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Multi-Step Synthesis by Using Modular Flow Reactors: The Preparation of Yne–Ones and Their Use in Heterocycle Synthesis

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The development of new and improved chemical processing techniques that conduct both complex and routine chemical transformations in a safe, reproducible and scalable fashion without recourse to costly route modification or redevelopment is very desirable. The introduction of continuous-flow reactor technologies offers the ability to test, optimise and create scalable syntheses rapidly by using a simple bench-top device.[1] In combination with the concept of immobilised reagents, scavengers and catch-and-release protocols, a powerful tool arises that can perform chemical transformations without the need for traditional workup procedures.[2] Moreover, these devices enable the rapid progression of a clean product flow stream from one synthetic transformation to the next in a multi-step sequence. Furthermore, the intrinsic design of the flow equipment allows real-time, in-line monitoring and accommodates high temperatures and pressures, which permit reactions to be performed that were previously difficult to carry out in conventional batch synthesis. The reaction setup also facilitates containment of hazardous reagents or intermediates and is readily scalable to provide bulk samples.

Herein, we report the palladium-catalysed acylation of terminal alkynes for the synthesis of yne–ones[3] and their further transformation into various heterocycles.[4] The reactions are performed as a continuous-flow procedure by using a commercially available pumping system and heated flow coils in combination with a suite of packed Omnifit glass tubes[5] containing appropriate scavenger materials to ensure the quality of the final product. We also present an extension of the simple flow configuration that allows for easy batch splitting through a four-way splitter device and the generation of a heterocyclic library.

For this work we used a commercially available synthesis platform, the Vapourtec R2+/R4 unit (Figure 1).[6] The Vapourtec integrates a twin pumping unit with an independent-

Figure 1. Vapourtec R2+/R4 flow system.

ly controlled four-channel air-circulated heating module. A low-pressure input valve is used to route either solvent or bulk stock solutions directly to the self-regulating HPLC pumps. Two additional Rheodyne 6-port–2-position switching valves can be used to introduce reagents or substrates into the main flow line through individual sample loop arrangements of user-defined variable volumes.

A positive system pressure was maintained by using an in-line 100 or 250 psi back-pressure regulator. The use of an appropriate back-pressure regulator allows superheating of solvents as required. Mixing of the reagent streams is achieved with a simple T-piece and the combined output is then directed through perfluoroalkoxy (PFA) tubing to the

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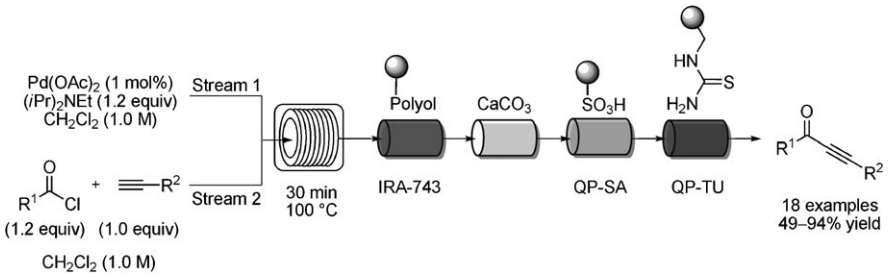
convection flow coil (CFC), which can be precisely heated to 150 °C. Upon exiting the CFC, the flow stream is cooled rapidly and is then directed to scavenger cartridges that consist of simple Omnifit glass columns packed with appropriate immobilised materials. The final flow line can then be collected and evaporated to give the purified product.

A rapid screening of reaction parameters was performed, which included reaction temperature, residence time (flow rate), internal pressure, solubility, reagent concentrations and stoichiometry. Practical conditions were determined that involved the introduction of a 1 M solution of $Pd(OAc)_2$ (1 mol %) and Hünig's base (1.0 equiv) in dichloromethane through an injection loop (Scheme 1, stream 1), which was then mixed through a T-piece with a 1 M solution of the acid chloride (1.2 equiv) and terminal acetylene (1.0 equiv) in dichloromethane (Scheme 1, stream 2). The mixture was then heated to 100 °C through a CFC (2×10 mL) to give a residence time of 30 min. Upon exiting the CFC, the flow stream was directed through a series of scavenger columns. Firstly, a tube packed with a Amberlite polyol resin (IRA-743) operating at room temperature effectively removed any excess acid chloride, subsequently the $CaCO_3$ cartridge deprotonates the ammonium salts and traps the HCl that was formed during the reaction. The sulfonic acid resin



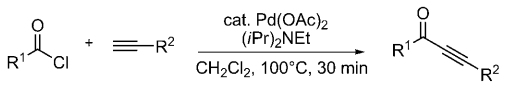
Scheme 1. Flow synthesis of yne–ones.

(QP-SA) scavenges the tertiary amine by protonation. Finally, a thiourea (QP-TU) resin removes any residual palladium contamination to give a pure yne–one product stream (Scheme 1). Evaporation of the solvent by using a Vapourtec V10 instrument affords the coupling products in excellent purity and good yield.

The whole system is maintained under positive pressure by using an in-line 100 psi back-pressure regulator. Typically, we used IRA-743 (3.0 g), $CaCO_3$ (3.0 g), QP-SA (5.0 g) and QP-TU (2.0 g) to perform three consecutive experimental runs on a 2.0 mmol scale to obtain clean reaction products (Scheme 1). After evaporation of the solvent the yne–ones required no additional purification.

From the examples depicted in Table 1, it can be noted that the couplings proceed smoothly for substrates with electron-donating and -withdrawing substituents. Functionalities such as halide, nitro and cyanide are all tolerated under the reaction conditions. Couplings proceeded successfully by using aromatic as well as aliphatic acid chlorides. However,

Table 1. Palladium-catalysed acylations for the synthesis of yne–ones.[a]

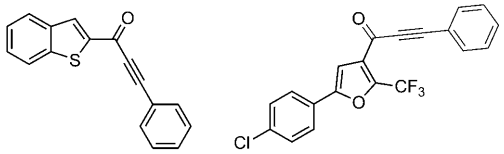


1 2 3

Entry	R^1	R^2	3	Yield [%]
1	4-F-C_6H_4	C_6H_5	**3a**	80
2[b]	4-CN-C_6H_4	C_6H_5	**3b**	63
3	4-CF_3-C_6H_4	C_6H_5	**3c**	94
4[b]	3,4-OCH_2O-C_6H_4	C_6H_5	**3d**	78
5	3-NO_2-C_6H_4	C_6H_5	**3e**	88
6	3-Br-C_6H_4	C_6H_5	**3f**	79
7	3-Br-C_6H_4	*n*Bu	**3f**	41
8	cinnamyl	C_6H_5	**3g**	95
9	C_6H_5	cyclohexenyl	**3h**	70
10	C_6H_5	C_6H_5	**3i**	89
11	C_6H_5	*n*Bu	**3j**	87
12	4-F-C_6H_4	$SiEt_3$	**3k**	49
13	Me	C_6H_5	**3l**	89
14	*t*Bu	C_6H_5	**3m**	65
15	cyclopropyl	C_6H_5	**3n**	72
16	*n*Pr	C_6H_5	**3o**	75
17	2,4-OMe-C_6H_4	C_6H_5	**3p**	86

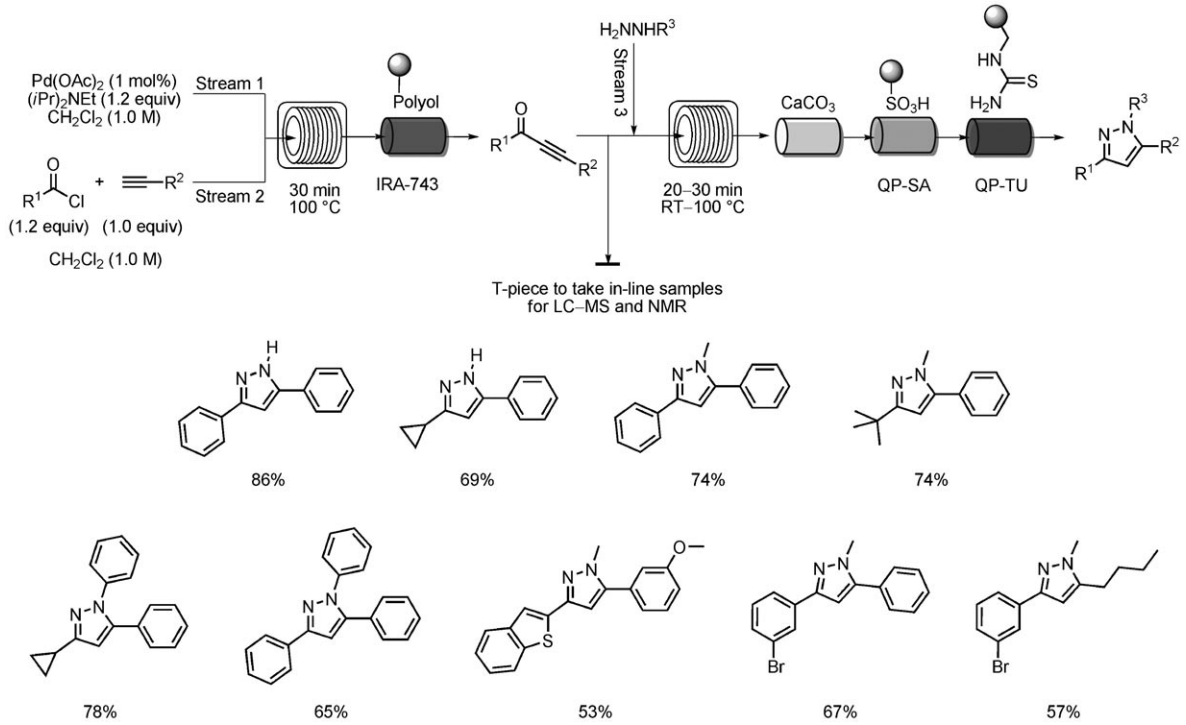
[a] Reactions conducted on a 2 mmol scale in dichloromethane for 30 min at 100 °C with $Pd(OAc)_2$ (1 mol %), iPr_2NEt (1.0 equiv), acid chloride (1.2 equiv) and terminal acetylene (1.0 equiv). [b] Small amounts of DMF were added to improve the solubility of the starting materials.

when aliphatic alkynes were used as starting materials, the yield for the corresponding yne–one dropped slightly. Similarly, not all substrates reacted smoothly. Esters and anhydrides did not undergo the desired coupling reaction with terminal acetylenes under the standard reaction conditions, whereas challenging substrates containing heterocyclic substituents, such as furans and thiophenes, led to yne–ones in high purity (>95% by ^1H NMR spectroscopy and LC–MS) and in good yield (Scheme 2).



Scheme 2. Formation of heterocyclic products.

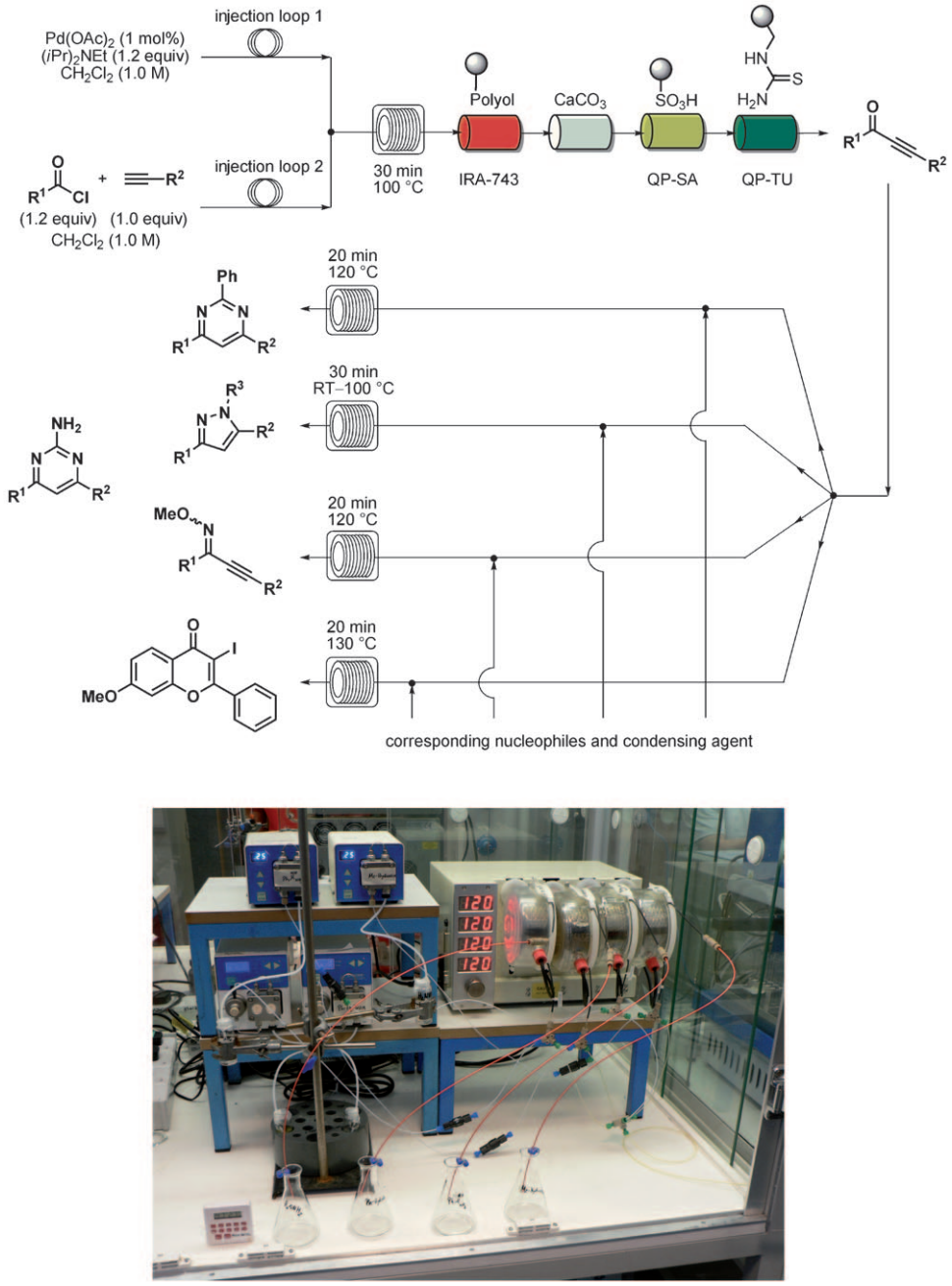
In an effort to expand the product diversity of these flow reactions, an additional pump providing a further hydrazine input stream (Scheme 3, stream 3) was used to prepare various pyrazoles in a single operation. The main stream containing the pure yne–one was processed as previously de-



Scheme 3. Two-step formation of pyrazoles from yne–ones.

scribed. However, the polyol IRA-743 resin needed to be placed after the yne–one formation to avoid amide formation by reaction of the hydrazine with residual acid chloride. After exiting the IRA-743 scavenger column, the yne–one solution passes into a T-piece that enables an in-line sample analysis. The use of an in-line UV detector can be used as a trigger for the pump that provides the hydrazine stream, thereby enabling a reduction in the amount of nucleophile required. The product was then mixed within a second T-piece with a solution of hydrazine (5.0 equiv) in ethanol (Scheme 3). The combined flow stream was then heated to 100 °C through a CFC (2×10 mL) to give a residence time of 20–30 min. Ammonium salts are formed during the reaction, but since the remaining acetylene did not hinder the heterocycle formation they both remained in the reaction mixture and were removed later in the sequence. Upon exiting the CFC, the pyrazole-containing flow stream was directed through a series of scavenger columns as shown in Scheme 3. Since the use of scavenger resin columns causes dispersion of the product, the carbonate, QP-SA and QP-TU columns were located at a late stage of the reaction sequence. Therefore, the high concentration of the yne–one stream is maintained and the mixing of which with the hydrazine is simplified. However, due to the excess of hydrazine used for the heterocycle formation, a larger amount of QP-SA scavenger resin was necessary (12 g for two experimental runs on a 2.0 mmol scale). Simple evaporation of the solvent provides pyrazole derivatives in a pure form (>95% by ^{1}H NMR spectroscopy and LC–MS) with good to excellent regioselectivity and good yield over two steps. Decreased regioselectivity was observed by conducting the reaction with phenyl hydrazine at 100 °C for 30 min. When methyl hydrazine was used at room temperature and when hydrazine was used at 80 °C then only one regioisomer was detected. The regioselectivity follows the literature precedent.[8] The reaction sequence is general and links an important coupling reaction to the generation of potentially hazardous and bioactive substrates and intermediates all contained within the flow system.

Although the above two-step sequence for the synthesis of pyrazoles proceeded smoothly, we wished to extend the sequence still further. We therefore generated the yne–one derivatives as shown in Scheme 1. After exiting the scavenger cartridges, the pure product line was divided into four equal side streams by using a splitter (Scheme 4). Each of the side arms was subsequently mixed through a T-piece with a stock solution of different nucleophiles to generate four different products based on the yne–one synthesised in the first step of the sequence. To obtain equal flow rates for each of the four channels, we attached commercial capillary peek tubing[7] (1/16×0.005) to the exit of each flow reactor acting as a tuneable back-pressure regulator (16 bar). By cutting the red tubing to the appropriate length, we equilibrated the four flow streams under the required reaction conditions. The relatively high back-pressure employed was required to maintain the dichloromethane in the liquid phase at the elevated reaction temperatures, thus avoiding decomposition of chemicals, which eventually leads to blockage of the flow reactor. In addition, we avoided cross-contamination of the nucleophile flow streams by using four one-way valves each connected to the four-way splitter device. The combined mixtures of yne–one and nucleophile



Scheme 4. Four-way split approach for the generation of a heterocyclic library.

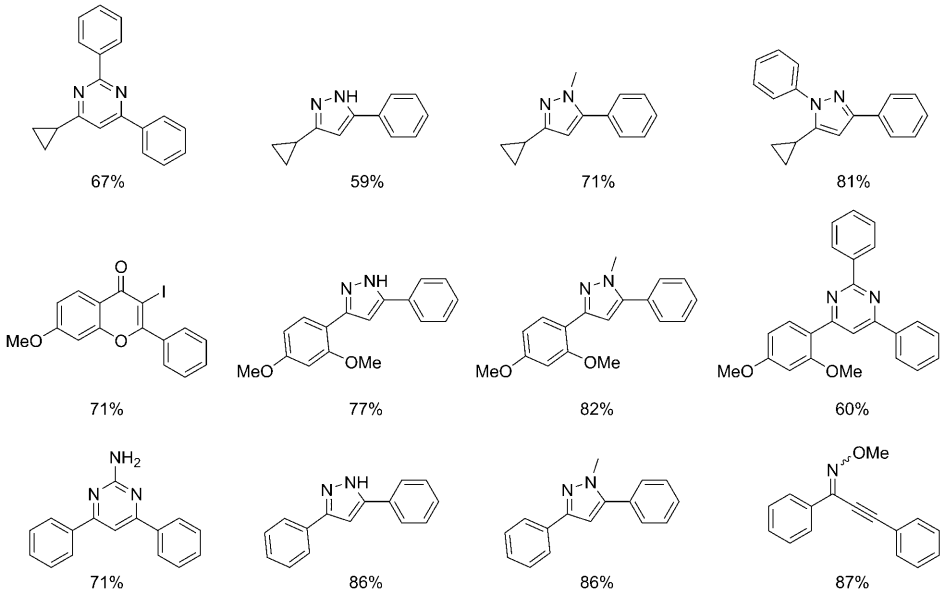
were heated independently to 120 °C through separate CFC units (10 mL) to give a residence time of 20–30 min. Upon exiting the CFC, the flow stream was rapidly cooled, collected and the solvent was evaporated. To remove the excess of the nucleophile used, the crude mixtures were dissolved in Et_2O and extracted with aqueous 1 N HCl. After evaporation of the solvent, the products were obtained in high purity (>95% by ^{1}H NMR spectroscopy and LC–MS) and good yield. In this way key intermediates, for example, pyrimidines, pyrazoles, oximes, guanidines and flavones, have been synthesised and required only a simple aqueous workup (Scheme 5).

For the synthesis of pyrimidines, the yne–one flow stream was mixed through a T-piece with a 1 M solution of benzamidine (5.0 equiv) in a solvent mixture of acetonitrile/ethanol (2:1). The reaction mixture was heated to 120 °C through a CFC (10 mL) to give a residence time of 20 min.

The formation of pyrazoles was achieved by mixing the yne–one flow line through a T-piece with a solution of hydrazine derivative in ethanol and the combined stream was then directed through PFA tubing to the CFC, which was heated to various temperatures depending on the hydrazine reactivity. Preparation of *N*-methyl-substituted pyrazoles proceeded smoothly at room temperature within 20 min. However, generation of N–H-pyrazoles required gentle heating at 80 °C for 30 min, whereas *N*-phenyl hydrazine required 30 min at 100 °C to give high conversion.

Since the 2-alkyn-1-one *O*-methyl oximes represent versatile intermediates for the synthesis of isoxazoles, we have also incorporated these in a continuous-flow process. Treatment of the oximes with various electrophiles (I_2, Br_2, ICl, PhSeBr) initiates the cyclisation to highly substituted isoxazoles. For the synthesis of 2-alkyn-1-one *O*-methyl oximes the yne–one flow line was mixed through a T-piece with a solution of $MeONH_2$·HCl (5.0 equiv) in methanol. The reaction mixture was then heated to 120 °C through a CFC (10 mL) to give a residence time of 20 min. The condensation product was obtained in quantitative yield as an *E*/*Z* mixture in a ratio of 3:1. Investigations into the continuous production of isoxazoles through a multi-component three-step sequence, that is, acylation, oxime formation and subsequent cyclisation, are currently on going in our laboratories.

For the preparation of guanidine derivatives, slightly harsher reaction conditions were required. The yne–one flow line was mixed through a T-piece with a solution of guanidine hydrochloride (5.0 equiv) in a solvent mixture of



Scheme 5. Formation of heterocycles by using the four-way split flow setup.

ethanol/water (1:1) followed by heating through a CFC maintained at 130 °C for 20 min.

Furthermore, we have generated a flavone derivative by using the four-way split flow setup. Mixing of the flow stream containing yne–one **3p** with a solution of ICl (5.0 equiv) in dichloromethane is achieved by using a T-piece. The ICl solution was injected into the yne–one line through an injection loop to avoid contact with the pump head. The combined reaction line was then directed into a CFC and the reaction proceeded at room temperature for 20 min. The product stream was collected in an aqueous solution of sodium thiosulfate to quench the excess electrophile. Phase separation gave the flavone derivative in excellent purity and good yield.

From the examples summarised in Scheme 5, it can be seen that the various transformations investigated proceed well and the procedure appears to be general. Furthermore, the process demonstrates the potential for library generation and rapid optimisation of reaction conditions in a safe, scalable and reproducible manner.

Further investigations, based on the use of yne–ones, into the synthesis of different heterocycles, incorporating the formation of terminal alkynes by using the Bestmann–Ohira reagent[9] developed previously in the group, are currently in progress. This approach offers the ability to produce a collection of heterocycles in a short time and is therefore of interest for pharmaceutical and medicinal applications.

In conclusion, we have presented the application of a modular flow reactor to achieve multi-component, multi-step transformations to give products in excellent purity without the necessity of common column chromatography. In the case of the four-way split approach, only a simple aqueous extraction was required to remove the excess nucleophile. The choice of appropriate scavenger materials ensures the removal of byproducts and impurities, which leads to the formation of the final product in high purity. In particular, we demonstrated the palladium-catalysed preparation of yne–ones and their further transformation into various heterocycles and 2-alkyn-1-one *O*-methyl oximes.

Experimental Section

General description for the synthesis of yne–ones in flow (Scheme 1): Two flow streams were driven by the Vapourtec R2+/R4. Stream 1 contained a solution of $Pd(OAc)_2$ (1 mol%) and $(iPr)_2NEt$ (1.0 M, 1.0 equiv, 2 mmol) in CH_2Cl_2, whilst the terminal acetylene (1.0 M, 1.0 equiv, 2 mmol) and the acid chloride (1.0 M, 1.2 equiv, 2.4 mmol) in CH_2Cl_2 were dispensed from stream 2. These streams were mixed through a T-piece before entering the CFC for 30 min at 100 °C. The stream was then directed through a series of scavenger columns: firstly IRA-743, secondly $CaCO_3$, thirdly QP-SA and finally QP-TU. Typically, IRA-743 (3.0 g), $CaCO_3$ (3.0 g), QP-SA (5.0 g) and QP-TU (2.0 g) were used to perform three consecutive experimental runs on a 2.0 mmol scale to obtain clean reaction products. A 100 psi back-pressure regulator ensured the system was pressurised before eluting into a reaction flask. Finally, the solvent was concentrated in vacuo to provide the desired yne–one derivative.

General description for the synthesis of pyrazoles from yne–ones in flow (Scheme 3): The yne–one derivatives were prepared as described above and in Scheme 1. The stream containing the yne–one (1.0 equiv, 2 mmol) followed the standard pathway and was passed through an IRA-743 scavenger column at a total flow rate of 500 μL min^{-1} driven by the Vapourtec R2+/R4 unit. This stream was mixed with a stream of hydrazine derivative (5.0 equiv, 10 mmol) in EtOH (1.0 M) through a second T-piece before the combined flow stream was passed through the second CFC (20–30 min residence time; RT–100 °C) and then directed through a series of scavenger columns as shown in Scheme 1. Finally, a 100 psi back-pressure regulator was used before eluting into a reaction flask. The solvent was removed in vacuo to provide the desired product.

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Keywords: alkynes · flow chemistry · heterocycles · supported reagents · yne–ones

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