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Manipulation of the stereochemical outcome and product distribution in the Henry reaction using CO_2 pressure

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The rate and stereocontrol of the Henry reaction in the presence of CO_2 can be controlled simply by manipulation of CO_2 pressure, and can be understood by consideration of the kinetic and thermodynamic aspects of the reaction.

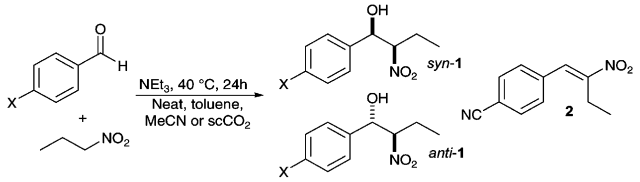
The Henry reaction is a particularly useful carbon–carbon bond forming reaction giving highly functionalised products of considerable synthetic utility.[1] In keeping with our interest in utilising supercritical carbon dioxide ($scCO_2$) as a reaction medium for synthetic chemistry,[2] this reaction seemed an ideal candidate for study. It is known to be an equilibrium process,[3] and has considerable potential for stereocontrol, both of which are of interest with regard to exploiting the tunability of $scCO_2$ to control the outcome of the reaction.[4] It has been reported to proceed more efficiently and with better selectivity at high pressures (> 750 MPa),[5] which although much higher than typical $scCO_2$ pressures (T_c = 304.2 K, P_c = 7.38 MPa), suggested that some interesting results may be possible.

One of the most attractive features of the Henry reaction is its potential for stereocontrol. Varying levels of diastereoselectivity have been reported depending on the catalyst and solvent systems, although this is generally modest,[3,6] even with modern complex asymmetric reactions,[7] and in many cases, is not considered.[8] Improvements such as selective protonation of double deprotonated nitroaldols pioneered by Seebach gives predominantly *syn* selectivity,[3] whereas use of dichloroisopropoxytitanium nitronates gives predominantly *anti* selectivity.[9] However, there remains considerable scope for improvement, which can be best achieved if a greater understanding of the factors controlling the stereochemical outcome of the reaction can be obtained.

We chose to investigate the reaction of a variety of aromatic aldehydes with 1-nitropropane in a variety of solvent systems which would allow us to gain valuable comparative information on both reaction rate and stereocontrol. NEt_3 was chosen as base, as it is well established for simple Henry reactions,[10] and is known to be very soluble in $scCO_2$.[11] Initial studies in $scCO_2$ showed an interesting contrast when compared with reactions in the absence of solvent, or as solutions in MeCN or toluene at comparable concentrations (0.05 M aldehyde) (Table 1). Highest conversions were obtained when reactions were conducted in the absence of solvent; in contrast only very low conversions were observed in toluene, a typical non-polar organic solvent. In comparison, in $scCO_2$ and MeCN, intermediate conversions were obtained, with $scCO_2$ being significantly greater than MeCN in all cases except benzaldehyde (entries 3 and 4). It is important to appreciate that the reactions in $scCO_2$ were not fully optimised (*vide infra*), but all were homogeneous throughout. Interestingly using MeCN and $scCO_2$ together (entry 12) gave significantly lower conversions than when either was used individually.

Along with conversions, stereocontrol also varied considerably depending on substrate and reaction conditions. In all cases, use of $scCO_2$ showed a significant shift in stereoselectivity away from the more usual *anti* isomer, towards the *syn* (Table 1). Although this could be due to a simple solvent effect, we decided to investigate one specific example in more detail - the reaction of *p*-cyanobenzaldehyde with 1-nitropropane at a variety of CO_2 pressures. Importantly this also included subcritical CO_2 pressures, which would enable comparisons with neat reactions, to allow further meaningful mechanistic information to be obtained. Throughout these studies, only the nitroaldol product, starting materials, and under certain conditions (*vide infra*), dehydration product **2**, were present in the crude reaction mixture after work-up.

Studies in a high pressure view cell showed this reaction to be a single homogeneous phase above approximately 10 MPa CO_2 pressure at 40 °C (indicated by vertical dotted line on Fig. 1, Scheme 1, X = CN). Here the conversion to the nitroaldol product is optimum for the homogeneous reaction (and much better than that obtained in conventional solution), but as pressure is increased a significant decrease in reaction rate is observed, as determined by lower conversion in a set period of time. We have reported a similar trend in our previous studies on the Baylis–Hillman reaction.[4] This rate change may be attributed to reduced fugacities of the reactive species,[12] or to the $scCO_2$ achieving more liquid-like densities at



Scheme 1 Henry reaction of 1-nitropropane and substituted benzaldehydes.

Table 1 Solvent comparison of Henry reactions

Entry	X	Solvent	Conv. (%)[a]	d.e. (%)[a]	Yield (%)
1	H	Neat	67	38 *anti*	41
2	H	Toluene	< 5	—	—
3	H	MeCN	49	49 *anti*	*
4	H	$scCO_2$[b]	31	0	21
5	NO_2	Neat	92	33 *anti*	60
6	NO_2	Toluene	< 5	—	*
7	NO_2	MeCN	28	40 *anti*	*
8	NO_2	$scCO_2$[c]	63	23 *anti*	51
9	CN	Neat	96	81 *anti*	94
10	CN	Toluene	11	59 *anti*	*
11	CN	MeCN	43	47 *anti*	*
12	CN	MeCN/$scCO_2$[d]	27	45 *anti*	*
13	CN	$scCO_2$[e]	59	8 *anti*	52
14	CO_2Me	Neat	75	42 *anti*	62
15	CO_2Me	Toluene	< 5	—	—
16	CO_2Me	MeCN	7	48 *anti*	*
17	CO_2Me	$scCO_2$[f]	18	16 *syn*	18
18	CF_3	Neat	76	50 *anti*	74
19	CF_3	Toluene	< 5	—	—
20	CF_3	MeCN	12	55 *anti*	*
21	CF_3	$scCO_2$[g]	60	33 *anti*	34

[a] All reactions were carried out using aldehyde (1 mmol), 1-nitropropane (2 mmol) and NEt_3 (0.7 mmol) in solvent (20 ml) when required; $scCO_2$ reactions were carried out in a 20 ml high pressure vessel. Conversion and d.e. obtained by ^{1}H NMR integration of crude product mixtures. [b] 9.35 MPa. [c] 9.69 MPa. [d] 9.59 MPa. [e] 9.49 MPa. [f] 8.65 MPa. [g] 8.94 MPa. *Not determined.

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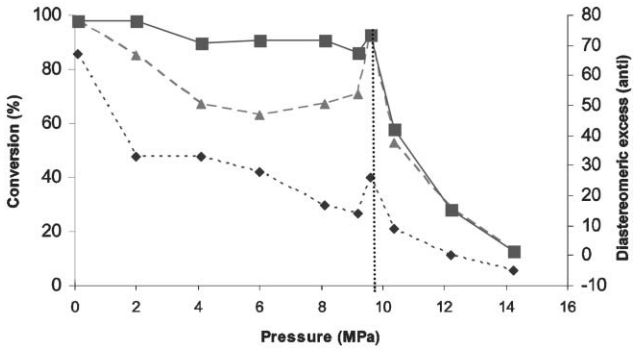

Fig. 1 Control of Henry reaction by variation of CO_2 pressure. ■ Total conversion including dehydration to **2**; ▲ conversion to nitroaldol product **1**; ◆ d.e. of **1** (*anti*).

higher pressures[13] – the conversion at 14 MPa is similar to what is observed in toluene at a similar concentration (entry 10, Table 1). Alternatively a combination of these two effects may be operating. Also of interest in this homogeneous region, is the lack of dehydration to the vinylnitro species[14] **2**, with the nitroaldol **1** being the major product.

At pressures below 10 MPa, we are in a two phase region, where a neat (or CO_2 expanded[11]) reaction is occurring under an atmosphere of super- or subcritical CO_2. Overall conversions here are excellent and are comparable to neat reactions (entry 9, Table 1), but interestingly significant amounts of dehydration[14] product **2** are now observed (*ca.* 30%, represented on the Fig. 1 by the difference between total conversion and that of nitroaldol **1**). Interestingly, this only occurs in the presence of CO_2. This may be a result of the Lewis acidity[4,15] of CO_2 dissolved in the neat reaction aiding the dehydration process. The polar nature of the neat reaction medium may promote the dehydration, which would also explain why no dehydration is observed in the relatively non-polar homogeneous $scCO_2$ solution.

The most interesting aspect of this study is the stereoselectivity. It can be seen from Fig. 1 that there is a gradual shift from *ca.* 70% *anti* to 5% *syn* on going from 0.1 to 14 MPa of CO_2 pressure. It is intriguing to note that this effect occurs almost linearly with pressure and independently of phase, other than a slight dip around 2 MPa (which may be due to facile dehydration of the predominant *anti* isomer), and an enhancement around the critical point, probably due to enhanced reaction rates (*vide infra*) resulting from reagent clustering.[16]

To explain these observations it is necessary to consider the reaction in more detail. It is known that the Henry reaction is reversible,[3] and in this case, what we believe we are observing is competing kinetic *vs.* thermodynamic control. At low CO_2 pressures, we have a neat reaction which is rapid, which also allows for rapid equilibration of the kinetic product mixture to the thermodynamically favoured *anti* isomer. However at higher pressures, the reaction is significantly slower, particularly under supercritical conditions, and kinetic control dominates, tending towards *ca.* 10% in favour of the *syn* isomer, with greatly reduced conversions. Such control has not been reported before for the Henry reaction, and provides valuable mechanistic insight into the factors controlling diastereoselectivity, which remains a problem even in some recent elegant asymmetric processes.[7]

The final point to comment on is the variation of stereocontrol at subcritical pressures. These reactions were all performed for 24 h to aid comparison with other results, but such neat reactions are usually 'complete' within a much shorter period of time. However, they will continue to equilibrate for the remaining period, with such equilibration being apparently more facile at lower CO_2 pressures. A possible explanation for this is the ability of CO_2 to interact with Lewis bases, in this case, either NEt_3, or less likely, the nitronate/nitronol nucleophile. It is known that CO_2 has a high affinity for NEt_3 forming expanded solutions,[11] and spectroscopic studies have also provided evidence for a weak Lewis acid–Lewis base interaction which would be expected to influence the efficiency of the base, and would be pressure dependent.[15] This would be expected to reduce the rate of equilibration, in accord with what is observed.

In conclusion, we have shown that the rate and stereocontrol of the Henry reaction in the presence of CO_2 can be controlled simply by manipulation of CO_2 pressure. This leads to a greater understanding of the kinetic and thermodynamic effects controlling the Henry reaction and is an excellent example of how fundamental studies in $scCO_2$ can lead to results of more widespread importance, particularly for the development of related diastereo- and enantio-selective C–C bond forming processes.†

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Notes and references

† Typical experimental procedure: A 20 ml high-pressure view cell was charged with aldehyde (1 mmol), triethylamine (0.7 mmol) and a stirrer bar. The vessel was sealed and pre-heated to 40 °C. 1-Nitropropane (2 mmol) was then injected along with additional CO_2 to achieve the desired pressure. This was left with stirring for 24 hours. The vessel was then vented through an ether solvent trap (50 ml) and 0.1 M HCl (10 ml) was injected into the vessel and stirred for 5 minutes. The vessel was rinsed with ether (3 × 10 ml) and combined with the HCl quench. The combined fractions were then extracted into further ether (3 × 10 ml), dried ($MgSO_4$), and solvent removed under reduced pressure to give the crude product which was further purified using column chromatography (20% ethyl acetate/petrol).

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