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Preparation of benzimidazole *N*-oxides by a two-step continuous flow process

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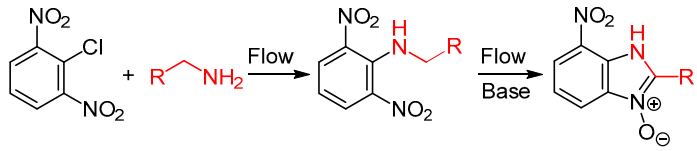


A continuous flow process for the synthesis of nitrobenzimidazole *N*-oxides from 2,6-dinitrochlorobenzene and amines or amino acids is reported. The process, performed in a two-step sequence, is faster than previously reported batch processes and avoids some of the isolation and purification steps.

Keywords: benzimidazoles, *N*-oxides, cyclization, flow chemistry, green chemistry, nucleophilic aromatic substitution.

The majority of bioactive compounds are heterocyclic molecules. Nitrogen-containing heterocyclic compounds are considered particularly privileged structures in drug development since they can increase binding efficiency and solubility and can facilitate the formation of salts. These properties are important in terms of oral absorption and bioavailability of the drug.[1,2]

Compounds derived from benzimidazoles and benzimidazole *N*-oxides exhibit a wide range of biological properties. They play roles in agrochemistry[3] as well as in human[4–8] and veterinary[9] medicine. This wide number of applications has fueled the study of different synthetic methods for the preparation of benzimidazole *N*-oxides, which cannot be obtained by direct oxidation of benzimidazoles. Thermal and photochemical cyclizations of 2-nitroaniline derivatives having electron-withdrawing substituents at the α-carbon next to the amino group are known to give benzimidazole *N*-oxides,[10] but the reaction fails in some cases.[11] Therefore, the development of new synthetic methods to obtain a variety of benzimidazole *N*-oxide derivatives is of interest.

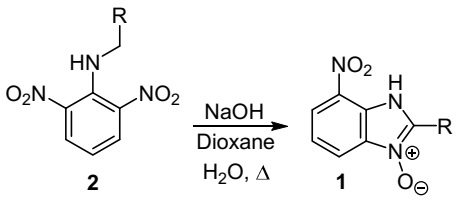
With increasing legislation and environmental awareness, chemists are under pressure to find cleaner, greener, and more sustainable ways of making their target compounds.[12] By adopting new technology, it is often possible to open up avenues for the development of new synthetic methods. To this end, continuous flow processing is becoming very useful for the development of medicinal chemistry.[13] Reactions can often be streamlined, multiple steps can be linked together, and reactions that were challenging in batch are now available for chemists to use. There is also better control of heating and mixing, allowing for reactions to be performed under very precise and reproducible conditions. While the synthesis of heterocycles, including benzimidazole derivatives, has been reported using flow processing,[14,15] to our knowledge, there are no reports of synthesis of benzimidazole *N*-oxides derivatives using this technology. We present our results here.

A series of nitrobenzimidazole *N*-oxides **1** has been previously prepared by means of the cyclization of *N*-substituted 2,6-dinitroanilines **2** (Scheme 1a). The method involves heating compound **2** at reflux with sodium hydroxide in a 1,4-dioxane–water 6:4 mixture as the solvent.[16–18] The disadvantage of this methodology is the need to synthesize compounds **2** as they are not commercially available. These starting materials were prepared by an S_NAr reaction of 2,6-dinitrochlorobenzene (**3**) and amine using DMF as solvent (Scheme 1b).[16–18]

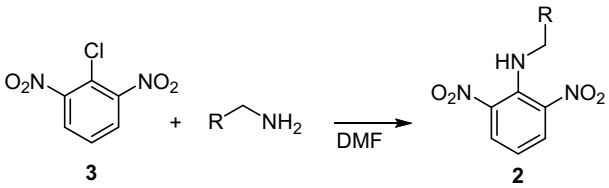
Our objective was to improve this method according to the principles of green chemistry.[19] The choice of solvent is the key to this.[20–23] Solvents such as 1,4-dioxane or DMF are hazardous and their substitution is required. To this

Scheme 1

(a) Preparation of benzimidazole *N*-oxides



(b) Preparation of *N*-substituted 2,6-dinitroaniline precursors

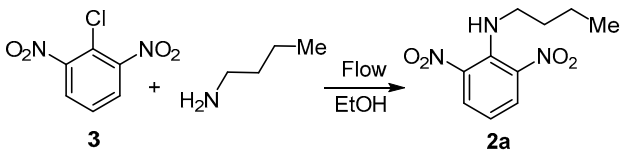


end, we attempted to perform the S_NAr reaction of compound **3** and a range of different amines and α-amino acids. Reactions were initially run in batch using microwave heating as a tool.[24] When performing reactions involving simple amines, we selected ethanol as the solvent, while in the case of α-amino acids a water–ethanol 1:1 mixture was used. We were successful in preparing a representative number of *N*-substituted 2,6-dinitroanilines. Reactions were performed at 95°C for 10 min employing a 1:2 stoichiometric ratio of compound **3** to amine (in order to neutralize the HCl liberated in the S_NAr reaction).

In planning to translate this methodology to continuous flow processing, we had to ensure that the reaction mixture remained homogeneous throughout. When working at elevated temperatures, use of a back pressure regulator allows for solvents and reaction mixtures to be heated well above their boiling points. However, if the product precipitates out of solution, blockage of the back pressure regulator or the exit tube can be a potential problem. While specialized equipment is available for processing slurries, when using most commercially available apparatus issues of heterogeneity can be a hurdle that needs to be overcome.

In an attempt to find optimal conditions for the first step of the process in flow, we selected the reaction of compound **3** with *n*-butylamine. Using a 0.15 M solution of compound **3** in ethanol and a 0.3 M solution of *n*-butylamine in ethanol and pumping each at a flow rate of 0.5 ml/min through a 10 ml capacity coil (1 ml/min combined flow rate; 10 min residence time) at 95°C gave a 71% conversion to compound **2a**. By increasing the residence time to 25 min (0.2 ml/min on each pump) and the temperature to 120°C we were able to obtain 100% conversion to compound **2a** (Scheme 2).

Scheme 2

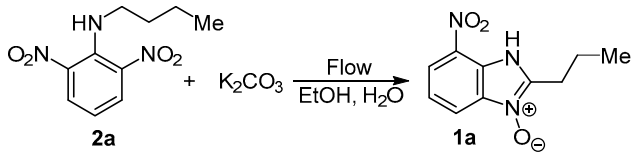


95°C, 10 min residence time: 71% conversion
120°C, 25 min residence time: 100% conversion

We turned our attention next to the second step of the process, the base-mediated cyclization of *N*-substituted 2,6-dinitroanilines to the corresponding benzimidazole *N*-oxides. In microwave-heated batch trials employing a water–dioxane 1:1 solvent mixture, we found that sodium hydroxide can be used as the base. However, along with the desired benzimidazole *N*-oxide we observed formation of 2,6-dinitrophenol, the result of a substitution reaction. By keeping the sodium hydroxide concentration lower than 0.2 M we were able to limit the formation of this by-product.[25,26] Moving to ethanol as a solvent, we observed a number of new by-products. We believed that this was due to the formation of sodium ethoxide which triggered the undesired side reactions. For this reason, we decided to transition to a milder base, selecting potassium carbonate.[27] We performed the reaction in batch using compound **2a** as a test substrate, adding a 0.3 M aqueous solution of K_2CO_3 to an ethanol solution of compound **2a**. Heating at 95°C for 20 min gave the desired benzimidazole *N*-oxide **1a** in quantitative conversion.

In transitioning to flow, we wanted to be able to take the product stream from the first reaction (conversion of compound **3** to compound **2**), introduce an aqueous solution of base, and then pass the mixture through a second 10 ml capacity coil. To achieve this, we needed to shorten the residence time for the second step from the 20 min we used in batch to around 10–11 min. We decided to perform a trial reaction. We prepared an ethanol solution of compound **2a** at the concentration it would come out of coil 1 and a 0.3 M aqueous solution of K_2CO_3. Pumping the solution of compound **2a** at a flow rate of 0.4 ml/min and the solution of base at flow rate of 0.5 ml/min through a 10 ml capacity coil (0.9 ml/min combined flow rate, 11.1 min residence time) at 120°C, gave a quantitative conversion to compound **1a** (Scheme 3).

Scheme 3



120°C, 11.1 min residence time: 100% conversion

With operating conditions for both steps of the reaction in hand, we moved to concatenating the two steps. The progress of the reaction could be clearly seen. There is a marked color change from yellow to red, attributed to the formation of a Meisenheimer complex (Fig. 1).[26] Turning our attention to product purification, we again wanted to take an approach with the tenets of green chemistry in mind. We developed a purification strategy that did not require chromatography. Instead, using only ethyl acetate as solvent, we obtained the pure product by aqueous–organic phase extraction. Working on the 0.25 mmol scale, we obtained a quantitative conversion of compound **3** and an 72% isolated yield of compound **1a**.

We next moved to probe the substrate scope of the methodology. Embarking on this endeavor, we discovered

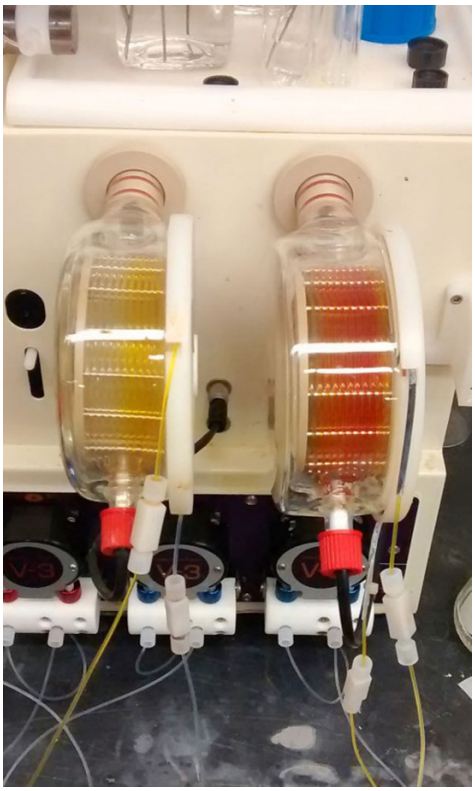


Figure 1. The conversion of compound **3** to compound **1a** using a two-step flow process.

a solubility problem when the outlet stream of the first reactor was mixed with the aqueous stream of base. We remedied this with the addition of an organic cosolvent to the base solution. We needed to choose a suitable solvent that would allow us to keep the organic components of the reaction in solution but at the same time assure the solubility of the mineral base. We decided to use 2-propanol as the cosolvent, an 11:2 volume ratio of water–2-propanol being optimal and allowing us to maintain a base concentration of 0.3 M. With this improvement, we prepared a series of six benzimidazole *N*-oxides (Table 1, entries 1–6). The flow configuration used is shown in Figure 2. Good to excellent yields of the *N*-oxide products **1** were obtained in each case. In the case of ethanolamine and ethylene diamine (Table 1, entries 5 and 6), rather than the expected 2-substituted nitrobenzimidazole, 7-nitro-1*H*-benzimidazole 3-oxide **1e** was formed. This product implies the loss of CH_2OH and CH_2NH_2 for the reaction with ethanolamine and ethylene diamine, respectively.

The reaction was also performed with two amino acids – β-alanine and γ-aminobutyric acid. To ensure complete solubility for the initial S_NAr reaction, we dissolved the amino acids in water along with two equivalents of $NaHCO_3$ in order to neutralize the carboxylic acid group and the HCl liberated in the reaction. With this modification we were able to obtain good yields of *N*-oxide products **1f**,**g** (Table 1, entries 7 and 8). The expected substituted nitrobenzimidazole *N*-oxide **1g** was obtained

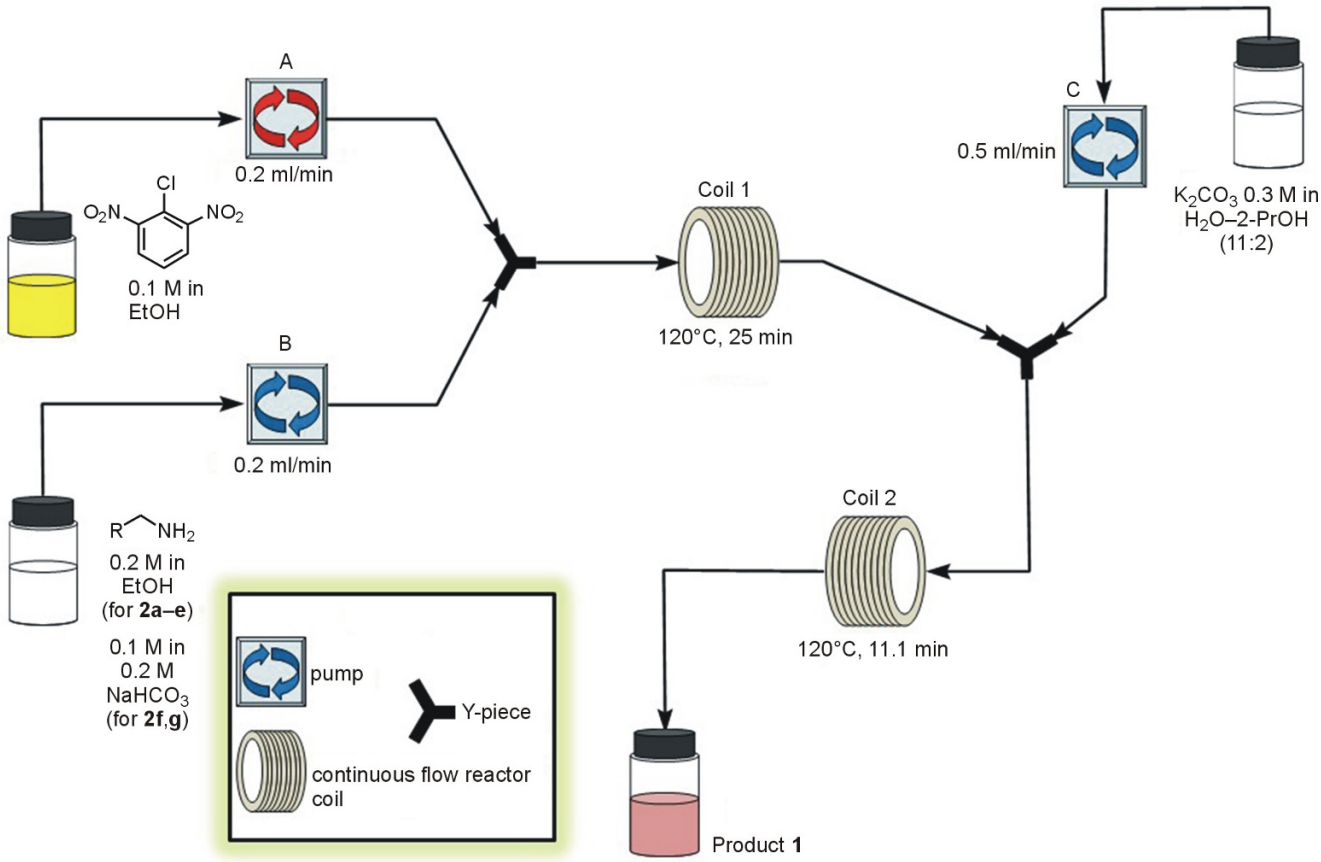
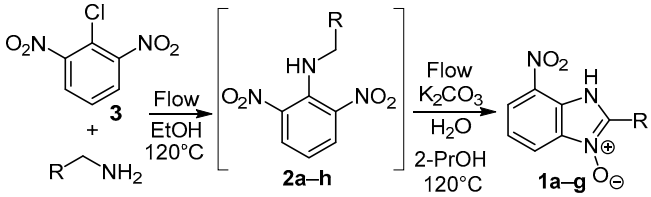
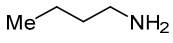
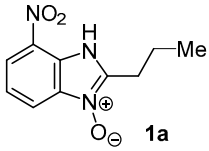
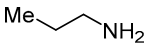
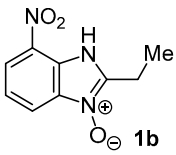
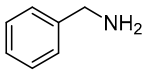
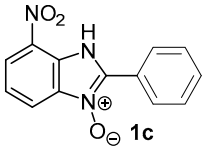
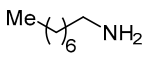
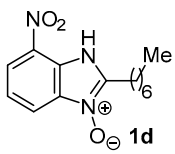
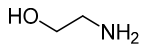
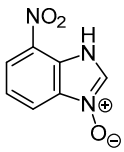
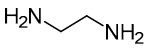
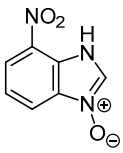
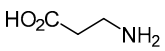
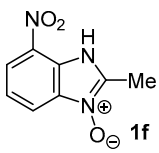
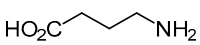
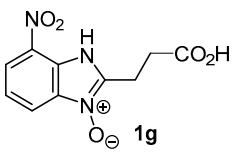


Figure 2. The flow configuration used for the preparation of nitrobenzimidazole *N*-oxides **1** in flow.

Table 1. Preparation of nitrobenzimidazole *N*-oxides **1a**–**g** in flow*



Entry	Amine	Product	Yield,** %
1		 **1a**	72, 72*** (75)[16]
2		 **1b**	59 (63)[17]
3		 **1c**	53
4		 **1d**	69
5		 **1e**	76 (42)[18]
6		 **1e**	90 (42)[18]
7		 **1f**	65 (69)[18]
8		 **1g**	80 (63)[18]

* Reactions performed on the 0.25 mmol scale.
** Literature yield in brackets over two steps in batch.
*** Reaction performed on the 1.0 mmol scale.

when using γ-aminobutyric acid but in the case of β-alanine, decarboxylation occurred upon cyclization yielding compound **1f**.

Where available, we compared product yields reported in the literature with those obtained using our greener continuous flow procedure. Our methodology resulted in similar yields, higher in three cases (Table 1, entries 5, 6, and 8), but with a great improvement from the perspective of sustainability due to the use of greener solvents, as well as the avoidance of chromatographic separation in the purification step. In addition, our flow approach is faster as compared with the previously reported methods and does not require the isolation and purification of the *N*-substituted aniline intermediate.

We did attempt to perform the reaction in one step, but adding a high concentration of base to the reaction mixture of compound **3** and the amine resulted in the formation of 2,6-dinitrophenol as the principal product. At a low concentration of base, the S_NAr product **2** is the principal product with little to none of the desired compound **1** being formed.

In summary, we have developed a continuous flow process for the synthesis of nitrobenzimidazole *N*-oxides from 2,6-dinitrochlorobenzene and amines or amino acids. The process, performed in a two-step sequence, is faster than previously reported batch processes and avoids some of the isolation and purification steps.

Experimental

^{1}H and ^{13}C NMR spectra were performed at 298 K on Bruker Advance (300 and 75 MHz, respectively) or Bruker Advance III (400 and 101 MHz, respectively) spectrometers in DMSO-d_6 and referenced to residual non-deuterated DMSO (2.50 and 39.5 ppm, respectively) in the deuterated solvent. Mass spectra were recorded using an Agilent Technologies 5975 mass spectrometer. High-resolution mass spectra were obtained using a JEOL AccuTOF-DART SVP 100 instrument in positive direct analysis in real time (DART) ionization method, using PEG as internal standard. Reactions were monitored by ^{1}H NMR and/or by TLC on silica gel plates (60 Å porosity, 250 μm thickness). TLC analyses were performed using hexane–EtOAc and Et_2O as the eluent, visualizing the compounds with UV light.

Flow configuration. Reactions were performed using a Vapourtec E series flow unit. The two reactor coils used were made of PFA and had an internal volume of 10 ml. PEEK Y-mixers (Y-connector, 0.02-in. through-hole) were purchased from Upchurch Scientific. The configuration shown in Figure 2 was assembled using the aforementioned equipment.

Preparation of 7-nitro-2-propyl-1*H*-benzimidazole 3-oxide (1a) (General method). To a glass vial was added 2-chloro-1,3-dinitrobenzene (**3**) (49.6 mg, 0.246 mmol, 1 equiv) and anhydrous EtOH to a total volume of 2.5 ml (0.1 M). To another vial was added *n*-butylamine (36.0 mg, 0.05 ml, 0.500 mmol, 2 equiv) and made up to 2.5 ml with anhydrous EtOH. A third vial was filled with 0.3 M K_2CO_3 solution in water–2-propanol, 11:2. With these solutions

prepared, the continuous flow process was initiated. The pumps assigned for substrate and amine were primed and flushed with anhydrous EtOH and the pump for the second step was primed and flushed with deionized water. The flow system was equipped with two 10-ml capacity coils in series (coil 1 and coil 2). Three pumps were employed (pump A, B, and C). The outlets of pumps A and B were joined to a Y-piece and the outlet of the Y-piece attached to the "reagent in" port of the first reactor coil. The "reagent out" port of the first reactor coil and the outlet of pump C were attached to a Y-piece and the outlet of the Y-piece attached to the "reagent in" port of the second reactor coil. The "reagent out" port of the second reactor coil was directly interfaced with a back pressure regulator after which there was a short length of tubing leading to a collection vessel. The flow system was primed using the equipment manufacturer's suggested start-up sequence. The entire system was flushed with EtOH for 5 min at a flow rate of 0.5 ml/min on each pump. The reactor coils were set at 120°C and the back regulator pressure set at 5 bar. Then, the substrate **3** and amine solutions were loaded into the reactor coil at a flow rate of 0.2 ml/min. Once these solutions were completely loaded, both pumps were set to pump anhydrous EtOH. After 5 min, pump C (pumping the aqueous base) was started at a flow rate of 0.5 ml/min. Once the product mixture was completely out of the system (observed clearly by the change from red to a colorless solution), all pumps were stopped. The resulting reaction mixture was transferred from the collection flask to a separatory funnel.

An extraction with ~15 ml of ethyl acetate was performed, in order to eliminate the all non-acidic products. The aqueous layer was acidified using 2 M aqueous HCl, until pH between 2 and 5 was reached. A color change from red to yellow in the solution was observed at this point. The aqueous layer was extracted with EtOAc (3×15 ml). The combined organic layers were washed with brine (~30 ml) and dried with Na_2SO_4. The solvent was removed under reduced pressure by rotary evaporation affording the pure benzimidazole *N*-oxide **1a** (39.0 mg, 72%) as a clear yellow solid. ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 7.95 (1H, d, *J* = 7.1, H-4); 7.72 (1H, d, *J* = 7.4, H-6); 7.29 (1H, t, *J* = 8.0, H-5); 2.85–2.78 (2H, m, CH_2); 1.83–1.65 (2H, m, CH_2); 0.93 (3H, t, *J* = 7.4, CH_3). ^{13}C NMR spectrum (101 MHz), δ, ppm: 155.2 (C-2); 137.8 (C-7); 135.1 (C-7a); 131.3 (C-3a); 121.2 (C-5); 118.2 (C-6); 115.5 (C-4); 27.5 ($\underline{C}H_2CH_2CH_3$); 20.2 ($CH_2\underline{C}H_2CH_3$); 13.8 ($CH_2CH_2\underline{C}H_3$). Mass spectrum, *m*/*z*: 222 $[M+H]^+$.

2-Ethyl-7-nitro-1*H*-benzimidazole 3-oxide (1b). To a glass vial was added 2-chloro-1,3-dinitrobenzene (**3**) (49.9 mg, 0.247 mmol, 1 equiv) and anhydrous EtOH to a total volume of 2.5 ml (0.1 M). To another vial was added *n*-propylamine (28.8 mg, 0.04 ml, 0.490 mmol, 2 equiv) and made up to 2.5 ml with anhydrous EtOH. A third vial was filled with 0.3 M K_2CO_3 in water–2-propanol, 11:2. The general method was followed, affording the pure benzimidazole 3-oxide **1b** (30.2 mg, 59%) as a clear yellow solid. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 12.15 (1H, s, NH); 8.00 (1H, d, *J* = 7.9, H-4); 7.87 (1H, d, *J* = 7.9, H-6); 7.40 (1H, t, *J* = 8.0, H-5); 2.95 (2H, q, *J* = 7.4, CH_2); 1.34 (3H, t, *J* = 7.3, CH_3). ^{13}C NMR spectrum (101 MHz), δ, ppm: 156.3; 137.8; 135.0; 131.2; 121.2; 118.1; 115.3; 19.2; 11.2. Mass spectrum, *m*/*z*: 208 $[M+H]^+$.

7-Nitro-2-phenyl-1*H*-benzimidazole 3-oxide (1c). To a glass vial was added 2-chloro-1,3-dinitrobenzene (**3**) (49.4 mg, 0.245 mmol, 1 equiv) and anhydrous EtOH to a total volume of 2.5 ml (0.1 M). To another vial was added benzylamine (50.0 mg, 0.051 ml, 0.470 mmol, 2 equiv) and made up to 2.5 ml with anhydrous EtOH. A third vial was filled with 0.3 M K_2CO_3 in water–2-propanol, 11:2. The general method was followed for the flow processing step. The resulting product mixture was transferred from the collection flask to a separatory funnel. An extraction with ~15 ml of ethyl acetate was performed, in order to eliminate the all non-acidic products. The aqueous layer was acidified using 2 M aqueous HCl, until pH between 2 and 5 was reached. A color change from red to yellow in the solution was observed at this point, along with formation of a precipitate. The precipitate was isolated by vacuum filtration, and washed with cold water, affording the pure benzimidazole 3-oxide **1c** (32.9 mg, 53%) as a clear yellow solid. ^{1}H NMR (400 MHz), δ, ppm (*J*, Hz): 12.61 (1H, s, NH); 8.31 (2H, dd, *J* = 6.6, *J* = 3.0, H Ar); 8.11 (1H, d, *J* = 7.7, H Ar); 8.01 (1H, d, *J* = 7.8, H Ar); 7.69–7.56 (3H, m, H Ar); 7.49 (1H, t, *J* = 8.0, H-5). ^{13}C NMR spectrum (101 MHz), δ, ppm: 150.7; 138.6; 136.7; 131.8; 131.4; 129.3; 129.2; 128.2; 122.6; 119.7; 116.7. Mass spectrum, *m*/*z*: 256 $[M+H]^+$. Found, *m*/*z*: 256.0697 $[M+H]^+$. $C_{13}H_{10}N_3O_3$. Calculated, *m*/*z*: 256.0722.

2-Heptyl-7-nitro-1*H*-benzimidazole 3-oxide (1d). To a glass vial was added 2-chloro-1,3-dinitrobenzene (**3**) (50 mg, 0.247 mmol, 1 equiv) and anhydrous EtOH to a total volume of 2.5 ml (0.1 M). To another vial was added octylamine (64 mg, 0.082 ml, 0.496 mmol, 2 equiv) and made up to 2.5 ml with anhydrous EtOH. A third vial was filled with 0.3 M K_2CO_3 in water–2-propanol, 11:2. The general method was followed for the flow processing step and the purification protocol used for compound **1c** was followed, affording the pure benzimidazole 3-oxide **1d** (47 mg, 69%) as a clear yellow solid. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 12.11 (1H, s, NH); 8.01 (1H, d, *J* = 8.0, H-4); 7.88 (1H, d, *J* = 7.9, H-6); 7.40 (1H, t, *J* = 8.0, H-5); 2.92 (2H, t, *J* = 7.7, CH_2); 1.79 (2H, quint, *J* = 7.5, CH_2); 1.45–1.13 (8H, m, $4CH_2$); 0.86 (3H, t, *J* = 6.7, CH_3). ^{13}C NMR spectrum (101 MHz), δ, ppm: 155.4; 137.8; 134.9; 131.2; 121.2; 118.2; 115.3; 31.1; 28.6; 28.3; 26.6; 25.5; 22.0; 13.9. Mass spectrum, *m*/*z*: 278 $[M+H]^+$. Found, *m*/*z*: 278.1495 $[M+H]^+$. $C_{14}H_{19}N_3O_3$. Calculated, *m*/*z*: 278.1505.

7-Nitro-1*H*-benzimidazole 3-oxide (1e). To a glass vial was added 2-chloro-1,3-dinitrobenzene (**3**) (50.0 mg, 0.247 mmol, 1 equiv) and anhydrous EtOH to a total volume of 2.5 ml (0.1 M). To another vial was added ethylenediamine (29.7 mg, 0.033 ml, 0.490 mmol, 2 equiv) and made up to 2.5 ml with anhydrous EtOH. A third vial was filled with 0.3 M K_2CO_3 in water–2-propanol, 11:2. The general method was followed, affording the pure benzimidazole 3-oxide **1e** (40.0 mg, 90%) as a clear yellow solid. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 12.45 (1H, s, NH); 8.71 (1H, s, H-2); 8.08 (1H, d, *J* = 7.9, H-4);

7.98 (1H, d, *J* = 8.0, H-6); 7.49 (1H, t, *J* = 8.0, H-5). ^{13}C NMR spectrum (75 MHz), δ, ppm: 143.0; 137.1; 132.4; 131.0; 122.2; 118.7; 116.2. Mass spectrum, *m*/*z*: 180 $[M+H]^+$.

2-Methyl-7-nitro-1*H*-benzimidazole 3-oxide (1f). To a glass vial was added 2-chloro-1,3-dinitrobenzene (**3**) (50 mg, 0.247 mmol, 1 equiv) and anhydrous EtOH to a total volume of 2.5 ml (0.1 M). To another vial was added β-alanine (22 mg, 0.247 mmol, 1 equiv), $NaHCO_3$ (42 mg, 0.500 mmol, 2 equiv) and made up to 2.5 ml with water–anhydrous EtOH, 1:1. A third vial was filled with 0.3 M K_2CO_3 in water–2-propanol, 11:2. The representative procedure was followed, affording the pure benzimidazole *N*-oxide **1f** (31 mg, 65%) as a clear yellow solid. ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 12.16 (1H, s, NH); 8.01 (1H, d, *J* = 8.0, H-4); 7.88 (1H, d, *J* = 7.3, H-6); 7.41 (1H, t, *J* = 8.0, H-5); 2.59 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz), δ, ppm: 152.3; 137.5; 135.1; 131.2; 121.0; 118.1; 115.5; 13.4. Mass spectrum, *m*/*z*: 194 $[M+H]^+$.

3-(7-Nitro-3-oxido-1*H*-benzimidazol-2-yl)propionic acid (1g). To a glass vial was added 2-chloro-1,3-dinitrobenzene (**3**) (50 mg, 0.247 mmol, 1 equiv) and anhydrous EtOH to a total volume of 2.5 ml (0.1 M). To another vial was added γ-aminobutyric acid (26 mg, 0.252 mmol, 1 equiv), $NaHCO_3$ (42 mg, 0.5 mmol, 2 equiv) and made up to 2.5 ml with water–anhydrous EtOH, 1:1. A third vial was filled with 0.3 M K_2CO_3 in water–2-propanol, 11:2. The general method was followed, affording the pure benzimidazole *N*-oxide **1g** (50 mg, 80%) as a clear yellow solid. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 12.30 (1H, s, NH); 8.01 (1H, d, *J* = 8.0, H-4); 7.89 (1H, d, *J* = 7.9, H-6); 7.41 (1H, t, *J* = 8.0, H-5); 3.15 (2H, t, *J* = 7.2, CH_2); 2.85 (2H, t, *J* = 7.2, CH_2). ^{13}C NMR spectrum (101 MHz), δ, ppm: 173.3; 154.3; 137.9; 135.1; 131.1; 121.5; 118.3; 115.5; 30.2; 21.1. Mass spectrum, *m*/*z*: 252 $[M+H]^+$.

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