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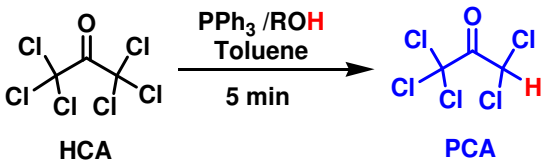
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An easy and short preparation of pentachloroacetone by selective dechlorination of hexachloroacetone under Appel conditions.

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ABSTRACT

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

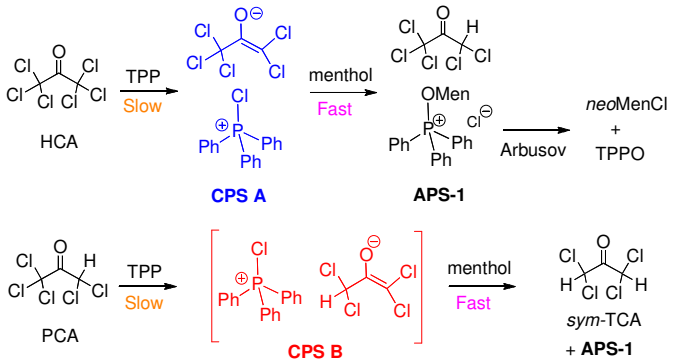
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Pentachloroacetone (PCA) was developed by Föhlisch and co-workers[1a,b] as a useful starting material for the generation of chloro-substituted oxyallyl intermediates, which are valuable components for [4+3] cycloaddition reactions. They used the method 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] synthesised 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 in laboratory chemicals suppliers' catalogues. To our knowledge, the only reported procedure for making polychlorinated acetone uses chlorine gas in the presence of an organic base for the non-selective 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 for 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 non-racemic 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 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.

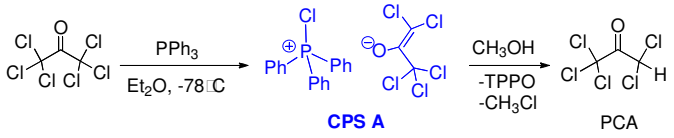
In preliminary investigations triphenylphosphine (TPP) was used in our standard process with HCA in the presence of menthol and various other alcohols. The alcohol has to be chosen judiciously with respect to its reaction by-product, which can complicate the purification of the PCA – e.g. in the case of menthol the product neomenthyl chloride made the isolation of PCA by distillation tedious. However, much more seriously, we also found that, commonly, multiple declorination 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. We concluded that the PCA formed in the reaction *via* the intermediate chlorophosphonium salt (**CPS A**, δ_P 64.5 ppm)[10] on route to the alkoxyphosphonium salt, (**APS-1,** δ_P 58.9 ppm)[11] probably competes with HCA for phosphine *via* the intermediate **CPS B** (δ_P 73.3 ppm) to form TCA, leaving behind unreacted HCA (Scheme 1). We assume that the rates of reaction of TPP 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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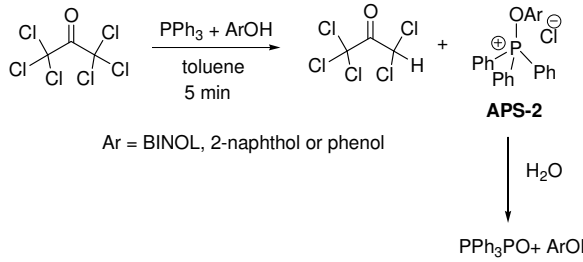
Scheme 1 Plausible route for the formation of both PCA and TCA under Appel conditions with menthol

A simple way to avoid the production of *sym*-TCA would be to form **CPS-A** initially in the absence of alcohol. Thus phosphine and HCA were mixed at -78 ˚C to pre-form **CPS A** quantitatively, followed by reaction with methanol in diethyl ether. As well 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, it has to be run rather dilute and low temperature has to be used to minimise a number of other possible reaction pathaways.[13] The is not ideal because the **CPS** is particularly susceptible to moisture. In addition, the by-product methyl chloride is also undesirable due to its toxicity.



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

An option would have been to switch to a higher alcohol but we discovered a better approach by use of an aromatic alcohol. In this case **CPS-A** does not have to be pre-formed because the reduced nucleophilicity of the alcohol slows down the second step in Scheme 1, which means that the PCA does not build up enough to compete with the HCA for phosphine. Better still, the aromatic alcohol 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 alcohol in dry toluene followed by the dropwise addition of HCA (Scheme 2, 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 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 aromatic alcohol which can be reused in the process if required. Various aromatic alcohols were tried such as BINOL and phenol but the 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.



Scheme 3: Synthesis of PCA using aromatic alcohols (Protocol B)

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 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 various electrophilic chlorine sources including PCA in the asymmetric Appel reaction.

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12. **Protocol A**: A dry double necked round bottom flask was charged with triphenylphosphine (2.0 g, 1 equiv., 7.6 mmol) dissolved in dry diethyl ether (80 mL). To this HCA (2.2 g, 1.1 equiv., 7.6 mmol) dissolved in dry diethyl ether (10 mL) was added dropwise at -78°C. The reaction was allowed to stir for 5-10 min. Dry methanol (0.34 mL, 1 equiv, 7.6 mmol) was added at -78°C to the reaction 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 triphenylphosphine oxide to precipitate out of the solution. The phosphine oxide was then filtered off and 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 an pathway known from the original work of Appel (ref [4]).
14. **Protocol B**: A dry double necked round bottom flask was charged with triphenylphosphine (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 δ 66.5). Once the addition of HCA was complete the reaction mixture was allowed to stir for 5-10 min and the salts filtered through a sintered funnel and washed twice with toluene (2 x 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%). ^{1}H-NMR (400 MHz, $CDCl_3$,) δ 6.7 (s, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$,) δ 179.5 (C=O), 92.3 (Cl_3C=O), 61.7 ($CHCl_2$-C=O), ^{13}C Dept-NMR (101 MHz, $CDCl_3$,) δ 61.4 (CH-C=O). FT-IR (KBr) ν_{max}/cm^{-1} 3019, 1786. Electrospray (ES^-) 227.84, 229.84, 230.84, 231.84, 233.84, 235.84. HRMS Calc. Mass 227.8470 Mass Found 227.8474. [see SI for NMR spectra]
15. Full spectral characterisation of the product PCA is given in the Supplementary Information