Synthetic Methods

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Continuous-Flow Synthesis of 1-Substituted Benzotriazoles from Chloronitrobenzenes and Amines in a C–N Bond Formation/Hydrogenation/Diazotization/Cyclization Sequence**

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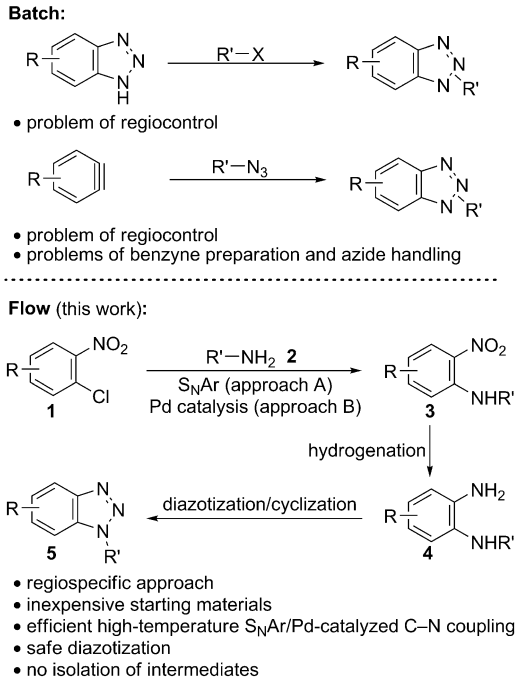
Substituted benzotriazoles represent key structural motifs in compounds that possess antibacterial, antimalarial, and antifungal activities.[1] They are also found in potassium channel activators,[2] inhibitors of various kinases,[3] and in selective agonists of human orphan G-protein-coupled receptor GPR109b.[4] In addition, benzotriazoles are versatile intermediates in the synthesis of important heterocycles, such as carbazoles, pyridoacridines, carbolines, and tetraazapentalenes.[5] They have also been extensively utilized as synthetic auxiliaries in benzannulation and alkylation reactions.[6]

Traditionally, 1-substituted benzotriazoles have been prepared by N-alkylation/arylation of benzotriazoles or [3+2] cycloaddition of azides and benzynes. The alkylation/arylation approach often suffers from poor regioselectivities because of the tautomeric nature of unsymmetrical benzotriazoles.[7] Moreover, the arylation reagents are usually limited to activated heteroaryl halides or aryl halides that possess strong electron-withdrawing groups. The regioselectivity of 1,3-dipolar cycloadditions of azides is largely dependent on the steric and electronic properties of benzynes, and mixtures of regioisomers are often formed.[8] Separation of 1-, 2-, and 3-substituted benzotriazoles is also oftentimes not trivial because of their similar physical properties.[9] In addition, the generation of unstable benzyne intermediates and the handling of azides on large scale present safety problems. Thus, the development of a safe and efficient method to prepare 1-substituted benzotriazoles in a regiospecific fashion is desirable.[10]

In this regard, we have designed a multistep synthesis consisting of a C–N bond formation/hydrogenation/diazotization/cyclization sequence starting from 2-chloronitrobenzenes and amines. Depending on the electronic properties of the chloronitrobenzene, the C–N bond-forming step can be achieved either by nucleophilic aromatic substitution (S_NAr; approach A) or by a Pd-catalyzed C–N cross-coupling reaction (approach B) followed by hydrogenation and diazotization/cyclization (Scheme 1). These multistep operations in batch mode are time-consuming and labor-intensive. Additionally, carrying out high-temperature processes and thermally sensitive diazotization reactions under batch conditions can be problematic.[11] Continuous-flow processes are useful alternatives to traditional batch procedures as has been demonstrated by both industrial and academic chemists.[12] We felt that a continuous-flow approach would be ideal in our multistep synthesis of benzotriazoles and would greatly enhance the practicality of this method.



Scheme 1. Multistep strategy for the synthesis of 1-substituted benzotriazoles under continuous-flow conditions.

Despite recent advances in multistep synthesis under continuous-flow conditions pioneered by Ley,[12,13] examples of such cases, including consecutive multiphase processes in a continuous line, are still rare.[14] For a sequence of multiphase reactions in flow, problems of mass- and heat-transfer between different phases, varying solubilities of intermediates over the course of the reaction, compatibility of solvents, as well as residence-time control for segmented flow all need to be considered. Herein, we report the development of a multistep continuous-flow synthesis of 1-substituted benzotriazoles under consecutive multiphase reaction conditions.

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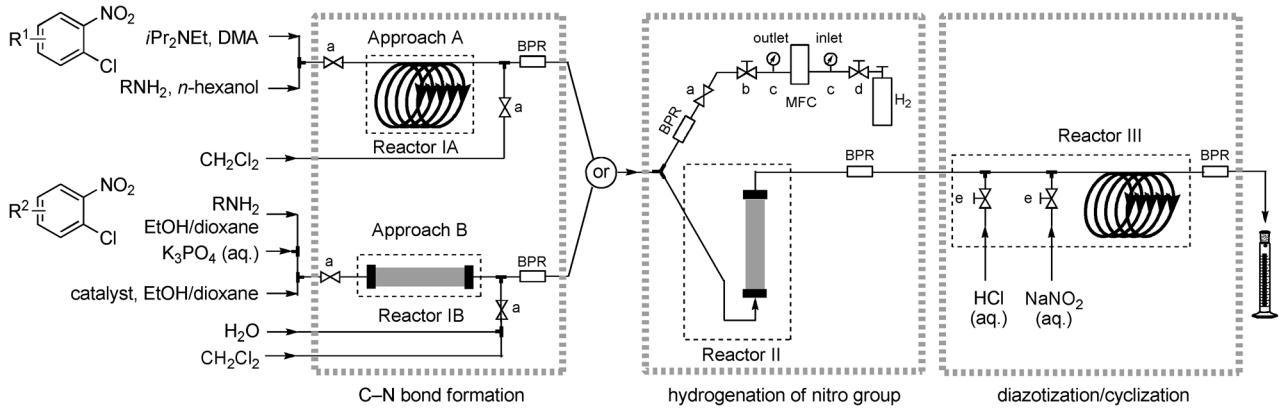
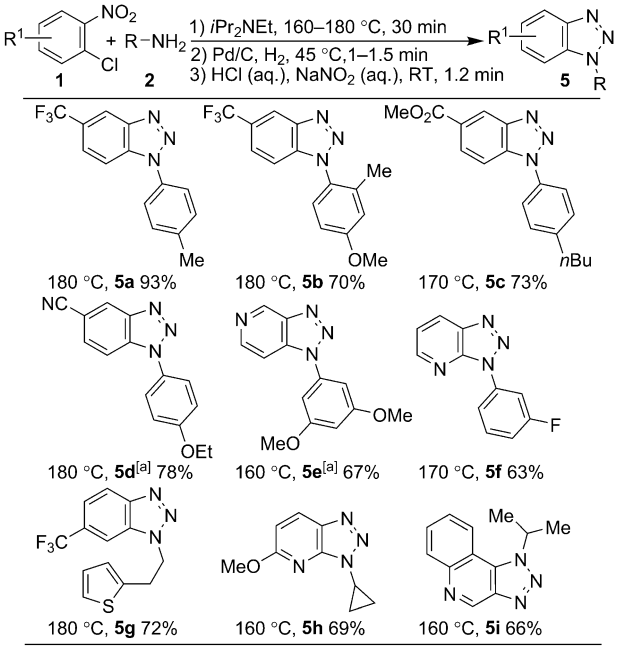


Figure 1. Continuous-flow setup for the C–N bond formation/hydrogenation/diazotization sequence of approach A and B. a) In-line check valve; b) on-off valve; c) pressure gauge; d) 2-stage regulator; e) 2-way valve; BPR: back-pressure regulator; MFC: mass flow controller. For more details, see the Supporting Information.

We began our studies on the C–N bond formation/hydrogenation/diazotization/cyclization sequence using approach A with the setup depicted in Figure 1 with 4-chloro-3-nitrobenzotrifluoride and *p*-toluidine as model substrates. In considering the solubility and reactivity constraints of downstream processes, a mixture of *N*,*N*-dimethylacetamide (DMA) and *n*-hexanol was chosen as the solvent for this S_NAr step.[15] In the flow setup, a solution of 4-chloro-3-nitrobenzotrifluoride and iPr$_2$NEt in DMA was mixed with *p*-toluidine in *n*-hexanol and introduced into reactor IA at 180 °C. After C–N bond formation was complete, the resulting mixture was diluted with CH_2Cl_2, and was mixed with H_2 gas.[16,17] The resulting gas/liquid segmented flow was passed through a vertically placed[18] packed-bed reactor II (packed with stainless steel spheres and 5% Pd/C particles) at 45 °C. After hydrogenation had finished, the resulting mixture was directly combined with aqueous HCl and aqueous $NaNO_2$, and the resulting stream was then introduced into reactor III to perform diazotization/cyclization.[19] Finally, the resulting mixture was collected and subsequently purified by column chromatography to afford **5a** in 93% yield of isolated product (Scheme 2).

With the optimized flow conditions in hand, the substrate scope with various electrophiles and both aromatic and aliphatic amines using approach A was investigated (Scheme 2). *Para*-, *meta*-, *ortho*-, and multi-substituted anilines could be successfully employed. Both electron-rich and electron-deficient anilines appeared to be effective nucleophiles. Substrates with electron-withdrawing groups (R^1), such as a trifluoromethyl, an ester, and a nitrile group, were converted to products in good yield. Of note, chloro-(nitro)heteroaryl substrates could also be used to efficiently access the corresponding triazolopyridines (**5e**, **5f**, and **5h**) or triazoloquinolines (**5i**). Although these S_NAr reactions were carried out at high temperatures, only 1.3 equivalents of amines, including those with low boiling points (e.g., isopropyl and cyclopropyl amine), were required, further demonstrating the advantage of this flow process. To overcome clogging problems that initially occurred in preparing **5d** and **5e**, which have limited solubilities under our conditions, reactor III was placed in a sonication bath at 45 °C.[20] With

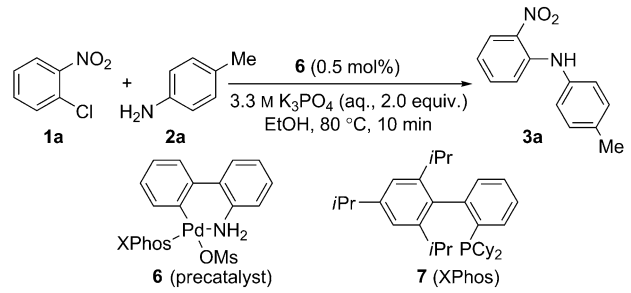


Scheme 2. Continuous-flow synthesis of 1-substituted benzotriazoles by an S_NAr C–N bond formation/hydrogenation/diazotization/cyclization sequence. Yields of isolated products (average of two runs) based on 1 mmol scale are shown. See the Supporting Information for details. [a] Sonication at 45 °C was used in the third step.

this setup, 1-substituted benzotriazoles could be prepared regiospecifically on a 1 mmol scale in approximately one hour.[21]

While approach A is successful for chloro(nitro)aromatic substrates with additional electron-withdrawing groups, it is not efficient for other substrates. To overcome this limitation, we developed a Pd-catalyzed version (approach B). After briefly optimizing the C–N coupling reaction in EtOH/H_2O with K_3PO_4 as the base at 80 °C, palladium precatalyst **6**[22] afforded the desired product **3a** in 97% yield (determined by GC analysis; Scheme 3).

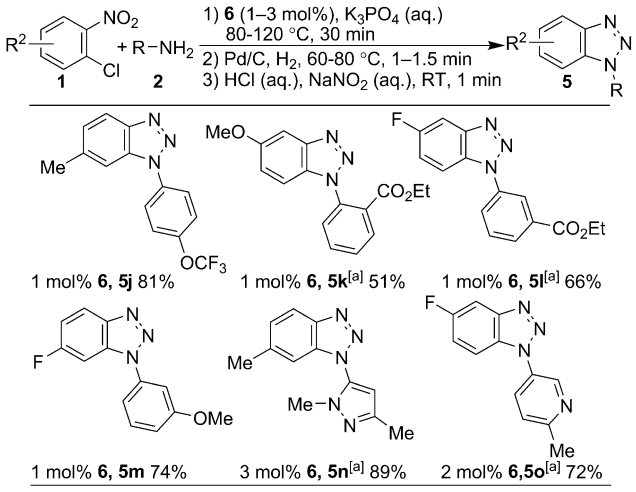
Having identified appropriate reaction conditions for Pd-catalyzed C–N bond formation, we next assembled a micro-



Scheme 3. Pd-catalyzed C–N coupling of 2-chloronitrobenzenes and amines.

fluidic system as shown in Figure 1, approach B.[23] In this flow setup, the combined biphasic solutions of substrates, base, and catalyst were first introduced into a packed-bed reactor IB (packed with stainless steel spheres) at 80 °C with sonication. After Pd-catalyzed C–N cross coupling was complete, the stream containing the intermediate was mixed with streams of water and CH_2Cl_2, and the resulting mixture was flowed into the hydrogenation reactor II and then the diazotization reactor III with the same setup as for approach A (see above). To achieve complete hydrogenation of the nitroaniline intermediate, a longer packed-bed hydrogenation reactor II[24] was used in approach B, and the reaction temperatures were increased to 60–80 °C.

1-Arylbenzotriazoles that bear electron-donating groups (methyl, methoxy) could be prepared with approach B (Scheme 4). Fluorine-substituted benzotriazoles, which were



Scheme 4. Continuous-flow synthesis of 1-substituted benzotriazoles by a Pd-catalyzed C–N bond formation/hydrogenation/diazotization/cyclization sequence. Yields of isolated products (average of two runs) based on 1 mmol scale are shown. See the Supporting Information for details. [a] Sonication at 45 °C was used in the third step.

difficult to obtain using the high-temperature S_NAr approach, could also be generated in good yields. Heterocyclic amines, such as 5-aminopyrazole and 3-aminopyridine, could be used as nucleophilic compounds to give the corresponding benzotriazoles **5n** and **5o** in good yields.

In summary, we have developed an efficient and regiospecific synthesis of 1-substituted benzotriazoles from chloronitrobenzenes and amines by a C–N bond formation/hydrogenation/diazotization/cyclization sequence under continuous-flow conditions. Two approaches beginning either with an S_NAr reaction or Pd catalysis were developed to prepare unsymmetrically substituted benzotriazoles with a range of substituents. Of particular note is that benzotriazoles that bear various N-substituted groups, including alkyl, aryl, and heteroaryl, can all be efficiently and regiospecifically accessed with the described method. This protocol represents a successful example of a continuous-flow method with consecutive multiphase processes.

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