Selective Debenzylation of *N*-Benzyloxypyrazinones in Flow

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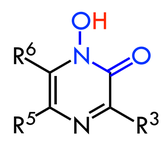
1. Introduction

✧ Hydroxamic acids
Known for:
- bioactive compounds in nature (e.g. aspergillic acid)
- strong binding ability with most of metal ions
- inhibition of specific enzymes involved in HIV and cancer progression (HDACs, MMPs, RNR)

✧ Removal of benzyl group from O-benzyl-protected hydroxamate precursors
- selectivity issue (overreduction to amides)
- require an appropriate catalyst system (e.g., Pd-C, $Pd(OH)_2$-C, Pd-$BaSO_4$, $AlCl_3$-C_6H_5Cl, BBr_3-CH_2Cl_2, …)

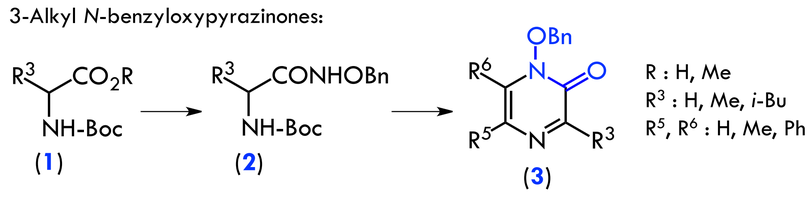
✧ Our goals
- design of novel aspergillic acid-like hydroxamic acids
- development of synthetic strategies for highly functionalised N-hydroxypyrazinones



R^3 : H, alkyl, carboxamide
R^5, R^6 : H, alkyl, aryl

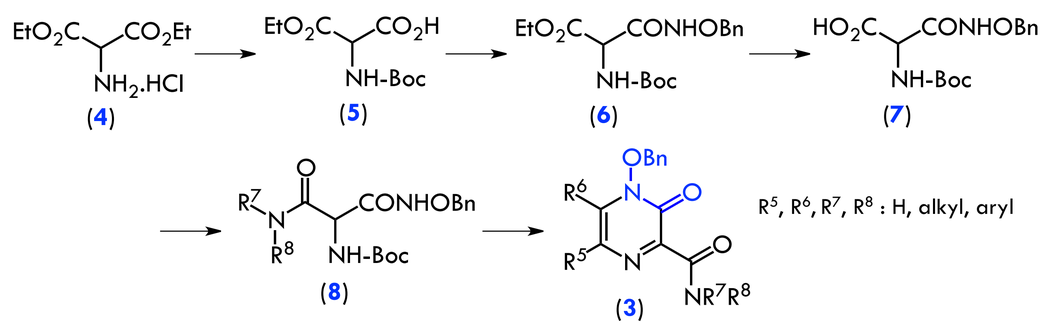
2. Synthesis of *N*-Benzyloxypyrazinones Precursors

✧ 3-Alkyl *N*-benzyloxypyrazinones:



R : H, Me
R^3 : H, Me, *i*-Bu
R^5, R^6 : H, Me, Ph

✧ 3-Carboxamide *N*-benzyloxypyrazinones:



R^5, R^6, R^7, R^8 : H, alkyl, aryl

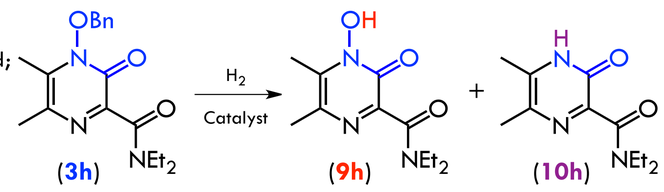
(For details, see http://dx.doi.org/10.1016/j.tetlet.2014.06.100)

3. Methodology for Debenzylation

✧ **Debenzylation in Batch:**

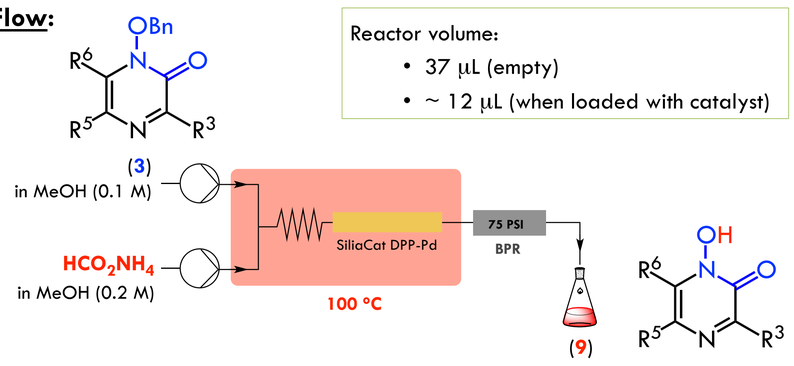
(Non-)Palladium catalysts were used; (**10h**) was the major product.

Using **5% Pd-$BaSO_4$ unreduced** gave 91% yield of (**9h**).



In batch the **yields** and **selectivity** are **not reproducible** when other substrates were deprotected.

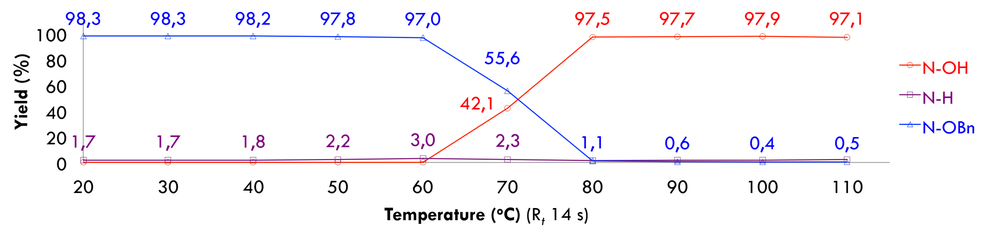
✧ **Debenzylation in Flow:**

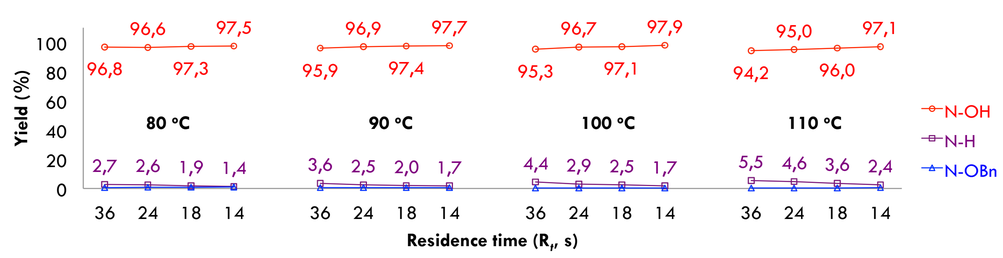


Reactor volume:
- 37 µL (empty)
- ~ 12 µL (when loaded with catalyst)

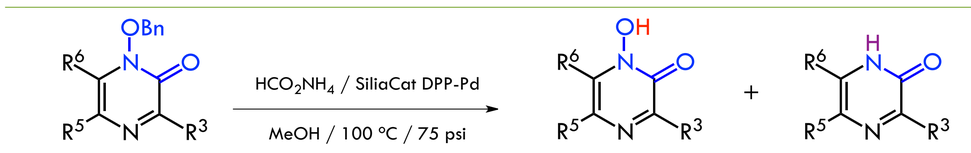
Conditions: (**3**) (0.1 mmol, 1 equiv., 0.1 M), **SiliaCat®DPP-Pd** (0.8 mol%), HCO_2NH_4 (0.2 mmol, 2 equiv., 0.2 M).

★ Studying the influence of temperature and residence time on debenzylation of compound **3h**:

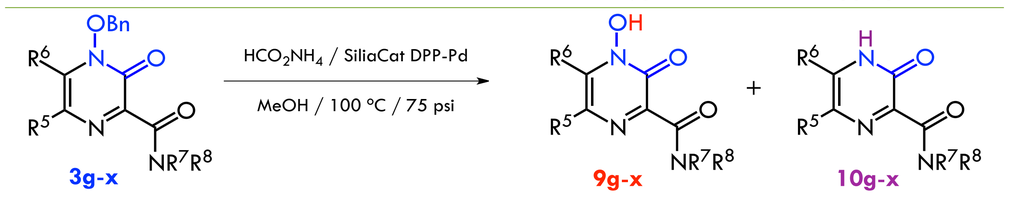




★ The ideal flow conditions for debenzylation of O-benzyl precursors: HCO_2NH_4 as hydrogen donor, SiliaCat® DPP-Pd as catalyst, reaction temperature above 100 °C and residence time of 14 s. These conditions were applied to synthesise other *N*-hydroxypyrazinones (**9a-x**).



Precursor	R^3	R^5	R^6	Yield of **9a-f** (%)	Selectivity (%) **9a-f : 10a-f**
3a	H	H	H	87	100 : 0
3b	H	Me	H	91	100 : 0
3c	H	Ph	H	89	94 : 6
3d	H	Me	Me	90	99 : 1
3e	Me	Me	H	93	100 : 0
3f	*i*-Bu	Ph	H	95	100 : 0



Precursor	R^5	R^6	R^7	R^8	Yield of **9g-x** (%)	Selectivity (%) **9g-x : 10g-x**
3g	H	H	Et	Et	92	100 : 0
3h	Me	Me	Et	Et	90	98 : 2
3i	Me	Me	H	Bn	72	85 : 15
3j	Me	Me	Me	Bn	91	96 : 4
3k	Me	Me	Et	Bn	94	97 : 3
3l	H	H	Me	4-$ClC_6H_4CH_2$	98	100 : 0
3m	Me	H	Me	4-$ClC_6H_4CH_2$	89	97 : 3
3n	Me	Me	Me	4-$ClC_6H_4CH_2$	91	95 : 5
3o	H	H	Me	2,4-$Cl_2C_6H_3CH_2$	95	100 : 0
3p	Me	H	Me	2,4-$Cl_2C_6H_3CH_2$	92	98 : 2
3q	Me	Me	Me	2,4-$Cl_2C_6H_3CH_2$	82	87 : 13
3r	H	H	Me	3-$FC_6H_4CH_2$	93	100 : 0
3s	Me	H	Me	3-$FC_6H_4CH_2$	96	100 : 0
3t	Ph	H	Me	3-$FC_6H_4CH_2$	73	87 : 13
3u	Me	Me	Me	3-$FC_6H_4CH_2$	81	89 : 11
3v	H	H	Me	4-$FC_6H_4CH_2$	94	100 : 0
3w	Me	H	Me	4-$FC_6H_4CH_2$	89	97 : 3
3x	Me	Me	Me	4-$FC_6H_4CH_2$	90	95 : 5

4. Conclusion

✧ Methodology for **debenzylation** of O-benzyl-protected hydroxamates has been studied in batch as well as in flow using catalytic transfer hydrogenation.

✧ A library of 24 *N*-hydroxypyrazinones (**9a-x**) have been synthesised in good to excellent yields with **high selectivity**.