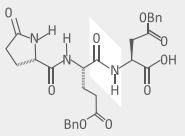
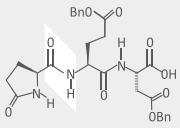
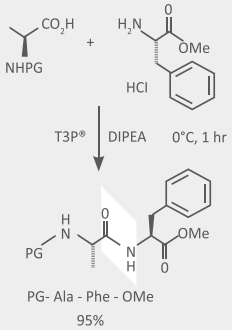
WE'VE GOT T3P® DOWN TO AN EXACT SCIENCE

T3P® – PROPANEPHOSPHONIC ACID ANHYDRIDE







The Coupling Reagent of the Future

T3P, propanephosphonic acid anhydride, is an exceptional reagent for amide/peptide bond formation. T3P is very easy to use and combines excellent reaction selectivity, almost no epimerization, high product purities and excellent yields. Because of its properties, hazardous additives, such as explosive HOBt, are not required. Additionally, the T3P reagent is nontoxic, nonallergenic/nonsensitizing and the salt by-products are nonhazardous and completely water soluble.

T3P also works well in other condensation reactions, such as esterifications. In addition, it may be used as a mild reagent for alcohol oxidations and the Lossen rearrangement.

T3P was developed for an industrial application because all known coupling reagents had severe technical disadvantages.

Recent Studies With T3P

In the last 10 years, T3P has attracted tremendous attention in research and development departments of almost all innovative pharmaceutical companies worldwide.

A number of citations report its excellent performance. T3P delivers process efficiencies that lead to more effective use of equipment while providing increased yields for more economical use of raw materials. At the same time, its application in industrial processes is very easy, yielding high-purity products.

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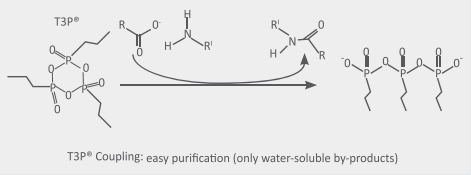


T3P® Coupling: easy purification (only water-soluble by-products)

Reaction Mechanism

T3P converts the oxygen of the carboxylic acid into a leaving group. The by-product formed by the leaving group can be easily extracted. The easy workup, mild reaction conditions and good conversion obtained with T3P make it ideal for commercial applications.

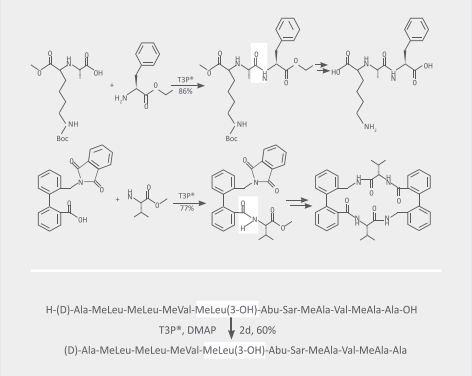
This is especially true for late stage synthetic steps or in the production of molecules with multiple chiral centers.

T3P: Peptide Coupling Performance Leader

In a performance comparison between T3P and other peptide coupling reagents for the preparation of a nonapeptide drug, it was found that T3P was superior to other reagents with regards to yield and low epimerization.[2]

	YIELD	EPIMERIZATION
T3P	86.6	1.8
DCC/HOBt*	60.5	5.9
EDC/HOBt*	67.3	11.1
TBTU	53.2	9.1
HBTU	65.6	16.1
PyClοP	4.1	-
PyBOP	63.4	14.2

*HOBt IS NOW CLASSIFIED AS AN EXPLOSIVE COMPOUND.[1]



H-(D)-Ala-MeLeu-MeLeu-MeVal-MeLeu(3-OH)-Abu-Sar-MeAla-Val-MeAla-Ala-OH
T3P®, DMAP, 2d, 60%
(D)-Ala-MeLeu-MeLeu-MeVal-MeLeu(3-OH)-Abu-Sar-MeAla-Val-MeAla-Ala

T3P as a Classical Peptide Coupling Reagent

T3P allows the synthesis of a peptide library with high yields and low epimerization resulting in a high throughput screening library without the need for costly column purification. Due to simple workup, with complete and easy removal of the by-product of T3P, this process is ideally tailored for high throughput screening equipment.[3]

T3P Is the Choice in Cyclizations

The selectivity of T3P allows cyclizations of high-value molecules like ciclosporin derivatives to proceed without additional steps to protect the MeLeu(3-OH) alcohol. This gives high yields that are otherwise unachievable.[4]

	PURIFICATION	YIELD	EPIMERIZATION	TOXICITY	PRICE/GRAM	OVERALL
T3P	• EASY	• HIGH	• LOW	• NOT TOXIC	• MEDIUM	• • • • •
EDC(WSC)	• EASY	• MEDIUM	• MEDIUM	• HIGH	• MEDIUM	• • • • •
TBTU/HBTU	• DIFFICULT	• HIGH	• LOW	• MEDIUM	• MEDIUM	• • • • •
PyClοP	• DIFFICULT	• HIGH	• LOW	• MEDIUM	• VERY HIGH	• • • • •
BOP	• DIFFICULT	• HIGH	• LOW	• VERY HIGH	• HIGH	• • • • •
DCC/HOBt	• VERY DIFFICULT	• MEDIUM	• MEDIUM	• HIGH	• LOW	• • • • •
DCC	• VERY DIFFICULT	• LOW	• HIGH	• HIGH	• LOW	• • • • •

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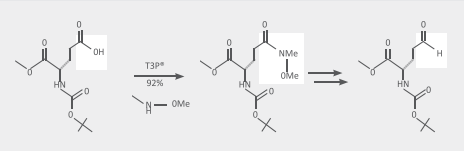
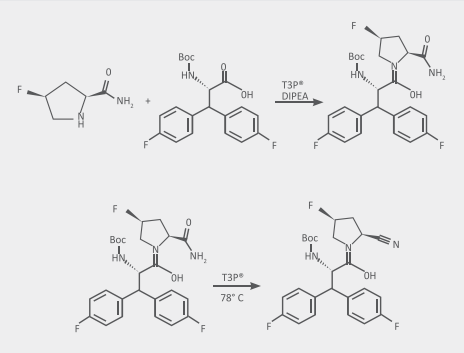


Mild Preparation of Weinreb Amides

Under mild conditions, T3P is the ideal activator for the formation of Weinreb amides. The selectivity of T3P results in almost no epimerization and high yields.

These Weinreb amides can be converted into aldehydes in high yield, while the chiral information is fully maintained.[5]

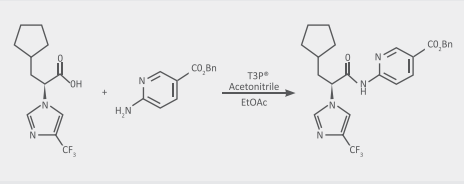


Preparation of Amides and Nitriles

T3P has been successfully applied in amide bond formation and in nitrile generation in an economic route to Denagliptin (GlaxoSmithKline).

In this synthesis, T3P gave superior yield over other alternative synthesis with no epimerization being observed.

T3P was found to be extremely cost-effective and provided a safe and efficient alternative to the use of HATU previously investigated.[6]



Amide Formation With Epimerization-Prone Substrates

With epimerization-prone substrates, T3P is the coupling reagent of choice. In development of a process for production of multi-kg quantities of a hepatoselective glucokinase activator (Pfizer) in which formation of an amide was the penultimate synthetic step, Dunetz [7,8] screened a wide range of traditionally used coupling reagents (e.g., DCC, EDC with or without HOBt, HATU etc.). T3P was selected for scale-up after showing that it was clearly superior in giving products minimal racemization and also being most suitable for scale-up. Further screening of T3P for amide formation with other racemization-prone substrates confirmed the general excellent application of T3P for such reactions.

Facts About T3P

MOLECULAR WEIGHT	318.19 G/MOL
EMPIRICAL FORMULA	$(C_3H_7O_2P)_3$
CAS NO.	68957-94-8
ASSAY T3P	> 50.0%
APPEARANCE	CLEAR COLORLESS TO BROWNISH
SHELF LIFE	DEPENDING ON SOLVENT, AT LEAST 1-2 YEARS IF STORED CORRECTLY

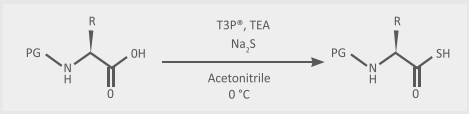
AVAILABLE SOLVENTS

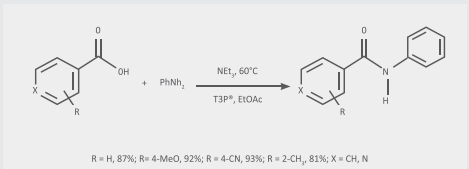
T3P is currently supplied as a 50% (w/w) solution in a variety of solvents allowing a greater adaptation and optimization to your process needs.

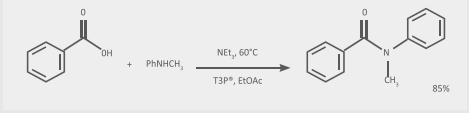
Solvents include:

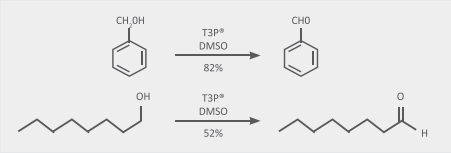
- Ethyl Acetate
- Butyl Acetate
- THF
- 2-MeTHF
- Toluene
- N,N-Dimethylformamide
- Chlorobenzene
- Methylene Chloride
- Acetonitrile
- Any other compatible solvent

Use of T3P often requires only a mixing stage at 0-25°C. High purity products can be easily isolated by hydrolysis of residual T3P and phase separation. This is a result of the ionic nature of the reaction by-products of T3P and removes the need for expensive chromatographic columns.









Selective Transformations of Multifunctional Molecules

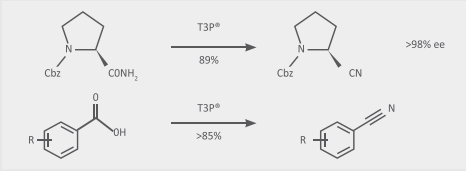
Research has shown that T3P is efficient for highly selective transformations of multifunctional molecules, including:

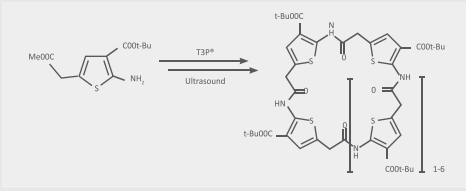
- Lossen rearrangement
- Synthesis of urea and carbamate derivatives[9]
- Formation of thioacids from N-protected amino acids and peptides.[10] Wide range of amino acids and peptides, including sterically hindered substrates, tested in this transformation giving typical yields of 80-95% with non-detectable levels of racemization; formed products were readily isolated using mild workup procedures
- Formation of anilides using free acids to obtain high yields[15]
- Formation of amino acid esters[11], such as:
  - Z-Tyr(BU)-O-cyclohexyl 91%
  - Z-Tyr(BU)-O-n-butyl 78%
  - Z-Tyr(BU)-O-n-hexyl 85%
  - Z-Tyr(BU)-O-isopropyl 83%
  - Z-Phe-OtBu 76%
  - Z-Asp(OtBu)-OEt 79%

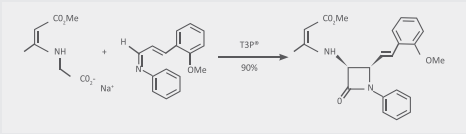
Formation of Substituted Heterocycles Water Removal Reagents with Acid Catalysis

T3P is a liquid organic equivalent to the highly reactive and hazardous P_2O_5 (phosphorous pentoxide) and PPA (polyphosphoric acid) chemical water removal reagents and, at the same time, it provides Lewis acid catalysis potential for reactions.[12]

Oxidation reactions, with very mild conditions (0-5 °C), easy workup and no heavy metals: The usual problems with the product separation from dicyclohexylurea by-product if DCC is used instead of T3P can be avoided.[15]







Conversion of acids to nitriles, with very mild conditions, high yields and easy application: Nitrile formation can be accomplished without interference with almost all other functional groups. A 96% isolated yield has been achieved already at a scale as high as several 100 kg in an example with a very complex substitution pattern.[15]

Synthesis of linear and cyclic oligoamides having a thiophene backbone has been carried out using T3P. The combination of an ultrasonic technique to diminish intramolecular backfolding of longer oligoamide chains and T3P as a coupling reagent leads to shorter reaction times and higher yields for both cyclic and linear oligomers.[13]

T3P can also be used in the formation of β-lactams, where very mild conditions are needed (0°C), in addition to full stereo control.[14]

Facts About T3P Safety and Ease of Handling

T3P is a reagent not classified as toxic or allergenic. It also reduces health and environmental risks in scaling up processes from the lab to commercial scale.

The T3P Process Development Service

The application of T3P is fundamentally different from any other commercially available coupling reagent.

AMRI has more than 25 years of experience in coupling reactions for a variety of chemical reactants from amides, heterocycles and esters and to carbon-carbon bonds.

This extensive knowledge base of coupling reactions allows AMRI to provide a free application program for T3P process development. With proper optimization support from AMRI, T3P is proven to be a better reagent than others in many cases.

The T3P application program is carried out under a confidentiality agreement and allows companies to maintain complete control of their intellectual property. Under the process development service, AMRI's expertise allows integration of the coupling and extraction steps required, and provides an optimum solution for commercial scale-up.

Quality Management

T3P is produced in an ISO 9001:2008 certified facility.

Availability

In Frankfurt Hoechst, Germany, we have large capacity and small-scale facilities dedicated to the manufacture of custom T3P solutions for our customers. A complementary T3P technical package is available upon request at clientservicesapi@amriglobal.com.

Notification

T3P is a registered trademark in accordance with statutory regulations. Before T3P can be released to our customers (even in sample quantities), we require the completion of end use declaration.

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