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Adaptation of an Exothermic and Acylazide-Involving Synthesis Sequence to Microreactor Technology

Luigi Rumi,[†] Christophe Pfleger,[‡] Paul Spurr,[‡] Uwe Klinkhammer,[‡] and Willi Bannwarth*,[†]

Institut für Organische Chemie und Biochemie, Albert-Ludwigs-Universität Freiburg, Albertstrasse 21, D-79104 Freiburg, and F. Hoffmann-La Roche Ltd., Pharmaceuticals Division, Technical Sciences, Kilolaboratory and Synthesis and Process Research, CH-4070 Basel, Switzerland

Abstract:

The original three-step batchwise synthesis of the pharmaceutical intermediate (1*R*,2*S*,4*S*)-(7-oxa-bicyclo[2.2.1]hept-2-yl)-carbamic acid ethyl ester (4) from (1*R*,2*S*,4*S*)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid ethyl ester (1) encompassed a highly exothermic hydrazine quenching step as well as an acylazide intermediate. After appropriately modifying the reaction conditions, all three steps could be adapted to a microreactor system and a continuous process which permitted the desired carbamate 4 to be prepared under safe operating conditions in yields of 96%, 94%, and 84% for the three individual steps.

1. Introduction

Chip-based microfluidic systems and microstructured continuous-flow reactors are becoming increasingly popular to overcome limitations associated with chemical synthesis in traditional batch reactors.[1−18] Due to their high surface-to-volume ratio, microreactors provide efficient heat transfer. Consequently, reaction temperatures can be accurately tuned and thus avoid hot spots often responsible for the formation of byproducts. A further consequence is that reactions that have been previously considered as unattractive for practical or safety reasons can be performed under safe conditions. A plethora of such reactions including those using phosgene,[19] phenol nitration,[20] glycosylation,[21,22] β-peptide synthesis,[23] the generation and reaction of *o*-bromophenyllithium,[24] formation of oligosaccharides,[25] fluorination,[26] trimethylaluminium-mediated amide bond formation,[27] oxidation with oxygen,[28] radical-based reduction and hydrosilylation,[29] as well as radical reactions of tin hydride[30] have had this technology applied. A further advantage is high miscibility due to molecular diffusion as a consequence of the laminar flow in the capillaries[4] which makes these especially suited for biphasic reactions where efficient mixing is a prerequisite for fast conversions.[31−33] Furthermore, microreactor technology has found applications in the synthesis of ionic liquids,[34] polymers,[35,36] C−C coupling reactions,[37−42]

* Corresponding author: Fax: +49 761 2038705. Tel: +49 761 2036073. E-mail: willi.bannwarth@organik.chemie.uni-freiburg.de.

† Institut für Organische Chemie und Biochemie, Albert-Ludwigs-Universität Freiburg.

‡ F. Hoffmann-La Roche Ltd., Pharmaceuticals Division, Technical Sciences, Kilolaboratory and Synthesis and Process Research.

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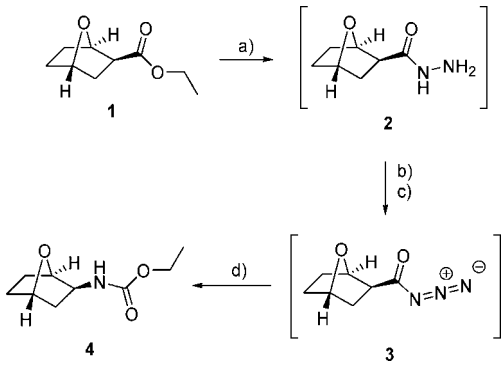
Scheme 1[a]



[a] Reagents and conditions: a) 1 (1.0 equiv), 1.9 equiv of 24% aq $N_2H_4.H_2O$, 95 °C, 24 h; b) HCl 25% (4 equiv), 0 °C; c) 10% aq $NaNO_2$ (2.7 equiv), 0 °C; d) DCM/EtOH 1:1, 45 °C, 20 h.

and biocatalytic transformations.[43,44] In recent years, microreactors have mainly been used in small-scale synthesis,[13,45,46] but in the meantime there have been increasing numbers of examples also covering their application in industrial production processes.[47−53]

2. Results and Discussion

The basis of our optimization and adaptation to a microreactor is the reaction sequence depicted in Scheme 1.[54,55] The target carbamate **4** is an intermediate to a receptor antagonist molecule.

The first step in the original batchwise[54] synthesis was the transformation of the ethyl ester **1** to the hydrazide **2**. In order to attain complete conversion, 1.9 equiv of aq hydrazine hydrate had to be employed at 95 °C for 24 h. Initially, the reaction was biphasic, but in the course of the conversion, the phase consisting of ester **1** was consumed as the resulting hydrazide was soluble in the aqueous phase.

The aqueous hydrazide solution was then cooled to 0 °C and acidified with 25% HCl, resulting in an exothermic reaction (ΔH: −102 kJ/mol)[56] to the protonation of the excess of hydrazine. Dropwise addition of a 10% aq sodium nitrite solution at 0 °C led not only to the formation of the acylazide **3** but also to a strongly exothermic reaction (ΔH: −599 kJ/mol)[56] because of the consumption of excess hydrazine forming N_2, N_2O, and H_2O and an associated vigorous gas evolution. The azide **3** was extracted into cold dichloromethane, and after the addition of the same volume of ethanol, the mixture was refluxed for 20 h to obtain the urethane **4** *via* a *Curtius* rearrangement. The overall yield of the crude urethane **4** after the three steps was in the range of 71−84%.

For the envisaged adaptation of the reaction sequence to the microreactor system, we were faced with a number of challenges. First and foremost, the excess hydrazine hydrate needed for an effective conversion of ester **1** to hydrazide **2** was identified as a severe problem due to the strong exothermicity arising from the acidification and azide formation steps thereafter, accompanied by the large volume of gas production. Furthermore, the potential instability of the acylazide intermediate **3** had to be taken into account in terms of handling, and last, the hydrochloric acid originally used had to be replaced by an alternative because of the corrosive properties of this substance on the stainless steel capillaries of the microreactor. The use of a glass reactor would have avoided this latter problem.

The initial focus was given to the reaction of ester **1** with aq hydrazine hydrate as this was the key to a successful throughput application of the microreactor technology. With the efficient miscibility in such reactors, we anticipated an acceleration of this biphasic transformation which would enable the utilization of equimolar amounts or a small excess of hydrazine hydrate in order to reduce the exothermicity in the ensuing acidification step.

For our studies we used a CYTOS Lab System by CPC-Cellular Process Chemistry GmbH (Figure 1) which is composed of the microreactor itself ($V = 2$ mL), three exchangeable RESIDOS residence time modules ($V = 15$ mL each), and fully integrated pumping and heating/cooling systems, the whole system being completely computer controlled.

The progress of hydrazide formation was studied initially using 1 equiv of hydrazine hydrate at 88 °C with different flow rates and residence times (Table 1). As expected, the conversion was enhanced with increasing residence times which was achieved by either reducing the flow rate or by inserting residence time modules. Elongation of the residence time with

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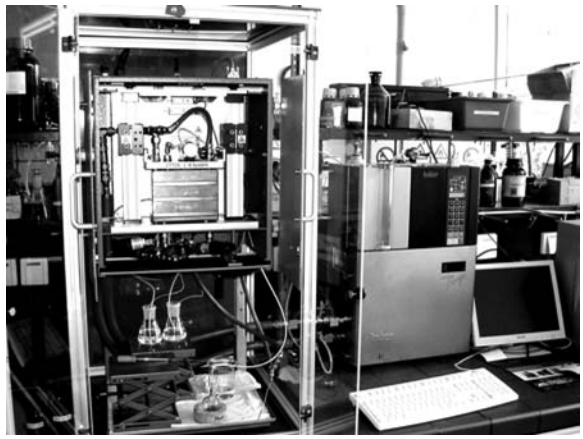

Figure 1. **CYTOS Lab System by CPC GmbH.**

Table 1. **Transformation of the ester 1 into the hydrazide 2 in the microreactor using 1.0 (entry 1−9) or 1.1 (entry 10) equiv of hydrazine hydrate, respectively**

entry	number of RESIDOS modules	T_i [°C]	flow rate [mL/min]	residence time [min]	conversion (HPLC) [%]
1	−	88	1.06	2	31
2	1	88	1.06	16	47
3	2	88	1.06	30	80
4	3	88	1.06	44	89
5	−	88	0.60	3	58
6	1	88	0.60	28	64
7	2	88	0.60	53	85
8	3	88	0.60	78	92
9	3	93	0.44	106	94
10	3	93	0.44	106	>96

1 equiv of N_2H_4 resulted in a constant improvement of the conversion, and with a residence time of 78 min, the conversion was as high as 92%. Raising the reaction temperature to 93 °C and increasing the amount of hydrazine hydrate to 1.1 equiv led after 106 min to a conversion of >96% to the desired hydrazide **2**. On cooling to 0 °C, the pure product **2** crystallized and was obtained by filtration and in yields of 88−96%.

For the next step, a suitable acid had to be identified as an alternative to hydrochloric acid. Sulphuric acid generated insoluble sodium sulfate which likely could cause clogging of the capillaries. Acetic acid proved to be too weak to protonate the hydrazide quantitatively. The best choice turned out to be phosphoric acid. For the azide transformation, an aqueous solution of hydrazide **2** was acidified with 2 equiv of 85% aq phosphoric acid in the microreactor at 2 °C with a residence time of 2 min. The resulting solution was injected along with a 10% aq sodium nitrite solution into the microreactor at the same maintained temperature and reacted at a flow rate of 0.5 mL/min each, corresponding to a residence time of 2 min. The conversion to the azide **3** occurred in the range of 83−94% as monitored by HPLC. Extraction with dichloroethane (DCE) yielded the pure azide with the impurities remaining in the aqueous phase. The DCE solution containing the azide was then used for the Curtius rearrangement.

Despite the intrinsic instability of the azide **3** and the negative reaction enthalpy of −100 kJ/mol, the rearrangement process was very slow at temperatures close to ambient. Thus, a solution of the azide in DCE and ethanol (1:1; v/v) was injected into the microreactor and circulated at a flow rate of 0.5 mL/min at 60 °C for 20 h. After HPLC analysis showed complete conversion of the azide, on evaporation of the solvent under reduced pressure, the urethane **4** was isolated in 84% yield.

3. Conclusion

In summary, microreactor technology could be successfully applied to the three-step synthesis of the desired urethane **4** intermediate from ester **1** *via* hydrazide **2** and acylazide **3**. Salient features of the microreactor preparation are the efficient biphasic transformation of ester **1** into the hydrazide **2**, avoiding large excesses of hydrazine hydrate and, hence, the high exothermicity encountered on subsequent manipulation in addition to the safe formation and handling of the azide **3** which was converted after Curtius rearrangement to the desired urethane **4**. Although the conversions, yields (batch: 71−84%, microreactor: 75%) and reaction times for the last two steps were in the same range, the transformation of the ester into the hydrazide experienced a remarkable acceleration in the microreactor (106 min vs 24 h). Compared to the batchwise synthesis of **4,** the microreactor preparation turned out to be efficient, safe, and straightforward, as well as resulting in high yields. The example illustrates the potential of microreactor devices to surmount critical highly exothermic synthetic steps and provide safe handling of potentially unstable compounds.

4. Experimental Section

All reagents were purchased from commercial sources (Aldrich, Fluka, Riedel-de Haën), with the exception of compound **1** which was synthesized in the laboratories of F. Hoffmann-La Roche Ltd., Basel. HPLC analysis was performed on an *Agilent-1100* system with a *Zorbax Eclipse XDB-C8 4.6 mm × 150 mm* column (Agilent). NMR spectra were obtained with a Bruker AM 400 (^{1}H 400 MHz, ^{13}C 100.6 MHz) or a Varian Mercury 300 (^{1}H 300 MHz, ^{13}C 75.5 MHz) and are reported in δ relative to $CHCl_3$ (^{1}H 7.26 ppm, ^{13}C 77.23 ppm) as an internal reference. MS spectra with chemical ionisation (CI) were obtained with a Finnigan MAT312 with ammonia as gas (0.4 mbar, 220 °C, 250 eV, 1 mA, 2 kV). MS spectra with electron impact ionisation (EI) were obtained with a Finnigan MAT8200 (230 °C, 70 eV, 1.0 mA, 3 kV). Elemental analyses were obtained with a Vario EL (Elementaranalysensysteme GmbH). Melting points were measured with an Electrothermal IA 9000 and are uncorrected.

The CYTOS Lab System by CPC-Cellular Process Chemistry GmbH is composed by the microreactor itself (V = 2 mL), consisting of microstructured stacked plates of stainless steel, three exchangeable RESIDOS residence time modules (V = 15 mL each), and fully integrated pumping and heating systems. The device was filled with the appropriate solvent by activating the two pumps simultaneously, whereas the temperature was adjusted using an external thermostat (Huber Unistat Tango). Prior to synthesis, the pumps of the microreactor system were calibrated to the desired flow rates. The temperature inside the microreactor and the attached residence units were adjusted accordingly. The system was washed by purging with the 2-fold installed volume of solvent before running a reaction.

4.1. Synthesis of 7-oxabicyclo[2.2.1]heptane-6-carboxylic acid hydrazide (2). *4.1.1. Batchwise Synthesis.* To ester **1** (15.0 g, 86.8 mmol) was added a 24% aq. solution of hydrazine

hydrate (35.3 g, 169 mmol, 1.95 equiv). The biphasic solution was vigorously stirred at 95 °C for 24 h. After TLC- and HPLC-control demonstrated complete conversion, the clear monophasic hydrazide solution was used directly for the next step.

4.1.2. Microreactor Synthesis. The vessel containing ester **1** was heated at 80 °C in order to reduce the viscosity of the ester. The ester and a 36% aq hydrazine hydrate solution (1.1 equiv) were pumped at 0.22 mL/min each into the microreactor (reactor with three residence time blocks, $V = 47$ mL, $T = 93$ °C). The product solution was then collected in a vessel and cooled to 0 °C. After filtration and washing with DCM (20 mL), the acid hydrazide was obtained as a colourless solid (isolated yields 88−96%, corresponding to the continuous formation of 11.6−12.7 g of hydrazide per h; mp 112 °C, Lit.[54] 118 °C).

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.49$ (2 H, m), 1.75 (2 H, m), 1.88 (2 H, m), 2.59 (1 H, dd, $J = 5.7$, 7.9 Hz, *H*CC=O), 3.83 (2 H, bs, NHN*H*$_2$), 4.67 (2 H, m, *H*C−O), 7.40 (1 H, bs, N*H*NH$_2$).

^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 29.2$, 29.7, 36.6, 48.9, 76.1, 79.2, 175.6.

MS (GC/MS-CI, NH_3, 130 eV): *m*/*z* (%) = 174 (12) [$(M + NH_4)^+$], 157 (100) [$(M + H)^+$], 142 (12).

Anal. Calcd for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.74; N, 17.94; Found: C, 53.61; H, 7.74; N, 18.01.

4.2. Synthesis of Ethyl 7-oxabicyclo[2.2.1]hept-2-yl Carbamate (4). *4.2.1. Batchwise Synthesis.* The aq acid hydrazide solution from the first step was cooled to 0 °C. DCM (174 mL) was added followed by the dropwise addition of 25% aq hydrochloric acid (50.2 g, 344 mmol, 3.96 equiv) and a 10% aq sodium nitrite solution (106.9 g, 154.9 mmol, 1.78 equiv). The biphasic system was stirred for 30 min during which the pH varied between 3−5. DCM (174 mL) was added, the organic phase was separated and dried over Na_2SO_4. After addition of ethanol (348 mL), the mixture was stirred at 45 °C for 36 h. After HPLC analysis indicated complete conversion, the solvent was removed under reduced pressure, and the product was obtained as a light-yellow oil (13.0 g, 81% overall from ester **1**).

4.2.2. Microreactor Synthesis. In a flask, the pure hydrazide (3.0 g, 19 mmol) was dissolved in water (6.6 mL). This solution and phosphoric acid 85% (2.4 mL, 38 mmol, 2 equiv) were pumped into the microreactor ($T = 2$ °C, $V = 2$ mL) at a total flow rate of 1 mL, corresponding to 0.33 g of hydrazide per min. The collected cold, protonated hydrazide solution and a 10% aq solution of sodium nitrite (13.2 mL, 1.32 g $NaNO_2$, 19.2 mmol, 1 equiv) were pumped into the microreactor ($T = 2$ °C, $V = 2$ mL) at a total flow rate of 1 mL/min. In both steps neither gas formation nor any exothermicity was observed. The azide solution was collected in a cooled vessel (0 °C) and analyzed by HPLC (83−94%, corresponding to the continuous formation of 4.5−5.1 g of azide per h). The azide **3** was then extracted into cold DCE (2 × 10 mL) (0 °C); ethanol (20 mL) was added to the DCE phase, and this solution was then pumped into the microreactor ($T = 60$ °C, $V = 47$ mL) with a flow rate of 0.5 mL/min. The solution was circulated in the reactor for 22 h. After HPLC analysis had indicated complete conversion of the azide, the solvent was removed under reduced pressure to obtain the pure urethane **4** (2.99 g, 16.1 mmol, 84% isolated yield, corresponding to the continuous formation of 0.13 g of carbamate product per h) as confirmed by GC/MS and elemental analysis.

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.23$ (3 H, t, $J = 7.1$ Hz, OCH_2CH_3), 1.41 (3 H, m), 1.68 (2 H, m), 1.98 (1 H, dd, $J =$ 8.1, 12.9 Hz), 3.83 (1 H, dd, $J = 6.0$, 7.9 Hz, C*H*−N), 4.10 (2 H, q, $J = 7.0$ Hz, OCH_2CH_3), 4.37 (1 H, d, $J = 5.3$ Hz, C*H*-O), 4.59 (1 H, dd, $J = 5.1$, 5.1 Hz, C*H*−O), 4.97 (1 H, bs, N*H*).

^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 14.6$, 26.1, 29.4, 40.5, 54.8, 60.8, 75.5, 81.4, 175.9.

MS (GC/MS-EI, 70 eV): *m*/*z* (%) = 185 (29) [M^+], 156 (14) [$(M - C_2H_5)^+$], 141 (98) [$(M - OC_2H_5)^+$], 128 (100), 96 (25) [$(C_6H_9O)^+$], 70 (26), 56 (38), 41 (18).

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.61; Found: C, 58.13; H, 8.19; N, 7.64.

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