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Reagent-free continuous thermal *tert*-butyl ester deprotection

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ABSTRACT

Continuous processing enables the use of non-standard reaction conditions such as high temperatures and pressures while in the liquid phase. This expands the chemist's toolbox and can enable previously unthinkable chemistry to proceed with ease. For a series of amphoteric amino acid derivatives, we have demonstrated the ability to hydrolyze the *tert*-butyl ester functionality in protic solvent systems. Using a continuous plug flow reactor at 120–240 °C and 15–40 min reaction times, no pH modification or additional reagents are needed to achieve the desired transformation. The method was then expanded to encompass a variety of more challenging substrates to test selectivity and racemization potential. The acid products were generally isolated as crystalline solids by simple solvent exchange after the deprotection reaction in good to high yield and purity.

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1. Introduction

Flow chemistry and continuous processing have expanded the operational spaces available to chemists. They offer wider possible temperature ranges and allow investigation of extreme conditions with improved process safety and precise control of residence time (τ). Although commonplace in many industries, continuous manufacturing has yet to gain widespread use for pharmaceutical production.[1] Recent encouragement from regulatory bodies,[2] as well as technological advances in equipment have prompted organizations to invest in developing this capability.[3] Our initial interest in continuous processing was guided by safety considerations for the use of energetic intermediates or transformations.[4] More recently our group has become interested in the concept of fume-hood production or Small Volume Continuous manufacturing,[5] which combines the expanded processing space of continuous flow with improved containment, reduced facility capital costs, and increased facility flexibility.

Carboxylic acids are a common motif in pharmaceutical development and there is a need to mask and unmask them using orthogonal protecting groups that can be selectively removed in the presence of other blocking groups. Many carboxylic acid protecting groups can be cleaved selectively by employing acidic or basic catalysts. However, these conditions can result in epimerization or decomposition of certain functional groups. Furthermore, the inclusion of acid or base can complicate the isolation of amphoteric substrates. For example, deprotection of an ester that contains a basic amine functionality and yields a highly water soluble carboxylic acid product could almost certainly be accomplished using standard acids such as HCl or MsOH at super-stoichiometric levels. This approach may even present a convenient isolation of a crystalline salt derivative of the product. However, if isolation of the free product is desired, this will be greatly complicated by the high solubility of the product in either high or low pH aqueous media; careful pH control will likely be necessary to avoid yield loss if an extractive method is used to shed the stoichiometric acid. An alternate to using acids or bases is to simply heat the protected substrate to facilitate thermal deprotection. This type of high temperature thermal deprotection is well precedented for *tert*-butylcarbamates (Boc amines), and has been used by us[6] and others[7] for chemical development and production in a continuous plug flow reactor (PFR, Scheme 1). While the analogous reaction for *tert*-butyl esters has been known for some time,[8] the potential utility and benefits of this transformation in continuous flow has yet to be explored or exemplified. The generally accepted mechanism for the thermal deprotection proceeds via a concerted 6-membered transition state to afford the carboxylic acid and isobutylene, as illustrated in Scheme 1.[9,10] This mechanism is supported by the lack of ester oxygen scrambling as demonstrated by an ^{18}O labeling experiment.[11] Additionally, the Thrope-Ingold effect forces the necessary transition-state conformation to be available at all times in the case of *tert*-butyl esters. The majority of methods that are reported to unmask an acid from a *tert*-butyl ester involve Lewis or Brønsted acid catalysis.[12] Some previous reports on the thermal cleavage of *tert*-butyl esters have employed gas phase pyrolysis.[8] This technique relies on sublimation of a substrate to the gas-phase at high temperatures (e.g. 200–400 °C). Gas phase pyrolysis is dif-

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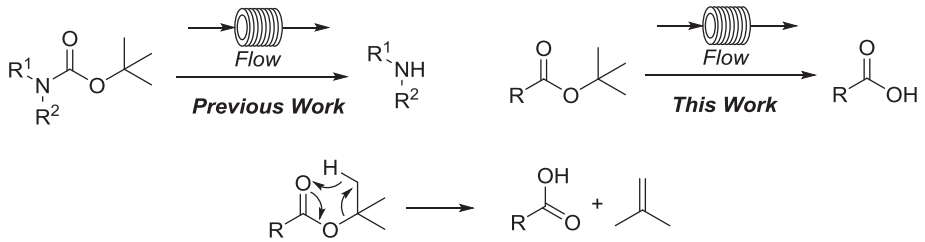

Scheme 1. Proposed mechanism for deprotection reaction.

ficult to translate from laboratory to production scale, and the substrates must have appropriate volatility to so that they do not decompose while heating to sublimation, limiting the scope of this transformation. To address this challenge, we sought to pursue *tert*-butyl ester cleavage under liquid-phase continuous flow conditions.[13] This technology can be readily scaled from lab to production and avoids the disadvantages associated with variable substrate volatility. Furthermore, as the thermal method does not rely on the introduction of acid or base, it is not necessary to purge or neutralize the catalyst, and the pure carboxylic acid product can be directly telescoped into a subsequent transformation or isolated post-reaction without generation of waste associated with acid neutralization.

As this method uses no pH adjustment or added reagents, it is expected to be compatible with many common carboxylic acid protecting groups, enabling selective deprotection of a *tert*-butyl ester over other esters. There is a consistent trend of ~5–8 kcal/mol difference in activation energy between *tert*-butyl esters compared to *iso*-propyl or ethyl, which implies the potential for selective hydrolysis of *tert-butyl* esters over other alkyl esters.[9] An excellent example of this selectivity was the ability to cleave a *tert*-butyl ester in the presence of a benzyl ester using thermolysis.[14] Herein we report our investigation into the continuous flow thermal deprotection of *tert*-butyl esters, and our findings regarding the scope, capability, ease, and convenience of this method, especially with regard to amphoteric amino acid derivatives where avoidance of pH manipulation may be desirable for isolation.

2. Equipment

PFRs are convenient tools that readily achieve high reaction temperatures well above the boiling point of common solvents, while maintaining the liquid phase due to pressurization provided by a backpressure regulator (BPR). PFRs are easily modeled and their mixing and axial dispersion characteristics can be calculated and understood. While many commercially available flow chemistry units that include PFRs are available, our group chooses to fabricate systems from readily available components.[15] These custom systems maintain greater flexibility in terms of scalability and general robustness as tubing diameter, length, and material of construction can be readily varied, as can the heat transfer fluid (often water or air). They are inexpensive as well, which allows for unique systems to be developed to best suit each chemical transformation, if desired. The pumping mechanism can be a large differentiator when selecting between a custom made or commercial system. Many commercially available systems rely on HPLC pumps that can be unreliable with regard to maintaining prime or flow rate accuracy. Flow rate accuracy is especially important early in development when small quantities of material are typically available and small reactors with low flow rates are normally used (<1 mL/min). Our pump of choice for development is normally high pressure syringe pumps due to the nearly pulseless fluid delivery, ability to achieve high pressures, and excellent accuracy/precision of volumetric flow rates. Achieving these characteristics at larger scale, for example >50 mL/min is relatively straightforward using a combination of a mass flow meter and a variety of high pressure pump types. Some of the most robust mechanisms for backpressure regulation at small scale in terms of fouling resistance and consistency of performance are simple nitrogen pressurization of a steel collection vessel or use of a dome-type BPR such as those made by Equilibar®.

3. Substrate preparation

A recent effort aimed at achieving a challenging late stage functionalization of complex heterocycles using photoredox catalysis[16] required preparation of substituted glycine derivatives; this effort afforded late stage introduction of a challenging C—C bond in order to diversify the scaffold, and would enable SAR for medicinal chemistry purposes. After initial experimentation with *tert*-butyl bromoacetate and secondary amines, a convenient preparative method was found that used inexpensive *tert*-butyl chloroacetate with the amines and triethylamine in THF solvent.[17] As most of the amines used were either highly volatile or highly water soluble, they could be used in slight excess relative to the chloroacetate, and triethylamine was used to neutralize the HCl liberated by the S_N2 reaction. The triethylamine·HCl salt was highly insoluble in the THF solvent, and could be filtered off upon reaction completion. Solvent exchange into ethyl acetate then allowed for aqueous washings to remove any remaining traces of salts or other water soluble impurities, and the desired esters could then be isolated after concentration in good to excellent yields and purity. Esters **3a–d** (Scheme 2) were readily prepared at 100 g scale. In some instances, small amounts of additional solids, observed to be triethylamine·HCl and/or the over alkylated ammonium salt from the desired product, continued to precipitate, and could be removed by filtration. A noteworthy exception to this approach was diphenylamine, which proved unreactive towards this method of C-N bond formation. Attempted Pd-catalyzed *N*-phenylation of **3e** with either PhBr or $PhB(OH)_2$ was unsuccessful in our hands. Use of sodium hydride to deprotonate the diphenylamine, followed by exposure to the bromoacetate afforded a modest yield of the desired product (57%), which was isolated by purification using flash column chromatography. Additionally, the *tert*-butyl esters of acetic, acrylic, and benzoic acid are commercially available and would also be evaluated in the thermal deprotection reaction.

4. Batch screening

When use of a PFR is suggested, it is often useful to conduct small batch screening reactions, which can readily be conducted in 0.5–1 mL volume pressure reactors constructed of Swagelok® (or similar) steel or hastelloy parts.[21] Previous experience with thermal cleavage of Boc[6] and ethoxyethyl[22] groups guided us to conduct preliminary studies using protic solvents, such as alcohols or aqueous THF in the range of 150–200 °C. Initial scouting was

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