One-Pot Synthesis of α-Haloketones Employing a Membrane-Based Semibatch Diazomethane Generator

Silvia Garbarino[1†], Javier Guerra[1,2], Peter Poechlauer[3], Bernhard Gutmann[1*] and C. Oliver Kappe[1*]

[1]*Institute of Chemistry, University of Graz, NAWI Graz, Heinrichstrasse 28, 8010 Graz, Austria*
[2]*Crystal Pharma SAU, Gadea Pharmaceutical Group-AMRI, Parque Tecnológico de Boecillo, Valladolid 47151, Spain*
[3]*DPx Fine Chemicals Austria GmbH & Co KG, St. Peter-Strasse 25, 4020 Linz, Austria*

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The crucial structural motive in viral protease inhibitors such as atazanavir and darunavir is a chiral aminoalcohol structure. The structure is generally introduced during the synthesis of the protease inhibitor via an α-chloroketone intermediate. The α-chloroketone can be synthesized in a multistep sequence from naturally occurring L-phenylalanine. Herein, we report a one-pot synthesis of an α-chloroketone starting from *N*-Boc-L-phenylalanine in a novel type of "tube-in-flask" semi-batch diazomethane generator. Activation of the amino acid to the mixed anhydride was carried out in the flask, while diazomethane was generated from in situ formed *N*-nitroso-*N*-methylurea within a gas-permeable tubing contained inside the flask. The diazomethane diffused through the gas-selective membrane into the flask, and reacted with the anhydride to the diazoketone (Arndt–Eistert reaction). The addition of aqueous hydrogen chloride provided the α-chloroketone and destroyed any excess of diazomethane. The desired product was isolated by extraction in excellent purity and yield (90%–96%).

Keywords: diazomethane, α-chloroketone, gas-permeable tubing, tube-in-flask reactor, Arndt–Eistert reaction

1. Introduction

In the late 1990s, a series of orally bioavailable viral protease inhibitors has gained approval for human immunodeficiency virus (HIV) treatment. Within 2 years of their introduction, annual death rates from AIDS in the developed world reduced dramatically [1]. As a consequence, viral protease inhibitors, such as saquinavir and atazanavir, have become listed by the World Health Organization (WHO) as Essential Medicines for a basic health care system (Scheme 1). The key structural unit in these protease inhibitors is a chiral aminoalcohol structure, formally derived from L-phenylalanine. A large body of research has been directed towards the synthesis of this chiral building block [1]. The most direct route involves halomethylation of *N*-protected-L-phenylalanine, followed by reduction of the haloketone to the *N*-protected amino-epoxide [1]. The protease inhibitor is then further assembled by a nucleophilic ring opening of the epoxide with the nitrogen of the C-terminal building block.

Even though a wide range of reagents and reaction conditions has been developed to accomplish the halomethylation, the most effective method remains the condensation of an activated amino acid with anhydrous diazomethane (CH_2N_2) to the α-diazoketone, followed by an α,α-substitution reaction with a hydrogen halide (Scheme 1) [1].

Diazomethane (CH_2N_2) is an exceptionally potent and versatile C1-building block in organic synthesis [2]. Reactions with diazomethane are typically fast and clean and proceed under mild conditions, often with nitrogen as the sole byproduct. However, diazomethane is a very poisonous and carcinogenic gas [2]. Furthermore, in its pure form, it is exceedingly sensitive to explosion, and CH_2N_2 is thus virtually exclusively used as a solution in diethyl ether [2]. Various specialized kits for the laboratory scale generation and purification of ethereal solutions of diazomethane have been developed and commercialized [2].

Recently, we and others demonstrated experimental setups for the continuous generation of anhydrous diazomethane [3–5]. Key to these methods was the use of semipermeable, microporous membranes which selectively allow hydrophobic, low-molecular weight compounds to cross [3–5]. For our approach, diazomethane was continuously produced within a gas-permeable Teflon AF-2400 tubing by basic decomposition of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald) [3, 4]. The permeable tubing was housed inside a thick walled, gas-impermeable outer tubing (tube-in-tube reactor) [3, 4]. The tube-in-tube reactor design, with an inner tubing made of a highly gas permeable AF-2400 membrane, was originally conceived in 2011 in the laboratories of S. V. Ley [6] and has become popular as a versatile tool to saturate gases into a liquid phase [6, 7]. Furthermore, the tube-in-tube reactor has been utilized to couple the synthesis of a gaseous reagent within the membrane tubing with concomitant selective transport of the gas through the membrane [3, 4, 8]. Thus, the tube-in-tube reactor allows simultaneous generation and purification of gaseous reagents [3, 4, 8]. The gas can be directly used for reactions in the outer chamber. This method was recently employed by our group for the continuous multistep synthesis of α-chloroketones starting from *N*-protected amino acids (Scheme 2a) [4]. The continuous synthesis of α-chloroketones started with the formation of the mixed anhydride from the corresponding amino acid in an organic phase (Scheme 2a). Diazomethane was concurrently generated in an aqueous phase and was separated into the organic phase through the permeable membrane. The CH_2N_2 reacted with the mixed anhydride in the organic phase to the α-diazoketone, and the diazoketone was finally decomposed with hydrochloric acid to the desired chloroketone [4]. The fully continuous synthesis necessitated five pumps, three residence tubes in addition to a tube-in-tube reactor for the generation and purification of the diazomethane (Scheme 2a). The experimental setup allowed the continuous on-demand generation and utilization of anhydrous CH_2N_2, without any need to isolate, store, or transport this highly toxic and explosive gas [4].

Even though flow reactions offer many distinct advantages over traditional batch processes, they also present additional challenges [9–11]. The set-up of a flow process requires the parallel and interactive development of the single process steps and the single equipment components: reaction parameters such as reaction time, temperature, solvent, stoichiometry, and concentrations are screened, and in parallel, plant features such as dimensions, mixer types, exchange areas for heat, and mass are adapted. The observed effects determine further adaptions and optimizations of the recipe. Therefore, next to the experimental work in the flow plant,

* Authors for correspondence: bernhard.gutmann@uni-graz.at (B. Gutmann), oliver.kappe@uni-graz.at (C. O. Kappe)
† Present address. University of Genova, Department of Chemistry, Via Dodecaneso 31, 16146 Genova, Italy

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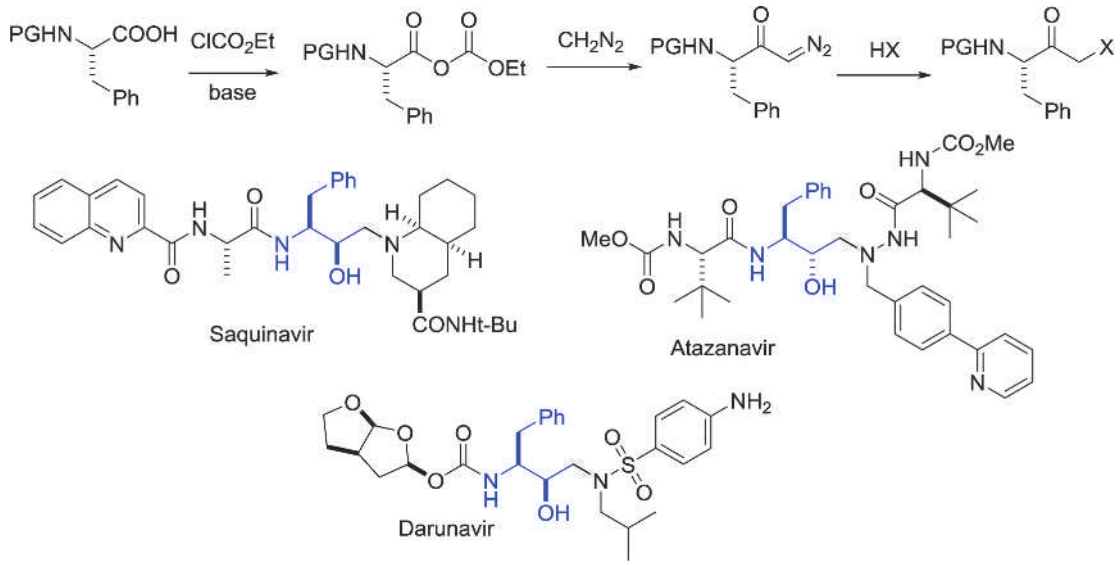
Scheme 1. Synthesis of α-chloroketones from diazomethane and *N*-protected-L-phenylalanine



ancillary experiments are part of the development coordinate. Likewise, analytical methods for process monitoring or even process control are established separately and integrated into the laboratory installation if required.

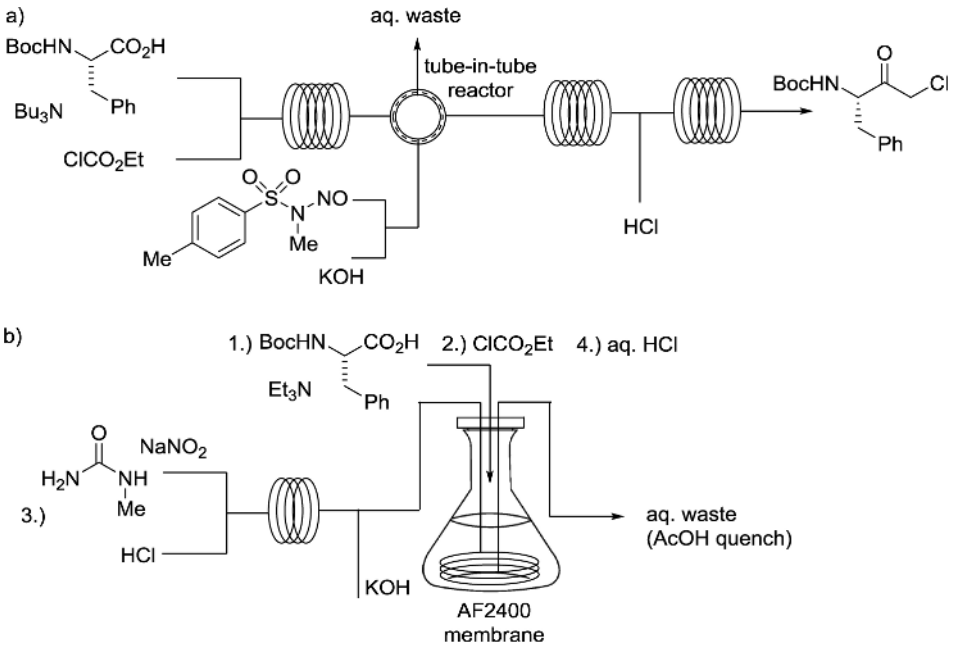
This additional effort of codevelopment may take more time than screening different reaction conditions in a small-scale vessel, especially if heterogeneous systems or precipitations occur [10], but it leads to a more detailed process understanding and allows screening of a wider parameter space. This effort may also lead to unforeseen and innovative plant concepts.

Herein, we utilize the concept of a "tube-in-flask" reactor for the laboratory-scale generation of α-chloroketones employing anhydrous diazomethane. The reactor was designed and developed with a focus on operational simplicity and flexibility [12]. Similar reactor designs have been previously developed in the laboratory of S. V. Ley for reactions with ozone [13] and in the laboratories of S. S. Stahl and T. W. Root for reactions with oxygen [14]. In their approach, the reaction mixture was carried in the AF-2400 tubing inside the flask, while the flask was filled with the respective gas [13, 14]. We have chosen a design where diazomethane is generated within the tubing and subsequently diffuses into the flask containing the substrate. The tube-in-flask reactor was used to develop and optimize the generation of water free diazomethane by a reaction sequence starting from *N*-methyl urea and sodium nitrite as simple and benign precursors. The diazomethane was directly utilized for the synthesis of an α-chloroketone in a semibatch–semiflow reaction (Scheme 2b).

2. Results and Discussion

2.1. Basic Concept. By far, the most common method to generate diazomethane is by base-catalyzed decomposition of *N*-methyl-*N*-nitroso amines with electron withdrawing substituents such as sulfonyl or carboxyl groups [2]. Prominent precursors are *N*-nitroso-*N*-methylurea (NNMU), *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine, and *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald®). Similar to CH_2N_2, these compounds are methylating agents, and

Scheme 2. Tube-in-tube (a) and tube-in-flask reactor (b) for the generation of CH_2N_2. a) Tube-in-tube reactor for ex-situ generation of CH_2N_2 and concomitant use for the generation of α-chloroketones . b) Simplified tube-in-flask reactor for the laboratory scale generation of CH_2N_2 from *N*-methylurea



since they methylate nucleobases in nucleic acids, they are carcinogenic, mutagenic, and teratogenic substances. The simplest CH_2N_2 precursor, NNMU, is furthermore shock-sensitive and unstable at temperatures above around 20 °C. It is thus no longer available from chemical suppliers, and it has become essentially obsolete as precursor for diazomethane. However, several researchers recently reported the generation of *N*-methyl nitrosamides in continuous-flow microreactors. Stark and coworkers described the continuous two-step synthesis of Diazald® by amidation of *p*-toluenesulfonyl chloride with methyl amine and subsequent nitrosation with $NaNO_2$ [15]. The subsequent basic decomposition of Diazald® in a microreactor was reported by the same group in a separate publication [16]. Furthermore, DPx owns a process for the continuous generation of diazomethane consisting of continuous synthesis of NNMU by nitrosation of *N*-methyl urea (NMU), basic decomposition of NNMU to diazomethane, and extraction of diazomethane with an organic solvent through a hydrophobic membrane [17]. Even though the organic solution of CH_2N_2 thus obtained is not free of water, it is sufficiently pure for various follow-up reactions [17].

Likewise, we envisaged generation of CH_2N_2 starting from simple and inexpensive chemicals (Scheme 2b). Since *N*-methylurea is not toxic and commercially attractive, and since the subsequent basic decomposition of the *N*-nitroso intermediate produces only carbon dioxide and ammonia in addition to the desired CH_2N_2, *N*-methyl urea was chosen as starting material also for the present study. Formation of the *N*-nitroso intermediate requires separate feeds for *N*-methylurea–$NaNO_2$ and for the acidic solution (Scheme 2b). A third feed is required for the subsequent basic decomposition to diazomethane. The combined solution finally enters the AF-2400 membrane tubing in an Erlenmeyer flask where formation of diazomethane is completed and molecular CH_2N_2 diffuses through the microporous, hydrophobic membrane into the flask. The aqueous phase of the reaction mixture, including all waste salts, is retained by the membrane and is directed into a quench solution (Scheme 2b).

2.2. Reactor Development and Optimization

2.2.1. Synthesis of the* N-*Nitroso*-N-*methylurea (NNMU). Initial experiments were performed in 8 mL batch vessels closed by a Teflon rubber septum. A solution of hydrochloric acid in various solvents was added through the septum with a syringe to an aqueous solution of *N*-methyl urea (NMU) and $NaNO_2$ (Table 1). *N*-methylurea readily dissolves at the envisaged concentrations in water (~0.5 M). The *N*-nitroso compound, on the other hand, slowly precipitated from the reaction mixture in most tested solvent systems. Homogeneous solutions were obtained with hydrochloric acid dissolved in DMSO–H_2O, DMF–H_2O, MeOH–H_2O, and *i*-PrOH (Table 1). The stoichiometry of the reagents for this set of experiments was NMU–$NaNO_2$–HCl= 1:1.1:1.3. This gave solutions of pH ~2. A detailed study by Snyder and Stock demonstrated that *N*-nitroso-*N*-methylurea decomposes at pH below 2 through denitrosation as well as hydrolysis [18]. Denitrosation regenerates the starting material, while acid-catalyzed hydrolysis forms mainly methylamine, nitrogen, and carbon dioxide [18]. Monitoring the reaction at 30 °C by ultraviolet–visible (UV–vis) analysis at the absorption maximum of NNMU at 391 nm (molar extinction coefficient is 95.14 L/mol cm at 391 nm) revealed that the absorption increases rapidly to a maximum and remains constant afterwards for at least 2 h without appreciable decrease (see Figure S1 in Supporting Information). These results indicate that the *N*-nitroso-*N*-methylurea is formed within a few minutes and is sufficiently stable under these reaction conditions. In contrast, the nitroso derivative decomposed quickly at higher temperatures, especially in alcoholic solvents (see Figure S2 in Supporting Information). The decomposition was accompanied by an increase in pressure (due to the generation of CO_2 and N_2) and slight increase in the pH (probably due to the formation of ammonia and methylamine). Unfortunately, formation of gas bubbles as well as the change of the extinction coefficient in different solvents and at different pH values rendered quantification of NNMU yield by UV–vis analysis unfeasible for this set of experiments.

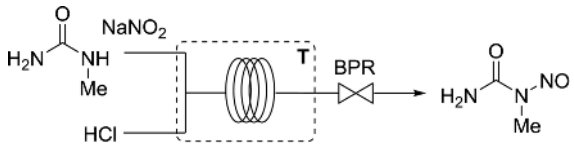
For the continuous-flow generation of the *N*-nitroso-*N*-methylurea, an aqueous solution of *N*-methylurea (1 M) and $NaNO_2$ (1.1 M) and a second solution of HCl in a solvent mixture (1.3 M) were pumped by two syringe pumps at equal flow rates into a Y-mixer in a water bath. The combined solution then went through a gas-tight 2 mL perfluoroalkoxy alkane (PFA) tubing. Due to the tight molecular structure of PFA, PFA tubing is recommended wherever low permeability and low diffusion rates are required. The PFA tubing was connected to an adjustable back-pressure regulator (BPR). The mixture leaving the system was collected and immediately analyzed by UV–vis measurements at 391 nm (Table 2). Back-pressures of 5 to 6 bar were necessary to keep most of the gas formed during the reaction dissolved in the liquid phase. At lower back-pressures, the gas bubbles pushed the reactor content through the reactor and reduced residences time considerably. According to UV–vis analysis, NNMU was formed with ~82% selectivity in DMSO–H_2O as solvent after a reaction time of 5 min at 40 °C. These yields compare well with those reported in the literature for the conversion of *N*-methylurea to NNMU [19]. Longer residence times or higher temperatures did not increase

Table 1. Batch generation of *N*-nitroso-*N*-methylurea (NNMU) from *N*-methylurea (NMU), $NaNO_2$, and HCl[a]

Solvent for HCl	*t*=0 min	*t*=30 min	*t*=120 min
i-PrOH–water 4:1	One phase	Precipitate	Precipitate
DMSO–water 4:1	One phase	One phase	One phase
DMF–water 4:1	One phase	One phase	One phase
THF–water 9:1	Two phases	Two phases	Two phases
EG–water 4:1	Precipitate	Precipitate	Precipitate
MeOH–water 4:1	One phase	One phase	One phase
i-PrOH	One phase	One phase	One phase

[a] Conditions: 1.0 mL of HCl in the indicated solvents (1.3 M) was pipeted to an aqueous 1.0 mL solution of *N*-methylurea and $NaNO_2$ (1.0 M and 1.1 M, respectively). EG=ethyleneglycol.

Table 2. Continuous-flow generation of *N*-nitroso-*N*-methylurea (NNMU) from *N*-methylurea (NMU) and $NaNO_2$[a]



	Ratio NMU–$NaNO_2$–HCl	Solvent (HCl)	Res. time (min)	*T* (°C)	UV–vis yield (%)[b]
1	1:1.1:1.3	DMSO–H_2O 4:1	5	40	82
2	1:1.1:1.3	DMSO–H_2O 4:1	10	40	82
3	1:1.1:1.3	DMSO–H_2O 4:1	5	50	83
4	1:1.1:1.3	*i*-PrOH	5	50	34
5	1:1.1:1.3	*i*-PrOH	5	30	50
6	1:1.1:1.3	DMF–H_2O 4:1	5	70	69
7	1:1.1:1.3	DMF–H_2O 4:1	5	50	71
8	1:1.1:1.3	DMF–H_2O 4:1	5	30	74
9	1:0.7:1.3	DMSO–H_2O 4:1	5	50	87
10	1:0.7:1.3	*i*-PrOH	5	50	83

[a] Conditions: An aqueous solution of NMU (1 M) and $NaNO_2$ was combined with HCl (1.3 M) at equal flow rates (0.2 mL/min). The solution went through a 2-mL PFA residence tube at the indicated temperature and left the system through a BPR at 6 bar. The pH was 2 or less for most of these experiments.

[b] The sample was analyzed by UV–vis monitoring (see Supporting Information for details). Res time = theoretical residence time calculated from residence volume and total flow rate.

the amount of NNMU appreciably (entries 2 and 3 in Table 2). Slightly lower yields were obtained with DMF as cosolvent (entries 6 to 8 in Table 2). Significantly less NNMU was generally obtained with *i*-PrOH as solvent (entries 4 and 5 in Table 2). Interestingly, using $NaNO_2$ as the limiting reagent, the amount of NNMU obtained in *i*-PrOH–H_2O approached that obtained with DMSO as cosolvent (entry 10 in Table 2). For further experimental results, see Table S1 in Supporting Information.

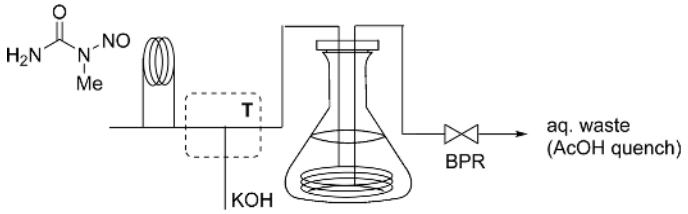
2.2.2. Generation of CH_2N_2 from* N-*Nitroso*-N-*methylurea (NNMU). The formation of CH_2N_2 was first studied employing the isolated *N*-nitroso-*N*-methylurea as the starting material. The NNMU, generated as described in Table 2, was not entirely soluble in most tested solvent mixtures at room temperature and generally precipitated after the back-pressure regulator. Thus, to investigate generation of diazomethane from NNMU under continuous-flow conditions, the nitroso compound was redissolved under heating, and the solution was then introduced into a 2-mL injection loop at 60 °C to prevent precipitation during the experiments. The NNMU was fed from the injection loop into the system and was combined with a 6-molar aqueous solution of KOH in a heated Y-mixer (Table 3). The combined solution subsequently went through the AF-2400 membrane of the tube-in-flask reactor. The tube-in-flask reactor consisted of a 50-mL standard Erlenmeyer flask. Into the reactor, 4 m of a Teflon AF-2400 tubing with 1.0 mm outer diameter and a wall thickness of 0.1 mm was coiled (Figure 1) [12]. Thus, the membrane tubing provides a residence volume of 2.0 mL and an outer surface area of 126 cm^2 [20]. Both ends of the AF-2400 tubing were connected to standard gastight PFA tubing. The PFA tubing penetrated the septum stopper, which was used to seal the Erlenmeyer flask (Figure 1). The aqueous mixture left the system through a back-pressure regulator into a quench solution of aqueous acetic acid. Diethyl ether was filled into the Erlenmeyer flask (35 mL). After 2.0 mL of a 0.5-M solution of NNMU was pumped through the reactor, 10 mL of the ethereal solution of CH_2N_2 was pipetted from the flask to 34.9 mg (0.286 mmol) of benzoic acid. The conversion of benzoic acid to methyl benzoate was used to determine the yield of CH_2N_2 with respect to NNMU (high-performance liquid chromatography [HPLC] at 215 nm). Diazomethane yields of 50 to 60% were obtained after residence times of only 3 min at a reaction temperature of 30 °C with both *i*-PrOH and DMSO as cosolvents (entries 1 and 2 in Table 3). Lower temperatures gave slightly lower yields even with longer residence times or higher back pressures (entries 3 to 5 in Table 3). With DMF as cosolvent, yields of 30% were obtained

Figure 1. The "tube-in-flask" reactor consisted of a 50-mL standard Erlenmeyer flask in which 5 m of a Teflon AF-2400 tubing was coiled

(entry 6 in Table 3). More experimental results can be found in Table S2 in Supporting Information.

2.2.3. Continuous Generation of CH_2N_2 from* N-*Methylurea (NMU). Both steps were finally combined to allow continuous generation of solutions of CH_2N_2 from NMU and $NaNO_2$ as starting materials. Thus, an aqueous solution of NMU (1 M) and $NaNO_2$ (1.1 M) was combined with a second feed of HCl (1.3 M) at equal flow rates. The mixture went through a first residence tubing (2 mL) at temperatures of 30 to 50 °C, and the resulting stream was then mixed with aqueous KOH. To prevent the formation of precipitates in the AF-2400 tubing, the concentration of the KOH solution was reduced to 4 M. The combined solution went through the AF-2400 membrane and was finally directed into an AcOH quench solution. Again, the concentration of CH_2N_2 in the Erlenmeyer flask was determined by the conversion of benzoic acid to methyl benzoate. The best results were obtained with DMSO as cosolvent (compare entries 1 to 3 in Table 4). Yields of 48% were obtained in DMSO–H_2O at 30 °C (entry 4 in Table 4). With 10 mL of the reagent solution, about 0.14 M ethereal solutions of diazomethane were obtained. The diazomethane yields

Table 3. Generation of diazomethane from NNMU[a]



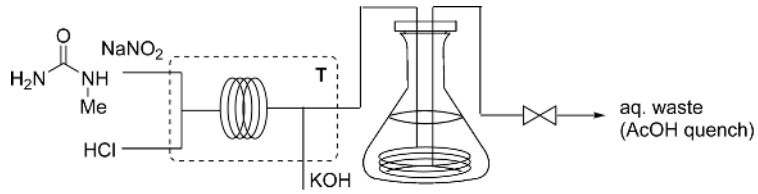
	Ratio NNMU–KOH	Solvent–H_2O 1:1 (NNMU)	Res time (min)	Y-mixer *T* (°C)	*P* (bar)	CH_2N_2 yield (%)[b]
1	1:8.4	DMSO–H_2O	3	30	6	56
2	1:8.4	*i*-PrOH–H_2O	3	30	6	58
3	1:8.4	DMSO–H_2O	3	22	6	44
4	1:8.4	DMSO–H_2O	3	22	9	47
5	1:8.4	DMSO–H_2O	6	22	6	42
6[c]	1:5.6	DMF/H_2O	3	30	6	30

[a] Conditions: 2.0 mL of NNMU (0.5 M) in the indicated solvent was pumped at a flow rate of 0.4 mL/min (0.2 mL/min for entry 5) from an heated injection loop into a Y-mixer. In the mixer, the stream was combined with a 6-M aqueous solution of KOH at a flow rate of 0.28 mL/min (0.14 mL/min for entry 5). Bubbles after the Y mixer were noticed in all experiments. The solution went through the Teflon AF-2400 tubing in the Erlenmeyer flask and was finally quenched in aqueous acetic acid. The Erlenmeyer flask was filled with 35 mL diethyl ether.

[b] The conversion of benzoic acid to methyl benzoate with the solution in the flask was used to assess CH_2N_2 yields. Conversions were determined in triplicate, and the average is reported with a standard deviation that was usually less than 3%.

[c] KOH concentration was 4 M. Res time=theoretical residence time calculated from the volume of the AF-2400 tubing and total flow rate.

Table 4. Generation of diazomethane from *N*-methyl-urea (NMU)[a]



	Ratio NMU–$NaNO_2$–HCl–KOH	Solvent–H_2O 4:1 (HCl)	*T* (°C)	CH_2N_2 yield (%)[b]
1	1:1.1:1.3:2.8	DMSO–H_2O	50	30
2	1:1.1:1.3:2.8	*i*-PrOH –H_2O	50	22
3	1:1.1:1.3:2.8	MeOH–H_2O	50	11
4	1:1.1:1.3:5.6	DMSO–H_2O	30	48
5	1:1.1:1.3:5.6	DMF–H_2O	30	20
6[c]	1:0.7:1.3:5.6	DMSO–H_2O	30	47
7[c]	1:0.7:1.3:5.6	DMF–H_2O	30	21

[a] Conditions: For a detailed experimental procedure, see Experimental section. Reactions 4 to 7 were performed with 4 M solutions of KOH. Reactions 1 to 3 were performed with solutions of 2 M KOH and 2 M NaCl to keep the ionic strength constant.
[b] The conversion of benzoic acid to methyl benzoate with the solution in the flask was used to assess CH_2N_2 yield. Conversions were determined in triplicate and the average is reported.
[c] $NaNO_2$ as limiting reagent. Res time=theoretical total residence time in the system.

were significantly lower with other cosolvents for the acidic solution, such as MeOH, *i*-PrOH, or DMF (see Table 4, and Table S3 in Supporting Information).

The overall diazomethane yields obtained from the continuous two-step reaction sequence were in good agreement with those expected from the yields of the individual reaction steps, suggesting that reagents or side-products from the NNMU synthesis do not interfere with the subsequent generation of CH_2N_2 (Table 5). With *i*-PrOH as the cosolvent, low yields were obtained for the NNMU synthesis, while the basic hydrolysis of NNMU and subsequent extraction of CH_2N_2 into the flask provided good results. With DMF and DMSO as solvent, comparable results were achieved for NNMU synthesis. However, generation of CH_2N_2 from NNMU or extraction of CH_2N_2 into the flask performed poorly in DMF–H_2O, resulting in low overall yields. With DMSO as cosolvent, stable yields of 45 to 50% were obtained.

2.3. Reactions in the Tube-in-Flask Reactor

2.3.1. Synthesis of Phenacyl Chloride from Benzoyl Chloride. To demonstrate that the diazomethane obtained through the AF-2400 membrane is indeed anhydrous, the acylation of CH_2N_2 with benzoyl chloride was attempted. The presence of water would lead to partial hydrolysis of the benzoyl chloride and subsequent methylation to methyl benzoate. For this reaction, the Erlenmeyer flask was cooled to 0 °C and charged with 35 mL diethyl ether and 6 mmol of benzoyl chloride. The generation of diazomethane was performed under the conditions reported in entry 4 in Table 4 (for details see the Experimental section). Thus, a 1.3-M solution of HCl in DMSO–H_2O 4:1 was pumped into the reactor at a flow rate of 200 μL/min. The solution was combined with a second solution containing *N*-methylurea (1 M) and $NaNO_2$ (1.1 M). After the residence tubing, the solution merged with the 4 M solution of aqueous KOH at a flow rate of 280 μL/min. The mixture went through the AF-2400 tubing, and the effluent solution was finally quenched in aqueous acetic acid. After 2 h, a faint yellow color (CH_2N_2) developed in the Erlenmeyer flask, suggesting that conversion of benzoyl chloride to the diazoketone was complete (4.0 equivalents of *N*-methylurea). HPLC analysis revealed that 4% of the benzoyl chloride was not consumed. Further, NMU was pumped through the reactor until complete conversion of the benzoyl chloride was obtained according to HPLC analysis. In total, 27.6 mmol of *N*-methylurea was consumed in this reaction. Since the reaction needs 2 equivalents of diazomethane, a CH_2N_2 yield of 43% with respect to NMU can be calculated for this reaction. Two equivalents of aqueous HCl were added to the flask, and the mixture was stirred for 30 min at 22 °C. Extraction gave the chloroketone in 91% yield. No methyl ester was detected by HPLC or ^{1}H-NMR analysis, confirming that the generated CH_2N_2 is anhydrous.

Table 5. Comparison of the CH_2N_2 yield obtained from separate reactions with that of the combined two-step flow process

Solvent for HCl	Yield 1st step (%)	Yield 2nd step (%)	Calc. CH_2N_2 yield (%)	Exp. CH_2N_2 yield (%)
i-PrOH	50 (30 °C)	58 (30 °C)	29	31 (40 °C)
DMSO	82 (40 °C)	56 (30 °C)	46	48 (30 °C)
DMF	74 (30 °C)	30 (30 °C)	22	20 (30 °C)

2.3.2. Three Step Synthesis of α-Chloroketone Starting from* N-*Boc-*L*-phenylalanine. Since the use of diethyl ether as solvent is strongly discouraged, if not forbidden, in industrial laboratories, methyl *tert*-butyl ether (MTBE) and 2-methyl tetrahydrofurane (2-Me-THF) were investigated as alternatives (see Table S4 in Supporting Information). The best results were obtained with the Boc protected L-phenylalanine (1.3 mmol) and triethylamine (1.5 equivalents) dissolved in anhydrous MTBE (10 mL). Ethyl chloroformate (1.5 equivalents) dissolved in MTBE (0.39 M) was pipetted into the flask at a reaction temperature of 0 °C. Large amounts of a white precipitate immediately formed in the flask (Et_3NHCl). Reactions which produce large amounts of solids currently cannot be carried out in microreactors. For our previously published fully continuous chloroketone synthesis, the formation of the precipitate was prevented by using tributylamine as base [4]. However, tributylamine is not removable from the reaction mixture by extraction and makes a chromatographic separation necessary. After the slurry in the flask was stirred for 7 min, the pumps were switched on to generate the diazomethane as described above. 7.35 mmol of *N*-methylurea was pumped through the flask while the temperature of the flask was kept between 0 and 4 °C. Complete conversion to the diazoketone in a remarkably clean reaction was obtained after a reaction time of 70 min (see Figure 2). Concentrated HCl (4.0 equiv) was then added at 0 °C under vigorous stirring (2 phases) before the mixture was slowly warmed to room temperature. HPLC analysis revealed that conversion of the diazoketone to the chloroketone was complete after reaction times of 100–180 min (Scheme 3). Workup by extraction provided the desired α-chloroketone in high purity and in 90 to 95% product yield (see Figures S4 and S5 in Supporting Information).

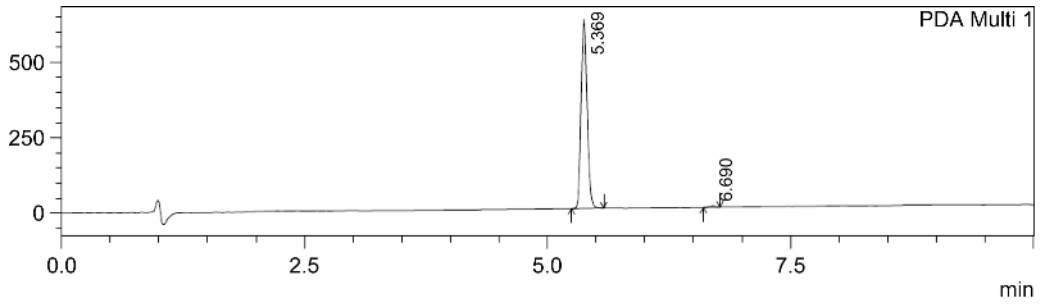
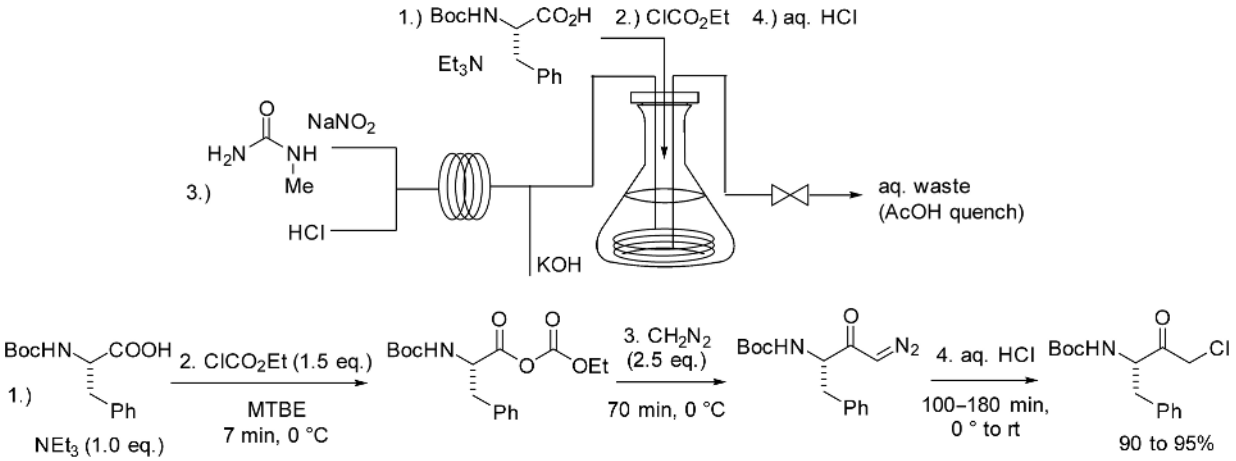


Figure 2. HPLC (215 nm) of the crude reaction mixture after activation of *N*-Boc-L-Phe-OH and reaction with CH_2N_2. The main product is the α-diazoketone (99.3%). The only detected side-product is *N*-Boc-L-Phe-OMe from methylation of unactivated Boc-Phe-OH (0.7%)

Scheme 3. Synthesis of α-chloroketone from *N*-Boc-L-phenylalanine in the tube-in-flask reactor



3. Conclusion

Among the most important aspects in chemical research during early development of reactions and reaction optimization are speed, operational simplicity, and flexibility of the experimental platform. Often, hundreds of experiments have to be performed to fully develop a chemical reaction or to thoroughly optimize the synthesis of a new compound. A simple and robust experimental setup is essential to accomplish this objective quickly and reliably. Herein, we have presented a simple and robust reactor for the generation of anhydrous CH_2N_2 from inexpensive and easy-to-handle precursors. *N*-Nitroso-*N*-methylurea (NNMU), a highly carcinogenic, mutagenic, teratogenic, and explosive compound, was formed in-situ by nitrosation of *N*-methylurea (NMU). The NNMU was directly decomposed by an aqueous base to diazomethane. The molecular diazomethane diffused through a gas-selective AF-2400 membrane into a standard Erlenmeyer flask, while the aqueous waste solution was retained by the membrane and directed into a quench solution. The two-step reaction sequence provided water-free diazomethane in around 48% yield. The concentration of CH_2N_2 in the flask was controlled by the filling volume in the flask and by the amount of NMU pumped through the reactor. Similarly, for reactions performed directly in the flask, the stoichiometry of CH_2N_2 was determined by the quantity of NMU fed through the system. In general, the reactor will be operated until the reaction at hand is completed.

Teflon AF-2400 is highly gas permeable but has a chemical and mechanical resistance comparable to standard fluoropolymers [3–8]. Specifically, Teflon AF-2400 is resistant to most standard laboratory chemicals and solvents. Furthermore, the tube-in-flask reactor readily accepts solids. The reactor presented herein is thus nearly universally applicable for reactions involving CH_2N_2 [12].

4. Experimental

4.1. General. ^{1}H-NMR spectra were recorded on a Bruker 300 MHz instrument. ^{13}C-NMR spectra were recorded on the same instrument at 75 MHz. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet. Low resolution mass spectra were obtained on a liquid chromatography–mass spectrometry (LC–MS) instrument using electrospray ionization (ESI) in positive or negative mode (Agilent 1100 LC/MS or Shimadzu LCMS-2020). Analytical HPLC (Shimadzu LC20) analysis was carried out on a C18 reversed-phase (RP) analytical column (150×4.6 mm, particle size 5 μm) at 37 °C using a mobile phase A (water–acetonitrile 90:10 (v/v)+0.1% TFA) and B (MeCN+0.1% TFA) at a flow rate of 1.5 mL/min. The following gradient was applied: linear increase from solution 30% B to 100% B in 10 min. All solvents and chemicals were obtained from standard commercial vendors and were used without any further purification.

Caution: Both *N*-nitroso-*N*-methylurea (NNMU) and CH_2N_2 are toxic, carcinogenic, mutagenic, and teratogenic substances. NNMU in isolated form is shock-sensitive and can decompose explosively. CH_2N_2 is a highly explosive, volatile substance even in diluted solution. Reactions with these substances should not be undertaken without proper safety precautions put in place.

4.2. General Procedure for the Generation of CH_2N_2 from *N*-Methylurea (NMU). For a picture of the experimental setup, see Figure S3 in Supporting Information. The Erlenmeyer flask was filled with 35 mL of diethyl ether and cooled to 0 °C. Water (feed A) and a 1.3-M solution of HCl in DMSO–H_2O 1:1 (feed B) were pumped into a Y-mixer (Upchurch Scientific) heated in a water bath to 30 °C (Asia syringe pump module). The flow rate for both feeds was 200 μL/min. The mixture went through a 2-mL PFA tubing (1.59 mm o.d., 0.8 mm i.d.) in the same water bath.

The mixture was combined with a 4-M aqueous solution of KOH at a flow rate of 280 μL/min in a second Y-mixer. The combined solution went through the Teflon AF-2400 membrane tubing in the Erlenmeyer flask (2.0 mL, 1 mm o.d., 0.8 mm i.d.). The effluent mixture was directed into a quench solution of aqueous acetic acid. When the reaction was started, feed A was switched from pure water to 10 mL of a solution containing NMU (1 M) and $NaNO_2$ (1.1 M). After the solution was consumed, feed A was switched back to water. The remaining NMU solution in the reactor was carried through the reactor with water, and the pumps were then stopped. Five milliliters of the ether solution was pipeted from the flask to 174 mg (1.43 mmol) of benzoic acid. The conversion of benzoic acid to methyl benzoate, as determined by HPLC analysis at 215 nm, was used to calculate CH_2N_2 yields. All analyses were done in triplicate, and the average values are reported.

4.3. Procedure for the Preparation of Phenacyl Chloride from Benzoyl Chloride. The Erlenmeyer flask was cooled to 0 °C and charged with 35 mL diethyl ether and 6 mmol of benzoyl chloride. The generation of diazomethane was performed as reported above. In total, 27.6 mmol of *N*-methylurea was fed through the reactor for this reaction (CH_2N_2 yield of 43%). Two equivalents of aqueous HCl were added to the flask, and the mixture was stirred for 30 min at 22 °C. The mixture was extracted with sat. $NaHCO_3$–Et_2O, the organic phase dried over $MgSO_4$, and the solvent was then removed under vacuum to give 843 mg (91%) of phenacyl chloride as a yellowish solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99–7.96 (m, 2H), 7.67–7.61 (m, 1H), 7.51 (dd, J=10.4, 4.7 Hz, 2H), 4.74 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.1, 134.2, 134.0, 128.9, 128.5, 46.1.

4.4. Procedure for the Synthesis of α-Chloroketone Starting from *N*-Boc-L-phenylalanine. *N*-Boc-L-phenylalanine (1.3 mmol) and triethylamine (1.5 equivalents) were dissolved in 10 mL anhydrous methyl *tert*-butyl ether (MTBE) in the Erlenmeyer flask. Ethyl chloroformate (1.5 equivalents), dissolved in MTBE (5 mL, 0.39 M), was pipeted into the flask at a reaction temperature of 0 °C. Large amounts of a white precipitate formed. After the mixture was stirred for 7 min, the pumps were switched on to generate the diazomethane as described above. 7.35 mmol of *N*-methylurea was pumped through the system while the temperature of the flask was kept between 0 and 4 °C. After 70 min, concentrated HCl (4.0 eq.) was added at 0 °C under vigorous stirring before the mixture was slowly heated to room temperature (100–180 min). The solution was extracted with saturated $NaHCO_3$ (15 mL) and brine (15 mL). The organic phase was dried with $MgSO_4$, and the solvent was removed under vacuum to provide 353 to 380 mg (90 to 96%) of (*S*)-*tert*-butyl (4-chloro-3-oxo-1-phenylbutan-2-yl)carbamate as a white solid: mp. 103–105 °C (lit. [4] 102–103 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.29 (m, 3H), 7.28–7.11 (m, J=6.4 Hz, 2H), 5.07–5.05 (m, J=6.9 Hz, 1H), 4.78–4.55 (m, 1H), 4.19 (d, J=16.3 Hz, 1H), 4.00 (d, J=16.3 Hz, 1H), 3.13–2.88 (m, J=7.2 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 155.2, 135.6, 129.3, 129.1, 128.9, 127.4, 80.5, 58.4, 47.6, 37.7, 28.2.

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Supporting Information

Electronic Supplementary Material (ESM) is available in the online version at doi: 10.1556/1846.2015.00046.

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