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# COPPER TRIFLATE CATALYZED BAEYER- VILLIGER OXIDATION OF KETONES

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**Abstract.** A simple, efficient and eco-friendly method for Baeyer-Villiger oxidation reaction has been developed. The reaction employed *m*-CPBA as the oxidant with $Cu(OTf)_2$ catalyst in $CH_2Cl_2$ at room temperature. Lactones or ester were synthesized in good to excellent yield (85-94 %). The catalyst could be reused twice without considerable loss in activity.

*Keywords:* oxidation, ketone, lactone, ester, catalyst.

*Classification numbers:* 1.1.2, 1.1.3

## 1. INTRODUCTION

Lactones and esters are important classes of substances that have been used extensively as synthetic intermediates in the preparation of a variety of fine or special chemicals such as drugs, steroids, pheromones, etc. [1, 2]. Up to now, many reports in literature have been found in synthesis of these types of compounds, and a well-known method for such a synthesis constitutes the Baeyer-Villiger oxidation of ketones [3, 4]. The reaction was first published by Adolf Baeyer and Victor Villiger in 1899 [5]. The use of Baeyer–Villiger oxidation in several stereoselective organic syntheses is known [6, 7].

Various oxidants such as m-chloroperbenzoic acid, trifluoroperacetic acid, peroxybenzoic acid and hydrogen peroxide, oxone etc. have been used for the Baeyer-Villiger oxidation [6]. Strong acids such as perchloric acid, sulfuric acid and toluenesulfonic acid were used to be employed as catalysts for the oxidation. Recently, several transition metal-based oxidation procedures [8-10] and metal-free organocatalytic methods [11] have been investigated, aimed at achieving the Baeyer- Villiger oxidation in higher yield and in an asymmetric manner. Many Lewis acids were also utilized as catalysts for the oxidation, such as $Sc(OTf)_3$ [12], hydrated silica-supported potassium peroxomonosulfate [13], titanium silicate [14]. Enzymatic Baeyer-Villiger oxidation has been an efficient strategy for more than ten years; most of the results from application of enzyne to the reaction have been summarized in recent reviews [15, 16]. In this study, the $Cu(OTf)_2$ has been used as the catalyst for the Baeyer-Villiger reaction for the first time with *m*-CPBA oxidant. Furthermore, the obtained lactones or esters have been synthesized in good to excellent yields and the catalyst was recovered and reused two times without considerable loss in activity.

## 2. MATERIALS AND METHODS

### 2.1. Experiment

All chemicals and dichloromethane for reaction solvent were purchased from Sigma-Aldrich company and used without further purification. All reactions were monitored by thin-layer chromatography (TLC) using silica gel (Merck, 60–120 mesh). Column chromatography was performed using Meck silica gel (40-63 μm) packed by the slurry method, under a positive pressure of air. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian Inova NMR Spectrometer ($^{1}H$ NMR running at 400 MHz or 500 MHz and $^{13}C$ NMR running at 100 MHz or 125 MHz) instrument. $CDCl_3$ was used as the NMR solvent. All products were characterized by comparison of their $^{1}H$ NMR and $^{13}C$ NMR spectra with those of in literature. Coupling constants (*J*) are reported in Hz, with signal multiplicities designated at singlet (s), doublet (d), doublet of doublet (dd), doublet of doublet of doublet (ddd), triplet (t), quartet (q), doublet of triplets (dt), multiplet (m), broad singlet (bs), doublet of quartets (dq).

### 2.2. General procedure for Baeyer- Villiger oxidation

The reactions were performed with ketones (2 mmol) and *m*-chlorobenzoperoxoic acid (*m*-CPBA) (4 mmol) in $CH_2Cl_2$ (10 mL). The mixtures were stirred at room temperature for 18 h. The course of the reaction was carefully followed by TLC. The reaction mixtures then were diluted with $CH_2Cl_2$ (30 ml) and filtered. The filtrates were washed with saturated $NaHCO_3$ solution (2 x 30 ml), brine (2 x 20 ml) and dried over $MgSO_4$ and filtered. The organic layers were concentrated in *vacuo* and the crude products were purified by column chromatography on silica gel to afford the corresponding products. The $Cu(OTf)_2$ residue (filtrate cake) was washed with $CH_2Cl_2$ (30 ml) and dried under reduced pressure at 150 °C for 2 h to a white solid, which could be reused almost without loss in activity.

### 2.3. NMR data for products

**Phenyl benzoate** (Table 2, entry 1). 337 mg, 85 % yield, colourless liquid

$^{1}H$ NMR (400 MHz, $CDCl_3$) δ 8.26-8.21 (m, 2H), 7.86 – 7.80 (m, 1H), 7.67 – 7.56 (m, 2H), 7.55 – 7.41 (m, 3H), 7.32-7.22 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 165.2, 151, 133.6, 130.2, 130.1, 129.5, 128.6, 125.9, 121.8. NMR spectroscopic data matched with the published data [17].

**5-Phenyloxepan-2-one** (Table 2, entry 2). 346 mg, 91 % yield, white solid

$^{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 2H), 7.26–7.21 (m, 1H), 7.21–7.16 (m, 2H), 4.40 (ddd, *J* = 13.0, 5.3, 2.3 Hz, 1H), 4.32 (ddd, *J* = 13.0, 10.2, 1.2 Hz, 1H), 2.90–2.71 (m, 3H), 2.20–1.98 (m, 3H), 1.91– 1.80 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 176.0, 145.1, 128.9, 127.0, 126.7, 68.4, 47.4, 36.9, 33.8, 30.5. NMR spectroscopic data matched with the published data [12].

**5-methyloxepan-2-one** (Table 2, entry 3). 230 mg, 90% yield, colourless oil

$^{1}H$ NMR (400 MHz, $CDCl_3$) δ 4.28 (ddd, *J* = 12.8, 5.6, 2.0 Hz, 1H), 4.17 (dd, *J* = 12.8, 10.4 Hz, 1H), 2.71–2.56 (m, 2H), 1.98–1.83 (m, 2H), 1.82–1.71 (m, 1H), 1.50 (dtd, *J* = 15.2, 10.8, 2.0 Hz, 1H), 1.33 (dtd, *J* = 14.0, 11.6, 2.4 Hz, 1H), 0.99 (d, *J* = 6.8 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 176.3, 68.3, 37.4, 35.4, 33.4, 30.9, 22.3. NMR spectroscopic data matched with the published data [12].

**Dihydrofuran-2(3H)-one** (Table 2, entry 4). 158 mg, 92 % yield, colourless oil

$^1$H NMR (400 MHz, $CDCl_3$)δ 4.33 (t, *J* = 7.2 Hz, 2H), 2.57–2.44 (m, 2H), 2.35–2.18 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.8, 68.6, 27.9, 22.3. NMR spectroscopic data matched with the published data [12].

**(1R,5S)-2-oxabicyclo[3.2.1]octan-3-one** (Table 2, entry 5). 237 mg, 94 % yield, colourless oil.

$^1$H NMR (500 MHz, $CDCl_3$) δ 4.84 (s, 1H), 2.70 (ddd, *J* = 18.5, 5.0, 2.0 Hz, 1H), 2.54 (d, *J* = 4.5 Hz, 1H), 2.46 (dd, *J* = 18.5, 1.5 Hz, 1H), 2.14 (td, *J* = 9.5, 2.5 Hz, 1H), 1.98 (d, *J* = 13.0 Hz, 2H), 1.94 – 1.89 (m, 3H), 1.73 – 1.62 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.9, 81.1, 40.8, 35.9, 32.6, 32.0, 29.4. NMR spectroscopic data matched with the published data [18].

**Tetrahydro-2H-pyran-2-one** (Table 2, entry 6). 178 mg, 89%, colourless oil

$^1$H NMR (400 MHz, $CDCl_3$) δ 4.38–4.29 (m, 2H), 2.54 (t, *J* = 7.2 Hz, 2H), 1.97–1.78 (m, 4H); 13C NMR (100 MHz, $CDCl_3$) δ 171.5, 69.5, 29.9, 22.4, 19.2. NMR spectroscopic data matched with the published data [19].

**Oxepan-2-one** (Table 2, entry 7). 189 mg, 91% yield, colourless oil

$^1$HNMR (400 MHz, $CDCl_3$) δ 4.28–4.17 (m, 2H), 2.71–2.57 (m, 2H), 1.90–1.80 (m, 2H), 1.81–1.69 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 176.3, 69.4, 34.7, 29.4, 29.1, 23.1 NMR spectroscopic data matched with the published data [18].

**7-Methyloxepan-2-one** (Table 2, entry 8). 238 mg, 93% yield, colourless oil

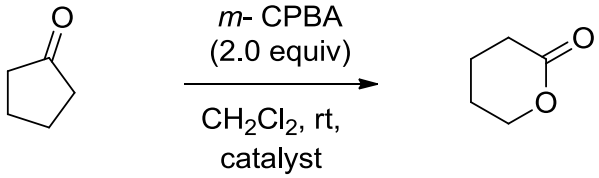
$^1$HNMR (400 MHz, $CDCl_3$) δ 4.43 (dq, *J* = 8.4, 6.4 Hz, 1H), 2.72–2.52 (m, 2H), 1.99–1.83 (m, 3H), 1.72–1.51 (m, 3H), 1.34 (d, *J* = 6.4 Hz), ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 175.7, 76.9, 36.4, 35.1, 28.4,23.0, 22.7. NMR spectroscopic data matched with the published data [18].

**5-(tert-butyl)oxepan-2-one** (Table 2, entry 9). 286 mg, 94 % yield, white solid

$^1$H NMR (400 MHz, $CDCl_3$) δ 4.32 (ddd, J = 12.8, 6.0, 2.0 Hz, 1H), 4.14 (dd, J = 12.8, 10.4 Hz, 1H), 2.69 (ddd, J = 14.4, 7.6, 1.6 Hz, 1H), 2.61–2.51 (m, 1H), 2.13–1.95 (m, 2H), 1.58–1.44 (m, 1H), 1.38–1.28 (m, 2H), 0.88 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 176.5, 68.8, 50.9, 33.6, 33.1, 30.5, 27.6, 23.9. NMR spectroscopic data matched with the published data [12].

## 3. RESULTS AND DISCUSSION

Our initial study was to find the optimal conditions for the Baeyer- Villiger oxidation. Cyclopentanone (2 mmol) was treated with *m*-CPBA (4 mmol) in $CH_2Cl_2$ (10 ml) at room temperature in stated time with different catalysts. The results were summarized at Table 1.



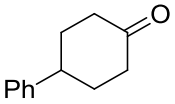
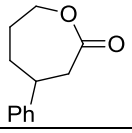
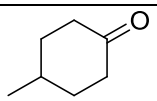
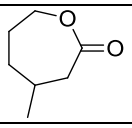
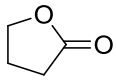
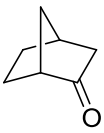
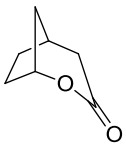
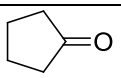
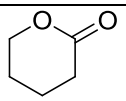
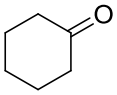
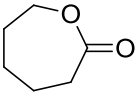
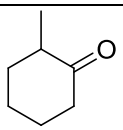
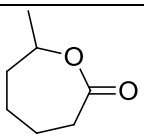
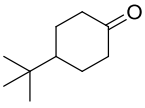
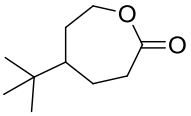

*Scheme 1*. Baeyer- Villiger oxidation of cyclopentanone under different conditions.

*Table 1.* Bayer- Villiger oxidation of cyclopentanone with different catalysts.

| Entry | Catalyst | Amount | Time | Yield (%) |
|---|---|---|---|---|
| 1 | $H_2SO_4$ conc | 0.5 equiv | 36 h | 86 |
| 2 | $HClO_4$ conc | 0.5 equiv | 36 h | 88 |
| 3 | $Sc(OTf)_3$ | 0.05 equiv | 36 h | 87 |
| 4 | $Sc(OTf)_3$ | 0.05 equiv | 24 h | 82 |
| 5 | $Cu(OTf)_2$ | 0.05 equiv | 18 h | 90 |
| 6 | $Cu(OTf)_2$ | 0.02 equiv | 18 h | 89, 88, 87* |

Conc: concentrated; h: hour; equiv: equivelent; * yield obtained for the first, second and third time, respectively.

*Table 2.* Bayer- Villiger oxidation of ketones using $Cu(OTf)_2$ as the catalyst.

| Entry | Ketone | Product | Yield (%) |
|---|---|---|---|
| 1 | PhCOPh | PhCOOPh | 85 |
| 2 |  |  | 91 |
| 3 |  |  | 90 |
| 4 |  |  | 92 |
| 5 |  |  | 94 |
| 6 |  |  | 89 |
| 7 |  |  | 91 |
| 8 |  |  | 93 |
| 9 |  |  | 94 |

Under $H_2SO_4$ and $HClO_4$ catalysts, good yields were observed but long reaction time was required (36 h; Table 1; entry 1, 2). With 5 % mol of $Sc(OTf)_3$ catalyst, 87 % of the lactone was isolated in 36 h (Table 1, entry 3). Reaction yield was inignificantly reduced when reaction duration was 24 h (82 %, Table 1, entry 4). A big improvement was observed when $Cu(OTf)_2$,a less expensive catalyst, was used. The lactone product was isolated in 90 % yield after 18 hours (Table 1, entry 5). Concerning about the environment, we then reduced the amount of $Cu(OTf)_2$ catalyst to 2 % mol and surprisingly, this led to very slight decraese in reaction yield (89 %, entry 6). In addition, $Cu(OTf)_2$ catalyst was recovered and reused for the second and third time with reaction yield of 88 and 87 %, respectively (Table 1, entry 6).

We then examined the optimal reaction conditions ($Cu(OTf)_2$ 2 % mol; time: 18 h; solvent: $CH_2Cl_2$; room temperature) for Baeyer- Villiger oxidation using *m*-CPBA as the oxidant for other ketones. The results were summarized in the table 2. With cyclic ketones, the corresponding lactones were formed in excellent yields (89-94 %, Table 2, entry 2-9), while lower yield (85 %) was observed with an acyclic ketone (Table 2, entry 1). With unsymmetrical ketones (Table 2, entry 5, 8), the observed products followed the migratory ability of substituents in Beayer- Villiger oxidation (tertiary > secondary > aryl > primary).

## 4. CONCLUSIONS

A new, efficient method for Baeyer- Villiger oxidation reaction of ketones by *m*- CPBA using $Cu(OTf)_2$ as the catalyst has been investigated. The reaction was carried out in $CH_2Cl_2$ solvent at room temperature. High yields of products and recycability of catalyst are the advantages of the synthesis. Although the mechanism of this transformation is thought to operate in agreement with other classical Baeyer-Villiger-type reactions effected by *m*- CPBA, it is being investigated in our laboratory and will be reported in due course.

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