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Continuous, on-demand generation and separation of diphenylphosphoryl azide

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ABSTRACT

Diphenylphosphorylazide (DPPA) has been synthesized in microfluidics with near-100% yield in sub-3 minute residence time, affordably, and with a process design that minimizes hazards associated with hydrazoic acid (HN_3) production. A pilot-plant scale continuous process for the on-demand synthesis of diphenylphosphoryl azide (DPPA) that can readily be integrated with subsequent transformations was designed, built, and validated. Using Corning's Low Flow reactor system coupled to a membrane separator and in-line Fourier Transform Infrared (FTIR), DPPA was safely produced at a rate of 1 mol/hr as a 2.0 M anhydrous toluene stream. Continuous FTIR was able to reliably monitor product quality, purity and concentration, showcasing the ease and utility of this continuous flow process for manufacturing common, safe pharmaceutical precursors.

1. Introduction

Diphenylphosphoryl azide (DPPA)—a well-known azide reagent used in peptide couplings,[1,2] Curtius rearrangements,[3–6] and Mitsunobu inversions[7–9]—is often encountered in pharmaceutical process development because it enables the most direct route to a desired product. However, DPPA comes with the risk associated with all azides and is expensive for scale up of these processes, limiting DPPA use in production lines. Hydrazoic acid (HN_3) formation is of the greatest concern. HN_3 has a gas phase autoignition as low as 8%, and is highly volatile at process conditions (b.p. 37 °C).[10] Further, it is shock sensitive in condensed form, and reacts readily with heavy metals to form explosive azide salts that are commonly used as commercial detonators.[11–14] HN_3 also poses critical health effects upon exposure, forming strong complexes with hemoglobin to block O_2 transport in the blood. The recommended airborne exposure limit is 40 times lower than hydrogen cyanide.[15]

A number of recent reviews showcase the unique advantages of continuous flow systems for reliable and safe chemical transformations of azides.[16–18] Surprisingly, despite its popularity in pharmaceutical development, continuous DPPA synthesis has not been explored.

Design of a continuous flow DPPA synthesis can address the traditional challenges with manufacturing routes requiring DPPA, resulting in a near-100%-yield process that is also safe (Scheme 1). By operating with enhanced mass-transfer, a continuous flow system diminishes safety concerns regarding HN_3 formation by minimizing potential for hydrolyzing both the diphenylphosphoryl chloride (DPPCl) precursor and product DPPA (Scheme 2).[19] Traditional DPPA synthesis often suffers from mass-transfer limitations of sodium azide in organic solvents that continuous flow systems improve,[20,21] and hydrazoic acid is quite safe in dilute solution (<17%, or <3.95 M w%, or 4.30 M v%).[22]

The goal of this work is to demonstrate a DPPA micro-scale synthesis from DPPCl and NaN_3 that incorporates safer process design by exploiting the advantages of continuous engineering, to determine the condition for optimal kinetics and yield of that reaction in preparation for scale-up.

Process safety is particularly important and is carefully considered in this design in addition to minimizing risk to lab members, because incorporating a safe operation window early on in development greatly facilitates the translation to a manufacturing process. These studies were undertaken through exploring a very narrow operational window in which the potential hazards were greatly minimized. In addition, the line incorporates safer process design by exploiting the advantages of continuous and

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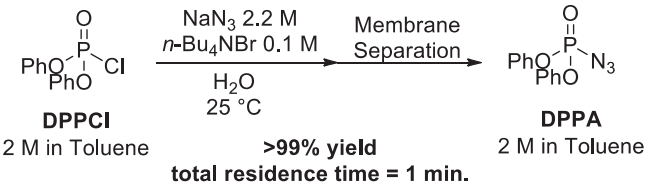
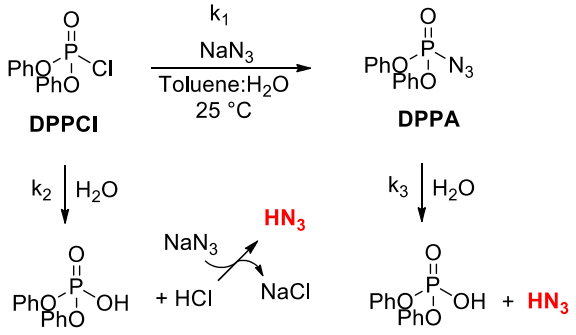


Scheme 1. Overall DPPA synthesis scheme and conditions for proposed continuous-flow DPPA manufacturing.



Scheme 2. The danger of hydrazoic acid production via hydrolysis from both starting material and product.

microfluidic-scale engineering, in-line separation, in-line Process Analytical Technology (PAT) product analysis with redundancy, and ensuring basic pH throughout the reaction.

The DPPA synthesis line made use of a small-scale flow reactor that has many advantages from a safety viewpoint, in comparison to conventional production technologies.[16–18] Specifically, unlike a traditional batch reactor, tube reactors can be run liquid-filled without any vapor-phase headspace. The greater surface area to volume ratio of tube reactors ensure that the reaction mixture can be quickly cooled and then quenched or pH-adjusted before exiting the reactor, eliminating concerns over hydrazoic acid volatility before the reaction mixture reaches a vessel with any headspace. The lower explosion limit of HN_3 in N_2 at pressures above ambient pressure is not known. By ensuring that HN_3 remains in solution, this problem is obviated and is an additional advantage of the flow approach The reduced reaction times at the higher temperatures could permit the use of a reactor of much smaller volume at the same throughput, greatly reducing the potential severity of an explosive or over-pressurization event, in comparison to a batch reactor of the same throughput.[22] Further, the process would be unsafe if the same screening reaction conditions were conducted in batch; attaining the observed efficiencies and kinetics requires a continuous process, which has not previously been achieved for DPPA synthesis.

It is necessary to minimize the DPPA product's contact time with water in order to ensure the safe development and operation of this on-demand process. For applications such as this where generation of toxic or unstable product is formed require continuous phase separation, because collection of the liquid process stream and its subsequent separation by gravity is too slow.[23] In-line membrane separation provides an effective and simple solution to minimize the DPPA product's contact time with water. The residence time through the membrane separator unit must be a fraction of the time through the reactor; this is achievable with the system introduced above. The closed system prevents the buildup of flammable solvent vapor, in addition to reducing the potential of operator exposure. Also, the more effective use of solvent will have significant economic and environmental benefits upon system scale-up, such as reducing overall solvent consumption, solvent inventory, and its waste disposal.

In this work, toluene was selected to use as solvent. Toluene has low volatility and will remain condensed even at the elevated temperatures of downstream processes. It also has a low dielectric constant, which decreases solvation of the reacting species, and thus increases in reaction rate are typically observed.

Due to the toxic nature of the reaction mixture, the use of in-line FTIR was the only way to safely screen such a range of conditions—conversion, end point, relative concentration, and even absolute concentration—in a short amount of time and with the presence of dangerous and unstable intermediates. Moreover, the ability to monitor for the presence of undesired species such as HN_3 provided a means to alert nearby scientists and plant personnel. Further, because conditions can be varied in continuous flow, the chemical process can be more rapidly optimized with in-line FTIR and can be maintained via standard process control systems. Since most of the equipment and instruments necessary to the process can be networked, the introduction of automation to investigate process space readily translates to a manufacturing environment, which should lead to significant reductions in the time. NaN_3 monitoring redundancy was also built into the process by using $FeCl_3$-impregnated colorimetric test strips to concurrently monitor for HN_3 vapor in the space above the experimental area. Residual water in the toluene process stream was also monitored offline using Karl Fischer titration (<0.1%) to ensure product stability.

Finally, maintaining a basic pH = 10 throughout the reaction should ensure that any azide present in the aqueous effluent stream remained ionized, effectively preventing the buildup of hydrazoic acid in the waste vessel's headspace (the pKa of hydrazoic acid is 4.72). In addition, basic conditions serve to prevent extraction of the neutral hydrazoic acid species into the organic permeate stream. This was achieved by appropriately buffering the aqueous feedstock. The waste vessel also contained a 2 M excess of aqueous NaOH relative to the amount of azide used throughout the process. As the product stream is also susceptible to potential hydrolysis, upon completion of its analysis, it too was sent to the waste vessel to quench.

2. Results/discussion

2.1. Process condition optimization

Optimized conditions for the process were determined by varying the ratio of DPPCl substrate to NaN_3 reagent, the number of equivalents of NaN_3, catalyst concentration and counter anion identity, and the activity of the water. Water activity and the hydration sphere, volume, electronegativity, and structure of the anions play a fundamental role in determining the relative ease of their extraction into the organic phase, and thus are critical to the kinetics. The successful development of an efficient phase-transfer process under liquid-liquid conditions relies on the selective extraction of a quaternary salt from an aqueous into an organic phase. The kinetic experiments on the formation of DPPA were conducted in a simple FEP tube reactor. The reaction kinetics were tracked based on a chemometric model using an in-line Mettler-Toledo FlowIR.

Delivering a stream of DPPA to downstream operations necessitated it to be produced at a high concentration due to its subsequent dilution in the next process. Since the next process was to be run at 1 M, the DPPCl concentration was first studied at 2 M.

Initial kinetic studies for the isothermal reaction were conducted at 23 °C to determine dependence on substrate and reagent concentration. Reaction rate trends were in line with expectations. The reaction proceeded quite quickly in toluene, ethyl acetate, and