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# An easy and short preparation of pentachloroacetone by selective dechlorination of hexachloroacetone under Appel conditions

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ABSTRACT

We report a very convenient laboratory preparation of pentachloroacetone (PCA) by selective dechlorination of hexachloroacetone (HCA) via reaction with triphenylphosphine in the presence of methanol or aromatic alcohols.



Pentachloroacetone (PCA) was developed by Föhlisch and co-workers[1a,b] as a useful starting material for the generation of chloro-substituted oxyallyl intermediates, which are valuable components for [4+3] cycloaddition reactions. They used the method for the synthesis of both tropones[1b,c] and hydroazulenes[1d] as well as many other seven-membered ring derivatives.[1b] Recently Rashatasakhon and Harmata[2] synthesized a rigid analog of the inhibitory neurotransmitter gamma-aminobutyric acid via an initial exhaustive dechlorination of the PCA adduct with a 2-substituted furan. However, as far as we know, this chemical is not available from laboratory chemical catalogs. To our knowledge, the only reported procedure for making polychlorinated acetone uses chlorine gas in the presence of an organic base for the nonselective substitution of hydrogen atoms in acetone. This results in a mixture of products that has to be separated in a tedious distillation step to give PCA in low yield.[3] Therefore, we believe it is useful to disclose our results on the preparation of PCA under Appel conditions,[4] which can be performed with readily available starting materials at room temperature with work-up by filtration and simple distillation.

Our interest in PCA arose through our discovery of the dynamic resolution of phosphines through asymmetric oxidation under Appel conditions with chiral nonracemic alcohols, such as menthol.[5] In our studies we found that the electrophilic chlorine source used in the reaction plays a major role in determining the selectivity.[6] Notably there was a 40% increase in selectivity when switching from carbon tetrachloride to hexachloroacetone (HCA).[7] Since PCA is produced in these reactions, we then wished to study the reaction using PCA as a cross-check on the chlorine source. In contemporary organic chemistry it remains a substantial challenge to perform selective dechlorination[8] and, to our knowledge, there are no reports of the replacement of one chlorine atom out of six with hydrogen. It was therefore pleasing to discover that the Appel reaction itself could be manipulated to make PCA exclusively.

In preliminary investigations triphenylphosphine ($Ph_3P$) was used in our standard process with HCA in the presence of menthol and various other alcohols. The alcohol has to be chosen judiciously with respect to its reaction by-product, which can complicate the purification of PCA; for example, in the case of menthol the product neomenthyl chloride made the isolation of PCA by distillation tedious. However, much more seriously, we also found that, commonly, multiple dechlorination occurs, producing an inseparable mixture of HCA, PCA and symmetrical tetrachloroacetone (*sym*-TCA).[9] We gained some insight into this problem on monitoring the reaction by $^{31}P$ NMR spectroscopy. We concluded that the PCA formed in the reaction via the intermediate chlorophosphonium salt (**CPS A**, $\delta_P$ 64.5)[10] en route to the alkoxyphosphonium salt, (**APS-1**, $\delta_P$ 58.9)[11] probably competes with HCA for phosphine via the presumed intermediate **CPS B** ($\delta_P$ 73.3) to form TCA, leaving behind unreacted HCA (Scheme 1). We assume that the rates of reaction of $Ph_3P$ with both HCA/PCA would be similar but the PCA can build-up in the presence of HCA if the reaction of **CPS-A** with the alcohol is faster.

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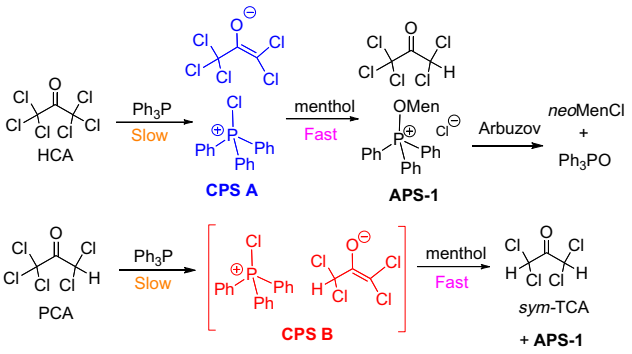
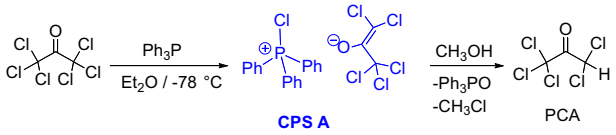



**Scheme 1.** Plausible route for the formation of both PCA and TCA under Appel conditions with menthol.

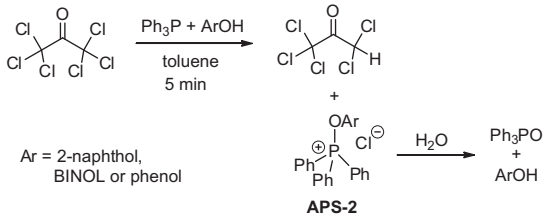
A simple way to avoid the production of *sym*-TCA would be to form **CPS-A** initially in the absence of alcohol. Thus $Ph_3P$ and HCA were mixed at −78 °C to pre-form **CPS A** quantitatively, followed by reaction with methanol in diethyl ether. As well as giving PCA exclusively (Scheme 2, Protocol A)[12] this also provided support for the proposals in Scheme 1. However the synthesis has some drawbacks. Although the materials are cheap, for operational reasons, they have to be run rather dilute and a low temperature has to be used to minimize a number of other possible reaction pathaways.[13] This is not ideal because **CPS** is particularly susceptible to moisture. In addition, the by-product, methyl chloride, is also undesirable due to its toxicity.

An option would have been to switch to a higher alcohol but we discovered a better approach by the use of a phenol. In this case **CPS-A** does not have to be pre-formed because the reduced nucleophilicity of the phenol slows down the second step in Scheme 1, which means that PCA does not build up enough to compete with HCA for phosphine. Better still, the phenol also leads to an aryloxyphosphonium salt. This stops the reaction at the **APS** stage, it being unable to undergo the required Arbuzov reaction under the reaction conditions. This salt is insoluble in the reaction medium and can simply be filtered, giving a very easy purification. The reaction can now be performed at room temperature by dissolving triphenylphosphine and phenol in dry toluene followed by the dropwise addition of HCA (Scheme 3, Protocol B).[14,15] Soon after the first drops of HCA enter the reaction flask, the aryloxyphosphonium salt (**APS-2**) precipitates. Filtration and removal of the solvent is then followed by distillation under reduced pressure from a small amount of triphenylphosphine oxide. Furthermore, hydrolysis of **APS-2** produces triphenylphosphine oxide, releasing the phenol which can be reused in the process if required. Various phenols were tried such as BINOL and phenol itself, but inexpensive 2-naphthol proved most convenient. Replacing toluene with diethyl ether as the solvent produced a mixture of HCA, PCA and *sym*-TCA, with the latter predominating, consistent with the speeding up again of the second step in Scheme 1.

In conclusion, we have presented an easy and convenient synthetic route for the selective preparation of pentachloroacetone in high yield through the Appel process. This process for making PCA is significant as there are no previously reported methods




**Scheme 2.** Synthesis of PCA using methanol (Protocol A).




**Scheme 3.** Synthesis of PCA using phenols (Protocol B).

available to perfom such a selective dechlorination of HCA. We hope this new method will allow other workers to further explore the usefulness of PCA. We will disclose later the results of the use of various electrophilic chlorine sources including PCA in the asymmetric Appel reaction.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.101.

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12. Protocol A: A dry double-necked round-bottomed flask was charged with $Ph_3P$ (2.0 g, 1 equiv, 7.6 mmol) dissolved in dry $Et_2O$ (80 mL). To this HCA (2.2 g, 1.1 equiv, 7.6 mmol) dissolved in dry $Et_2O$ (10 mL) was added dropwise at −78 °C. The reaction was allowed to stir for 5–10 min. Dry MeOH (0.34 mL, 1 equiv, 7.6 mmol) was added at −78 °C to the mixture which was then allowed to warm to room temperature. The solvent was removed using a rotary evaporator; cyclohexane (20 mL) was added to reaction mixture which caused $Ph_3PO$ to precipitate from the solution. The phosphine oxide was

filtered off and the solvent removed from the filtrate using a rotary evaporator. This was followed by distillation at reduced pressure (bp 55–60 °C at 0.3 mm Hg) to give PCA as a colourless oil (1.33 g, 76%).

13. For example, a second phosphine can react with the CPS to form a bis-phosphonium salt, which in turn can lead to several derived products (this is a pathway known from the original work of Appel).[4]
14. Protocol B: A dry double-necked round-bottomed flask was charged with $Ph_3P$ (2.0 g, 1 equiv, 7.6 mmol), 2-naphthol (1.1 g, 1 equiv, 7.6 mmol), and dry toluene (10 mL). To this mixture was added HCA (2.0 g, 1 equiv, 7.6 mmol) dissolved in dry THF (5 mL) slowly and dropwise. As the first drops of HCA entered the reaction mixture a white solid precipitated ($^{31}P$ NMR $\delta$ 66.5). Once the addition of HCA was complete the mixture was allowed to stir for 5–10 min and the salts filtered through a sintered funnel and washed twice with toluene (2 × 10 mL). The solvent was removed using a rotary evaporator, followed by distillation at reduced pressure (bp 55–60 °C at 0.3 mm Hg) to give PCA as a colourless oil (1.50 g, 85%). $^1H$ NMR (400 MHz, $CDCl_3$,) $\delta$ 6.7 (s, 1H). $^{13}C$ NMR (101 MHz, $CDCl_3$,) $\delta$ 179.5 (C=O), 92.3 ($Cl_3C$=O), 61.7 ($CHCl_2$-C=O), $^{13}C$ DEPT-NMR (101 MHz, $CDCl_3$,) $\delta$ 61.4 (CH-C=O). FT-IR (KBr) $\nu_{max}/cm^{-1}$ 3019, 1786. Electrospray ($ES^-$) 227.84, 229.84, 230.84, 231.84, 233.84, 235.84. HRMS Calcd Mass 227.8470; Found 227.8474 [see Supplementary data for NMR spectra].
15. Full spectral characterisation of PCA is given in the Supplementary data.