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One-pot synthesis of amines from biomass resources catalyzed by HReO₄ João A. T. Caetano and Ana C. Fernandes^{*}

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Abstract – This work describes the one-pot synthesis of furfurylamines from carbohydrates catalyzed by HReO₄. These one-pot three-reaction and four-reaction processes allow the conversion of xylose and xylan, respectively, into a large variety of secondary and tertiary amines with good overall yields and chemoselectivity.

Keywords: Biomass, carbohydrates, reductive amination, furfurylamines, perrhenic acid.

Introduction

Sustainable conversion of biomass into drugs, chemicals, biofuels, and various materials is one of the most challenging tasks for the modern chemistry and industry. In particular, the conversion of carbohydrates into valuable nitrogen compounds represents an interesting possibility for the sustainable synthesis of biologically active amines.¹⁻⁷

Amines derived from furfural (furfurylamines) have diverse applications, including in the preparation of polymers, biologically active compounds and also as intermediates in the synthesis of pharmaceuticals such as antiseptic agents, antihypertensives and diuretics (e.g. Furosemide, Figure 1).



Figure 1 – Furosemide

Reductive amination, involving the reaction of carbonyl compounds with amines, remains one of the most versatile and useful synthetic routes for the synthesis of amines. The synthesis of furfurylamines has been investigated only from furfural and 5-hydroxymethylfurfural by reductive amination using Au,⁸ Fe/Ni,⁹ Ru,¹⁰ Pt,¹¹ Ir,¹¹ Zn,¹²

or enzymes¹³ as catalysts. To best of our knowlegde, the one-pot synthesis of amines from carbohydrates has never been reported.

Several years ago, our group has developed an efficient methodology for the synthesis of secondary and tertiary amines by direct reductive amination of aldehydes catalyzed by oxo-rhenium complexes using silanes as reducing agents.¹⁴ However, the catalytic activity of HReO₄ was not evaluated in this study.

In continuation of our work on the reduction and deoxygenation of several organic compounds such as sulfoxides,¹⁵ *N*-oxides,^{15a} aromatic nitro compounds,¹⁶ esters,¹⁷ amides,¹⁸ imines,¹⁹ alkenes,²⁰ nitriles,²¹ epoxides,²² carbonyl compounds,²³ and carbohydrates²⁴ catalyzed by oxo-rhenium and oxo-molybdenum complexes, here we investigated the one-pot conversion of xylose and xylan into several furfurylamines catalyzed by HReO₄ (Figure 2).



Figure 2 - One-pot conversion of xylose and xylan into furfurylamines.

Results and discussion

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Initially, we investigated the conversion of xylose into furfural, which is an important chemical that can be obtained from biomass, and it is currently used in the production of various resins, pharmaceuticals, herbicides, stabilizers and fuel, such as liquid hydrocarbons or 2-methyltetrahydrofuran.²⁵ In order to find the best reaction conditions, the conversion of xylose into furfural catalyzed by HReO₄ in dioxane was studied using different amounts of catalyst and temperatures. The best result (80%) was obtained in the presence of 5 mol% of HReO₄ at 140 °C after 2h (Table 1, entry 1). At 120 °C, the furfural yield decreased to 60% (Table 1, entry 2). The reaction performed with 2.5 mol% of HReO₄ gave the furfural with 70% yield (Table 1, entry 3). Increasing the amount of HReO₄ to 10 mol% at 140 °C, led to a similar yield of furfural (80%) to that obtained in the presence of 5 mol% of HReO₄ (Table 1, entry 4). Finally, no reaction was observed in the absence of catalyst (Table1, entry 5).

ł	HO OH HREC	D ₄ (5 mol%), Dioxane	- С Н	
Entry	HReO ₄ (mol%)	Temp. (°C)	Time (h)	Yield (%) ^b
1	5	140	2	80
2	5	120	2	60
3	2.5	140	3	70
4	10	140	2	80
5	_	140	24	No reaction

Table 1 – Conversion of xylose into furfural catalyzed by HReO₄^a

^a The reactions were carried out with 1 mmol of xylose.

^b Yields determined by ¹H NMR spectroscopy using mesitylene as standard.

The direct synthesis of furfurylamines from xylose catalyzed by HReO₄ was investigated using different silanes. The best result (76%) was obtained employing tertiary silane Me₂PhSiH as reducing agent (Table 2, entry 1). The reaction with primary silane PhSiH₃, which is generally the most reactive silane, gave furfurylamine in a slightly lower yield (70%), probably due to some polymerization of phenylsilane at high temperature (Table 2, entry 2). The conversion of xylose was also tested using polymethylhydrosiloxane (PMHS), a cheaper, easy-to-handle and environmentally friendly silicone industry byproduct, however this reducing agent proved to be less efficient, producing the amine in only 35% yield after 3 h (Table 2, entry 3). In contrast to Me₂PhSiH, the tertiary silanes Et₃SiH and Pr₃SiH were less effective. No furfurylamine was formed using these silanes after 1h (Table 2, entries 4 and 6), but after 18 h, the product was obtained in 54% and 19% yields, respectively (Table 2, entries 5 and 7). Finally, the formation of furfurylamine was not observed using triphenylsilane (Table 2, entry 8) or in the absence of silane (Table 2, entry 9).

Table 2 – One-pot synthesis of furfurylamine using different silanes^a

$H_{0} \xrightarrow{O}_{OH} OH \frac{1) \text{ HReO}_{4} (5 \text{ mol}\%), \text{ dioxane, 140 °C, 2 h}}{2) 4-Fluoroaniline, Silane, 1h} O$					
Entry	Silane	Time (h) ^b	Yield (%) ^c		
1	Me ₂ PhSiH	1	76		
2	PhSiH ₃	1	70		

3	PMHS	3	35
4	Pr ₃ SiH	1	0
5	Pr ₃ SiH	2.5	62
6	Et ₃ SiH	1	0
7	Et ₃ SiH	18	54
8	Ph ₃ SiH	18	No reaction
9	Without silane	18	No reaction

^a The reactions were carried out with 1 mmol of xylose and 1.2 mmol of silane.

^b Reaction time after addition of the silane.

^c Isolated yields.

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To evaluate the general applicability of HReO₄ as catalyst for the one-pot synthesis of furfurylamines from xylose, this reaction was explored with a variety of anilines (Table 3). Initially, we tested the reaction of xylose using 4-fluoroaniline catalyzed by 2.5 mol% of HReO₄, obtaining the amine in 65% yield (Table 3, entry 1). This reaction was also explored with a higher amount of catalyst (5 mol%), leading to the formation of product with a better yield of 76% (Table 3, entry 2). Then, we decided to study the conversion of xylose into a wide range of furfurylamines using 5 mol% of HReO₄. Generally, moderate to good overall yields of the secondary amines were obtained. The best yields were observed in the reactions with anilines containing electron-withdrawing groups, which promote the attack of the silane to the imine. In contrast, no reaction was observed using benzylamine and cyclohexylamine. This method was also tested with *N*-methylaniline in order to evaluate the efficiency of this catalyst in the synthesis of a tertiary amine, giving the amine with an overall yield of 71% (Table 3, entry 14). This methodology is also chemoselective tolerating several functional groups including -CN, -CO₂Me, -SO₂Me, -CF₃, -F, -Br, -CI, -OMe.

Table 3 - One-pot synthesis of furfurylamines from xylose catalyzed by HReO₄^a



		F	
1	F		65 ^c
2	H ₂ N		76
2	0	OMe	80
3	OMe	HN	80
	H ₂ N		
4	ĊI		75
4	CI	HN HN	/5
	H ₂ N ² V		
~	o Br	Br	71
2	H ₂ N		/1
		CN CN	
6	CN		71
	H ₂ N		
_	05	CF ₃	
7	CF3	HN .0.	65
	H ₂ N		
0			(0)
8	H ₂ N		60
		 0 <u></u> 0	
9		HN	59
	H ₂ N		
10		HN	73
	H ₂ N		
11	NH ₂	HN HN	67
	~ ~		
12	\sim	HN	55 ^d
	H ₂ N		
		OMe	e ed
13	OMe	HN HN	56°
	H ₂ N		
14		N	75
			, 0

^a The reactions were carried out with 1.0 mmol of xylose, 1.0 mmol of aniline and 1.2 mmol of Me₂PhSiH.

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^dYields determined 2h after the addition of silane.

To study the scope of this reaction, we also investigated the synthesis of furfurylamines from other carbohydrates such as arabinose, ribose and the polysaccharide xylan. These reactions were carried out with 4-fluoroaniline using dimethylphenylsilane as reducing agent in the presence of higher amount of HReO₄ (10) mol%). The reaction of arabinose, the second most abundant pentose in biomass after xylose, gave the furfurylamine in only 29% yield (Figure 3). Low yields for the conversion of arabinose were also reported before by other authors. For example, Gallo²⁶ found that the furfural yield obtained from arabinose was approximately half of that from xylose using H₂SO₄ solution. Garrett²⁷ studied the kinetics of the conversion of arabinose and xylose into furfural and observed that the reaction rate of xylose was much higher than that of arabinose, proposing that the steric positioning of the hydroxyls in the pentose is the controlling factor leading to different reactivities. Dussan²⁸ further suggested that the distribution of isomers of pentose is another factor affecting the reactivity. In xylose, the β -pyranose form is the predominant form, whereas the α -pyranose is the predominant for arabinose. As the α -pyranose tautomer is more stable than β -pyranose, it is more difficult to dehydrate it to furfural. The reaction of ribose catalyzed by HReO₄ also gave furfural in only 36% yield (Figure 3). In



Figure 3 - Synthesis of furfurylamines from arabinose and ribose.

contrast, the reaction of xylan produced the furfurylamine with a better yield (57%) (Table 4, entry 3). Then, we decided to explore the reaction of xylan with different

^b Isolated yields.

^c Using only 2.5 mol% of HReO₄.

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anilines obtaining the corresponding furfurylamines in 62-58% yields (Table 4). These results demonstrate that HReO₄ also catalyzes the hydrolyse of the glycosidic bonds of xylan.







^b Isolated yields.

The catalytic activity of HReO₄ on the conversion of xylose was also tested in gram scale. The reaction carried out from 10 mmol (1,5 g) of xylose with 4-flouroaniline using dimethylphenylsilane as reducing agent in the presence of 5 mol% of HReO₄ gave the corresponding furfurylamine with 43% yield. Using a higher amount of HReO₄ (10 mol%), the furfurylamine was obtained with 58% yield.

Conclusion

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This work describes the first methodology for the one-pot conversion of monoand polysaccharides into amines catalyzed by an oxo-rhenium complex. This methodology is chemoselective and produces a large variety of secondary and tertiary amines with good overall yields. This one-pot multi-reaction process has also the advantage of minimize chemical wastes, reduce cost, time and the separation of intermediate compounds.

HReO₄ also efficiently catalyzed the conversion of xylose into furfural, which has been identified as one of the most promising chemical platforms for the synthesis of value-added chemicals and fuels. These results extend the scope of the use of oxorhenium complexes as efficient catalysts for the synthesis of valuable amines from renewable resources and open a new area of research for these complexes.

Experimental Section

General information

Carbohydrates, anilines, silanes and the catalyst HReO₄ (75-80% aqueous solution) were obtained from commercial suppliers and were used without further purification. Flash chromatography was performed on MN Kieselgel 60M 230-400 mesh. ¹H NMR, ¹³C NMR and ³¹P NMR spectra were measured on a Bruker Avance II⁺ 400 MHz and

300 MHz spectrometers. Chemical shifts are reported in parts per million (ppm) downfield from an internal standard.

General procedure for the conversion of xylose into furfural catalyzed by HReO₄

To a Schlenk flask equipped with a J. Young tap containing a solution of xylose (1.0 mmol) in 1,4-dioxane (10 mL) was added HReO₄ (5 mol%). The reaction mixture was stirred in a closed Schlenk at 140 °C during 2 h. The yield of furfural was determined by spectroscopy ¹H NMR using mesitylene as internal standard.

General procedure for the one-pot synthesis of furfurylamines

To a Schlenk flask equipped with a J. Young tap containing a solution of carbohydrate (1.0 mmol of pentose) in 1,4-dioxane (10 mL) was added HReO₄ (5 mol%). The reaction mixture was stirred in a closed Schlenk at 140 °C during 2 h. Then, the reaction mixture was cooled at room temperature and aniline (1.0 mmol) and dimethylphenylsilane (1.2 mmol) was added. After 1h at 140°C, the reaction mixture was evaporated and the residue was purified by flash chromatography with appropriate mixtures of *n*-hexane:ethyl acetate, affording the furfurylamines.

Conflicts of interest

There are no conflicts to declare.

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Graphical abstract



HReO₄ as an efficient catalyst for *one-pot* conversion of xylose and xylan into a large variety of amines with good overall yields.