Synthesis of 3-Nitropyrrolidines via Dipolar Cycloaddition Reactions Using a Modular Flow Reactor

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Abstract: The generation and subsequent use of unstabilised azomethine ylides in dipolar cycloaddition reactions within a flow microreactor is demonstrated. The 3-nitropyrrolidines produced were furthermore subjected to chemoselective hydrogenation reactions using the H-Cube® system. To ensure product purities in excess of 90–95%, immobilised scavengers were successfully employed.

Key words: microreactor, flow chemistry, pyrrolidine, dipolar cycloaddition, solid-supported reagents

The synthesis of highly functionalised heterocyclic compounds is of central importance to most modern medicinal chemistry programmes[1] since these building blocks are readily manipulated to compounds with favourable pharmacophoric properties. Accordingly, the synthetic chemist is expected to deliver these entities in a flexible, high-yielding fashion yet avoiding time-consuming purification procedures as well as hazardous or obnoxious chemical inputs wherever possible.[2] In recent studies we[3] and others[4] have attempted to address some of these issues by using modular flow reactors in concert with automation methods and in-line immobilised reagents and scavengers packed into glass columns to effect clean product formation.

We have already demonstrated the success of these methods in the preparation of various heterocyclic scaffolds such as oxazoles,[5] oxazolines,[6] pyrazoles,[7] triazoles,[8] thiazoles, and imidazoles[9] using a variety of flow microreactors. Here we show how these devices can be applied further to the efficient assembly of 3-nitropyrrolidines and related structures as potentially useful building blocks for synthesis since pyrrolidine-based compounds have been shown to display a wide variety of biological activities.[10] These structures can be found in alkaloids such as nicotine or in amino acids typified by proline, as well as many drug substances such as the anticonvulsant Levetiracetam or the oral antihyperglycemic agent Vildagliptin (Figure 1). In addition, many chiral pyrrolidines have been described as privileged structures with numerous applications in the field of asymmetric organocatalysis.[11]

In our investigations below we make use of the R2+/R4 flow system commercially available from Vapourtec.[12] This modular platform consists of a dual pumping unit which delivers the dissolved starting materials into a mixing device and directs the combined reaction stream through a selection of convection flow coils (CFC) and/or glass tubes[13] filled with solid-supported reagents and scavengers that can be maintained at a desired temperature and pressure. Furthermore, this system can be run with the Flow Commander software also available from Vapourtec[12] allowing for the use of a front-end liquid handler and a UV-directed fraction collector.

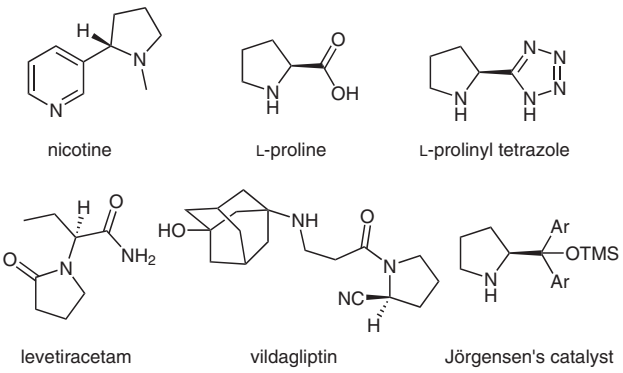

Figure 1 Biologically and synthetically interesting pyrrolidines

For the preparation of 3-nitropyrrolidine derivatives and in order to access more structural variety in the pyrrolidine ring, we have chosen to use a dipolar cycloaddition process involving nonstabilised azomethine ylides and nitro alkenes.[14] This reaction also readily allows for the subsequent differentiation of both nitrogen functionalities and hence increases the flexibility towards any subsequent transformation (Scheme 1).

In order to perform initial cycloaddition studies, toluene was selected as the preferred solvent to dissolve both the nitro alkene as well as the commercially available *N*-(methoxymethyl)-*N*-(trimethylsilyl)benzylamine coupling partner at concentrations up to 0.2 M. The further addition of 1.0 equivalent of TFA to the nitro alkene solution was found to be crucial in order to generate the dipole even at the elevated temperatures of the flow reaction. When these stock solutions were mixed in a standard static mixing tee and flowed through a 10 mL CFC heated to 120 °C, with a residence time of between 30–90 minutes, the corresponding 3-nitropyrrolidine was formed. Subsequent optimisation led to the observation that acetonitrile, in most cases, was a superior solvent to toluene as it was

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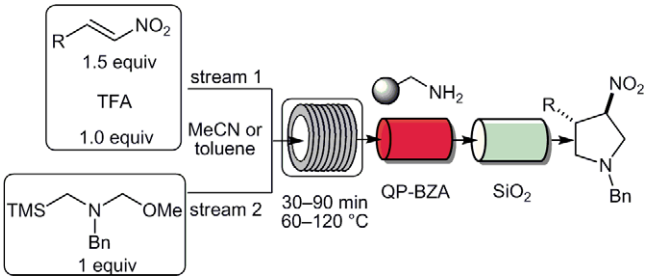
more easily removed, and the starting materials could be prepared at higher concentrations (up to 0.5 M). Furthermore, real time product analysis via LC-MS was more convenient in acetonitrile as opposed to toluene due to the high UV absorption of the toluene signal at key monitoring wavelengths.



Scheme 1 Optimised flow set-up for formation of 3-nitropyrrolidines

We have also shown that by passing the exiting flow stream through a glass column packed with an immobilised benzylamine scavenger resin (QP-BZA,[15] 2.5 equiv) followed by a plug of silica gel (1 cm path length), it was possible to remove any unreacted nitro alkene and simultaneously release the desired nitropyrrolidine from its initially formed TFA salt. By using the above set of conditions a small collection of 3-nitropyrrolidines (Figure 2) was quickly generated using temperatures ranging from 60–120 °C and affording high-purity products in good isolated yields.

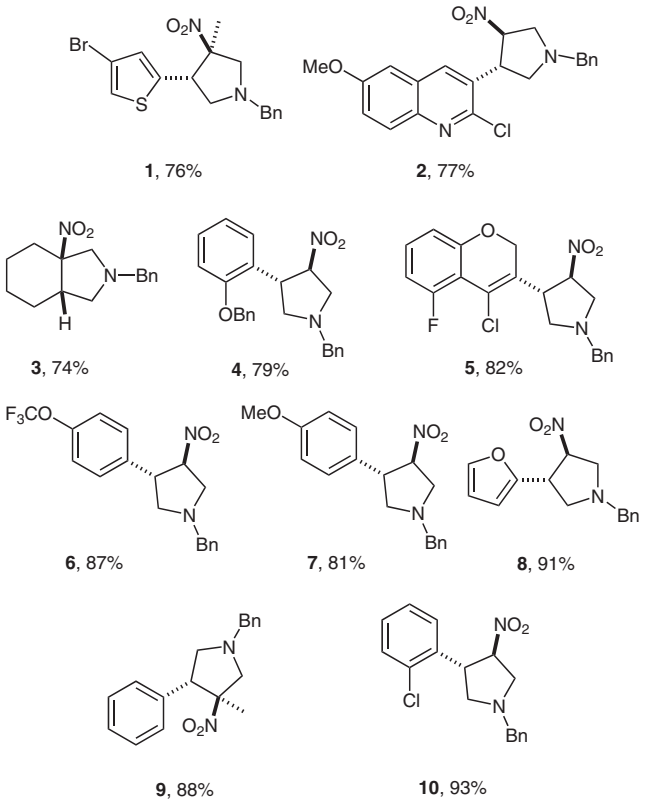


Figure 2 Collection of 3-nitropyrrolidines prepared in flow

By being able to carefully adjust the reaction parameters of the flow reactor more sensitive nitropyrrolidines such as those with labile halides on heterocyclic ring systems (**1**, **2**, and **5**) or the bicyclic octahydroisoindoline derivative **3** could also be readily obtained in high yield.

Having prepared this first set of nitropyrrolidine derivatives we wished to further simplify our protocol by avoiding the use of the strong TFA acid in order to generate the reactive dipole. In relation to some of our earlier studies on monolithic reactor cartridges we were attracted by the concept of a reloadable fluoride monolith which we had previously found very powerful in a number of trifluoromethylation reactions using Ruppert's reagent ($TMS-CF_3$) in a flow process.[17b] After preparation and charging of this ion-exchange monolith according to previously published literature procedures[3e,16,17] we started our investigations in the azomethine ylid cycloaddition chemistry. We were pleased to confirm that indeed high conversions of the starting materials could be achieved even at reduced temperatures of between 50–80 °C in comparison to our original procedure. Furthermore, we were able to reduce the overall reaction time including the QP-BZA-assisted removal of excess nitro alkene starting material to less than one hour. Using the fluoride monolith also resulted in increased yields of 3-nitropyrrolidine products when compared to the previous method using TFA (Figure 3, compounds **1**, **3**, **9**). Encouraged by these new results we expanded the initial work by varying the type of dipolarophile. Again, a small collection of differently substituted pyrrolidine products was prepared (Figure 3) including interesting substituents such as sulfonates, phosphonates, and esters. Starting from D-menthyl acrylate we also investigated the impact of a chiral auxiliary on the diastereomeric ratio of the product outcome. However, under all conditions evaluated (time, temperature, stoichiometry, and solvent modifications) only a 1:1 mixture of diastereomers was ever observed by NMR analysis.

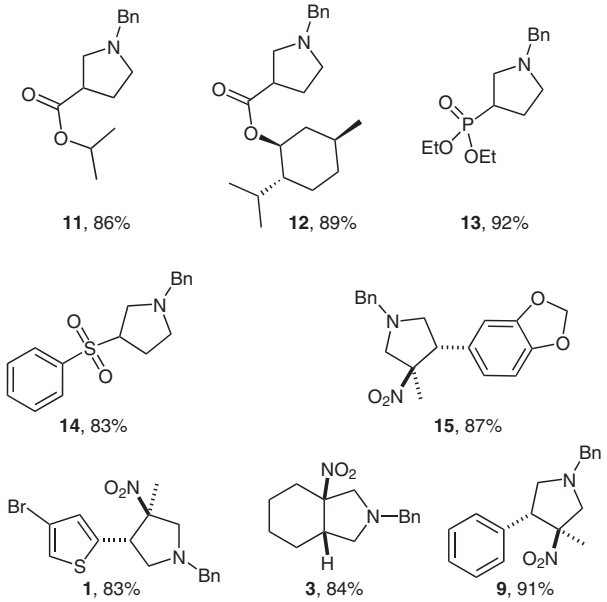
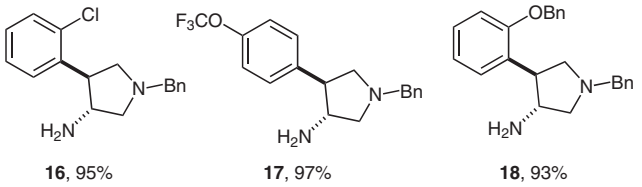


Figure 3 Pyrrolidines prepared using a fluoride monolith in flow

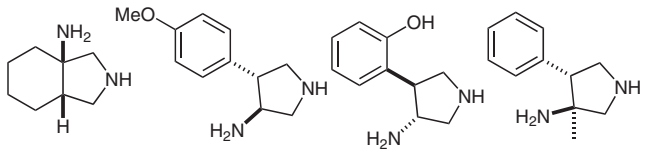
To further elaborate these 3-nitropyrrolidine derivatives into other building blocks we exploited their inherent chemoselectivity. This was accomplished by selective hydrogenation of the nitro group over the benzyl group using the H-Cube® flow hydrogenator.[18] Employing an ethanol–ethyl acetate (1:1 mixture) solvent system the clean reduction of the nitro group to the corresponding amine was achieved on passage through a Raney Nickel filled cartridge at 60 °C in the presence of catalytic amounts of acetic acid (Figure 4).



16, 95% **17**, 97% **18**, 93%

Figure 4 Raney nickel mediated reduction of nitropyrrolidines

Alternatively, when the flow catalyst cartridge was filled with 10% Pd on charcoal both reduction of the nitro group and concomitant removal of the benzyl protecting group can be realised. All of the resulting 3-aminopyrrolidines were obtained with no loss of stereochemical integrity in very good yields and purities after removal of the acetate counterion. This was easily achieved by elution of the output stream through a column of polymer-supported carbonate[19] (1.0 equiv based on 3-nitropyrrolidine starting material) followed by solvent removal (Figure 5).



19, 90% **20**, 97% **21**, 93% **22**, 95%

Figure 5 Pd/C-mediated reduction and debenzylation of 3-nitropyrrolidines

In summary, we have demonstrated a particularly convenient preparation of 3-nitropyrrolidines and related compounds using a flow chemical reactor and appropriate inline workup cartridges to avoid conventional clean up procedures.[20] The further elaboration of the products by chemoselective hydrogenation chemistry using a flow hydrogenator was also achieved to give a new range of building blocks for organic synthesis programmes.

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(13) 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 10 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.
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(18) The H-Cube® flow hydrogenator is commercially available from ThalesNano Nanotechnology Inc., Graphisoft Park, H-1031 Budapest, Záhony u. 7, Hungary; Website: http://www.thalesnano.com.
(19) MP-carbonate is a basic anion-exchange resin (3.2 mmol/g) commercially available from Biotage. Website: http://www.biotage.com.
(20) In a typical flow experiment stock solutions of the alkene component (1.5 equiv, containing 1.0 equiv TFA in MeCN) and *N*-(methoxymethyl)-*N*-(trimethylsilyl)benzylamine (1.0 equiv in MeCN) were prepared and injected into the two individual sample loops of the R2+ unit of the Vapourtec system. The resulting streams were mixed in a static mixing tee and then directed into a flow coil (10 mL volume, 1.0 mm i.d., temperature 60–120 °C) mounted on the R4 unit to give residence times between 30–90 min depending on the reactivity of the substrate used. After leaving this coil the reaction mixture was directed into a glass column (typically 10 cm length, 10 mm bore) containing the scavenging resin (QP-BZA, 2.5 equiv and a 1 cm plug of silica). The purified product was then collected and isolated after solvent removal.
For Experiments Involving the Use of the Fluoride Monolith
The two starting materials were dissolved at the same concentrations in MeCN and injected into the two corresponding sample loops of the R2+ [alkene 1.5 mmol in MeCN and *N*-(methoxymethyl)-*N*-(trimethylsilyl)benzylamine 1.0 mmol in MeCN]. After mixing both streams in a T-piece the resulting mixture was directed into the fluoride monolith (in a column; 10 cm length, 15 mm bore, ca. 12 mmol fluoride) heated between 50–80 °C with a combined flow rate of 200 μL/min. The exiting stream was then passed through a glass column (10 cm length, 10 mm bore) containing the scavenging resin (QP-BZA, 2.5 equiv) for final in-line purification.
For the chemoselective reduction of 3-nitropyrrolidines using the H-Cube® system in full hydrogen mode the starting material was dissolved in a EtOH–EtOAc (1:1) solvent system (0.2–0.5 M; containing catalytic amounts of AcOH) and passed through the appropriate catalyst cartridge heated to 60 °C with a flow rate of 1.0 mL/min. In order to remove the acetate counterion the out flow stream is subsequently directed through a glass column containing 1 equiv polymer-supported carbonate.[19]