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[3 + 2] Cycloaddition of acetylenes with azides to give 1,4-disubstituted 1,2,3-triazoles in a modular flow reactor

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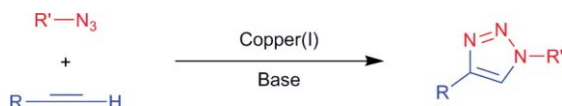
The cycloaddition of acetylenes with azides to give the corresponding 1,4-disubstituted 1,2,3-triazoles is reported using immobilised reagents and scavengers in pre-packed glass tubes in a modular flow reactor.

Introduction

In this and the following communication,¹ we describe applications and further concepts for the use of modular continuous flow reactor systems. These methods are gaining popularity for the preparation of fine chemicals at the micro- and meso-fluidic levels² as well as for small-scale manufacturing production.³

Our own efforts in this area have focused on flow hydrogenation,⁴ microwave-assisted flow chemistry⁵ and the use of microfluidic chips together with pre-packed tubes containing immobilised reagents and scavengers to effect the multi-step synthesis of natural products,⁶ peptides⁷ and medicinally relevant heterocyclic systems.⁸ The appropriate use of flow techniques allows direct access to target compounds in high purity, avoiding technically demanding and time consuming work-up and purification procedures common to conventional batch-chemistry processes.

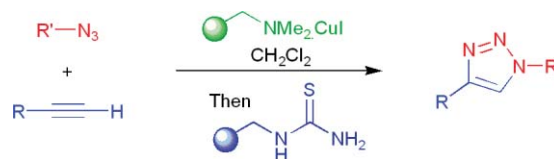
The pioneering work of Huisgen⁹ on the [3 + 2] cycloaddition of acetylenic compounds with azides leading to 1,4-disubstituted 1,2,3-triazoles, followed by recent modifications by Mendal¹⁰ and Sharpless (Click chemistry),¹¹ has become an important strategy in a variety of applications; including organic synthesis (Scheme 1), material science and cell biology.¹² In this paper, we report on the use of a small footprint modular flow reactor to accomplish this useful transformation on gram scale with a variety of acetylene and azide building blocks. As reported in our previous communications describing flow-chemistry applications,^{4,8} the flow reactor and pumping system is based on a modified automated HPLC unit and fraction collector. The work described herein was carried out using the Syrris AFRICA^{®13} flow pumping system, a commercially available platform which can be readily adapted to incorporate the necessary sequence of pre-packed flow columns when combined with a Vapourtec R4^{®14} column heater unit.



Scheme 1 Copper(I)-mediated 1,2,3-triazole formation.

Results and discussion

Recently, Girard¹⁵ described the successful immobilisation of a copper(I) iodide species to a solid support, an Amberlyst A-21 free base¹⁶ (PS-NMe₂), and applied it as a catalyst in a batch-mode cycloaddition reaction. Our own experiments under flow conditions reported here also use a copper-modified Amberlyst A-21 resin, which produces the highest loading resin (1.33 mmol g⁻¹ by mass increase) whilst retaining the basic functionality necessary for the mechanism of the cycloaddition reaction.¹⁷ As the copper is only attached to the resin by weak co-ordination to the amine lone pair, the copper species is expected to leach to some extent into the solution phase. Indeed this is confirmed by the blue or green tinted solutions obtained when these reactions are run in batch mode. This problem is easily solved by the use of Quadrapure[™] TU (QP-TU) metal-scavenging resin.¹⁸ Stirring the resin with the batch solution results in complete removal of the colour from the solution in less than 30 minutes (Scheme 2).



Scheme 2 Improved batch method.

Our initial investigations into a flow-based process revealed that excess azide was required to drive the reaction to completion in only a single pass through the flow reactor. The excess azide, contaminating the triazole product, could be removed by flowing the reaction solution through a column of phosphine resin (PS-PPh₂),¹⁹ thus capturing the azide onto the solid phase as an iminophosphorane *via* a Staudinger reaction (Scheme 3).^{6b}

In practice, the azide (0.15–0.2 M, 1.5–2 equiv.) and terminal alkyne (1 equiv.) components are dissolved in DCM and injected into a manual load reagent loop, which is connected in-line with the flow system. Multiple reagent stores can be configured in this way for successive iterative additions of different reagent combinations. The contents of a particular reagent loop (typically 1 mL or 5 mL) are then introduced into the flow stream and pumped through the columns containing the supported reagents, generating the specified 1,2,3-triazole product.

Glass Omnifit[®] columns²⁰ containing the PS-NMe₂, CuI complex (0.1 equiv), QP-TU (100 mg) and then PS-PPh₂ (3 equiv.) are

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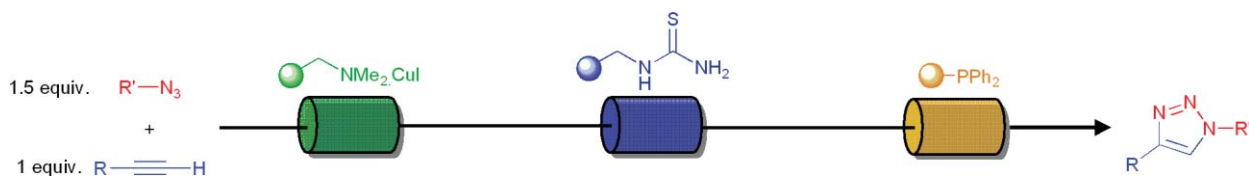


Table 1 Products obtained

Entry number	Product	Isolated yield	Entry number	Product	Isolated yield
1		93%	8		93%
2		85%	9		88%
3		85%	10		91%
4		91%	11		81%
5		89%	12		85%
6		87%	13		70%
7		75%	14		88%

placed in series. The columns are prewashed with DCM, then the reagent solution is introduced at 30 $\mu\text{L min}^{-1}$. After the calculated time for the starting materials to have passed through all of the columns has elapsed (time equivalent to filling the reagent loop three times), the flow rate is increased to 250 $\mu\text{L min}^{-1}$ to elute the product from the columns. A back-pressure regulator was placed in-line at the exit of the flow stream and set to ~ 7 bar (100 psi) to ensure a uniform flow stream. The resulting solution was then concentrated using a Vapourtec V-10[®] solvent evaporator,²¹ providing a solid product ready for analysis. Following this procedure, the products in Table 1 were obtained without the need for further purification; all purities were assessed as being >95%, as determined by LC-MS and ¹H- and ¹³C-NMR.

Normally the flow reactions were operated to deliver 20–200 mg of product; however in one experiment 1.5 g of the triazole (entry 2, Table 1) was produced as a continuous flow process after 3 hours. This modified process used 2 equiv. of propargylic alcohol, 400 mg of PS-NMe₂, CuI and 200 mg of QP-TU, and was flowed at 100 $\mu\text{L min}^{-1}$, followed by washing at 250 $\mu\text{L min}^{-1}$. The excess propargylic alcohol was removed *in vacuo*, to give the product in 85% yield and >95% purity.

In addition to the potential scalability demonstrated above, this continuous flow system has additional advantages over conventional batch procedures for the preparation of 1,2,3-triazoles. For example, both the acetylenes (prepared *via* a Sonogashira reaction), and the azides^{6b} can be generated in-line by flow-chemistry methods. From a safety view point, this ability to form and trap reactive intermediates in-line without manual intervention by the chemist reduces their exposure to such potentially explosive and highly toxic chemical inputs.

Furthermore, the nature of the flow process means that the reactants are exposed to a much higher apparent concentration of the copper catalyst, allowing reduced catalyst loading. Finally, due to the very short residence/reaction times and the easy exclusion of oxygen from the system, Glaser homocoupling, a common side reaction in this type of synthesis, is prevented ensuring that the products require no further purification.

Conclusion

In conclusion, the application of a modular flow reactor to the continuous preparation of 1,4-disubstituted 1,2,3-triazoles described above illustrates further the potential of these systems for the on-demand preparation of chemical substances.

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19 PS-PPh₃; triphenylphosphine polymer-bound [14664]. Commercially available from Sigma-Aldrich. Website: <http://www.sigmaaldrich.com>.

20 Commercially available Omnifit[®] glass chromatography columns with adjustable height end pieces (plunger). Typically, the polymer-supported reagent is placed in an appropriately sized Omnifit[®] column, usually 6.6 mm bore by 150 mm length, or shorter, and the plungers are adjusted to relevant bed heights and the polymer swelled/washed with solvent. Website: <http://www.omnifit.com>.

21 Vapourtec V-10[®] rapid solvent evaporator. Commercially available from Biotage. Website: <http://www.biotage.com>.