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Clean and selective oxidation of aromatic alcohols using silica-supported Jones' reagent in a pressure-driven flow reactor

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Abstract—By exploiting the high surface to volume ratio obtained within continuous flow reactors, we are able to oxidise selectively an array of primary alcohols to either the aldehyde or carboxylic acid, depending on the flow rates employed, demonstrating a degree of reaction control unattainable in traditional stirred reactors.

The selective oxidation of primary and secondary alcohols to aldehydes and ketones is a fundamental synthetic transformation[1] that can be achieved using a plethora of reagents; of these, chromium(VI) reagents are among the most efficient. The synthetic utility of the technique is however often marred by concomitant over-oxidation, leading to the formation of complex reaction mixtures. In addition, chromium(VI) based reagents are largely viewed as being undesirable, due to the generation of toxic residues and acidic waste-water. To address the problem of chromium contamination, numerous supported analogues have been developed enabling the spent oxidising agent to be filtered from the reaction products;[2] in addition, the use of a co-oxidant enables the oxidising agent to be recycled.[3] The complete removal of such materials from reaction products can, however, prove problematic due to mechanical degradation of the support as a result of prolonged stirring/agitation. In addition, the use of solid-supported oxidising agents can require long reaction times[4] and elevated reaction temperatures,[5] whilst being low-yielding.[6]

With this in mind, continuous flow reactors have found use as powerful synthetic tools enabling operational flexibility, reduced reaction times and system automation, resulting in a technique that is suitable for both high-throughput synthesis and lead generation. The main drawback of the technique, however, is how to purify the reaction products prepared in continuous flow systems. By coupling the advantages associated with solid-supported reagents with those of flow reaction methodology, the problems associated with reagent

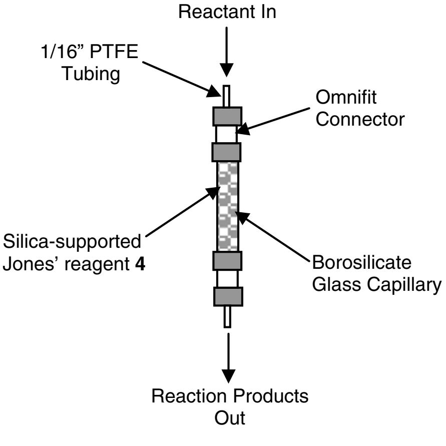
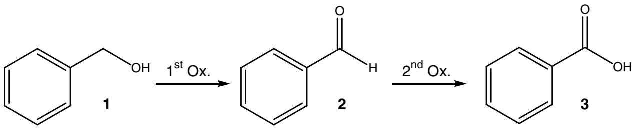


Figure 1. Schematic illustrating the flow reactor used for the selective oxidation of primary alcohols.



Scheme 1. Schematic illustrating the oxidation of benzyl alcohol **1** to afford benzaldehyde **2** and benzoic acid **3**.

Keywords: Selectivity; Continuous flow; Oxidation; Jones' reagent.

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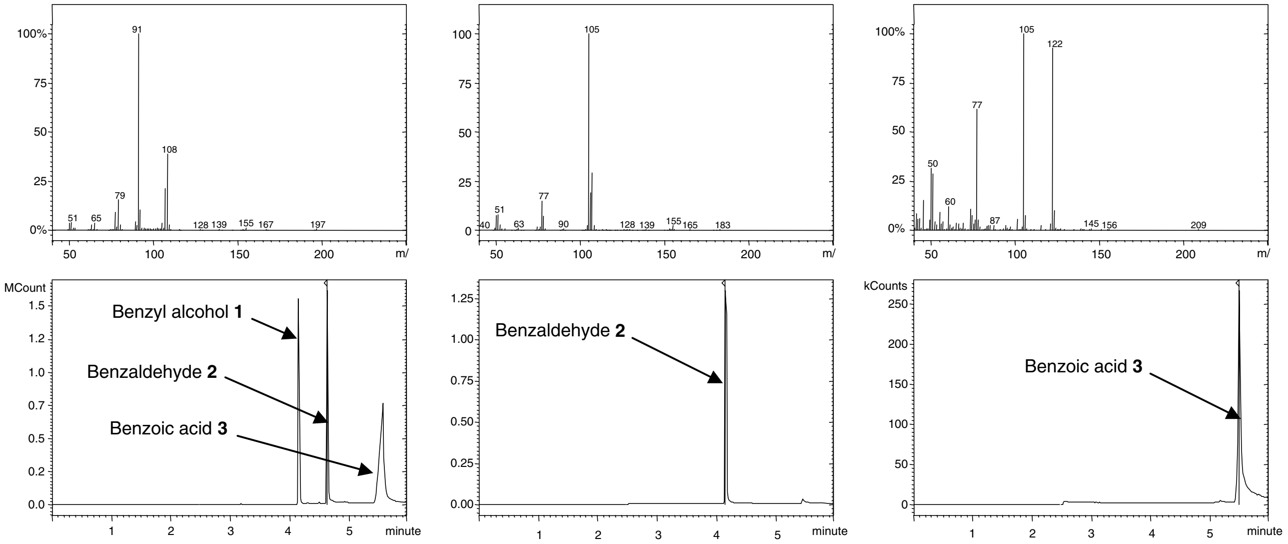

a. Batch Reaction (20 min) b. Flow Reactor (650 µl min^{-1}) c. Flow Reactor (≤50 µl min^{-1})

Figure 2. Gas chromatograms and mass spectra illustrating the products synthesised in (a) a stirred batch reactor, (b) a flow reactor operated at 650 µl min^{-1} and (c) a flow reactor operated at 50 µl min^{-1}.

Table 1. Summary of the results obtained for the oxidation of an array of primary alcohols, using silica-supported Jones' reagent **4**, in a flow reactor

Entry	Primary alcohol	Flow rate (µl min^{-1})	Product distribution	
			Aldehyde[a] (%)	Carboxylic acid[a] (%)
1	Benzyl alcohol **1**	650	100 (99.1)[b]	0
		50	0	100 (99.6)
2	3,5-Dimethoxybenzyl alcohol	650	100 (99.5)	0
		50	0	100 (99.3)
3	4-Bromobenzyl alcohol	650	100 (99.0)	0
		50	0	100 (98.3)
4	4-Chlorobenzyl alcohol	650	100 (99.3)	0
		50	0	100 (99.4)
5	4-Cyanobenzyl alcohol	650	100 (98.5)	0
		50	0	100 (99.0)
6	Methyl-4-formylbenzyl alcohol	650	100 (99.2)	0
		50	0	100 (99.6)
7	4-Methylbenzyl alcohol	650	100 (99.2)	0
		50	0	100 (95.6)
8	4-Benzyloxybenzyl alcohol	650	100 (99.5)	0
		50	0	100 (99.8)
9	4-Aminobenzyl alcohol	650	100 (100)	0
		50	0	100 (99.8)
10	4-Dimethylaminobenzyl alcohol	650	100 (99.3)	0
		50	0	100 (99.6)
11	Biphenyl-4-yl methanol	650	100 (99.7)	0
		50	0	100 (99.5)
12	(5-Nitrothiophen-2-yl)-methanol	650	100 (99.8)	0
		50	0	100 (99.7)
13	2-Benzyloxybenzyl alcohol	650	100 (99.7)	0
		50	0	100 (99.8)
14	2-Naphthalen-2-yl-methanol	650	100 (99.9)	0
		50	0	100 (99.9)
15	4-Acetylbenzyl alcohol	650	100 (99.8)	0
		50	0	100 (99.8)

[a] $n = \geqslant 15$.

[b] The number in parentheses represents the % isolated yield.

recovery/recycle are readily overcome enabling the continuous synthesis of compounds in both high purity and excellent yield.

Building on our recent syntheses of analytically pure α,β-unsaturated compounds[7] and dimethyl acetals in continuous flow reactors,[8] we report herein the preliminary results obtained for the selective oxidation of primary (and secondary) alcohols in a pressure-driven flow reactor (Fig. 1).

As Scheme 1 illustrates, when a primary alcohol **1** is oxidised, precautions must be taken to ensure that the desired aldehyde **2** is not further oxidised to the corresponding carboxylic acid **3**. In practice, this can be achieved by distillation of the aldehyde as it forms, this technique is however restricted to molecules of low molecular weight.

We therefore proposed that by conducting the reaction in a continuous flow reactor, where the residence time of a reagent can be carefully controlled, selective oxidation of the primary alcohol could be achieved. In addition to the obvious advantage of enhanced product selectivity, in the case of acidic oxidants, such as Jones' reagent (H_2CrO_4), the use of silica-supported analogues proves advantageous as heavy metal contamination of the product is avoided, as even in its reduced form, the chromium residues are retained by the support.[9] Unlike previous examples where EOF-based flow reactors have been employed,[10] due to solvent incompatibilities with the supported oxidising agent **4**,[†] a simple pressure-driven system was constructed.

In order to perform a flow reaction, 0.150 g (0.150 mmol) of silica-supported Jones' reagent **4** was packed into a borosilicate glass flow reactor (0.3 cm (i.d.) × 3.0 cm (length)) and a solution of benzyl alcohol **1** (0.01 M in DCM) pumped through the reactor, using a syringe pump (Harvard Apparatus), at the desired flow rate. The reaction products were collected from the reactor outlet at 1 min time intervals and analysed by GC–MS (number of samples (n) = $\geqslant 15$). After chromatographic analysis, the reaction products were combined, concentrated in vacuo, the 'crude' product dissolved in $CDCl_3$ and analysed by NMR spectroscopy; all known compounds prepared had spectroscopic data consistent with the literature. In order to confirm product purity and reagent **4** stability, the reaction products were also analysed by ICP-MS; whereby $\leqslant 6.9 \times 10^{-5}\%$ w/w Cr was detected in all samples.

As Figure 2b illustrates, when operating the flow reactor at 650 μl min^{-1}, providing a reagent residence time of 9.7 s,[11] over-oxidation to benzoic acid **3** was successfully prevented and quantitative conversion of benzyl alcohol **1** to benzaldehyde **2** was obtained.

Interestingly, when the reactor was operated at 300 μl min^{-1} (residence time = 21 s), the reaction products contained a mixture of unreacted starting material **1**, benzaldehyde **2** and benzoic acid **3**, replicating the lack of reaction control exhibited in the stirred, batch reactor (Fig. 2a). However, by further reducing the flow rate to $\leqslant 50$ μl min^{-1} (residence time = $\geqslant 126$ s), quantitative conversion to the carboxylic acid **3** was observed (Fig. 2c). Having demonstrated the ability to synthesise selectively either benzaldehyde **2** or benzoic acid **3** in excellent yield and purity (Table 1), the reaction was repeated using an array of substituted primary alcohols. As illustrated in Table 1, excellent selectivity was obtained for all primary alcohols investigated; importantly, no functional group incompatibilities were observed.

Table 2. Summary of the results obtained for the oxidation of secondary alcohols, using silica-supported Jones' reagent **4**, in a flow reactor

Entry	Secondary alcohol	Conversion[a] (%)	Yield[b] (%)
1	1-Phenylpropan-1-ol	100	100
2	1-Phenylethanol	100	100
3	1-(4-Aminophenyl)ethanol	100	98.8
4	Diphenylmethanol	100	99.6
5	1-(4-Iodophenyl)ethanol	100	99.6
6	1-(4-Nitrophenyl)ethanol	100	100
7	1-(4-Hydroxyphenyl)ethanol	100	99.3
8	1-Phenylbutan-1-ol	100	100
9	1-(4-Methylphenyl)ethanol	100	99.5
10	1-(4-Bromophenyl)ethanol	100	99.2
11	1,3-Diphenylpropan-1-ol	100	100
12	1-(4-Chlorophenyl)ethanol	100	99.0
13	Cyclopentanol	100	99.2
14	Cyclohexanol	100	100
15	2-Methylcyclohexanol	100	99.7

[a] $n = \geqslant 15$.

[b] Flow reactor operated at 650 μl min^{-1}.

In order to demonstrate the versatility of the aforementioned methodology, a series of secondary alcohols was subsequently oxidised within the flow reactor. As Table 2 illustrates, in all cases, quantitative conversion of the alcohol to the respective ketone was observed, affording all products in excellent yield and purity; again no substrate dependancy was observed.

Finally, the oxidation of aliphatic primary alcohols (C_2–C_8) was investigated; however, in all cases leaching of oxidising agent from the silica support was observed (indicated by colouration of the reaction products), an observation that was attributed to an increase in the polarity of the reactant stream, compared to that observed for the primary aromatic alcohols. Consequently, this particular supported oxidising agent is limited to the oxidation of aromatic alcohols in a flowing system; this could however be overcome by the use of covalently bound oxidising agents.

Owing to the unique reaction conditions obtained as a result of incorporating supported reagents into continuous flow reactors, we have demonstrated the ability to oxidise selectively an array of primary alcohols to their respective aldehydes (residence time = 9.7 s) or carboxylic acids (residence time = 126 s), depending on the flow rate employed (Table 1).

[†] When the flow reactions were performed using water, acetonitrile, tetrahydrofuran or diethyl ether as the reaction solvent, chromium release was observed (determined by a distinct orange colouration of the product stream). In comparison, when performing the reaction in dichloromethane, no colouration of the reaction products was observed (confirmed by ICP-MS analysis of the product stream, $\leqslant 6.9 \times 10^{-7}\%$ w/w Cr).

Using this approach, we have successfully synthesised 15 aromatic aldehydes and their respective carboxylic acids, along with the oxidation of 15 secondary alcohols; in all cases, excellent yields and product purities were obtained, irrespective of functionality (Table 2).

In conclusion, the strategy employed herein provides a route to product selectivity and system reproducibility that is unobtainable in traditional stirred or shaken reactors. With these factors in mind, further investigations are currently underway within our laboratories to explore the use of co-oxidants, enabling the solid-supported oxidising agent to be recycled.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.05.157.

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11. The total volume of the flow reactor, once packed, was determined experimentally to be 105 μl. Therefore when operating the reactor at flow rates of 650, 300 and 50 μl min^{-1}, residence times of 9.7, 21 and 126 s were obtained, respectively.