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A Multistep Flow Process for the Synthesis of Highly Functionalized Benzoxazoles

Jörg Sedelmeier,* Fabio Lima,† Alain Litzler, Benjamin Martin, and Francesco Venturoni*

Novartis Pharma AG, Fabrikstrasse 14, 4002 Basel, Switzerland

joerg.sedelmeier@novartis.com; francesco.venturoni@novartis.com

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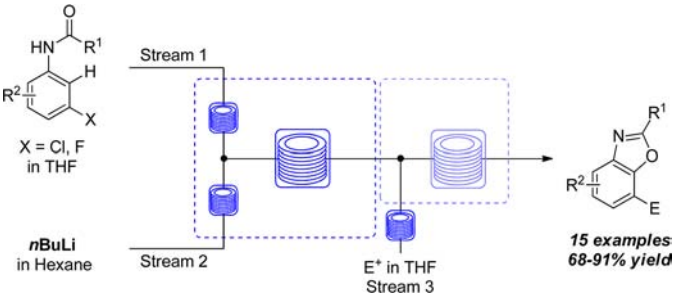
ABSTRACT



An efficient and scalable transformation of 3-halo-*N*-acyl anilines to the corresponding benzoxazoles within a continuous flow reactor is reported. This transformation proceeds *via* base-mediated deprotonation, ortho-lithiation, and intramolecular cyclization to provide unstable lithiated benzoxazole moieties. The subsequent in-line electrophilic quench results in the formation of substituted benzoxazoles in high yield and quality. Continuous flow technology allowed for accurate temperature control and immediate in-line quench while minimizing the hold-up time for the unstable lithiated intermediates thereby minimizing associated byproduct formation.

The benzoxazole moiety and the related α-hydroxy anilines represent an important pharmacophore in many biologically active compounds. Substituted benzoxazoles have been shown to exhibit antitumor, hypoglycaemic, antiallergic, antihistaminic, antiparasitic, herbicidal, antitubercular, antihelmintic, COX-2 inhibitory, antifungal, antibacterial, anticancer, anticonvulsant, HIV reverse transcriptase inhibitor, and insecticidal activities, among others.[1] As such, a variety of synthetic methods for the formation of benzoxazoles have been developed,[2] and we adopted such an approach[2f] in the synthesis of benzoxazole **10a** (Scheme 2), a key intermediate of a recent research investigation. We focused our attention toward continuous flow techniques since major drawbacks in traditional batch chemistry had already been observed, including quality-critical deviations such as formation of dimeric benzoxazoles, as well as complete loss of batches on multikilogram scale due to the lack of robustness. The continuous manufacturing system used for our investigation is of in-house design and integrates precooling loops for all reagent streams, two tubular reactors, three Syrdos2 continuous syringe pumps,[3] pressure sensors for each reagent stream, and a Coriolis mass flow controller unit[4] to monitor the overall flow rate (Figure 1). The entire setup is controlled by HiTecZang software[5] allowing for online monitoring of flow rates, mass flow, temperatures, and system pressures. The integrated software control features enable automatic safety shut-down or emergency actions based upon user predefined parameters thereby increasing the overall safety of the continuous flow process. To efficiently remove the reaction heat generated in the mixing zones, narrow-bore metal T-pieces (Swagelok)[6] have been used. Perfluoroalkoxy (PFA) tubing with an inner diameter (id) = 0.78 mm served as residence volumes and have been precisely cooled to the desired temperatures using cryostat baths.

Although outside of the scope of this manuscript, the benzoxazoles can subsequently be hydrolyzed to the corresponding *ortho*-hydroxy anilines (Figure 1).[7]

The initial benzoxazole synthesis was optimized using the pivaloyl protected aniline **2a**[8] as a substrate, with the

† Current address: Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States.

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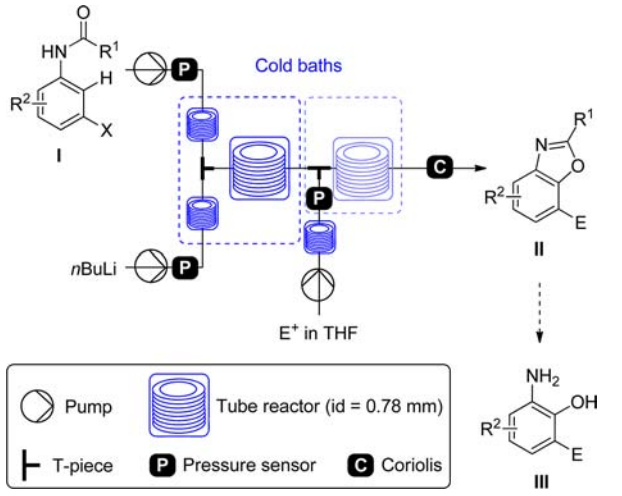

Figure 1. General reactor setup.

solvent, residence time, mixing efficiency, reaction temperature, reagent concentration, and stoichiometries being systematically investigated. On combination with 2 equiv of *n*-butyllithium the protected aniline **2a** underwent base-mediated elimination of the 3-chloro substituent to afford the aryne intermediate **4a**, followed by intramolecular cyclization. Trapping of moiety **5a** with a THF solution of acetic acid as the model electrophile provided the benzoxazole **6a** (Scheme 1).[9]

The optimal preparation of **6a** was achieved using a 0.25 M concentration of aniline derivative **2a** (1.0 equiv) in tetrahydrofuran, a 1.25 M solution of *n*-butyllithium (2.4 equiv) in hexane, and a 0.75 M solution of the corresponding electrophile (3.0 equiv) in tetrahydrofuran. The lithiation chemistry occurred at −10 °C with a residence time of 300 s, whereas the electrophilic quench required −5 °C and a 60 s reaction time. Maintaining a temperature as close to −10 °C as possible for the lithiation chemistry was found to be a critical process parameter, since any warmer temperatures led to the formation of undesired byproducts[10] over a prolonged reaction time. Calorimetric investigations showed an instantaneous reaction and the exothermic nature (510 kJ/mol) of the base-mediated transformation; it resulted in an adiabatic temperature rise of about 55 °C (considering a 0.17 M solution) in the first mixing zone.[11] To efficiently remove the reaction heat generated, an appropriate mixing device had to be identified. In order to avoid hot spots it was decided that a nonoptimal mixing regime would serve to dissipate the reaction energy over the length of the tubular reactor, avoiding thermal accumulation in a single mixing point (adiabatic conditions). This reasoning led us to choose a metal Swagelok T-piece as a mixing device.[12] To further facilitate and control the heat dissipation all reagent streams were prechilled before mixing. Adhering to the above protocol ensured a high-quality product **6a** that required only a simple extractive workup followed by evaporation of the solvent.

In order to demonstrate the substrate scope and synthetic value of the continuous flow process, conditions for the direct conversion of **2a** to various benzoxazoles

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(4) Mass flow controller Bronkhorst Schweiz. http://www.bronkhorst.ch/en/ (accessed Oct 30, 2013).

(5) HiTec Zang Automation and Evaluation Software. http://www.hitec-zang.de/en/laboratory-automation/software.html (accessed Oct 30, 2013).

(6) Swagelok. http://www.swagelok.com/ (accessed Oct 30, 2013).

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(10) As major byproducts the corresponding dimers (for structure see Supporting Information, Figure 1) and the protodehalogenated benzoxazole (when using an electrophile other than acid) have been observed during the batch optimization process.

(11) Experiment was performed in a METTLER RC1 reaction calorimeter. Software: WinRC NT V.7. Glass reactor 0.9 L equipped with 4-bladed glass propeller stirrer, glass cover, and glass inserts.

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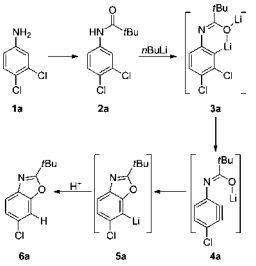
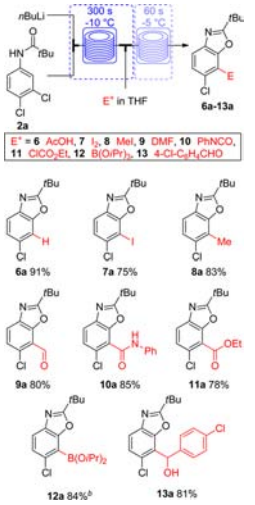
Scheme 1. Model Reaction and Reaction Mechanism



Scheme 2. Transformation of Aniline **2a** to Benzoxazole Derivatives Using Various Electrophiles[a]



[a] **2a** in dry THF (0.25 M, 0.750 mL/min), *n*-butyllithium in hexane (1.25 M, 0.360 mL/min), electrophile in THF (0.75 M, 0.750 mL/min); residence time in first reactor = 300 s, and residence time in second reactor = 60 s. [b] Yield based on ^{1}H NMR.

by quenching with different electrophiles were devised (Scheme 2).

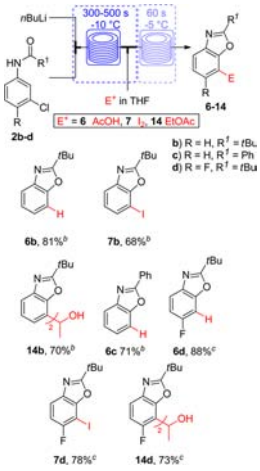
Following the described flow protocol, functionalities such as iodine, alkyl, esters, aldehydes, amides, boronic esters,[13] and alcohols could be introduced into the 7-position of the benzoxazole moiety[14] enabling further modifications.

In an effort to expand on the product diversity of these flow reactions, additional modifications to the aniline moiety were investigated (Scheme 3). Regarding the substitution pattern on the aromatic ring, the electron-deficient 3,4-dichloroaniline **2a** (Scheme 2) and the 3-chloro-4-fluoroaniline moiety **2d** showed comparable

(13) Boronic ester **12a** was revealed to be instable at ambient conditions and would require immediate consumption. The concept of production and immediate usage of boronic intermediates has been demonstrated recently by Buchwald, S., Prof.; Shu, W.; Pellegatti, L.; Oberli, M. A.; Buchwald, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 10665–10669.

(14) For an overview of electrophiles being used, see Table 1 in the Supporting Information.

Scheme 3. Expansion of Benzoxazole Diversity[a]



[a] **2b**–**d** in dry THF (0.25 M, 0.750 mL/min), *n*-butyllithium in hexane (1.25 M, 0.360 mL/min), electrophile in THF (0.75 M, 0.750 mL/min). [b] Residence time in the first reactor = 500 s, and residence time in the second reactor = 60 s. [c] Residence time in the first reactor = 300 s, and residence time in the second reactor = 60 s.

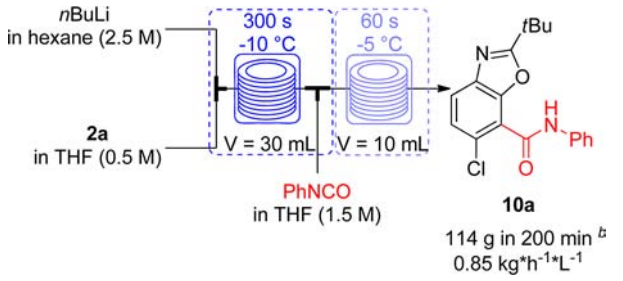
chemical behavior. However, in contrast, we encountered a significantly slower and less exothermic reaction for the monochloroaniline derivatives (**2b**, **2c**). A plausible explanation is that the proton in the 2-position is less acidic than those in **2a** and **2d**; therefore, the reactor volume (residence time) was adjusted accordingly, keeping the overall flow rates (mixing efficiency) unchanged.

With a protocol available to prepare a broad variety of different benzoxazoles (**6**–**14**), we turned our attention toward scale-up of the continuous manufacturing process. We considered this to be an important proof-of-concept effort due to the exothermic nature of the two consecutive reaction steps, the potential clogging of the reactor system with lithium salts, and the generation of undesired byproduct formation in case of insufficient temperature control. Our aim was to demonstrate that the flow setup could be operated under steady state conditions for several hours, thereby generating multigram quantities of benzoxazole product. The integrated control and safety features were managed by the software, which constantly monitors the system temperature, flow rates, and pressures, which encouraged us to directly scale the two-step sequence to a 100 g scale.

With this aim in mind, we maximized the throughput of the transformation by adapting the concentration of the feedstock solutions, flow rates, and the reactor volumes (Scheme 4), without observation of clogging or quality issues related to hot spots.

Under the adjusted reaction conditions a 0.5 M solution of **2a** (100 g, 406 mmol, 4 mL/min) was reacted with a 2.5 M solution of *n*-butyllithium (1.92 mL/min) at a total flow rate of 5.92 mL/min using a reactor volume of 30 mL. The reaction stream was quenched in-line with a 1.5 M solution of phenyl isocyanate in THF (4 mL/min) prior to a 10 mL residence coil. The final reaction mixture

Scheme 4. Scale-up of Key Intermediate **10a**[a]



[a] **2a** in dry THF (0.5 M, 4.0 mL/min), *n*-butyllithium in hexane (2.5 M, 1.92 mL/min), PhNCO in THF (1.5 M, 4.0 mL/min); residence time in the first reactor = 300 s, and residence time in the second reactor = 60 s. [b] Throughput of product (space-time-yield) has been normalized to production time [1 h] and reactor volume [1 L].

was collected into saturated aqueous ammonium chloride solution over a period of 200 min. After extraction, phase separation, removal of solvent, and crystallization from heptane/EtOAc, the corresponding benzoxazole **10a** was isolated in 86% yield (114 g, 348 mmol). A throughput of 0.85 kg (**10a**) per hour per liter of reactor volume was thus achieved. During the extended processing period, no operational issues were encountered due to fouling of the reactor, and isolation of the desired product occurred in comparable yield and purity as for the small-scale flow reaction.

In summary, we have developed an efficient, rapid, and reproducible process for the formation of benzoxazoles under continuous flow conditions. We demonstrated the reliable and robust scale-up by running the continuous manufacturing process in steady state mode processing 400 mmol of starting material. The value of this process lies in the use of readily available and inexpensive aniline precursors delivering highly functionalized benzoxazole products in good yields and purities.

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Supporting Information Available. Experimental procedures and full characterization (^{1}H and ^{13}C NMR data and spectra, UV and HRMS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.