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# Synthesis of 3-Aryl/benzyl-4,5,6,6a-tetrahydro-3a*H*-pyrrolo[3,4-*d*]isoxazole Derivatives: A Comparison between Conventional, Microwave-Assisted and Flow-Based Methodologies

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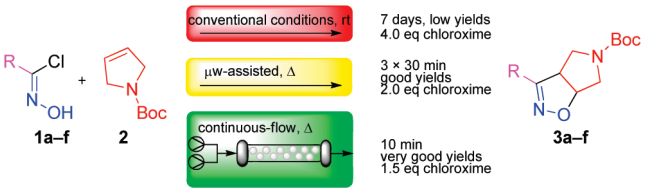


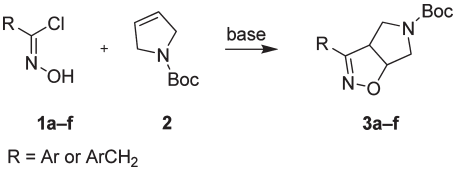

Two modern synthetic technologies to perform 1,3-dipolar cycloaddition reactions were compared. This study puts in evidence the power of microwave-assisted and flow-based methodologies compared to the conventional one in terms of reaction time and yield, and demonstrates the potential of flow chemistry in terms of time, automation, and scaling up opportunities.

The 1,3-dipolar cycloaddition offers a convenient one-step route for the construction of a variety of complex five-membered heterocycles. 1,3-Dipolar cycloadditions of *in situ* generated nitrile oxides with alkenes are well-documented and provide access to $\Delta^2$-isoxazolines.[1] Aldoximes are established precursors of nitrile oxides, and different classes of reagents have been used in the literature for the conversion of aldoximes to nitrile oxides.[2] The outcome of the reaction is strongly dependent on the nature of the dipolarophile. With sluggish dipolarophiles, the 1,3-dipole must be generated slowly so as to disfavor dimerization of the nitrile oxide to give furoxan (1,2,5-oxadiazol-2-oxide) as an unwanted side product. Slow generation of the nitrile oxide can be achieved by addition of an organic base by means of a syringe pump to a solution of the stable precursor hydroximoyl halide and the dipolarophile.[3] Alternatively, an efficient strategy involves the use of a heterogeneous mixture of an organic solvent, e.g., ethyl acetate, and an inorganic base, e.g., $NaHCO_3$ or $KHCO_3$.[4] Both methods allow the maintenance of a low concentration of the dipole, thus preventing dimerization and promoting its reaction with the dipolarophile. The drawback of the above-described strategy is the slowness of the reaction, which can take up to several days or weeks.

Microwave-assisted methodology is a well established way to improve a reaction outcome and speed up the process. The advantage of such a methodology applied to 1,3-dipolar cycloaddition has been highlighted.[5] Besides, flow chemistry is an emerging technology to implement and expedite classical organic reactions.[6] Very recently, this methodology has been successfully applied to cycloaddition reactions.[7]

In this paper we analyzed and compared the usefulness of these two modern methodologies applied to the synthesis of bicyclic-$\Delta^2$-isoxazolines of general structure **3**, derived from 1,3-dipolar cycloaddition of differently substituted nitrile oxides to *N*-Boc-$\Delta^3$-pyrroline **2** (Scheme 1).

**SCHEME 1. General Reaction Scheme**




3-Aryl-(or benzyl-)4,5,6,6a-tetrahydro-3a*H*-pyrrolo[3,4-*d*]-isoxazole derivatives are biologically interesting molecules, since they can be considered as frozen analogues of arylalkylamines, thus being useful tools for structure−activity studies in different medicinal chemistry areas. As a matter of fact, such a scaffold has been used in several biologically active compounds, including nicotinic receptor ligands,[8] antibacterial agents,[9] and neuroleptics.[10]

The target molecules can be obtained according to the reaction depicted in Scheme 1. As previously reported with other types of hydroxamoyl halides, alkene **2** has a poor reactivity, and unless the generated dipole is highly reactive (e.g., bromonitrileoxide), the cycloaddition reaction gives low

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**TABLE 1. Reaction of Chloroximes 1 with *N*-Boc-$\Delta^3$-Pyrroline 2 under Conventional Reaction Conditions at Room Temperature**

| entry | R | equiv of **1**[a] | solvent | time (days) | yield[b] (%) |
|---|---|---|---|---|---|
| **a** | Ph | 4 | EtOAc | 7 | 40 |
| **b** | *p*-$NO_2$-$C_6H_4$ | 4 | EtOAc | 7 | 28 |
| **c** | *p*-$CH_3O$-$C_6H_4$ | 4 | EtOAc | 7 | 45 |
| **d** | $PhCH_2$ | 4 | EtOAc | 7 | 32 |
| **e** | *p*-$NO_2$-$C_6H_4$-$CH_2$ | 4 | EtOAc | 7 | < 2 |
| **f** | *p*-$CH_3O$-$C_6H_4$-$CH_2$ | 4 | EtOAc | 7 | 35 |

[a]Added portionwise to the reaction mixture. [b]Isolated yield.

**TABLE 2. Optimization of Reaction Conditions for the Cycloaddition of Chloroxime 1a (R = Ph) to *N*-Boc-$\Delta^3$-Pyrroline 2, under Conventional Heating or Microwave Irradiation**

| entry | equiv of **1a**[a] | solvent | time (h) | *T* (°C) | yield[d] (%) |
|---|---|---|---|---|---|
| 1 | 2.0 | EtOAc | 72 | reflux[b] | 42 |
| 2 | 2.0 | EtOAc + $H_2O$ (1%) | 72 | reflux[b] | 51 |
| 3 | 1.5 | EtOAc | 2 × 0.5 | 80[c] | 35 |
| 4 | 2.0 | EtOAc | 3 × 0.5 | 80[c] | 48 |
| 5 | 2.5 | EtOAc | 4 × 0.5 | 80[c] | 41 |
| 6 | 3.0 | EtOAc | 5 × 0.5 | 80[c] | 34 |
| 7 | 2.0 | EtOAc + $H_2O$ (1%) | 3 × 0.5 | 80[c] | 66 |
| 8 | 2.0 | EtOAc + $H_2O$ (2%) | 3 × 0.5 | 80[c] | 47 |
| 9 | 2.0 | EtOAc + $H_2O$ (1%) | 3 × 0.5 | 90[c] | 56 |
| 10 | 2.0 | EtOAc + $H_2O$ (1%) | 3 × 0.5 | 100[c] | 44 |

[a]Added portionwise to the reaction mixture. [b]Conventional heating. [c]Microwave irradiation. [d]Isolated yield.

yields.[11] Thus, a slow generation of the dipole is required. We initially carried out the reaction under conventional reaction conditions: the nitrile oxide was generated *in situ* by treating chloroxime **1** with excess solid $NaHCO_3$ in EtOAc, in the presence of alkene **2**, and the reaction was carried out at room temperature.[9,11] As a result of the partial dimerization of the dipole, the addition of further aliquots of chloroxime over time was necessary. The series of differently substituted chloroximes **1a**−**f** was prepared from the corresponding aldehydes according to a procedure reported in the literature.[2a] The cycloaddition reaction proceeded slowly, yielding less than 50% of the desired product after 7 days (Table 1). The yield was strongly dependent on the nature of the chloroxime ranging from 45% (entry c, R = *p*-$CH_3O$-$C_6H_4$) to as low as < 2% (entry e, R = *p*-$NO_2$-$C_6H_4$-$CH_2$).

The detailed results are reported in Table 1.

We then optimized the reaction conditions using chloroxime **1a** as a model substrate. When the reaction was carried out under conventional heating by refluxing in EtOAc, the yield was comparable to that obtained at room temperature (Table 2, entry 1 vs Table 1, entry a), but reaction time was reduced from 7 to 3 days and only 2 equiv of **1a** were consumed. The yield can be further improved up to 51% by adding a small percentage of water (1% v/v) to the reaction medium (Table 2, entry 2). The potential usefulness of the microwave-assisted methodology was then investigated. We performed a series of experiments by varying the reaction conditions, i.e., the number of equivalents of **1a**, time, temperature, and percentage of added water, with the aim of fine-tuning the best reaction conditions (Table 2).

The use of solid $NaHCO_3$ (4 equiv) as a base was kept as a constant in all the experiments.

Microwave irradiation was performed by setting the temperature to the desired value. The average microwave output power ranged from 5 to 20 W, and the registered pressure ranged from 30 to 50 psi. Cooling was kept off while irradiating. Heating cycles of 30 min each were applied. The first equivalent of chloroxime was added at the beginning of the experiment, and further 0.5 equiv portions were added before every additional heating cycle, since monitoring by TLC showed the presence of unreacted alkene **2**, while chloroxime **1a** was completely consumed. The highest yield was obtained after the addition of 2 equiv of chloroxime and 3 heating cycles (Table 2, entry 4). As observed under conventional heating conditions, the addition of a small percentage of water (1% v/v) to the reaction medium had a positive effect on the reaction outcome (Table 2, entry 7 vs 4). Increasing the temperature over 80 °C was counterproductive (Table 2, entries 9 and 10 vs 7).

**TABLE 3. Microwave-Assisted Cycloaddition of Chloroximes 1a−f to *N*-Boc-$\Delta^3$-Pyrroline 2**

| entry[a] | R | time (h) | yield[b] (%) |
|---|---|---|---|
| **a** | Ph | 3 × 0.5 | 66 |
| **b** | *p*-$NO_2$-$C_6H_4$ | 3 × 0.5 | 60 |
| **c** | *p*-$CH_3O$-$C_6H_4$ | 3 × 0.5 | 67 |
| **d** | $PhCH_2$ | 3 × 0.5 | 50 |
| **e** | *p*-$NO_2$-$C_6H_4$-$CH_2$ | 3 × 0.5 | 47 |
| **f** | *p*-$CH_3O$-$C_6H_4$-$CH_2$ | 3 × 0.5 | 57 |

[a]Results obtained using the optimized conditions reported in Table 2, entry 7. [b]Isolated yield.

Thus, we selected as optimal conditions those reported in entry 7. While operating under these conditions, we extended our procedure to a series of differently substituted chloroximes **1a**−**f**. The data reported in Table 3 demonstrate that this methodology is versatile and can be fruitfully applied to the synthesis of a series of 3-substituted isoxazolines **3**. In fact, all derivatives were obtained in acceptable yields (47−67%). Notably, the reaction time was significantly reduced from 7 days (at room temperature) or 3 days (refluxing under conventional heating) to 1.5 h, and very importantly, the outcome of the reaction was not anymore dependent on the nature of the chloroxime. Indeed, we were able to obtain derivative **3e** in 47% yield (compare entry **e** in Table 1 and in Table 3).

The main limitation of the described methodology is related to the possibility of scaling up the reaction. In fact, microwave devices commonly available in a research laboratory are designed to fit 0.2−35 mL sealed tubes, allowing performance of the reaction up to a maximum total volume of 25 mL. This entails the need to repeat the reaction several times in order to produce the desired cycloadduct in multigram scale. Moreover, as pointed out above, the procedure, albeit optimized, requires multiple operator interventions to add additional aliquots of chloroxime over time.

Thus we decided to investigate the feasibility of this type of cycloaddition reaction under continuous-flow conditions.[12] For this purpose, we used the R2+/R4 flow system commercially available from Vapourtec.

First, we chose the appropriate base among a selection of polymer-supported (PS) bases (i.e., PS-sodium carbonate, Amberlyst A-21, PS-DBU,[13] PS-BEMP[14]), as well as solid

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(13) 1,8-Diazabicyclo[5.4.0]undec-7-ene, polymer bound (PS-DBU).

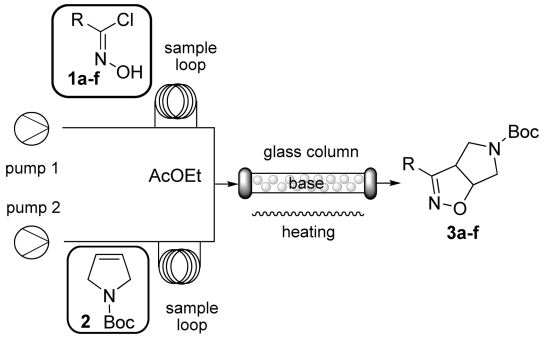
(14) 2-*tert*-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine, polymer bound (PS-BEMP).

**TABLE 4. Cycloaddition of Chloroxime 1a (R = Ph) to *N*-Boc-$\Delta^3$-Pyrroline 2 under Continuous-Flow Conditions[a]**

| entry | equiv of **1a**[b] | residence time (min) | *T* (°C) | yield[c] |
|---|---|---|---|---|
| 1 | 1.0 | 30 | 80 | 50 |
| 2 | 1.5 | 30 | 80 | 60 |
| 3 | 2.0 | 30 | 80 | 63 |
| 4 | 1.5 | 10 | 80 | 45 |
| 5 | 1.5 | 10 | 90 | 69 |
| 6 | 4.5 | 10 | 90 | 87 |
| 7 | 1.5 | 10 | 100[d] | 45 |

[a]Reactions conducted on a 0.25 mmol scale of *N*-Boc-$\Delta^3$-pyrroline **2** in EtOAc (0.25 M solution), using solid $K_2CO_3$ as a base (4.0 equiv). [b]All solutions were prepared in 1 mL of EtOAc. [c]Isolated yield. [d]A further increase in the temperature up to 130 °C causes a dramatic reduction of the yield (8%).

**SCHEME 2. Schematic Representation of the Cycloaddition Reaction in Flow**




$NaHCO_3$ and $K_2CO_3$.[15] Initially, the reaction was performed using a 0.25 M solution of **2** (0.25 mmol) in EtOAc (1 mL) and an equimolar solution of chloroxime **1a** (Table 4, entry 1). The solutions were introduced into the flow stream (EtOAc) through two injection loops, mixing was achieved with a simple T-piece, and the combined output was then directed through a glass column containing the base (4 equiv), heated at 80 °C, in which the reaction took place (Scheme 2). The total flow rate was set in a way that the residence time of the reagents in the column was 30 min. The final flow line was then collected and evaporated to give the crude material, which was purified by column chromatography. A positive system pressure was maintained by using an in-line 100 psi back-pressure regulator.

All of the PS-bases turned out to be inefficient in the cycloaddition reaction, since the product **3** was isolated in unacceptable yield ( < 10%). Only solid $K_2CO_3$ gave a good result (50% yield), and so it was selected for the subsequent optimization phase. A rapid screening of reaction parameters was performed, which included reaction temperature, residence time (flow rate), and stoichiometry.

As shown in Table 4, under continuous-flow conditions it was possible to obtain cycloadduct **3a** in good yield (69%, entry 5) in only 10 min using 1.5 equiv of chloroxime **1a** (0.37 M in EtOAc). This represents a significant improvement over the above-described microwave-assisted methodology, since the reaction time was considerably reduced from 1.5 h to 10 min with a comparable satisfactory yield (69% vs 66%). Increasing the temperature to 100 °C was detrimental for the reaction yield (Table 4, entry 7 vs 5).

**TABLE 5. Cycloaddition of Chloroxime 1a−f to *N*-Boc-$\Delta^3$-Pyrroline 2 under Continuous-Flow Conditions[a]**

| entry[a] | R | time (min) | yield[b] (%) |
|---|---|---|---|
| **a** | Ph | 10 | 69 |
| **b** | *p*-$NO_2$-$C_6H_4$ | 10 | 60 |
| **c** | *p*-$CH_3O$-$C_6H_4$ | 10 | 73 |
| **d** | $PhCH_2$ | 10 | 71 |
| **e** | *p*-$NO_2$-$C_6H_4$-$CH_2$ | 10 | 67 |
| **f** | *p*-$CH_3O$-$C_6H_4$-$CH_2$ | 10 | 64 |

[a]Results obtained using the optimized conditions reported in Table 4, entry 5. [b]Isolated yield.

Since unreacted starting material was recovered in all of the performed experiments, we resolved to test the reaction using a larger excess of chloroxime **1a** (entry 6). In this case, complete conversion of the alkene was observed, and the yield was improved to 87%, but the isolation of the product was hampered by the presence of a large amount of furoxan and other byproducts and required intensive and time-consuming purifications by column chromatography. Therefore, we selected the conditions reported in Table 4, entry 5 as the optimal ones and validated our synthetic protocol by applying such optimized conditions to the series of chloroximes **1a**−**f**. In all cases (Table 5), the cycloadducts were obtained in good yield (60−73%), very short time (10 min), and using as low as 1.5 equiv of chloroxime.

In conclusion, we have compared three different methodologies to prepare 3-substituted-4,5,6,6a-tetrahydro-3a*H*-pyrrolo[3,4-*d*]isoxazole derivatives by means of 1,3-dipolar cycloaddition. Under conventional reaction conditions the reaction proceeded very slowly (7 days) with low yield (≤45%), and it was sometimes impossible to obtain the desired product (i.e., compound **3e**). Running the reaction under microwave irradiation resulted in both a yield increase, especially in the case of poorly reactive dipoles, and a considerable acceleration of the process from 7 days to 1.5 h. Yet, multiple operator interventions and excess of chloroxime were needed. Notably, if conventional heating was applied, the reaction was speeded up to a much lesser extent (3 days) and no increase in the yield was observed.

Finally, through a flow-chemistry approach, we further reduced reaction times from 1.5 h to 10 min and additionally increased the yields. This process could be easily scaled up by simply letting the instrument run for longer time and using a larger base-containing column, without any intervention from the operator.[16]

Our analysis clearly emphasizes the power of the flow-based technique and the unparalleled advantages of its application to the cycloaddition chemistry, in terms of time, yield, automation, and scaling-up opportunities. In perspective, the combination of microwave-assisted and flow-based methodologies could enable the achievement of further progresses in the field of cycloaddition chemistry.

## Experimental Section

**General Procedure for the Cycloaddition Reaction.** To a solution of *N*-Boc-$\Delta^3$-pyrroline **2** (169 mg, 1.0 mmol) in EtOAc (5 mL) were added solid $NaHCO_3$ (420 mg, 5.0 mmol) and the proper chloroxime **1** (**1a**−**f**, 4 equiv added portionwise: 1 equiv the first day, 0.5 equiv/day for the next six days). The mixture was vigorously

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stirred at room temperature for 7 days. Water was added to the reaction mixture, and the organic layer was separated. The aqueous layer was further extracted with EtOAc, and the combined organic phase was dried over anhydrous sodium sulfate. The solvent was evaporated, and the crude material was purified by silica gel chromatography (cyclohexane/EtOAc 7:3) to give the corresponding cycloadduct **3a**−**f**.

**General Procedure for the Microwave-Assisted Cycloaddition Reaction.** The proper chloroxime (**1a**−**f**, 1.0 mmol) was dissolved in EtOAc (5 mL) at room temperature in a 10 mL CEM pressure vessel equipped with a stirrer bar. *N*-Boc-$\Delta^3$-pyrroline **2** (169 mg, 1.0 mmol), solid $NaHCO_3$ (336 mg, 4.0 mmol), and $H_2O$ (50 $\mu$L) were added, and the vial was sealed and heated in a CEM Discover microwave synthesizer to 80 °C (measured by the vertically focused IR temperature sensor) for 30 min. The reaction cycle was repeated another two times, each time adding additional 0.5 equiv of chloroxime **1** (2 equiv total). The solid was filtered off, and the solution was dried over anhydrous sodium sulfate. The solvent was evaporated, and the crude material was purified by silica gel column chromatography (cyclohexane/EtOAc 7:3) to give the corresponding cycloadduct **3a**−**f**.

**General Procedure for the Cycloaddition Reaction Using the R2+/R4 Flow Reactor.** A 0.25 M solution of *N*-Boc-$\Delta^3$-pyrroline **2** (1.0 mmol) in EtOAc (4 mL) and a 0.37 M solution of the proper chloroxime **1a**−**f** (1.5 mmol) in EtOAc (4 mL) were prepared. The two reactant streams were mixed using a simple T-piece and delivered to a glass column (6.6 mm i.d. by 100 mm length) filled with $K_2CO_3$ (4.0 mmol, 540 mg) heated at 90 °C at a total flow rate of 0.1 mL $min^{-1}$, equating to a residence time of about 10 min. A 100 psi backpressure regulator was applied to the system. The solvent was evaporated, and the product was purified by silica gel column chromatography (cyclohexane/EtOAc 7:3) to give the corresponding cycloadduct **3a**−**f**.

***tert*-Butyl 3-Phenyl-6,6a-dihydro-3a*H*-pyrrolo[3,4-*d*]isoxazole-5(4*H*)-carboxylate (3a).** White solid; mp 146−147 °C (dec). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.40 (s, 9H); 3.51−3.70 (m, 3H); 3.90 (d, $J$ = 12.6 Hz, 1H); 4.15−4.25 (m, 1H); 5.28 (ddd, $J$ = 1.1; 5.5; 9.3 Hz, 1H); 7.35−7.45 (m, 3H); 7.55−7.65 (m, 2H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 28.5; 49.8; 51.6; 53.7; 80.4; 85.7; 127.1; 128.5; 129.2; 130.5; 154.3; 158.1.

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**Supporting Information Available:** General experimental procedures, characterization data, and copies of $^1$H and $^{13}$C NMR spectra of synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.