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Communications to the Editor

An Integrated Microreactor for the Multicomponent Synthesis of α-Aminonitriles[1]

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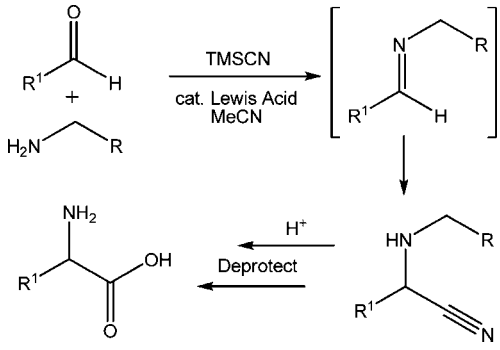
Abstract:

Initial steps have been taken to develop an integrated microreactor, capable of performing multicomponent reactions consisting of both solution phase and heterogeneously catalyzed steps. Using the multicomponent Strecker reaction as a model, five α-aminonitriles were synthesized in excellent yields (>99.5%) and analytical purity, under continuous flow conditions.

Introduction

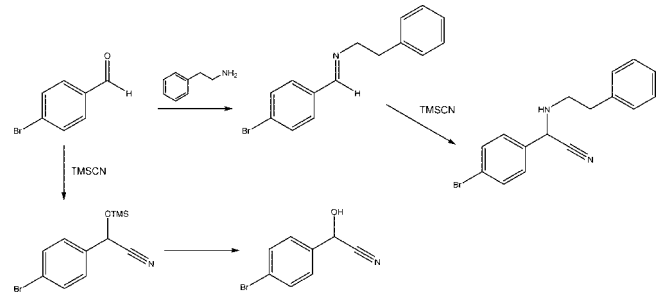
With interest in nonproteinogenic α-amino acids on the increase, there is a growing demand for novel and efficient techniques that enable the synthesis of such non-natural compounds. Although many synthetic procedures have been reported, few are suitable for the incorporation of alkyl imine substrates, often resulting in low yields and selectivities. One synthetically useful approach is the Strecker reaction, which as Scheme 1illustrates, is a three-component reaction between a

Scheme 1. **Schematic illustrating the synthesis of α-aminonitriles and their subsequent use in the preparation of non-natural amino acids**



carbonyl-containing compound, an amine, and a cyanide source.[2] The resulting α-aminonitrile can then be hydrolysed, followed by deprotection, to afford an array of non-natural amino acids, or be used as a precursor in the preparation of nitrogen-containing heterocycles and 1,2-diamines.[3,4] Despite its synthetic utility, the use of expensive Lewis acid catalysts, harsh reaction conditions and somewhat variable yields preclude the use of the Strecker reaction on a production scale. In addition a major drawback of the one-pot Strecker reaction is the competing cyanohydrin formation, as illustrated in Scheme 2, which is particularly problematic when employing aromatic aldehyde precursors; as the respective aldimine forms slowly, leaving the aldehyde available for competing cyanohydrin formation, resulting in poor reaction selectivity.

Scheme 2. **Illustration of the model reaction evaluated within an integrated microreactor and the competing cyanohydrin formation found to occur in conventional batch reactors**



Owing to the new and interesting opportunities for the management of chemical reactions that microreaction technology offers, such as enhanced process safety and rapid reaction optimization, efficient catalyst recycle and production volume flexibility,[5] we embarked upon the development of a microfluidic system capable of integrating solution-phase and heterogeneously catalyzed reaction steps in a single reactor. By using this approach we aimed to evaluate if sequential reactant addition, coupled with the use of a solid-supported Lewis acid catalyst, would allow for the efficient and selective synthesis of α-aminonitriles (Figure 1), compared to the conventional one-pot methodology.

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(1) Presented in part at the 234th American Chemical Society National Meeting, Boston, MA, 2007. Wiles, C. *Abstr. Pap. Am. Chem.* **2007**, ORGN 105.

(2) Strecker, A. *Liebigs Ann. Chim.* **1850**, *75*, 27.

(3) Groger, H. *Chem. Rev.* **2003**, *103*, 2795.

(4) Weinstock, L. M.; Davis, P.; Handelsman, B.; Tull, R. *J. Org. Chem.* **1967**, *32*, 2823.

(5) (a) For recent reviews of the technology, see: Fukuyama, T.; Rahman, M. T.; Sato, M.; Ryu, I. *Synlett* **2008**, *2*, 151. (b) Wiles, C.; Watts, P. *Eur. J. Org. Chem.* **2008**, http://dx.doi.org/10.1002/ejoc.200701041. (c) Wiles, C.; Watts, P. *Chem. Commun.* **2007**, 443. (d) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300. (e) Geyer, K.; Codee, J. D. C.; Seeberger, P. H. *Chem. Eur. J.* **2006**, *12*, 8434.

(6) **Caution!** All experiments should be performed within a fumecupboard in order to avoid inhalation of HCN, which may be liberated upon hydrolysis of trimethylsilylcyanide (TMSCN) should the reaction not go to completion.

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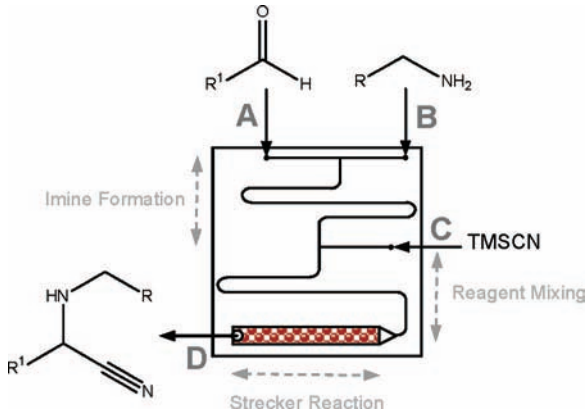


Figure 1. **Schematic illustrating the reactor manifold designed for the evaluation of the multicomponent Strecker reaction, under continuous flow.[6]**

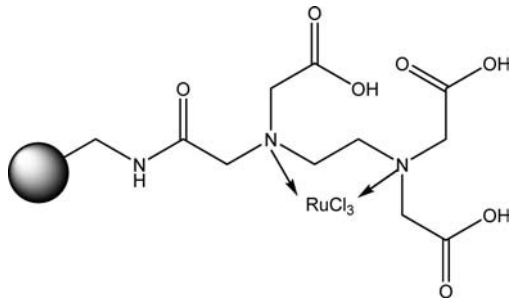


Figure 2. **Polymer-supported ethylenediaminetetraacetic acid ruthenium (III) chloride (PS-$RuCl_3$), the Lewis acid catalyst evaluated within the microreactor.**

Results and Discussion

As a result of the hydrolytic instability of many imines, which often leads to difficulties in their isolation and purification, it was desirable to generate these reactive intermediates in situ in order to achieve our aim of providing a simple and efficient route to the selective synthesis of α-aminonitriles. With this in mind, a borosilicate glass microreactor with an overall footprint of 3.0 cm × 3.0 cm × 0.6 cm was fabricated. As Figure 1 illustrates, the reaction manifold consists of a T-intersection where the aldehyde (inlet A) and amine (inlet B) are mixed under diffusion and reacted within a central channel (150 μm (wide) × 50 μm (deep) × 5.6 cm (long)) to afford the aldimine. Subsequent introduction of the cyanide source, in this case trimethylsilyl cyanide (TMSCN), through inlet C enables the reagents to mix, again under diffusion, before nucleophilic addition of the cyanide anion to the imine occurs within the catalyst bed (0.3 cm (wide) × 200 μm (deep) × 2.1 cm (long)) which was dry-packed with polymer-supported ethylenediaminetetraacetic acid ruthenium (III) chloride (PS-$RuCl_3$) (0.01 g, 0.26 mmol g^{-1}, 50 to 100 mesh), (Figure 2). PEEK tubing (360 μm o.d. × 150 μm i.d. × 10 cm) and FEP tubing (1/16 in. o.d. × 380 μm i.d. × 4 cm) was subsequently glued in place, using epoxy resin (Bondmaster, UK), at the inlets and outlet, respectively. As Figure 3 illustrates, fluidic interconnections were made between the reactor and syringes (Hamilton, Switzerland) using a series of commercially available connectors (Supelco, UK).

Prior to evaluating the performance of the reactor for the multicomponent reaction illustrated in Scheme 2, the reaction conditions required for the in situ preparation of the aldimines was first investigated. To achieve this, solutions of 2-phenylethylamine (0.4 M in MeCN) and 4-bromobenzaldehyde (0.4 M in MeCN) were introduced from separate inlets (A and B) into the microchannel network, under pressure-driven flow (5−100 μL min^{-1}), where they were reacted for a specified period of time prior to collection and analysis of the reaction mixture (at outlet C, 0.2 M in MeCN) by GC−MS. As illustrated in Figure 4a, employing a flow rate of 100 μL min^{-1} (residence time <0.2 s) afforded incomplete conversion of 4-bromobenzaldehyde to the respective imine, [1-(4-bromophenyl)meth-(*E*)-ylidene]phenethylamine. Further optimization of the reaction conditions, however, afforded quantitative synthesis of [1-(4-bromophenyl)meth-(*E*)-ylidene]phenethylamine, when operating over a flow rate range of 1−25 μL min^{-1}, which corresponds to a residence time of between 21.6 and 0.9 s. Having successfully achieved our first aim, which was to efficiently prepare an imine, the next step of the investigation was to evaluate the synthesis of the respective α-aminonitrile under continuous flow.

In order to determine the optimal flow rate required to perform the nucleophilic addition step and identify the rate-limiting step, we initially focused on the use of a preformed imine, [1-(4-bromophenyl)meth-(*E*)-ylidene]phenethylamine. Using the reactor illustrated in Figure 1, a solution of [1-(4-bromophenyl)meth-(*E*)-ylidene]phenethylamine (0.2 M in MeCN) was introduced from inlet A and a solution of TMSCN (0.2 M in MeCN) from inlet C; the reactants mixed in the central channel prior to reaction within the catalyst bed, which contained PS-$RuCl_3$. The resulting reaction products were collected at outlet D (0.1 M) after 2.5 h, concentrated in vacuo, prior to dissolution of the resulting solid in $CDCl_3$ and analysis by NMR spectroscopy, whereby comparison of the integrals

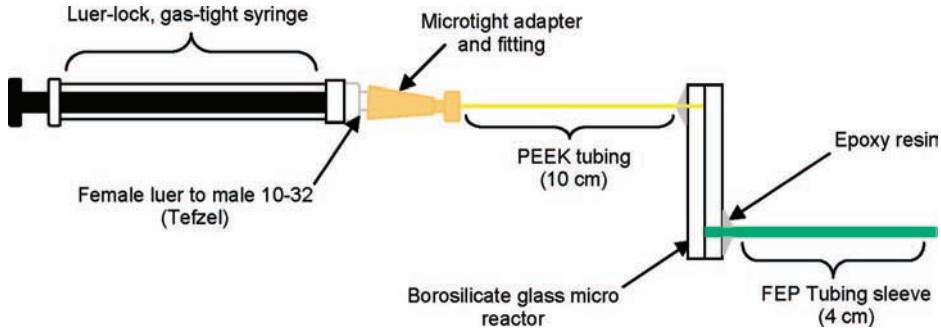


Figure 3. **Interconnection strategy used to deliver/remove solutions to/from the microreactor.**

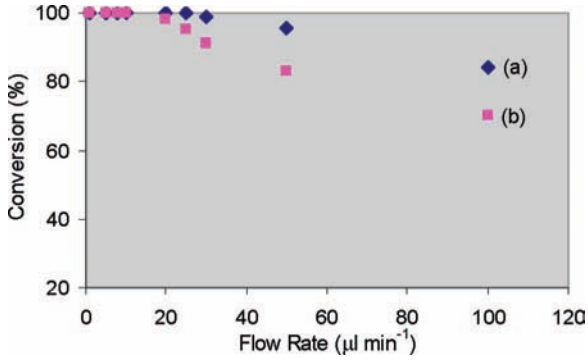


Figure 4. **Summary of the reaction conditions evaluated for the synthesis of (a) [1-(4-bromophenyl)meth-(*E*)-ylidene]phenethyl-amine and (b) 2-(4-bromophenyl)-2-(phenethylamino)-acetonitrile.**

(imine δ 8.1 ppm and α-aminonitrile δ 4.8 ppm) afforded quantification of the percentage conversion achieved. As Figure 4b illustrates, employing a flow rate of 100 μL min^{-1} afforded 70.0% conversion to the desired α-aminonitrile, which was subsequently improved upon by increasing the reactant residence time, as a function of flow rate, to afford quantitative conversion of the imine to 2-(4-bromophenyl)-2-(phenethylamino)acetonitrile. Having confirmed that both reaction steps could be conducted under flow conditions and identified the cyanation as the rate-limiting step, the in situ generation of the imine, [1-(4-bromophenyl)meth-(*E*)-ylidene]phenethylamine followed by the synthesis of 2-(4-bromophenyl)-2-(phenethylamino)acetonitrile was investigated in series.

As Figure 4 illustrates, quantitative conversion is attainable for both steps and in line with this observation, the multicomponent reaction was performed at a total flow rate of 10 μL min^{-1}. To conduct a reaction, 4-bromobenzaldehyde (0.4 M) was introduced from inlet A, 2-phenylethylamine (0.4 M) from inlet B, and TMSCN (0.2 M) from inlet C (1:1:1). The reaction products were collected at outlet D, over a period of 2.5 h, and concentrated in vacuo to afford 2-(4-bromophenyl)-2-(phenethylamino)acetonitrile as a pale-yellow solid (0.047 g, 99.5%). Analysis of the material by ^{1}H NMR spectroscopy confirmed quantitative conversion to the desired product, and unlike analogous batch reactions, whereby 18% cyanohydrin formation was observed, no competing cyanation of the aldehyde was detected (Figure 5). To further evaluate the purity of the α-aminonitrile synthesized under continuous flow conditions, the material was also evaluated by ^{13}C NMR, IR spectroscopy, MS and elemental analysis. To compare the purity of products synthesized under flow conditions with those prepared in batch, a sample of 2-(4-bromophenyl)-2-(phenethylamino)acetonitrile was evaluated by Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) as a means of determining the proportion of Ru leached from the catalyst. Using this approach, the material synthesized in batch was found to contain 440 ppm of Ru, compared to that prepared within the flow reactor that contained a proportion of Ru below the instruments limit of detection and

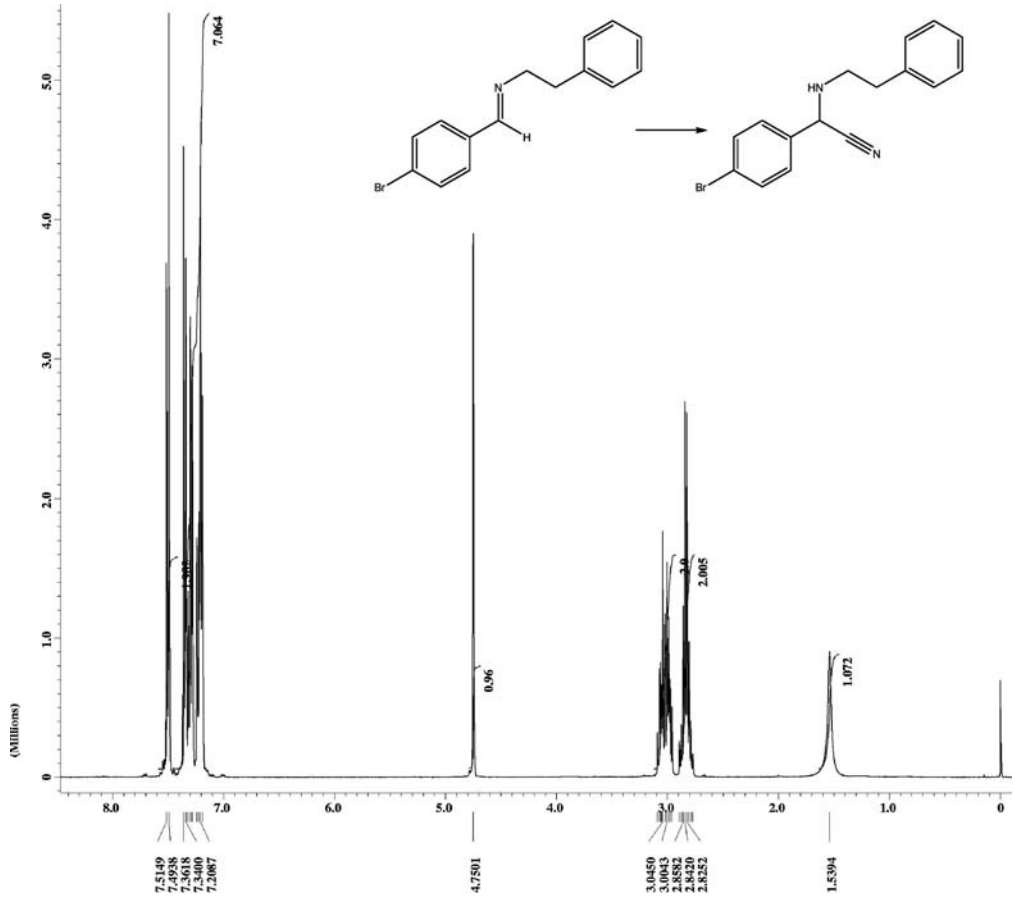


Figure 5. **^{1}H NMR spectra of 2-(4-bromophenyl)-2-(phenethylamino)acetonitrile synthesized in a microreactor (no additional purification performed).**

comparable with the blank; an observation that is attributed to mechanical degradation of the catalyst in a stirred reactor. Finally to confirm that the PS-$RuCl_3$ was acting as a catalyst, the reaction was performed in its absence, packing the catalyst bed with PS-EDTA[7] Under the aforementioned reaction conditions, no α-aminonitrile formation was observed; instead we observed quantitative formation of the imine as expected.

Generality of the Technique. Having demonstrated the ability to synthesize an α-aminonitrile with excellent selectivity under continuous flow conditions, we subsequently evaluated the preparation and reaction of a series of hydrolytically unstable imines. As Table 1 illustrates, a further four amines were investigated, ranging from aromatic derivatives to a cyclic aliphatic amine, which afforded an iminium ion as the reactive intermediate. Using this approach it was found that the optimal flow rate for aromatic derivatives (entries 1−4) was 10 μL min^{-1}, compared to the more reactive pyrrolidine (entry 5) which afforded quantitative conversion to the α-aminonitrile at a flow rate of 20 μL min^{-1}.

In an attempt to increase the throughput of the system, conducting the reactions at an elevated temperature was investigated. Employing the aforementioned reaction conditions, the microreactor was placed in a silicone oil bath and heated to 40 °C. Upon initial purging of the system with anhydrous MeCN, at a total rate of 10 μL min^{-1}, coloration of the solvent stream was noted at outlet D, an observation that was attributed to leaching of Ru from the catalyst. Consequently further investigations will focus on other methods of increasing reactor throughput such as increased reactant concentration and alternative catalysts.

Conclusions

In summary, we report herein a reactor capable of performing multicomponent reactions consisting of both solution phase and polymer-assisted steps. This approach, not only afforded superior selectivity when compared to analogous batch reactions, due to sequential reactant addition, but also enabled an impressive catalytic turnover in excess of 289 for the five examples reported herein. Furthermore, the technique described affords a simple route to the synthesis of α-aminonitriles without the need for additional purification steps, whilst preventing catalyst leaching (compared to a typical stirred protocol where degradation led to the release of 440 ppm of Ru into the reaction product). With this in mind, further investigations are currently underway within our laboratories in order to increase reactor throughput, product diversity and chemoselectivity, the results of which will be published in due course.

Experimental Section

Materials. All solvents were purchased as puriss grade (>99.5%) over molecular sieves (H_2O < 0.005%) from Fluka (Gillingham, UK), and unless otherwise stated, chemicals were purchased from Sigma-Aldrich (Gillingham, UK) and used as received. Prior to use, polymer-supported ethylenediaminetetraacetic acid ruthenium (III) chloride (0.26 mmol Ru g^{-1}, 50−100 mesh, 1% cross-linked with DVB) and ethylenediamineacetic acid acetamide (3.0−4.0 mmol N g^{-1}, 50−100 mesh, 1% cross-linked with DVB), polymer bound were sieved to afford a particle size distribution of 38−75 μm (Endcotts, UK).

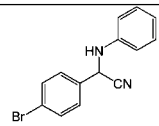
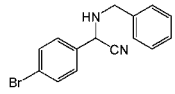
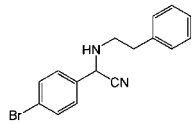
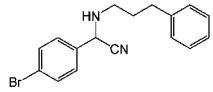
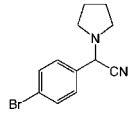
Instrumentation. ^1H and ^{13}C NMR spectra were obtained at room temperature as solutions in deuterochloroform ($CDCl_3$) using tetramethylsilane (TMS) as an internal standard. The spectra were recorded using a Jeol GX400 spectrometer and the chemical shifts given in parts per million (ppm) with coupling constants reported in Hertz (Hz). The following abbreviations are used to report NMR data, s = singlet, d = doublet, t = triplet, brs = broad singlet, m = multiplet, and C_0 = quaternary carbon. In the case of previously prepared compounds, all spectral data obtained was consistent with the literature. Gas chromatography−mass spectrometry (GC−MS) was performed using a Varian GC (CP-3800) coupled to a Varian MS (2000) with a CP-Sil 8 (30 m) column (Phenomenex, UK) and ultrahigh-purity helium (99.999%, Energas, UK) carrier gas. Samples were analyzed using the following method, injector temperature 200 °C, helium flow rate 1 mL min^{-1}, oven temperature 60 °C for 1 min then ramped to 270 at 25 °C min^{-1}, with a 2.5 min filament delay. Elemental analyses were performed using a Carlo Erba EA1108 CHN analyzer. Infrared spectra (4000−600 cm^{-1}) were recorded using a Perkin-Elmer Paragon 1000 FT-IR spectrometer and peaks reported in wavenumbers (cm^{-1}). Melting points were measured on a Gallenkamp melting point apparatus and are reported uncorrected, based on three replicates. Mass spectra were obtained using a Shimadzu QP5050A instrument and an EI ionization source. Reactant delivery to the microreactor was controlled by the use of a displacement pump (MD-1001, Bioanalytical Systems Inc.), capable of delivering three solutions at flow rates between 0.1 to 100 μL min^{-1} (calibrated for a 1 mL syringe). The borosilicate glass microreactor was fabricated in-house using photolithography, wet-etching and thermal annealing and had channel dimensions of 150 μm (wide) × 50 μm (deep) × 5.6 cm (long) and a catalyst bed of 3 mm (wide) × 150 μm (deep) × 2.1 cm (long)).

General Batch Protocol. To perform the Strecker reaction under batch conditions, the aldehyde (0.15 mmol) and amine (0.15 mmol) were added to a stirred vessel containing polymer-supported ethylenediaminetetraacetic acid ruthenium (III) chloride (0.01 g, 0.026 mmol) in anhydrous MeCN (5 mL). After 20 min at room temperature, TMSCN (0.15 mmol) was added and the reaction mixture stirred for an additional 24 h. After which time the reaction mixture was filtered, under suction, to remove the catalyst and the filtrate concentrated in vacuo. The resulting reaction mixture was dissolved in $CDCl_3$ (doped with TMS) and analyzed by ^1H NMR spectroscopy.

General Microreaction Protocol. To perform a reaction, the aldehyde and amine (0.4 M in MeCN) were introduced into the reactor from inlets A and B, employing 500 μL syringes, to afford, upon mixing, a 0.2 M solution of the respective imine. TMSCN (0.2 M in MeCN) was subsequently introduced from inlet C, using a 1 mL syringe, and the reaction mixture was pumped through the catalyst bed, prior to collection within a preweighed sample vial at outlet D. Varying the flow rate enabled the effect of reactant residence time to be evaluated;

(7) Ethylenediaminetetraacetic acid acetamide polymer bound (3.62 mmol N g^{-1}, 50−100 mesh) is commercially available from Sigma-Aldrich.

Table 1. **Results obtained for the synthesis of five α-aminonitriles, derived from 4-bromobenzaldehyde (unless otherwise stated, a run time of 2.5 h was employed)**

entry	product	flow rate, μl min^{-1} [a]	yield, g	yield, mmol	throughput, mg hr^{-1}
1		10	0.043 (100) [b]	0.149	17.2
2		10	0.045 (100)	0.149	18.1
3		10	0.047 (100)	0.149	18.9
4		10	0.049 (100)	0.149	19.7
5		20	0.040 (100)	0.149	31.8 [c]

[a] Based on the total flow obtained from three fluidic inputs. [b] Percent conversion determined via comparison of the ^{1}H NMR integrals observed for the imine and α-aminonitrile. [c] Run time = 1.25 h.

once optimized, the reactor was operated for 2.5 h, after which time the reaction products were concentrated in vacuo prior to dilution with $CDCl_3$ (doped with TMS) and analysis by ^{1}H NMR spectroscopy. In the case of previously unreported compounds, the NMR sample was concentrated in vacuo and the crude reaction product further evaluated by elemental analysis, IR spectroscopy and mass spectrometry. It is important to note that no additional product purification was performed prior to analytical evaluation of the reaction products described herein.

2-(4-Bromophenyl)-2-(phenylamino)acetonitrile (Entry 1).[8] Employing 4-bromobenzaldehyde and aniline as precursors, the microreaction was conducted at a total flow rate of 10 μL min^{-1} to afford the title compound as a white crystalline solid (0.043 g, 99.9%); δ_H (400 MHz, $CDCl_3$/TMS) 3.65 (1H, brs, NH), 5.32 (1H, d, *J* 3.7, CH), 6.66 (2H, d, *J* 8.4, 2 × ArH), 6.85 (1H, t, *J* 7.7, ArH), 7.20 (2H, t, *J* 7.7, 2 × ArH), 7.36 (2H, d, *J* 7.7, 2 × ArH) and 7.47 (2H, d, *J* 8.4, 2 × ArH); δ_C (100 MHz, $CDCl_3$/TMS) 49.8 (CH), 112.3 (2 × CH), 114.9 (CN), 116.9 (CH), 122.6 (C_0Br), 128.3 (2 × CH), 129.1 (C_0), 131.3 (2 × CH), 131.4 (2 × CH) and 143.7 (C_0).

2-(Benzylamino)-2-(4-bromophenyl)acetonitrile (Entry 2). Employing 4-bromobenzaldehyde and benzylamine as reactants, the micro reaction was conducted at a total flow rate of 10 μL min^{-1} to afford 2-(benzylamino)-2-(4-bromophenyl)acetonitrile as a pale yellow oil (0.045 g, 99.9%); (Found C, 60.10; H, 4.56; N, 9.06, $C_{15}H_{13}N_2Br$ requires C, 59.82; H, 4.35; N, 9.30%); ν_{max}/cm^{-1} 701.0, 736.7, 788.2, 823.5, 1454.1, 1488.2, 1551.6, 1591.1, 2303.6, 2846.5, 3030.4, 3053.5 and 3322.5; δ_H (400 MHz, $CDCl_3$/TMS) 1.85 (1H, brs, NH), 3.82 (1H, d, *J* 12.9, C*H*H), 3.94 (1H, d, *J* 12.9, CH*H*), 4.81 (1H, s, CH), 7.28−7.41 (5H, m, 5 × ArH), 7.44 (2H, d, *J* 8.4, 2 × ArH) and 7.54 (2H, d, *J* 8.4, 2 × ArH); 51.2 (CH_2), 52.9 (CH), 118.3 (CN), 123.3 (C_0Br), 127.8 (CH), 128.4 (2 × CH), 128.7 (2 × CH), 129.0 (2 × CH), 132.1 (2 × CH), 133.7 (C_0) and 137.8 (C_0); *m*/*z* (E.I.) 303 (30), 302 (20), 301 (30), 274 (13), 272 (5), 195 (5), 194 (11), 106 (21), 92 (50), 91 (100) and 65 (20).

2-(4-Bromophenyl)-2-(phenethylamino)acetonitrile (Entry 3). Conducting the reaction at a total flow rate of 10 μL min^{-1} and employing 4-bromobenzaldehyde and 2-phenylethylamine as reactants, the title compound was obtained as a pale yellow solid (0.047 g, 99.5%); mpt. 91−92 °C; (Found C, 61.06; H, 4.96; N, 8.69, $C_{16}H_{15}N_2Br$ requires C, 60.97; H, 4.80; N, 8.89%); ν_{max}/cm^{-1} 701.2, 750.6, 770.8, 811.9, 1419.6, 1450.0, 1542.2, 1581.0, 2347.4, 2896.1, 3002.7, 3056.1 and 3315.8; δ_H (400 MHz, $CDCl_3$/TMS) 1.54 (1H, brs, NH), 2.62−2.86 (2H, m, CH_2), 2.95−3.10 (2H, m, 2 × CH_2), 4.75 (1H, s, CH), 7.12 (3H, m, 3 × ArH), 7.23 (2H, m, 2 × ArH), 7.43 (2H, d, *J* 8.4, 2 × ArH) and 7.50 (2H, d, *J* 8.4, 2 × ArH); δ_C (100 MHz, $CDCl_3$/TMS) 35.7 (CH_2), 47.8 (CH_2N), 53.6 (CH), 118.2 (CN), 122.9 (C_0Br), 128.2 (C_0), 128.5 (4 × CH), 128.6 (2 × CH), 131.8 (2 × CH), 133.6 (CH) and 138.8 (C_0); *m*/*z* (E.I.) 317 (80), 316 (50), 315 (82), 290 (10), 288 (8), 197 (75), 196 (100), 170 (44), 169 (48), 91 (34), 90 (31), 89 (34), 77 (19) and 65 (21).

2-(4-Bromophenyl)-2-(3-phenylpropylamino)acetonitrile (Entry 4). Employing 4-bromobenzaldehyde and phenylpropylamine as reactants, the microreaction was conducted at a total flow rate of 10 μL min^{-1}, to afford 2-(4-bromophenyl)-

(8) El-Ahl, S. A. *Synth. Commun.* **2003**, *33*, 989.

2-(3-phenylpropylamino)acetonitrile as a pale-yellow gum (0.049 g, 99.9%); (Found C, 61.95; H, 5.29; N, 8.48, $C_{17}H_{17}N_2Br$ requires C, 62.02; H, 5.20; N, 8.51%); ν_{max}/cm^{-1} 699.7, 746.6, 817.7, 1453.0, 1487.2, 1573.3, 1589.1, 2226.6, 2855.9, 2935.0, 3025.1 and 3316.0; δ_H (400 MHz, $CDCl_3$/TMS) 1.48 (1H, brs, NH), 1.76 (2H, m, CH_2), 2.61−2.74 (4H, m, 2 × CH_2), 4.61 (1H, s, CH), 7.12−7.30 (5H, m, 5 × ArH), 7.32 (2H, d, *J* 8.5, 2 × ArH) and 7.46 (2H, d, *J* 8.5, 2 × ArH); δ_C (100 MHz, $CDCl_3$/TMS) 30.8 (CH_2), 32.9 (CH_2), 46.2 (CH_2), 53.5 (CH), 118.2 (CN), 122.6 (C_0), 125.6 (CH), 128.0 (2 × CH), 128.1 (4 × CH), 131.1 (2 × CH), 133.7 (C_0) and 141.8 (C_0); *m*/*z* (E.I.) 329 (1), 328 (15), 304 (8), 303 (4), 301 (10), 199 (93), 198 (90), 197 (100), 196 (99), 169 (20), 118 (65), 91 (85), 77 (17) and 65 (25).

2-(4-Bromophenyl)-2-(pyrrolidin-2-yl)acetonitrile (Entry 5).[9] Employing 4-bromobenzaldehyde and pyrrolidine as precursors, the micro reaction was conducted at a total flow rate of 20 μL min^{-1}, affording the title compound as a pale yellow oil (0.040 g, 99.9%); δ_H (400 MHz, $CDCl_3$/TMS) 1.82 (4H, m, 2 × CH_2), 2.57−2.67 (4H, m, 2 × CH_2), 5.00 (1H, s, CH), 7.38 (2H, d, *J* 10.9, 2 × ArH) and 7.48 (2H, d, *J* 10.9, 2 × ArH), NH not observed; δ_C (100 MHz, $CDCl_3$/TMS) 23.1 (2 × CH_2), 49.8 (2 × CH_2), 58.3 (CH), 115.3 (CN), 122.4 (C_0Br), 128.9 (2 × CH), 131.9 (2 × CH) and 133.1 (C_0).

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