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Diazo Compounds

Fluoroalkyl-Substituted Diazomethanes and Their Application in a General Synthesis of Pyrazoles and Pyrazolines

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Abstract: A novel continuous-flow approach for the synthesis of fluoroalkyl-substituted diazomethanes has been developed. Utilizing a cheap, self-made microreactor fluoroalkyl-substituted amines were transformed into the corresponding diazomethanes using *tert*-butyl nitrite and acetic acid as catalyst. These diazomethanes were employed in [2+3] cycloaddition reactions with olefins and alkynes, yielding valuable pyrazolines and pyrazoles in good to excellent yields.

The synthesis of functionalized, fluorinated heterocycles is of major interest to both the pharmaceutical and agrochemical industry. Fluorinated compounds often possess highly desired properties, such as high lipophilicity and favorable metabolic stability. Thus, the incorporation of fluorine into pharmaceutically active molecules plays a significant role in lead finding/optimization processes. New operationally simple and broadly applicable synthetic methods are highly desired to streamline synthesis of this important class of building blocks.[1,2]

Fluoroalkyl-substituted pyrazoles are a privileged class of heterocycles and find widespread application in drug discovery programs (Figure 1).[3,4] For example, COX inhibitors Celecoxib **1a**[4a,b] and Deracoxib **1b**[4b] contain a tri- and a difluoromethylated central pyrazole moiety, respectively. Similarly, the antiviral AS-136 A **3**,[4c] factor Xa inhibitor Razaxaban **5**,[4d] and TRPV-1 modulator **6**[4e] possess a central trifluoromethylated pyrazole ring. Moreover, sulfonyl-substituted fluoroalkylated pyrazoles **4**[4f] as well as long-chain perfluoroalkylated pyrazoles ($R_F = C_2F_5$, **2**)[4g] find prominent applications as insecticides or as ligands of Pt^{II} complexes in opto-electronic devices ($R_F = C_3F_7$, C_4F_9).[4h]

Thus, the development of new, efficient, easily scalable, and broadly applicable synthetic methods for the rapid synthesis of fluoroalkyl-substituted pyrazoles is of high interest. The [2+3] cycloaddition reaction of fluoroalkyl-substituted diazomethanes with olefins and alkynes provides an atom-economic approach for the direct synthesis of this structural class.

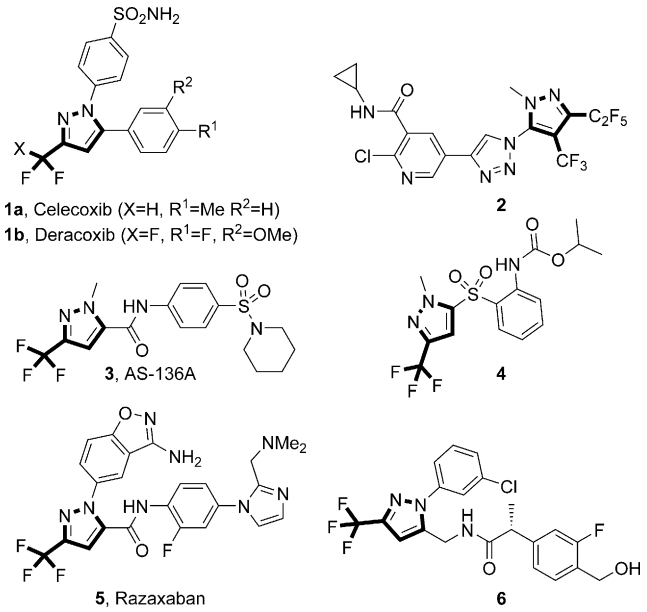

Figure 1. Fluoroalkyl-substituted pyrazoles.

Recently, the synthesis of trifluoromethyl diazomethane from primary amines has been reported.[5–7] Morandi and Carreira reported on the utilization of inorganic nitrites for the preparation of trifluoromethyl diazomethane and applications in cyclopropanation reactions.[5a] The synthetic applicability of trifluoromethyl diazomethane was further investigated in the past years by different research groups,[5] for example in cyclopropanation[5b,d] and cycloaddition reactions.[5e,f] Recently, Mykhailiuk reported a new strategy for the preparation of these versatile reagents using an organic nitrite for the acid-catalyzed synthesis of difluoromethyldiazomethane and its application in [2+3] cycloaddition reactions.[6,7] Yet, a generally applicable method for the simple preparation of fluoroalkyl-substituted diazomethanes and their application to organic synthesis is still highly desired.

The challenge when working with diazomethanes is risk hazards, which renders the utilization of special glass equipment necessary. In particular, scale-up and multi-gram synthesis of small molecules for development programs of drug candidates require strong safety precautions when working with diazo compounds. Thus the development of a safe and robust method for the continuous-flow synthesis of diazomethane analogues is of great interest.[8,9]

Herein, we report on the continuous-flow synthesis of fluoroalkyl-substituted diazomethanes[9m] using commercially avail-

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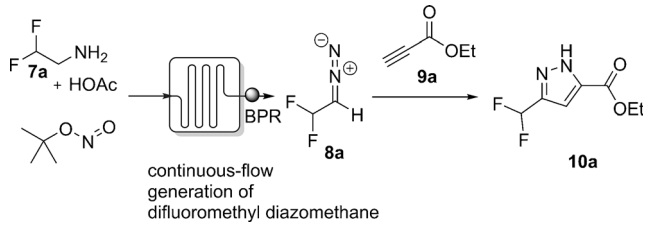
able amines and *tert*-butyl nitrite and the application of these valuable reagents in cycloaddition reactions. For the continuous-flow synthesis of diazomethanes we utilize a simple, self-made microreactor based on cheap, commercially available PTFE tubing (inner diameter: 0.8 mm, length: 2 m, reactor volume: 1 mL and an additional 20 psi back pressure regulator). Using this technology, we could realize a broadly applicable general protocol for the continuous-flow synthesis of fluoroalkyl-substituted diazomethanes and their subsequent application in the synthesis of pyrazoles and pyrazolines.

We started our investigations towards the synthesis of fluoroalkyl-substituted diazomethanes by evaluating our self-made microreactor in the synthesis of difluoromethyl diazomethane and the subsequent addition to ethyl propiolate as a model substrate (Scheme 1).



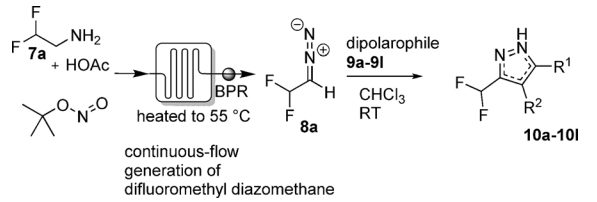
Scheme 1. Continuous-flow generation of difluoromethyl diazomethane and subsequent application in [2+3] cycloaddition reactions (BPR = back-pressure regulator).

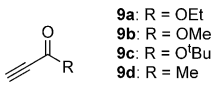
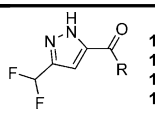
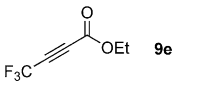
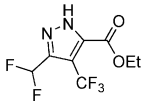
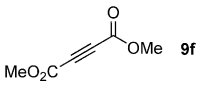
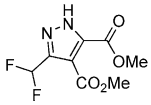
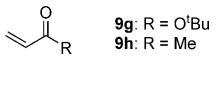
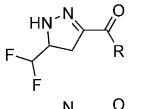
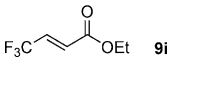
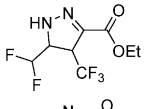
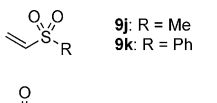
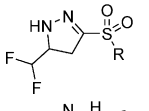
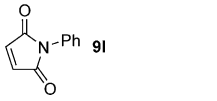
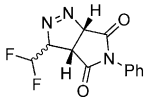
First, we evaluated the role of the Brønsted acid catalyst for the preparation of difluoromethyl diazomethane by monitoring the yield of the addition reaction to ethyl propiolate. To our surprise, acetic acid proved to be the best catalyst for the synthesis of difluoromethyl diazomethane; all other Brønsted acids examined provided the difluoromethylated product in significantly decreased yield. Using chloroform as solvent, 5 mol% of acetic acid catalyst and a reaction temperature of 55 °C for the preparation of difluoromethyl diazomethane proved to be the optimal reaction conditions, and we could isolate the desired pyrazole **10a** in excellent yield (93%).[10]

With the optimal conditions in hand, we investigated next the reaction of difluoromethyl diazomethane, generated in continuous-flow from primary amines and *tert*-butyl nitrite, with a range of different, structurally diverse, electron-poor alkynes and olefins (Table 1).

We were able to show that the addition of difluoromethyl diazomethane to different propiolic (**9a–c**) and acrylic acid esters (**9g**) provided the desired pyrazoles and pyrazolines in good to excellent yields. Further investigations on electron-poor alkynes and olefins revealed that the ketones **9d** and **9h** as well as disubstituted alkynes **9e** and **9f** and olefins **9i** provided the desired difluoromethylated pyrazoles and pyrazolines in very good yields and with excellent selectivities. In particular, we could demonstrate, that double fluoroalkyl-substituted pyrazole **10e** and pyrazoline **10i** could be easily obtained using this methodology. This structural class is of particular importance as double fluoroalkyl-substituted pyrazoles find widespread use as agrochemicals. In a similar way, cyclic olefins **9l** react to the corresponding bicyclic systems **10l**.

Table 1. Substrate scope of difluoromethyl substituted pyrazoles and pyrazolines.[a]



Dipolarophile	Product Yield[b]
 **9a**: R = OEt **9b**: R = OMe **9c**: R = O^{t}Bu **9d**: R = Me	 **10a**: R = OEt 93% **10b**: R = OMe 72% **10c**: R = O^{t}Bu 68% **10d**: R = Me 99%
 **9e**	 **10e** 71%[c]
 **9f**	 **10f** 74%
 **9g**: R = O^{t}Bu **9h**: R = Me	 **10g**: R = O^{t}Bu 85% **10h**: R = Me 84%
 **9i**	 **10i** 59%
 **9j**: R = Me **9k**: R = Ph	 **10j**: R = Me 83% **10k**: R = Ph 82%
 **9l**	 **10l** 80%[d]

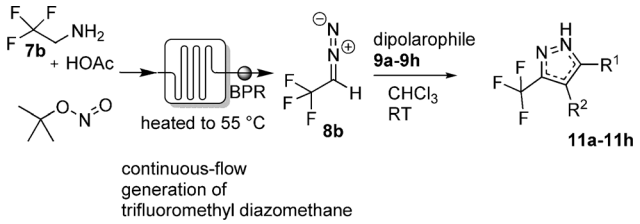
[a] Reaction conditions: 0.5 mmol **9a–9l**, 2,2-difluoroethylamine (2 eq), *tert*-butyl nitrite (2.4 eq), AcOH (0.1 eq). A 0.1 mmol L^{-1} solution of 2,2-difluoroethylamine and AcOH and *t*BuONO in $CHCl_3$ was added using a syringe pump (flow rate 100 μL min^{-1}) into a microreactor heated to 55 °C (PTFE tubing, volume 1 mL, 20 psi BPR). The solution was added into a reaction flask containing substrate and stirred for 14 h at RT. [b] Isolated yield. [c] 0.25 mmol **9e**, 2,2-difluoroethylamine (4 eq), *tert*-butyl nitrite (4.8 eq), AcOH (0.2 eq). [d] Mixture of diastereoisomers.

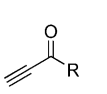
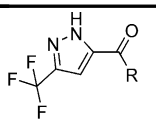
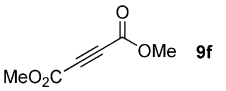
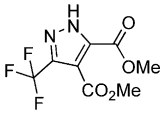
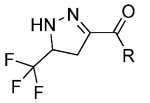
We also investigated the reaction of vinyl sulfones with fluoroalkyl-substituted diazomethanes for the first time, which opens up a highly efficient atom-economic path towards fluoroalkylated, sulfonated pyrazolines **10j** and **10k**. This structural class is important for applications in pharmaceutical and agrochemical industry for bioisosteric replacement of carbonyl groups. Surprisingly, only few applications have been disclosed yet, which might be due to limited synthetic methods for their rapid synthesis.

In further investigations we applied this protocol to the continuous-flow preparation of trifluoromethyl diazomethane. In contrast to previously described methods, we employed an organic nitrite and catalytic amounts of acetic acid for the prepa-

ration of trifluoromethyl diazomethane. The advantage of this method being, that no extraction, other workup, or purification procedure is necessary for the application of this reagent in chemical synthesis. We examined the [2+3] cycloaddition with a selection of different alkynes and olefins, which reacted smoothly to the desired trifluoromethylated pyrazoles and pyrazolines (Table 2).

Table 2. Substrate scope of the [2+3] cycloaddition of trifluoromethyl diazomethane yielding trifluoromethylated pyrazoles and pyrazolines.[a]



Dipolarophile	Product Yield[b]
 **9a**: R = OEt **9b**: R = OMe **9c**: R = O^{t}Bu **9d**: R = Me	 **11a**: R = OEt 98% **11b**: R = OMe 77% **11c**: R = O^{t}Bu 64% **11d**: R = Me 69%
 **9f**	 **11f** 89%
 **9g**: R = O^{t}Bu **9h**: R = Me	 **11g**: R = O^{t}Bu 99% **11h**: R = Me 86%

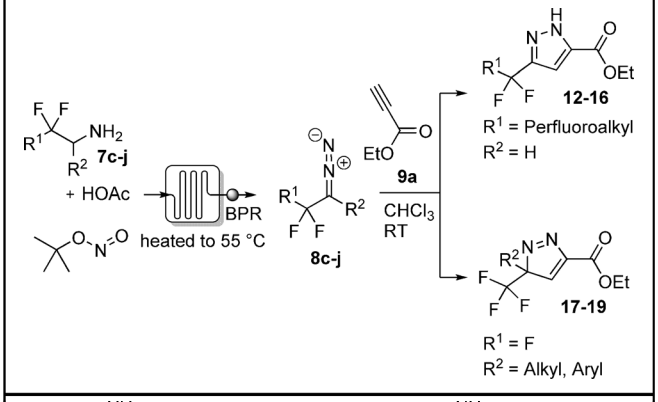
[a] Reaction conditions: 0.5 mmol **9a–9h**, 2,2,2-trifluoroethylamine (**7b**, 2 eq), *tert*-butyl nitrite (2.4 eq), AcOH (0.1 eq). A 0.1 mmol L^{-1} solution of 2,2-difluoroethylamine and AcOH and *t*BuONO in $CHCl_3$ was added by syringe pump (flow rate 100 μL min^{-1}) into a microreactor heated to 55 °C (PTFE tubing, volume 1 mL, 20 psi BPR). The solution was added into a reaction flask containing substrate and stirred for 14 h at RT. [b] Isolated yield.

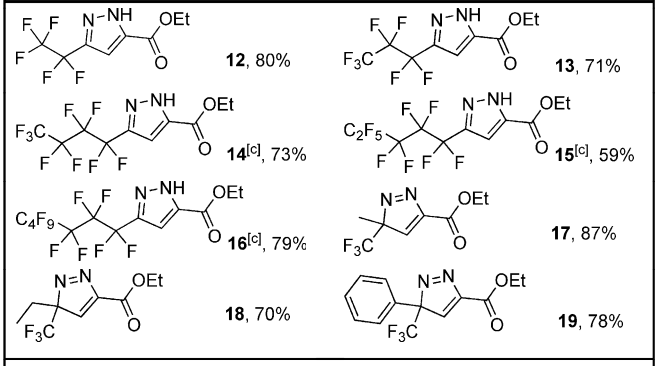
In a next step, we became interested in the general applicability of this protocol for the preparation of different fluoroalkyl-substituted diazomethanes. Thus we decided to investigate a range of different perfluoroalkyl-substituted methanamines using our protocol (Table 3).

Indeed, we were able to demonstrate that different perfluoroalkyl-substituted methanamines react with *tert*-butyl nitrite to the corresponding perfluoroalkyl-substituted diazomethanes. These diazomethanes were subjected under our standard reaction conditions to the [2+3] cycloaddition with ethyl propiolate yielding the desired perfluoroalkyl-susbtituted pyrazoles (Table 3, **12**–**16**) in good to excellent isolated yields. It should be noted that the corresponding monofluoromethyl substituted pyrazole was not obtained under these reaction conditions.

Further investigations concentrated on branched primary amines using our continuous-flow protocol. We could demonstrate that valuable α-branched trifluoromethyl diazomethanes could be generated using different aliphatic and aromatic substituted 2,2,2-trifluoroethylamine derivatives and *tert*-butyl nitrite as a cheap organic nitrite source. Application in the [2+3] cycloaddition reaction with ethyl propiolate yielded the desired 3*H*-pyrazoles (Table 3, **17**–**19**) in excellent yields.

Table 3. Substrate scope of fluoroalkyl-substituted diazomethanes and their application in a [2+3] cycloaddition reaction with ethyl propiolate.[a]

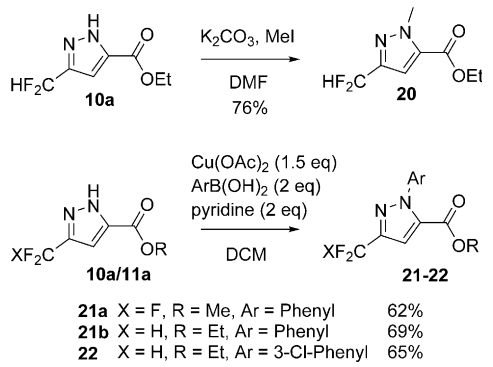




[a] Reaction conditions: 0.5 mmol **9a**, amine **7c–7j** (2 eq), *tert*-butyl nitrite (2.4 eq), AcOH (0.1 eq). A 0.1 mmol L^{-1} solution of **7c–7j** and AcOH and *t*BuONO in $CHCl_3$ was added by syringe pump (flow rate 100 μL min^{-1}) into a microreactor heated to 55 °C (PTFE tubing, volume 1 mL, 20 psi BPR). The solution was added into a reaction flask containing substrate and stirred for 14 h at RT. [b] Isolated yield. [c] 0.25 mmol **9a**, amine (4 eq), *tert*-butyl nitrite (4.8 eq), AcOH (0.2 eq).

Finally, we performed a series of derivatization reactions of the herein-described pyrazoles **10a** and **11a**. Methylation provided the *N*-methyl pyrazole **20** in excellent yield and Chan–Lam coupling proved very efficient for the introduction *N*-aryl substituents using aromatic boronic aicds (**21**, **22**) (Scheme 2).[11] This way, we could demonstrate that upon simple derivatization of previously described building blocks, valuable intermediates for broad application in medicinal and agrochemical industry can be obtained, for example for the synthesis of factor Xa inhibitors or TRPV-1 modulators such as **5** and **6** in Figure 1.

In summary, we herein report on the acid-catalyzed synthesis of fluoroalkyl-substituted diazomethanes in continuous-flow using an organic nitrite source and the application of these reagents in cycloaddition reactions. We were able to demonstrate for the first time that a range of different linear and substituted fluoroalkyl diazomethanes can be efficiently generated in a safe and operationally simple way. These diazomethanes were applied in [2+3] cycloaddition reactions with a broad variety of different olefins and acetylenes yielding fluoroalkyl-



Scheme 2. Application of fluoromethyl substituted pyrazoles in *N*-alkylations and *N*-arylation reactions.

substituted pyrazolines and pyrazoles in good to excellent yield.

Keywords: cycloaddition · diazo compounds · fluorine · heterocycles · microreactors

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[10] For details, see the Supporting Information.

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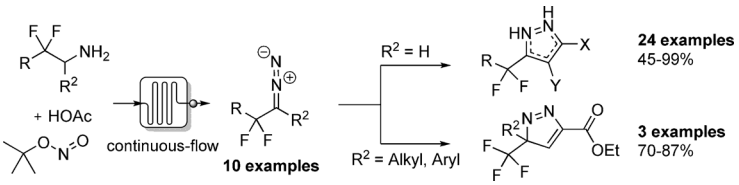

Fluoroalkyl-substituted diazomethanes could be generated from primary amines using a continuous-flow microreactor. These valuable reagents were applied in the synthesis of fluoroalkyl-substituted pyrazolines and pyrazoles (see scheme).

Diazo Compounds

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Fluoroalkyl-Substituted Diazomethanes and Their Application in a General Synthesis of Pyrazoles and Pyrazolines