Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information

A fully automated, multistep flow synthesis of 5-amino-4-cyano-1,2,3-triazoles

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General Information

Unless specified, reagents were obtained from commercial sources and used without further purification. QuadraPure™ sulfonic acid resin (QP-SA) and QuadraPure™ dimethylamine resin (QP-DMA) were obtained from Johnson Matthey and used without further purification. 1,5,7-triazabicyclo[4.4.0]dec-5-ene polystyrene (PS-TBD) was obtained from Biotage (part number 800321) and used without purification. 4-Nitroaniline was dissolved in MeCN and filtered through a plug of silica before use.

Solvents were obtained from Fisher Scientific, and H_2O was deionised before use. EtOH (absolute, analytical reagent grade) and MeCN (HPLC grade) were used as supplied, without further purification. EtOAc (technical grade) and petroleum ether (technical grade) were distilled before use. PE 30–40 refers to petroleum distillate collected between 30 and 40 °C. Dry THF refers to either analytical grade THF dried over calcium hydride and lithium aluminium hydride with triphenylmethane as an indicator and distilled under an atmosphere of dry argon, or unstabilised HPLC grade THF passed through activated alumnia under an atmosphere of dry argon immediately before use. Dry MeCN refers to HPLC grade MeCN dried over calcium hydride and distilled under an atmosphere of dry argon immediately before use.

Malononitrile reaction columns were loaded and washed with dry THF. Stock solutions of starting materials for aryl azide and triazole syntheses were made up in freshly distilled MeCN. Azide and triazole syntheses were performed using HPLC grade MeCN (without further purification) as the system solvent.

Manual flow reactions were carried out using the commercially available Vapourtec R2+/R4 flow system, and automated flow sequences were carried out using the reactor system described below, together with a Vapourtec R4 convection heater to heat the malononitrile reaction column and convective flow coil (CFC). Automated sequences were controlled by Gilson Trilution®LC or Unipoint™ software. Polymer-supported reagents were packed in glass Omnifit® columns and connected to the flow system with standard tubing connectors. Convective flow coils and glass heating jackets for columns and CFCs are commercially available from Vapourtec. A GeneVac EZ-2 Plus evaporator was used for purification of triazole products.

In-line IR monitoring was carried out using a Mettler-Toledo ReactIR™ 45m, fitted with a 24 h mercury cadmium telluride (MCT) detector and MultiplexIR™ attachment. The system was operated with a 51 μL flow cell with an integrated attenuated total reflectance (ATR) gold sealed diamond (DiComp™) sensor and a 10 μL flow cell with an ATR gold sealed silicon (SiComp™) sensor. Data collection and subsequent processing were carried out using iC IR™ software (version 4.1).

The automated reactor system is shown above. All component parts are commercially available from Gilson, Inc. and easily assembled without the aid of specialist knowledge. The flow reactor (see p. 6 for a schematic) comprises of two 307 HPLC pumps (5 mL pump heads, Pump A and Pump B), a 233XL autosampler with two 10 mL PEEK sample loops (Sample Loop A and Sample Loop B) and a 402 syringe pump (10 mL syringe and 10 mL dispensing loop). The system included five Valvemates. One Valvemate with a two-position, six port Rheodyne 7060 head served as the Solvent Divert Valve, used to direct the output of Pumps A and B through the reactor or away to waste during the filling of Sample Loops A and B. Another Valvemate with two-position, six port Rheodyne 7060 head was used as Valve A to direct the flow stream for Step 1 or Step 2. Two Valvemates with six-position, seven port Rheodyne 7000 heads (Valve B and Valve C) were used together as a column switcher. A 156 UV/Vis detector was used to monitor the reactor output, and material was collected either through a 315 fraction collector with 402 syringe pump (10 mL syringe and 3 mL dispensing loop), or using another Valvemate with six-position, seven port Rheodyne 7000 head (Valve D) to dispense directly into collection flasks. In the PS-TBD scavenging procedure used in the synthesis of Table 2, Entry 6, a twin ten-position, eleven port Vici-Valco valve, controlled by a multiposition actuator control module (model no. EMTCA-CE) served as a second column switcher.

Flash column chromatography was carried out on silica gel [Breckland 60 (0.040–0.063 mm)].

Melting points were measured with a SRS OptiMelt apparatus.

Elemental analysis was performed by the Microanalytical Laboratories at the Department of Chemistry, University of Cambridge. Limit: ±0.5%.

IR spectra were recorded neat on a Perkin-Elmer Spectrum One FT-IR spectrometer using Universal ATR sampling accessories. Letters in parentheses refer to the relative absorbency of the peak: w – weak (<40% of the most intense peak), m – medium (40–75% of the most intense peak), s – strong (>75% of the most intense peak).

^{1}H NMR spectra were recorded on a Bruker DPX-400 (400 MHz), a Bruker Avance 500 (500 MHz) with dual cryoprobe, or a Bruker DRX-600 (600 MHz) spectrometer using the deuterated solvent as internal deuterium lock. Chemical shift data are given in units δ relative to tetramethylsilane (external standard), calibrated based on residual monoprotic solvent. The multiplicity of a signal is indicated as: br – broad, s – singlet, d – doublet, t – triplet, q – quartet, sept – septet, m – multiplet, dd – doublet of doublets, dt – doublet of triplets, etc. Coupling constants (*J*) are recorded to the nearest 1 Hz.

^{13}C NMR spectra were recorded on a Bruker DPX-400 (100 MHz), a Bruker Avance 500 (125 MHz) with dual cryoprobe, or a Bruker DRX-600 (150 MHz) spectrometer with broadband proton decoupling using the deuterated solvent as internal deuterium lock. Chemical shift data are given in units δ relative to tetramethylsilane (external standard), calibrated based on deuterated solvent. Coupling constants (*J*) are recorded to the nearest 1 Hz.

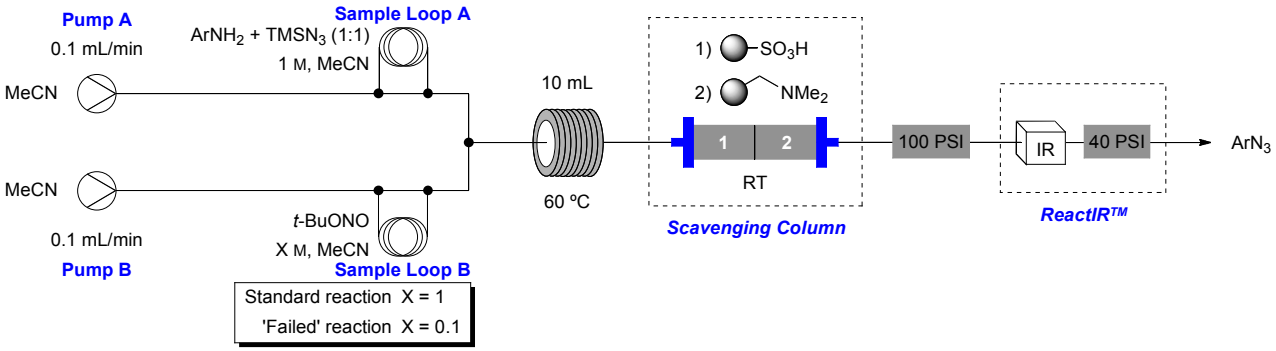
Liquid chromatography-mass spectrometry (LCMS) was performed on an Agilent HP 1100 series chromatograph (Mercury Luna 3µ C18 (2) column) attached to a Waters ZQ2000 mass spectrometer with ESCi ionisation source in ESI mode. Elution was carried out at a flow rate of 0.6 mL/min using a reverse phase gradient of MeCN–water containing 0.1% formic acid. Gradient = 0–1 min: hold MeCN 5%, 1–4 min: ramp MeCN 5–95%, 4–5 min: hold MeCN 95%, 5-7 min: ramp MeCN 95–5%, 7–8 min: hold MeCN 5%. Retention times are reported as Rt.

High resolution mass spectra (HRMS) were recorded on a Waters Micromass LCT Premier spectrometer using time of flight with positive electrospray ionisation (ESI^+) or a Bruker BioApex II 4.7e FTICR utilising ESI^+. The mass reported is that containing the most abundant isotopes (^{35}Cl and ^{79}Br). Limit: ±5 ppm.

X-Ray crystal structure determination was performed by Dr John E. Davies at the Department of Chemistry, University of Cambridge using a Nonius Kappa CCD detector.

***Safety Warning*:** While flow processing does address many of the safety concerns associated with azide synthesis, these reactions should still be carried out with caution, and with the awareness that starting materials and product mixtures may contain hazardous components.
Trimethylsilyl azide is toxic, volatile, latex-permeable and absorbed by the skin. Furthermore, trimethylsilyl azide may be hydrolised to hydrazoic acid, which is volatile, highly toxic and extremely explosive. Aryl azide products may also be explosive and/or toxic.
Malononitrile is toxic and may polymerise/decompose violently upon heating (≥100 ºC).[1]

Scavenging Experiments



Scavenging test reactions:
Sample Loop A (1 mL, 1 mmol scale) was filled with a stock solution of aniline starting material and trimethylsilyl azide (1:1, 1 M in MeCN) and Sample Loop B (1 mL, 1 mmol scale) was filled with a stock solution of *tert*-butyl nitrite (0.1 or 1 M in MeCN for 'standard' and 'failed' reactions, respectively). These two sample loops were simultaneously switched into line and the starting material solutions were pumped through the system at 0.1 mL/min each, driven by Pumps A and B with a constant stream of MeCN. The starting materials mixed in a T-piece and the reaction solution (at a combined flow rate of 0.2 mL/min) passed through a 10 mL CFC heated at 60 ºC. For all reactions, the flow stream passed through a 100 psi backpressure regulator prior to exiting the system. For reactions with scavenging and/or ReactIR™ monitoring, the Scavenging Column and/or ReactIR™ were incorporated as shown above.

Scavenging Column: For reactions with scavenging, the flow stream exiting the CFC passed through a 10 mm i.d. × 8 cm height glass column (at room temperature) packed with QP-SA (1.3 g) followed by QP-DMA (1.3 g) before entering the 100 psi backpressure regulator.

ReactIR™: For reactions with ReactIR™ monitoring (see below for further details), the flow stream exiting the 100 psi backpressure regulator passed through the ReactIR™ 10 µL flow cell (SiComp™ sensor), then exited the flow system through a 40 psi backpressure regulator.

The presence of trimethylsilyl azide or hydrazoic acid was detected by a qualitative colourimetric test.[2] Two drops of the output stream were collected from the reactor exit every two min. These samples were immediately tested by adding 2 drops of ferric chloride solution (1 wt% in H_2O). Yellow colour indicated a negative result, while orange or red colour indicated the presence of undesired azide contaminants. Control tests indicated that trimethylsilyl azide could be clearly detected in MeCN at concentrations of 0.005 M or greater, and that *tert*-butyl nitrite, 3,5-bis(trifluoromethyl)aniline and 1-azido-3,5-bis(trifluoromethyl)benzene neither gave false positive results nor interfered with the detection of undesired azide contaminants in a positive control sample.

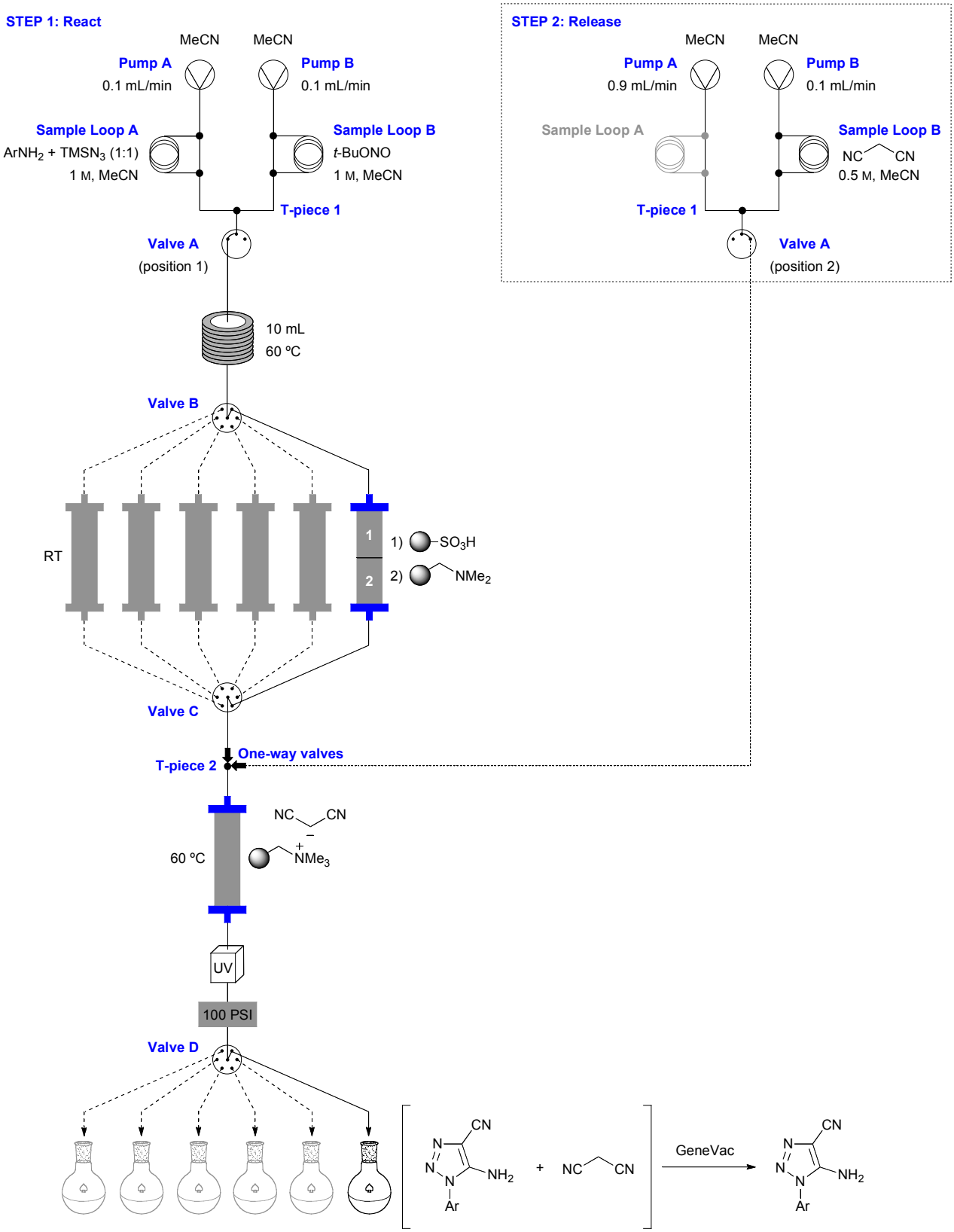
The presence of unreacted aniline starting material was determined by ^{1}H NMR analysis of the reaction output. The output stream was collected in a flask cooled to –78 ºC, where the crude product solution was frozen solid until all the material was collected. When all of the product had been collected, this output solution was melted rapidly by stirring in a room temperature water bath, then an aliquot was taken for immediate analysis by ^{1}H NMR to determine the ratio of starting aniline to azide product. (Control experiments indicated that this temperature quench/analysis protocol was sufficient to prevent any significant further conversion to the desired product in the collection flask before analysis.)

ReactIR™ monitoring:
Reference IR spectra were recorded using the MultiplexIR™ attachment, by injection of the relevant solutions into both the 10 μL flow cell with SiComp™ sensor and 51 μL flow cell with DiComp™ sensor. Reaction monitoring was carried out using the MultiplexIR™ attachment with the 10 μL flow cell and SiComp™ sensor, with 16 scans taken every 30 seconds.

All reaction and reference spectra presented in this publication are shown after subtraction of MeCN solvent background, with no further manipulation. The representative spectrum shown for each scavenging test reaction was chosen as a spectrum from the most concentrated region of the reaction plug, as determined by the intensities of the trimethylsilyl azide (ν = 2141) and/or 1-azido-3,5-bis(trifluoromethyl)benzene (ν = 2122 cm^{-1}) N=N=N bands, as well as the Si-Me_3 bands (ν = 1255 and 850 cm^{-1}) visible in all test reaction plugs. For test reactions with scavenging, no trimethylsilyl azide was detected by the ReactIR™ (or the ferric chloride colourimetric test) at any point during the reaction.

A note on general applications:
This scavenging procedure was designed and evaluated for azide synthesis on 1 mmol scale, with a fresh scavenging column used for each reaction. In order to apply this scavenging protocol on larger scales, we would recommend scaling the scavenger column geometry proportionally, but scaling up with caution and monitoring as described to ensure that scavenging is equally effective on scale. This small-scale scavenging process was developed with the goal of achieving complete removal of contaminants in case of reaction failure, rather than maximal usage of the scavenging cartridge for typical reactions with high conversion. On larger scales therefore, it may be desirable to reduce the amount of scavenger resins used, or to develop protocols for reuse or regeneration of the scavenger resins. However, we have only evaluated a single-use procedure with an excess of scavenger resins as described, and given the hazardous nature of the contaminants and the low cost of the resins employed, we would recommend this single-use, excess scavenger protocol whenever practical.

Automated Flow Synthesis of 5-Amino-4-cyano-1,2,3-triazoles (Table 2)



Automated flow synthesis of 5-amino-4-cyano-1,2,3-triazoles:
Preparation:
Malononitrile reaction columns were generated using the Vapourtec R2+/R4 flow system. A 15 mm i.d. glass column was filled to 3 cm height with a slurry of A900 hydroxide resin in ethanol. This column was then connected to the flow system and washed with dry THF at 1 mL/min for 20 min, causing the resin to shrink. The column plunger ends were adjusted to approximately 1.5 cm height and the column was then loaded by washing with excess malononitrile (10 mmol, 1 M in dry THF) at a flow rate of 1 mL/min. The resulting malononitrile column was washed at 1 mL/min with dry THF to remove excess malononitrile and residual water (as determined by Karl Fischer analysis of the output stream). The loaded malononitrile reaction column could then be sealed and stored for several weeks on the benchtop, or connected to the automated flow system for immediate use.

In preparation for each series of reactions, a loaded malononitrile reaction column was connected to the automated reactor, housed in the Vapourtec R4 heating unit. Starting material solutions in Teflon sealed vials were loaded into the autosampler, and pre-packed scavenging columns (10 mm i.d. glass columns, each packed with 1.3 g QP-SA followed by 1.3 g QP-DMA and adjusted to 8 cm height) were connected between Valves B and C. The reactor system was primed with MeCN and the Vapourtec R4 heating unit was set manually to 60 ºC, then the automated sequence was initiated.

Step 1:
Pumps A and B (system solvent MeCN) were started with a flow rate of 0.1 mL/min each, directed through a Valvemate (Solvent Divert Valve) to waste. Valve A was set to position 1, which connected the T-piece 1 fluid path to the CFC. Valves B and C were set to select a fresh scavenging column and Valve D was set to select a fresh collection flask. Sample Loop A was filled with 1 mL of a MeCN stock solution containing aniline starting material (1 mmol) and trimethylsilyl azide (1 mmol), with front and back end air gaps. The autosampler needle was washed after injection and Sample Loop A switched into line. Next, Sample Loop B was filled with 1 mL of a MeCN stock solution containing *tert*-butyl nitrite (1 mmol), with front and back end air gaps. The autosampler needle was washed after injection and Sample Loop B switched into line.

The Solvent Divert Valve was used to simultaneously switch Pumps A and B into line. This directed the system solvent into Sample Loops A and B, driving the starting material plugs to meet at T-piece 1. The combined reaction mixture then flowed through the CFC (10 mL, 60 ºC) and the resulting crude azide intermediate was purified by passage through a scavenging column (between Valves B and C). The purified azide then progressed through T-piece 2 (*via* a one-way valve) into the malononitrile reaction column (60 ºC). The reactor output was then directed through the UV detector and a 100 psi backpressure regulator before exiting the system through Valve D into a collection flask. The duration of Step 1 was 280 minutes, during which time the injection ports for Sample Loops A and B were rinsed with MeCN.

Step 2:
The Solvent Divert Valve redirected the flow from Pumps A and B to waste, whilst the flow rates changed to 0.9 mL/min and 0.1 mL/min, respectively. Valve A was switched to position 2, bypassing the CFC and scavenging column to connect directly to T-piece 2 (through a one-way valve). Sample Loop B was filled with 9 mL of malononitrile wash solution (0.5 M in MeCN), with front and back end air gaps. The autosampler needle was washed after use and Sample Loop B switched into line.

The Solvent Divert Valve was used to simultaneously switch Pumps A and B into line, delivering the malononitrile plug from Sample Loop B to be diluted at T-piece 1. The resulting 0.05 M solution was pumped at a combined flow rate of 1 mL/min into the malononitrile reaction column *via* T-piece 2.

The reactor output was then directed through the UV detector and a 100 psi backpressure regulator before exiting the system through Valve D into the same collection flask. The duration of Step 2 was 270 minutes, during which time the injection ports for Sample Loop B was washed with MeCN.

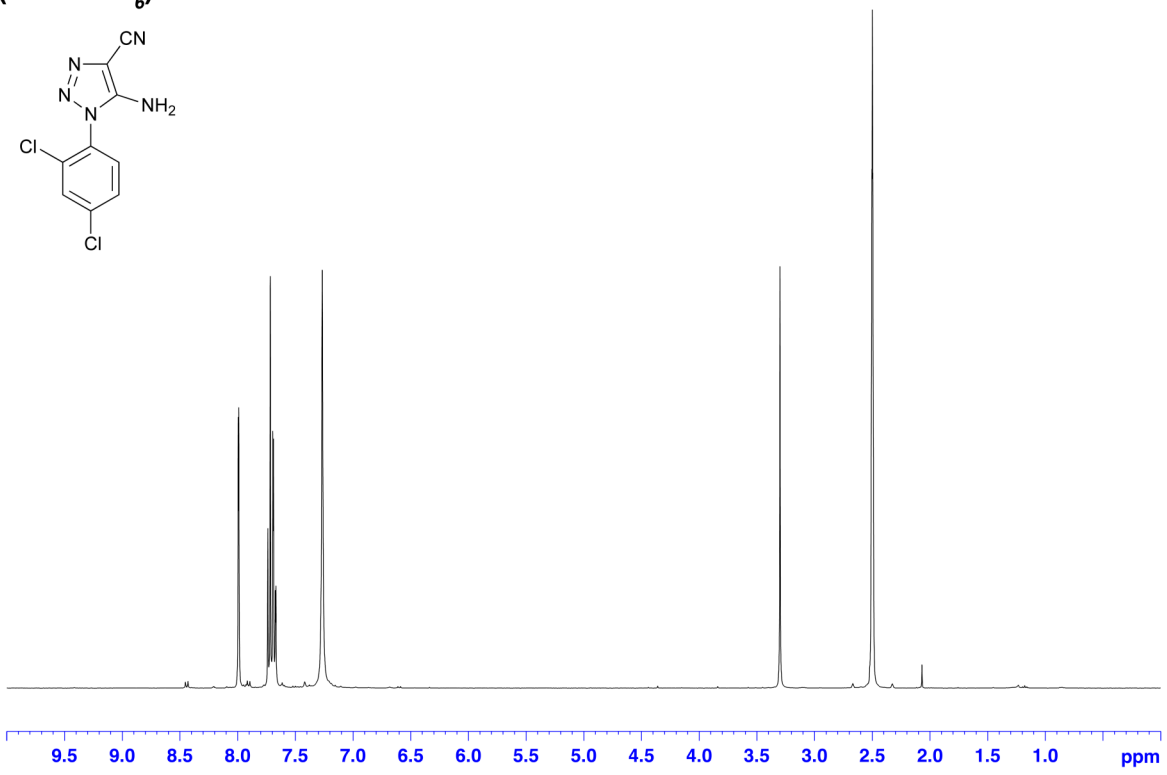
Subsequent runs:
For each iterative reaction, the same sequence (Steps 1 and 2) was repeated under software control, with new starting material solutions selected from the autosampler and a fresh scavenging column and reaction flask selected by Valves B, C and D.

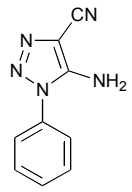
Workup:
The contents of each reaction flask were concentrated and transferred to the GeneVac for removal of malononitrile and MeCN by evaporation (60ºC, HPLC setting, 14 h 45 min).

All characterisation data reported below was obtained for samples synthesised using the general automated procedure described above and isolated by evaporation with no further purification unless otherwise specified.

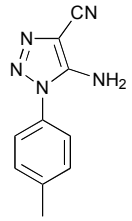
A representative spectrum is shown below: 5-amino-1-(2,4-dichlorophenyl)-1*H*-1,2,3-triazole-4-carbonitrile (Table 2, Entry 9) was isolated following the general automated flow synthesis and evaporation procedure, with no further purification.

5-amino-1-(2,4-dichlorophenyl)-1H-1,2,3-triazole-4-carbonitrile (Table 2, Entry 9) (DMSO-d_6)

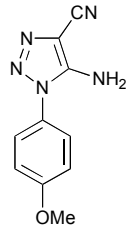




5-amino-1-phenyl-1*H*-1,2,3-triazole-4-carbonitrile[3] (Table 2, Entry 1)
1 mmol scale, 83% yield (154 mg) of brown solid. IR (neat) ν_{max}/cm^{-1} 3325 (w), 3200 (w), 2245 (w), 1651 (m), 1597 (m), 1584 (m), 1505 (m), 1457 (m), 1365 (w), 1324 (m), 1295 (w), 1242 (w), 1168 (w), 1073 (w), 1033 (m), 985 (m), 760 (m), 745 (s), 729 (m), 688 (s), 664 (m); ^{1}H NMR (600 MHz, DMSO-d_6): δ_H = 7.63-7.56 (5H, m), 7.15 (2H, s, br); ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 147.8 (C), 134.0 (C), 129.8 (2 × CH), 129.7 (CH), 124.9 (2 × CH), 113.4 (C), 101.3 (C); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.63-7.56 (3H, m), 7.53-7.51 (2H, m), 4.86 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 146.7 (C), 133.8 (C), 130.6 (CH), 130.5 (2 × CH), 124.5 (2 × CH), 112.5 (C), 104.2 (C); LCMS Rt 3.85 min, *m*/*z* (ESI^+) 186 ($[M+H]^+$); HRMS *m*/*z* (ESI^+) found 186.0786 ($[M+H]^+$, $C_9H_8N_5$ requires 186.0780).

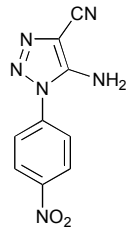


5-amino-1-(4-methylphenyl)-1*H*-1,2,3-triazole-4-carbonitrile[4] (Table 2, Entry 2)
1 mmol scale, 73% yield (146 mg) as a light brown solid. IR (neat) ν_{max}/cm^{-1} 3325 (w), 3203 (w), 2246 (w), 1650 (s), 1597 (w), 1582 (w), 1521 (m), 1483 (w), 1323 (m), 1290 (w), 1242 (w), 1173 (w), 1115 (w), 1027 (m), 988 (m), 845 (w), 806 (s), 759 (w), 692 (w); ^{1}H NMR (600 MHz, DMSO-d_6): δ_H = 7.44 (2H, d, *J* = 9 Hz), 7.42 (2H, d, *J* = 9 Hz), 7.08 (2H, s, br), 2.41 (3H, s); ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 147.8 (C), 139.5 (C), 131.5 (C), 130.2 (2 × CH), 124.8 (2 × CH), 113.5 (C), 101.2 (C), 20.7 (CH_3); LCMS Rt 4.12 min, *m*/*z* (ESI^+) 200 ($[M+H]^+$); HRMS *m*/*z* (ESI^+) found 200.0940 ($[M+H]^+$, $C_{10}H_{10}N_5$ requires 200.0936).



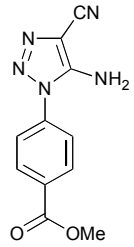
5-amino-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole-4-carbonitrile (Table 2, Entry 3)
General procedure: 1 mmol scale, 10% yield (21 mg) as a brown solid. *Modified procedure*: The general procedure was run with the following modifications: the scavenging column was removed from its standard position between Valves B and C. The scavenging step was instead carried out using a 10 mm i.d. glass column containing 2.67 g QP-SA followed by 2.67 g QP-DMA, which was incorporated between the malononitrile reaction column and the UV detector. Step 1 was carried out as in the general procedure for 280 min. Step 2 was carried out for 345 min, by which time all material had exited the reactor as indicated by the UV detector. 1 mmol scale, 73% yield (157 mg) as a light brown solid. Elemental analysis found C 55.6, H 4.2, N 32.4% ($C_{10}H_9N_5O$ requires C 55.8, H 4.2, N 32.5%); IR (neat) ν_{max}/cm^{-1} 3366 (w), 3303 (w), 3158 (w), 3016 (w), 2967 (w), 2930 (w), 2841 (w), 2234 (m), 1900 (w), 1656 (m), 1638 (m), 1610 (w), 1584 (m), 1519 (s), 1493 (m), 1455 (w), 1443 (m), 1365 (w), 1318 (m), 1303 (m), 1248 (s), 1183 (m), 1172 (m), 1106 (m), 1045 (m), 1024 (s), 989 (m), 839 (s), 822 (m), 803 (w), 723 (m), 688 (m); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 7.46 (2H, d, *J* = 9

Hz), 7.14 (2H, d, J = 9 Hz), 7.05 (2H, s, br), 3.84 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 160.1 (C), 148.1 (C), 126.9 (2 × CH), 126.6 (C), 115.0 (2 × CH), 113.6 (C), 101.0 (C), 55.6 (CH_3); LCMS Rt 4.03 min, m/z (ESI$^+$) 216 ([M+H]$^+$); HRMS m/z (ESI$^+$) found 216.0886 ([M+H]$^+$, $C_{10}H_{10}N_5O$ requires 216.0885); X-ray crystallography: File reference CCDC 791579; Formula: $C_{10}H_9N_5O_1$; Unit cell parameters: a 27.8326(7) b 6.2301(2) c 11.8916(3) α 90.00 β 94.99(3) γ 90.00 space group C2/c.



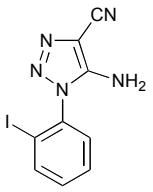
5-amino-1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carbonitrile[5] (Table 2, Entry 4)

General procedure: 1 mmol scale, 66 mg total (26% yield of 5-amino-1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carbonitrile + 5% 4-nitroaniline) as a yellow solid. *Modified procedure*: The only modification to the general procedure was setting the malononitrile reaction column to room temperature (rather than 60 ºC). 1 mmol scale, 87% yield (200 mg) as a yellow solid. Elemental analysis found C 46.9, H 2.7, N 36.1% ($C_9H_6N_6O_2$ requires C 47.0, H 2.6, N 36.5%); IR (neat) ν_{max}/cm^{-1} 3370 (w), 3329 (w), 3205 (m), 3082 (w), 2244 (m), 1652 (s), 1617 (m), 1590 (m), 1542 (m), 1530 (s), 1505 (s), 1477 (w), 1418 (w), 1349 (s), 1308 (s), 1297 (m), 1245 (w), 1197 (w), 1116 (m), 1088 (w), 1030 (m), 987 (m), 853 (s), 759 (w), 748 (m), 713 (w), 688 (m); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 8.44 (2H, d, J = 9 Hz), 7.91 (2H, d, J = 9 Hz), 7.42 (2H, s, br); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 148.1 (C), 147.4 (C), 139.1 (C), 125.7 (2 × CH), 125.1 (2 × CH), 113.1 (C), 101.7 (C); LCMS Rt 4.07 min, m/z (ESI$^+$) 231 ([M+H]$^+$); HRMS m/z (ESI$^+$) found 231.0624 ([M+H]$^+$, $C_9H_7N_6O_2$ requires 231.0630).



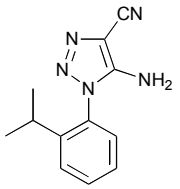
methyl 4-(5-amino-4-cyano-1*H*-1,2,3-triazol-1-yl)benzoate (Table 2, Entry 5)

1 mmol scale. The automated reactor shut down automatically mid-reaction, due to high system pressure caused by precipitate formation. Flushing the system with acetonitrile enabled recovery of 37% (91 mg) as an off-white solid. Elemental analysis found C 54.0, H 3.6, N 28.3% ($C_{11}H_9N_5O_2$ requires C 54.3, H 3.7, N 28.8%); IR (neat) ν_{max}/cm^{-1} 3381 (w), 3327 (w), 3205 (w), 2247 (w), 1725 (s), 1651 (s), 1608 (m), 1578 (w), 1516 (w), 1479 (w), 1434 (m), 1414 (m), 1367 (w), 1327 (w), 1284 (s), 1186 (w), 1160 (w), 1104 (s), 1022 (m), 985 (m), 956 (m), 864 (w), 843 (w), 827 (w), 771 (s), 713 (w), 695 (m); ^{1}H NMR (600 MHz, DMSO-d_6): δ_H = 8.16 (2H, d, J = 8 Hz), 7.76 (2H, d, J = 8 Hz), 7.33 (2H, s, br), 3.91 (3H, s); ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 165.4 (C), 147.9 (C), 137.8 (C), 130.7 (2 × CH), 130.2 (C), 124.8 (2 × CH), 113.2 (C), 101.6 (C), 52.5 (CH_3); LCMS Rt 4.13 min, m/z (ESI$^+$) 244 ([M+H]$^+$); HRMS m/z (ESI$^+$) found 244.0839 ([M+H]$^+$, $C_{11}H_{10}N_5O_2$ requires 244.0835).



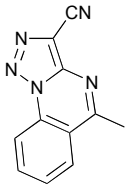
5-amino-1-(2-iodophenyl)-1*H*-1,2,3-triazole-4-carbonitrile (Table 2, Entry 6)

General procedure: It was not possible to isolate this low-melting product using the standard evaporation protocol as it was prone to bumping during evaporation. *Modified procedure*: The general procedure was carried out as previously described, however malononitrile was removed using an in-line scavenging process instead of evaporation. A 15 mm i.d. glass column packed with 11.25 g of PS-TBD was incorporated between the malononitrile reaction column and the UV detector. Step 2 was carried out for 770 min in order to ensure that all material had exited the reactor. The resulting product solution was free from malononitrile but contaminated with by-products from the scavenging process, so was concentrated and purified by flash column chromatography (EtOAc–PE (30-40), 3:7, then 1:1). 1 mmol scale, 55% yield (171 mg) as a white foam. Elemental analysis found C 35.0, H 2.1, N 22.2% ($C_9H_6N_5I$ requires C 34.8, H 1.9, N 22.5%); IR (neat) ν_{max}/cm^{-1} 3358 (w), 3313 (w), 3238 (w), 3194 (w), 2231 (m), 1637 (s), 1585 (m), 1497 (m), 1462 (w), 1441 (w), 1323 (m), 1310 (m), 1280 (w), 1223 (w), 1104 (w), 1047 (w), 1022 (m), 982 (m), 947 (w), 866 (w), 765 (s), 737 (m), 707 (m), 671 (w); ^{1}H NMR (600 MHz, DMSO-d_6): δ_H = 8.09 (1H, d, J = 8 Hz), 7.62 (1H, ddd, J = 8, 8 and 1 Hz), 7.57 (1H, dd, J = 8 and 1 Hz), 7.39 (1H, ddd, J = 8, 8 and 1 Hz), 7.13 (2H, s, br); ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 148.4 (C), 139.7 (CH), 136.3 (C), 132.6 (CH), 129.8 (CH), 129.6 (CH), 113.5 (C), 100.4 (C), 98.5 (C); LCMS Rt 4.19 min, m/z (ESI$^+$) 312 ([M+H]$^+$); HRMS m/z (ESI$^+$) found 311.9760 ([M+H]$^+$, $C_9H_7N_5I$ requires 311.9746).



5-amino-1-(2-(propan-2-yl)phenyl)-1*H*-1,2,3-triazole-4-carbonitrile (Table 2, Entry 7)

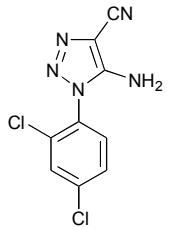
1 mmol scale, 85% yield (194 mg) as a pink solid. IR (neat) ν_{max}/cm^{-1} 3380 (w), 3313 (w), 3244 (w), 3195 (w), 3071 (w), 2964 (w), 2867 (w), 2233 (m), 1640 (m), 1589 (m), 1507 (m), 1482 (w), 1459 (w), 1384 (w), 1362 (w), 1315 (m), 1230 (w), 1168 (w), 1081 (m), 1044 (m), 989 (m), 775 (s), 707 (m), 668 (m); ^{1}H NMR (400 MHz, CD_3CN): δ_H = 7.62-7.61 (2H, m), 7.45-7.40 (1H, m), 7.29 (1H, d, J = 8 Hz), 5.39 (2H, s, br), 2.56 (1H, sept, J = 7 Hz), 1.16 (6H, d, J = 7 Hz); ^{13}C NMR (100 MHz, CD_3CN): δ_C = 149.7 (C), 148.0 (C), 132.7 (CH), 132.1 (C), 128.9 (CH), 128.5 (CH), 128.4 (CH), 113.9 (C), 103.0 (C), 29.1 (CH), 23.7 (2 × CH_3, br); LCMS Rt 4.54 min, m/z (ESI$^+$) 228 ([M+H]$^+$); HRMS m/z (ESI$^+$) found 228.1249 ([M+H]$^+$, $C_{12}H_{14}N_5$ requires 228.1249); X-ray crystallography: File reference CCDC 791582; Formula: $C_{12}H_{13}N_5$; Unit cell parameters: a 33.4277(8) b 6.1102(2) c 12.4082(3) α 90.00 β 106.375(2) γ 90.00 space group C2/c.



5-methyl[1,2,3]triazolo[1,5-*a*]quinazoline-3-carbonitrile[6] (Table 2, Entry 8)

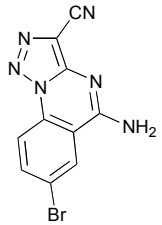
1 mmol scale. The automated reactor shut down automatically mid-reaction, due to high system pressure caused by precipitate formation. The material collected in the output flask before reactor shutdown contained a yellow crystalline solid, which was identified as the title compound. ^{1}H NMR

(400 MHz, DMSO-d_6): δ_H = 8.70 (1H, d, J = 8 Hz), 8.51 (1H, d, J = 8 Hz), 8.24 (1H, dd, J = 8 and 8 Hz), 7.96 (1H, dd, J = 8 and 8 Hz), 3.04 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 167.9 (C), 142.7 (C), 136.2 (CH), 132.2 (C), 129.1 (CH), 128.5 (CH), 118.8 (C), 115.3 (CH), 112.1 (C), 111.4 (C), 22.9 (CH_3); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.76 (1H, d, J = 8 Hz), 8.25 (1H, d, J = 8 Hz), 8.11 (1H, ddd, J = 8, 8 and 1 Hz), 7.85 (1H, ddd, J = 8, 8 and 1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 166.6 (C), 142.6 (C), 135.9 (CH), 132.9 (C), 129.1 (CH), 127.7 (CH), 119.1 (C), 116.4 (CH), 113.6 (C), 111.5 (C), 23.3 (CH_3); LCMS Rt 4.34 min, m/z (ESI$^+$) 210 ([M+H]$^+$); HRMS m/z (ESI$^+$) found 210.0778 ([M+H]$^+$, $C_{11}H_8N_5$ requires 210.0774); X-ray crystallography: File reference CCDC 791580; Formula: $C_{11}H_7N_5$; Unit cell parameters: a 10.1129(2) b 14.7360(5) c 7.3628(2) α 90.00 β 118.152(3) γ 90.00 space group Cc.



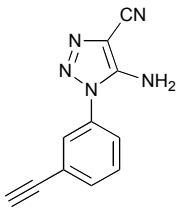
5-amino-1-(2,4-dichlorophenyl)-1*H*-1,2,3-triazole-4-carbonitrile (Table 2, Entry 9)

1 mmol scale, 53% yield (135 mg) as a yellow solid. Elemental analysis found C 42.6, H 2.0, N 27.5, Cl 27.8% ($C_{11}H_9N_5O_2$ requires C 42.5, H 2.0, N 27.6, Cl 27.9%); IR (neat) ν_{max}/cm^{-1} 3372 (w), 3307 (w), 3152 (w), 2232 (s), 1660 (w), 1639 (s), 1596 (m), 1586 (m), 1568 (w), 1509 (s), 1469 (m), 1391 (w), 1323 (m), 1280 (w), 1254 (w), 1231 (m), 1148 (m), 1098 (m), 1066 (m), 1035 (m), 989 (s), 867 (m), 836 (m), 814 (s), 715 (w), 698 (w), 657 (m); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 7.99 (1H, d, J = 2 Hz), 7.73 (1H, d, J = 9 Hz), 7.68 (1H, dd, J = 9 and 2 Hz), 7.27 (2H, s, br); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 149.0 (C), 136.5 (C), 132.8 (C), 131.6 (CH), 130.2 (CH), 130.2 (C), 128.9 (CH), 113.3 (C), 100.2 (C); LCMS Rt 4.48 min, m/z (ESI$^+$) 254 ([M+H]$^+$); HRMS m/z (ESI$^+$) found 254.0010 ([M+H]$^+$, $C_9H_6N_5Cl_2$ requires 254.0000).

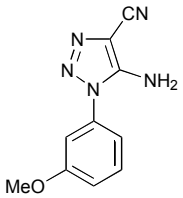


5-amino-7-bromo[1,2,3]triazolo[1,5-*a*]quinazoline-3-carbonitrile (Table 2, Entry 10)

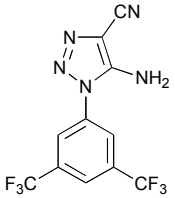
1 mmol scale. The automated reactor shut down automatically mid-reaction, due to high system pressure caused by precipitate formation. The yellow crystalline material recovered from the malononitrile reaction column was identified as the title compound. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 8.74 (1H, d, J = 2 Hz), 8.64 (2H, d, br), 8.37 (1H, d, J = 9 Hz), 8.21 (1H, dd, J = 9 and 2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 157.8 (C), 145.4 (C), 137.6 (CH), 132.3 (C), 128.3 (CH), 120.6 (C), 117.6 (CH), 113.3 (C), 113.0 (C), 106.2 (C); LCMS Rt 4.43 min, m/z (ESI$^+$) 289 ([M+H]$^+$); HRMS m/z (ESI$^+$) found 288.9850 ([M+H]$^+$, $C_{10}H_6N_5$ requires 288.9837); X-ray crystallography: File reference CCDC 791583; Formula: $C_{10}H_5Br_1N_6$; Unit cell parameters: a 7.2576(2) b 8.4262(2) c 8.8405(2); α 97.305(1) β 110.101(1) γ 90.585(1) space group P-1.



5-amino-1-(3-ethynylphenyl)-1*H*-1,2,3-triazole-4-carbonitrile (Table 2, Entry 11)
1 mmol scale, 60% yield (126 mg) as an off-white solid. IR (neat) ν_{max}/cm^{-1} 3390 (w), 3324 (w), 3292 (w), 3248 (w), 3204 (m), 3074 (w), 2246 (m), 1648 (s), 1604 (w), 1590 (m), 1580 (m), 1498 (m), 1477 (w), 1427 (m), 1366 (w), 1334 (w), 1320 (m), 1308 (w), 1247 (w), 1165 (w), 1103 (w), 1086 (w), 1023 (m), 990 (m), 883 (m), 852 (m), 805 (s), 763 (w), 686 (m), 661 (m); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 7.67-7.61 (4H, m), 7.21 (2H, s, br), 4.36 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 148.0 (C), 134.3 (C), 132.9 (CH), 130.3 (CH), 128.0 (CH), 125.7 (CH), 123.2 (C), 113.3 (C), 101.3 (C), 82.4 (CH), 82.1 (C); LCMS Rt 4.24 min, *m*/*z* (ESI$^+$) 210 ([M+H]$^+$); HRMS *m*/*z* (ESI$^+$) found 210.0781 ([M+H]$^+$, $C_{11}H_8N_5$ requires 210.0780).



5-amino-1-(3-methoxyphenyl)-1*H*-1,2,3-triazole-4-carbonitrile (Table 2, Entry 12)
1 mmol scale, 76% yield (163 mg) as a light brown solid. Elemental analysis found C 55.5, H 4.2, N 32.2% ($C_{10}H_9N_5O$ requires C 55.8, H 4.2, N 32.5%); IR (neat) ν_{max}/cm^{-1} 3385 (w), 3326 (w), 3203 (m), 3015 (w), 2962 (w), 2840 (w), 2246 (m), 1651 (s), 1610 (m), 1597 (s), 1501 (m), 1488 (s), 1470 (m), 1454 (m), 1431 (m), 1369 (w), 1317 (s), 1282 (w), 1255 (m), 1234 (s), 1178 (m), 1156 (m), 1088 (m), 1040 (s), 1020 (s), 991 (m), 893 (w), 867 (s), 838 (s), 791 (s), 760 (m), 686 (s), 663 (m); ^{1}H NMR (500 MHz, DMSO-d_6): δ_H = 7.51 (1H, dd, *J* = 8 and 8 Hz), 7.16-7.11 (5H, m), 3.83 (3H, s); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C = 160.0 (C), 147.8 (C), 135.0 (C), 130.7 (CH), 116.9 (CH), 115.8 (CH), 113.4 (C), 110.3 (CH), 101.2 (C), 55.5 (CH_3); LCMS Rt 4.05 min, *m*/*z* (ESI$^+$) 216 ([M+H]$^+$); HRMS *m*/*z* (ESI$^+$) found 216.0885 ([M+H]$^+$, $C_{10}H_{10}N_5O$ requires 216.0885).



5-amino-1-(3,5-bis(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole-4-carbonitrile (Table 2, Entry 13)
1 mmol scale, 61% yield (196 mg) as a brown solid. Elemental analysis found C 41.4, H 1.6, N 21.9% ($C_{11}H_5N_5F_6$ requires C 41.1, H 1.6, N 21.8%); IR (neat) ν_{max}/cm^{-1} 3354 (w), 3317 (w), 3176 (w), 2235 (w), 1650 (m), 1596 (m), 1501 (w), 1473 (w), 1459 (w), 1398 (m), 1343 (w), 1328 (m), 1277 (s), 1194 (m), 1173 (s), 1137 (s), 1104 (m), 1038 (m), 914 (w), 897 (s), 849 (m), 825 (m), 763 (w), 720 (m), 701 (m), 684 (s), 667 (m); ^{1}H NMR (500 MHz, DMSO-d_6): δ_H = 8.36 (3H, s), 7.46 (2H, s, br); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C = 148.7 (C), 135.6 (C), 131.71 (2 × C, q, *J* = 34 Hz), 126.96 (2 × CH, m), 123.73 (CH, m), 122.73 (2 × CF_3, q, *J* = 273 Hz), 113.3 (C), 101.3 (C); LCMS Rt 4.79 min, *m*/*z* (ESI$^+$) 322 ([M+H]$^+$); HRMS *m*/*z* (ESI$^+$) found 322.0536 ([M+H]$^+$, $C_{11}H_6N_5F_6$ requires 322.0527).

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