Azide monoliths as convenient flow reactors for efficient Curtius rearrangement reactions†

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The preparation and use of an azide-containing monolithic reactor is described for use in a flow chemistry device and in particular for conducting Curtius rearrangement reactions *via* acid chloride inputs.

Introduction

In the preceding article we described a simple flow reactor for performing Curtius rearrangements starting from carboxylic acids with concomitant trapping of the intermediate isocyanate with various nucleophiles.[1] In this paper we wish to further exemplify this Curtius chemistry by using alternative monolithic reactor devices as immobilised azide sources for the conversion of acid chlorides.

Both traditional solution-phase and solid-phase synthetic approaches have associated problems and limitations. For example, the requirement for extensive iterative work-up and purification procedures make solution-phase synthesis an unattractive method for multi-step parallel operations. Likewise, generating libraries of compounds in high purity at reasonable scales (high milligram to gram scale) can be problematic when conventional solid-phase combinatorial chemistry is employed. Alternatively, an increasingly popular approach to circumvent many of these issues is the application of solid-supported reagents, catalysts and scavengers to expedite solution-phase synthesis and purification.[2] This approach combines the most advantageous aspects of both solution- and solid-phase synthesis, allowing the construction of advanced chemical architecture through the use of multi-step sequences.[3]

The application of solid-supported reagents to high-throughput chemistry can be further improved by transferring the batch environment into a continuous flow process.[4,5] In this way flow synthesis offers many advantages compared to normal batch mode.[6] For example, it is usually safer because at any given time only small amounts of reagent are present in the reactor. This small volume also circumvents many of the engineering issues such as heat and mass transfer. In addition, the reaction can be easily scaled by allowing the reaction to run for a longer period of time or at a higher flow rate, thereby giving access to more material with only minor alterations to the reactor. The simple modular design of the reactors also enables easy expansion of the system by the addition of supplementary units facilitating scale-out operations. Unfortunately, the incorporation of solid-supported reagents into flow processes can cause some problems due to their nature and format. By far the most common support systems for organic synthesis have been the gel-type polystyrene-based resins[7] or co-polymers thereof prepared as small beads (defined by low crosslinking). The physical compressibility of these materials tends to obstruct the flow stream leading to large pressure drops, especially when used with thermodynamically compatible 'good' solvents—solvents that effectively solvate and swell the resins. Conversely, in the presence of a 'poor' solvent the beads shrink, causing the active sites to become less accessible to the reactants and enabling the reaction mixture to by-pass and channel around the exterior of the beads, decreasing the chance of successful reactions (Fig. 1).[8]

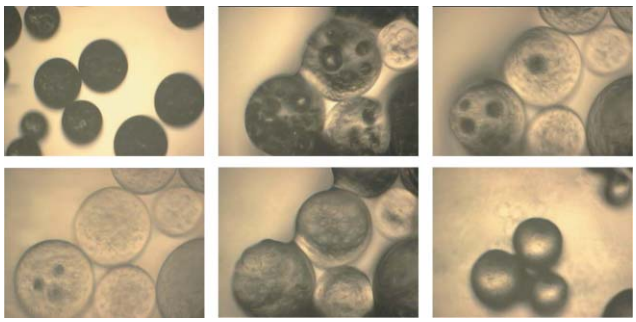

Fig. 1 Effect of solvents on the swelling characteristics of polystyrene beads (2% DVB crosslinked). Top (left to right): the expansion of polystyrene beads in DCM. Bottom (left to right): the contraction of pre-swollen polystyrene beads in Et_2O.

Macroporous beads (highly crosslinked) are an alternative to gel-type or microporous beads. These beads are permanently porous in nature regardless of solvent being used, making them preferential for use in flow systems. Nevertheless, the active sites within the cavities of these beads are only accessible to the passing solution through the relatively slow process of diffusion which becomes more of a concern as the molecular dimensions of the reactants increase.[9] An additional problem can also be that of by-passing, since even an ideally packed column containing monodispersed beads has approximately one quarter its total volume as void space.[10] Therefore, when a solution is forced through a packed bed column, it will tend to circumnavigate the beads instead of passing through them, thereby severely affecting the chemical efficiency of the system and often requiring larger columns.

To overcome some of these drawbacks, monoliths have been proposed and developed for use in solid-supported continuous

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† We dedicate this publication to Professor Andrew B. Holmes, friend and colleague, on the occasion of his 65th birthday.

flow synthesis.[10,11] Monoliths are a single continuous piece of porous material which can be made from either an organic or inorganic material.[10–12] Although inorganic monoliths have been widely used in catalysis, it is the alternative organic polymer structures that have found wider synthetic application.[13] Their readily tailored morphologies make them ideal constructs for use in synthesis due to easier control of pore dimensions, tuneable microchannel construction and their greater scope for chemical functionalisation. The most versatile systems are the rigid macroporous polymeric monoliths, as developed by Frechet and Svec in the early 1990's,[10,11f] which can be manufactured in any shape and size, making them ideal for use in micro- and meso-flow systems.[11a]

The Curtius rearrangement of acyl azides is a common reaction for the preparation of isocyanates and their secondary products and is widely used in the synthesis of pharmacologically active compounds.[14] To increase the safety profile of the active reagent, azide anions have therefore been immobilised onto ion-exchange resins as a safer alternative for use in organic synthesis.[15] These polymer-supported azide systems have then been demonstrated to reduce handling risks associated with shock, impact and exposure hazards. We have chosen to prepare azide-functionalised monolithic reaction columns to facilitate Curtius rearrangement reactions within a flow reactor.

Results and discussion

Preparation of macroporous monolithic reactor columns (quaternary ammonium ion exchange systems—azide form)

The physical characteristics of the macroporous monoliths are highly dependant upon the relative composition of the monomers, the nature and amount of any porogen used and the specific conditions employed to promote polymerisation. Significant experimentation was performed to identify a robust monolith-forming blend that could be reproducibly prepared and possessing both high porosity, to reduce back-pressure in the flow system, and a high stability, to withstand derivatization and repeated use.[11a] Our initial target was therefore to prepare Merrifield-type monoliths (functionalised with benzyl chloride) which could be easily modified to create multiple immobilised delivery systems by well documented transformations.

All polymerisation experiments were performed within 15 mm i.d. × 100 mm Omnifit glass columns[16] which were sealed at both ends and thermally incubated within a VapourTec R4 multi-channel convective heating device[17] (Fig. 2). AIBN was determined as the best polymerisation initiator permitting a stable monolithic matrix to form under elevated temperature (80 °C) over a period of 20 h. In practice, a homogeneous mixture of vinylbenzyl chloride (VBC; 30% v/v), divinyl benzene (DVB crosslinker; 20% v/v), 1-dodecanol (50% v/v) as the porogen and AIBN (1% wt relative to VBC + DVB) were loaded into the glass column. The system was then sealed using a set of fritted end pieces (lower end plugged) and maintained under positive pressure (20 psi, top connector) while the curing process was conducted. After 20 h the column was cooled to ambient temperature using the R4 system and extensively washed with dry THF (R2+ unit set to a flow rate of 1.0 mL min^{-1} for 2 h). The washing procedure removed the porogen and residual non-polymeric material, resulting in a rigid white monolith that completely filled the glass column (Fig. 2b). All

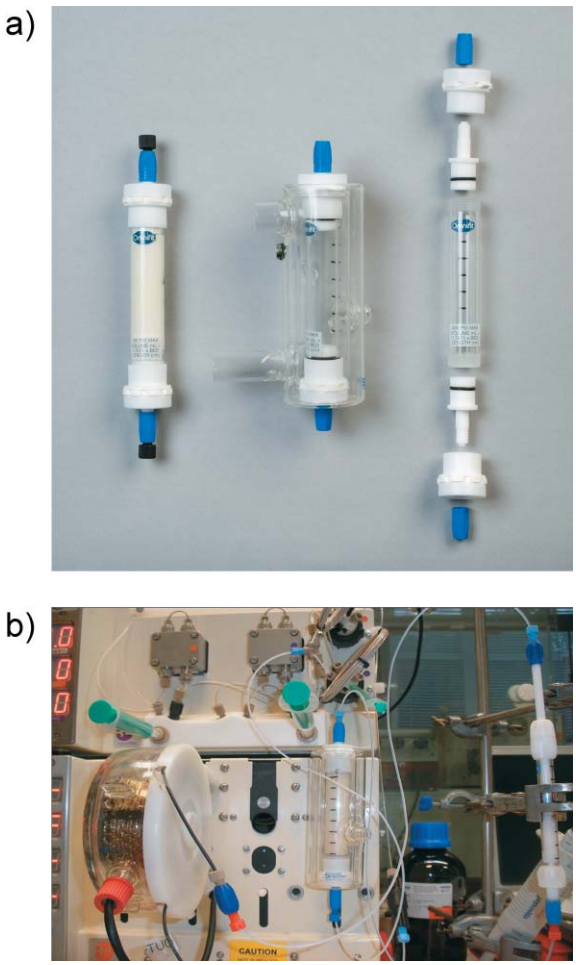


Fig. 2 a) R4 reactor column components, disassembled sections (left) and assembled unit (right); b) monolith-containing column; c) R2+ and R4 reactor unit with monolith column inserted for reaction.

monoliths prepared exhibited excellent batch-to-batch consistency and gave almost identical analytical data.

Mercury Intrusion Analysis (MIA) of this Merrifield-type monolith established the median pore size to be 3147 nm and the surface area to be 4.93 m^2 g^{-1} as determined by nitrogen absorption and BET measurements (Fig. 3). The internal volume of the monolithic column was calculated as 12.55 mL (1.77 cm^2 × 7.1 cm) consisting of a total void space of 6.4 mL based on a porosity of 51% (MIA, also being consistant with the use of 50% porogen). The structural integrity of the monolith is maintained across a range of solvents by the high crosslinking of the structure, 44% based on the theoretical incorporation of DVB. In pressure tests a maximum value of only 2.2 bar was recorded for flow rates of up to 5 mL min^{-1} using MeCN as the solvent. Indeed, the monoliths possessed a near-linear correlation between pressure and flow rate. Even at higher flow rates (10 mL min^{-1}) the hydrodynamic compressibility of the system was excellent, registering only 4.6 bar, implying very little channel collapse or closure. Elemental analysis (C, H and Cl) indicated a functionalisation of 3.5 mmol g^{-1} compared to a theoretical value of 3.95 mmol g^{-1} (complete VBC incorporation). In practice this high loading value would not be possible to fully exploit in the further chemical functionalization due to the highly cross-linked matrix created. Only certain sites

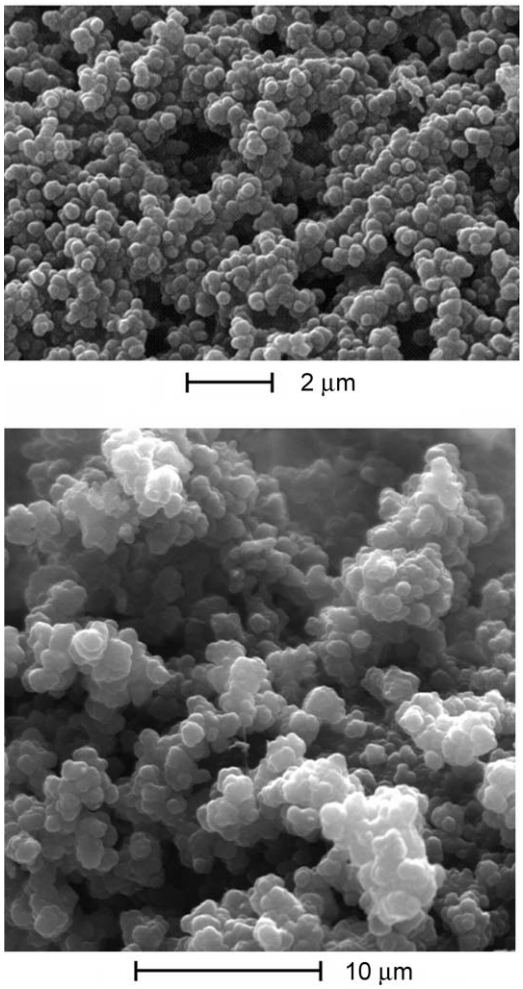


Fig. 3 SEM images of the macroporous Merrifield-type monolith.

would be accessible to solution-phase species, and typically an expected post-polymerisation loading of 40–60% of the theoretical loading is attainable.

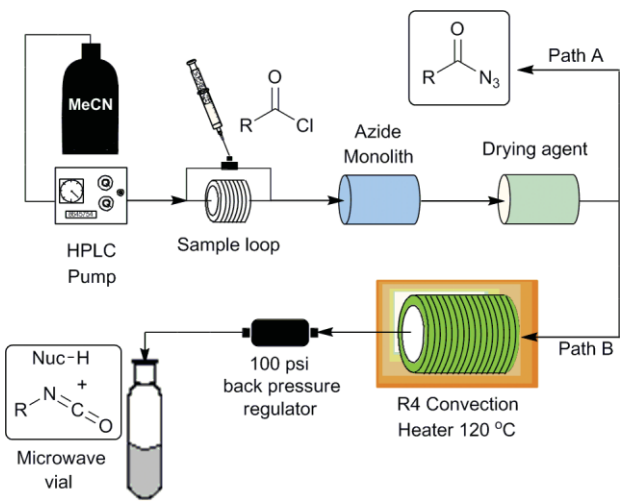
Next, the Merrifield-type monolith was converted to its quaternary ammonium form by reaction with triethylamine. A solution of the amine in toluene (1 : 4 v/v; 2.5 equiv.) was pumped through the column at 0.2 mL min^{-1} at 60 °C over a period of 48 h (output solution was recycled). The column was then flushed consecutively with toluene, DCM, MeOH and water, each at 1.0 mL min^{-1} for 30 min (system temperature 60 °C). Finally, an aqueous solution of sodium azide was prepared (0.1 M; 40 mL) and passed through the monolith structure at 0.25 mL min^{-1} at ambient temperature to generate the azide-exchanged column. A sequential washing sequence involving water (1 mL min^{-1}, 1 h), water–MeCN (1 : 1) and MeCN, each pumped at 1.0 mL min^{-1} for 1 h ensured only immobilised azide remained. This affords a monolithic structure with an azide loading of 2.0 mmol g^{-1} according to C, H and N analysis. Employing the R2+ and R4 system, a small batch of azide-functionalised monoliths were readily prepared (four simultaneous reactions can be conducted on the R4 unit using the R2+ system for solvent washing and reagent dispensing).

Having established a convenient and reliable procedure for the generation of the azide-functionalised monoliths, we turned our attention to preparing larger units to conduct scaled synthesis. For synthetic expedience we aimed to make a series of monoliths with effective azide loadings of 3, 7 and 15 mmol per cartridge. The dimensions for these column bodies were 6.6, 10 and 15 mm i.d. by 100 mm, respectively. Our fabrication process proved robust, allowing all desired sizes of the monoliths to be prepared. Indeed, the variously sized monoliths showed excellent agreement in both their physical and chemical parameters. However, our observations are that much larger monoliths would certainly require an alternative approach, as the internal structures show a marked degradation as the dimensions of the system are scaled. Obvious signs of cavitation and collapse of the internal polymeric network can be detected in these larger monoliths. This can be easily monitored and characterised by the increased pressure drop across the construct and noticeable channelling of coloured solutions through the matrix. Furthermore, clear shrinking of the polymer core occurs during the curing process, significantly reducing the cohesion of the polymer core to the glass wall of the column and thereby rendering the system useless for flow applications. Ways of artificially stabilising the monolith morphology by introducing additional buttressing and structural supports are under investigation.

Curtius rearrangement of acyl chlorides using the azide ion-exchanged monolith in the R2+ and R4 flow reactor

The newly prepared monoliths were then used to convert acyl chlorides to their corresponding isocyanates *via* their acyl azide intermediates. The rearranged isocyanates were also further reacted with various nucleophiles to obtain secondary carbamate and urea products.[1]

In a typical experiment (Scheme 1; Path A), 1 mmol of the starting material was introduced to the main flow stream *via* a 1 mL injection loop as a 1 M solution in MeCN. The material was delivered to the monolithic reactor (15 mmol column) using MeCN as the system solvent at a flow rate of 0.5 mL min^{-1}. Since the pore volume of the monolithic reactor is approximately 6.5 mL, the residence time for the reactor was assumed to be 13 min. The conversion of the acyl chlorides to the corresponding azides happens at ambient temperature and is therefore easily achieved by simply directing the starting material through the azide-exchange



Scheme 1 Flow reactor for Curtius rearrangements.

monolith. Initially, we collected and characterised the output from the monolith to enable identification of the acyl azide product, which could be isolated in quantitative yield by simply removing the solvent (see Experimental section; 3-bromobenzoyl azide **1**). This approach was then modified to create a small collection of compounds by thermally rearranging the acyl azide intermediates to their corresponding isocyanates and reacting these with various nucleophiles (Fig. 4).

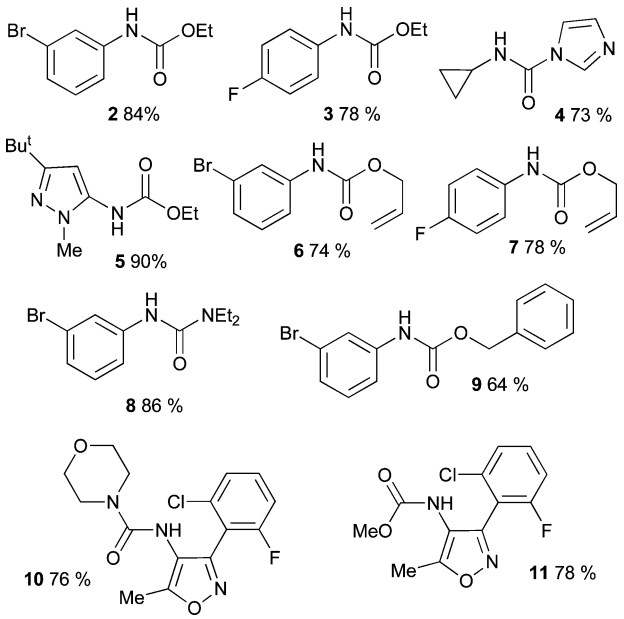


Fig. 4 Products from Curtius rearrangements and trapping of the corresponding isocyanates.

For these extended reaction sequences, the acyl azide solution (prepared as above) was directed to a secondary column packed with a dehydrating agent ($MgSO_4$ or Na_2SO_4; 1 g) (Scheme 1; Path B). This acted to remove any possible traces of water from the reaction stream and was found to be essential for the success of the reaction. Following the Curtius rearrangement, the presence of even small quantities of water rapidly led to the formation of the carbamic acid, and then through spontaneous decarboxylation to the corresponding amines and eventual urea by-products. The presence of a small drying column entirely eliminated this problem.

Next, the solution feed from the drying column was passed through a 10 mL convection flow coil (CFC) which was heated at 120 °C promoting the rearrangement to the isocyanate.[17] A back-pressure regulator (100 psi) was added in-line after the reactor to enable the superheating of the MeCN reaction mixture. The output stream from the coil reactor containing the newly formed isocyanate was collected directly into a 25 mL microwave vial that already contained the appropriate nucleophile (1–4 equiv.) for the subsequent addition reaction. The solution was collected for a period of 1.5 h (with the initial 35 min aliquot being discarded), and then the vial was sealed and heated under microwave irradiation[18] at 100 °C for 10 min to ensure that the reaction between the isocyanate and nucleophile had gone to completion. The final product was then obtained by simply removing the solvent or in certain cases by first passing the solution through a small bond elute silica gel cartridge[19] prior to solvent removal. This gave the product in good yield and excellent purity (>95% as determined by LC-MS and ^{1}H-NMR; Fig. 4).

In these reactions a single monolith could be used to produce between 1 and 10 mmol of the product with a steady-state output of up to 30 mmol of acyl azide per hour. Therefore a series of columns can be sequentially employed and by alternating between different monoliths a small set of compounds produced. Alternatively, it is possible to scale reactions by integrating multiple monoliths through split reactant lines, rapidly increasing the throughput of material. We have also demonstrated the feasibility of using larger monoliths (20 mmol) as reactors for the conversion of a sequence of different acyl chlorides separated by solvent plugs without observing cross-contamination. In addition, parallelisation is possible using the two dedicated HPLC pumps of the R2+ unit to feed two independent channels and their associated monoliths and CFC reactors. In practice, further auxiliary Knauer K120 HPLC pumps can also be readily configured with the system to deliver extra reagent feeds, giving additional synthetic scope and flexibility. It was also shown that the depleted monoliths could be easily regenerated by eluting with a new solution of sodium azide as previously described for their original preparation. Such columns retained their original loading and reactivity as demonstrated by their subsequent reactions.

Conclusion

In conclusion, a new monolithic azide exchange reactor has been developed and tested. This monolithic cartridge has been shown to be ideally suited for flow chemistry purposes, and when used in combination with other flow reactor components is a powerful tool for performing Curtius rearrangements and other azide-related chemistries. Taking into account the high achievable loading of the azide cartridge (up to 10 mmol reactive loading), the multiple usage of each unit to create libraries, as well as its parallel operation for scaling up reactions, both without compromising upon safety, certainly indicates a significant synthetic potential.

Experimental

Unless otherwise stated, reaction solutions were prepared in MeCN (distilled over calcium hydride) in 5 ml glass volumetric flasks. ^{1}H-NMR spectra were recorded on a Bruker Avance DPX-400 or DRX-500 spectrometer with residual chloroform as the internal reference ($CHCl_3$ δ_H = 7.26 ppm). ^{13}C-NMR spectra were also recorded in $CDCl_3$ on the same spectrometer with the central peak of the residual solvent as the internal reference (δ_C = 77.0 ppm). COSY, DEPT 135 and HMQC spectroscopic techniques were used to aid the assignment of signals in the ^{13}C-NMR spectra. Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer neat. Letters in the parentheses refer to relative absorbency of the peak: w, weak, <40% of the main peak; m, medium, 41–74% of the main peak; s, strong, >74% of the main peak. LC/MS analysis was performed on an Agilent HP 1100 chromatograph (Luna Max RP column) attached to an HPLC/MSD mass spectrometer. Elution was carried out using a reversed-phase gradient of MeCN–water with both solvents containing 0.1% formic acid. The gradient is described in Table 1. For HRMS a LCT Premier Micromass spectrometer was used.

Table 1 LC-MS conditions

Time/min	MeCN (%)	Flow rate/mL min^{-1}
0.00	5	1
3.00	95	1
5.00	95	1
5.50	5	1
8.00	5	1

Preparation of the Merrifield-type monolith

A stock solution of divinylbenzene (technical grade containing a mixture of isomers; 5.2 mL; 36.5 mmol; 80% technical grade), 4-vinylbenzene chloride (7.8 mL; 55.3 mmol; 90% purity grade), 1-dodecanol (13.0 mL; 63.5 mmol) and AIBN (130 mg; 0.8 mmol) was prepared. A 15 mm × 100 mm Omnifit column was filled from this stock solution and both end of the column were sealed by plugs (VapourTec) and the system maintained under positive pressure (20 psi, top connector) while the curing process was conducted.[20] The VapourTec R4 convective heating unit was used to heat the column at 80 °C for 20 h. A white polymeric monolith resulted. This monolith was washed with THF at 1 mL min^{-1} for 2 h at 60 °C using the R2+ and R4 combination unit. The back-pressure for the washing step was only 0.1 bar. Elemental analysis C, H and Cl of the monolithic column (C; 78.73% H; 6.77% Cl; 12.53%) gave results equating to a loading of 3.5 mmol g^{-1}.

Preparation of quaternary ammonium chloride ion-exchange monolith

A stock solution of triethylamine (25 ml) in toluene (75 mL) was prepared. This solution was pumped through the Merrifield monolith prepared in the previous step at a flow rate of 0.2 ml min^{-1} for 48 h, the column being maintained at 60 °C. The column was then washed with dichloromethane at 1 mL min^{-1} for 30 min. The system back-pressure steadily increased to 12 bar during the washing step. The wash solvent was then changed to methanol and the column eluted at 1 mL min^{-1} for 30 min. The system back-pressure returned to 0.1 bar. Finally the column was washed with water at 1.0 mL min^{-1} for an additional 30 min. This monolith was then ready for further ion-exchange functionalisation.

Preparation of azide exchange monolith

A stock solution of sodium azide (2.5 g) was dissolved in water (40 mL). The solution was passed through the monolith column prepared in the previous step at 0.25 mL min^{-1}. The column was then washed sequentially with water (1 mL min^{-1}, 1 h), water–MeCN (1 : 1) and MeCN, each pumped at 1.0 mL min^{-1} for 1 h each. Elemental analysis: C 77.21%, H 6.53%, N 10.75%, equating to a loading of 2.0 mmol g^{-1} of immobilized azide.

A typical Curtius reaction

A solution of 3-*tert*-butyl-1-methyl-1*H*-pyrazole-5-carbonyl chloride (201 mg, 1.0 mmol) in acetonitrile (1.0 mL) was injected into the 1 mL sample loop of the R2+ unit. The valve was set to load and the material pumped through the azide monolith using acetonitrile as the system solvent at a flow rate 0.5 mL min^{-1}. The output of the monolith reactor was directed through a column packed with anhydrous sodium sulfate (1.0 g) then into a 10 mL CFC which was heated at 120 °C (R4 unit). A back-pressure regulator (100 psi) was added in-line after the reactor to enable the superheating of the MeCN reaction mixture. The output stream from the coil reactor containing the newly formed isocyanate was collected directly into a 25 mL microwave vial containing ethanol (0.5 mL). The solution was collected for a period of 1.5 h (with the initial 35 min aliquot being discarded) then the vial sealed and heated under microwave irradiation at 100 °C for 10 min. The solvent was then removed to obtain ethyl 3-*tert*-butyl-1-methyl-1*H*-pyrazole-5-ylcarbamate **5** (180 mg; 90%) as a pale yellow oil.

3-Bromobenzoyl azide (1). Flow rate 0.5 mL min^{-1}, 1 mmol, Yield: quantitative, Rt = 4.66 min, (no corresponding mass found); ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 8.16 (1H, t, J = 8.0 Hz), 7.95 (1H, dt, J = 7.5, 1.5 Hz), 7.73 (1H, dq, J = 8.0, 1.5 Hz), 7.34 (1H, t, J = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 123.19 (C), 128.35 (CH), 130.60 (CH), 132.77 (CH), 132.92 (C), 137.57 (CH), 171.64 (C); IR: ν 2137.2 (s), 1771.9 (s), 1691.0 (s), 1592.2, 1568.4 (m), 1472.2, 1421.7 (m), 1374.9, 1278.8 (m), 1228.9 (s), 1166.1 (s), 1067.6 (m), 1036.1 (m), 994.9 (s), 868.8, 802.0, 725.0 (s), 670.0 cm^{-1}; HRMS calculated for $C_7H_5BrN_3O$ 224.9536, found 224.9532.

Ethyl 3-bromophenylcarbamate (2). Flow rate 0.5 mL min^{-1}, 2 mmol, Yield: 84%, Rt = 4.48 min, M + H m/z = 244.1; ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 7.65 (1H, m), 7.15–7.35 (3H, m), 6.72 (1H, br. s), 4.24 (2H, q, J = 8.5 Hz), 1.31 (3H, t, J = 8.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 14.89 (CH_3), 61.92 (CH_2), 117.52 (CH), 121.98 (CH), 123.13 (C), 126.72 (CH), 130.68 (CH), 139.74 (C), 153.76 (C); IR: ν 3310.4 (m), 2980.3, 2936.2, 2137.8, 1702.1 (s), 1590.9 (s), 1529.1 (s), 1479.9 (s), 1422.4 (s), 1389.2 (m), 1304.1 (m), 1275.6 (s), 1222.9 (s), 1168.6 (m), 1095.5 (m), 1074.1 (s), 1062.7 (s), 995.2 (m), 915.8, 852.1 (m), 772.4 (s), 730.5, 681.4 (m) cm^{-1}; calculated for $C_9H_{11}BrNO_2$ 243.9973, found 243.9968.

Ethyl 4-fluorophenylcarbamate (3)[21]. Flow rate 0.5 mL min^{-1}, 2 mmol, Yield: 77%, Rt = 4.16 min, m/z = 138.00 (acylium ion); ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 7.27–7.24 (2H, m), 6.94–6.89 (2H, m), 6.59 (1H, s), 4.14 (2H, q, J = 8.0 Hz), 1.22 (3H, t, J = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 14.90 (CH_3), 61.68 (CH_2), 116.06 (2 × CH, d, J = 22.5 Hz), 120.87 (2 × CH), 134.33 (C), 154.22 (C), 159.36 (C, d, J = 240.7 Hz); IR: ν 3311.6 (m), 2990.8, 2924.5 (m), 2155.4, 1696.5 (s), 1610.1 (m), 1531.4 (s), 1509.1 (s), 1411.3 (m), 1387.8, 1365.3, 1303.2 (m), 1208.3 (s), 1156.5 (m), 1098.3 (m), 1064.4 (s), 1012.5 (m), 930.2, 830.1 (s), 782.0 (m), 767.8 (s), 744.3 (s) cm^{-1}; calculated for $C_9H_{11}FNO_2$ 184.0774, found 184.0780.

***N*-Cyclopropyl-1*H*-imidazole-1-carboxamide (4).** Flow rate 0.5 mL min^{-1}, 1 mmol, Yield: 73%, Rt = 1.02 (no corresponding mass found); ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 8.35 (1H, s), 8.16 (1H, s), 7.48 (1H, s), 6.91 (1H, s), 2-74-2.72 (1H, m), 0.74–0.73 (2H, m), 0.60–0.59 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 6.89 (2 × CH_2), 23.90 (CH), 108.29 (C), 130.21 (C), 136.18 (C), 150.07 (C); IR: ν 3122.7 (m), 3013.9 (m), 2839.2, 1707.3 (s), 1536 (s), 1518.8 (s), 1377.4 (m), 1354.9 (m), 1321.5 (s), 1291.0 (s), 1225.1 (m),1195.5, 110.1, 1064.0 (s), 1020.0, 949.9, 912.4, 846.1 (m), 749.5 (m), 654.7 (m) cm^{-1}; calculated for $C_7H_{10}N_3O$ 152.0820, found 152.0818.

Ethyl 3-*tert*-butyl-1-methyl-1*H*-pyrazole-5-ylcarbamate (5). Flow rate 0.5 mL min^{-1}, 1 mmol, Yield: 90%, Rt = 3.96 min, M + H m/z = 226.3; ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 6.33 (1H, s), 6.04 (1H, s), 4.3 (2H, q, J = 8.0 Hz), 3.70 (3H, s), 1.33 (3H, t, J = 8.0 Hz), 1.29 (9H, s); ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 14.42 (CH_3), 31.98 (CH_3), 32.18 (C), 34.93 (CH_3), 62.03 (CH_2), 96.12 (C), 135.17(C), 153.98(C), 160.97 (C); IR: ν 3275.9, 2959.2 (s), 2867.2, 1709.2 (s), 1570.7 (s), 1461.3 (m), 1361.9 (m), 1230.7 (s), 1095.9, 1061.6 (s), 990.4, 779.6 (m) cm^{-1}; calculated for $C_{11}H_{20}N_3O_2$ 226.1556, found 226.1553.

Allyl 3-bromophenylcarbamate (6)[14]. Flow rate 0.5 mL min^{-1}, 1 mmol, Yield: 74%, Rt = 4.63 min, M + H m/z = 215.14 (carbamic acid); ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 7.67 (1H, s), 7.31–7.29 (1H, m), 7.21–7.14 (2H, m), 6.87 (1H, s), 5.99 (1H, ddt, J = 17.2, 10.4, 5.5 Hz), 5.37 (1H, app. dq, J = 17.2, 1.5, 1.5 Hz), 5.29 (1H, app. dq, J = 10.4, 1.5, 1.5 Hz), 4.68 (1H, app. dt, J = 5.5, 1.5, 1.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 66.51 (CH_2), 118.92 (CH_2), 122.08 (CH), 122.87 (CH), 123.14 (C), 126.86 (CH), 130.70 (CH), 132.60 (CH), 139.57 (C), 153.44 (C); IR: ν 3309.9 (m), 3083.3, 2946.5, 1706.6 (s), 1649.0, 1590.8 (s), 1530.4 (s), 1481.2 (s), 1421.0 (s), 1305.1 (m), 1275.3 (s), 1223.4 (s), 1167.8, 1095.7 w), 1073.6 (m), 1057.8 (m), 995.2 (m), 934.1, 867.9, 774.9 (m), 681.7 (m) cm^{-1}; calculated for $C_{10}H_{10}BrNO_2Na$ 277.9800, found 277.9787.

Allyl 4-fluorophenylcarbamate (7). Flow rate 0.5 mL min^{-1}, 1 mmol, Yield: 78%, Rt = 4.36 min, M + Na m/z = 219.1; ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 7.39–7.34 (2H, m), 7.04–6.98 (2H, m), 5.97 (1H, ddt, J = 17.2, 10.4, 5.5 Hz), 5.37 (1H, *ap.* dq, J = 17.2, 1.5, 1.5 Hz), 5.27 (1H, *ap.* dq, J = 10.4, 1.5, 1.5 Hz), 4.68 (1H, *ap.* dt, J = 5.5, 1.5, 1.5 Hz), ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 66.33 (CH_2), 115.99 (2 × CH, d, J = 22.5), 118.73 (CH_2), 120.87 (2 × CH) 132.73 (CH), 134.16 (C), 153.87 (C), 159.40 (C, d, J = 241.2); IR: ν 3315.0 (m), 2094.1, 1707.8 (s), 1614.2 (m), 1540.0 (s), 1512.3 (s), 1410.8(s), 1308.2 (m), 1221.0 (s), 1158.2, 1102.6, 1061.2 (s), 995.9, 935.1, 834.4 (s), 791.0, 769.1 cm^{-1}; calculated for $C_{10}H_{11}FNO_2$ 196.0774, found 196.0775.

3-(3-Bromophenyl)-1,1-diethylurea (8). Flow rate 0.5 mL min^{-1}, 1 mmol, Yield: 86%, Rt = 4.34 min, M + H m/z = 273.2; ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 7.63 (1H, m), 7.26 (1H, m), 7.04–7.10 (2H, m), 6.57 (1H, *br.* s), 3.33 (4H, q, J = 7.5 Hz), 1.17 (6H, t, J = 7.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 13.85 (CH_3), 42.32 (CH_2), 118.44 (CH), 122.30 (C), 122.80 (CH), 125.54 (CH), 129.91 (CH), 140.83 (C), 154.39 (C); IR: ν 3321.3(m), 2976.4 (m), 2931.1 (m), 2871.9, 2028.5, 1636.8 (s), 1595.3 (m), 1585.0 (s), 1519.4 (s), 1477.0 (s), 1452.4 (m), 1422.2 (s), 1401.6 (m), 1378.8 (m), 1364.9, 1301.4 (s), 1279.0 (s), 1241.6 (s), 1222.2 (m), 1162.6 (s), 1099.2, 1071.7 (m), 1085.0 (m), 1051.9, 993.9 (m), 977.0 (m), 936.3, 897.7 (m), 876.2 (m), 830.9, 790.2, 773.4 (s), 753.4 (m), 733.0 (m), 686.0 (m), 670.3 (m) cm^{-1}; calculated for $C_{11}H_{16}BrN_2O$ 271.0446, found 271.0439.

Benzyl 3-bromophenylcarbamate (9)[14]. Flow rate 0.5 mL min^{-1}, 1 mmol, Isolated yield following filtration through silica: 64%, Rt = 4.97 min, M + H m/z = 307.6; ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 7.67 (1H, s), 7.43–7.37 (5H, m), 7.30 (1H, s), 7.22–7.15 (2H, m), 6.75 (1H, s), 5.22 (2H, s); ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 67.69 (CH_2), 117.57 (CH), 122.03 (CH), 123.16 (C), 126.92 (CH), 128.73 (2 × CH) 128.88 (2 × CH), 129.05 (CH), 130.70 (CH), 136.19 (C), 139.49 (C), 153.44 (C); IR: ν 3396.9, 3307.6 (m), 1705.7 (s), 1594.4 (s), 1531.3 (s), 1481.4 (m), 1454.9, 1422.4 (m), 1305, 1275.7 (s), 1222.2 (s), 1095.4, 1073.6 (m), 1054.3 (m), 995.5, 870.5, 776.6 (m), 742.3, 697.5 (m), 681.8 cm^{-1}; calculated for $C_{14}H_{13}BrNO_2$ 306.0130, found 306.0132.

***N*-(3-(2-Chloro-6-fluorophenyl)-5-methylisoxazole-4-yl)morpholine-4-carboxamide (10).** Flow rate 0.5 mL min^{-1}, 1 mmol, Yield: 76%, Rt = 3.82 min, M + H m/z = 340.2; ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 7.38 (1H, m), 7.30 (1H, d, J = 8.0 Hz), 7.10 (1H, dt, J = 8.5, 1.0 Hz), 5.86 (1H, br. s), 3.59 (4H, t, J = 4.5 Hz), 3.29 (4H, t, J = 4.5 Hz), 2.40 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 11.45 (CH_3), 44.36 (2 × CH_2), 66.27 (2 × CH_2), 114.66 (CH, d, J = 22.5 Hz), 115.03 (C), 116.69 (C, d, J = 18.4 Hz), 125.64 (CH, d, J = 3.6 Hz), 131.74 (CH, d, J = 9.4 Hz), 134.74 (C, d, J = 3.9 Hz), 153.92 (C, d, J = 0.8 Hz), 155.07 (C), 160.79 (C, d, J = 251.7 Hz), 165.27 (C); IR: ν 3286.8 (m), 2967.0, 2922.3, 2899.0, 2857.1, 2244.2, 1637.0 (s), 1572.3 (s), 1504.8 (s), 1456.3 (s), 1438.0 (s), 1390.0 (m), 1335.8, 1296.6 (m), 1251.8 (s), 1184.0 (m), 1149.3, 1115.2 (s), 1070.4 (m), 1019.5, 999.3 (m), 898.1 (s), 779.7 (s), 730.0 (s), 676.8 cm^{-1}; calculated for $C_{15}H_{16}ClFN_3O_3$ 340.0864, found 340.0880. X-ray data: File reference: CCDC 675581; Formula: $C_{15}H_{15}Cl_1F_1N_3O_3{\cdot}0.5(CH_2Cl_2)$; Unit cell parameters: a 25.8310(4), b 8.8237(2), c 19.7540(4), α 90.00, β 128.919(1), γ 90.00; space group $C2/c$.

Methyl 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-ylcarbamate (11). Flow rate 0.5 mL min^{-1}, 1 mmol, Yield: 74%, Rt = 4.12 min, M + H m/z = 285.2; ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 7.38 (1H, m), 7.29 (1H, d, J = 8.0 Hz), 7.10 (1H, d, J = 8.5 Hz), 5.95 (1H, br. s), 3.62 (3H, br. s), 2.44 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 11.37 (CH_3), 53.21 (CH_3), 114.96 (CH, d, J = 21.6 Hz), 116.60 (C, d, J = 18.4 Hz), 126.08 (CH, d, J = 3.6 Hz), 132.28 (CH, d, J = 9.4 Hz), 135.44 (C, d, J = 4.0 Hz), 153.89 (C, d, J = 0.8 Hz), 155.56 (C), 161.21 (C, d, J = 251.6 Hz), 165.64 (C); IR: ν 3274.0 (m), 2956.4, 2250.6, 1718.2 (s), 1646.9 (m), 1612.3 (m), 1573.5 (s), 1530.2 (m), 1502.0 (m), 1457.7 (s), 1409.6 (m), 1373.8, 1343.3, 1251.8 (s), 1186.0, 1072.3 (s), 98.3, 902.0 (s), 786.9 (s), 734.8 (s) cm^{-1}; calculated for $C_{12}H_{11}FN_2O_3$ 285.0442, found 285.0450.

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