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A continuous flow synthesis and derivatization of 1,2,4-thiadiazoles

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ABSTRACT

A continuous flow process is presented that enables the efficient synthesis and derivatization of 1,2,4-thiadiazole heterocycles. Special attention was given to the safe handling of the versatile yet hazardous trichloromethane sulfenylchloride reagent including its in-line quenching in order to eliminate malodourous and corrosive by-products. Based on this flow method gram quantities of 5-chloro-3-phenyl-1,2,4-thiadiazole were safely prepared allowing for further elaboration of this valuable building block by reaction with different nitrogen-, sulfur- and oxygen-based nucleophiles. This synthetic approach was subsequently applied to generate a series of bromophenyl-5-chloro-1,2,4-thiadiazoles providing a valuable entry towards further structural diversification on this important heterocyclic scaffold.

1. Introduction

Thiadiazoles represent a unique subclass of bioactive five-membered aromatic heterocycles containing one sulfur and two nitrogen atoms.[1–4] The presence of these heteroatoms increases both the membrane permeability as well as the ability to act as versatile hydrogen bond acceptors. Due to the spacial similarity of vinyl groups to ring embedded sulfur atoms thiadiazoles can be considered isosteres of diazines[5,6] adding to their potential to serve as fragments of bioactive structures.[7–10] Thiadiazoles can occur in four distinct regioisomeric forms (**1**–**4**) enriching their structural diversity with respect to local polarization and vector space occupied by both carbon bound substituents R_1 and R_2 (Fig. 1).

Amongst the possible thiadiazole isoforms the 1,2,4-thiadiazole scaffold is an important structure as it resembles the ubiquitous pyrimidine moiety. The synthesis of 1,2,4-thiadiazoles can be accomplished by a variety of methods including oxidative ring closure,[11,12] multicomponent reactions[13] or [3 + 2]-cycloadditions.[14] A further option which is more amenable to subsequent functionalization on the heterocyclic scaffold is based on reacting various amidines with trichloromethane sulfenylchloride (**5**, Scheme 1).[15] Although very versatile this reagent poses several safety risks as it is unstable and readily decomposes into highly corrosive and malodorous species.[16] In order to mitigate these hazards we decided to harness the benefits of flow reactor technology[17–26] to study the safe and efficient use of trichloromethane sulfenylchloride en route to 5-chloro-1,2,4-thiadiazoles that would allow further functionalization reactions to take place at the activated 5-position of this scaffold.

2. Results and discussion

In order to safely employ trichloromethane sulfenylchloride we opted to utilize a Vapourtec R-series flow system[27] as it is amenable to using either the injection sample loops (for small scale reactions) or pumping directly from reagent bottles (for scale up operations).

Stock solutions of trichloromethane sulfenylchloride (**5**, 0.45 M in EtOAc) and hydrated benzamidine hydrochloride salt (**6**, 0.4 M in 1.5 M aqueous NaOH) were freshly prepared before each set of experiments and used up within 2–3 h. As depicted in Scheme 1 the reagent solutions were loaded into the sample loops (PTFE, 2–5 mL each) and subsequently pumped at equal flow rates to unite at a T-piece (PEEK, 1.3 mm ID). The initial mixing resulted in an emulsion that then separated into individual droplets due to the biphasic nature of the solvent system. This stream was then directed through two tubular coiled reactors (PTFE, 10 mL each, ambient temperature, no active cooling) followed by a 75 psi back-pressure regulator prior to be collected into a round-bottom flask.

Using this set-up allowed us to rapidly screen a selection of conditions and quickly confirm the viability of preparing the desired 5-chloro-1,2,4-thiadiazole building block **7** in a short residence time of only 5 min with yields up to 80%. Importantly the improved heat transfer offered by this flow approach meant that the reaction can be performed at ambient temperature without decomposition or run-away phenomena being observed. Although the desired

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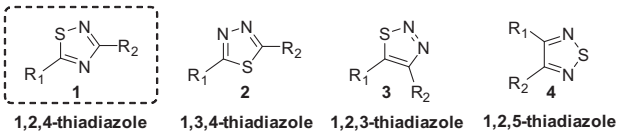
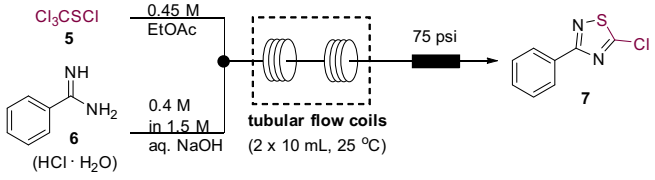


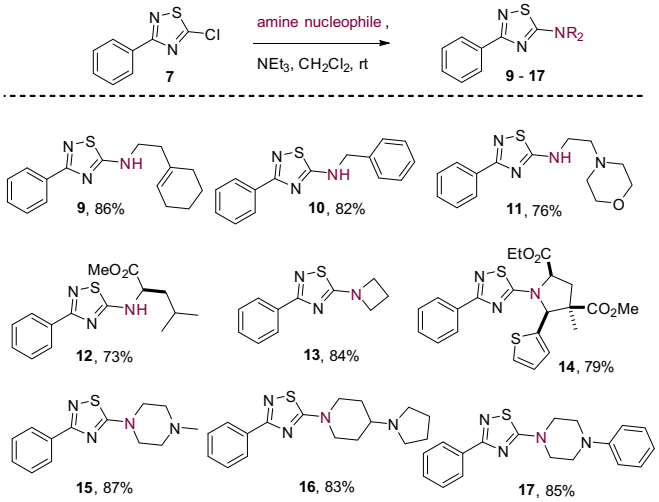
Figure 1. Regioisomerism of thiadiazoles (**1**–**4**).



Scheme 1. Flow reactor set-up.

reaction reaches completion in <5 min we elected to use a residence time of 30 min in order to further ensure complete hydrolysis of any residual reagent **5** in addition to any of its hazardous by-products in the alkaline aqueous co-solvent. This is very selective as the desired product **7** resides preferentially in the organic phase which minimizes its hydrolysis to the corresponding 5-hydroxy derivative (**8**). This is more difficult to achieve in a batch process showcasing another benefit of this flow process. Encouraged by these results we decided to test the scale up of **7** by processing a 20-fold amount of starting materials in an analogous fashion (20 mmol scale). Pleasingly this directly translated into an efficient access to multi-gram quantities of the desired 5-chloro-1,2,4-thiadiazole **7** which was isolated in pure form after aqueous extraction and filtration over a short plug of silica with hexanes as the eluent yielding 3.25 g of **7** (83%).

With sufficient quantities of compound **7** in hand we proceeded to study its functionalization via reaction with different nucleophiles in a simple parallel batch process. We therefore dissolved aliquots of **7** in CH_2Cl_2 (1.0 mmol, 2.5 M) and added the desired nucleophile (1.1 equiv.) and triethylamine as base (1.1 equiv.). The reactions were stirred at 25 °C until complete conversion of **7** was indicated by tlc (typically 2–8 h) followed by evaporation and purification by silica gel chromatography. Pleasingly, this approach allowed us to quickly generate a small selection of reaction products based on various nitrogen nucleophiles including aliphatic as well as variable cyclic amine species (Scheme 2).



Scheme 2. Functionalization of **7** with amine nucleophiles.

Furthermore, we established that substituted thioimidazoles obtained via a Marckwald multicomponent reaction[28] are equally competent nucleophiles analogously delivering interesting sulfide linked architectures in good yield (Fig. 2). Finally, we found that 5-phenoxy substituted 1,2,4-thiadiazoles can be generated by treating a solution of **7** (0.5 M, THF) at room temperature with phenols in the presence of polymer-substituted BEMP as base leading to the clean and high-yielding formation of the desired adduct **21** (Fig. 2).

The connectivity of selected reaction products (**13** and **20**) was confirmed by single crystal X-ray diffraction experiments (Figure 3). This also revealed an interesting π-stacking phenomenon between the thiadiazole ring and a nearby aryl moiety in the case of sulfide linked entities (e.g. **20**).

In an extension of our studies we decided to investigate the formation of 5-chloro-1,2,4-thiadiazole building blocks that would enable functionalization in a bidirectional sense. To this end we opted to incorporate bromo-substituents located at different positions of the phenyl moiety enabling future diversification by means of metal mediated amination or cross-coupling reactions (Fig. 4).

The required bromophenylamidine substrates (**22**–**24**) were prepared by reacting ortho-, meta- and para-bromobenzonitrile (0.5 M, THF) with a solution of NaHMDS (1.5 M, 1.2 equiv., THF, 1 h, rt) rendering after treatment with aqueous hydrochloric acid the desired bromophenylamidine HCl-salts **22**–**24** (see experimental section for full details). Having gained a quick access to these substrates we applied them towards the flow-synthesis of the corresponding thiadiazole derivatives (Scheme 3). In order to avoid any potential solubility issues we modified the initial set-up by first mixing trichloromethane sulfenylchloride (**5**, stream 1, 0.45 M, EtOAc) with the bromophenylamidine HCl-salt (**22**–**24**, stream 2, 0.4 M, H_2O) prior to adding a stream containing NaOH (stream 3, 1.5 M, H_2O). The resulting biphasic reaction mixture was then again directed through two flow coils maintained at

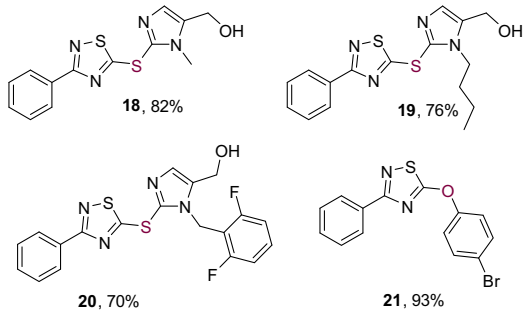


Figure 2. Structures of sulfur- and oxygen-linked products 18–**21.**

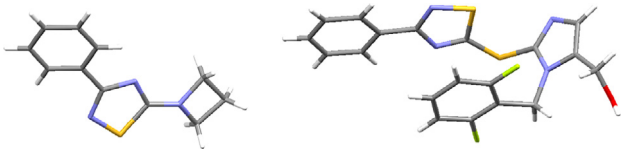


Figure 3. X-ray crystal structures of **13** (left) and **20** (right).

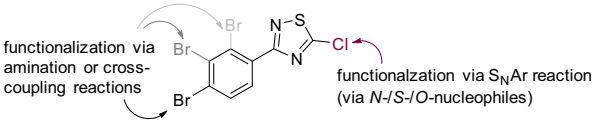


Figure 4. Key scaffold for bidirectional diversification.