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# Facile azide formation via diazotransfer reaction in a copper tube flow reactor

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ABSTRACT

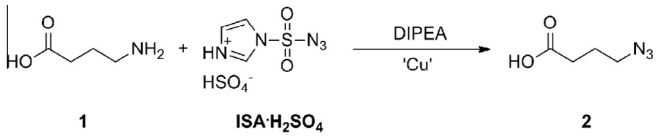
A copper tube flow reactor is used in the conversion of primary amines into organic azides using imidazole-1-sulfonyl azide hydrogen sulfate. The catalyst is generated in situ from the metallic copper. The reaction can be quenched in acidic environment or via a cycloaddition of the azides formed with an alkyne. The possibility to perform this azide-alkyne cycloaddition using the copper released from the reactor is demonstrated with the synthesis of both a 1,2,3-triazole derivative of benzylamine and of a more complex BODIPY–DOTA adduct.



Flow chemistry is a useful tool for the synthetic chemist.[1–4] The ease with which flow reactors can be constructed by utilizing standard tubing, connector pieces, and syringe pumps, the possibility to tightly control reaction time and reaction temperature, the small quantities of product required for optimization are great advantages. Furthermore, safety issues such as toxicity and explosive decomposition of reagents are mitigated by the closed system and small reaction volumes.[1–5] The latter argument shows great potential for flow chemistry in the synthesis of organic azide.

Organic azides are a class of compounds with potential highly toxic and explosive properties.[6] Despite these attributes they are valuable and versatile intermediates in organic synthesis.[7] Organic azides can be synthesized from primary amines via a diazotransfer reaction.[8,9] Triflyl azide is most commonly used as a diazotransfer reagent.[10] Its short shelf life and highly explosive nature in neat form render this product rather unattractive.[11,12] The introduction of imidazole-1-sulfonyl azide (**ISA**) and more recently its hydrogen sulfate salt (**ISA·$H_2SO_4$**, Scheme 1) as a stable, easy to prepare, and manipulate reagent has given the diazotransfer reaction a whole new set of applications.[13–19]

Recently, the possibility to perform the diazotransfer reaction under continuous flow conditions has been demonstrated by Delville et al.[20] However, issues with solubility of some of our compounds prompted us to use a different solvent system and a different catalyst. While screening for appropriate catalysts in the preparation of performing the diazotransfer reaction under continuous flow conditions, it was found that it was possible to catalyze the reaction by using copper turnings. Oxidation of metallic copper under the influence of a sulfonyl azide results in the formation of a catalytic active Cu(II)-sulfonylamide complex.[21,22] This prompted us to investigate the possibility to perform this reaction under flow conditions using a copper tube reactor. The use of metallic copper as a source of an ionic catalyst system has previously been demonstrated, for example, in the synthesis of 1,4-disubstituted 1,2,3-triazoles.[23,24] The use of copper flow reactors has already been successfully applied in the synthesis of 1,4-disubstituted 1,2,3-triazoles and several coupling reactions.[25–40] To the best of our knowledge, the application of copper tube flow reactors was not reported for the diazotransfer reaction.




1 ISA·$H_2SO_4$ 2

**Scheme 1.** Synthesis of γ-azidobutyric acid via a copper catalyzed diazotransfer reaction using imidazole-1-sulfonyl azide.

A general procedure was developed via the optimization of the synthesis of γ-azidobutyric acid (**2**) starting from γ-aminobutyric acid (**1**) and **ISA·$H_2SO_4$** (Scheme 1). A 500 μL internal volume reactor was constructed using copper GC tubing (Fig. 1). The reactor was connected to two syringes via a T-mixing piece. A 10:3:3

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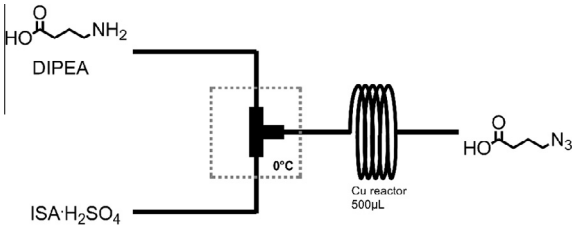



**Figure 1.** Set up of the copper tube flow reactor.

mixture of methanol/dichloromethane/water was chosen as the solvent since this monophasic mixture is reported to result in a minimal precipitation of salts from the diazotransfer reaction.[7,41] This mixture also proved to have better solvating properties for the reagents used. The amine and diazotransfer reagent were dissolved in separate stock solutions that were brought in two separate syringes. Stock solution A is 145 mM in reagent **1**. Stock solution B contains a solution with variable quantities of **ISA·H$_2$SO$_4$** (according to the number of equivalents needed). Base was added as a second component to solution A in a fixed ratio to **ISA·H$_2$SO$_4$** (Supplementary material). When the base is premixed with **ISA·H$_2$SO$_4$**, premature decomposition of this reagent is observed in the syringe as formation of gas bubbles. An ice bath was used to immerse the T-mixer to prevent decomposition while combining the mixtures before bringing them into the copper tube flow rector at room temperature. Upon leaving the reactor the reaction mixture was directly quenched by adding the reaction mixture to acetic anhydride. Reaction time and equivalents of **ISA·H$_2$SO$_4$** were optimized and monitored via LC/MS (Figs. 2 and 3).

Using less than three equivalents of **ISA·H$_2$SO$_4$** relative to the amine results in an incomplete conversion of the amine. At the same time it was observed that a precipitate forms in the reactor. By using three or more equivalents of **ISA·H$_2$SO$_4$** this problem is alleviated. A comparable rate of amine conversion is observed when three or four equivalents of **ISA·H$_2$SO$_4$**. However, overall formation of azide is lower in the case where four equivalents are used. Addition of five equivalents results in both lower conversion of the amine and less formation of the azide. At shorter retention times the amine does not completely convert to the azide. Longer retention times result in lower yields of the azide. This could be due to further reduction of the formed azides in the presence of copper.[21,42] Generally, the amine is converted optimally when a

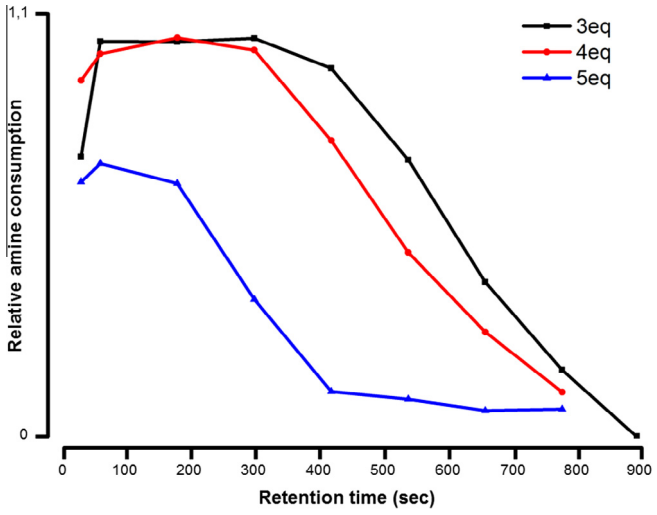



**Figure 2.** Influence of the number of equivalents of **ISA·H$_2$SO$_4$** and the retention time in the reactor on the conversion of amine **1** relative to an internal standard.

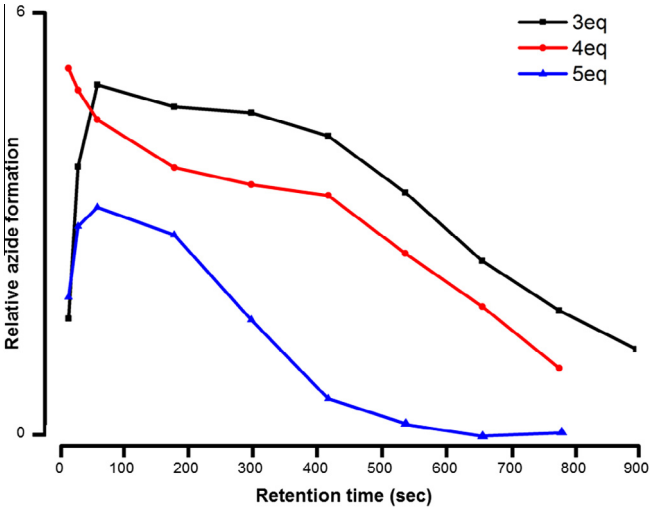
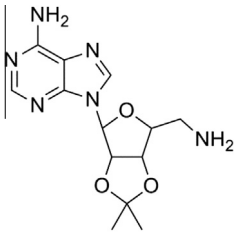



**Figure 3.** Influence of the number of equivalents of **ISA·H$_2$SO$_4$** and the retention time in the reactor on the formation of azide **2** relative to an internal standard.

**Table 1**
Diazotransfer reaction at room temperature, 3 equiv of ISA·H$_2$SO$_4$, 300 s retention time in a 500 µL copper tube flow reactor. Yields are isolated yields

| Entry | | Amine | Product | Yield (%) |
|---|---|---|---|---|
| 1 | **1a** | Ethyl 4-aminobutyrate·HCl | **1b** | 59 |
| 2 | **2a** | Benzylamine | **2b** | 77 |
| 3 | **3a** | Fmoc-Lys-OH·HCl | **3c** | 74 |
| 4 | **4a** |  | **4c**[a] | 65 |
| 5 | **5a** | *p*-Anisidine | **5b** | 44 |
| 6 | **6a** | *p*-Toluidine | **6b** | 26 |
| 7 | **7a** | *p*-Chloroaniline | **7b** | 7 |
| 8 | **8a** | 4-Aminobenzonitrile | **8b** | / |

[a] Synthesis in a 150 µL copper tube flow reactor, reaction was quenched by introducing the reaction mixture to a 3:1 solution of methanol/acetic acid.

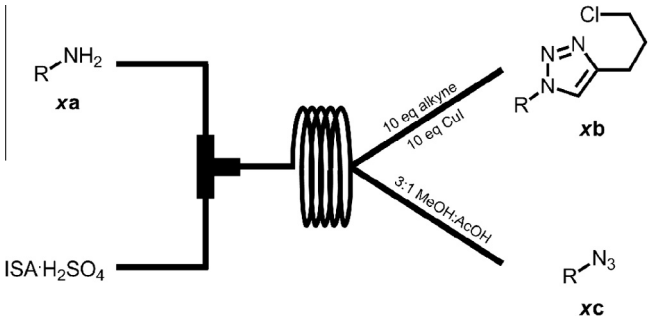
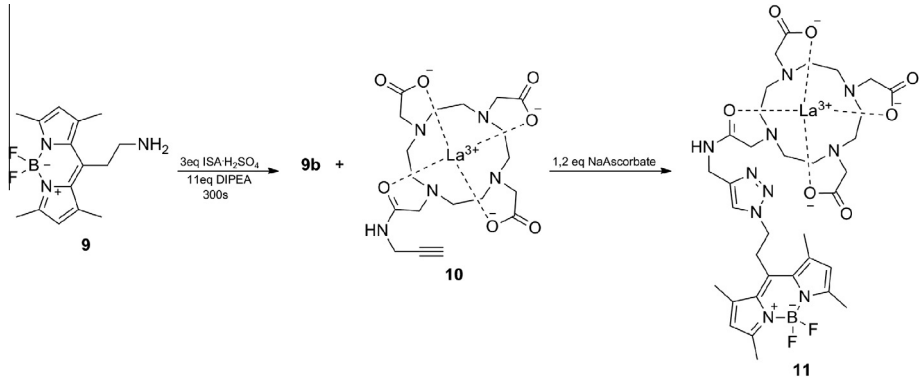



**Figure 4.** The diazotransfer reaction of ***xa*** is either quenched by introducing the mixture to a solution of 5-chloro-1-pentyne and CuI forming triazole ***xb***, or quenched by introducing the mixture to a 3:1 solution of methanol and acetic acid forming azide ***xc***.

retention time of the mixture in the reactor of 60–300 s is used. The scope and limitations were studied at room temperature using 3 equiv of **ISA·H$_2$SO$_4$** and a retention time of 300 s (Table 1). The




**Scheme 2.** Synthesis of the BODIPY functionalized complex **11** by performing a diazotransfer reaction on amine **9**, followed by a Cu AAC with alkyne **10**.

reaction was quenched by introducing the mixture to a solution of 10 equiv of 5-chloro-1-pentyne and CuI or in a 3:1 solution of methanol and acetic acid, resulting in the formation of the triazole ***x*b** or azide ***x*c**, respectively (Fig. 4).

For ease of purification the ethyl ester of γ-aminobutyric acid was used to determine the isolated yield and the acidic quench was replaced with a quench using a mixture of 10 equiv of 5-chloro-1-pentyne and CuI yielding the corresponding 1,4-triazole via a copper(I) catalyzed azide-alkyne cycloaddition (Cu AAC). This quenches the reaction and yields a less volatile compound. Product **1b** was obtained in a 59% overall isolated yield over the two reaction steps. Conversion of benzylamine and Fmoc-Lys-OH proceeded with yields of 77% and 74%, respectively. The diazotransfer to compound **4a** resulted in selective transformation of the alkyl amine, leaving the hetaryl amine intact. Product **4c** was obtained in a 65% yield. Conversion of aromatic amines proved to be more problematic due to the instability of their corresponding azides. To prevent this undesired degradation during purification, all the organic azides were converted to their respective 1,4-triazoles by introducing the reaction mixture to a 5-chloro-1-pentyne/CuI solution. The isolated yield of these compounds decreases from 44% for **5b** to 26% for **6b** to 7% for **7b**, with no conversion observed for **8a**. This decreases within the aromatic amines and compared to the alkyl amines corresponds to a decrease in nucleophilicity of the nitrogen atom. This confirms the need of a nucleophilic amine in the diazotransfer reaction as proposed in the mechanism of Nyffeler et al. and the elucidated mechanism of Stevens et al.[7,41,43]

After each run the increase of the internal volume of the copper tube reactor was checked by weighing the reactor. This increase due to the previously mentioned oxidation of Cu(0) amounted to less than 0.5% of the total internal volume and was deemed insignificant.

To verify the possibility of cascading the diazotransfer reaction with the Cu AAC using the copper ions formed in the reactor tube, the synthesis of compound **2b** was repeated in one continuous process. The azide of compound **2a** was introduced to a solution 1.5 equiv of 5-chloro-1-pentyne and 1.5 equiv of sodium ascorbate. The reaction mixture was left stirring overnight and compound **2b** was isolated in a 57% overall yield. The same procedure was used in the synthesis of compound **11** (Scheme 2). The azide of compound **9** could not be isolated in batch diazotransfer reactions. Hence, azide **9b** was synthesized in situ by performing the herein developed flow procedure in a 150 μL copper tube flow reactor. The reaction mixture was introduced to a flask containing 1.5 equiv of sodium ascorbate and 1.5 equiv of **10**. The reaction was left stirring overnight and was purified via HPLC. The previously elusive BODIPY functionalized complex **11** was obtained in a 9% overall isolated yield starting from **9**.

In conclusion, a straightforward flow protocol is developed for the synthesis of azides via a diazotransfer reaction using a copper tube flow reactor. This procedure requires less diazotransfer reagent, a lower retention time, and no addition of catalyst to any of the stock solutions compared to the procedure of Delville et al.[20] It was shown that the reaction proceeds with higher yields using alkyl amines compared to aryl amines. Diazotransfer reactions to aryl amines are more efficient if the amine is more nucleophilic. The possibility to perform the Cu AAC using the copper released from the system is demonstrated by the synthesis of compound **2b** and compound **11**. Once constructed, the copper tube flow reactor, the easily applicable procedure and the possibility of cascading the diazotransfer reaction with the Cu AAC puts a wide range of azides and 1,4-triazoles within easy reach of a wide variety of scientists.

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## Supplementary data

Supplementary data (experimental procedures, characterization data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.02.036.

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