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An optimized and scalable synthesis of propylphosphonic anhydride for general use

Hana Pizova, Pavel Bobal *

Department of Chemical Drugs, Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences Brno, Palackeho 1/3, 612 42 Brno, Czech Republic

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ABSTRACT

Propylphosphonic anhydride (T3P®) is an effective coupling and dehydrating agent, which has been used for a large number of chemical transformations. An efficient and versatile synthetic method is described to synthesize propylphosphonic anhydride (T3P®) in pure form, in an overall yield of 51% in four steps from commercially available diethyl phosphonate.

Propylphosphonic anhydride (**1**), (PPAA, T3P®) was originally developed as a coupling reagent for peptide synthesis,[1,2] but it is also used as a dehydrating agent with many advantages. These include high reaction yields, low impurity profiles due to the water solubility of the by-products formed from this reagent, and associated with easy work-ups. The reduced epimerization tendency and low toxicity make propylphosphonic anhydride a reagent of choice, even for large-scale synthesis.

There are more than 200 scientific articles and patent applications published describing the utilization of T3P® for different types of transformations. From this large number of papers we must at first mention the use of T3P® as a peptide-coupling promoter.[1–4] It is superior to many widely used phosphorus-containing coupling reagents.[4] As a coupling reagent, it has also found application in the synthesis of Weinreb amides,[5,6] esters,[7] β-lactams,[8] hydroxamic acids,[9] and acid azides.[10] Several methods utilize T3P® in dehydration processes, for example, the direct conversion of aldehydes into nitriles,[11] formamides into isonitriles and carboxylic acids or amides into nitriles,[12] and alcohols into alkenes.[13] The other applications of this reagent for the formation of various heterocycles have been compiled in a review article.[14] T3P® has also been successfully used as a promoter of Beckmann,[15] Curtius,[16] and Lossen[17] rearrangements.

Although propylphosphonic anhydride is commercially available as 50 wt % solution the solvent range is quite limited. Generally it is sold in ethyl acetate and*N*,*N*-dimethylformamide (DMF). But for many applications, these two solvents are not appropriate. Ethyl acetate often contains significant amounts of ethanol and acetic acid, which might interfere with the reacting substances forming either ethyl esters or derivatives of acetic acid. This can often lower the yield of the reaction. In addition, at elevated temperatures, ethyl acetate might react with certain components of the reaction mixture. The other solvent in which T3P® is commercially available is *N*,*N*-dimethylformamide. This solvent has many advantages over ethyl acetate such as better stability to nucleophiles and better solubility properties. On the other hand, liberation of dimethylamine from DMF under certain conditions may hamper many reactions. Furthermore, removal of DMF from the reaction mixture is rather difficult and often makes chromatographic purification necessary. In general, one criterion for selection of a suitable solvent for a reaction is its stability, that is, the solvent does not react with the components in the reaction mixture. Therefore, for many reactions, the solvent of choice is an inert one. If we think about amide bond formation, solvents such as toluene, methylene chloride, or ether-type solvents are appropriate. This fact encouraged us to investigate the synthesis of T3P® in neat form with further application in a solvent of choice.

However, the synthesis of T3P® in an economical fashion from simple starting materials is difficult. Hence there is a need to develop improved and convenient methods for the synthesis of

* Corresponding author. Tel.: +420 54156 2927.
E-mail address: bobalp@vfu.cz (P. Bobal).

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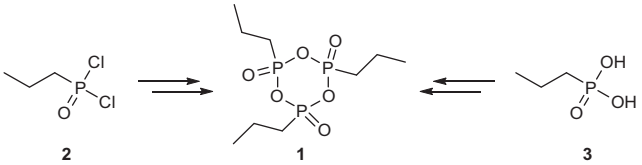
propylphosphonic anhydride (T3P®) from readily available dialkyl phosphonates.

Besides Wissmann's procedure[1,2] the synthesis of T3P® **1** has been described vaguely in the patent literature[18–20] without any optimized procedure (Scheme 1). Many patent procedures have been tested without satisfactory results. In the original procedure[1] for the synthesis of T3P®, propylphosphonic dichloride (**2**) was used as the starting material. Its partial hydrolysis followed by heating led to formation of T3P® **1**, which was used without further purification by distillation. The drawback of this procedure was the liberation of a large amount of HCl and the fact that propylphosphonic dichloride (**2**) is not readily available nowadays. In addition, the synthesis of propylphosphonic dichloride (**2**) using $AlCl_3$ and PCl_3[21] or PCl_5[22] is rather unpleasant. The other method consists of two steps.[18] In the first step, propylphosphonic acid (**3**) is treated with acetic anhydride at elevated temperature to form an oligomeric phosphonic acid anhydride intermediate **4** (Fig. 1), which is then distilled under reduced pressure.

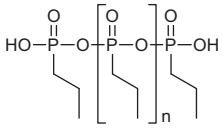
Of the two methods, the latter would appear to be the more convenient. Therefore our attention was focused on the optimization of this procedure. The starting propylphosphonic acid is available in a limited quantity as a laboratory reagent. So we decided to start the synthesis from trialkyl phosphites or dialkyl phosphonates.

Traditionally, alkyl phosphonates are prepared via the Michaelis–Arbuzov[23,24] or the Michaelis–Becker reactions.[25] Thus, we initially tested the Michaelis–Arbuzov reaction[23,24] of 1-bromopropane with triethyl phosphite (**5**). The reaction was carried out from 70 °C to 90 °C. According to GC–MS analysis, formation of a mixture of products occurred. Besides the desired diethyl propylphosphonate (**6**) and residual phosphite **5**, formation of diethyl ethylphosphonate (**7**) and triethyl phosphate (**8**) as side products was observed (Scheme 2). The first side product (**7**) was formed from liberated bromoethane, and triethyl phosphate (**8**) was the product of oxidation of triethyl phosphite (**5**). In order to reduce the formation of side products the reaction was carried out with a large excess of bromopropane, but the effect on the impurity profile was negligible. Attempts to separate the products formed were unsuccessful. We also tested the Michaelis–Becker reaction[25] according to the patent procedure.[22] Unfortunately, the reaction of 1-bromopropane with dimethyl phosphonate (**9**) in the presence of NaH as the base in anhydrous diethyl ether did not give the desired intermediate. According to GC–MS analysis, formation of dimethyl propylphosphonate (**11**) was not achieved, probably due to the low reaction temperature or the poor solubility of the



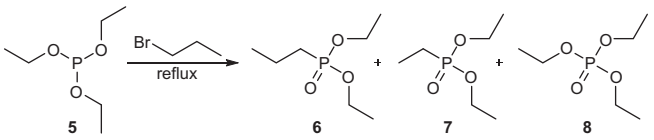
2 1 3

Scheme 1. Synthesis of propylphosphonic anhydride (T3P®).



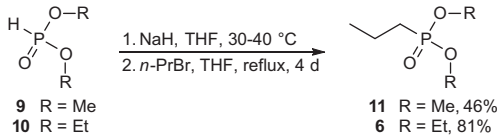
4

Figure 1. The general structure of oligomeric phosphonic acid anhydride intermediate **4**.



5 6 7 8

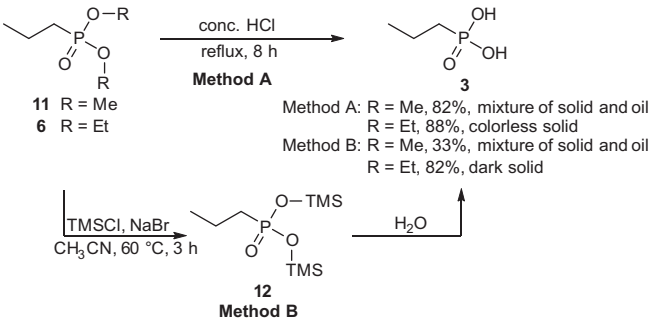
Scheme 2. Michaelis–Arbuzov reaction of 1-bromopropane with triethyl phosphite.



9 R = Me
10 R = Et

11 R = Me, 46%
6 R = Et, 81%

Scheme 3. Michaelis–Becker reaction of dialkyl phosphonates.



11 R = Me
6 R = Et

3

Method A: R = Me, 82%, mixture of solid and oil
R = Et, 88%, colorless solid
Method B: R = Me, 33%, mixture of solid and oil
R = Et, 82%, dark solid

12
Method B

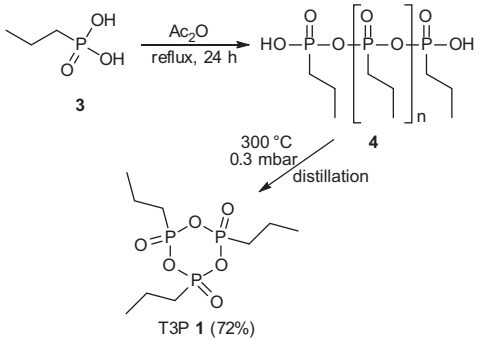
Scheme 4. Scope of the hydrolysis of dialkyl phosphonates.

sodium salt of dimethyl phosphonate in diethyl ether. To overcome this problem, the solvent was exchanged for anhydrous tetrahydrofuran. In this case, dimethyl propylphosphonate (**11**) containing a small amount of methyl propyl propylphosphonate was isolated in 46% yield (Scheme 3).

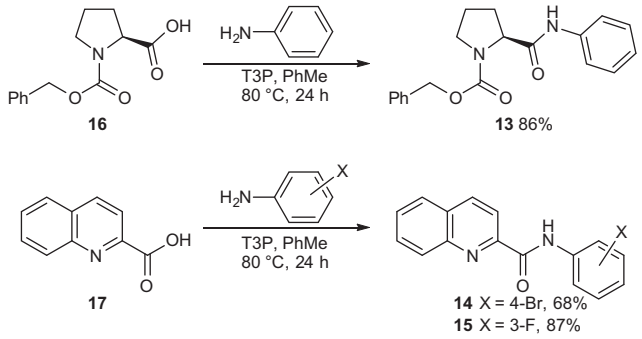
Hydrolysis of the phosphonate prepared was performed by two methods (Scheme 4). The first tested (method A) was hydrolysis with concentrated hydrochloric acid.[22] During heating, the reaction mixture became dark in color and the resulting acid was difficult to purify. All attempts to optimize the recrystallization failed and the crystalline product **3** contained a large amount of a yellow oily residue. Purification via the disodium salt together with extraction with an organic solvent and subsequent conversion back into the acid was successful, but lengthy and difficult, because the acid was highly soluble in water. However, we managed to isolate the acid **3** in 29% yield.

We next attempted to progress through transesterification to silyl ester **12** and its subsequent hydrolysis (method B) to the acid **3**.[26–28] The reaction proceeded without problems, but we again encountered the same problem with an oily residue present in the crystalline propylphosphonic acid after isolation, and the yield of this reaction was only 33%. Furthermore, the intermediate was contaminated with iodine formed from the Me_3SiCl/KI system used in this transformation.

A significant improvement was achieved when instead of dimethyl phosphonate (**11**), the diethyl homologue **6** was used. The Michaelis-Becker reaction of diethyl phosphonate (**10**) with 1-bromopropane proceeded without the formation of a mixed ester and the product was isolated in 81% yield after distillation (Scheme 3). The transesterification into silyl ester **12**, followed by hydrolysis in aqueous medium at room temperature led to an acid in 71% yield (Scheme 4). The formation of iodine was eliminated by



Scheme 5. Synthesis of propylphosphonic anhydride (**1**).



Scheme 6. Examples of tested amide couplings.

using Me_3SiCl/NaBr and the yield reached 82%, however, the purity of the product was not satisfactory. On the other hand, simple hydrolysis with concentrated hydrochloric acid was superior and pure off-white propylphosphonic acid (**3**) was isolated in 88% yield.

The transformation into T3P® was carried out in refluxing acetic anhydride for 24 h with subsequent distillation of oligomeric phosphonic acid anhydride intermediate**4** (Scheme 5). We found that reflux in acetic anhydride for 8 hours as described in a patent[18] was not sufficient, so we extended the time to 24 h. Residual acetic anhydride and acetic acid were removed under reduced pressure on a rotary evaporator. Distillation was carried out in a simple short-path bulb-to-bulb distillation apparatus (Kugelrohr) at a pressure of 0.3 mbar. In order to achieve a sufficient degree of cyclization to propylphosphonic anhydride (**1**), the temperature during the distillation had to reach 300 °C.

Propylphosphonic anhydride (**1**) was isolated as a colorless, highly viscous oil and could be stored in pure form in a closed container for several months without decomposition. After warming it could be removed from the container and transferred to a reaction flask. Compatible solvents such as toluene, tetrahydrofuran, methylene chloride, etc., can be added and the reagent applied for further use as a solution. Standard 50 wt % solutions were tested in amide formation. We have demonstrated the efficacy of the T3P® prepared in this manner for the synthesis of heterocyclic anilides**13**–**15** and have compared this method with traditional procedures.[29–31] The results were compared with those cited in the literature and it was found that the anilides (Scheme 6) prepared using this protocol were obtained in comparable or improved yields and purities.

In conclusion, we have developed an optimized and versatile method for the synthesis of cyclic propylphosphonic anhydride (T3P®), which can be conveniently applied to a wide variety of chemical transformations. This simple process, which features four simple high-yielding steps from commercially available diethyl phosphonate, represents a superior alternative method to produce this important green reagent in comparison with literature reports. The prepared propylphosphonic anhydride either neat, or as a solution in the solvent of a choice, shows activity comparable with or better than commercial solutions. In addition, a few examples of amide bond formation have been highlighted with very good results. Investigations on the use of this reagent in amide coupling for the synthesis of new biologically active compounds are underway in our laboratory.

Representative procedures are described

Diethyl propylphosphonate (**6**).[22] To a mixture of 17.4 g (0.73 mol) of NaH (free of mineral oil) in 100 ml of anhydrous THF was added a solution of 50.0 g (0.36 mol) of dry diethyl phosphonate (**10**) in 50 ml of anhydrous THF at 30–40 °C, and the mixture was stirred overnight. Next, a solution of 49.0 g (0.4 mol) of 1-bromopropane in 50 ml of anhydrous THF was added dropwise and the mixture was heated under reflux for 4 d under an argon atmosphere. To the mixture was slowly added 130 ml of H_2O followed by extraction with Et_2O (3 × 150 ml). The organic layer was dried over anhydrous $MgSO_4$ and the solvents were removed under reduced pressure. Distillation of the residue gave 52.7 g (81%) of diethyl propylphosphonate (**6**).

Propylphosphonic acid (**3**).[22] Method A. A mixture of 20.00 g (0.11 mol) of diethyl propylphosphonate (**6**) and 100 ml of concentrated HCl was heated under reflux for 8 h. Next, one half of the volume of acid was removed by atmospheric distillation and the remainder was evaporated to the dryness under reduced pressure on a rotary evaporator. The crude solid was triturated with hexane and filtered to yield 12.1 g (88%) of propylphosphonic acid (**3**) as off-white crystals.

Method B. To a solution of 3.00 g (0.02 mol) of diethyl propylphosphonate (**6**) in 10 ml of dry MeCN, 5.43 g (0.05 mol) of TMSCl and 5.14 g (0.05 mol) of dry NaBr were added. The mixture was heated at 60 °C for 3 h. Precipitated NaCl was filtered off and the solvent and low boiling materials were evaporated under reduced pressure. The residue was treated with 10 ml of H_2O and stirred at room temperature overnight. The mixture was washed with hexane (2 × 10 ml) and evaporated to dryness. The residue was triturated with hexane and the remaining solid material was filtered to give 1.46 g (71%) of propylphosphonic acid (**3**).

Propylphosphonic anhydride (**1**).[18] Propylphosphonic acid (**3**) 10.00 g (0.08 mol) was dissolved in 53 ml (0.56 mol) of Ac_2O in a round-bottomed flask. The solution was heated under reflux for 24 h under an argon atmosphere. Residual Ac_2O and AcOH were evaporated under reduced pressure on a rotary evaporator and the oligomeric phosphonic acid anhydride **4** was distilled using a Kugelrohr apparatus at 300 °C/0.3 mbar to yield 6.17 g (72%) of cyclic propylphosphonic anhydride (**1**) as a colorless viscous oil, which could be dissolved in inert organic solvents with the aid of sonication.

Acknowledgements

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Supplementary data

Supplementary data (Further experimental details, GC data, NMR and MS spectra for compounds **1**, **3**, **6** and **13**–**15**.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.02.126.

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