

# SYNLETT Spotlight 198

## T3P: A Convenient and Useful Reagent in Organic Synthesis

Compiled by Ariel L. Llanes García



This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

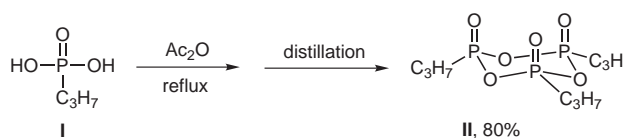
Ariel L. Llanes García was born in 1971 in Santa Clara, Cuba. He received his B.Sc. from Central University of Las Villas in 1994 and he obtained his M.Sc. degree from the University of La Havana in 1999. In the same year, he moved to Campinas, SP, Brazil, where he is currently working towards his Ph.D. under the supervision of Prof. Carlos Roque D. Correia at the State University of Campinas. His research is focused on the development of new synthetic methodologies using cross-coupling reactions with palladium-based catalysts.

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### Introduction

T3P is a highly reactive *n*-propyl phosphonic acid cyclic anhydride (**II**, Scheme 1) originally designed as a coupling agent.<sup>1</sup> T3P works both as coupling and as water removal reagent, offering several advantages over traditional reagents, such as high yields and purity, low toxicity, broad functional group tolerance, low epimerization tendency without any additives, and easy work-up (only water-soluble by-products, eliminating the need of chromatographic columns).<sup>1,2</sup> It can be prepared from the reaction of propyl phosphonic acid (**I**, Scheme 1) with acetic anhydride at a temperature preferably in the range of 70–110 °C; then the oligomeric phosphonic acid anhydride intermediate is distilled at 0.01–50 mbar and a temperature range of 200–350 °C. The cyclic anhydride **II** is immediately dissolved in an inert organic solvent.<sup>3,4</sup>



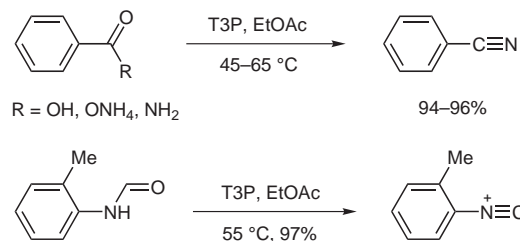
**Scheme 1** Preparation of T3P

Although T3P has been mainly used as an effective and mild condensation reagent in peptide and peptidomimetic synthesis,<sup>1–3,5</sup> new applications have recently been developed for this reagent, which include direct conversion of carboxylic acids into nitriles,<sup>6</sup> dehydrations of amides to nitriles,<sup>6</sup> formation of Weinreb amides,<sup>7</sup>  $\beta$ -lactam synthesis,<sup>8</sup> ester formations,<sup>9</sup> thiohydroxamic acid anhydride syntheses,<sup>10</sup> preparation of heterocycles,<sup>11</sup> alcohol oxidations,<sup>12</sup> and acylations.<sup>13</sup> The diverse advantages and applications of T3P show its potential as a reagent in organic synthesis.

### Abstracts

(A) Direct conversion of carboxylic acids and amides into nitriles, and conversion of formamides into isonitriles:

Meudt and co-workers<sup>6</sup> have reported a novel method for producing nitriles and isonitriles by using dehydration reactions with T3P. This methodology furnishes excellent yields by reacting a) carboxylic acid amides, ammonium salts of carboxylic acids, or carboxylic acids in the presence of ammonia or ammonium salts or b) formamides or mixtures of amines with formic acid or ethyl formate, with T3P.



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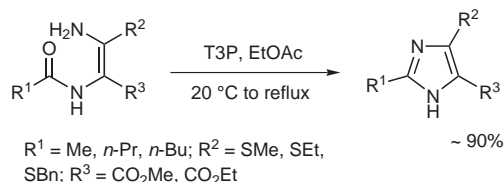
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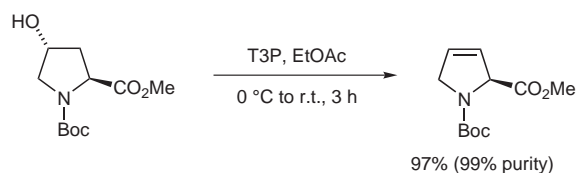
## (B) Preparation of substituted heterocycles:

S-Alkyl(aryl)imidazole derivatives can be prepared in high yields and very high purities by cyclization of the corresponding aminoacrylic acid esters in the presence of T3P.<sup>11</sup>



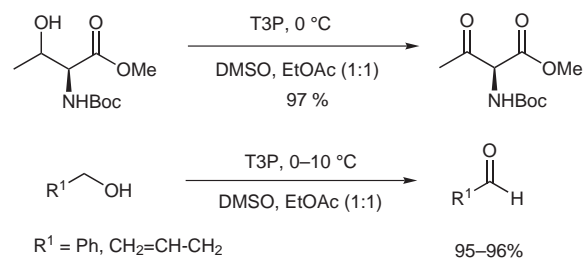
## (C) Alkene synthesis from alcohols:

Alkenes can be prepared by the reaction of primary, secondary, or tertiary alcohols with T3P under very mild conditions, without isomerization and in high yields and purities.<sup>14</sup>



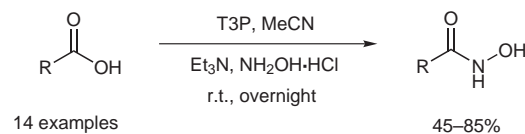
## (D) Alcohol oxidation:

Meudt and co-workers<sup>12</sup> have reported a very mild method, free of heavy metals, for the production of aldehydes and ketones by reacting primary and secondary alcohols with T3P in the presence of DMSO. This method is a variation of the Swern oxidation and avoids the use of the expensive and hazardous oxalylchloride. Furthermore, this variation improves the selectivity on commercial scale.

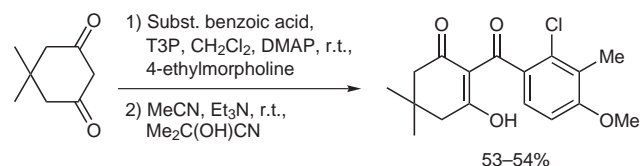


## (E) Hydroxyamidation of carboxylic acids:

Appendido and co-workers<sup>15</sup> showed that T3P is a selective reagent to convert carboxylic acids into hydroxamic acids. The method was especially suitable for labile substrates, whose activation via chloride is not trivial, for  $\alpha,\beta$ -unsaturated acids, which do not tolerate large excess of hydroxylamine, and for hydroxyacids, whose oxyamidation with other protocols would require hydroxyl protection.



(F) Acylation reactions (C–C coupling reactions): T3P was used for mild acylation reactions on pharmacophores like 1,3-cyclohexanediones and 1-substituted 5-pyrazolols, giving moderate yields.<sup>13</sup>



## References

- (1) (a) Wissmann, H.; Kleiner, H.-J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 133. (b) Escher, R.; Bünning, P. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 277.
- (2) Glauder, J. *Speciality Chemicals Magazine* **2004**, *24*, 30; and references cited therein.
- (3) Wehner, M.; Kirschbaun, B.; Deutscher, L.; Wagner, H. J.; Hoessl, H. PCT Int. Appl. WO 2005014604, **2005**; *Chem. Abstr.* **2005**, *142*, 198208.
- (4) T3P is a trade name and it is commercially available as a 50% (w/w) solution in DMF, EtOAc, or BuOAc.
- (5) (a) Zadnard, R.; Schrader, T. *J. Am. Chem. Soc.* **2005**, *127*, 904. (b) Rzepecki, P.; Gallmeier, H.; Geib, N.; Cernovska, K.; König, B.; Schrader, T. *J. Org. Chem.* **2004**, *69*, 5168. (c) Davies, J. S. *J. Pept. Sci.* **2003**, *9*, 471.
- (6) Meudt, A.; Scherer, S.; Nerdinger, S. PCT Int. Appl. WO 2005070879, **2005**; *Chem. Abstr.* **2005**, *143*, 172649.
- (7) Burkhart, F.; Hoffmann, M.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1191.
- (8) Crichfield, K. S.; Hart, J. E.; Lampert, J. T.; Vaid, R. K. *Synth. Commun.* **2000**, *30*, 3737.
- (9) Wedel, M.; Walter, A.; Montforts, F.-P. *Eur. J. Org. Chem.* **2001**, 1681.
- (10) (a) Hartung, J.; Schwarz, M. *Synlett* **2000**, 371. (b) Schwarz, M. *Synlett* **2000**, 1369.
- (11) Holla, W.; Napierski, B.; Rebenstock, H.-P. Ger. Offen. DE 19802969, **1999**; *Chem. Abstr.* **1999**, *131*, 131507.
- (12) Meudt, A.; Scherer, S.; Böhm, C. PCT Int. Appl. WO 2005102978, **2005**; *Chem. Abstr.* **2005**, *143*, 440908.
- (13) Hermann, S. Ger. Offen. DE 10063493, **2002**; *Chem. Abstr.* **2002**, *137*, 47003.
- (14) Meudt, A.; Scherer, S.; Böhm, C. PCT Int. Appl. WO 2005123632, **2005**; *Chem. Abstr.* **2005**, *144*, 69544.
- (15) (a) Ech-Chahad, A.; Minassi, A.; Berton, L.; Appendido, G. *Tetrahedron Lett.* **2005**, *46*, 5113. (b) Appendido, G.; Minassi, A.; Berton, L.; Moriello, A. S.; Cascio, M. G.; De Petrocellis, L.; Di Marzo, V. *J. Med. Chem.* **2006**, *49*, 2333.