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Waste Minimized Multistep Preparation in Flow of β-Amino Acids Starting from α,β-Unsaturated Carboxylic Acids

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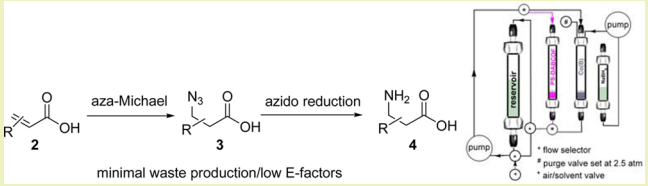
Supporting Information

ABSTRACT: An efficient protocol for the synthesis of β-amino acids starting from easily accessible α,β-unsaturated carboxylic acids based on the combination of two heterogeneous catalytic systems is reported. This multistep approach is based on the direct β-azidation of α,β-unsaturated carboxylic acids and subsequent azido group reduction performed in flow conditions. It has been demonstrated that the catalysts can be easily recovered and reused conserving its complete efficiency. The green metrics calculations proved the high environmental efficiency of the protocol characterized by very low waste production.



KEYWORDS: *Cobalt boride, Multistep process, Waste minimization, Amino acids*

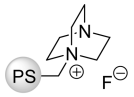
INTRODUCTION

Although less abundant than α-amino acids, β-amino acids are common motifs in many natural products with valuable pharmacological properties, such as antibacterial,[1] antituberculosis,[2] antibiotic[3,4] and antitumor activities.[5] Moreover, β-amino acids are precursors of various biologically active compounds, such as β-lactams and key components in potent enzyme inhibitors including pepstatin and amastatin.[6] β-peptides are also very important due to their conformational properties and biological activities. Therefore, many different methods for the synthesis of β-amino acids have been developed including α-amino acid homologation,[7−9] addition of enolates or enolate equivalents to imines,[10] conjugate addition of N-nucleophiles to electron-deficient olefins[11] and nucleophilic ring-opening reaction of β-lactones.[12−14]

Among these methods, Michael addition of the azido ion to α,β-unsaturated carboxylic acids with subsequent reduction of the azido group into the corresponding amino group represents an interesting approach to β-amino acids. Representatively, Miller and co-workers reported the conjugate addition of azide ion to α,β-unsaturated carbonyl compounds, using simple tertiary amines as catalysts under mild conditions.[15−17]

In the past few years, we have reported the use of polystyrene-supported ammonium fluorides (Amberlite IRA900F, Amb-F and PS-DABCOF$_2$) as catalytic systems for the β-azidation of α,β-unsaturated ketones in water[18] or under solvent-free conditions (SolFC).[19,20]

We recently reported the use of an efficient and recoverable bifunctional supported catalyst **1**, PS-DABCOF (Figure 1), able to promote the β-azidation of α,β-unsaturated carboxylic acids under SolFC.[21] This bifunctional catalyst contains a Lewis basic and a Brønsted basic sites installed into a single diazabicyclo moiety. The presence of these two different functional groups allows simultaneous interaction of both the electrophile and nucleophile to the catalyst facilitating the direct β-azidation of the α,β-unsaturated carboxylic acids (**2**) without the preliminar protection of the carboxylic functionality.[21] Furthermore, the use of this solid catalyst allows a facile isolation of the desired β-azidoacids (**3**), by simple filtration of the reaction mixture.



PS-DABCOF (**1**)

Figure 1. Bifunctional polystyrene-supported catalyst PS-DABCOF (**1**).

In fact, this protocol allowed us to significantly reduce the waste production during the process, compared to the previously reported three-step procedure. Thus, we demonstrated the efficiency of our recently reported batch protocol with the synthesis of several β-azido carboxylic acids (**3**) with an average E-factor[22−25] value of ca. 27.[21] If compared to the reported three-step procedure, which features an average E-factor value of ca. 3400, a 99.2% waste reduction was obtained following our protocol.

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Our research program has recently focused on the design and optimization of ecofriendly synthetic strategies based on the use of water[18,26−29] or SolFC,[30−34] in combination with heterogeneous catalysts.[35−40] In our view, waste minimization (E-factor minimization),[22−25] is crucially important for the modern chemical industry and we are exploring the application of flow approach as an efficient strategy to reach this goal.

The use of flow chemistry may offer several advantages over traditional batch reactors especially in the products isolation step which requires only minute amounts of an organic solvent, and in the easy and reproducible recovery of the heterogeneous catalysts and their repetitive use in consecutive processes.[41−44]

To develop a sustainable protocol featuring minimal production of waste, we decided to set a flow procedure for the synthesis of β-azido acids. Moreover, according our previous reports in this field, the flow approach can be very effective in maintaining the chemical and physical integrity of a heterogeneous catalyst thus allowing better performance on large scale.[18,34−36]

In this contribution, we report a multistep protocol for the synthesis of β-amino acids based on β-azidation of α,β-unsaturated carboxylic acids (**2**) and subsequent azido group reduction. To this end, we have initially designed an E-factor minimized flow-based protocol for the preparation of β-azido carboxylic acids (**3**) and then developed a novel procedure for the cobalt boride-catalyzed reduction of the azido group in flow, affording the corresponding β-amino acids (**4**).

EXPERIMENTAL SECTION

Materials. Unless otherwise stated, all chemicals were purchased and used without any further purification. Gas chromatography (GC) analyses were performed on a Hewlett-Packard HP 5890A equipped with a capillary column DB-35MS (30 m, 0.53 mm), flame ionization detection (FID) and hydrogen as gas carrier. Gas chromatography with electron impact mass spectrometry (GC-EIMS) analyses were carried out by using a Hewlett-Packard HP 6890N Network GC system/5975 mass selective detector equipped with an electron impact ionizer at 70 eV.

All ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 or 400 MHz, and at 50.3 or 100.6 MHz respectively, using a Bruker DRX-ADVANCE 200 MHz or a Bruker DRX-ADVANCE 400 MHz spectrometers (see the Supporting Information for details). Chemical shifts are reported in ppm and coupling constants in hertz. Elemental analyses were realized by using a FISONS instrument EA 1108 CHNS. Thin layer chromatography analyses were carried out on silica gel using UV and/or ninhydrine as revealing systems.

Representative Experimental Procedure for the Continuous-Flow β-Azidation of α,β-Unsaturated Carboxylic Acids with PS-DABCOF (1) as Catalyst. Acrylic acid (**2a**) (100 mmol, 7.2 g) was charged in a glass column functioning as a reservoir, and $TMSN_3$ (150 mmol, 19.91 mL) was slowly added. PS-DABCOF (**1**) (15 mol %, 5.4 g), suitably dispersed in 1 mm diameter solid glass beads, was charged into a second glass column. The equipment was installed into a thermostated box and connected, by using the appropriate valves, to a pump. The reaction mixture was continuously pumped (flow rate 1.0 mL/min) through the catalyst column at 60 °C for 0.5 h to reach the complete conversion to 3-azidopropionic acid (**3a**). After this time, the air/solvent valve was opened and the pump was set to work at 5 mL/min in order to transfer the product into the reservoir and empty the PS-DABCOF (**1**) column. To recover completely the product and clean the reactor, ethyl acetate (2 × 5 at 1.5 mL/min, 0.1 mL/mmol of acrylic acid (**2a**)) was pumped from the air/solvent valve through the catalyst column for 10 min (each fraction) and then collected in the reservoir. The solvent was removed (90% of recovered solvent) under vacuum to furnish pure 3-azidopropionic acid (**3a**) (>99% purity by GLC and ^{1}H NMR analyses) in >99% yield (11.4 g, 99.9 mmol). The catalyst was reused for three consecutive runs without substantial loss of efficiency.

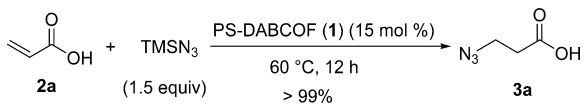
Representative Experimental Procedure for the Multistep Continuous-Flow β-Azidation/Azido Reduction of α,β-Unsaturated Carboxylic Acids. Acrylic acid (**2a**) (100 mmol, 7.2 g) was charged in a glass column functioning as reservoir and $TMSN_3$ (150 mmol, 19.91 mL) was slowly added. PS-DABCOF (**1**) (15 mol %, 5.4 g), suitably dispersed in 1 mm diameter solid glass beads, was charged into a second glass column. The equipment was installed into a thermostated box and connected, by using the appropriate valves, to a pump. The reaction mixture was continuously pumped (flow rate 1.0 mL/min) through the catalyst column at 60 °C for 0.5 h to reach the complete conversion to 3-azidopropionic acid (**3a**). After this time, the air/solvent valve was opened and the pump was set to work at 5 mL/min in order to transfer the product into the reservoir and empty the PS-DABCOF (**1**) column. To recover completely the product and clean the reactor, ethanol (2 × 5 mL at 1.5 mL/min, 0.1 mL/mmol of acrylic acid (**2a**)) was pumped from the air/solvent valve through the catalyst column for 10 min (each fraction) and then collected in the reservoir. At this point, we have set up two additional columns labeled as Co(B) and $NaBH_4$. The first column was charged with previously prepared cobalt boride from $CoCl_2{\cdot}6H_2O$ (10 mol %, 2.38 g) and $NaBH_4$ (2 equiv with respect to $CoCl_2{\cdot}6H_2O$, 0.756 g), suitably dispersed in 1 mm diameter solid glass beads; the second one was charged with a freshly prepared ethanolic solution of $NaBH_4$ (110 mmol, 4.16 g) and, by using the appropriate valves, was connected to a syringe pump. The two pumps were run in order to allow the continuous flow of both solutions of β-azido carboxylic acid **3a** and hydride through the catalyst column for the time necessary for its complete conversion to 3-aminopropionic acid (**4a**). At this stage, the pump was left to run in order to recover the reaction mixture into the reservoir. Then EtOH (2 × 2.5 mL at 1.5 mL/min) was added from the air/solvent valve to wash the catalyst and then was collected into the reservoir.

The solution of product in ethanol was then acidified and passed throughout an ion-exchange resin (DOWEX50W8X-400, 1.7 mequiv/mL, 42.7 g) charged in a column. Elution was performed with NH_4OH 1 M. After evaporation, 90% of EtOH was recovered and the pure product **4a** (>98% purity by ^{1}H NMR analysis) was obtained in 93% yield (93 mmol, 8.27 g).

RESULTS AND DISCUSSION

On the basis of our previously reported batch protocol for the β-azidation of α,β-unsaturated carboxylic acids under SolFC[21] and on the single-step flow approach for the β-azidation of acrylic acid (**2a**) (Scheme 1),[45] we have designed a new flow procedure operating in cyclic mode capable in reproducing the batch protocol for representative substrates (Figure 2).

Scheme 1. β-Azidation of Acrylic Acid (2a)



The protocol has been applied to α,β-unsaturated carboxylic acids **2a−f** affording the corresponding β-azido carboxylic acids **3a−f** in good to excellent yields. The results are reported in Table 1.

The reactions were performed on a relatively large 100 mmol scale. The results of the flow procedure show significant improvements over the batch protocol with respect to waste minimization (low E-factor), consistently with our goal of minimizing the waste produced in the process. Noteworthy, the flow protocols was found beneficial over the batch protocol in terms of reproducibility. Thus, since the large-scale batch protocol requires efficient mechanical stirring to ensure efficient

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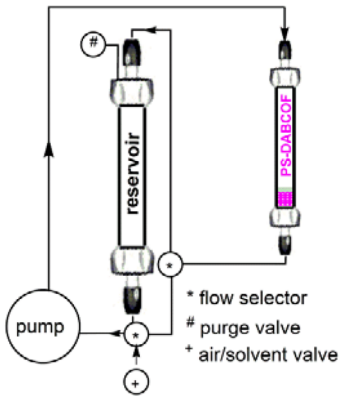
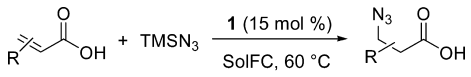


Figure 2. Flow reactor for the preparation of β-azido carboxylic acids **3a–f**.

Table 1. Results for the β-Azidation of α,β-unsaturated Carboxylic Acids 2a–f in Flow and SolFC



2a-f **3a-f**

entry	α,β-Unsaturated acid **2**	time (h)	yield (%)[a]	E_{kernel}	E_{excess}	E_{aux}	E_{tot}	PMI
1	**2a**	0.5	> 99	0.63	0.50	0.08	1.21	2.21
2	**2b**	12	> 99	0.56	0.45	0.07	1.08	2.08
3	**2c**	24	94	0.55	0.39	0.06	1.00	2.00
4	**2d**	24	95	0.46	0.33	0.05	0.84	1.84
5	**2e**	72	87[b]	0.63	1.55	0.06	2.24	3.24
6	**2f**	72	92[b]	0.49	1.27	0.05	1.81	2.81

[a]Isolated yield of the corresponding pure products (**3**). [b]Reaction conditions: 80 °C, 3 equiv of $TMSN_3$, 30 mol % cat.

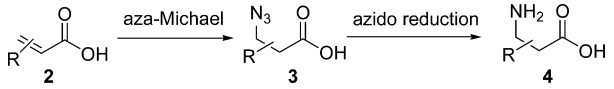
mass transfer, the solid catalyst is finely crunched which leads to its difficult and irreproducible recovery. On the contrary, increasing the scale of the flow process makes it even more efficient, because it is also possible to proportionally reduce the amount of organic solvent needed to isolate the product and clean the reactor.

According to Andraos algorithm,[46] we also calculated several key green parameters: the overall yield, the E-factors,[22−25] and the process mass intensity PMI.[47] the E-factors are calculated by estimating the waste originating from byproducts and unreacted starting materials (E-kernel), excess reagent consumption (E-excess), and auxiliary material consumption arising from the reaction solvent, catalysts, workup and purification materials (E-aux).

In the batch protocol, the average E-factor value for the preparation of β-azido carboxylic acids (**3**) was 27, whereas the flow procedure features an average E-factor value of ca. 2.3 with a consequent 91.2% reduction of waste.

Following our goal toward β-amino acids (**4**), we developed a procedure for the reduction of the azido group that could be combined with the β-azidation protocol in a multistep fashion. This will allow to access the final products (**4**) directly starting from α,β-unsaturated carboxylic acids (**2**) (Scheme 2).

Scheme 2. Multistep procedure for the synthesis of β-amino acids (4) starting from α,β-unsaturated carboxylic acids (2)



2 **3** **4**

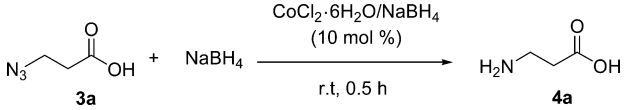
The reduction of the azido group to an amino group has been widely investigated. For example, non-hydride[48−52] and hydride-based[53−57] reducing agents have been extensively employed often showing limitations such as the need in large excess of hydride, long reaction time and insufficient functional group compatibility.

It was demonstrated in the past that the combination of $NaBH_4$ with $CoCl_2$ is a potent reducing system for various functional groups.[58,59] A few years ago, we demonstrated for the first time that also the reduction of the azido group is possible using this reducing system even if conducted in water (using in this case $CoCl_2{\cdot}6H_2O$).[60]

In protic solvents such as ethanol (EtOH) or methanol (MeOH), the $CoCl_2{\cdot}6H_2O/NaBH_4$ system produces a black solid that is identified as cobalt boride Co(B), which is an active catalytic species for the decomposition of borohydride to hydrogen.[58,59] The black Co(B) can be isolated by filtration leading to a relatively stable compound (except when dried under vacuum, in which case it can becomes pyrophoric if dried. ***Caution!***).[58,59]

We initially verified the use of $CoCl_2{\cdot}6H_2O/NaBH_4$ reducing system for the synthesis of β-amino acids and found that the reduction of β-azido acid **3a** proceeds efficiently in the presence of 0.1 equiv of Co(B) as a catalyst and 1.5 equiv of $NaBH_4$ as reducing agent in EtOH, MeOH or water (Table 2).

Table 2. $CoCl_2{\cdot}6H_2O/NaBH_4$ catalyzed reduction of β-azido acid 3a in MeOH, EtOH or H_2O



3a **4a**

entry	medium	$NaBH_4$ (equiv)	conversion[a] (%)
1	MeOH	1.5	>99
2	EtOH	1.5	>99
3	H_2O	1.5	>99

[a]Complete conversion was evaluated by TLC analyses; isolated yield of **4a** was in all cases ca. 90%.

For the design of the multistep flow protocol, we selected EtOH as medium and optimized the amount of the hydride source. The multistep protocol for the synthesis of β-amino acids (**4**) via the β-azidation of **2a–f** under SolFC and subsequent reduction of the intermediate β-azido acids **3a–f** in EtOH (5M), was performed in the flow reactor depicted schematically in Figure 3. The results obtained are reported in Table 3.

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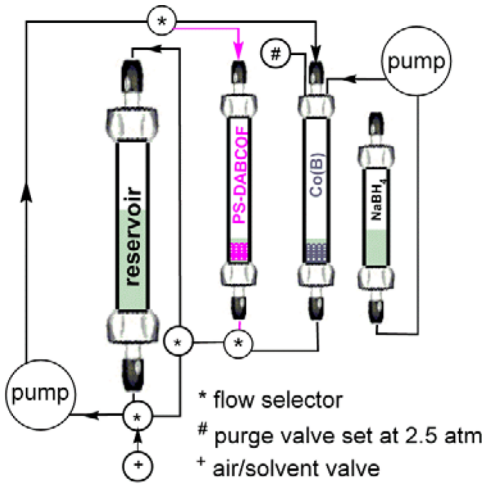

Figure 3. Flow reactor for the preparation of β-amino acids **4a–f**.

In flow, the reductions proceeded well in the presence of 1.1 equiv of $NaBH_4$ for β-azido acids **3a** and **3b**, 1.25 equiv for **3c**, **3d** and **3e** and with 1.5 equiv for the reduction of **3f**.

The multistep flow protocol allowed for the preparation of β-amino acids **4a–f** in 82–94% yields and E-factor values ranging from 11.9 to 20.7. These values include the ion-exchange resin purification necessary to isolate pure final products **4a–f**.

According to the Andraos algorithm,[46] we also calculated some parameters for the multistep approach, to evaluate the greenness and efficiency of our new synthetic protocol. Thus, for the reactions performed on the 100 mmol scale, the results show low E-factors values. In particular, a component that importantly contributes to the overall value of the E-factor is E-auxiliary. This parameter includes reaction solvents, workup and purification materials, and in this particular case its relatively high impact stems from the purification of the crude β-amino acid **4a–f** through an ion-exchange resin. These calculations are useful for the actual evaluation of the sustainability level reached in optimization processes and the low values obtained of all the green parameters stress the efficacy of our protocol at larger laboratory scales.

In conclusion, we have developed an efficient and sustainable approach for the synthesis of β-amino acids starting from unprotected α,β-unsaturated carboxylic acids. The process comprises the β-azidation of the substrates, catalyzed by a bifunctional heterogeneous catalyst under SolFC, followed by a cobalt boride-promoted azido group reduction. In particular, the use of SolFC for the first step and a careful tuning of reaction conditions for the second step allowed a considerable reduction of the environmental impact of the synthesis. In both processes, catalysts have been recovered and reused with unchanged efficiency. The environmental efficiency of the protocol and the results obtained have been evaluated and satisfactory results have been obtained as highlighted by the fundamental green metrics calculations.

■ ASSOCIATED CONTENT

Supporting Information

Full characterization of compounds **4a–f** and copies of the ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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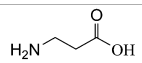
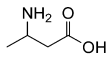
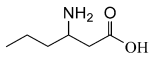
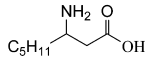
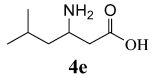
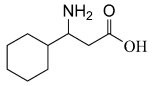
Notes

The authors declare no competing financial interest.

Table 3. Multistep Flow Synthesis of β-Amino Acids 4a–f

Entry	Acid	β-azido acid **3**	$NaBH_4$ (equiv)	β-amino acid **4**	Yield (%)[a]	E_{kernel}	E_{excess}	E_{aux}	E_{tot}	PMI
1	**2a**	**3a**	1.1	 **4a**	93	1.72	0.74	18.20	20.7	21.7
2	**2b**	**3b**	1.1	 **4b**	94	1.47	0.63	15.50	17.6	18.6
3	**2c**	**3c**	1.25	 **4c**	90	1.26	0.57	12.76	14.6	15.6
4	**2d**	**3d**	1.25	 **4d**	91	1.04	0.46	10.40	11.9	12.9
5	**2e**	**3e**	1.25	 **4e**	82	1.36	2.02	12.65	16.0	17.0
6	**2f**	**3f**	1.5	 **4f**	87	1.06	1.67	10.11	12.8	13.8

[a]Isolated yield of the pure products **4a–f**.

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