

Tin-Free Radical Carboazidation

Philippe Panchaud* and Philippe Renaud

Abstract: The radical carboazidation of alkenes could be achieved in water using triethylborane as initiator. This efficient process is complete in one hour at room temperature in an open system. These new tin-free azidation and carboazidation conditions are environmentally friendly and enable reactions to be run with an excess of either the alkene or the radical precursor. Furthermore, 3-pyridinesulfonyl azide could be used in order to avoid tedious purifications, especially when the reaction product has a similar chromatographic behavior to benzenesulfonyl azide, our original azidation reagent.

Keywords: Amination · Azides · Radicals · Synthetic methods · Tin-free

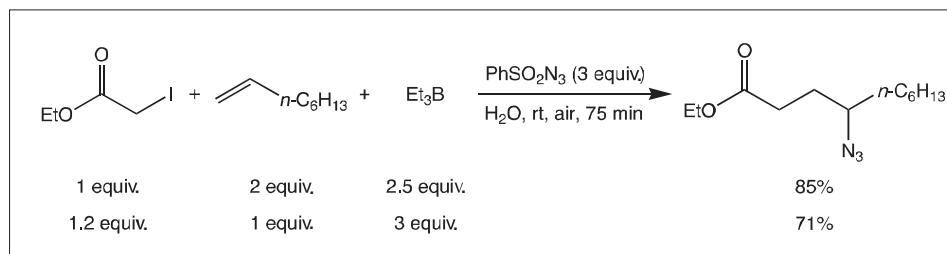
Introduction

We recently reported a useful radical carboazidation of alkenes and its application towards concise synthesis of the core of different alkaloids [1][2]. This efficient procedure uses hexabutylditin as radical chain transfer reagent. Organotin reagents are widely used in radical chemistry, especially because they are known to sustain efficiently radical chains [3]. However, their toxicity and the difficulties encountered to remove traces of tin byproducts greatly limit their use for preparative purposes. The development of tin-free conditions for the carboazidation reaction are therefore strongly needed [4]. Furthermore, several total syntheses of natural compounds under investigation in our laboratories are based on the carboazidation of structurally complex alkenes. Since these alkenes are produced through multistep syntheses, we became very concerned about the current need to use them in a twofold excess to achieve the carboazidations in high yields. Ideally, the new conditions should work equally well with an excess of either the radical precursors or the alkene. Moreover, we frequently faced purification problems caused by the very similar chromatographic behavior of benzenesulfonyl azide (used in threefold excess) and reaction products. In order to facilitate the purification step, we decided to develop another azidation reagent possessing a different polarity [5].

Radical azidation with ethanesulfonyl azide and dilauroyl peroxide (DLP) was the first system developed for tin-free azidation [6][7]. These reaction conditions proved to be problematic for carboazidation reactions. Indeed, large amounts of DLP as initiator are necessary for the reaction to proceed to completion and side products resulting from the decomposition of DLP considerably complicate the purification of the final products. Recently, Oshima and coworkers demonstrated that the system triethylborane/oxygen is a general and efficient method for radical initiation [8][9] that is particularly suitable to run atom transfer reactions [10][11]. Since radical carboazidations occur *via* an initial transfer of iodine atom or xanthate group, the triethylborane method became an obvious choice for us. Furthermore, Oshima and coworkers reported excellent results by running reactions in aqueous media [12].

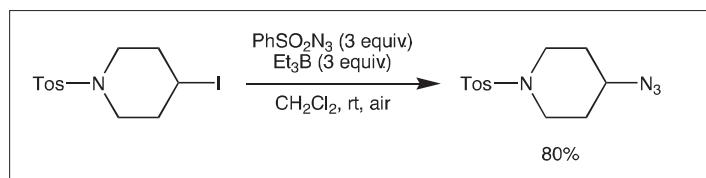
Results and Discussion

We started our investigations by testing this initiation system on the carboazidation of 1-octene. The ditin-mediated reaction involving 1 equiv. of ethyl 2-iodoacetate and 2 equiv. of 1-octene proceeds in 79% yield [2]. The triethylborane-induced reaction conditions, involving an identical stoichiometry and 2.5 equiv. of initiator, delivered the alkyl azide in 85% yield (Scheme 1) [13]. This result being encouraging, the carboazidation with an excess of ethyl 2-iodoacetate was also examined. For this procedure, 1.2 equiv. of radical precursor were loaded and 3 equiv. of triethylborane should have been added to reach reaction completion. Despite a minor decrease in yield, these conditions nicely extend the scope of our carboazidation process by providing the opportunity to choose a procedure adapted to a defined synthetic strategy (excess of alkene *versus* excess of iodide). Interestingly, this triethylborane procedure not only allows the use of ditin and benzene to be avoided but it also permits the reaction time to be reduced considerably, the heating to be suppressed and the work under an inert atmosphere is no longer necessary. Nevertheless, an excess of triethylborane



Scheme 1. Triethylborane-induced carboazidations

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Scheme 2. Azidation of a N-protected iodopiperidine

should be added since the reaction is not a chain process in contrast to our initial expectations [14].

The simple azidation of the N-tosyl-4-iodopiperidine was investigated next (Scheme 2). The reaction was conducted in water but unreacted starting material was always recovered along with alkyl azide in low yield. These disappointing results are caused by the low solubility of the piperidine derivative in water. Gratifyingly, running the reaction in methylene chloride gave the azidation product in 80% yield. This demonstrates again the convenience and the efficiency of the newly developed procedure since this azide was synthesized with similar yields using the DLP-induced azidation (81%) and the ditin-mediated reaction (89%) [7][15].

In order to test further the utility of this tin-free procedure, a tandem radical annulation–azidation was examined. The one-pot radical addition of the iodomalonate derivative to 1-octene followed by successive cyclization and azidation gave the tertiary azide in 72% yield as a 4:1 inseparable mixture of diastereoisomers (Scheme 3) [16]. The *cis* stereochemistry was assigned to the major isomer on the basis of precedent only [17].

Then the use of a new reagent, namely 3-pyridinesulfonyl azide [5], was tested for these tin-free conditions. It appeared that the carboazidation of 1-octene was again feasible by using an excess of either the alkene or the radical precursor (Scheme 4). It is of interest to mention that these results are comparable to those obtained with benzenesulfonyl azide under similar conditions and that the purification of the azide is much more easier in this case. This illus-

trates well the nice complementarity of the two reagents since the yields of the carboazidation remain constant while two reagents of different polarity were used.

Conclusion

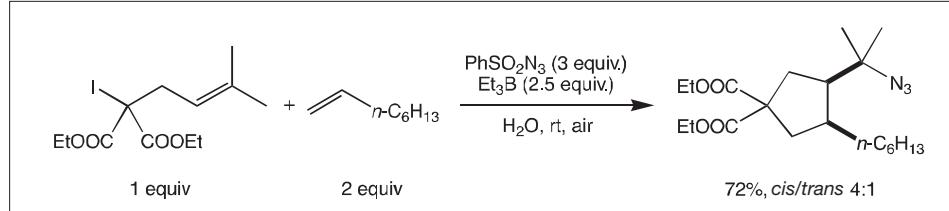
In conclusion, we have developed an efficient and convenient procedure which allows simple azidation as well as carboazidation and more complex tandem reactions. Compared to previously reported methods, this procedure enables reactions under tin-free conditions and benzene is advantageously replaced by water. When required (for instance for solubility reasons), other solvents are fully compatible with these reaction conditions. Finally, the reaction is run in an open system within one hour at room temperature. These improvements, together with the possibility to use two different and complementary azidation reagents, are expected to render radical azidation processes more suitable for preparative purposes. Applications in the total synthesis of nitrogen-containing biologically active compounds, encouraged by the possibility to use an excess of either the radical precursor or the alkene, are currently being investigated.

Acknowledgements

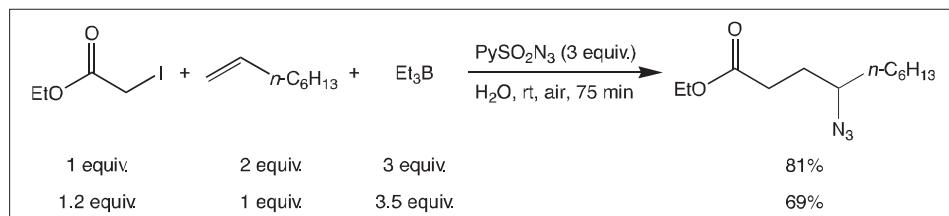
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Scheme 3. Tin-free tandem radical annulation–azidation



Scheme 4. Tin-free carboazidation using 3-pyridinesulfonyl azide

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