

KMnO₄-Mediated Oxidation as a
Continuous Flow Process

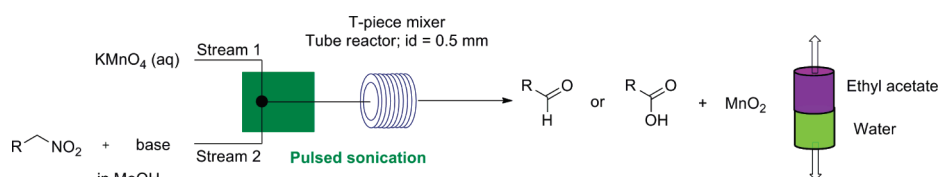
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ABSTRACT



An efficient and easily scalable transformation of alcohols and aldehydes to carboxylic acids and nitroalkane derivatives to the corresponding carbonyls and carboxylic acids using permanganate as the oxidant within a continuous flow reactor is reported. Notably, the generation and downstream processing of MnO₂ slurries was not found to cause any blocking of the reactor when ultrasound pulses were applied to the flow system.

Over the past few years, flow chemistry has been extensively used by the chemical community as a valuable replacement or supplement to traditional batch-processing methods. The associated benefits such as improved mass and heat transfer, safer and more reproducible performance,¹ and the ability to conduct multistep sequences² have been demonstrated by numerous laboratories.³ However, an often mis-stated limitation of continuous flow chemistry is the inability of microreactors to cope with reactions that lead to precipitates due to the potential for reactor clogging. Although this is a concern, specifically engineered reactors have been constructed to deal with the problems associated with slurry transport.⁴ Unfor-

tunately, these solutions are less easily accommodated when using standard commercial flow equipment. We encountered such a problem of solid generation when attempting to conduct permanganate mediated Nef oxidation as a continuous flow process in a Uniqsis FlowSyn reactor.⁵ We found that the oxidation of alcohols and aldehydes to carboxylic acids and the Nef oxidation⁶ of nitroalkanes to their carbonyl derivatives proceeded smoothly by treatment with alkaline

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potassium permanganate under flow conditions. However, stoichiometric quantities of manganese dioxide were formed that deposited in the reactor causing fouling of the system. This prevented a truly continuous process from being realized as the system needed to be periodically stopped in order to clean the T-piece connector. A simple modification to the reactor setup involving submerging the T-piece mixer and a short length of the subsequent reactor tubing within an ultrasound bath⁷ proved ideal for dispersing the aggregate manganese dioxide that immediately formed (Figure 1). Once

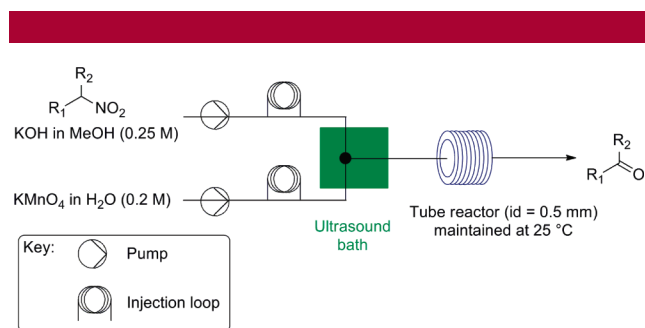


Figure 1. General reactor setup.

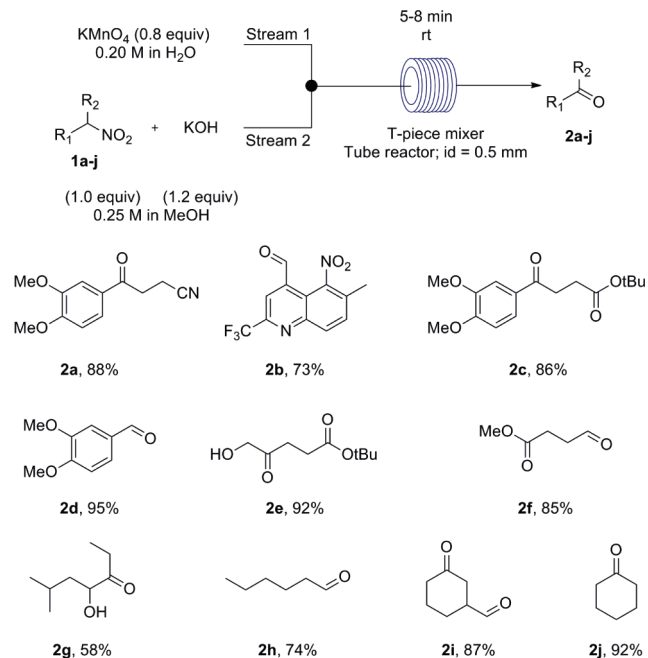
passed the mixing point, the reaction mixture was easily pumped through the remaining coil reactor exiting as a fine suspension that showed no signs of coating the internal tubing, therefore allowing a continuous flow process.

While the Nef oxidation of aliphatic nitro compounds can be achieved via a large number of different reaction conditions⁸ our choice of oxidant was made due to the fact that potassium permanganate is a cheap reagent and the manganese dioxide byproduct can be easily isolated and used in other oxidation processes.⁹ This significantly reduces the environmental and financial impact of employing the permanganate as an oxidant.¹⁰ Furthermore, high chemoselectivity can be achieved; the use of a single equivalent of the oxidant smoothly converts nitroalkanes into aldehydes (or ketones), whereas an excess results in the clean generation of the carboxylic acids.¹¹

The flow reactor consists of two HPLC pumps which deliver stock solutions from reservoirs being mixed at a T-piece. The resulting reaction stream was then progressed through a PFA (per-fluoro-alkoxy) tubular coil (14 mL internal volume) where the reaction takes place. The final flow stream was collected, the phases were separated, and the organic layer evaporated to afford the product. The initial

Nef oxidation was optimized using 1,2-dimethoxy-4-(nitromethyl)benzene (**1a**) as the substrate, with the solvent, base, residence time (flow rate), reaction temperature, reagent concentrations, and stoichiometries being systematically varied (Scheme 1). The reactions were rapidly screened as

Scheme 1. Nef Oxidation of Nitroalkanes to the Corresponding Carbonyl Compounds



small flow plugs of reagents and analyzed by LC–MS and proton NMR for both conversion and associated purity. It was quickly discovered that protic, water-miscible solvents such as methanol and ethanol were crucial for achieving high, rapid, and clean reactions.¹² Other solvents such as hexane and dichloromethane which formed biphasic systems gave noticeably slower reactions, even in the presence of various phase-transfer catalysts. Ultimately, methanol proved to be the best solvent giving full solubility of the in situ generated nitronate species prepared during the Nef process. The effect of the base was also investigated. Amine bases such as Hünig's base, triethylamine, and 1,1,3,3-tetramethyl guanidine (TMG) were all as equally efficient for the formation of the required nitronate anion as were inorganic bases such as KOH and K₂CO₃. In each case, the reactions were found to proceed very rapidly as they were extremely exothermic. Consequently, careful control of stoichiometries and flow rates and ensuring effective dissipation of the heat generated were required in order to realize good conversions.

Finally, optimal conditions were determined that involved introduction of a 0.25 M solution of the nitroalkane (1.0 equiv) and KOH (1.2 equiv) in methanol via an injection

(7) An U300H Ultrasound bath from Ultrawave was used (<http://www.ultrawave.co.uk/>). Although constant sonication was effective, we found that only short pulses of irradiation were actually required; for example, 5 s every minute.

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(12) No analysis for oxidation products derived from the alcohol solvents was conducted during the reactions; following workup, these products were also not detected. It is known that the relative rates of oxidation of MeOH and EtOH are substantially slower than for higher order species.

loop (1, 2, or 5 mL) as stream 1 which was then mixed within a T-piece mixer with a 0.2 M aqueous solution of KMnO_4 (0.8 equiv) similarly dispensed from an injection loop (1, 2, or 5 mL) as stream 2 (Scheme 1). Interestingly, it was determined that even substoichiometric quantities of the permanganate oxidant gave excellent conversions within short residence times of between 5–8 min (14 mL tube reactor). On exiting the reactor, the reaction output was collected into a vigorously stirred biphasic system comprising saturated aqueous sodium chloride (50 mL; for 5 mL sample loop) and ethyl acetate (20 mL; for 5 mL sample loop). The ethyl acetate layer was decanted and the aqueous portion repeatedly re-extracted with further aliquots of ethyl acetate (dried over MgSO_4). The solvent was removed in vacuo using a Vapourtec V10 system providing the desired product in high yield and purity >95% (as determined by ^1H NMR and LC–MS) with no overoxidation being detected.

As can be seen from the examples depicted in Scheme 1 the oxidation of both benzylic and aliphatic nitroalkanes proceeded smoothly with additional functionalities such as esters, alcohols, and nitriles being tolerated. However, some limitations were encountered; nitroalkanes possessing an amino group β to the nitro functionality gave exclusively elimination to the nitro olefin. Furthermore, with the exception of a single example, **2g** attempted oxidation of nitro-aldol products led to C–C bond cleavage. Nevertheless, this procedure provides a valuable alternative to the classical methods of preparing aromatic building blocks using Friedel–Crafts acylation or formylation.¹³ High yields of essentially analytically pure compounds can be prepared from easily synthesized starting materials. For example, compound **2g** is derived from a base-catalyzed nitro-aldol reaction, whereas substrates **2a,c,e,i** arise from nitroalkane conjugate addition into the corresponding unsaturated systems. Finally, direct substitution of a halide furnishes compounds **2b,h,j**. Each of these sequences can be performed as a flow-based protocol generating diversely functionalized noncommercial nitro-containing materials. Indeed, the number of commercially available nitromethylene-substituted aliphatic and aromatics are very limited.¹⁴ As a consequence, we wished to demonstrate a flow synthesis of one such substrate at scale for use in the Nef chemistry and as a key intermediate within an additional natural product program.

The nitro derivative 1,2-dimethoxy-4-(nitromethyl)benzene (**1d**) was generated on a multigram scale (177 g) using the flow sequence depicted in Figure 2. A concerted procedure involving initial deprotonation with a 2-fold excess of base, followed by reaction of the resulting enolate with isopropyl nitrate and subsequent hydrolysis of the ethyl ester with aqueous NaOH gave a reaction stream containing reactive intermediate **3**. This was flowed into a collection tank containing a stirred solution of 2.5 M HCl which spontaneously induced decarboxylation of **3**, and the resulting product precipitated from solution as a yellow solid. The desired product could be isolated in moderate yield by direct filtration of the mixture (114.3 g; 58%). Additional material could be further recovered by extraction of the acid solution with dichloromethane giving an overall yield of 177.3 g, 90%. This

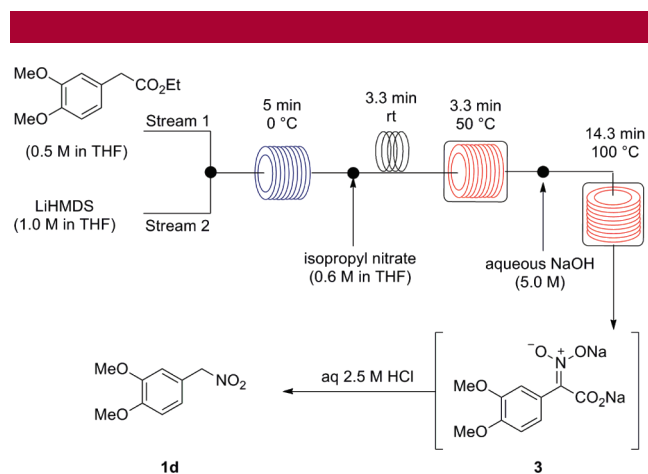


Figure 2. Reactor setup for the synthesis of 1,2-dimethoxy-4-(nitromethyl)benzene (**1d**).

large-scale synthesis clearly demonstrates the value of flow based processing for the generation of novel building blocks.

With methods available to prepare significant quantities of nitro adducts, we turned our attention to the corresponding scale up of the Nef oxidation. We considered this to be an important proof of principle due to the potential for exothermic run-away as evidenced by the rapid heat liberation of the small scale reactions. Our aim was therefore to demonstrate that the flow reactor could be operated under a steady state as a continuous flow process for a number of hours, thereby generating multigram quantities of product. The integrated control features that constantly monitor the system temperature and pressure enabling automatic shutdown (based upon user selected parameters) gave us confidence in directly scaling the sequence by a factor of 200.

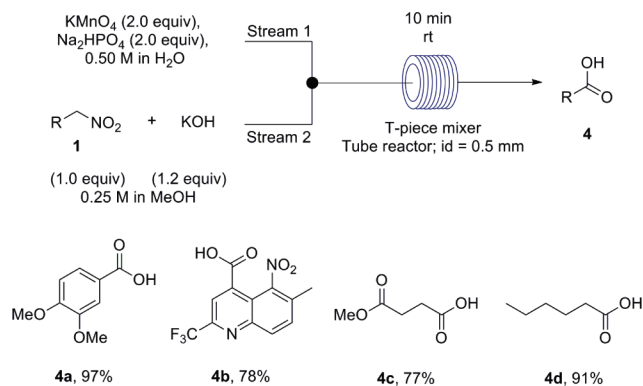
A 0.25 M solution of methyl 4-nitrobutanoate (**1f**) (7.36 g, 50.0 mmol) was processed at a flow rate of 1.40 mL/min (using only a 14 mL coil reactor) to yield 5.05 g (43.5 mmol, 87%) of the corresponding aldehyde **2f** over a period of 3.3 h. As well as yielding the product in essentially the same yield, chemoselectivity, and high purity as for the small-scale reaction demonstrating good consistency, we also encountered no issues due to manganese dioxide fouling of the reactor. The general principle of using short pulses of ultrasonic irradiation proved highly efficient at preventing build-up of solid within the reactor.

In order to further expand the synthetic potential of the continuous flow process, conditions for the direct conversion of nitroalkanes **1** into the corresponding acids **4** were devised (Scheme 2). Optimal conversions were achieved by combining a 0.25 M solution of a primary nitroalkane (1.0 equiv) and KOH (1.2 equiv) in methanol as stream 1 with a 0.50 M buffered solution of KMnO_4 (2.0 equiv) and Na_2HPO_4 (2.0 equiv) in water as stream 2 using the same reactor setup as described above. The output stream was dispensed into a vigorously stirred biphasic mixture of ethyl acetate and aqueous 1 M HCl saturated with sodium chloride and containing a substoichiometric amount of sodium thiosulfate (as a reducing agent for excess permanganate). Under these conditions, the in situ generated manganese dioxide was

(13) PTC/US98/11194.

(14) A SciFinder search (24/05/10) for nitromethylene substrates supplied at synthetically useful quantities (≥ 10 g) returned a list of only 25 compounds.

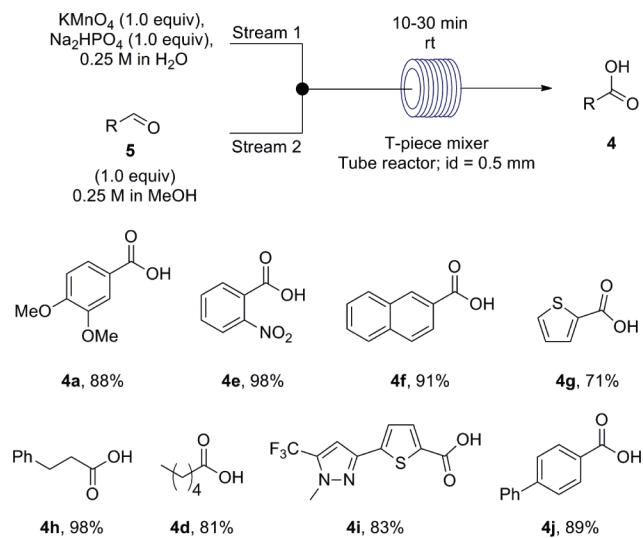
Scheme 2. Transformation of Nitroalkanes to the Corresponding Carboxylic Acids



solubilized permitting a simple extractive workup. This provided the desired product in high yield and excellent purity. While only four examples were examined using this process (Scheme 2), we found the reaction to be very reliable.

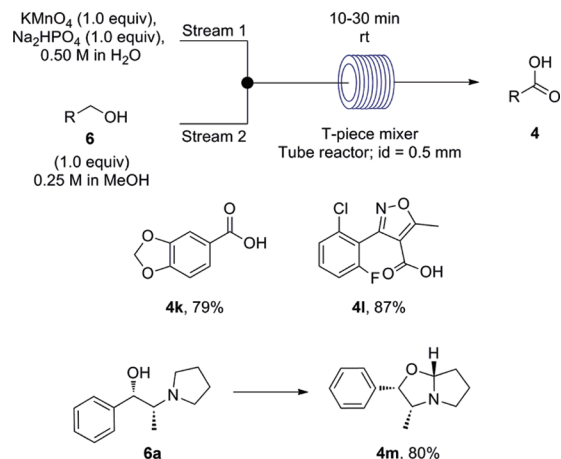
As an obvious extension to this protocol, we also examined the KMnO_4 -mediated oxidation of alcohols and aldehydes to carboxylic acids.¹⁵ The most effective conditions found were to coelute a 0.25 M solution of the alcohol (for **4k** and **4l**) or aldehyde (1.0 equiv) in methanol as stream 1 with a 0.25 M solution of KMnO_4 (1.0–2.0 equiv) and Na_2HPO_4 (1.0–2.0 equiv) in water as stream 2. An identical reactor setup and workup protocol as described previously was employed, furnishing again the products in high yields and purities (Schemes 3 and 4).

Scheme 3. Transformation of Aldehydes to the Corresponding Carboxylic Acids



These conditions were additionally applied to the oxidation of (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidiny)-1-propanol (**6a**) where

Scheme 4. Transformation of Alcohols to the Corresponding Carboxylic Acids and Aminal Formation



the oxidation of the tertiary amine to an iminium species proceeded faster than the oxidation of the benzylic alcohol (Scheme 4). The resultant aminal **4m** was obtained in high yield with a dr of 19:1 via intramolecular trapping of this reactive electrophile by the adjacent hydroxyl group. This series of reactions highlights the complementary nature of this facile oxidation process that can be tailored to deliver aldehydes (ketones) or acids as required.

In summary, we have developed an efficient, rapid, and easy to conduct process for the KMnO_4 -mediated oxidation of alcohols, aldehydes, and nitroalkanes under flow conditions. The value of the transformation is in using cheap reagents that deliver oxidation products in high yields and excellent purities following simple workup and evaporation of the solvent. As part of this study, we have successfully shown that MnO_2 slurries can be handled within a flow reactor by application of ultrasonication. Furthermore, we have demonstrated the ease of scale-up by running the flow setup at steady state processing 50 mmol of starting material. The simple experimental setup in combination with the benefits given by continuous flow technology renders this procedure synthetically very interesting.

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Supporting Information Available: Experimental procedures and full characterization (^1H and ^{13}C NMR data and spectra, IR, and HRMS) for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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