Scalable in Situ Diazomethane Generation in Continuous-Flow Reactors

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ABSTRACT: Diazomethane is a valuable derivatizing agent but very difficult to handle for large-scale chemical transformations. We report here the base-induced decomposition of N-methyl-N-nitrosourea under continuous-flow conditions that enables the production up to 19 mol d^{-1} of diazomethane, at a total flow rate of 53 mL min^{-1}.

INTRODUCTION

Diazomethane is a highly reactive and selective reagent for the synthesis of pharmaceuticals and fine chemicals.[1] However, its acute toxicity and explosive characteristics strongly discourage a large-scale use in synthesis. Discontinuous preparations up to 2−300 mmol of diazomethane, through the reaction of solid nitrosoamides or ureas with bases, has been reported in special safety glassware.[2] Also, strategies for industrial-scale production of diazomethane have been described, although the equipment needed for its safe handling is elaborate and expensive.[3] Important gains can be achieved by transferring the batchwise diazomethane synthesis to continuous-flow processing in microstructured reactors where large surface-area-to-volume ratios allow precise reaction control through efficient heat and mass transfer.[4] Struempel and co-workers[5] reported the production of diazomethane in a continuous microreactor setup through the base-induced decomposition of N-methyl-N-nitroso-p-toluenesulfonamide (MNTS, Diazald) that, in turn, can be prepared in a continuous multistep synthesis starting from p-toluensulphonyl chloride.[6] Other common diazomethane precursors are N-methyl-N'-nitro-N-nitroso guanidine (MNNG) and N-methyl-N-nitrosourea (MNU). MNTS is classified as a self-reacting solid[7] that can undergo explosions by shock, friction, heating, and other sources of ignition,[8] whereas MNU is a flammable solid[9] but is supplied as a water/acetic acid slurry that may reduce flammability during transportation and storage. According to the safety data sheet, MNNG is a nonflammable, nonexplosive solid.[10] On the other hand, toxicity data[7,9−11] and price are in favor of MNTS which has a much lower acute toxicity and is less expensive than MNNG and MNU.[12] However, we believe that the commercial formulation of MNU is safer to transport and store if compared to MNTS[13] and may reduce toxicity hazards with respect to MNNG that, as a solid reagent, is affected by an easier exposure route through inhalation.

In this contribution we report an optimized continuous generation of diazomethane through the base-induced decomposition of MNU. For the flow experiments we used Corning Advanced-Flow Reactors. The continuous process conditions were first optimized in a small-volume *LowFlow* reactor and then scaled-up into a *GEN1* reactor of larger size with limited need for further optimization that, in the conditions described in the Experimental Section, is capable of processing more than 19 mol d^{-1} of diazomethane.

RESULTS AND DISCUSSION

The diazomethane generation efficiency, from the KOH-promoted decomposition of MNU, was demonstrated on the model compound benzoic acid, assuming that the yield of methyl benzoate is equivalent to that of diazomethane (Scheme 1).[5] Excess benzoic acid was used to convert diazomethane and to neutralize the excess base from the first reaction step.[14]

Scheme 1. Methylation of benzoic acid with diazomethane produced in situ by basic decomposition of N-methyl-N-nitrosourea with KOH
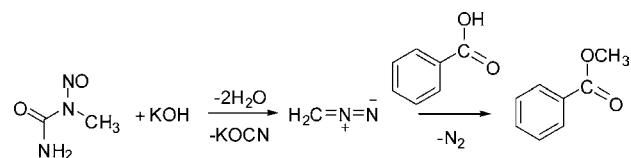
To prevent particulate formation and clogging of the flow-reactor, a series of batch tests were carried out to determine the optimum solvent system for the reactions illustrated in Scheme 1. From the data reported in Table 1, the solvent system reported in entry 6 gave optimal reagent solubility, less particulate formation, and moderate yields, if compared to the solvents used in the other trials (entries 1−5). In particular, a 1:1 mixture of Et$_2$O and diethyleneglycol diethylether (DEG) solubilized nicely the MNU feed (0.5 M), whereas KOH and benzoic acid feeds were solubilized by water (1.5 M) and ethanol (1.5 M), respectively.[3,5]

To achieve the continuous-flow synthesis of diazomethane, Corning Advanced-Flow *LowFlow* reactor assembly was first employed to test the conditions of entry 6 (Table 1) that gave the highest batchwise yield without particulate formation. Figure 1 shows the glass microstructured module sequence of the flow reactor, in which each module has a HEART-shaped

Table 1. Solvent tests that were carried out under batchwise conditions at 25 °C (MNU 0.5 mmol, MNU/KOH/benzoic acid = 1:1.5:3)[a]

entry	solvent (MNU)	solvent (KOH)	solvent (benzoic acid)	precipitate	phases	yield (%)
1	DEG	2-PrOH	DEG	N	1	33
2	DEG	EtOH	EtOH	Y	1	32
3	THF	EtOH	EtOH	Y	1	19
4	EtOH	EtOH	EtOH	Y	1	19
5	Et$_2$O	EtOH	EtOH	Y	1	70
6	Et$_2$O/DEG[b]	H$_2$O	EtOH	N	2	55

[a]MNU: N-methyl-N-nitrosourea; DEG: diethyleneglycol ethylether; THF: tetrahydrofuran. [b]1:1 v/v.
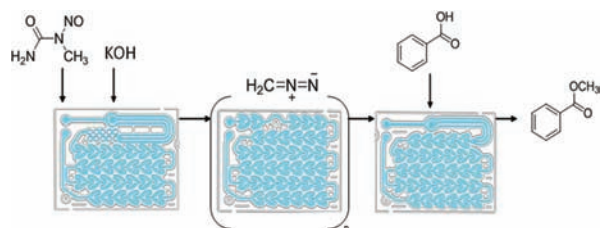
Figure 1. Module schematics of Corning Advanced-Flow *LowFlow* reactor.

design,[15] that efficiently handles the liquid−liquid two-phases emulsion created by the solvent combination of entry 6. In the *Low Flow*, each glass fluidic module has an inner path of 0.45 mL (see the Experimental Section for further details).

Reactor assembly and experimental conditions were rapidly screened searching for the best values of temperature, reagents stoichiometry and residence time.

Under optimized conditions, a constant yield of 75% of methyl benzoate was achieved at room temperature for a residence time of 19 s, a total flow-rate of 3.2 mL min^{-1} and 1.5 mol equiv of KOH (Table 2, entry 1). Longer reaction times, obtained by changing either flow rates or the volume of the reactor, probably favor diazomethane decomposition, whereas higher amounts of base results in extensive saponification of the benzoate ester (Table 2, entries 2−6). During all experiments, no clogging problems were encountered.

Once identified the best reaction parameters in the *Low Flow* system, a scale up was carried out on larger *GEN1*-type fluidic modules (see Experimental Section for details) with minimal adjustments. Under optimized conditions, a nearly quantitative yield of methyl benzoate was obtained at room temperature for

a residence time of 28 s, a total flow-rate of 52.8 mL min^{-1} and 1.3 mol equiv of KOH (Table 3, entry 4).

One can notice that the optimized conditions for the *LowFlow* and *GEN1* systems differ markedly (Table 2, entry 1 vs Table 3, entry 4). The reason for this variation could be related to a different glass microstructure of the channels that, in turn, determine distinctive flow characteristics within the heart-shaped mixing elements. Mixing is a fundamental process that affects mass transfer rate, hence, the observed difference. It is worth mentioning, however, that the internal volume of the *GEN1* system is almost 10-fold that of the *LowFlow* counterpart. In order to maintain comparable residence times, the flow rates used for the *LowFlow* setup have been increased substantially when diazomethane was prepared in the *GEN1* system. In addition, low flow rates in a *GEN1* setup may produce flow pulsations that hamper data reproducibility.

Water content in the commercial MNU slurries differs noticeably within different production lots. Product specifications indicate, for instance, a generic acetic acid content ≤5% and an amount of water (by Karl Fischer) ≤ 45%. The MNU employed for *GEN1* experiments had a rather different content of water if compared to the lot used with *LowFlow* setup experiments (27% vs 41% w/w). Water was added to MNU stock solutions for the *GEN1* experiments to achieve both comparable water content and elimination of particulate. Accordingly, the concentration of MNU (calculated over dry basis weight) decreased. Although the effect of different water content in MNU starting slurries may deserve further studies, it was beyond the scope of this work.

The stability of the process was tested in longer runs without observing any clogging of the reactor setup that is shown in Figure 2. A mean operative yield of 90% of methyl benzoate was obtained under the optimized conditions reported in entry 4 of Table 3.

It is worth noting that the production of diazomethane, in the two-phase solvent system described above, is strongly affected by mixing. The highest diazomethane conversions were obtained for a MNU/KOH flow ratio of 1.66 that was kept constant both in the *Low Flow* and *GEN1* systems.

■ CONCLUSION

In conclusion, this study has shown the effectiveness of flow reactors to handle the preparation of hazardous diazomethane through a base-induced decomposition of N-methyl-N-nitrosourea. Process scale-up was quickly and efficiently achieved on a modular continuous-flow platform that allowed the production and use of diazomethane up to 19 mol d^{-1} at a total flow rate of 53 mL min^{-1}, while maintaining the amount of

Table 2. Selected low flow results at 25 °C (MNU 0.6 M in 1:1 Et$_2$O/DEG;[a] KOH 1.5 M in H$_2$O; benzoic acid 1.5 M in EtOH)[b]

entry	MNU flow rate (mL min^{-1})	KOH flow rate (mL min^{-1})	MNU:KOH	acid flow rate (mL min^{-1})	residence time 1[c] (s)	residence time 2[d] (s)	yield (%)
1[e]	2.0	1.2	1:1.5	2.4	18.7	5.3	75
2[e]	1.0	0.6	1:1.5	1.2	37.5	10.7	7
3[f]	2.0	1.2	1:1.5	2.4	39	5.3	15
4[f]	2.0	1.5	1:1.8	2.4	36.1	5.1	5
5[f]	2.0	1.0	1:1.2	2.4	42	5.6	33
6[f]	2.0	0.8	1:1	2.4	45	5.8	6

[a]Water 4% (v/v), CH$_3$CO$_2$H 0.26% (v/v) from commercial MNU (see Experimental Section). [b]MNU: N-methyl-N-nitrosourea; DEG: diethyleneglycol ethylether. [c]Residence time before addition of benzoic acid. [d]Residence time after addition of benzoic acid. [e]Total reactor volume 0.9 mL. [f]Total reactor volume 1.35 mL.

Table 3. Selected GEN1 results at 25 °C (MNU 0.45 M in 1:1 Et$_2$O/DEG[a]; KOH 1.0 M in H$_2$O; benzoic acid 1.5 M in EtOH)[b]

entry	MNU flow rate (mL min^{-1})	KOH flow rate (mL min^{-1})	MNU:KOH	acid flow rate (mL min^{-1})	residence time 1[c] (s)	residence time 2[d] (s)	yield (%)
1[e,f]	25	11.25	1:1.5	31.5	24.6	5.5	29.3
2[f]	35	21	1:1.3	31.5	16	5.5	40
3[e,f]	33	10.56	1:1.1	29.7	20.5	6.6	55.7
4[g]	33	19.8	1:1.3	29.7	28.4	5.8	97
5[h]	33	19.8	1:1.3	29.7	19.2	5.8	87
6[h]	23.75	14.25	1:1.3	21.37	26.7	8.1	72

[a]Water 3% (v/v), CH$_3$CO$_2$H 0.18% (v/v) from commercial MNU (see Experimental Section). [b]MNU: N-methyl-N-nitrosourea; DEG: diethyleneglycol ethylether. [c]Residence time before addition of benzoic acid. [d]Residence time after addition of benzoic acid. [e]KOH solution concentration 1.5 M in H$_2$O. [f]Total reactor volume 14.86 mL. [g]Total reactor volume 24.98 mL. [h]Total reactor volume 16.92 mL.
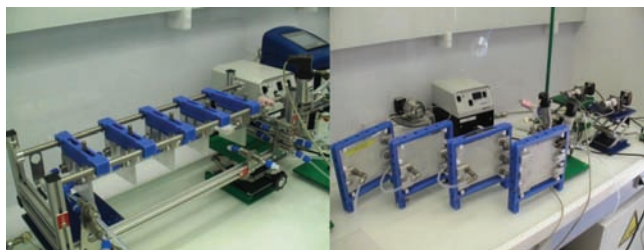

Figure 2. Corning Advanced-Flow *LowFlow* (left) and *GEN1* reactors.

diazomethane itself in the reactor limited to 6.5 mmol. This process productivity could, at least in principle, fulfill the needs of small pharma or fine chemical companies. Best reaction parameters were first developed on a small-volume flow reactor (0.9−1.35 mL) for minimal reagents consumption. Then a 10-fold production improvement was achieved by increasing the flow reactor dimensions (15−25 mL) with a very limited optimization effort. This scale-up procedure complements the so-called numbering-up approach, where a series of identical flow reactors are run in parallel.[8]

■ EXPERIMENTAL SECTION

All chemicals and solvents were used as received. N-Methyl-N-nitrosourea (MNU, 50−70% aqueous slurry stabilized with 3% w/w acetic acid, Sigma Aldrich) contains a variable amount of water that depends on the production lot as indicated on the package. KOH 86% (Fischer Scientific); benzoic acid (Sigma Aldrich, purity ≥99.5%); diethyl ether 99.8% (Sigma Aldrich); diethylene glycol 99% (Sigma Aldrich); methyl benzoate 99.5% (Sigma Aldrich). In the reaction balance, 0.1 equiv of KOH is needed to neutralize the stabilizing acetic acid. MNU concentrations were calculated on dry weight basis.

Batch Reactions. In a 4-mL glass vial MNU (53% dry basis, 100 mg, 0.5 mmol) was dissolved in the selected solvent (Table 1, 1 mL) and stirred at 25 °C for 5 min. Then a solution of KOH (0.5 mL, 1.5 equiv) in the selected solvent was added in about one minute with a syringe. After 5 min at room temperature, excess benzoic acid (1.5 M, 1 mL) was added quickly. The crude mixtures were analyzed by gas chromatography on a GC Agilent 7890A equipped with an Agilent dimethylpolysiloxane Rtx 50 column (30 m × 320 μm, 0.25 μm film thickness) and FID detector. The product methyl benzoate was identified through a standard reference compound and quantified with toluene as an internal standard.

Flow Experiments. Continuous flow studies were carried out in Corning Advanced-Flow *LowFlow* and *GEN1* modules that were grouped into continuous-flow synthesis units by assembling single-injection and residence time modules (Figure

1). Single-injection modules mixed two feeds at once and have a heart-shaped glass flow path for optimum phases split/mixing and mass exchange enhancement. Residence time modules have a heart-shaped structure as well. Typical channel width and height for the *GEN1* system were in the 1 mm × 1 cm and in the 600 μm × 1 mm range, respectively, and a total volume up to 10 mL per module (see Table 3). *LowFlow* modules are a compact, low-volume version of *GEN1* modules. Typical channel dimensions are 10 times smaller than those of *GEN1* modules, with a total volume of 0.45 mL. All modules have an external path for circulating a thermal fluid. In all experiments, temperature was kept at 25 °C with the aid of a circulating thermostat that was connected to the external path. Both *LowFlow* and *GEN1* systems could be operated from −25 °C up to 200 °C. The limit pressure at 100 °C was 9 and 10 bar for *LowFlow* and *GEN1*, respectively. The pressure that was recorded during diazomethane production at the various flow rates, reported in Tables 2 and 3, was in the 4.0−5.0 bar range. The continuous-flow synthesis units were equipped with Pt 100 thermocouples and HD3604T gauge pressure transducers within the reaction and thermal fluid circuits. Temperature and pressure were recorded with an ALMEMO 2590 unit. A three-way gauge was mounted at the outlet of the synthesis units for reactor equilibration purposes and sample collection. Advanced technical information on Corning reactors are available via the web at www.corning.com/reactors.

In a typical *LowFlow* experiment, solutions of MNU in a 1:1 diethyl ether/diethylene glycol mixture (0.45 M), KOH in water (1.5 M), and benzoic acid in ethanol (1.5 M) were delivered to the flow reactor through three pumps (two Fuji PEEK HYM super metering pumps for MNU and acid feeds and an Encynova Novasync 2-1 pump for KOH feed). The stock solution of MNU was prepared by dissolving 10.2 g of commercial slurry (water content = 4.2 mL) in 100 mL of ether/glycol mixture. Flow experiments with the *GEN1* system were carried out using glass modules of 8.39, 8.53, 8.06, and 6.80 mL that were combined to give the volumes indicated in Table 3. A stock solution of MNU for *GEN1* experiments was prepared by dissolving 32.5 g of commercial slurry (water content = 8.7 mL) in 500 mL of ether/glycol. Additional water (5 mL) was added to prevent particulate formation. The KOH was dissolved in water (1.0 or 1.5 M for entry 2, Table 3) and benzoic acid in ethanol (1.5 M). The solutions were delivered by means of *mzr*-7255 pumps.

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(8) The following statement is reported about diazomethane precursors: "*although this material (Diazald) has been kept at room temperature for years without significant change, there has been reported one instance in which a sample stored for several months detonated spontaneously. For long periods of storage, it is recommended that the material be recrystallized and placed in a dark bottle*", in De Boer, T. J., Backer, H. J., Rabjohn, N., Ed. In *Organic Synthesis*; John Wiley & Sons: New York, 1963; Collect. Vol. *IV*, p 495.

(9) www.sigmaaldrich.com/catalog/ProductDetail.do?lang=it&N4=N4766|SIGMA&N5=SEARCH_CONCAT_PNO|BRAND_KEY&F=SPEC

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(11) http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB. LD_{50} (Diazald) = 2700 mg/kg; LD_{50} (MNU) = 110 mg/kg; LD_{50} (MNNG) = 114 mg/kg. The higher LD_{50} value is probably the reason why Diazald is usually preferred for diazomethane preparations. However it is reported that in a favorable environment (i.e. in the stomach) even a weakly or non-carcinogenic compound, such as Diazald, may give rise to strong carcinogenic products via trans-nitrosation reactions. Börzsönyi, M.; Saigó, K.; Török, G.; Pintér, A.; Tamás, J.; Kolar, G.; Spiegelhalder, B. *Neoplasma* **1988**, *35*, 257.

(12) Cost and toxicity issues should be carefully considered, although the latter concern can be handled by using continuous-flow methodologies.

(13) www.unece.org/trans/danger/publi/adr/adr2011/11contentse.html. (ADR 2011, International Carriage of Dangerous Goods) Annex 1, part 1 (1.1.3.6.3 page 10). MNTS (ADR/RID: 3234, transport category 1, maximum quantity per transport unit: 20 kg); MNNG (ADR/RID: 1325, transport category 2, maximum quantity per transport unit: 333 kg); MNU (ADR/RID: 1325, transport category 3, maximum quantity per transport unit: 1000 kg).

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