Acyl Azide Synthesis and Curtius Rearrangements in Microstructured Flow Chemistry Systems

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The synthesis and utilisation of acyl azides in a flow apparatus combined with an automated extraction unit is described. This process safely provides multi-100 g quantities of a labile diacyl azide (**3**) as an intermediate that could not be generated safely by classic batch methods. Its subsequent conversion to the desired amine (**4**) represents an example for process intensification. The same set-up with an output capacity of >30 g/h was used for the unattended synthesis of benzoyl azide as the final product in solution (*tert*-butyl methyl ether (TBME), 0.5 M).

Keywords: acyl azide synthesis, Curtius rearrangement, continuous extraction, process safety

1. Introduction

Acyl azides are useful starting materials for non-nucleophilic amine introduction via Curtius rearrangement to generate substituted urea, amines, amides [1] or guanidines [2]. Synthesis, conversion and work-up of acyl azides are delicate processes due to the compounds' inherent potential of vigorous decomposition [3]. Safety was, therefore, the crucial point when our group planned a universal process for the manufacture and conversion of acyl azides in bulk quantities (100–500 g). Owing to the intrinsic advantages flow chemistry offers, namely precise temperature control, minimised hold-up volumes and optional intermediate post-processing [4], we decided to set up a liquid/liquid process using commercially available equipment. Rapid mixing and efficient heat exchange are strategic edges of flow chemistry. Furthermore, it has been previously mentioned that flow mode alone may significantly enhance process performance (namely safety) by instant interception of reactive intermediates [5]. This should allow both isolation of the acyl azide into an appropriate solvent and its subsequent thermal degradation to the corresponding amine. In order to produce the desired product quantities, a phase separation unit with a throughput capacity of >10 mL/min had to be built [6].

The labile character of acyl azide derivatives hindered their isolation in pure form, but first tests indicated that handling them in solution should be safe. For the manufacturing process, only extraction and washing operations were considered whereas distillation and crystallisation operations were not. This required that all involved materials be water soluble, except the products. For this reason, synthesis of the described acyl azides **3** and **6** started with readily available hydrazides in aq. HCl and NaNO$_2$ [7] rather than from non-basic precursors [8].

2. Results and Discussion

To avoid cumbersome leaving group operations, the approach towards racemic diamine **4** was based on a double Curtius rearrangement (Scheme 1). Conversion of diester **1** (racemate) to dihydrazide **2** in batch mode did not give any problems even for multi-100 g quantities [9]. The differential scanning calorimetry (DSC) [10] analysis of diacyl azide **3**, prepared from a test batch experiment in smaller scale, revealed the hazard potential to exceed the company safety criteria for multi-100 g scale synthesis. The energy release of a 1 M solution (toluene) started

Scheme 1. Synthesis of amine **4**·2HCl (racemate). (a) NH$_2$NH$_2$; (b) NaNO$_2$; (c) heat; (d) aq. HCl
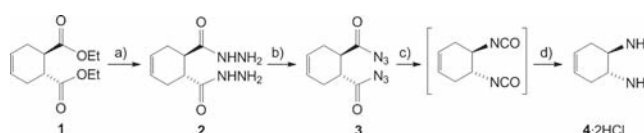
below room temperature and the energy liberated was 364 J/g. These data excluded intermediate **3** from being synthesised in significant amounts but enforced its direct submission to the follow-up conversion.

In the flow chemistry approach, both reagents, hydrazide dihydrochloride **2** and NaNO$_2$, were injected into the glass microreactor (MR) (Sigma-Aldrich type S02, Figure 1, [10]) as aqueous solutions (Figure 2). The extraction medium, toluene, was injected from a third storage container rather than as part of one of the reagent solutions to assure proper feeding rates. The non-sensitive premixing of aq. NaNO$_2$ and toluene took place in a simple T-piece. Both the conversion to diacyl azide **3** and the extraction were initiated inside the glass MR and completed in the attached polytetrafluoroethylene (PTFE) tube (1/8 inch ID (inner diameter), volume 200 mL).

One of the project objectives was the continuous removal of by-products and non-reacted starting materials. To achieve an interim separation, the raw mixture was firstly sampled into a separation funnel. All water-soluble compounds were periodically drained off with the aqueous phase. Diazide **3** in the upper
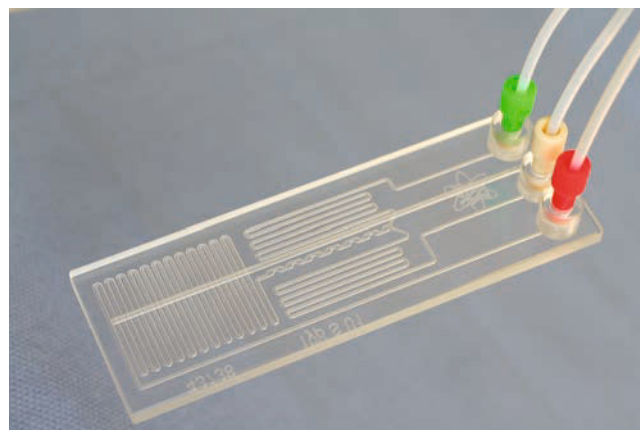
Figure 1. Glass microreactor, type Sigma-Aldrich S02
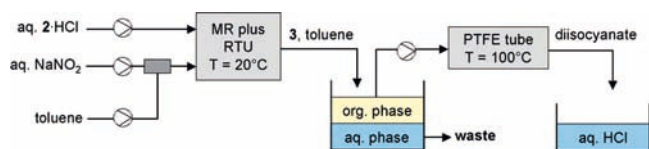
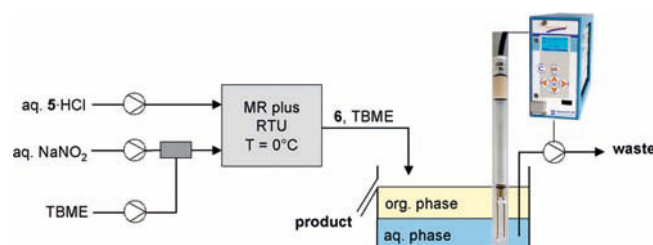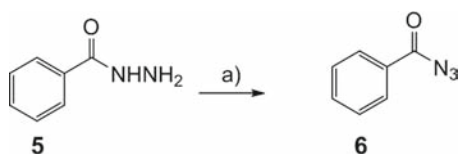**Figure 2.** Set-up for the synthesis of diamine **4**·2HCl

organic phase was continuously pumped through a heated PTFE (1/8 inch ID, volume 100 mL), and it underwent double Curtius rearrangement at 100 °C. In order to minimise risk, the total volume of the interim organic phase never exceeded 30 mL, representing a maximum of 3.5 g of intermediate **3**. Each campaign was run for 8 h. Typical flow rates are as follows: hydrazide **2** (0.7 M in 5% aq. HCl) 12.0 mL/min; $NaNO_2$ (1.69 M in water), 11.2 mL/min; toluene (pure), 16.0 mL/min, residence time (stage 1) ~5.4 min. The flow rate of the pump in stage 2 was correlated with the toluene feeding rate from stage 1, and this resulted in a residence time of ~10 min in stage 2. The formed diisocyanate was not isolated but directly converted into the final product. Quenching the raw mixture from stage 2 on aq. HCl and recrystallisation (ethanol) provided amine **4** as dihydrochloride in 49% yield (>99% purity, argentometric titration), with a non-optimised output of 14.6 g/h. As a positive side effect, this raw mixture was easier to purify than the material obtained from the test batch experiment.

In order to eliminate the manual phase separation, we looked for a more convenient and automated solution. This was found in the form of an impedance probe (Aquasant comp.), whose usefulness was demonstrated in the course of the acyl azide **6** synthesis starting from commercially available hydrazide **5** (Scheme 2). Since aromatic acyl azides were found to be more stable than their aliphatic counterparts, it was the intention to deliver acyl azide **6** as the final product in solution, rather than using it only as an intermediate.

The reagent arrangement for acyl azide **6** synthesis was similar to those of intermediate **3** (Figure 3), although the interim solution was not submitted to later conversion but allowed to enter a glass tube with a drainage on the side, where the product solution was transferred to the sampling container (Figure 4). The water/organic solvent phase frontier was kept in a defined range by the impedance controller in connection with another piston pump that regularly removed the aqueous waste phase [11]. It operated reliably during the entire campaign of 3–4 h. Even in other applications, loaded with lingering solid formation inside the aqueous medium, the phase boundary was clearly identified by the measuring system.

The desired standard concentration (0.5 M) of the dissolved product **6** was adjusted either by enhancing the extraction medium flow rate or by later diluting the complete batch. Typical flow rates are as follows: hydrazide **5** (0.45 M in 0.5 M aq. HCl), 10 mL/min; $NaNO_2$ (1.3 M in water), 3.8 mL/min; *tert*-butyl methyl ether (TBME) (pure), 5.0 mL/min, residence time (including extraction) ca. 1.5 min. Acyl azide **6** was obtained in 80% yield (96.0% purity, high-performance liquid chromatography (HPLC)) with a non-optimised output of ca. 30 g/h (net amount). Extraction with fresh TBME of an aliquot taken


Figure 3. Set-up for the synthesis of acyl azide **6**

from the milky aqueous phase in the separation unit showed acyl azide **6** as the major product besides traces of the starting material (HPLC analysis). This suggested that there is room for improvement of the extraction, but the process was accepted as proof-of-principle without further optimisation. DSC analysis showed an energy release of 187 J/g (two onsets) for the 0.5 M solution of acyl azide **6** and a thermal stability up to 75 °C (Radex (rapid detection of exothermity) test for 8 h). On the basis of these values, acyl azide **6** dissolved in TBME (0.5 M) was deemed suitable as a commercial product [12].

3. Conclusion

We present safe and direct access to acyl azides and their controlled degradation to amines (Curtius rearrangement) in multi-100 g scale. Both processes are not optimised and promise room for improvement in terms of yield and output. The approach towards diamine **4** via diacyl azide **3** in continuous mode represents an example of process intensification. The safe handling of the highly hazardous intermediate **3** in flow mode enabled access to product **4** in the most straightforward synthesis approach. Furthermore, obtaining easier to purify final product mixtures (versus those obtained from batch procedures) lowered labour costs and material resources. For unattended operation, a phase separation unit was built that fulfilled

Scheme 2. Synthesis of acyl azide **6**. (a) aq. $NaNO_2$
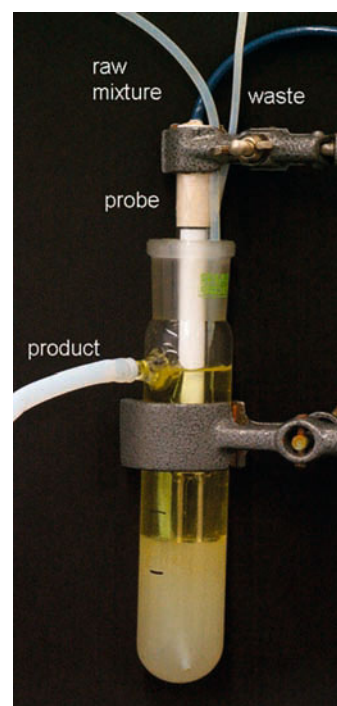
Figure 4. Phase separation unit

the input capacity of >10 mL/min and demonstrated potential for much higher throughputs in test runs. To further prove the advantage of the presented method, we take the liberty to note that the here-described materials **4** and **6** (in solution) are meanwhile commercially available [13].

4. Experimental Section

4.1. Instruments for Chemical Synthesis and Safety Analysis. All reagents were pumped by piston pumps (type ISMATEC *Reglo-CPF* Digital equipped with pump head *RH0. CKC-LF/FMI 13*, volume 50 μL). PTFE tubing (type Supelco no. 58699, OD (outer diameter) 3.2 mm and ID 1.5 mm) was used for connection and residence time unit (RTU). The system's inner pressure was monitored by sensors (type profimess) at the outlets of pump A and B, before entering the subsequent element. All elements were taken from the Microreaction Explorer Kit (Sigma-Aldrich no. 19979). Safety analysis: DSC, Mettler Toledo 821 with HP-Au M20 pan; Radex, SYSTAG TSC 5000.

CAUTION: Organic azides are sensitive towards shock, temperature, friction, light and other influences and may decompose with enormous violence. For detailed safety investigations and safety recommendations see literature [3].

4.2. (+/−)-trans-4-Cyclohexene-1,2-diamine dihydrochloride (4)

4.2.1. Solution A. (+/−)-*trans*-Cyclohex-4-ene-1,2-dicarboxylic acid dihydrazide (505 g, 2.548 mol) was dissolved into conc. HCl (600 mL) and distilled water (2540 mL). The concentration (dihydrochloride) was 0.7 mmol/mL and the flow rate was 12.00 mL/min or 8.40 mmol/min.

4.2.2. Solution B. Sodium nitrite (393.4 g, 5.701 mol) was dissolved into distilled water (3000 mL). The concentration was 1.69 mmol/mL and the flow rate 11.16 mL/min or 18.86 mmol/min.

4.2.3. Solution C. Toluene pure: The flow rate was 16.00 mL/min.

4.2.4. Set-up. Pump A was connected with one of the MR inlets. Pumps B and C were connected with a T-piece (type Supelco, no. 58750-U), and the outlet was directly connected with the other MR inlet. A PTFE coil (volume 200 mL) was attached to the MR outlet. Both the micoreactor and the PTFE coil were immersed in a water bath (without circulation) adjusted to 20 °C. The outlet was placed on top of a separation funnel (volume 100 mL). The funnel's drainage was opened just wide enough to establish a steady state volume (ca. 40 mL of the aqueous phase). The upper organic layer containing the product was continuously removed by another pump (same flow rate as that of pump C, also realising a steady state volume) and submitted to a second PTFE coil (volume 200 mL), which was heated to 100 °C with an oil bath. The outlet was placed in an Erlenmeyer flask (volume 10 L) containing aq. HCl (32%, 600 mL).

4.2.5. Operation. All pumps were calibrated with the respective solvent prior to use. Pump C was activated 3 min before pumps A and B in order to dissolve any instantly formed organic material. The reaction was run for 8 h. The diazide intermediate appeared as a light yellow liquid and the final product as off-white precipitate. After sampling was finished, all lines were flushed with water or toluene.

4.2.6. Work-up. The collected product solution was diluted with ethanol (250 mL) and then evaporated to yield a brown solid (387.6 g). The raw product was stirred with ethanol (500 mL) and then filtrated to yield 232.9 g (1.26 mol; 49% yield) off-white powder.

4.2.7. Analytical Data. ^{1}H NMR (600 MHz, D$_2$O) δ 2.43 (2H, m), 2.66 (2H, m), 3.88 (2H, m), 5.80 (2H, m); ^{13}C NMR (75 MHz, D$_2$O) δ 25.3, 46.7, 122.7; mp > 320 °C.

4.3. Benzoyl Azide Solution (6)

4.3.1. Solution A. Phenyl hydrazide (100.0 g, 0.735 mol) was dissolved into aq. HCl (816 mL, c = 1.0 M) and a total volume of 1.63 L was established by the addition of distilled water. The concentration (hydrochloride) was 0.45 mmol/mL and the flow rate 10.0 mL/min or 4.5 mmol/min.

4.3.2. Solution B. Sodium nitrite (64.6 g, 0.940 mol) was dissolved into distilled water (300 mL) and a total volume of 0.720 L was established by the addition of distilled water. The concentration was 1.3 mmol/mL and the flow rate was 3.8 mL/min or 4.94 mmol/min.

4.3.3. Solution C. TBME (pure): The flow rate was 5.0 mL/min.

4.3.4. Set-up. Pump A was connected with one of the MR inlets. Pumps B and C were connected with a T-piece (type Supelco, no. 58750-U), and the outlet was directly connected with the other MR inlet. A PTFE coil (volume 25 mL) was attached to the MR outlet. Both the micoreactor and the PTFE coil were immersed in a water/ice bath (without circulation). The outlet was placed on top of a sample tube (ID 30 mm, Figure 4) with an onside spill. The metallic detecting element of the impedance probe [11] inside the glass tube was positioned below the spill. The product solution from the spill was collected in an Erlenmeyer flask. The set points at the impedance control unit were chosen to keep the upper organic level in a range of 30–50 mL. The inlet of the piston pump connected with the control unit was fixed at the glass tube's bottom. The pump was activated at regular intervals and operated with a flow rate of ~20 mL. The extracted aqueous phase was sampled on aq. NaOH (1 M). On the basis of the total flow rate of 18.8 mL/min, a residence time of 1.5 min was assumed.

4.3.5. Operation. All pumps were calibrated with the respective solvent prior to use. Pump C was activated 3 min before pumps A and B in order to dissolve any instantly formed organic material, and the spilled solution was collected in a waste container. Product sampling commenced with the change of the product tube from the waste container to the glass tube 7 min after pumps A and B were activated. The material was collected for 80 min as a light yellow liquid. After sampling was finished, all lines were flushed with water or TBME. The real flow rate of reference compound A (phenyl azide) was 9.9 mL/min, found by measuring the consumed volume.

4.3.6. Work-up. The collected product solution was washed with saturated NaHCO$_3$ solution (3 × 50 mL) until the pH stayed >8, followed by washing with saturated NaCl solution (50 mL). The organic phase was dried (Na$_2$SO$_4$, 20 g), and the solid was filtered off and washed with TBME (30 mL) to provide 375 mL product solution. ^{1}H NMR analysis (benzlock) of the solution indicated a concentration of 0.76 M based on the residual solvent signal, representing a net amount of 41.9 g (285 mmol) with 96.0% purity (HPLC). The final concentration of 0.5 M was established by further addition of TBME (170 mL). The material was stored at −18 °C to keep its original quality.

4.3.7. Yield Calculation. Invested amount (phenyl hydrazide, **5**) = real flow rate (mL/min) × sampling time (min) × concentration (mmol/mL) = 356.4 mmol. Obtained amount (benzoyl azide, **6**) = 285 mmol. Yield (%) = 100 × (285/356.4) = 80%.

4.3.8. Analytical Data. FTIR (neat) 693, 967, 1174, 1241, 1492, 1691, 2128, 2170 cm^{-1}; ^{1}H NMR (600 MHz, TBME, benzlock) δ 7.91 (2H, t, J = 7.3 Hz), 8.08 (1H, t, J = 6.9 Hz), 8.47 (2H, d, J = 7.1 Hz); ^{13}C NMR (150 MHz, TBME, benzlock) δ 128.9, 129.5, 131.4, 134.7, 171.9.

Abbreviations

DSC: differential scanning calorimeter
ID: inner diameter
OD: outer diameter

MR: microreactor
Radex: rapid detection of exothermity
RTU: residence time unit
TBME: tert-butyl methyl ether

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10. The glass microreactor type S02 is available with the Sigma-Aldrich Microreaction Explorer Kit, article number 19979. Also see www.sigmaaldrich.com/mrt.

11. Impedance glass probe SGK 180/40 and control unit MIL 8130 were purchased from Aquasant Messtechnik AG (Bubendorf, Switzerland).

12. For United Nation criteria on chemical products, see http://www.unece.org/trans/danger/publi/manual/manual_e.html

13. Sigma-Aldrich product numbers: **4**, 726184; optical pure isomers 726311 and 726338; **6**, 778486. For further information and other azides, see www.sigmaaldrich.com.