# Safe use of Nitromethane for Aldol Reactions in Flow

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**Abstract**

Using a simple flow reactor, the safe use of nitromethane at elevated reaction temperatures was demonstrated in a nitro aldol reaction of different aldehydes. The reaction products were isolated in good yields after a short reaction time.

**Introduction**

Nitromethane has been shown to have extensive energetic properties and been used as a fuel and explosive for many years [1]. Its explosive properties were first reported in 1958 in a rail tanker accident [2], although it was not considered to be a dangerous compound at the time. Although insensitive by itself, upon mixture with oxidants, amines or microbeads detonation can be triggered readily [3]. This obviously poses a risk when nitromethane is being used in chemical synthesis. It has been shown that the presence of as little as 3% of an amine can cause detonation within a confined space. Therefore, nitromethane as a highly energetic compound is utilised in organic synthesis in many ways such as conjugate addition reactions under a limited set of reaction conditions [4]. Scale-up of these reactions remains a challenge particularly at high nitromethane concentrations.

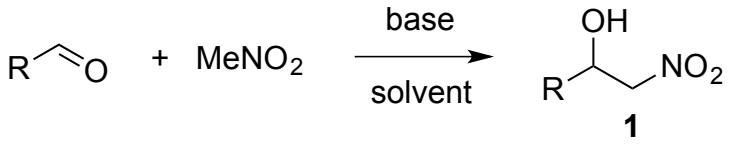
Carbon-carbon bond formation is at the core of organic synthesis and has been widely studied for decades. The Henry reaction, or the nitro-aldol reaction, between nitroalkanes and carbonyl compounds to produce nitro alcohols was discovered in 1895. The reaction has been used in many important syntheses to date. Classically the nitroaldol reaction is promoted by the presence of a base in an organic solvent, and conducted at room temperature. The most common bases and solvents used for this reaction are metal hydroxides, carbonates, bicarbonates and alkoxides in water or ethanol. Many reviews have been written within the area of the nitroaldol reaction under batch conditions [5, 6]

but only a few of publications have concerned the use of continuous flow technologies [7, 8, 9, 10, 11, 12].

As the nitroaldol reaction can be catalysed via basic or Lewis acidic reaction conditions, there is the potential for side reactions depending on the electrophile used. It is therefore paramount to control the basicity of the reaction medium and the time of the reaction. Due to the detrimental effects of these conditions, nitroaldol reactions are usually left to considerably long reactions times and performed at low temperatures. Although side products such as elimination products are unwanted, it does show the versatility of such products due to the apparent ease of transformation. A few publications have reported the formation of such aforementioned side products in flow [13,14]. As stated, a problem presented with the nitro aldol reaction is the subsequent elimination of the alcohol to form β-nitrostyrene products. This paper sets out to show that this does not have to be the case. The majority of conditions used to create β-nitrostyrenes use long reaction times. By reducing the time the nitro alcohol is in contact with the basic reaction conditions elimination is less likely to occur. This is aided by flow chemistry, as the reactants are only in the reactive zone for a designed period.

## Results and discussion

Our approach started by identifying reaction conditions that would be applicable under continuous flow conditions. Solvents and concentrations had to be carefully chosen to avoid precipitation as clogging can be problem in flow chemistry. Initially a common base was used in condensation reactions such as triethylamine. A polar solvent was chosen to stabilise the formation of charged intermediates and therefore allow for increased reaction rates. Methods for batch conditions have been well established, therefore moving straight to flow was thought to be the most efficient route.




**Scheme 1.** Nitroaldol (Henry) reaction

The flow reaction was carried out as shown in Figure 1. One syringe containing the base dissolved in ethanol (0.5 M) and a second syringe containing 4-nitrobenzaldehyde (R = 4-$NO_2$-$C_6H_4$) (0.1 M) dissolved in ethanol containing 10 equivalents of nitromethane (1 M). The reaction was then performed using a PTFE coil (1 mL, 0.5 mm i.d.) with a Comet mixer [15] attached for enhanced mixing. Residence times within the reactor coil were 30 min at room temperature. Upon quenching with 10% aqueous hydrochloric acid, the

product **1a** was extracted using dichloromethane. Due to the small scale of the reactions, the excess nitromethane was easily removed in vacuo. Inline evaporation and recycling of nitromethane also has been reported [12]. The results are summarized in Table 1.

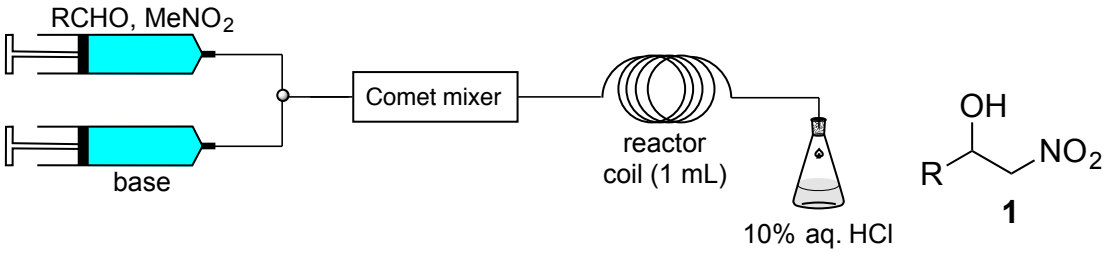



**Figure 1.** Reaction set up. Henry reaction in flow

| Entry | Base | **1a** (R = $C_6H_4$-4-$NO_2$) Yield (%) |
|---|---|---|
| 1 | $NEt_3$ | 51 |
| 2 | Hünig's base[a] | 21 |
| 3 | DBU[b] | 75 |
| 4 | DABCO[c] | 24 |
| 5 | DMAP[d] | 23 |
| 6 | Proton Sponge[e] | 27 |
| 7 | *n*-butylamine | traces |
| 8 | DBN[f] | 92 |
| 9 | TBD[g] | 90 |
| 10 | KOH | 81 |

**Table 1.** Bases investigated for the catalysis of the nitro aldol reaction using 4-nitrobenzaldehyde, nitromethane in ethanol at RT and 30 min residence time. a) $NEt_2$*i*Pr; b) 1,8-Diazabicyclo[5.4.0]undec-7-ene; c) 1,4-diazabicyclo[2.2.2]octane; d) 4-dimethylaminopyridine; e) 1,8-bis(dimethylamino)naphthalene; f) 1,5-Diazabicyclo[4.3.0]non-5-ene; g) 1,5,7-triazabicyclo[4.4.0]dec-5-ene

1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) (Table 1, entry 8) and similar bases such as DBU and TBD proved to be superior bases for this transformation under the chosen conditions. As expected due to the lower pKa values of $NEt_3$ and other bases, yields were considerably lower. Different solvents have then been screened with DBN as base and the optimal solvent system was found to be ethanol likely due to the highly polar nature of such a solvent stabilising the charged intermediates. Methanol (Table 2, entry 2) and acetonitrile (Table 2, entry 3) showed comparable yields.

| Entry | Solvent | **1a** (R = 4-$NO_2$- |
|---|---|---|

| | | $C_6H_4$) Yield (%) |
|---|---|---|
| 1 | Ethanol | 92 |
| 2 | Methanol | 91 |
| 3 | Acetonitrile | 86 |
| 4 | Toluene | 20 |
| 5 | Tetrahydrofuran | 58 |
| 6 | Dichloromethane | 22 |
| 7 | Chloroform | 18 |
| 8 | Diethyl ether | 41 |
| 9 | 2-Propanol | 82 |
| 10 | *tert*-Butanol / Dichloromethane | 80 |

**Table 2.** Bases investigated for the catalysis of the nitro aldol reaction using 4-nitrobenzaldehyde and nitromethane at RT and 30 min residence time.

Subsequently, a variety of aldehydes were investigated in the Henry reaction. Electron poor aldehydes showed good to excellent yields although for substrates containing one or more electron donating substituents the yields dropped dramatically. Modifications to this method were investigated in order to increase the yields when using electron rich substrates. Simple copper(II) salts have been shown to catalyse the nitroaldol reaction without the addition of a base, acting as a Lewis acid [16]. Although reaction times are long it was thought that, in co-catalysis with a base, reaction yields could be enhanced further. This was indeed the case as demonstrated for 4-tolylaldehyde (Table 3, entry 8) and 4-anisaldehyde (Table 3, entry 9) when copper(II) acetate as added. Copper(II) sulfate and copper(II) bromide had similar effects while cobalt(II) chloride or nickel(II) chloride formed an insoluble precipitate upon addition of the base. Similarly, a combination of copper(II) acetate and KOH formed an insoluble precipitate.

| Entry | Substrate | **1** Yield (%)[a] | **1** Yield (%)[b] |
|---|---|---|---|
| 1 | 4-nitrobenzaldehyde | 92 | 81 |
| 2 | 4-fluorobenzaldehyde | 70 | 76 |
| 3 | 4-chlorobenzaldehyde | 65 | 72 |
| 4 | 4-bromobenzaldehyde | 63 | 72 |
| 5 | 4-tolylaldehyde | 40 (74[c]) | 60 |
| 6 | 4-anisaldehyde | 12 (61[c]) | 10 |

| | | | |
|---|---|---|---|
| 7 | 2-bromobenzaldehyde | 54 | 52 |
| 8 | furfuraldehyde | - | 45 |
| 9 | cinnamaldehyde | - | 65 |
| 10 | cyclohexanecarboxaldehyde | - | 55 |
| 11 | phenacetaldehyde | - | 62 |
| 12 | octanal | - | 42 |

**Table 3.** Substrates used in the nitro aldol reaction with nitromethane, solvent: EtOH. a) Reaction performed with DBN as base at RT and 30 min residence time; b) Reaction performed with KOH as base at 60 ºC and 10 min residence time; c) Reaction performed in the presence of 10 mol% $Cu(OAc)_2$.

DBN is much more expensive than many other bases, but it shows the highest yields in the initial screen of the Henry reaction. Other inexpensive bases such as KOH did still perform reasonably well compared to DBN (Table 1, entry 10). The much lower price of this base can also allow for scale up being much more applicable. In addition, as KOH is an inorganic base, an aqueous separation can be used which is more facile compared to chromatography needed to separate many of the organic bases. As well as with the conditions used in combination with copper salts a second set of conditions using KOH was devised due to the low cost of using this base and ease of separation. Using ethanol as the solvent and heating to 60 °C allowed for almost full conversion in 10 minutes of residence time. As shown also in Table 3 (last column), yields were generally good for all aldehydes. As expected the electron-rich substrates showed lower yields than electron-poor aromatic aldehydes, but full conversion could not be reached under these conditions without extending the residence time much further. But also aliphatic aldehydes such as cyclohexanecarboxaldehyde, octanal and phenylacetaldehyde (Table 3, entries 10-12) showed reasonable yields within 10 min reaction time.

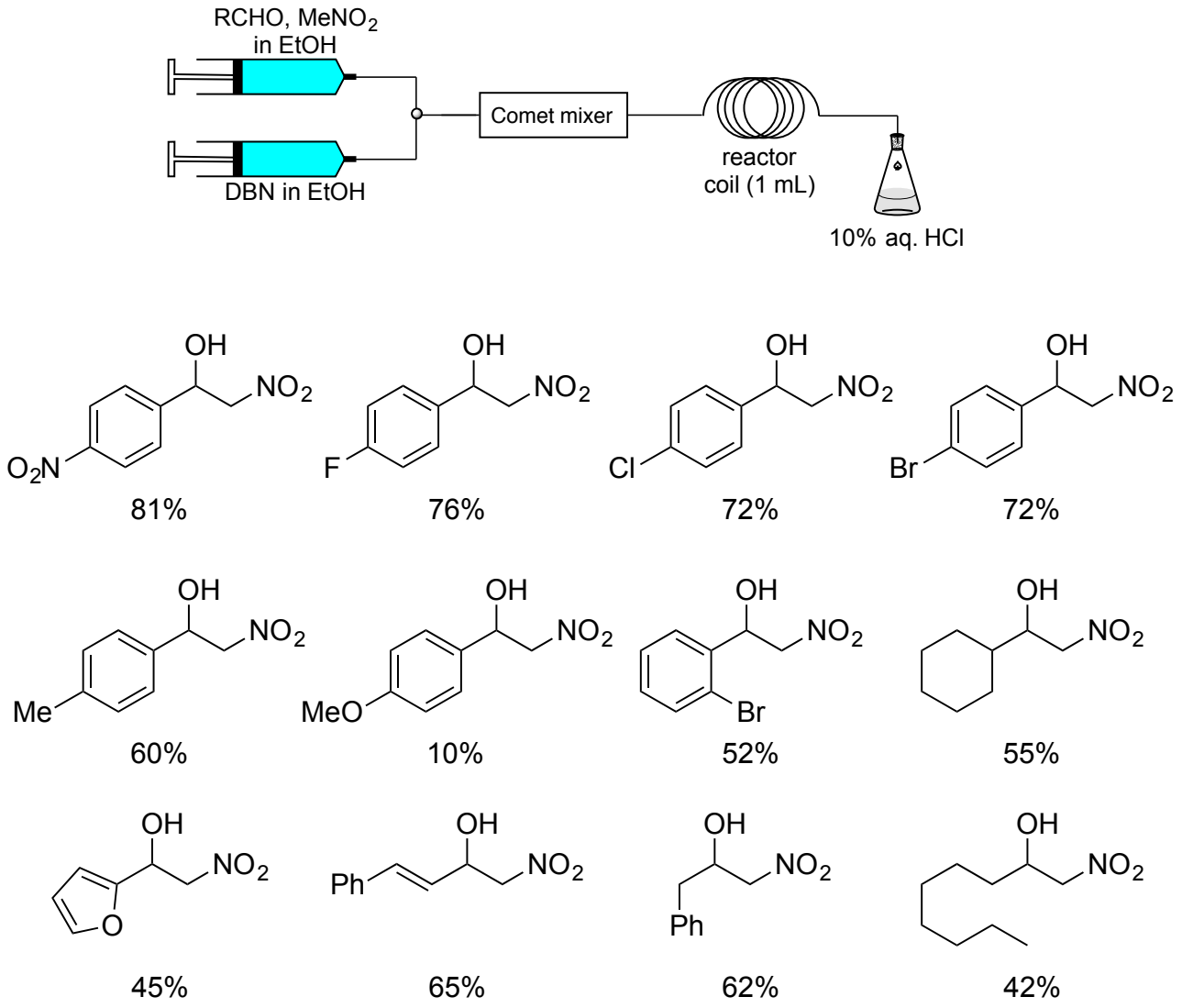
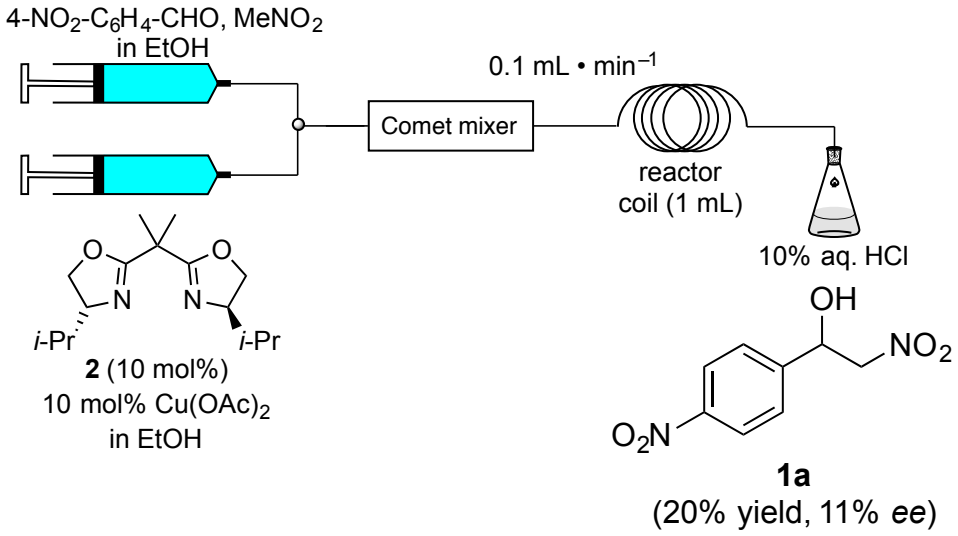



**Figure 3.** Products synthesised by Henry reactions in flow

Although stereochemical reactions are often associated with long reaction times and low temperatures, recent work in flow chemistry has shown that it does not necessarily have to be the case. Odedra and Seeberger have shown that stereocemical reactions can be achieved at elevated temperatures in short reaction times [17]. Two different techniques were investigated for the formation of the chiral nitroalcohols, copper(II) catalysis, and phase transfer catalysis. As copper showed a large affinity towards Lewis acid catalysts, batch conditions within the literature were adapted for continuous flow. A report by Evans and coworkers reported a similar system to the one established in flow (Figure 1) [16]. In the batch protocol, the use of $Cu(OAc)_2$ in alcoholic solvents using bisoxazoline ligand **2** showed very good control of stereochemical induction of up to 94% *ee*. Unfortunately it was not possible to transfer the reaction to flow conditions without almost complete loss of stereoselectivity as shown in Scheme 2.




**Scheme 2.** Asymmetric nitroaldol reaction using flow conditions

Unless highly electron-poor substrates such as nitrobenzaldehyde are used, conversion times are long. To circumvent this, it was hoped that using a base in combination would allow for an increase in reaction rate. The reaction rate was indeed increased, but to the detriment of the stereoselectivity as only racemic product was obtained.

Secondly, tandem chiral phase transfer catalysis (CPTC) was attempted in flow, this sought to utilise the inherent surface to volume ratio increase when switching from batch to flow conditions [18]. As PTC relies on the interaction between the organic and aqueous phase, the use of segmented flow was thought to be beneficial. Although an initial batch reaction using *N*-benzyl chinconidine hydroxide as catalyst provided a small enantiomeric excess (9%) in the Henry reaction product, a transfer to flow reaction conditions was not possible due to precipitation.

One of the advantages of continuous flow chemistry is the ability to couple multiple steps together. As amino alcohols have been shown to be very useful intermediates for a variety of compounds such as chiral ligands, heterocycles and catalysts themselves, the combination of a Henry reaction with a subsequent reduction was envisioned. Numerous reduction methods for nitroalkanes are available. We recently have already reported on the easy reduction of Henry-reaction products to aminoalcohols using a Pd/C catalyst in a packed-bed column with ammonium formate as hydrogen donor [19]. However, the direct combination of the two flow processes did only result in a retro-Henry reaction taking place probably due to the presence of excess nitromethane in the reduction process. The nitromethane is being reduced preferentially, allowing the acidic conditions to catalyse the retro-Henry process.

## Conclusions

The safe use of nitromethane as a versatile building block in the nitro aldol reaction was demonstrated by employing an inexpensive base such as potassium hydroxide in a flow system at elevated temperatures. A large range of aldehydes could be transformed to the corresponding Henry reaction products in good yields.

## Method

### General method for the nitro aldol reaction in flow synthesis:

A syringe was charged with the aldehyde (2 mmol) and nitromethane (10 mmol), dissolved in EtOH (2 mL). A second syringe was charged with the base (0.5 mmol) dissolved in EtOH (2 mL). Both syringes were mounted on a syringe pumpe, attached to a T-joint and the comet micromixer and to the PTFE reactor coil (1 mL, 0.5 mm i.d.). The mixture was pumped at a flow rate of 0.05 mL • $min^{-1}$ per syringe (0.1 mL • $min^{-1}$ overall) and quenched into 10% aq. HCl. The product was extracted with dichloromethane and purified using column chromatography. The spectroscopic data of all products **1** are in agreement with published data [20].

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## References

1. Utkin, A. V.; Mochalova, V. M. *Combust. Explos. Shock Waves* **2015***, 51*, 63.
2. Railroad Accident Investigation No. 213, Retrieved 08. June 2016 from http://www.blet602.org/Historic_accidents/Mt.%20Pulaski_6.1.1958.pdf.
3. Sullivan, J.; Sunderland, W. *Liquid Explosive in Pipes*, 1994.
4. Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933.
5. Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915.
6. Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315.

7. Biradar, A. V.; Sharma, K. K.; Asefa, T. *Appl. Catal. A Gen.* **2010**, *389*, 19.
8. Kawai, K.; Ebata, T.; Kitazume, T. *J. Fluor. Chem.* **2005**, *126*, 956.
9. Hashimoto, K.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2014**, *16*, 3496.
10. Tsubogo, T; Oyamada, H.; Kobayashi, S. *Nature* **2016**, *520*, 329.
11. Roberge, D. M.; Noti, C.; Irle, E.; Eyholzer, M.; Rittiner, B.; Penn, G.; Sedelmeier, G.; Schenkel, B. *J. Flow Chem.* **2014**, *4*, 26.
12. Deadman, B. J.; Battilocchio, C.; Sliwinski, E.; Ley, S. V. *Green Chem.* **2013**, *15*, 2050.
13. Ishitani, H.; Saito, Y.; Tsubogo, T; Kobayashi, S. *Org. Lett.* **2016**, *18*, 1346.
14. Soldi, L.; Ferstl, W.; Loebbecke, S.; Maggi, R.; Malmassari, C.; Sartori, G.; Yada, S. *J. Cat.* **2008**, *258*, 289.
15. The micromixing device 'Comet X-01', available from Techno Applications Co., Ltd, 34-16-204, Hon, Denenchofu, Oota, Tokyo 145-0072, Japan, was used.
16. Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692.
17. Odedra, A.; Seeberger, P. H. *Angew. Chem. Int. Ed.* **2009**, *48*, 2699.
18. Alvarez-Casao, Y.; Marques-Lopez, E.; Herrera, R. P. *Symmetry* **2011**, *3*, 220.
19. Hutchings, M.; Wirth, T. *Synlett* **2016**, *27*, in press. DOI: 10.1055/s-0035-1561624
20. Blay, G.; Domingo, L. R.; Hernández-Olmos, Pedro, J. R. *Chem. Eur. J.* **2008**, *14*, 4725.