

# Multistep Flow Procedure for the Waste-Minimized Preparation of *N*-Boc- $\beta$ -Amino Ketones

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A clean and efficient protocol for the synthesis of a wide variety of *N*-Boc- $\beta$ -amino ketones **3a-g** has been defined using flow approach. The multistep procedure is based on the  $\beta$ -azidation of unsaturated ketones, consecutive reduction of the azido group, and concomitant amino group protection, and furnishes the desired products in good yields and very low E-factors ranging from 3.1 to 5.6. In batch conditions and by water as reaction medium, poorer yields and complicated reaction mixtures are obtained. Adoption of the flow approach, which combines transformations performed in solvent-free conditions and in EtOAc, has been essential in order to avoid side reactions, poisoning of the reduction catalyst, and use of minimal amount of reactants.

**Keywords:** azides, green chemistry, enones, solvent-free conditions, polystyrene-supported catalysts

The development of new synthetic strategies to prepare  $\beta$ -amino ketones is an interesting topic in medicinal chemistry mainly it can provide the construction of privileged structural endowed with a wide variety of biological properties [1]. Moreover,  $\beta$ -amino ketones can be converted into the corresponding  $\beta$ -amino acids [2] and  $\gamma$ -amino alcohols [3], which are also biologically important molecules and can serve as chiral ligands for asymmetric synthesis.

Carbon–carbon bond formation between imines and enolates (Mannich-type reaction) is one of the classical and powerful methods for the construction of  $\beta$ -amino carbonyl functionality [1, 4]. On the other hand, carbon–nitrogen bond formation between  $\alpha,\beta$ -unsaturated carbonyl compounds and nitrogen nucleophiles (aza-Michael reaction) provides an alternative route to this functionality [4a, 5].

During the last few years, we have investigated the use of solvent-free conditions (SolFC) [6] or water [7] to realize new environmentally efficient synthetic processes and we are also paying much attention to polymer-supported organocatalysts that may represent powerful tools for the development of cost effective processes [8]. We have also been interested in the use of flow chemistry [9] that can be a very efficient technology to reduce the E-factor [10] and more in general the environmental cost of synthetic processes. Highlights of these protocols are the recovery of the products by using the minimal amount of organic solvent, as well as the reproducible recovery of the solid catalyst and its repetitive use in consecutive processes.

Recently, we have reported the preparation of high-loading fluoride sources based on 1,4-diazabicyclo[2.2.2]octane (DABCO) moiety, to be used as catalysts for the activation of Si–N bond. Our attention was directed towards porous supports specifically designed for their use in water. The proposed protocol allowed the efficient promotion of the  $\beta$ -azidation of  $\alpha,\beta$ -unsaturated ketones **1**, and also the waste production in the preparation of  $\beta$ -azido ketones **2** was significantly minimized [8d]. In the same contribution, we have also proved that it is possible to prepare *N*-Boc- $\beta$ -amino ketones **3** by combining the  $\beta$ -azidation with the azido group reduction and its protection steps performed in aqueous medium (Scheme 1). A combination of Pd on Al<sub>2</sub>O<sub>3</sub> and HCOOH was used as reducing system, and Boc<sub>2</sub>O was used as protective agent. At this

concern, it should be noted that although Pd-catalyzed reduction of azido group is a widely studied method in literature [11], we first reported that Pd on alumina in combination with formic acid is an efficient reduction system in water [8d]. *N*-Boc was chosen as an amino protecting group due to its easy manipulation and chemical stability.

The protocol was representatively used for the preparation of **3a** and **3b**.

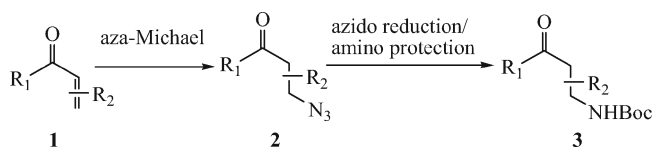
As mentioned in the literature [12], the need for coupling azido group reduction and *N*-protection is justified by the fact that  $\beta$ -amino ketones are very unstable and easily decompose during the isolation/purification processes; therefore, the simple reduction of  $\beta$ -azido ketones is not possible but *in situ* *N*-protection is necessary.

In the progress of our investigations and in the effort of extending the scope of the reported procedures to define a general protocol for the preparation of *N*-Boc- $\beta$ -amino ketones **3**, we have encountered several problems and the reported procedure using water as reaction medium gave unsatisfactory results. The major issues encountered could not be resolved even after numerous experiments aimed at the optimization of the reaction time and the amounts of reactants. Very poor results were especially obtained by performing the multistep one-pot process under batch conditions and were mostly related to the decomposition of the reduction system before completion of the desired process. Therefore, when either our reported batch or flow procedures were extended to substrates other than **1a** and **1b**, the resulting reaction mixtures were complex and poor yields of the desired product **3** were obtained.

We have concluded that by adopting the reported procedure [8d], if the green use of an equimolar amount of HCOOH is maintained, complete azido group reduction could not be reached, while using an excess of formic acid, the Boc<sub>2</sub>O reagent used to introduce the *N*-Boc protection group was compromised leading to a mixture of products, therefore, requiring a classic purification step and a significant increase of waste (E-factor). This major chemical issue leading to such synthetic limitation has been ascribed to the high specificity of the solid fluoride source for water as reaction medium while the efficiency of the reduction step is limited by water itself.

Therefore, we have concluded that a flow procedure and a more convenient reaction medium in combination with an

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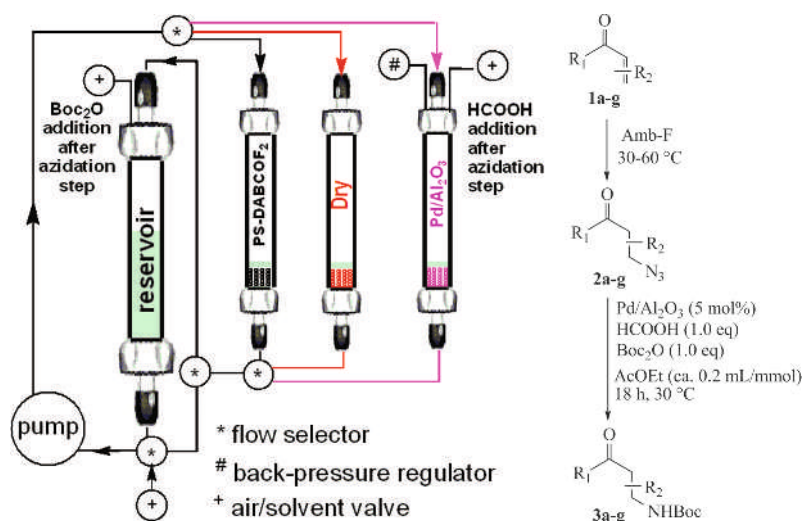
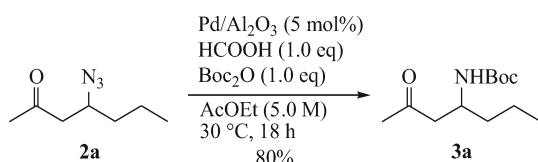
**Scheme 1.** Multistep procedure for *N*-Boc- $\beta$ -amino ketones synthesis

adequate fluoride source need to be identified in order to reach the highest efficiency for the multistep preparation of **3**.

In this contribution, we report our study towards the definition of a waste-minimized and general multistep flow procedure for the preparation of *N*-Boc- $\beta$ -amino ketones **3** based on the  $\beta$ -azidation of  $\alpha,\beta$ -unsaturated ketones **1** and subsequent reduction/protection step of  $\beta$ -azido ketones **2** (Scheme 1).

We have planned to define a general protocol by replacing water as medium and define the solid fluoride-catalyzed  $\beta$ -azidation step in flow and under SolFC. This approach is very efficient for the minimization of waste and would allow to use the minimal amount of organic solvent to move the resulting reaction mixture from the first reactor ( $\beta$ -azidation) through the second reactor for the reduction step. This would allow to reduce the waste deriving from the use of two different reaction media.

In the current study, we have found that in the aza-Michael addition in the model batch reaction of (*E*)-hepten-3-en-2-one (**1a**) with  $TMSN_3$  at 60 °C and under SolFC, the most convenient ratio between catalytic efficiency and availability was obtained by using 10 mol% of Amberlyst-F (Amb-F) [8a]. Very good results have been also obtained by using high-loading fluoride sources based on 1,4-diazabicyclo[2.2.2]octane (DABCO) that we have prepared using a gel-type chloromethylated resin [8d] (see Table S1 in the Supporting Information for details). Although it has lower loading, Amb-F confirmed a very good efficiency. In fact, while obvious advantages may arise from the use of high-loading catalysts in view of a large scale solvent-free process in batch or in flow, within the context

**Scheme 2.** Azido reduction of **2a** followed by *N*-Boc-protection**Figure 1.** Flow protocol for the preparation of *N*-Boc- $\beta$ -amino ketones **3a-g**

of this study aimed at the definition of a general flow protocol, we decided to focus the attention on the use of Amb-F, that is largely available at low cost.

Searching for the best reaction conditions we found that the representative reduction process of **2a** in  $AcOEt$  5 M using 5 mol% of  $Pd/Al_2O_3$  in the presence of just 1.0 equivalent of  $HCOOH$  and 1.0 equivalent of  $Boc_2O$  allowed to obtain the desired *N*-Boc- $\beta$ -amino ketone **3a** in 80% yield (Scheme 2). The use of equimolar amounts of reagents does allow the highest chemical efficiency, and it is also crucial for the success of the procedure. In fact, using different ratios of reagents, decomposition processes of both the  $\beta$ -amino ketone and protecting agent occur.

In addition, the reducing system is also very sensitive to the amount of  $TMSN_3$ . In fact, the one-pot approach reported in Scheme 1 is effective only when the excess of azide is almost consumed during the azidation step; otherwise, poisoning of the  $Pd$  catalyst was observed hampering the reduction step.

By combining the results obtained, we have defined a flow protocol that enabled us to realize the chemically and environmentally efficient one-pot synthesis of *N*-Boc- $\beta$ -amino ketones **3a-g**. First of all, the adoption of the flow approach allowed to reach the needed chemical efficiency, which was not possible under batch conditions, to recover and reuse the catalysts preserving their chemical and physical stability and also to minimize the waste produced; in particular, the amount of organic solvent needed to isolate the final products has been minimized.

The schematic representation of the reactor is illustrated in Figure 1 (thermostated box is not shown for clarity).

Representatively, the procedure for the one-pot synthesis of *N*-Boc- $\beta$ -amino ketone **3a** is briefly described.

**1a** (50 mmol) was charged in a glass column (15 mL) functioning as reservoir, and  $TMSN_3$  (1.1 equivalents) was slowly added into it. Amb-F (10 mol% measured respect to enone **1a**) was charged into a glass column (10 mL), and the reaction mixture was continuously pumped through it with a flow rate of 1.5 mL/min at 60 °C for 2.5 h. At this point, the reaction mixture was pumped through a drying/neutralizing column of sodium sulphate/potassium carbonate (2:1 mixture, 5.0 g) (dry), and then the pump was left to run in order to recover the reaction mixture into the reservoir.

Ethyl acetate ( $2 \times 5$  mL, 0.2 mL/mmol of **1a**) was pumped through the catalyst and dry columns for 30 min (each fraction) to wash it and then collected into the reservoir. Melted  $Boc_2O$  (0.95 equiv.) was pumped into the reservoir, while a solution of formic acid (0.95 equiv.) in ethyl acetate was pumped into a

**Table 1.** Preparation of *N*-Boc- $\beta$ -amino ketones **3a–g** using continuous-flow reactor

Entry	Enone	$\beta$ -Azidation				$\beta$ -Azido ketone	Reduction product	Yield (%) <sup>a</sup>	E-factor <sup>b</sup>
		Amb-F (mol%)	TMSN <sub>3</sub> (eq)	T(°C)	t(h)				
1	<b>1a</b>	10	1.1	60	2.5	<b>2a</b>		82	3.5
2	<b>1b</b>	10	1.1	60	6	<b>2b</b>		83	3.1
3	<b>1c</b>	10	1.1	30	5	<b>2c</b>		87	3.6
4	<b>1d</b>	25	3	30	4	<b>2d</b>		81	5.1
5	<b>1e</b>	25	1.5	30	6	<b>2e</b>		81	4.1
6	<b>1f</b>	50	1.5	60	24	<b>2f</b>		75 <sup>c</sup>	5.6
7	<b>1g</b>	50	3	60	18	<b>2g</b>		81	3.6

<sup>a</sup> Isolated yield of the pure products **3**.<sup>b</sup> See Supporting Information.<sup>c</sup> 60/40 mixture of diastereoisomers.

glass column charged with Pd/Al<sub>2</sub>O<sub>3</sub> (5 mol%). The formic acid solution was continuously pumped through the Pd-column for 30 min, and then the entire reaction mixture was continuously pumped through the Pd-column at 30 °C for 18 h until the reduction/protection process was complete. At this point, the pump was left to run in order to recover the reaction mixture into the reservoir. Ethyl acetate (2 × 5 mL) was pumped through the catalyst column for 30 min (each fraction) and then collected into the reservoir. After the evaporation of the solvent *N*-Boc- $\beta$ -amino ketone **3a** was obtained in pure form in 82% yield. In some cases, a further excess of TMSN<sub>3</sub> (see Table 1, entries 4 and 7) is necessary to complete the azidation step of some substrates, and the flow approach also furnished an effective solution to avoid palladium catalyst poisoning with the adoption of a drying/neutralizing column before the reduction step. It should be noted that, in batch conditions, the decomposition of TMSN<sub>3</sub> was sometimes observed, hampering to reach a complete conversion while, in the flow conditions, this phenomenon is dramatically minimized.

Consequently, by using the flow approach, it is possible to efficiently recycle the palladium catalyst for representative three

consecutive runs with unchanged efficiency, while in batch, results were poor and the reuse was not possible. In Table 1, we have also reported the E-factor values obtained with our flow protocol.

This one-pot flow procedure revealed to be very efficient also from an environmental point of view. In fact, with the use of a flow procedure, we were able to achieve very low E-factor values for the synthesis of *N*-Boc- $\beta$ -amino ketones **3a–g** (Table 1) [13].

In conclusion, the optimized flow protocol allowed to directly obtain *N*-Boc- $\beta$ -amino ketones **3a–g** in a one-pot procedure with good yields and very low E-factor ranging from 3.1 to 5.6 (Table 1) [13]. This protocol is characterized by the use of minimal amount of reagents, minimal amount of organic solvent (both during the reaction and the workup), and by a simple procedure for the recovery and reuse of the catalytic system. These features make the entire process useful from both synthetic and environmental points of view.

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### Supporting Information

Electronic Supplementary Material (ESM) is available in the online version at: doi: 10.1556/JFC-D-13-00027.

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13. See Supporting Information for E-factor calculation.