considered.

further investigated: acetonitrile and chlorobenzene. The reaction in acetonitrile (**entry 7**) after 25 h at 80 °C shows only 15% formation of COP. Although the solvent is generally suitable for the reaction and only 2% byproduct is formed, conversion is very slow and time consuming. Finally, the reaction in chlorobenzene (**entry 8**, Fig. S13) at 80 °C shows after 7 h 49% product, but also 10% opened ring byproduct. Longer reaction times do not show any increase in the yields, but instead degradation of COP was detected (51%).

In summary, from the solvent studied, benzene and toluene remain the most suitable reaction media. However, as toluene is not inert in radical reactions, the coupling products might be contaminants of the product. Greener solvents, such as ethyl acetate and propylene carbonate[34] were suitable for the oxidation of CP, but lower yields are accessible. For radical reactions generally only few inert solvents are convenient, e.g. benzene, chlorobenzene, acetonitrile, carbon tetrachloride or tetrachloroethane. The less hazardous-ranked solvents chlorobenzene and acetonitrile might be used, but both did not show satisfying results in our studies. Therefore, we consider benzene still to be the most eligible solvent for this reaction.

4. Conclusion

High demands on purity, pricing and delivery issues of COP still require in-house synthesis of this precursor molecule. Using oxygen from air instead of pure oxygen from a gas tank, has a strong economical impact, is easy to perform and avoids wasting of oxygen. Additionally, this is the first report on the acceleration of this reaction by the addition of catalytic amounts of $CoCl_2$ to reduce the reaction times from days to hours. A screening of different solvents revealed that the highest conversions can be achieved in toluene and benzene, while other "greener" solvents might be used, but are hampered by low reaction kinetics and the ring-opening of the product over prolonged reaction times. This minor, but crucial replacement of the oxygen source dramatically facilitates the synthesis of COP (at least in the university lab), which is required in high and pure amounts for the preparation of phosphoryl choline derivatives and cyclic monomers for poly(phosphoester)s. Further issues might include the further dilution of air (or oxygen) with inert gas, but we considered the ease of air beneficial. Also conducting the reaction in a continuous reactor setup in a green solvent might be a strategy for future industrial relevance that might be considered. Our strategy presented herein overcomes the commercial availability and establishes easy access to this important precursor molecule.

Conflict of interest

The authors declare no competing financial interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.05.037.

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