Synthesis of *N*-Hydroxypyrazin-2(1*H*)-ones via Selective *O*-Debenzylation of 1-Benzyloxypyrazin-2(1*H*)-ones Using Flow Methodology

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This paper describes the selective and reproducible debenzylation of benzyloxypyrazinones using flow chemistry to yield *N*-hydroxypyrazinones. Flow methodology enabled us to avoid overreduction of the compounds to pyrazin-2(1*H*)-ones.

Keywords: debenzylation, flow chemistry, 1-hydroxypyrazin-2(1*H*)-one, hydroxamic acid, aspergillilic acid

1. Introduction

Hydroxamic acids, also occurring in bioactive compounds from natural origin (e.g., aspergillilic acid), are well-known for their strong binding ability with many metal ions [1]. This explains their potential to inhibit specific metal-containing enzymes involved in human immunodeficiency virus [HIV] [2–4] and cancer progression (histone deacetylases [HDACs], mitochondrial membrane permeabilities [MMPs], ribonucleotide reductase [RNR]) [5–7]. Our group has previously been working on the design and synthesis of highly functionalized pyrazinones [8–14]. In the current paper, we focus on our newly developed synthesis of *N*-hydroxypyrazinones. These can be prepared via the base catalyzed condensation of a glyoxal derivative with either an α -amino hydroxamic acid (previous work) [15–20] or an *O*-protected α -amino hydroxamic acid (this work). The latter synthesis requires a deprotection step [21–24] but is warranted to have a better compatibility with different classes of functional groups as well as reaction conditions.

2. Results and Discussion

In order to avoid potential selectivity problems when preparing more complex systems (like the 3-carboxamide derivatives described in this paper) and in order to avoid difficulties in purification steps, we chose to work via the *O*-benzyl-protected precursors. We recently reported on the synthetic procedures that allow to prepare such 1-benzyloxypyrazin-2(1*H*)-ones from simple starting materials elsewhere (Scheme 1) [25].

Reductive debenzylation of *O*-benzyl hydroxamates has been reported before in the literature, though yields are sometimes low and over-reduction to amides is a known problem [21, 26–30]; however, an appropriate catalyst system (e.g., Pd–BaSO₄) can solve this problem in a number of cases [31–33]. Our debenzylation studies commenced with 1-benzyloxypyrazin-2(1*H*)-one (**3a**) using batch chemistry (Table 1) with hydrogen gas and different palladium catalysts (e.g., Pd–C and Pd–BaSO₄). This showed that the hydrogenolysis is fast and more selective for the desired compounds **4a** with the less reactive Pd-based catalysts at high temperature (Entry 6, Table 1). Since a characteristic ultraviolet (UV) absorption maximum of the core pyrazinone scaffold is present in the range of 320–370 nm (depending on pH) [34–36], a high-performance liquid chromatography–ultraviolet–mass spectrometry (HPLC–UV–MS) method has been used to quantify the relative conversion and selectivity of the reactions in this study. It is based on the integration of relative peak areas of reactant and product/byproduct at the indicated wavelength (for details, see Supporting Information).

However, when the same conditions were applied to 1-benzyloxypyrazin-2(1*H*)-one 3-carboxamide derivatives **3g–zb**, removal of the benzyl group most of the time was met with failure due to over-reduction. An excellent selectivity of **4h** over **5h** (91%, HPLC–UV–MS, 350 nm) once was obtained when performing the debenzylation of **3h** with 5% Pd–BaSO₄ (unreduced form) under hydrogen gas (1 bar, balloon). Moreover, the selectivity obtained in all these reactions was not reproducible even with the same substrates. Efficient control of the contact time between reagent and products and the catalyst seemed to be of the utmost importance. Therefore, we decided to switch from conventional batch hydrogenation conditions to flow technology using a catalytic transfer hydrogenation where residence times are more easily tuned and controlled.

The reactions under flow conditions were performed in the microflow system using a catalyst reactor (Chemtrix) and a backpressure regulator (Figure 1). We carefully screened and optimized the factors that could affect the selectivity and the conversion of the debenzylation process under flow conditions.

Product solubility is one of the most critical factors and may be a limitation of flow chemistry in general [37–39]; the formation of precipitate during the reaction may block the micro-channels and build up pressure, which could break the glass reactor [40, 41]. After screening different solvents, we found methanol being the best candidate: it could properly dissolve reasonable amounts of most of our substrates as well as the resulting debenzylation products. Besides that, its polarity is also favorable for the hydrogenolysis. Ethanol and isopropanol were able to dissolve the substrate benzyl hydroxamates but not the hydroxamic acid products.

Many hydrogen donors can be used in catalytic transfer hydrogenation, such as formic acid and its salts, isopropanol, cyclohexene, cyclohexadiene, hydrazine, phosphinic acid, etc. [42–44]. In situ hydrogen formation in the reaction mixture increases the gas–liquid–solid phase interaction, helps to control the stoichiometry of the reagents, and, most importantly, helps to avoid the risk of fire and explosion associated with using hydrogen gas (especially when dealing with larger scale synthesis). We used ammonium formate, which shows more advantages in comparison to the others [43, 45–49], as a hydrogen donor. Ammonium formate acts as a hydrogen equivalent that may be presented either in the adsorbed form on palladium or in the palladium hydride form [49]. Study on the decomposition of ammonium formate shows that it brings to the reaction not only hydrogen but also ammonia and carbon dioxide [45, 50, 48, 49]. These gases were observed as bubbles formed downstream of the backpressure regulator.

The pressure in the reaction mixture was fixed using a backpressure regulator set at 5 bar. This also allowed us to work above the boiling point of methanol up to 110 °C.

An appropriate catalyst was needed for the debenzylation, both in terms of reactivity and in terms of reactor specifications.

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Scheme 1. Synthesis of 1-benzyloxy-pyrazin-2(1*H*)-ones **Table 1.** Batch debenzoylation of 1-benzyloxy-pyrazin-2(1*H*)-one (3a)

Entry	Catalyst	Condition	Selectivity (%) ^a	
			4a	5a
1	5 % Pd-C	2 bar/rt/5 min	0	100
2	5 % Pd-C	1 bar/rt/10 min	25	75
3	5 % Pd-C	1 bar/rt/30 min	20	80
4	5 % Pd-C	1 bar/reflux/5 min	60	40
5	5 % Pd-BaSO ₄ ^b	1 bar/reflux/5 min	80	20
6	5 % Pd-BaSO ₄ ^c	1 bar/reflux/5 min	95	5

Reagents and conditions: **3a** (0.1 mmol, 0.1 M), H₂ (in a Parr apparatus or with a balloon), palladium catalyst (5 %wt.).
^a Quantitative conversion (quantification at 350 nm via RP HPLC–UV–MS).
^b Pd–BaSO₄ reduced form.
^c Pd–BaSO₄ unreduced form.

Horn and Cerato–Noyerie recently reported the development of a convenient in situ PdCl₂-based catalyst for hydrogenation in glass microreactors [51]. We found an alternative Pd source

Figure 1. Schematic representation for the debenzoylation experimental setup in flow**Scheme 2.** Debzoylation of representative precursor **3h** in flow

with appropriate particle size specifications in the form of SiliaCat® DPP-Pd which has been shown to be a useful catalyst for many kinds of Pd-catalyzed reactions (Heck, Sonogashira, Kumada, Suzuki, Stille reactions, and Buchwald aminations) in flow [52–54]. This catalyst was used in the optimization of temperature and residence time for the debenzoylation in flow using the model system 1-benzyloxy-*N,N*-diethyl-5,6-dimethylpyrazin-2(1*H*)-one-3-carboxamide (**3h**) with ammonium formate in methanol (Scheme 2).

Reagents and conditions: **3h** (0.25 mmol, 0.1 M, 2.5 mL, 1.0 equiv.), HCO₂NH₄ (0.5 mmol, 0.2 M, 2.5 mL, 2.0 equiv.), SiliaCat® DPP-Pd (12 mg).

The optimization was performed in the setup described in Figure 1 and Scheme 2. The two solutions were pumped into the reactor containing SiliaCat® DPP-Pd catalyst. Product/byproduct and starting material (if not fully converted) passed through the backpressure regulator before being collected in vials, which were used for HPLC–UV–MS analysis. Temperature (20–110 °C) and residence time (*R_t* 14–36 s) were varied, and the results are summarized in Figure 2 (temperature effect) and Figure 3 (residence time effect).

As shown in Figure 2, the reaction only occurs with acceptable conversions above 60 °C, the temperature above which ammonium formate efficiently decomposes in the presence of Pd. The conversion is more or less constant and complete in a wide range of temperatures (80–110 °C) at a residence time of 14 s without losing selectivity for the formation of the desired product (**4h**, N–OH form, 97–98%) over the over reduced product (**5h**, N–H form, 1–2%).

At 80 °C, complete conversion is seen with the residence time of 14 s. Increasing the residence time favors the formation of over reduced species (Figure 3). The same trend is observed at higher temperatures, with relatively larger amounts of over reduced compounds formed at longer residence time (up to 5.5% at 110 °C using a residence time of 36 s).

Based on these results, it is considered that the optimal condition for debenzoylation of 1-benzyloxy-pyrazin-2(1*H*)-one 3-carboxamide **3h** in this flow setup with HCO₂NH₄/SiliaCat® DPP-Pd in methanol are a temperature above 80 °C and a residence time of 14 s. Using these conditions, the turnover number of the catalyst was determined to be at least 100 in a long-run debenzoylation of compound **3h** (for details, see Supporting Information).

For testing the further scope of the procedure, we preferred to perform the reactions at 100 °C since the higher temperature would be beneficial in keeping all of the reaction partners in solution. In this way, we managed to convert the compounds **3a–zb** into a library of aspergillidic acid-like hydroxamic acids in

Figure 2. Temperature effect on debenzylolation of **3h** in flow (at residence time of 14 s, about 6 dead volumes were allowed to pass after modifying the temperature before the conversions were determined, conversion at 350 nm, HPLC–UV–MS)

good to excellent yields (Table 2). In case of secondary amides **3i,o,r,t,x**, yield and selectivity were improved dramatically when decreasing the residence time to 10 s (Entry 9, 15, 19, 21, and 25, Table 2). Moreover, *N*-debenzylation of the carboxamide was not observed in our examples **3i–k** (Entry 9–11, Table 2). All the compounds **4a–zb** show satisfactory analytical data and test positive for the hydroxamate function in aqueous ferric chloride solution (dark red color) and aqueous copper (II) acetate solution (green color).

To test the scalability of the protocol, a follow-up experiment was performed with compound **3h** in a milliflow system (X-Cube) equipped with a catalyst cartridge containing SiliaCat® DPP-Pd (188 mg). Excellent conversion (96%) and selectivity (98%) were obtained at a flow rate of 3.0 mL/min (for details, see Supporting Information). In this way, 2.2 g of **3h** has been converted into the corresponding 1-hydroxypyrazin-2(1*H*)-one 3-carboxamide **4h** (1.4 g, 90% isolated yield) at 110 °C, 30 bar backpressure with a flow rate of 3.0 mL/min.

In summary, with the application of flow technology and catalytic transfer hydrogenation, we have succeeded in delivering a reproducible methodology for the selective debenzylolation of *O*-benzyl protected cyclic hydroxamates, with a potential of scaling up from milligram scale to gram scale on suitable flow operations. This solved reproducibility problems experienced earlier using batch reaction conditions and finally allowed the efficient, safe, and reproducible synthesis of a library of 28 *N*-hydroxypyrazin-2(1*H*)-one analogues.

3. Experimental Section

3.1. General Experimental Methods. All reagents were obtained from commercial sources and used as purchased

without further purification. All solvents were analytical or HPLC or LC–MS grade and were used as supplied. Palladium-based catalysts were purchased from Sigma-Aldrich. SiliaCat® DPP-Pd was bought from SiliCycle and sieved one more time to obtain the particle size 80–120 mesh before packing into the microreactor. Debenzylation reactions under batch conditions were magnetically stirred under a hydrogen atmosphere (balloon) or shaken in a Parr hydrogenation apparatus. Reactions under flow conditions were performed on a Labtrix® Start system and an X-Cube system. The course of all reactions was monitored by HPLC–UV–MS (Prevail C18 2.1×150 mm 3 μm column, quadrupole ion trap, 350 or 375 nm) using atmospheric pressure ionization electrospray (API–ES) in positive mode. Preparative HPLC (Luna C18 21.2×150 mm 5 μm column, photodiode array detector) was used to purify the *N*-hydroxypyrazin-2(1*H*)-one products. Solvents were evaporated in a rotavapor at 40 °C. A bench-top lyophilizer was used to dry water-containing samples. Yields refer to yields of isolated compounds after chromatography; selectivities were determined on the crude mixtures by HPLC–UV–MS at the indicated wavelength. Nuclear magnetic resonance (NMR) spectra were recorded on 400 MHz and 600 MHz FT-NMR spectrometers in the indicated deuterated solvents; chemical shifts are expressed in δ scale (ppm) using tetramethylsilane as an internal standard, and coupling constants *J* are reported in Hertz (Hz). Low-resolution MS spectra were recorded on the LC–APCI–MS in positive mode. High-resolution MS spectra were recorded on a microTOF-Q instrument using electrospray ionization (ESI) in positive mode.

3.2. Flow Systems. The Labtrix® Start system (Chemtrix) is equipped with a reactor holder, a temperature controller, a standard syringe pump, gastight syringes (1.0 and 2.5 mL), polytetrafluoroethylene (PTFE) tubing (1/32" OD×0.009" ID), an IDEX

Figure 3. Residence time effect on debenzylolation of **3h** in flow (at different temperatures, conversion at 350 nm, HPLC–UV–MS)

Table 2. Scope of debenzoylation of 1-benzoyloxypyrazin-2(1*H*)-ones in flow

Entry	Precursor	R ²	R ³	R ⁴	Yield of 4a-f (%) ^a	Selectivity (%) ^b		
						4a-f	5a-f	
1	3a	H	H	H	87	100	0	
2	3b	H	Me	H	91	100	0	
3	3c	H	Ph	H	89	94	6	
4	3d	H	Me	Me	90	99	1	
5	3e	Me	Me	H	93	100	0	
6	3f	<i>i</i> -Bu	Ph	H	95	100	0

Entry	Precursor	R ³	R ⁴	R ⁵	R ⁶	Yield of 4g-zb (%) ^a	Selectivity (%) ^b	
							4g-zb	5g-zb
7	3g	H	H	Et	Et	92	100	0
8	3h	Me	Me	Et	Et	90	98	2
9	3i	Me	Me	H	Bn	72	85	15 ^{c,d}
10	3j	Me	Me	Me	Bn	91	96	4
11	3k	Me	Me	Et	Bn	94	97	3
12	3l	H	H	Me	3-FC ₆ H ₄ CH ₂	93	100	0
13	3m	Me	H	Me	3-FC ₆ H ₄ CH ₂	96	100	0
14	3n	Ph	H	Me	3-FC ₆ H ₄ CH ₂	73	87	13 ^e
15	3o	Me	Me	H	3-FC ₆ H ₄ CH ₂	53	62	38 ^{c,d}
16	3p	Me	Me	H	3-FC ₆ H ₄ CH ₂	91	93	7 ^{c,d,f}
17	3p	Me	Me	Me	3-FC ₆ H ₄ CH ₂	81	89	11
18	3q	H	H	Me	4-FC ₆ H ₄ CH ₂	94	100	0
19	3r	Me	H	H	4-FC ₆ H ₄ CH ₂	93	96	4 ^{c,d,f}
20	3s	Me	H	Me	4-FC ₆ H ₄ CH ₂	89	97	3
21	3t	Me	Me	H	4-FC ₆ H ₄ CH ₂	92	96	4 ^{c,d,f}
22	3u	Me	Me	Me	4-FC ₆ H ₄ CH ₂	90	95	5
23	3v	H	H	Me	4-ClC ₆ H ₄ CH ₂	98	100	0
24	3w	Me	H	Me	4-ClC ₆ H ₄ CH ₂	89	97	3
25	3x	Me	Me	H	4-ClC ₆ H ₄ CH ₂	91	94	6 ^{c,d,f}
26	3y	Me	Me	Me	4-ClC ₆ H ₄ CH ₂	91	95	5
27	3z	H	H	Me	2,4-Cl ₂ C ₆ H ₃ CH ₂	95	100	0
28	3za	Me	H	Me	2,4-Cl ₂ C ₆ H ₃ CH ₂	92	98	2
29	3zb	Me	Me	Me	2,4-Cl ₂ C ₆ H ₃ CH ₂	82	87	13 ^e

Reagents and conditions: **3a-zb** (0.1 mmol, 0.1 M, 1.0 equiv.), HCO₂NH₄ (0.2 mmol, 0.2 M, 2.0 equiv.), SiliaCat® DPP-Pd (12 mg), 100 °C, R₁ 14 s.

^a Isolated yield.

^b Quantification at 350 nm (HPLC–UV–MS).

^c Quantification at 375 nm (HPLC–UV–MS).

^d Precipitate could be avoided by diluting starting materials 3 times of usual or using a mixture of MeOH–toluene.

^e Substrate contained impurities (~ 8 %, HPLC–UV–MS, 350 nm).

^f Reactions were performed at 80 °C and R₁ 10 s.

All reactions were determined to have quantitative conversion via HPLC–UV–MS.

5 bar backpressure regulator, and a catalyst reactor model 3026 (Chemtrix). The schematic diagram of the experiment setup is shown in Figure 1. The X-Cube system (ThalesNano) is equipped with two HPLC pumps (flow rate 0.1–3.0 mL/min), inlet and outlet pressure systems (max 150 bar), a heater unit, a SiliaCat® DPP-Pd CatCart column, stainless steel tubing (0.5 mm ID), and PTFE tubing (1/8" OD×1/16" ID).

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Supporting Information

Electronic Supplementary Material (ESM) containing data (general procedures for synthesis and characterization of all products, the copies of ¹H, ¹³C NMR, and HRMS of new compounds) associated with this article is available in the online version at doi: 10.1556/JFC-D-14-00036.

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