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# Baeyer–Villiger oxidation in compressed $CO_2$†

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*Received (in Cambridge, UK) 19th March 2002, Accepted 10th June 2002*

**The aerobic Baeyer–Villiger oxidation of a wide range of ketones, both cyclic and acyclic to the corresponding esters or lactones can be efficiently carried out in compressed carbon dioxide in the presence of an aldehyde as co-reductant**

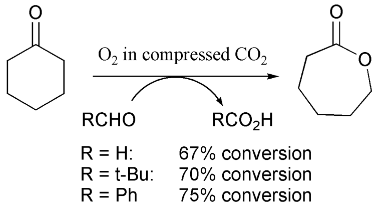
Selective oxidation of organic compounds is an important area of synthetic chemistry, the Baeyer–Villiger reaction being one of the most prominent examples.[1] In this context, the use of molecular oxygen as primary oxidant represents a particularly attractive approach and at the same time a scientific challenge.[2] The Baeyer–Villiger oxidation is generally carried out as a solution phase process with certain boundary conditions for the choice of the solvent. The solvent should possess high solubility for oxygen and organic substrates, it should be stable towards oxidation to avoid contamination by solvent degradation products, and it should be non-inflammable for safety reasons. Therefore, chlorinated solvents are generally preferred solvents for Baeyer–Villiger oxidation despite the environmental and toxicological hazards connected with their use.

Recently, compressed $CO_2$ (liquefied or supercritical) has emerged as an alternative reaction medium in organic synthesis.[3] It is environmentally friendly, non-toxic, and highly miscible with many gases, thus circumventing potential problems associated with limited mass-transfer in conventional gas–liquid reaction systems. Especially for oxidation reactions, safety considerations are undoubtedly the most convincing argument for the use of compressed $CO_2$ as reaction medium. In fact, it is *a priori* non-inflammable and non-oxidisable, and acts as an efficient diluting agent raising the explosion limit so that even relatively high substrate and oxygen concentrations can safely be employed. Intrigued by these obvious advantages, attempts have been made to employ compressed $CO_2$ for synthetic processes using oxygen in the presence of homogeneous[4a–d] and heterogeneous[4e–g] catalysts, or with aldehydes as co-reductants.[5]

Oxidation processes based on molecular oxygen as primary oxidant can be achieved with aldehydes as oxygen transfer agents and sacrificial co-reductants. Various reactions of this type occur under very mild reaction conditions in common organic solvents in the presence of metal catalysts (Mukaiyama conditions).[6] Certain aldehyde-based oxidations, including the Baeyer–Villiger reaction,[7] are also known to proceed in the absence of a catalyst, but the use of chlorinated solvents is essential for synthetic efficiency. Recently, some of us reported that highly efficient catalyst-free epoxidation of olefins[5a] and oxidation of alkanes[5b] can be achieved in compressed $CO_2$. The stainless steel of the reactor wall is responsible for the generation of an active oxidative species, most likely through its ability to promote the formation of acylperoxy radicals.

In the present communication we report on the use of oxygen–aldehyde mixtures for Baeyer–Villiger reactions using compressed carbon dioxide as the reaction medium. The oxidation occurs without the need for a catalyst and converts the starting ketones to their corresponding lactones efficiently and with high selectivity. Conversion in $CO_2$ is considerably higher than in conventional organic solvents under comparable conditions.

The study was initiated by screening various oxidants on their capability to selectively convert cyclohexanone to caprolactone in liquid or supercritical $CO_2$.‡ Hydrogen peroxide (30% in water) remained ineffective as oxidant even when hexafluoropropan-2-ol,[8] a catalytic amount of $Ph_2Se_2$,[9] or dimethyl carbonate[10] were added as potential activators. In contrast, the molecular oxygen–aldehyde combination led to high conversion even in the absence of any additives, affording the desired cyclic esters with good to excellent yields. Addition of catalytic amounts of $Cu(OAc)_2$ or $Sc(OTf)_3$ to the reaction mixture did not improve the conversion further. Among various commercially available aldehydes, benzaldehyde gave the best result leading to 75% conversion of the ketone under standard conditions (Scheme 1). Replacing the aldehydes with the corresponding acetals[11] did not result in the formation of caprolactone.



**Scheme 1**

The influence of the reaction conditions was investigated in more detail using cyclohexanone (**A**) and 3-*n*-octylcyclobutanone (**B**) as substrates and pivalaldehyde as the co-reductant (Table 1).

The amount of aldehyde had a major impact on the reaction course and high conversion required an aldehyde–substrate ratio of 3 : 1 (entry 2, 5). In contrast, the partial oxygen pressure

**Table 1** Baeyer–Villiger reaction of cycloalkanones in compressed $CO_2$ under different reaction conditions using pivalaldehyde as co-reductant

| Entry | Substrate[a] | Aldehyde/ eq. | $CO_2$/g | $pO_2$/bar | *T*/°C | Conv. (%) |
|---|---|---|---|---|---|---|
| 1 | A | 3 | 7.3 | 5 | rt | 71 |
| 2 | A | 3 | 7.4 | 20 | rt | 74 |
| 3 | A | 3 | 7.0 | 30 | rt | 70 |
| 4 | A | 3 | 15.1 | 20 | rt | 39 |
| 5 | A | 1.5 | 8.3 | 20 | rt | 41 |
| 6 | B | 3 | 9.0 | 20 | rt | 100 |
| 7 | B | 3 | 18.6 | 20 | 60 | 42 |
| 8 | B | 10 | 17.2 | 20 | 60 | 91 |

[a] Substrate A: cyclohexanone, substrate B = 3-*n*-octylcyclobutanone. [b] Determined by GC using *n*-decane as internal standard.

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† **Safety warning**: The use of compressed gases and especially oxygen in the presence of organic substrates requires appropriate safety precautions and must be carried out using suitable equipment only.

DOI: 10.1039/b202727e

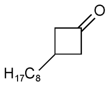
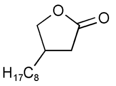
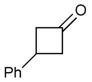
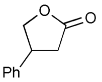
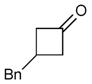
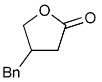
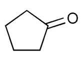
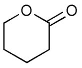
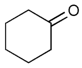
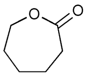
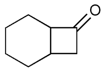
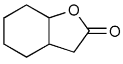
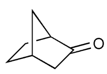
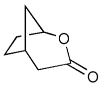
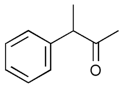
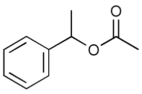
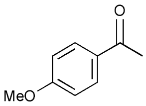
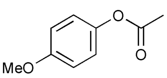
did not affect the oxidation significantly in the range of 5–30 bar (entries 1–3). The noticeable effect of temperature reflects partly an intrinsic response of the reaction rates and partly the phase behaviour of the reaction medium. The rate of the aldehyde auto-oxidation increases more strongly with increasing temperature as compared to the Baeyer–Villiger process. Consequently, a larger excess of aldehyde is required to achieve similar ketone conversion at higher temperatures (entry 7, 8). At the same time, the temperature increase results in transition from a biphasic (liquid and gaseous $CO_2$) to a monophasic (supercritical) reaction mixture as confirmed by visual inspection. The resulting dilution of substrates over the whole reactor volume makes the oxidation also less effective as demonstrated by dilution with liquid $CO_2$ at room temperature (entry 3, 4). Similar observations were made in Baeyer–Villiger reactions of 3-benzylcyclobutanone and bicycloctanone.

The Baeyer–Villiger oxidation of **A** was run in conventional organic solvents under conditions comparable to those of Table 1, entry 1 (3 equiv. of aldehyde, rt, atmospheric pressure of $O_2$, 24 h). In the absence of steel, a modest conversion of 23% was achieved in $CH_2Cl_2$ only. In the presence of steel shavings, conversion were 44% (toluene), 25% (ethyl acetate) and 27% ($CH_2Cl_2$). These data demonstrate that $CO_2$ is a "greener" replacement for $CH_2Cl_2$ providing significant advantages for the efficiency of the oxidation process.

An initial assessment of the scope of the reaction under a standard set of reaction conditions demonstrated that a wide range of ketones, both cyclic and acyclic can be oxidised efficiently (Table 2).

Various 3-substituted cyclobutanones are readily converted to their corresponding lactones (entries 1–3). Cyclopentanone and cyclohexanone react smoothly under these conditions giving δ- and ε-lactone, in 70% and 75% conversion, respectively (entries 4 and 5). Larger rings, such as cycloheptanone and cyclooctanone, did not undergo ring expansion.[5b] The bicyclic ketones, bicyclo[4.2.0]octan-7-one and bicyclo-[2.2.1]heptan-2-one, were transformed readily into hexahydrobenzofuran-2-one (entry 6) and 2-oxabicyclo[3.2.1]octan-3-one (entry 7), respectively, following the expected regioselectivity. The acyclic substrates 3-phenylbutan-2-one and *p*-methoxybenzophenone underwent oxidation too (entries 8 and 9), the higher conversion being obtained with the latter substrate. Also in these cases, the oxygen inserted exclusively into the C–C-bond between the carbonyl and the most substituted carbon atom.

**Table 2** Baeyer–Villiger oxidation in compressed $CO_2$[a]

| Entry | Substrate | Co-reductant | Product | Conv. (%)[b] |
|---|---|---|---|---|
| 1 |  | Pivalaldehyde |  | 100 |
| 2 |  | Benzaldehyde |  | 82 |
| 3 |  | Pivalaldehyde |  | 75 |
| 4 |  | Pivalaldehyde |  | 70 |
| 5 |  | Benzaldehyde |  | 75 |
| 6 |  | Benzaldehyde |  | 64 |
| 7 |  | Benzaldehyde |  | 92 |
| 8 |  | Pivalaldehyde |  | 48 |
| 9 |  | Benzaldehyde |  | 79 |

[a] For the reaction conditions see note‡. [b] Determined by GC using n-decane as internal standard.

In conclusion, we have demonstrated that Baeyer–Villiger reactions can be performed very efficiently in compressed $CO_2$ at room temperature using oxygen as primary oxidant and an aldehyde as co-reductant. No additional catalyst is required and good to excellent yields were achieved for a wide range of cyclic (up to C6) and acyclic ketones. These results emphasise the large potential of compressed $CO_2$ as a benign and safe ('green') reaction medium for oxidation processes in fine chemical synthesis.

## Notes and references

‡ The reactions were performed in a stainless steel high pressure reactor (25 mL) equipped with thick walled glass windows. In a typical experiment, the ketone (1 mmol), the aldehyde (3 mmol) and a weighed amount of $CO_2$ (9 g) were introduced into the reactor. The reactor was then charged with $O_2$ from a storage vessel, whereby the partial pressure was controlled by the use of calibration curves.[5] After 18 h, the autoclave was carefully vented through a cryo-trap (acetone–dry ice, −50 °C) to collect the product. The autoclave and the trap were washed with MTBE and the combined sample was directly submitted to GC and GC-MS analysis (*n*-decane was used as internal standard).

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