Continuous-Flow Synthesis

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Multistep Synthesis Using Modular Flow Reactors: Bestmann–Ohira Reagent for the Formation of Alkynes and Triazoles**

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In the late 1990s we initiated a research programme to develop methods to assist in the automation of organic synthesis.[1] While we recognize the flexibility and impressive power of modern molecular assembly it is not without its problems, especially during extended synthetic sequences common to the preparation of many drug substances or complex natural products. The issues that arise are not simply due to atom and step economy of the process (which are obviously important) but to many other factors. The main one of these being the number of additional unit operations needed to deliver pure products. Moreover, extended reaction optimization is often required which involves both routine and repetitive experimentation. All of these demand a skilled workforce and are time-consuming in their execution. We began our efforts in the area by developing the concept of immobilized reagents for multistep processes,[2] including applications to complex natural-product synthesis.[3] The aim was to achieve chemical transformations without the use of conventional work-up procedures of chromatography, crystallization, distillation, or water washes typical of batch-mode operations. These methods were combined with immobilized scavenging and reaction quenching, together with fast serial processing using microwaves[4] or catch-and-release methods and phase-switching techniques[5] leading to many further synthetic opportunities. However, it was always part of our vision that additional efficiency gains could be achieved by transfering these methods to multistep, continuous, flow-based chemical processing using computer-controlled modular pumping systems with flow tubes packed with the immobilized reagents and scavengers.[6,7] These devices avoid traditional work-up protocols allowing progression of the pure product flow stream to the next step of the synthetic process. The flow-based equipment used in this work accommodates extended working hours, in-line reaction monitoring and optimization, high pressure through superheating of solvents, containment of hazardous or transient species and ready scalability.

Here we report on the application of the Bestmann–Ohira reagent (**1**)[8] for the preparation of terminal acetylenes during flow conditions using commercially available pumping systems and heated flow coils in combination with a suite of packed Omnifit glass tubes[9] containing appropriate scavenger materials to ensure the quality of the exiting product. Furthermore, we have incorporated the process in an extended sequence of reactions that allows for the eventual conversion of alcohols, azides and the Bestmann–Ohira reagent to afford triazoles by multicomponent couplings through multistep operation of the flow equipment.

In order to conduct the flow experiments we chose a commercially available synthesis platform, the Vapourtec R2+/R4 combination (Figure 1).[10] While this equipment

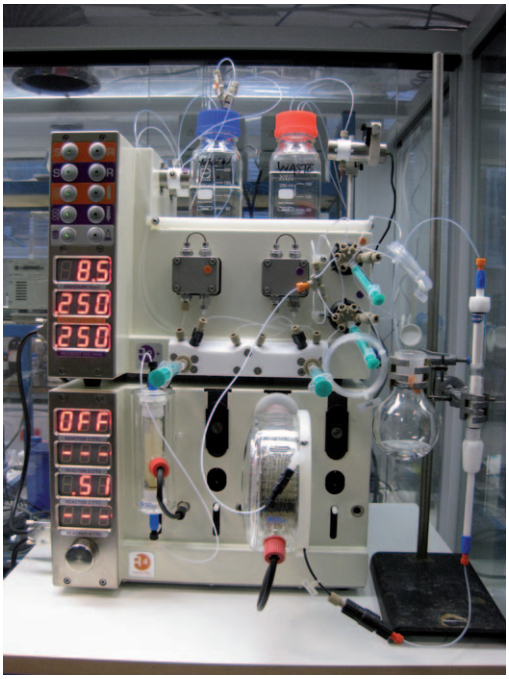

Figure 1. Vapourtec R2+/R4 flow system.

served our purposes well, any similar HPLC or syringe pumping device could in principle suffice. The Vapourtec integrates a twin-pumping and reagent selection module as the top-stage unit with an independent controlled four-channel air-circulated heating lower stage component. A low pressure input selection valve is used to route either solvent or bulk stock solutions directly to the self-regulating Knauer K-120 HPLC pumps. Two additional Rheodyne 6-port-2 position switching valves can be used to introduce

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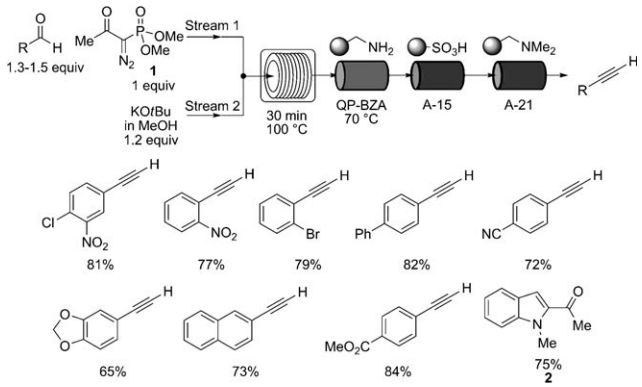
reagents or substrates to the main flow line through individual sample loop arrangements.

Pressure within the system is maintained using an in-line 100 psi back-pressure regulator. 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 convection-flow coil (CFC) which can be precisely heated up to 150 °C with further use of back-pressure regulation should superheating of solvents be required. Following exit from the CFC the rapidly cooled flow line may then be directed to various scavenger (or reagent) cartridges which often consist of Omnifit glass columns packed with appropriate immobilized species. The final flow stream can be collected and evaporated to afford the product or linked to a UV-triggered liquid handling unit to automate the whole process. Crucial to the successful operation of the system is the ability to adjust the reaction parameters, especially flow-rate, temperature, and pressure in real-time. Furthermore, with appropriate software, rapid optimization and reaction profiling can be achieved along with enhanced safety monitoring leading to the potential for 24/7 working mode. Finally, useful practical conditions were determined that involved introduction of an appropriate aldehyde (1.3 equiv) together with the Bestmann–Ohira reagent (**1**) (1 equiv) in methanol (or MeCN) through an injection loop as stream 1 which was then mixed through a T-piece with potassium *tert*-butoxide (1.2 equiv) in methanol as stream 2 (Scheme 1). The mixture was then heated to 100 °C through a



Scheme 1. Flow synthesis of terminal alkynes.

CFC (10 mL) to give a residence time of around 35 min. On exiting the CFC the flow stream was directed through a series of scavenger columns. Firstly, a tube packed with a Quadrapure-benzylamine resin (QP-BZA) operating at 70 °C effectively removed any excess aldehyde, subsequently the next Amberlyst-15 sulfonic acid (A-15) cartridge removes the base and protonates any phosphoric residues coming from the reagent. Finally, the Amberlyst-21 dimethyl amine (A-21) resin cleans up and removes any remaining acid material to give a pure acetylene product stream (Scheme 1, yields of isolated products based on transformation of compound **1**).

The whole system is maintained under positive pressure using an in-line back-pressure regulator. In typical runs of around 1.5 mmol of aldehyde input we used 3.5 g of QP-BZA and a total of 3.5 g of mixed A-15 and A-21 to isolate the clean reaction products in the yields indicated (Scheme 1). From the examples reported it should be noted that halides, nitro compounds, esters, and cyanides may be tolerated under the reaction conditions. However, when *N*-methyl-2-formylindole was used as a starting material the methyl ketone (**2**) was isolated in 75 % yield rather than the expected corresponding acetylene. We rationalized that the more polar acetylene undergoes further hydrolysis using residual water catalyzed by the A-15. Ion exchange resins such as A-15 are well known to be hygroscopic in nature and difficult to completely dry. In support of this if the reaction scheme was modified to replace the A-15 by an alumina-filled cartridge then polar aldehyde substrates were smoothly converted to the corresponding acetylenes (Figure 2) in high purity (> 95 % by ^{1}H NMR) and good yield.

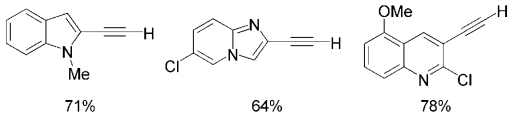
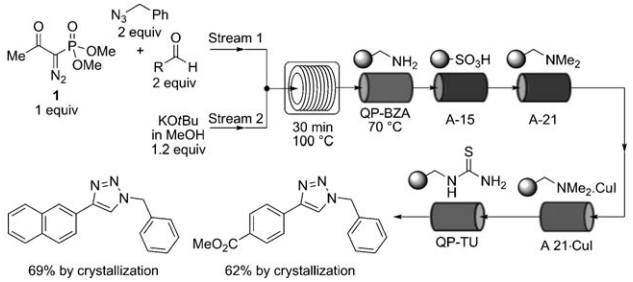


Figure 2. Formation of heterocyclic examples by substitution of A-15 for alumina.

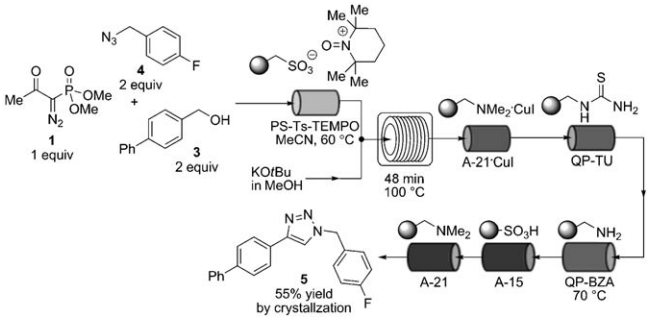
The next advance arises from our interest in achieving further use of the synthesized products through multicomponent, multistep operation of the flow equipment. Accordingly when the first input stream of aldehyde and reagent (**1**) additionally contains an azide in MeCN (Scheme 2) the reactions follow the normal pathway after mixing but on



Scheme 2. Two-step formation of triazoles from aldehydes.

passage through the CFC and scavenging columns the initial acetylene product then undergoes a further cycloaddition with the azide.[11] This is achieved by flowing through an immobilized copper(I) catalyst using A-21 (A-21·CuI) as a basic support material to give the triazole product.[12] Further scavenging is necessary to ensure any leached copper during this cycloaddition processes is effectively removed in one process through a Quadrapure-thiourea (QP-TU) flow tube. While only two examples were examined using this concept (Scheme 2) we believe the reaction to be fairly general and links together an important product coupling process (azide and acetylene) with the preparation of potentially hazardous substrates (azides and acetylenes) all contained within the flow system.

While the above sequence of reactions proceeded well we felt that a further extension was merited. Since aldehydes as starting materials are sometimes less available than the precursor alcohols and are prone to over-oxidize, form hydrates, or in some cases polymerize, we devised a new flow strategy to triazoles beginning with alcohols as the primary input (Scheme 3).



Scheme 3. Three-step synthesis of a triazole **5** from alcohol **3**.

In this configuration an alcohol (**3**) is introduced to a flow reaction loop co-mixed with the Bestmann–Ohira reagent (**1**) and an appropriate azide (**4**) in MeCN. This mixture passed through an Omnifit tube packed with pre-activated PS-TsO-TEMPO at a metered flow rate of 200 μL min^{-1} at 60 °C which selectively oxidizes the alcohol to the corresponding aldehyde in situ without affecting the other components of the mixture. The output from this column was then mixed in the normal way with potassium *tert*-butoxide in methanol through a T-piece and then onto the CFC operating at 100 °C. This was followed by passage through A-21·CuI reagent to bring about the cycloaddition reaction. Four in-line scavenger flow tubes in the sequence QP-TU→QP-BZA→A-15→A-21 then completed the product clean-up and delivered the triazole (**5**) in 55 % yield in a purity of over 95 % as determined by both ^{1}H NMR and LCMS.

In conclusion we have demonstrated the effectiveness of the modular flow reactors to work in combination with a variety of immobilized reagents and scavenger materials to achieve multicomponent, multistep coupling reaction to give clean products without the need for intermediate work-up or manipulation. In particular we demonstrated how a relatively complicated mixed component and by-product reaction stream could be controlled and automated to facilitate the preparation of acetylenes using the Bestmann–Ohira reagent and these products could be further transformed to triazoles.

Experimental Section

General description for the synthesis of terminal alkynes in flow: Two flow streams driven by the Vapourtec R4/R2+; stream 1 containing a solution of the aldehyde (0.13 M, 1.3 equiv, 1.3 mmol) and the Bestmann–Ohira reagent (**1**) (0.1 M, 1 equiv, 1 mmol) in MeOH or MeCN and stream 2 containing the methoxide source (KO*t*Bu in MeOH, 0.12 M, 1.2 equiv, 1.2 mmol). These were mixed at a T-piece before entering the CFC for 30 min at 100 °C. The stream was then directed through a series of reagent columns containing QP-BZA (3.5 g) heated to 70 °C and then a mixed bed of A-15/A-21 (3.5 g in total). A 100 psi BPR ensured the system was pressurized, before eluting into a reaction flask. Finally, the solvent was concentrated in vacuo to provide the desired alkyne.

Formation of triazoles from aldehydes: Two flow streams driven by the Vapourtec R4/R2+; stream 1 containing a solution of the aldehyde (0.2 M, 2 equiv, 2.0 mmol), azide (0.2 M, 2 equiv, 2.0 mmol), and the Bestmann–Ohira reagent (**1**) (0.1 M, 1 equiv, 1 mmol) in MeCN and stream 2 containing the methoxide source (0.12 M, 1.2 equiv, 1.2 mmol). These were mixed at a T-piece before entering the CFC for 30 min at 100 °C. The stream was then directed through a series of reagent columns beginning with QP-BZA (3.5 g) heated to 70 °C and a mixed bed of A-15/A-21 (3.5 g in total), A-21·CuI (3 g), and QP-TU (500 mg). A 100 psi BPR ensured the system was pressurized, before eluting into a reaction flask. Finally, the solvent was reduced in vacuo and crystallization provided the desired 1,2,3-triazole.

Formation of triazole **5** from alcohol **3**. A stream driven at 200 μL min^{-1} by the Vapourtec R4/R2+ containing a 0.1 M MeCN solution of the biphenyl-4-ylmethanol (**3**) (0.1 M, 184 mg, 1 mmol), 1-(azidomethyl)-4-fluorobenzene (**4**) (0.1 M, 151 mg, 1 mmol), and the Bestmann–Ohira reagent (**1**) (0.05 M, 86 mg, 0.5 mmol) was passed through a column of pre-activated PS-Ts-TEMPO heated to 60 °C and then through a 100 psi back-pressure regulator. This stream was mixed with a stream of KO*t*Bu in MeOH (0.1 M.) in a T-piece before the combined stream was passed through two CFC's (19 mL in total, 48 min residence time) heated to 100 °C then directed through a series of reagent columns of A-21·CuI (3 g), QP-TU (500 mg), QP-BZA (3.5 g, heated to 70 °C) then a mixed bed of A-15/A-21 (6 g in total). Finally, a 100 psi back-pressure regulator was used before eluting into a reaction flask. The solvent was removed in vacuo and crystallization provided the desired 1,2,3-triazole **5**. (90 mg, 55 % yield). **5**: ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 8.68$ (s, 1 H, Aryl-H), 7.93 (d, $J = 8.3$ Hz, 2 H, Aryl-H), 7.74 (d, $J = 8.8$ Hz, 2 H, Aryl-H), 7.70 (dd, $J = 8.3$, 1.1 Hz, 2 H, Aryl-H), 7.49–7.41 (m, 4 H, Aryl-H), 7.39 (m, 1 H, Aryl-H), 7.23 (t, $J = 9.1$ Hz, 2 H, Aryl-H), 5.65 ppm (s, 2 H, CH$_2$); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 158.3$ (d, $J = 246.0$ Hz, CF), 146.7 (C), 139.9 (C), 139.8 (C), 132.6 (d, $J = 3.2$ Hz, C), 131.2 (d, $J = 8.4$ Hz, CH), 130.1 (C), 129.9 (CH), 128.4 (CH), 128.0 (CH), 127.4 (CH), 126.6 (CH), 122.5 (CH), 116.4 (d, $J = 21.5$ Hz, CH), 53.1 ppm (CH$_2$); IR (thin film): $\tilde{\nu}_{max}$ = 3037 (w), 1607 (m), 1513 (m), 1483 (m), 1409 (m), 1317 (w), 1237 (m), 1217 (m), 1156 (m), 1044 (m), 975 (w), 842 (m), 805 (m), 761 (s), 724 (m), 690 cm^{-1} (m); LCMS: $R_t = 4.92$ min; $[M+H] = 330.12$; HRMS ($[M+H]$, $C_{21}H_{17}N_3F$) calculated 330.1407, found 330.1395.

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