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Generation and Synthetic Application of Trifluoromethyl Diazomethane Utilizing Continuous Flow Technologies

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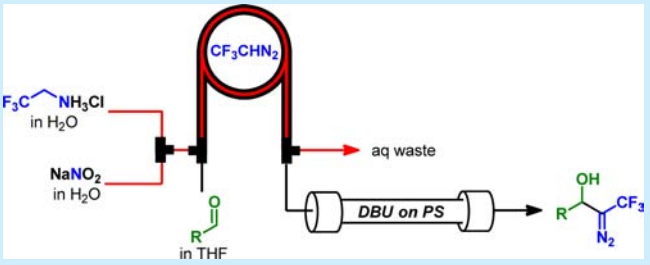
Supporting Information

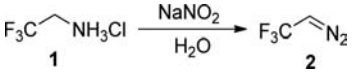
ABSTRACT: A continuous process for the synthesis and inline separation of anhydrous trifluoromethyl diazomethane in a single continuous flow process is presented. The diazo building block is generated from the corresponding amine and $NaNO_2$ under acidic, aqueous conditions and subsequently diffuses through a gas-permeable membrane into an organic stream. To avoid storage and transportation of the hazardous compound, a representative downstream process in a packed-bed reactor yielding highly functionalized building blocks was developed.



Incorporation of fluorine atoms into organic molecules can often dramatically enhance their physical, biological, and chemical properties.[1,2] These remarkable effects have led to widespread application of organofluorine compounds in pharmaceutical, agrochemical, and materials sciences.[1,2] One of the most popular fluorine-containing moieties undoubtedly is the trifluoromethyl group, which often improves the metabolic stability, lipophilicity, and binding selectivity of the corresponding unsubstituted analogues.[1,2] Many reagents and protocols for the selective trifluoromethylation of small molecules have thus been advanced over the past decades, resulting in a rapidly growing research field.[3]

A particularly interesting building block for the preparation of trifluoromethylated compounds is trifluoromethyl diazomethane (**2**), which was first generated in 1943 by diazotation of 2,2,2-trifluoroethylamine hydrochloride (**1**, Scheme 1).[4] Although this

Scheme 1. Synthesis of Trifluoromethyl Diazomethane



gaseous reagent (bp 13 °C) represents a versatile trifluoromethyl source, for a long period of time, only a very limited number of synthetic applications were reported. This is most likely explained by the explosive and potentially toxic properties of this material.[5] To challenge this limitation, Morandi and Carreira have recently developed an elegant protocol for the in situ generation of **2** and its subsequent utilization for iron-catalyzed cyclopropanation reactions.[6] A plethora of applications for **2** were subsequently reported by in situ generation of diazo building block **2** in biphasic environments or related strategies.[7−11] Still, the toxicity and thermal instability of the volatile reagent **2** poses severe safety risks in larger-scale batch processes.

Continuous flow technology offers the unique possibility to address these safety hazards by producing hazardous intermediates on demand.[12] Moreover, subsequent transformations and purification steps can easily be integrated in multistep processes to avoid storage and transportation of such compounds. It is thus not surprising that there is an ongoing interest in the application of this technology for the generation and use of diazo compounds.[13] For example, Ley and co-workers have recently developed a robust continuous protocol for the synthesis and utilization of diazo species by oxidation of the corresponding hydrazones with MnO_2 in a packed-bed reactor.[14]

In 2012, the continuous production of ethyl diazoacetate (EDA) from glycine ethyl ester and $NaNO_2$ in H_2O was described.[15] Immediately after the diazotation, a continuous extraction and phase separation was successfully applied to deliver EDA for further cyclopropanation reactions. Similar strategies were used to optimize the formation of EDA under mono- and biphasic flow conditions.[16−18] In the latter case, membrane-based microseparators were used to separate the organic and aqueous phase.[16,17] Diazomethane, a highly volatile and hazardous reagent, has also been generated by continuous processing strategies in aqueous media.[13,15,19] Notably, the highly reactive methylation agent can be efficiently separated from the aqueous mixture by gas-permeable membranes, that is, using a commercially available tube-in-tube reactor, resulting in an anhydrous diazomethane solution.[20−22]

Based on these findings, we hypothesized that **2** should also be able to penetrate the hydrophobic, gas-permeable Teflon AF-2400 membrane of the tube-in-tube device. This would result in a steady stream of the dry building block for subsequent downstream processes. Notably, this technique would also facilitate a convenient access to solutions of **2** in water-miscible

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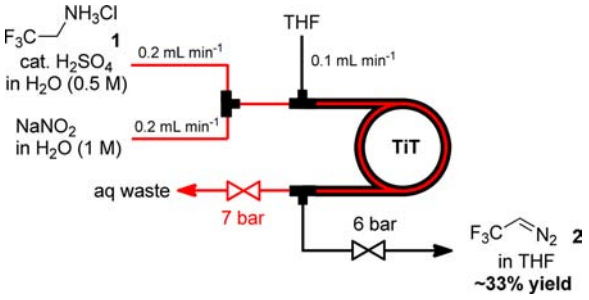
organic solvents such as THF or MeCN, which would require tedious distillation or stripping techniques in batch.[8a] To prove this assumption, an aqueous solution of **1** (0.5 M) with catalytic amounts of H_2SO_4 was mixed with $NaNO_2$ (1 M, H_2O) in the inner tube made out of Teflon AF-2400 (2 mL), resulting in a total flow rate of 0.4 mL min^{-1} (Scheme 2).[23] Simultaneously,

Scheme 2. Continuous Preparation and Separation of 2 in a Tube-in-Tube (TiT) Reactor

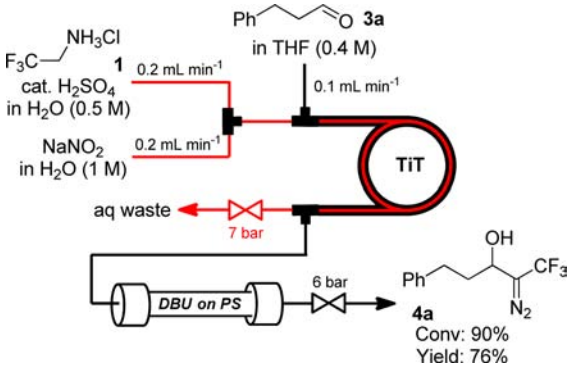


dry THF was pumped through the outer tube made out of a gas-impermeable perfluoroalkoxy polymer (~6 mL) at a flow rate of 0.1 mL min^{-1}. Visual inspection of both streams indicated that **2** indeed passed the membrane because the organic solution turned deep yellow, whereas the collected aqueous phase was completely colorless. To estimate the amount of CF_3CHN_2, the collected THF solution was subsequently allowed to react with sulfuric acid (1 M). By measuring the amount of generated N_2, we calculated that the continuous process resulted in ~33% of **2** based on **1**.[23]

With this proof of principle in hand, we ultimately moved on to integrate a subsequent consumption of the reactive intermediate **2** in a downstream process. A base-catalyzed aldol reaction, which was already intensively studied for EDA, was chosen as the model reaction.[17,18,24] Initial optimization experiments were performed with 3-phenylpropionaldehyde (**3a**) in the presence of catalytic amounts of DBU in the outer tube at different conditions.[23] Unfortunately, even at a residence time of 2 h, a maximum of 80% conversion under steady-state conditions was observed. This is in good agreement with earlier observations for this transformation using EDA in batch, where reaction times up to 24 h are required.[24] To circumvent these drawbacks, stoichiometric amounts of DBU[18] or ultrasonication[19] was studied to obtain acceptable yields in continuous flow mode. We assumed that the utilization of an immobilized catalyst in a packed-bed reactor could be a promising alternative because it not only affords a higher effective molarity of the catalyst during the reaction but also removes the necessity of subsequent quenching and catalyst separation.[25,26] Thus, we connected the membrane-based trifluoromethyl diazomethane generation unit with a cartridge reactor (2.4 mL total volume) filled with ~1.2 g of commercially available, polymer-supported DBU (Scheme 3).

After a short optimization study, we found that sufficient conversion (90%) for the model reaction can be obtained by applying flow rates of 0.2 mL min^{-1} for the amine (**1**, 0.5 M, H_2O) and $NaNO_2$ (1 M, H_2O) feeds entering the inner tube and 0.1 mL min^{-1} for the organic stream (**3a**, 0.4 M, THF) in the outer tube.[23] This corresponds to 2.5 equiv of the diazo precursor **1** and 5 equiv of $NaNO_2$ under steady-state conditions. Notably, the residence time for the coupling reaction in the packed-bed reactor was only 10 min at room temperature. Column

Scheme 3. Continuous Flow Setup for the Two-Step Process



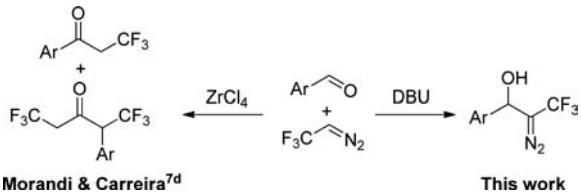
chromatography resulted in 76% isolated yield of the desired diazo compound **4a**.

With the optimized conditions in hand, we further investigated the scope of the reaction for a diverse set of aldehydes, resulting in valuable trifluoromethyl-functionalized diazo building blocks (Table 1).

In general, aliphatic aldehydes provided moderate to excellent yields (entries 1−5). In the case of aldehyde **3f**, we could not identify the corresponding product at all, which indicates a deactivation of the aldehyde by the conjugated system (entry 6). This effect could be further demonstrated by reacting various substituted benzylic aldehydes (entries 7−10). When the aldehyde functionality is activated by a slightly electron-withdrawing bromo substituent (**3h**), a conversion significantly higher than that for unsubstituted benzaldehyde (**3g**) was observed. As anticipated, strong electron-withdrawing substituents like trifluoromethyl (**3i**) or nitrile functionalities (**3j**) resulted in considerably higher conversions to the corresponding diazo compounds. Notably, the structure of **4j** was confirmed by single-crystal X-ray analysis.[23] Cyclohexanone (**3k**) did not provide significant amounts of the coupling product under the applied conditions (entry 11).

A similar condensation protocol with Lewis acid catalysts such as $ZrCl_4$ at low temperatures is known to furnish the corresponding trifluoroethyl-substituted ketones after hydride migration in the case of aliphatic ketones.[7d] Benzylic aldehydes were shown to undergo aryl migration, leading to double homologation, affording bis(trifluoromethyl)-substituted ketones (Scheme 4). In contrast, the above-discussed base catalysis offers a highly selective alternative since no aryl migration occurs.

Scheme 4. Lewis-Catalyzed vs Base-Catalyzed Condensation



After a few experiments were run under the optimized conditions, a significant decrease in conversion was observed. We assume that a byproduct or intermediate from the diazotation step passes the membrane and slowly deactivates the immobilized catalytic material. It was thus necessary to periodically regenerate the supported catalyst by rinsing the packed-bed reactor with a 0.5 M solution of DBU in THF.[23,27]

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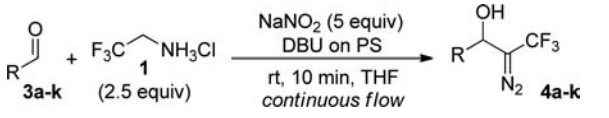
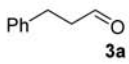
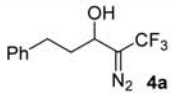
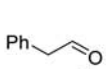
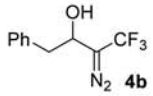
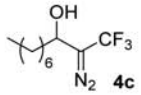
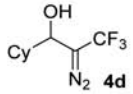
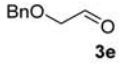
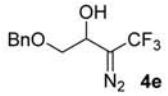
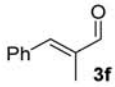
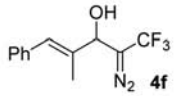
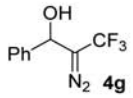
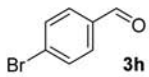
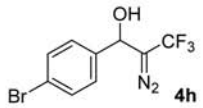
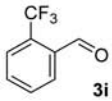
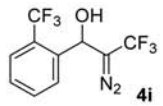
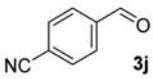
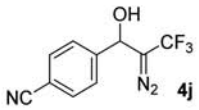
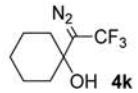
Table 1. Condensation of 2 with Aldehydes in Flow[a]



entry	substrate	product	conv (%)[b]	yield (%)
1	 3a	 4a	90[c]	76
2	 3b	 4b	57	46
3	 3c	 4c	86	71
4	 3d	 4d	80	65
5	 3e	 4e	80	72
6	 3f	 4f	<1	--
7	 3g	 4g	49	41
8	 3h	 4h	60	50
9	 3i	 4i	80	66
10	 3j	 4j	82	66
11	 3k	 4k	6[d]	--

[a]For conditions of the continuous process, see Scheme 2. [b]Determined by ^{1}H NMR using trichloroethylene as internal standard (IS). [c]Pyridine was used as IS. [d]Determined by ^{19}F NMR using α,α,α-trifluorotoluene as IS.

For the laboratory scale experiments described herein, this strategy was appropriate. Nevertheless, we decided to study this phenomenon in more detail. A long-run experiment over 6 h under slightly modified conditions showed a significant decrease of the catalyst performance after 3 h (Figure 1). When immobilized TBD was used instead of DBU, a similar drop in conversion occurred after 2 h. We hypothesized that by installing a second packed-bed reactor filled with a weak, catalytically inactive base between the trifluoromethyl diazomethane

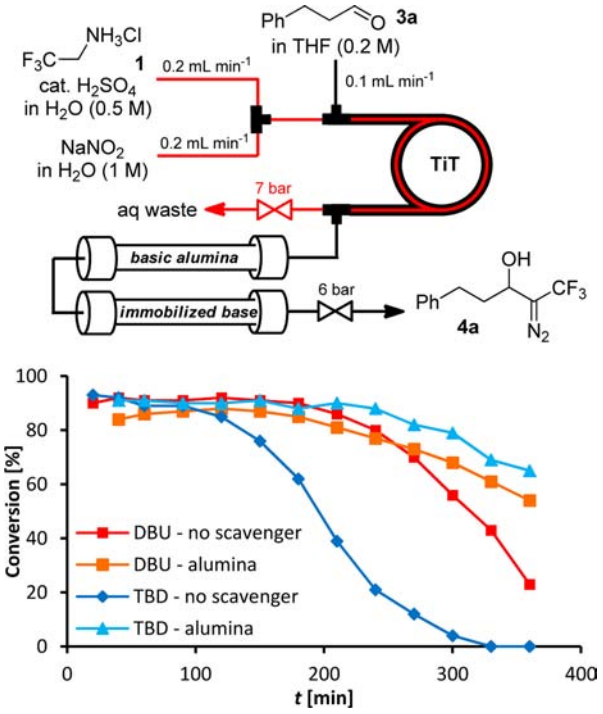


Figure 1. Long-run experiments with and without basic Al_2O_3.

generation unit and the catalyst cartridge the source of deactivation may be trapped, leading to a stable condensation process. A weak base like Al_2O_3 indeed extended the lifetime of the catalytically active species, showing a less drastic decrease of product formation (Figure 1).[23]

In summary, we have developed a simple and convenient protocol for the synthesis of anhydrous trifluoromethyl diazomethane using continuous flow technology. The diazo compound is generated from the corresponding amine and $NaNO_2$ under acidic, aqueous conditions and subsequently diffuses through a gas-permeable membrane into an organic stream. To avoid storage and transportation of the hazardous compound, the possibility of downstream processing is described in a subsequent aldol reaction, resulting in highly functionalized building blocks. Key to the success was the utilization of an immobilized catalyst in a packed-bed reactor for an efficient condensation process. The on-demand generation, separation, and consumption of CF_3CHN_2 described herein dramatically reduces safety risks and may open new doors for the application of this valuable trifluoromethyl source.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00194.

Experimental procedures, characterization data of new compounds, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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