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Remarkable rate acceleration of the solvent-free Baeyer–Villiger reaction on the surface of $NaHCO_3$ crystals for sterically congested cyclic and acyclic ketones

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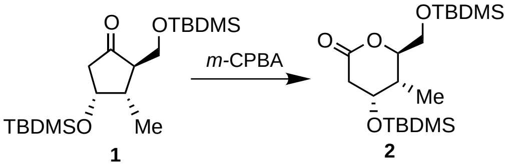
Abstract—Baeyer–Villiger reactions of sterically crowded cyclic and acyclic ketones are remarkably accelerated by carrying out the reactions under solvent-free conditions in the presence of powdered $NaHCO_3$. The corresponding lactones and esters have been obtained in excellent yields. © 2002 Elsevier Science Ltd. All rights reserved.

The Baeyer–Villiger reaction is an oxidative transformation of ketones into esters by peracid, which is important for functional group transformation as well as for ring expansion in organic synthesis.[1] Baeyer–Villiger reactions of cyclic ketones into lactones have been employed extensively for stereocontrolled syntheses of substituted heterocycles and functionalized carbon chains. Because the reaction is reliable for controlling the regio- and stereochemistries of the product, it is widely used as a key ring expansion step for the synthesis of natural products, including antibiotics, steroids, and pheromones.[1b,2,3] The rate of the Baeyer–Villiger reaction depends on the sizes of substituents adjacent to the carbonyl group. It has been reported that the oxidation reaction of the ketone having a bulky group adjacent to the carbonyl requires a long time.[4–6] In this letter, we describe a remarkable acceleration in the rate of the Baeyer–Villiger reaction for sterically congested ketones by the addition of powdered sodium bicarbonate under solvent-free conditions.



When we examined the Baeyer–Villiger reaction of highly substituted cyclopentanone (**1**)[7,8] with *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 at room temperature, the rate of the reaction was quite slow and eventually the corresponding δ-lactone (**2**)[8] was obtained regio- and stereoselectively in 75% yield after 1 week. Several other conditions have been investigated and the results are shown in Table 1. The addition of $NaHCO_3$[9] was not effective for accelerating the rate of the reaction of **1** with *m*-CPBA in CH_2Cl_2 (entry 2). This poor reactivity of **1** may be explained in terms of the steric hindrance to the carbonyl face. Bulky 2-TBDMSoxymethyl and 4-TBDMSoxy groups cover both the faces of the carbonyl group, thus preventing nucleophilic attack of *m*-CPBA. Refluxing the mixture for 4 days resulted in decomposition of **1** mainly (entry 3). A solid state reaction of crystalline **1** with *m*-CPBA developed by Toda and co-workers[10,11] shortened the reaction time to 4 days and afforded **2** in 67% yield along with a 31% recovery of **1** (entry 4). A mixture of **1**, 2 equiv. of *m*-CPBA, and 1 equiv. of $NaHCO_3$ was well ground and allowed to stand at room temperature for 4 days, giving 74% of **2** and 24% of **1** (entry 5). We found that further acceleration of the reaction was achieved by the following technical improvement. Thus, finely powdered $NaHCO_3$ was suspended in a CH_2Cl_2 solution of **1** and *m*-CPBA and then the whole mixture was concentrated. The residue was allowed to stand at room temperature for 3 days to give **2** in 95% yield (entry 7). A similar reaction in the absence of $NaHCO_3$ gave **2** in 78% yield after 4 days (entry 6). These results suggest that spreading the substrate ketone and oxidant uniformly on the surface of $NaHCO_3$ is important for acceleration of the reaction. We carefully examined the

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Keywords: Baeyer–Villiger reactions; stereospecific reactions; lactones; esters; solvent-free reaction.

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Table 1. Baeyer–Villiger reactions of **1**

Entry	*m*-CPBA (equiv.)	$NaHCO_3$ (equiv.)	Solvent	Temperature	Time	Yield of **2** (%)	Recovery of **1** (%)
1	3	None	CH_2Cl_2	Rt	7 days	75	6
2	3	3	CH_2Cl_2	Rt	7 days	74	24
3	3	3	CH_2Cl_2	Reflux	4 days	26	16
4[a]	2	None	None	Rt	4 days	67	31
5[a]	2	1	None	Rt	4 days	74	24
6[b]	2	None	None	Rt	4 days	78	15
7[b]	2	1	None	Rt	3 days	95	0
8[c]	2	1	None	Rt	10 h	96	0

[a] The reaction mixture was ground with an agate pestle and mortar once a day.[10]

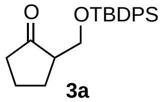
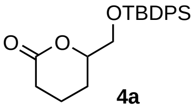
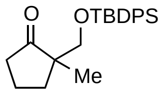
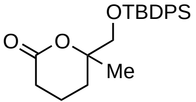
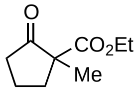
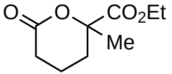
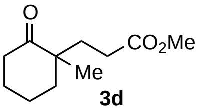
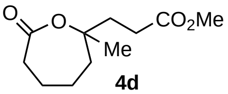
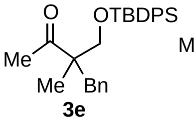
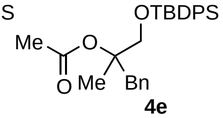
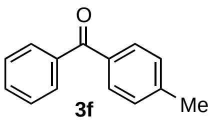
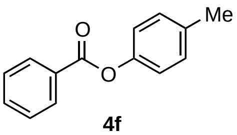
[b] To a solution of ketone and *m*-CPBA in CH_2Cl_2 was added $NaHCO_3$ and then the solvent was evaporated off.

[c] Ref. 12.

reaction and found that the rate of the reaction gradually decreases over 3 h. Interestingly, dissolving the solid reactant in CH_2Cl_2 and immediate evaporation of the solvent restarted the reaction, but the reaction nearly stopped again after 3 h. Repetition of this process twice every 3 h (ca. 10 h) eventually gave **2** in 96% yield (entry 8).[12]

In a solid state Baeyer–Villiger reaction, grinding the substrate with the explosive *m*-CPBA could be danger-

Table 2. $NaHCO_3$-promoted solvent-free Baeyer–Villiger reactions of ketones

Entry	Ketone	Product	Solvent-free in the presence of $NaHCO_3$[a]		in CH_2Cl_2	
			Time	Yield (%)	Time	Yield (%)[b]
1	 **3a**	 **4a**	10 min	quant	10 min	28 [c,d] (72)
2	 **3b**	 **4b**	4 h	93	4 h	13 [c] (85)
3	 **3c**	 **4c**	3 h	96	5 d [c,e]	59 [c,e]
4	 **3d**	 **4d**	1 h	83	6 h [f]	65 [f]
5	 **3e**	 **4e**	24 h	99	——	——
6	 **3f**	 **4f**	11 h	96	24 h [g]	12 [g]

[a] According to the typical procedure in Ref. 12.

[b] Yields in parentheses indicate the recovery of ketones.

[c] The reaction was performed in the presence of $NaHCO_3$ at room temperature.

[d] Ref. 13.

[e] Ref. 5a.

[f] The reaction was carried out in the presence of Li_2CO_3 at reflux.[6]

[g] $CHCl_3$ was used as a solvent.[10]

ous. Such a process, however, is not required in our method. Although we have not experienced any accidents, we recommend that for safety a small volume of solvent should be left during the evaporation process and then the remaining mixture is allowed to solidify by spontaneous evaporation of the solvent in a flask or on a large plate.

This method is quite general and effective for Baeyer–Villiger reactions of hindered ketones. Some additional examples under these new conditions as well as the reactions carried out in CH_2Cl_2 are shown in Table 2.[8] The crystalline α-substituted cyclopentanone (**3a**) reacted with *m*-CPBA in the presence of $NaHCO_3$ under the new solvent-free conditions for only 10 min to give **4a** in quantitative yield, whereas a similar reaction of **3a** in CH_2Cl_2 for 10 min gave 28% of **4a** along with 72% of unreacted **3a** (entry 1).[13] A similar reaction of the α,α-disubstituted cyclopentanone (**3b**) was completed within 4 h by the new procedure and afforded **4b** in 93% yield, while the oxidation of **3b** in CH_2Cl_2 for the same reaction time was not completed and gave only 13% of **4b** and 85% of unreacted **3b** (entry 2). The oily cyclopentanone (**3c**) having an electron-withdrawing ester group at the α-position, for which the Baeyer–Villiger reaction in CH_2Cl_2 in the presence of $NaHCO_3$ required 5 days,[5a] was also oxidized under the new conditions within 3 h to produce lactone (**4c**) in 96%. The Baeyer–Villiger reaction of cyclohexanone (**3d**), which is a key step of the efficient synthesis of 4,4-disubstituted γ-butyrolactones,[6] was accelerated by using our new procedure (entry 4). An acyclic ketone (**3e**) having quaternary carbon at the α-position was allowed to react under the new conditions for 24 h to give 99% of the corresponding ester (**4e**) exclusively (entry 5). A similar acceleration was observed in the case of the reaction of the aromatic ketone (**3f**) (entry 6).

In conclusion, an inorganic base, $NaHCO_3$, accelerated the solvent-free Baeyer–Villiger reaction of ketones with bulky substituents to give the corresponding esters and lactones in excellent yields. Repetition of a dissolution and evaporation technique every 3 h is extremely effective for shortening the reaction time.

Acknowledgements

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7. Compound **1** was easily prepared from (2*S*,3*S*,4*R*)-4-*tert*-butyldimethylsilyloxy-2-methoxycarbonyl-3-methyl-2-cyclopentanone[14] in 95% yield in three steps: (i) reduction with lithium aluminum hydride; (ii) monosilylation with TBDMSCl and imidazole; (iii) oxidation with tetrapropylammonium perruthenate.
8. All new compounds reported herein exhibited satisfactory spectral data.
9. Sodium bicarbonate is known to promote the Baeyer–Villiger reaction, see: Whitesell, J. K.; Matthews, R. S.; Helbling, A. M. *J. Org. Chem.* **1978**, *43*, 784–786.
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11. For a review of solvent-free reactions, see: Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025–1074.
12. Typical procedure is as follows: to a solution of ketone (1 mmol) and *m*-CPBA (2 mmol) in CH_2Cl_2 (3–5 ml) was added finely ground $NaHCO_3$ (1–2 mmol) and then the suspension was concentrated to be a solid residue. When the reaction was not completed after 3 h, a small volume of CH_2Cl_2 was added to the mixture and the whole mixture was concentrated to a solid. This process (a dissolution and evaporation) was repeated every 3 h.
13. Taylor et al. reported that the similar reaction in CH_2Cl_2 in the presence of $NaHCO_3$ at rt for 3.75 h gave the lactone in 100% yield, see: Taylor, R. J. K.; Wiggins, K.; Robinson, D. H. *Synthesis* **1990**, 589–590.
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