Flow-Mediated Synthesis of Boc, Fmoc, and Ddiv Monoprotected Diamines

Flow Mediated Synthesis of Boc, Fmoc and Dd*iv* Mono-Protected Diamines

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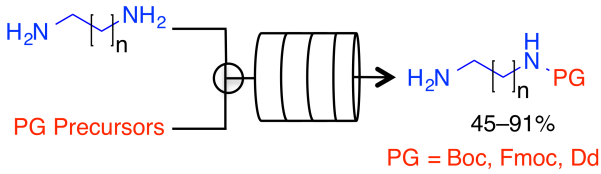
Supporting Information Placeholder



ABSTRACT: A series of mono-protected aliphatic diamines (21 examples) were synthesised via continuous flow methods. The carbamates and enamines were obtained in 45–91% yields using a 0.5 mm diameter PTFE tubular flow reactor. Using readily accessible protecting group precursors, the procedure serves as an attractive alternative to existing batch-mode synthetic routes by providing direct, multi-gram access to *N*-Boc, *N*-Fmoc and *N*-Dd*iv* protected compounds, with productivity indexes of 1.2–3.6 g/h.

The use of protecting groups to facilitate the construction of structurally complex molecules is an indispensable strategy in organic synthesis.[1] However, the selective mono-protection of a multi-functional molecule is often difficult to achieve due to competing reactive sites on the unprotected substrate and reactivity of the mono-protected product. The problem is exacerbated in a conventional batch environment as a result of system inhomogeneity, resulting in a mixture of protected products.[2] Mono-protected aliphatic diamines are important chemical precursors, widely used as spacers,[3] linkers[4] and scaffolds,[5] and various strategies have been introduced to achieve mono-protection,[6] including the use of passivated protecting group precursors,[7] chemical auxiliaries to differentiate the reactivity of amino groups,[8] solid-phase functionalisation,[9] and stoichiometric control.[10] These batch methods, however, have limited success and are often inconsistent as well as unpractical. The mono-acylation of diamines in a microreactor under ultrasonic irradiation has been reported.[11] This syringe pump-driven method, which is restricted to a fixed volume of reactants, produced good results (≥ 87% yields) with piperazine and homopiperazine when acid chlorides were used as the acylating agent; however, isolated yields for series of aliphatic diamines or protecting group chemistry was not reported.

Flow synthesis serves as an attractive alternative to the aforementioned batch methods by inducing reaction selectivity through spatial and temporal manipulation under continuous flow conditions.[12] This tight window of reaction control limits the propagation of undesirable side reactions, and consequently delivers higher yields compared to batch reactions. Continuous flow reactors have been used in a variety of synthetic endeavours to promote reaction selectivity and particle size control, mainly due to the superior physical transport properties, thermal control and mixing ability exhibited by narrow reaction chambers.[13]

Here, the selective and scalable mono-protection of symmetrical aliphatic diamines via continuous flow synthesis using a polytetrafluoroethylene (PTFE) tubular reactor is demonstrated. The flow reactor (SI, Figure S1–S2) was self-assembled from commercially available parts as a robust and scalable synthesizer compared to chip reactors that are often susceptible to material plugging. The carbamates, *tert*-butyloxycarbonyl (Boc) and 9-fluorenylmethyloxycarbonyl (Fmoc), and the enamine 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-isovaleryl (Dd*iv*), are popular protecting groups and were therefore selected to protect a series of diamines. Boc anhydride (Boc_2O), Fmoc-succinimide (Fmoc-OSu) and 2-(1-hydroxy-3-methylbutylidene)-5,5-dimethyl-cyclohexane-1,3-dione (Dd*iv*OH) are typically used to generate the *N*-carbamate and enamine derivatives, respectively (Scheme 1).

The reaction between 1,6-diaminohexane **1a** and Boc_2O was used to optimise the reaction parameters for mono-Boc protection. The reaction set-up for the continuous flow mediated mono-protection of diamines consisted of two steps (Figure 1). During the pre-conditioning stage, the reactants were fed into their respective PTFE channels (0.5 mm internal diameter [I.D.], 0.18 mL internal volume), immersed in a water bath at 0 °C. This step reduces the

time required for the reactants to reach thermal equilibrium within the flow reactor and promotes reaction reproducibility. The reactants were mixed in the T-mixer and the reaction proceeded along the PTFE flow reactor (0.5 mm I.D., 2.0 mL internal volume). Upon exiting the reactor, the reaction stream was immediately quenched with an excess of the silica-based trisamine scavenger in MeOH at –10 °C.

Scheme 1 Formation of Boc and Fmoc *N*-carbamates and Dd*iv* enamines from primary amines.

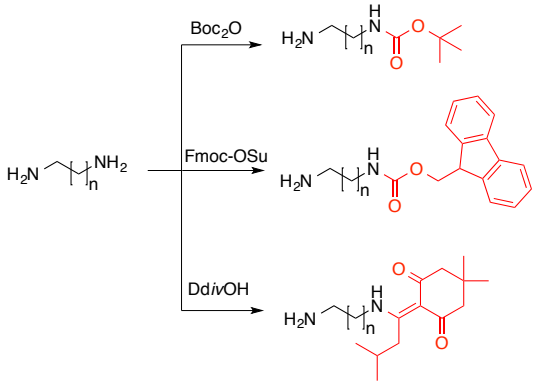
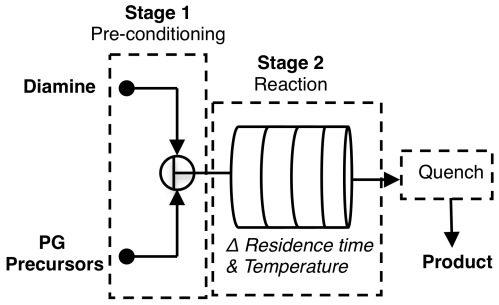
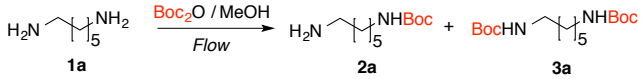


Figure 1 Reaction set-up for the flow synthesis of mono-protected diamines.



Initially, the effect of reactant stoichiometry on the mono-protection yield was investigated (Table 1). Concentrations of 0.10 M in MeOH for both reactants (diamine **1a** and Boc_2O) resulted in a 42% yield of *N*-Boc-1,6-diaminohexane **2a** along with a significant amount of the di-protected product **3a**. When the stoichiometric ratio of the diamine was raised from 1.0 to 2.0 equivalents by adjusting the flow rates, the yield of **2a** increased accordingly (64%) and the occurrence of di-protection was noticeably suppressed (entries a–f, Table 1). Reducing the residence time from 1.0 to 0.5 min did not show any appreciable influence on the reaction selectivity (entries f *vs*. h, Table 1) but a 2.0 min residence time led to a ~10% drop in product yield (entries f *vs*. i, Table 1). Similarly, raising the reaction temperature to 25 °C had a detrimental effect on the formation of **2a** (entry g, Table 1).

Table 1 Optimisation of the synthesis of mono-*N*-Boc-1,6-diaminohexane **2a** in a 0.5 mm I.D. tubular flow reactor.[i]



entry	equiv **1a**	temp (°C)	time (min)	yield **2a** (%)[ii]	ratio[iii] of **2a**:**3a**
a	1.0	0	1.0	42	1:0.56
b	1.2	0	1.0	48	1:0.40
c	1.4	0	1.0	54	1:0.36
d	1.6	0	1.0	52	1:0.34
e	1.8	0	1.0	57	1:0.26
f	2.0	0	1.0	64	1:0.19
g	2.0	25	1.0	53	1:0.22
h	2.0	0	0.5	63	1:0.12
i	2.0	0	2.0	53	1:0.35

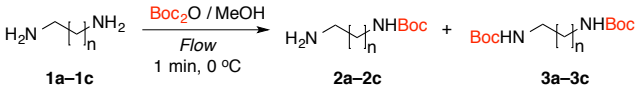
[i]2 mmol scale, 0.10 M Boc_2O (limiting reagent). [ii]Average isolated yield of replicate experiments after column chromatography (n = 3, variation in yields within ± 3% points). [iii]The molar ratio of **2a**:**3a** (isolated products).

The intricate relationship between the internal diameter of tubular flow reactors and the degree of reaction selectivity was explored (microreactors ≤ 1 mm I.D., mesoscale reactors > 1 mm I.D.). Thus, the Boc carbamation of 1,6-diaminohexane **1a**, 1,4-diaminobutane **1b** and 1,2-diaminoethane **1c** were performed in 0.5, 1.0 and 1.6 mm I.D. tubular flow reactors. The 0.5 mm I.D. flow reactor consistently gave mono-Boc-products **2a**–**2c** in 64–65% yields with good product to side-product ratios (> 4:1) (Table 2). Moreover, an excellent reproducibility (variation in yields within ±3% points) was demonstrated with replicate experiments (n = 3–5). In contrast, lower yields were observed in reactors with larger tubular I.D.'s (1.0 and 1.6 mm). This may be attributed to the efficiency of the mixing process in flow, which determines the homogeneity of the solution and is essential in reducing the occurrence of side-reactions.[14] With the Boc carbamations, sonication of the flow reactor did not have notable effect on the conversion. In a batch environment, inefficient mechanical stirring often leads to poor mixing, which creates localised concentration hotspots of reactants.

The continuous flow method was applied to the synthesis of mono-Fmoc diaminoalkanes. The most commonly used solution strategy relies on a three-step method, involving the mono-Boc protection of the diamine, followed by the Fmoc protection of the remaining free amino moiety, and finally Boc deprotection.[15] The mono Fmoc-carbamation of **1a** with Fmoc-OSu followed the optimised conditions for the flow synthesis of *N*-Boc-1,6-diaminohexane **2a**. For the Fmoc carbamation, DMF was used as the reaction solvent (good solubility for both the starting materials and the resulting Fmoc-protected compounds) and the reaction stream was quenched with HCl in cold MeOH (–10 °C, pH 2–3). Using Fmoc-Osu as the

limiting reagent (0.05 M) and 2.0 equivalents of **1a**, the flow procedure (0.5 min, 0 °C) gave a 45% yield of *N*-Fmoc-1,6-diaminohexane **4a**, showing that Fmoc-protected carbamates can be obtained in reasonable yields in a single step without the need for a sacrificial protecting group.

Table 2 The effect of the flow reactor's I.D. on the reaction mono-selectivity.[i]



1a–1c **2a–2c** **3a–3c**

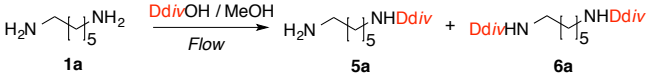
entry	diamine	reactor i.d. (mm)	yield[ii] (%)	product ratio[iii] (%)
a	**1a**, n = 5	0.5	64	**2a** 84:**3a** 16
b	**1a**, n = 5	1.6	51	**2a** 81:**3a** 19
c	**1b**, n = 3	0.5	65	**2b** 83:**3b** 17
d	**1b**, n = 3	1.6	59	**2b** 72:**3b** 28
e	**1c**, n = 1	0.5	64	**2c** 81:**3c** 19
f	**1c**, n = 1	1.6	50	**2c** 74:**3c** 26

[i]2 mmol scale, 0.10 M Boc_2O (limiting reagent). [ii]Average isolated yield of replicate experiments (n = 5, variation in yields within ± 3% points). [iii]The molar ratio of isolated products.

Having successfully synthesised the mono-carbamated diamines, the flow synthesis of enamine derivatives was investigated using the Dd*iv* protecting group, commonly used in solid-phase synthesis.[16] In the reaction between **1a** and Dd*iv*OH, temperature was found to play a very significant role in promoting flow-based enamination (Table 3). No product was observed below 90 °C with a residence time of 2.0 min. However, using 2.0 equivalents of **1a** and a residence time of 1 min at 130 °C, 81% conversion to the mono-protected enamine **5a** was observed (entry l, Table 3). Lowering the reaction temperature from 130 to 120 °C (entry j, Table 3) or reducing the concentration of **1a** consistently gave lower conversion to the mono-protected product (entries d and h *vs*. l, Table 3), while mono-selectivity was adversely affected with only 29% conversion to **5a** when the residence time was increased from 1.0 to 2.0 min (entry m, Table 3).

Based on the established optimal reaction parameters for each protecting group, the scope of continuous flow carbamation and enamination was examined with a series of aliphatic diamines of varying alkyl and ethylene glycol chain lengths (Table 4). The scale of syntheses was increased to 10 mmol to produce 1–3 g of the mono-protected compounds using a 4.0 mL internal volume flow reactor (0.5 mm I.D.). For alkyl diamines, the isolated yields of the mono-Boc and mono-Fmoc protected products **2a–2e** and **4a–4e** were 51–77%, demonstrating good overall selectivity (Table 4). Similar selectivity was also observed with the ethylene glycol-based diamines **2f–2g** and **4f–4g**. Interestingly, substituting Fmoc-OSu with Fmoc-Cl as the protecting group precursor led to significantly lower yields (25–42%) of the mono-Fmoc carbamates. Meanwhile, excellent yields (80–91%) of mono-protected enamines **5c–5d** were obtained with shorter members of the compund family. With the shorter diaminoalkanes, this may be due to steric hindrance provided by the first Dd*iv* group on a protected amine, thus decreasing the reactivity of the remaining free amino functionality. The longer chain mono-protected enamines **5a–5b** and **5e–5g** were obtained in ≥ 58% yield.

Table 3 Optimisation of the flow synthesis of mono-*N*-Dd*iv*-1,6-diaminohexane **5a**.[i]

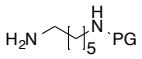
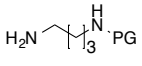
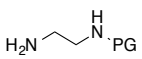
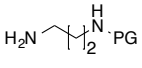
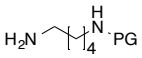


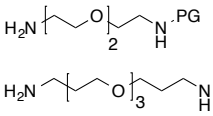
1a **5a** **6a**

entry	equiv **1a**	temp (°C)	time (min)	conversion to **5a**(%)[ii]	ratio of **5a**:**6a**[iii]
a	1.2	90	2.0	0	–
b	1.2	120	1.0	53	1:0.30
c	1.2	120	2.0	44	1:0.39
d	1.2	130	1.0	57	1:0.29
e	1.2	130	2.0	53	1:0.43
f	1.5	120	1.0	65	1:0.30
g	1.5	120	2.0	66	1:0.50
h	1.5	130	1.0	71	1:0.40
i	1.5	130	2.0	65	1:0.53
j	2.0	120	1.0	75	1:0.28
k	2.0	120	2.0	64	1:0.30
l	2.0	130	1.0	81	1:0.24
m	2.0	130	2.0	29	1:2.48

[i]200 μmol scale, 0.10 M Dd*iv*OH (limiting reagent). [ii]Measured by HPLC with UV detection at 254 nm, methyl benzoate as an internal standard. [iii]Integrated peak ratio of **5a** and **6a**, respectively.

Table 4 Continuous flow synthesis of Boc, Fmoc and Dd*iv* mono-protected diamines.

compound	protecting group and yield[i]		
	Boc	Fmoc	Dd*iv*
	**2a** (61%)	**4a** (45%)	**5a** (58%)
	**2b** (65%)	**4b** (51%)	**5b** (72%)
	**2c** (64%)	**4c** (63%)	**5c** (91%)
	**2d** (77%)	**4d** (59%)	**5d** (80%)
	**2e** (59%)	**4e** (62%)	**5e** (72%)



2f (65%) **4f** (61%) **5f** (63%)

2g (67%) **4g** (51%) **5g** (71%)

[i]Average isolated yield of replicate experiments (n = 3). General flow conditions: 10 mmol scale, diamine (2.0 equiv), 0.05 M Fmoc-OSu or 0.10 M Boc_2O and Dd*iv*OH.

To further demonstrate the potential of the flow method, a 20 g scale synthesis of *N*-Boc-1,6-diaminohexane **2a** was successfully completed.

Since amines protected with another dimedone-based protecting group, 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethylene (Dde) are susceptible to *N*→*N*' migration,[17] the stability of the mono-Dd*iv* protected compounds were of interest. The isovaleryl handle of Dd*iv* was designed to provide steric hindrance, reducing the likelihood of group migration. In order to determine the stability of the mono-Dd*iv* diamines **5a**–**5g**, their solution (1.1–2.2 mM) half-lives were established by HPLC analysis to be 8.4–25.4 h at 80 °C (SI, Table S1), confirming the suitability of these *N*-Dd*iv* protected compounds as synthetic building blocks.

In summary, 21 mono-protected *N*-Boc, *N*-Fmoc and *N*-Dd*iv* diamines were synthesised via continuous flow with productivity indexes of 1.2–3.6 g/h. Under flow conditions, short residence times and low reaction temperatures (≤ 1 min, 0 °C) favoured the mono-carbamation reaction, whereas mono-enamination of the diamines required a high reaction temperature (1 min, 130 °C). The selective incorporation of the Boc, Fmoc and Dd*iv* protecting groups onto a series of diamines demonstrated the versatility of the method. In generating the mono-protected compounds, each type of reaction responded to adjustments in physical conditions (temperature, residence time and solvent) to provide a good degree of selectivity without the use of any chemical auxiliaries. This easily scalable method gives unprecedented one-step, multi-gram scale access to valuable mono-protected building blocks, thus improving the efficiency and atom economy of conventional protecting group chemistry.

Supporting Information

Flow instrumentation, experimental procedures, compound characterisation, and the stability study of Dd*iv*-protected compounds are included in the supporting information. This material is available free of charge via the Internet at http://pubs.acs.org

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