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Continuous Flow Generation and Reactions of Anhydrous Diazomethane Using a Teflon AF-2400 Tube-in-Tube Reactor

Federica Mastronardi, Bernhard Gutmann, and C. Oliver Kappe*

Institute of Chemistry, University of Graz, Heinrichstrasse 28, A-8010 Graz, Austria

oliver.kappe@uni-graz.at

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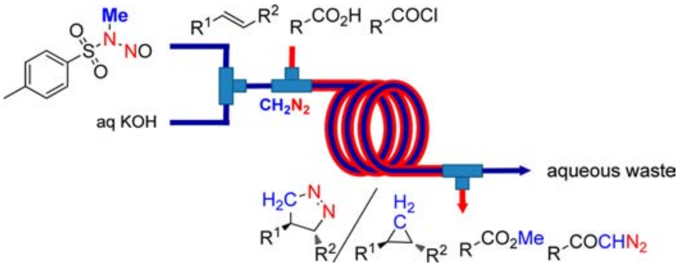
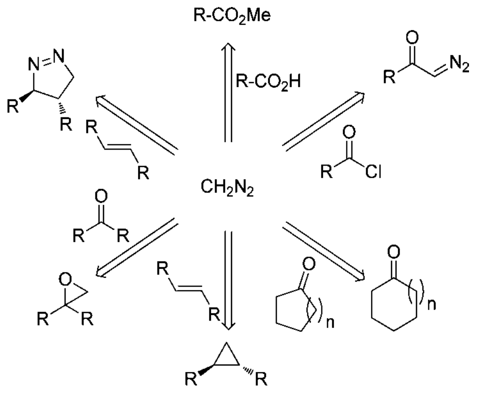
ABSTRACT



A continuous process for generation, separation, and reactions of anhydrous diazomethane in a tube-in-tube reactor was developed. The inner tube of the reactor is made of hydrophobic, gas-permeable Teflon AF-2400. The diazomethane is formed in the inner tube and then diffuses through the permeable membrane into the outer chamber and subsequently reacts in the solution carried within. This technique allows safe and scalable reactions with dry diazomethane to be performed on a laboratory scale.

Diazomethane (CH_2N_2) is one of the most valuable and versatile C_1 building blocks in organic chemistry (Scheme 1).[1] It is a potent methylation agent for carboxylic acids, phenols, alcohols, and a plethora of other nucleophiles, such as nitrogen and sulfur heteroatoms.[1] It is also essential for Arndt–Eistert homologation chemistry via α-diazoketones and for ring expansion or homologation of ketones.[1,2] As a powerful 1,3-dipole, diazomethane participates in Huisgen [2 + 3] cycloaddition reactions with unsaturated compounds to form the corresponding nitrogen-containing heterocycles.[3] Alternatively, in the presence of suitable catalysts, it forms cyclopropanes, epoxides, or aziridines from alkenes, ketones, or imines, respectively, by [1 + 2] additions (Scheme 1).[1] Reactions with diazomethane are usually very fast and take place under mild conditions, often producing nitrogen as the sole byproduct.

Scheme 1. Versatile Reactivity of Diazomethane



Unfortunately, working with diazomethane presents several serious safety hazards.[4] Diazomethane is a highly

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(1) (a) Black, T. H. *Aldrichimica Acta* **1983**, *16*, 3–10. (b) Pizey, J. S. *Synthetic Reagents*; John Wiley & Sons: New York, 1974; Vol. 2, pp 65–142.

(2) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091–1160.

(3) Maas, G. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002; pp 539–622.

(4) The dangerous nature of CH_2N_2 is well appreciated: (a) Schoental, R. *Nature* **1960**, *188*, 420–421. (b) Lewis, C. E. *J. Occup. Med.* **1964**, *6*, 91–93. (c) Lewinn, E. B. *Am. J. Med. Sci.* **1949**, *218*, 556–562. (d) de Boer, T. J.; Backer, H. *J. Org. Synth.* **1963**, *4*, 250–253.

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poisonous and irritating compound. The severe toxicity of diazomethane is particularly problematic because of its high volatility (bp = -23 °C).[4] Furthermore, diazomethane is extremely sensitive to friction, heat, light, and mechanical shock and tends to decompose explosively.[4] Thus, any sharp glass edges have to be strictly avoided when working with diazomethane, and the ends of glassware should be rounded in a flame. Specialized kits for the preparation of diazomethane on various scales (up to 300 mmol) are commercially available.[1] Due to its instability and toxicity, the use of diazomethane in the laboratory is often considered to be problematic or risky, and therefore, this extremely powerful reagent today is not often used in synthetic organic chemistry laboratories.

Hazardous reagents are preferably produced on demand by continuous flow processes. Production and consumption of the material can be integrated in multistage processes to eliminate the need to handle reactive reagents and to keep the total amount of stored material as low as possible.[5] In 2002, an industrial process for the continuous generation of up to 60 t of diazomethane gas per year was described by Proctor and Warr.[6] Diazomethane was produced from a feed containing *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald) in DMSO and a second feed of potassium hydroxide in water. The generated diazomethane gas was continuously transported by a N_2 stream to a reaction vessel where it was quenched with a solution of benzoic acid in DME.[6] More recently, Kim and coworkers presented a dual-channel microreactor for the continuous generation, separation, and subsequent reaction of diazomethane.[7] The microreactor was fabricated from poly(dimethylsiloxane) (PDMS) and consisted of two parallel channels separated by a 45 μm thick PDMS membrane (60 μL residence volume). The PDMS membrane is permeable to gases and small organic molecules. The diazomethane was produced from Diazald and KOH in one channel of the microreactor and subsequently diffused through the membrane where it formed the product in the second channel.[7] Unfortunately, the output of the PDMS microreactor was quite small (daily output ~1 mmol). Furthermore, many common nonpolar organic solvents, such as THF, $CHCl_3$, or Et_2O, diffuse into the PDMS polymer and cause the material to swell and are therefore incompatible with the PDMS device. Moreover, nonpolar solutes can be absorbed in the PDMS material and get lost from the reaction stream.[8]

Herein, we describe a process in which generation, separation, and chemical transformations of diazomethane are integrated in a robust, commercially available tube-in-tube reactor. The tube-in-tube device was originally developed in the Ley laboratory as a gas-addition tool for continuous processes.[9–12] The inner tube of the device is made of Teflon AF-2400 (0.8 mm inner diameter, 1 mm outer diameter, 4 m length). Teflon AF-2400 has a chemical resistance and mechanical strength comparable to that of PTFE but has a highly porous, amorphous structure.[11] Accordingly, the AF-2400 tube serves as a robust, hydrophobic, permeable membrane which selectively allows gases, but not liquids, to cross.[9–11] This membrane is enclosed within a thick-walled impermeable outer tube (PTFE; 1.59 mm inner diameter, 3.2 mm outer diameter, 4 m length). Typically, the gas (e.g., CO, CO_2, H_2, ethene, ethyne, or SO_2) is carried between the outer tube and the inner tube.[9] It crosses the semipermeable membrane and dissolves into the liquid carried within.[9] We contemplated a continuous generation of diazomethane in the inner chamber of the tube-in-tube device by combining a liquid stream of a Diazald solution with a stream of a strong base (e.g., KOH).[13] If the highly volatile diazomethane gas is able to penetrate the hydrophobic AF-2400 membrane, this strategy should give a steady stream of the dry reagent into the outer tube, without the need to distill or strip the reactive reagent from the reaction solution. Handling, transport paths, and storage time of the highly explosive diazomethane are thereby reduced to a minimum.

Initial optimization experiments with the tube-in-tube device were performed using benzoic acid (**1a**) as reagent in the outer tube as indicated in Figure 1 (for optimization details, see Table S1 in the Supporting Information). Reactions of diazomethane with carboxylic acids are generally quantitative and essentially instantaneous. The conversion of benzoic acid to the ester therefore characterizes the efficiency of diazomethane formation and the separation efficiency of diazomethane into the outer tube. Rapid transportation of the freshly formed diazomethane into the organic phase is essential to prevent decomposition in the aqueous phase (the half-life of CH_2N_2 in water at 20 °C and pH 7.2 is ≈12 min).[6] The rate with which diazomethane is transferred through the membrane

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(5) For continuous flow reactions involving diazomethane, see: (a) Martin, L. J.; Marzinzik, A. L.; Ley, S. V.; Baxendale, I. R. *Org. Lett.* **2011**, *13*, 320–323. (b) Rossi, E.; Woehl, P.; Maggini, M. *Org. Process Res. Dev.* **2012**, *16*, 1146–114. (c) Struempel, M.; Ondruschka, B.; Daute, R.; Stark, A. *Green Chem.* **2008**, *10*, 41–43.

(6) Proctor, L. D.; Warr, A. J. *Org. Process Res. Dev.* **2002**, *6*, 884–892.

(7) (a) Maurya, R. M.; Park, C. P.; Lee, L. H.; Kim, D.-P. *Angew. Chem., Int. Ed.* **2011**, *50*, 5952–5955. (b) For industrial applications, see: Poechlauer, P. *Chim. Oggi* **2012**, *30*, 51–54.

(8) Lee, J. N.; Park, C.; Whitesides, G. M. *Anal. Chem.* **2003**, *75*, 6544–6554.

(9) For selected references using a variety of gases, see the following. (a) O_3: O'Brien, M.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2010**, *12*, 1596–1598. (b) CO_2: Polyzos, A.; O'Brien, M.; Petersen, T. P.; Baxendale, I. R.; Ley, S. V. *Angew. Chem., Int. Ed.* **2011**, *50*, 1190–1193. (c) CO: Koos, P.; Gross, U.; Polyzos, A.; O'Brian, M.; Baxendale, I.; Ley, S. V. *Org. Biomol. Chem.* **2011**, *9*, 6903–6908. (d) H_2: O'Brian, M.; Taylor, N.; Polyzos, A.; Baxendale, I. R.; Ley, S. V. *Chem. Sci.* **2011**, *2*, 1250–1257. (e) Newton, S.; Ley, S. V.; Casas Arcé, E.; Grainger, D. M. *Adv. Synth. Catal.* **2012**, *354*, 1805–1812. (f) NH_3: Cranwell, P. B.; O'Brian, M.; Browne, D. L.; Koos, P.; Polyzos, A.; Peña-Lopéz, M.; Ley, S. V. *Org. Biomol. Chem.* **2012**, *10*, 5774–5779.

(10) For an analysis of mass transfer and scalability of the tube-in-tube reactor, see: Yang, L.; Jensen, K. F. *Org. Process Res. Dev.* **2013**, *17*, 927–933.

(11) The use of the tube-in-tube device employing two liquid feeds similar to the strategy reported herein has only been reported very recently. (a) Generation of CO: Brancour, C.; Fukuyama, T.; Mukai, Y.; Skrydstrup, T.; Ryu, I. *Org. Lett.* **2013**, *15*, 2794–2797. (b) Generation of CH_2O: Buba, A. E.; Koch, S.; Kunz, H.; Löwe, H. *Eur. J. Org. Chem.* **2013**, 4509–4513.

(12) The tube-in-tube device (gas addition module) is available from Uniqsis Ltd. See www.uniqsis.com for more details.

(13) For a continuous flow production of Diazald, see: (a) Struempel, M.; Ondruschka, B.; Stark, A. *Org. Process Res. Dev.* **2009**, *13*, 1014–1021. (b) See also ref 7b.

depends on several parameters, such as temperature and residence time, in addition to solvent, concentration of reagents, and pH in the inner tube. Water greatly reduces the solubility of diazomethane in the reaction mixture, thus, increasing separation efficiency and decreasing the amount of diazomethane lost in the waste stream. However, since water also reduces the solubility of the Diazald, a compromise between Diazald solubility and transport rate of diazomethane is required.[14]

After considerable experimentation varying solvents, reagent concentrations, and flow rates for all three feeds involved (Figure 1),[14] we have found that quantitative conversions to methyl benzoate (**2a**) were obtained applying flow rates of 200 μL/min for the KOH (0.6 M, MeOH/H_2O 1:1), the Diazald (0.3 M, MeOH), and the benzoic acid (**1a**, 0.15 M, THF) feeds. Solutions of the base and Diazald (2 equiv relative to benzoic acid **1a**) feeds were combined in a T-mixer, and the combined mixture went through a short PFA coil (200 μL) before entering the inner channel of the tube-in-tube reactor (Figure 1). The aqueous waste stream leaving the inner tube of the reactor was fed into concentrated acetic acid to decompose any unconsumed diazomethane. It should be noted that the temperature of the PFA coil connecting the T-mixer and the tube-in-tube device did not rise noticeably, even though the reaction of Diazald with KOH to CH_2N_2 is fast and highly exothermic. The product mixture from the outer tube was collected in a receiver flask with an acetic acid quench solution, and the mixture was analyzed by HPLC-UV. Using the flow rates stated above, this corresponds to a residence time of ~16 min for the methylation process.

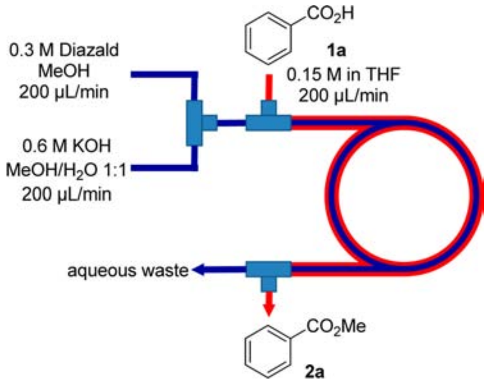

Figure 1. Continuous esterification of benzoic acid with diazomethane in a tube-in-tube reactor. A graphical image of the setup is shown in the Supporting Information.

Apart from **1a**, other aromatic carboxylic acids (**1b**–**d**), both with electron-donating and -withdrawing groups, provided full conversion to the corresponding esters (**2b**–**d**) under these general reaction conditions (Figure 2a). The esters were isolated by an extraction procedure in good to quantitative yields. As expected, methylation of 5-phenyltetrazole led to a mixture of the 1- and 2-methyltetrazoles (**3**).[15] The [2 + 3] cycloaddition of the diazomethane to *N*-phenylmaleimide gave the respective 1-pyrazoline (**4**) in essentially quantitative conversions (Figure 2b).[3] The pure product was isolated in 76% yield by flash chromatography.

Diazomethane adds to alkenes to form cyclopropanes via metal–carbene intermediates in the presence of Pd, Cu, Rh, and various other transition metal catalysts.[16,17] Cyclopropanes are useful synthetic intermediates and frequently employed as building blocks in organic syntheses.[17] Furthermore, the cyclopropyl unit occurs in various natural products and biologically active substances.[18] Using 4-phenyl-3-buten-2-one in combination with 1 mol % of $Pd(OAc)_2$ in the outer tube, the respective cyclopropane (**5**) was formed in 84% conversion (HPLC-UV at 235 nm) applying the general reaction conditions without any further reoptimization. Flash chromatography provided the pure product in 59% yield (Figure 2c).

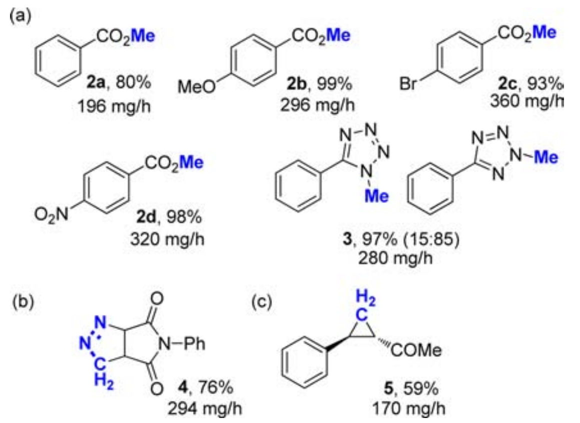

Figure 2. Continuous in situ generation and reactions of diazomethane: (a) methylations of various nucleophiles; (b) [2 + 3] cycloadditions; (c) cyclopropanation of alkenes (1% mol of $Pd(OAc)_2$). Isolated yields; for general conditions, see Figure 1 and the Supporting Information.

Finally, we attempted the acylation of diazomethane with acid chlorides (Arndt–Eistert reaction).[2] The resulting α-diazocarbonyl compounds are versatile precursors for a wide variety of chemical transformations under mild conditions.[1,2] The product stream of the outer tube was fed directly into 6 M aqueous HCl to convert the generated diazo compound to the α-chloroketone (Figure 3). When a

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[14] Further optimization data are presented in the Supporting Information.

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[17] For reviews on the application of cyclopropanes in organic synthesis, see: (a) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C. *Chem. Rev.* **1989**, *89*, 165–198. (b) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196. (c) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051–3060.

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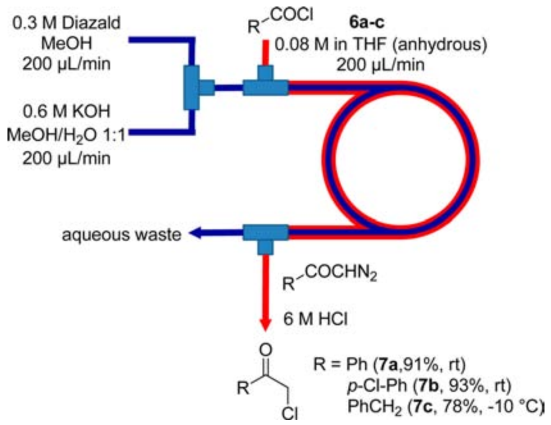

Figure 3. Continuous flow Arndt−-Eistert reaction using the tube-in-tube reactor. Isolated yields; rt = room temperature.

0.15 M solution of benzoyl chloride (**6a**) in anhydrous THF in the outer tube and 2 equiv of Diazald in the inner tube was employed, 63% of the acid chloride was converted to the corresponding α-chloroketone (**7a**). As the acylation of diazomethane liberates 1 equiv of HCl, part of the diazomethane is sequestered by the strong acid. Gratifyingly, when 3.8 equiv of Diazald was employed in the inner tube, the two-step conversion of the acid chloride (**6a**) to the α-chloroketone (**7a**) was improved to 98% (Figure 3). Importantly, no methyl benzoate could be detected in the product mixture, confirming that indeed anhydrous diazomethane penetrates the membrane into the outer tube, while water is retained in the inner tube. The resulting phenacyl chloride (**7a**) was isolated by extraction with Et_2O/aqueous $NaHCO_3$ in 91% yield. Similar results were obtained using *p*-chlorobenzoylchloride and phenylacetyl chloride as starting materials, albeit in the latter instance, the conditions were slightly modified in order to obtain 95% conversion (78% isolated yield) of the corresponding homologated acid chloride (**7c**) (see the Supporting Information for details).

In conclusion, we demonstrated the continuous generation, separation, and reaction of diazomethane in a tube-in-tube continuous flow reactor. The diazomethane is generated in the inner tube of the reactor from a feed of Diazald and a feed of potassium hydroxide. Dry diazomethane subsequently diffuses through a hydrophobic membrane into an outer tube where it dissolves and reacts in the solution carried within. Diazomethane is an exceptionally useful C_1 building block for a variety of reactions. However, the low boiling point, high toxicity, and extreme explosiveness of diazomethane have in the past severely limited its widespread use in laboratories and industry. The on-demand generation and direct separation/consumption of diazomethane in a commercially available microreactor environment, as described herein, eliminates human exposure to the reagent and reduces the risk of explosive decomposition. Therefore, this technique may allow a plethora of synthetic reactions using this powerful reagent to be explored and performed in the future and may revive interest in diazomethane chemistry.

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Supporting Information Available. Experimental procedures, optimization of reactions, and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.