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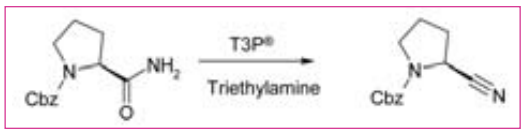
Recent advances in high-performance condensations

ABSTRACT

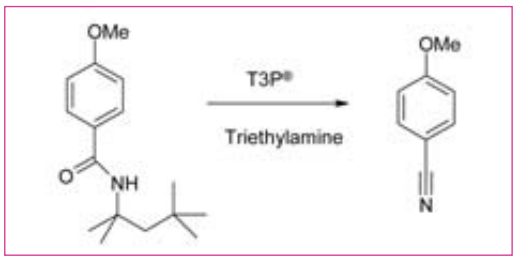
Propane phosphonic acid anhydride, T3P®, is a condensation reagent which has shown wide applicability in amide / peptide bond formations. The advantages obtained when using T3P® include high yields, high selectivity, very low epimerisation, easy work-up and non-toxicity. We have now expanded the application of this reagent to other chemistries. T3P® may be used in the ready conversion of acids and amides to nitriles, the formation of isonitriles from formanilides and in Moffat-type oxidations of alcohols to aldehydes. This review examines these applications and gives a partial insight into the scope of use of this reagent. It is concluded that a test of T3P® in all kinds of condensations can be recommended, especially in those reactions where many functional groups are present.

REVIEW

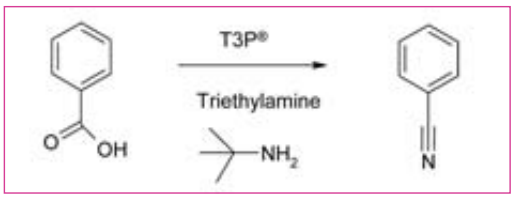
Propane phosphonic acid anhydride, T3P®, a reagent which is produced in large quantities by Archimica, has found many applications in amide and peptide bond formation reactions over the past years in the pharmaceutical and speciality fine chemical industries.
The reasons for its success are its beneficial properties in such chemistries, especially its very high selectivity, its very low level of racemisation/epimerisation compared to other coupling reagents, its easy application and its non-toxic properties.
These, combined with the high yields typically obtained, result in the development of very economic processes.
One of the major trends in today's organic chemistry is selectivity, as it ensures absence of tedious and costly purification procedures and results in economic processes while at the same time avoiding formation of even trace amounts of potentially hazardous by-products.
This is especially true for pharmaceutical fine chemicals, but increasingly so for many other areas of chemistry. A very important source for highly selective new chemistries can be the identification of new applications using existing, readily available reagents.
This article covers new applications of T3P® which have recently been developed and which have in common that all the advantages of this unique reagent are fully maintained, resulting in high purity products in high yields and very economic processes (1).
The first new application to be mentioned in this overview is the conversion of amides to nitriles. As a first example, subjecting Octanoic acid amide to T3P® at 5°C for a short period of time results in quantitative conversion to the respective nitrile, which can be isolated in very attractive yields by simple distillation.
The same procedure also converts aromatic amides to their nitriles. This procedure allows such transformations also in multifunctional molecules, for which "traditional" nitrile-forming chemistries often fail due to side reactions with other functionalities. One convincing example demonstrating the outstanding selectivity of this reaction is the elimination of Z-protected proline amide to its nitrile without any detectable racemisation (2).



It would be even more desirable to develop a method for the direct conversion of acids to nitriles, as acids are much more common as naturally and commercially available raw materials.
This too can readily be achieved with propane phosphonic acid anhydride by simply adding a nitrogen source. Suitable nitrogen sources may be ammonia gas, an ammonium salt and a base, or a tertiary amine which cleaves off the respective olefin after initial amide bond formation.
To mention just one example for such a final cleaving procedure of a tertiary amine, the conversion of the amide shown below to 4-Methoxybenzonitrile is possible in 96 percent yield.

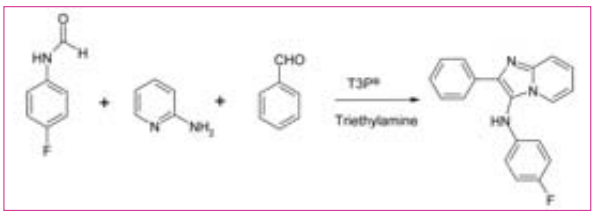


The direct transformation of acids to nitriles works accordingly, with the combination of a tertiary alkylamine and T3P®, in attractive overall yields.

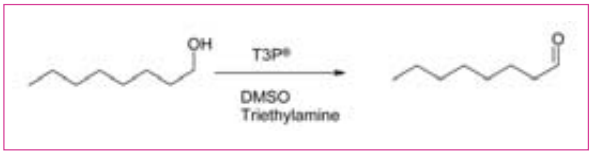


In another new application, T3P® can convert formanilides into isonitriles which can be subjected to a broad range of downstream reactions. In this respect, a mixture of formanilides and T3P® could be considered a "stable storage form" for isonitriles.

One attractive example is depicted below, showing a three component reaction and resulting in formation of an imidazopyridine in a quite straightforward process. Numerous other applications are possible and could potentially generate a large variety of heterocyclic products from single precursors. Again, several functional groups will not interfere because of the high selectivity of the reagent.



A last new application of this versatile reagent is oxidations. For conversions of alcohols to aldehydes, several selective methods have been developed in the past. However, they often suffer from severe practical problems.
For instance, in the classical Moffatt oxidation in which dicyclohexylcarbodiimide (DCC) is applied, removing the side-product dicyclohexylurea is problematic and such applications are often completely uneconomic. Overall, the problem of non-toxic, inexpensive and highly selective reagents for such oxidations without the need for tedious workup procedures is still to be solved.
We have found that the application of T3P® in Moffatt-type oxidations using DMSO results in very selective oxidation reactions. In a first example, an isolated yield of 75 percent of benzaldehyde was achieved in a small-scale experiment starting from benzyl alcohol, DMSO and T3P® at 0°C. So as to expand this chemistry to aliphatic substrates, octanal was synthesised from the respective alcohol at 0°C in good yields.
In both cases, no over-oxidation to the respective carboxylic acids was observed. Workup in all cases was very easy, due to the high water solubility of ring-opened T3P®. Thus, after completion of the oxidation, the mixture was hydrolysed by addition of water, the phases were separated, and the product was isolated in high purity by simple distillation.



These new applications of propane phosphonic acid anhydride are not fully optimised, as they have been developed to demonstrate the potential of this reagent in highly selective chemistries with model reactants.
It is safe to say that in all kinds of condensations, a test of T3P® can be recommended, especially in those reactions where more than just the functional groups involved in the desired reaction are present.

REFERENCES AND NOTES

1. Detailed procedures are available on request from the author.
2. Patents have been filed for these and many other reactions. For free of cost-licenses, please contact the author.

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