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Rapid Access to Substituted Amides and Dipeptides via prop-2-ynyl-triphenylphosphonium bromide: An Allene-mediated Coupling Strategy

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Abstract

Efficient synthesis of amide and peptide bonds remains a central objective in organic and medicinal chemistry, particularly in natural product synthesis. There are many different types of conventional coupling reagents such as carbodiimides, uranium salts, and phosphonium-based activators which frequently generate stoichiometric waste, induce racemization, and require extensive purification. In this study, we report a rapid, metal-free, and operationally simple precursor (highly reactive allene intermediates) for the synthesis of substituted amides and dipeptides employing prop-2-ynyl-triphenylphosphonium bromide. In the presence of triethylamine, prop-2-ynyl-triphenylphosphonium bromide undergoes base-promoted isomerization to generate an allene species in situ, which reacts with *N*-protected amino acids to provide activated ester intermediates. Subsequent coupling with *C*-protected amino acid esters affords the corresponding amides and dipeptides through clean –CONH– bond formation, enabling efficient amino acid conjugation. The method was successfully applied to prepare a series of many different substituted dipeptides in a very effective way while isolated yields were up to 85% without chromatographic purification. The present synthesis protocol offers significant advantages such as operational simplicity, waste minimization, broad substrate scope, and so on, which lead a better efficiency to facilitate peptide coupling processes.

Keywords: *Synthesis, dipeptides, phosphonium salts, coupling, wittig-type reagents*

1. Introduction

The formation of amide and peptide bonds is one of the most powerful and important transformations in the field of synthetic organic chemistry that supports the production of several essential pharmaceuticals, biologically active (amides/peptides) and different functional materials. Despite significant advances in this area of research, most established coupling methodologies rely on dehydrative activation using different reagents such as dicyclohexylcarbodiimide (DCC), carbonyldiimidazole (CDI), and uranium or phosphonium salts, where certain processes frequently generate problematic by-products (impurities) that typically necessitate laborious

purification, particularly in the pharmaceutical and biotechnology industries [1-3]. Importantly, many traditional methods of peptide synthesis and chiral compound manipulation can lead to partial racemization, especially with sterically hindered or sensitive amino acid derivatives [4].

Recent years have witnessed growing interest in a variety of fields of alternative bond-forming strategies that exploit highly reactive intermediates under mild and environmentally benign conditions. Among these, allenes have indeed become highly valuable and versatile building blocks in organic synthesis due to their unique electronic properties and ambident reactivity [5-6]. Significantly, allenes readily participate in a wide variety of organic transformations, including nucleophilic additions, cycloadditions, and transition-metal-catalyzed processes, due to their unique structure and reactivity, particularly they are using in the field of peptide and amide synthesis [7].

Prop-2-ynyl-triphenylphosphonium bromide was originally introduced as a Wittig-type reagent, specifically used to synthesize allenes or conjugated dienes; however, under basic conditions it undergoes rapid propargyl–allene isomerization to form a highly reactive allene species [8]. These rearranged intermediate displays pronounced electrophilicity that can be intercepted by a variety of nucleophiles under mild conditions [9]. Earlier many studies demonstrated that the in situ generated allene can react with *N*-protected amino acids to afford activated ester intermediates, which subsequently undergo nucleophilic substitution with amines and amino acid derivatives to yield amide products [10]. Nevertheless, those preliminary protocols afforded only moderate yields, leading to a lower amount of the desired product.

In view of recent advances in the field of allene chemistry (asymmetric synthesis and peptide functionalization methodologies) [11-13], we sought to refine and optimize this strategy to provide a practically high-yield production route to substituted amides/dipeptides. In this study, we described an improved one-pot metal-free protocol for amides/dipeptides synthesis based on prop-2-ynyl-triphenylphosphonium bromide (Scheme 1), enabling rapid access to structurally diverse peptides under mild reaction conditions with minimal waste generation.

2. Experimental Section

2.1 General information

Melting points were determined using a standard open-capillary melting point apparatus, and therefore, no mathematical correction is applied. Infrared (IR) spectra were recorded using FTIR-8400 and Perkin-Elmer 883 spectrometers, where samples were prepared with KBr pellets for solid compounds and then analyzed as neat films for liquid samples. The progress of all reactions was routinely monitored by thin-layer chromatography (TLC) on pre-coated silica gel plates, with visualization achieved under ultraviolet light and/or by staining. The required products were purified by column chromatography using silica gel (60–120 mesh) as the stationary phase.

2.2 General procedure for peptide synthesis

Prop-2-ynyl-triphenylphosphonium bromide (1.0 equiv.) was dissolved in anhydrous chloroform (15 mL) in a dry, nitrogen-flushed, two-necked round-bottomed flask equipped with a magnetic stir bar, reflux condenser, and a calcium chloride drying tube. To this stirred solution, triethylamine (1.2 equiv.) was added dropwise at room temperature (RT), and the reaction mixture

was maintained under continuous stirring for approximately 5 min to allow in situ generation of the reactive allene intermediate. The progress of allene formation was monitored by thin-layer chromatography (TLC). Afterward, a tosyl (Ts)-protected amino acid (1.0 equivalent) was added (portion wise) in the first step and then triethylamine (1.2 equivalent) was added in the second step to the reaction mixture for maintaining a basic environment. The resulting suspension materials were stirred at RT for 30 min and then heated at reflux in a water bath, while additional 30 min was applied to ensure complete formation of the activated ester intermediate with in the period of time. After completion of these stages as mentioned, the reaction mixture was allowed to cool in a natural way to room temperature.

Further, a suitably protected amino acid ester (1.0 equivalent) was then added to the reaction vial and then trimethylamine (1.2 equivalent) was added as a final portion, after that the reaction mixture was stirred at ambient temperature for 3 to 4 h very carefully. Here, the reaction progress was monitored step by step using Thin Layer Chromatography (TLC) until the starting materials were completely consumed in a required reaction time as mentioned.

Upon completion, the solvent was removed under reduced pressure using a rotary evaporator, and the resulting crude residue was triturated with diethyl ether (Et_2O) to selectively dissolve the peptide products while leaving the carbonyl-containing by-product as an insoluble solid. The ether layer was separated, and the organic phase was washed successively with 2 M hydrochloric acid, saturated aqueous sodium bicarbonate solution (5%), and distilled water for removing residual inorganic impurities and excess base. The organic layer was then dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude peptide products, which were further purified by recrystallization from ethyl acetate to yield analytically pure substituted dipeptides (Scheme 1).

3. Results and Discussion

3.1 Reaction design and mechanistic rationale

The key feature of the present methodology is the in-situ preparation of an allene intermediate from prop-2-ynyl-triphenylphosphonium bromide (1) in the presence of triethylamine. Subsequently, base treatment rapidly converts the propargyl phosphonium salt into the corresponding allene (**2**) through a rearrangement pathway previously documented for related systems [8, 9] Afterward, this transient allene reacts with the carboxylate oxygen of an *N*-protected amino acid to furnish an activated ester intermediate (3). This intermediate is characterized by enhanced electrophilicity at the acyl carbon, allowing rapid nucleophilic attack by C-protected amino acid esters or amines (4) to give the corresponding amide or dipeptide (5) via acyl substitution with acetylmethylenetriphenyl phosphonium bromide salt (6) [10]. To compared with carbodiimide-mediated coupling, the present method avoids urea by-product formation and proceeds under relatively mild, neutral-to-basic conditions, which reducing the risk of epimerization [3], [14]. Significantly, recent mechanistic investigations of allene-mediated transformations support this reactivity profile, which attributing the high efficiency of such processes to favourable orbital overlap and low activation barriers for nucleophilic capture [5-6].

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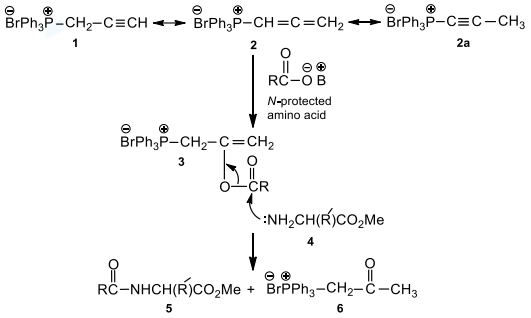

Scheme: 1

3.2 Optimization of reaction conditions

Initial experiments demonstrated that removal of residual hydrochloride salts from amino acid esters by washing (aqueous ammonia washing) led to significant material loss, may be due to the hydrolysis of the linkage. To address this limitation, the present protocol was redesigned to eliminate any pre-neutralization step. Importantly, triethylamine was introduced in three separate portions (0.3 equivalents each), allowing controlled generation of the allene intermediate while maintaining a consistently mild basic environment. The different types of allenes were produced under the optimized reaction conditions at RT within a very short time (5 to 10 min), while *N*-protected amino acids were subsequently added to the reaction (Scheme 1). The reaction mixture was then heated under gentle reflux on a water bath (about 30 minutes) to complete the reaction and then, the reaction mixture was subsequently cooled to RT in very simple natural way. After that a C-protected amino acid ester, along with excess amount of triethylamine (TEA) was then added to the reaction vial, while the mixture was stirred for 3 to 4 hours at RT. In the same order, reactions reached to complete within 1 to 4 hours, where the reactions were monitored by thin-layer chromatography (TLC, MeOH:CH_2Cl_2 1:4) at various times during the reaction. We use a very simple aqueous quench process to extract desired organic products from a quenched aqueous reaction mixture and in several cases the desired products crystallized directly from the crude reaction mixture, while no need to apply for chromatographic purification Importantly, it is a very simple and easy work-up procedure for separating the desired products from reaction mixture.

3.3 Substrate scope

Here, the optimized protocol was successfully applied to produce a broad range of dipeptides such as amino acids bearing aliphatic, aromatic, and heteroatom-containing side chains as shown in Figure 1. Significantly, the optimized protocol demonstrated the generality and robustness of the methodology as mentioned. Tosyl (Ts) was used as the preferred *N*-protecting group due to the excellent stability of Ts under the basic reaction conditions and at the following stage the Ts was easily removed under mild reductive conditions. A diverse series of substituted dipeptides was synthesized in good to excellent isolated yields 77% to 85% systematically using this simple synthesis protocol (entries 1-9, Fig. 1). Importantly, substrates with amino acids containing aromatic side chains such as phenylalanine and tyrosine derivatives gave slightly higher yields, may be attributed to favorable electronic effects that facilitate the coupling process.

On the other hand, substrates with highly hindered aliphatic side chains showed modestly reduced reactivity and comparatively low yields. Notably, this approach offers a broad substrate scope, high efficiency and provides facile access to a variety of phenylalanine and tyrosine derivatives compared to other recently reported

peptide coupling synthesized protocols that rely on activated esters, photochemical activation, or transition-metal-catalyzed processes [12], [13], [14], [15]. Therefore, the present protocol highlighted the metal free allene-mediated coupling strategy by avoiding the use of expensive/toxic transition-metal catalysts.

3.4 By-products recovery and reuse technique

A significant advantage of the present technique is the simple, efficient and straightforward recovery of the carbonyl-containing by-products which are formed from the phosphonium salt during the reaction. Here, the crude product mixture was concentrated under reduced pressure after completion of the coupling reaction and then a residue is formed. Thus, a residue was triturated with diethyl ether (Et_2O) and further washed several time with Et_2O to provide the pure by-product. The desired peptide products were readily dissolved under these conditions, while there were inorganic and carbonyl-rich by-products that did not dissolve under the conditions like insoluble solids. The ketonic by-products were systematically isolated in high yield with high purity in simple methods (shaking, washing, and extraction) without requiring sophisticated chromatographic purification technique. Importantly, preliminary recycling studies demonstrated that the recovered material could be efficiently recycled and reused in subsequent Wittig-type transformation and carbonyl olefination reactions as a precursor by maintain the synthetic protocol as described the present study. More importantly, the reuse technique of this protocol not only reduces many different toxic, hazardous chemical wastes and improves the overall synthesis process, compared with traditional processes but also significantly contributes to the sustainability profile of the methodology.

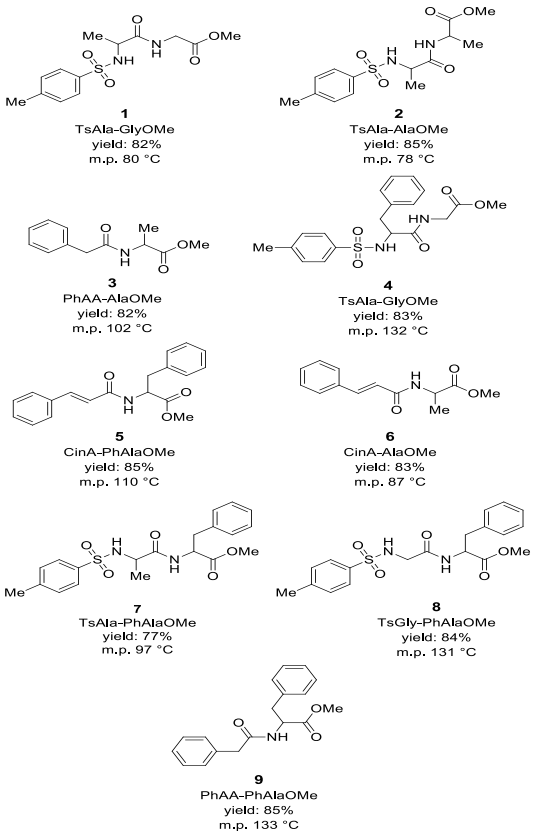

Figure 1: Substituted dipeptides synthesized using the allene-mediated coupling protocol.

The recovery and reuse of reaction by-products are in line with contemporary green chemistry and sustainable synthesis practices, where circular reagent utilization and waste minimization are considered essential design principles in modern organic synthesis [16].

3.5 De-protection and final peptide formation

Efficient removal of the tosyl (Ts) protecting group was achieved by refluxing the protected

dipeptides under mild conditions in a zinc/acetic acid (Zn/AcOH) system. This reductive treatment proved highly effective, enabling the simultaneous cleavage of both the *N*-tosyl group and additional sidechain protecting groups in a single operational step, thereby directly furnishing the corresponding free dipeptides in good to excellent isolated yields. The reaction proceeded in a clean and reproducible manner, with negligible peptide backbone degradation and detectable racemization, as confirmed through spectroscopic and chromatographic analyses. Although modern peptide synthesis often depends on carefully designed orthogonal protecting group strategies and multiple sequential deprotection steps [17], the methodology described herein offers the practical advantage of effecting global deprotection through a simple, one-pot reductive process. Importantly, this synthesis protocol offers several advantages over traditional synthesis methods, including efficiency, versatility, simplicity, straightforward synthesis protocol, shorter reaction times and fewer purification steps which makes this protocol more attractive for small- to medium-scale peptide synthesis, where step economy and efficiency are key considerations.

4. Conclusion

A simple, practical, efficient and straightforward methodology has been developed for the synthesis of many different substituted amides and dipeptides using in situ generated highly reactive prop-2-ynyltriphenylphosphonium bromide as a convenient allene precursor. Importantly, the protocol proceeds without expensive or toxic transition-metal catalysts under completely metal-free conditions, and displaying a remarkable level of functional group tolerance (across a wide variety of amino acid substrates). With the above parameters, the methodology affords several key facilities such as high isolated yields, reduced by-product formation, easy recovery, recycle and potential reutilization of carbonyl-containing by-products, which enhancing the overall atom economy and the sustainability profile of the present process in a right way.

In addition, this allene-mediated strategy offers a streamlined and scalable alternative which compared to conventional peptide coupling approaches that often require multiple steps, specialized reagents, or rigorous purification. It's operational simplicity, broad substrate scope, offering both economic attractiveness and high efficiency make it particularly more attractive for the synthesis of small molecules, substituted (highly functionalized) amides, peptides and many different essential molecules.

These, along with essential molecules, it is anticipated to find broad application in both academic and industrial settings where rapid and reliable peptide assembly is required. Significantly, the simplicity, broad substrate scope, and high efficiency of this methodology make it highly popular in the field of synthesis chemistry for the preparation of small molecules, substituted amides, and peptides, and this method can be used in industrial application where rapid and reliable functionalized amides/peptides are required.

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