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Purified mCPBA, a useful reagent for the oxidation of aldehydes

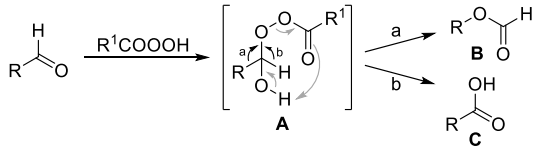
Alexander Horn and Uli Kazmaier*[a]

Keywords: Bayer Villiger oxidation / Enolformates / Epoxides / α-Hydroxyketones / Peracids

Purified mCPBA is an useful reagent for the oxidation of several classes of aldehyde. While linear unbranched aliphatic aldehydes are oxidized to the corresponding carboxylic acids, α-branched ones undergo BV oxidation to formates. α-Branched α,β-unsaturated aldehydes provide enolformates and/or the epoxides thereof, which can be saponified to α-hydroxy ketones with an shortening of the carbon chain by 1 carbon. Unbranched α,β-unsaturated aldehydes undergo an interesting BV oxidation / epoxidation / formate migration / BV oxidation cascade, resulting in formyl-protected hydrates with an overall loss of two carbon atoms.

Introduction

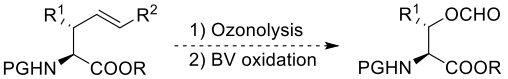
The Baeyer-Villiger (BV) oxidation, already discovered in 1899,[1] became one of the fundamental oxidation processes in organic synthesis. While in their original work Baeyer and Villiger used Caro's acid (H_2SO_5) to oxidize menthone towards the corresponding lactone, a wide range of peracids are generally used nowadays, while the oxidation power of the peracids correlates with the acidity of the corresponding carboxylic acid.[2] Weaker oxidation reagents such as H_2O_2 do not undergo BV oxidation but require „activation", either by transition metal complexes,[2] or nitriles, which generate imido peracids *in situ*.[3] Especially the oxidation of ketones became a standard protocol in organic synthesis and finds also widespread application in industry.[4] In contrast, reports of successful BV oxidations of aldehydes are extremely rare.[4] While some electron rich aromatic aldehydes can be oxidized already with H_2O_2 in the presence of SeO_2,[6] a process which is known as Dakin oxidation,[7] aliphatic aldehydes behave different. In general, not the desired formates **B** are formed, but carboxylic acids **C** as oxidation products. This might be caused by direct oxidation of aliphatic aldehyde, and/or by a faster migration of the hydrogen atom (b) [compared to the alkyl substituent (a)] in the primarily formed Criegee intermediate **A** (Scheme 1).



Scheme 1. Baeyer-Villiger oxidation of aliphatic aldehydes

Therefore, one might expect that increasing the electron density in the alkyl substituent might accelerate the alkyl group migration, what is in agreement with an observation made by the Knochel group, that α-quaternary aldehydes undergo BV-oxidation towards the *tert*.-alcohol derivatives.[8] Other, less α-substituted aldehydes have not been applied in this study. In 2012, Ochiai and Nakanishi described for the first time a BV oxidation of unbranched aliphatic aldehydes using hypervalent λ^3-bromanes.[9] These reagents have to be prepared from explosive BrF_3,[10] which is highly sensitive towards water and most organic compounds, what is a severe limitation of this protocol.

We became interested into BV oxidations of aldehydes during our efforts in stereoselective syntheses of β-hydroxyamino acids. Such amino acids can be obtained e.g. *via* aldol reaction of chelated enolates.[11] Although good diastereoselectivities can be obtained, the control of the absolute configuration is not a trivial issue. Therefore, we were interested to obtain the same type of amino acids from γ,δ-unsaturated amino acids, which can easily be obtained either *via* Claisen rearrangement or *via* Pd-catalyzed allylic alkylation in a highly enantio- and diastereoselective fashion.[12] While the Claisen rearrangement gives rise to *syn*-products,[13] the opposite *anti*-diastereomers can be obtained *via* allylic alkylation.[14] The absolute configuration can be controlled either by using chiral allyl alcohol derivatives[15] or chiral ligands.[16] Therefore, an oxidative degradation of the unsaturated side chain might be an attractive protocol (Scheme 2).



PG: Protecting group

Scheme 2. Planned synthesis of β-hydroxylated amino acid derivatives

Results and Discussion

We began our investigations with the oxidation of phenylpropionaldehydes.[17] With 3-phenylpropionaldehyde **1a** first the BV oxidation was investigated with the mild imidoperacids using a variety of nitriles. Best results were obtained with trichloroacetonitrile, which gave high conversion rates in a range of unpolar

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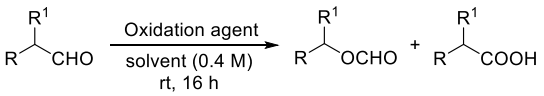
solvents such as CH_2Cl_2, $CHCl_3$, toluene, ether or ethyl acetate (Table 1, entry 1), but did not provide the desired BV product **2a**, but the carboxylic acid **3a**. Polar and protic solvents (THF, DMF, alcohols, H_2O and mixtures thereof) showed only moderate conversion. Interestingly, fluorinated alcohols gave good conversion, and for the first time some significant amounts of the desired BV product **2a** (entries 2 and 3), but still not in a preparatively useful amount. Therefore, we decided to investigate also the commonly used peracids. With commercial m-chloroperbenzoic acid (mCPBA) a clean reaction was observed providing the carboxylic acid **3a** as the sole product (entry 4). Oxidation of the secondary aldehyde **1b** gave a comparable result although the conversion was lower in this case (entry 5).[18] Also here, the desired formate **2b** was formed only in tiny amounts. This situation did not change by using the imido peracids. As a last attempt, we decided to purify the commercial mCPBA according to a protocol described by Aggarwal *et al*.[19] The mCPBA was washed with phosphate buffer and was dried over $MgSO_4$. With this purified peracid, the situation changed dramatically. While the conversion was the same as in the previous reaction, the product ratio changed completely (entry 6). Under these conditions, the desired formate **2b** was the sole product. Interestingly, applying the purified peracid to the linear aldehyde **1a** showed no influence, neither on the conversion rate nor product ratio (entries 4 and 7). Now the question arose, if the strong effect observed for **1b** results from the α-branching, or if a (α-substituted) benzyl group migrates more easily. Therefore, we investigated also the oxidation of α-unbranched phenylacetaldehyde **1c** (entry 8). Already after 1 h, complete conversion was observed and the formate could be isolated in 59% yield. In addition, phenylacetic acid **3c** was obtained in 25% as by-product. According to these results, the migration tendency of the substituents can be arranged: *sec*.-benzyl > benzyl > H > alkyl.

Table 1. BV-oxidation of aliphatic aldehydes **1**



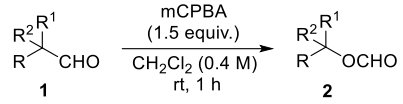
1a R = Bn, R^1 = H **2** **3**
1b R = Ph, R^1 = Me
1c R = Ph, R^1 = H

Entry	Aldehyde	Ox.-agent (equiv.)	Solvent	Conversion [%]	Ratio **2**:**3**
1	**1a**	H_2O_2·urea (1.5) Cl_3CCN (2.5) $KHCO_3$ (0.5)	Et_2O	88	1:99
2	**1a**	ibid.	TFE[a]	75	14:86
3	**1a**	ibid.	HFIP[a]	75	20:80
4	**1a**	mCPBA (1.5)[b]	CH_2Cl_2	100	1:99
5	**1b**	ibid.	CH_2Cl_2	65	5:95
6	**1b**	mCPBA (1.5)[c]	CH_2Cl_2	65 (51)[d]	99:1
7	**1a**	ibid.	CH_2Cl_2	100	1:99
8	**1c**	ibid.	CH_2Cl_2[e]	100 (59)[d]	70:30

[a] TFE: trifluoroethanol; HFIP: hexafluoroisopropanol. [b] commercial mCPBA (<77%). [c] Purified mCPBA (>90%). [d] Isolated yield. [e] Reaction time: 1 h

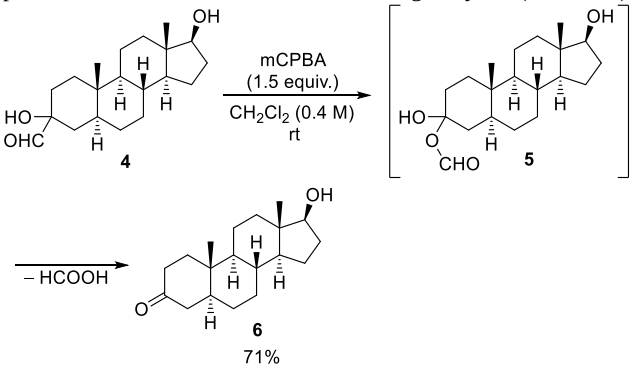
With our primary goal in mind, the stereoselective synthesis of β-hydroxy amino acids, the results of the linear aldehydes are irrelevant and we therefore focused on α-branched aldehydes (Table 2). In all cases, already after 1 h at room temperature, a complete conversion was observed and the desired formates were formed almost exclusively. Because of the volatility of the methylated derivatives (bp: 68−83°C) the formates **2d** and **2e** could not be isolated in significant amounts. But in the case of the larger derivatives **2f** and **2g** the products could be obtained in high yields.

Table 2. BV-oxidation of α,β-unsaturated aldehyde **7**



Entry	Aldehyde	R	R^1	R^2	Formate	Conv. [%]	Yield [%]
1	**1d**	Me	Me	Me	**2d**	100	
2	**1e**	Me	Me	H	**2e**	100	
3	**1f**	Et	Et	H	**2f**	100	99
4	**1g**	Bu	Et	H	**2g**	100	85

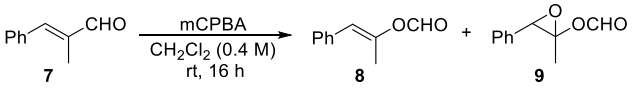
To illustrate, that this approach is not limited to simple aldehydes but can also be applied to complex structures, we investigated the oxidation of steroidal aldehyde **4**. Its BV oxidation should result in the formation of a monoformylated hydrate **5**, which eliminates formic acid to give ketone **6**. And indeed, under our optimized conditions **6** could be isolated in good yield (Scheme 3).



Scheme 3. BV oxidation of steroidal aldehyde **4**

Next, we focused on α,β-unsaturated aldehydes such as **7** (Table 3).[20] The electron-poor double bond should not be effected by the mCPBA, and with this α-branched aldehyde, we expected **8** to be the preferred product. Under our standard reaction conditions using 1.5-equiv. mCPBA **8** was indeed formed, but as a 1:1 mixture with epoxide **9** (enrty 1). Since full conversion was observed, the excess of mCPBA underwent a Prileschajew epoxidation of the now electron-rich double bond. Reducing the excess of mCPBA resulted in a lower conversion rate (enrty 2,3), because the epoxidation competes with the BV oxidation, the first step of the sequence. With an excess, the reaction could be shifted completely to the side of epoxide **9**, which could be isolated in excellent yield (entry 4).

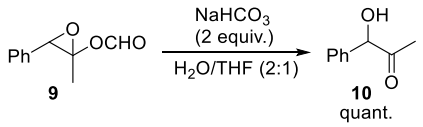
Table 3. BV-oxidation of α,β-unsaturated aldehyde **7**



Entry	Equiv. mCPBA	Conversion [%]	Ratio **8**:**9**
1	1.5	100	51:49
2	1.0	85	84:16
3	1.2	96 (67)[a]	74:26
4	2.5	100 (85)[b]	2:98

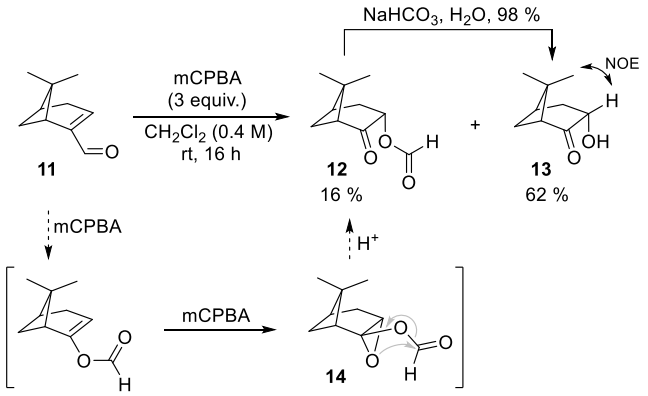
[a] Yield determined by NMR [b] Isolated yield

Saponification of **9** provided α-hydroxyketone **10** in almost quantitative yield. Therefore, the sequence BV oxidation / epoxidation / saponification is a straightforward protocol for the conversion of α-substituted α,β-unsaturated aldehydes into α-hydroxyketones (Scheme 4).



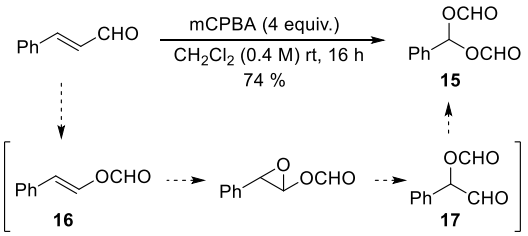
Scheme 4. Hydrolysis of epoxyformate **9**

That this protocol is not limited to cinnamaldehydes but can also be applied to other systems is illustrated with the conversion of myrtenal **11** (Scheme 5). With an excess of mCPBA the α-hydroxyketone **13** was formed directly as the major product, accompanied by a small amount of formate **12**. Its saponification provided **13** almost quantitatively, so that the hydroxy ketone was isolated in 77% overall yield. One might assume that the epoxyformate intermediate **14** formed primarily undergoes ring opening catalyzed by the acid, resulting in a formate shift onto the secondary alcohol. The configuration of its stereogenic center was confirmed by nmr showing a NOE between one of the geminal methyl groups and the α-proton of the alcohol.



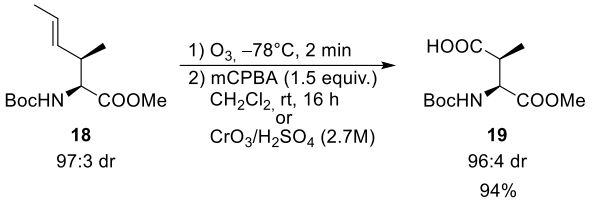
Scheme 5. Oxidation of myrtenal **11**

To figure out, if an α-substituent on the double bond is required or not, we subjected also unsubstituted cinnamaldehyde to the optimized conditions. In this case, diformate **15** was obtained in good yield and as sole product, probably formed in the reaction cascade shown in scheme 6. The reaction might start with a classical BV oxidation to provide the corresponding vinylformate **16** which undergoes epoxidation / formyl shift. In this case formylated α-hydroxyaldehyde **17** is formed which undergoes a second BV oxidation, comparable to steroid **4**, providing a yield of 74% for the whole cascade.



Scheme 6. Oxidation of cinnamaldehyde

Finally, coming back to our earlier intension, we tried to apply the BV oxidation also to our γ,δ-unsaturated amino acids. Several β-substituted and different *N*- and *C*-protected amino acids such as **18** have been subjected to ozonolysis and subsequent BV oxidation, using several conditions. While ozonolysis was not a problem, giving yields for the corresponding aldehydes in the range of 80−92%, the BV oxidation towards β-formylated amino acids failed in all cases. Only β-substituted aspartates (**19**) could be observed. The same products and yields were also obtained in oxidations using Jones reagent.



Scheme 7. Oxidative degradation of γ,δ-unsaturated amino acids

Conclusions

In conclusion, we could show that oxidation of aldehydes with purified mCPBA is an interesting entry to several classes of compounds depending on the aldehyde used. While linear unbranched aliphatic aldehydes are oxidized to the corresponding carboxylic acids, α-branched ones undergo BV oxidation to formates. α-Branched α,β-unsaturated aldehydes provide enolformates and/or the epoxides thereof, which can be saponified to α-hydroxy ketones with an shortening of the carbon chain by 1 carbon. Unbranched α,β-unsaturated aldehydes undergo an interesting BV oxidation / epoxidation / formate migration / BV oxidation cascade, resulting in formyl-protected hydrates with an overall loss of two carbon atoms. β-Formylated amino acid does not undergo BV-oxidation but oxidation to the corresponding substituted aspartates. Further attempts towards BV oxidations of amino acids are currently under investigation.

Experimental Section

General remarks: All air- or moisture-sensitive reactions were carried out in dried glassware (>100 °C) under an atmosphere of nitrogen. Dried solvents were distilled before use: Dichloromethane was purchased from Sigma-Aldrich. The products were purified by flash chromatography on silica gel (0.063−0.2 mm). Mixtures of EtOAc and petroleum ether were generally used as eluents. Analytical TLC was performed on pre-coated silica gel plates (Macherey-Nagel, Polygram® SIL G/UV254). Visualization was accomplished with UV-light, Ceric Ammonium Sulfate solution, $KMnO_4$ solution or ninhydrin solution. Melting points were determined with a MEL-TEMP II (Laboratory Devices) melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-400 [400 MHz (^1H) and 100 MHz (^{13}C)]. Chemical shifts are reported in ppm relative to TMS or internal solvent. Mass spectra were recorded with a Finnigan MAT 95 spectrometer (quadrupole) using the CI technique.

Purification of mCPBA[19]

Preparation of the buffer solution (pH 7.5): In a 1 L volumetric flask 0.1 N NaOH (410 mL) and 0.2 M KH_2PO_4 (250 mL) were mixed. The flask was filled up to 1 L with distilled water, the solution was stirred vigorously for 2 minutes, while the pH was controlled via pH meter.

Purification of mCPBA: Commercial mCPBA (30.0 g, 70−75 %) was dissolved in Et_2O (200 mL) and washed thrice with buffer solution (pH 7.5) (150 mL). The organic layer was dried ($MgSO_4$) and carefully evaporated to afford mCPBA (18.3 g, 91−99 % purity) as dry, white solid. The peracid was transferred to a plastic container and stored at +4 °C for up to 6 months without decomposition. The purity was determined by NMR spectroscopy.

Caution! It has been determined that 95−100% mCPBA can be detonated by shock or sparks, while the commercial 70−85% mCPBA is not shock-sensitive. It should be stored in a refrigerator in tightly closed containers.

General procedure A: Baeyer-Villiger Oxidation of aliphatic aldehydes: The corresponding aldehyde (1.0 equiv.) was dissolved in CH_2Cl_2 (0.4 M according to the aldehyde), purified mCPBA

(91−98%, 1.5 equiv.) was added and the reaction mixture was stirred at room temperature until complete consumption of the starting material was observed (TLC). After dilution with CH_2Cl_2 the organic layer was washed with sat. $Na_2S_2O_3$, sat. $NaHCO_3$ (3x) and sat. NaCl, dried (Na_2SO_4) and evaporated in vacuo.

1-Phenylethyl formate (2b):[21] According to general procedure A **1b** (134 mg, 1.00 mmol) was reacted with purified mCPBA (91%, 284 mg, 1.50 mmol) for 16 hours at room temperature. Flash chromatography (silica, petroleum ether/ethylacetate 9:1) provided **2b** (76.7 mg, 511 µmol, 51%) as a colourless liquid. R_f = 0.48 (petroleum ether/ethyl acetate 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59 (d, J = 6.7 Hz, 3 H), 6.01 (q, J = 6.6 Hz, 1 H), 7.28−7.38 (m, 5 H), 8.09 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 72.2, 126.1, 128.1, 128.6, 140.9, 160.3 ppm. HRMS (CI): *m*/*z* calcd. $C_9H_{11}O_2$ $[M+H]^+$ 151.0754; found 151.0759.

Benzyl formate (2c):[22] According to general procedure A freshly distilled **1c** (120 mg, 1.00 mmol) was reacted with purified mCPBA (91%, 284 mg, 1.50 mmol) over night. Aqueous work-up provided **2c** (79.9 mg, 587 µmol, 59%) as a colourless liquid. R_f = 0.30 (pentane/diethyl ether 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.22 (d, J = 0.6 Hz, 2 H), 7.34−7.41 (m, 5 H), 8.16 (t, J = 0.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 65.7, 128.3, 128.5, 128.6, 135.1, 160.8 ppm. HRMS (CI): *m*/*z* calcd. $C_8H_9O_2$ $[M+H]^+$ 137.0597; found 137.0601.

Pentan-3-yl formate (2f): According to general procedure A 2-Ethylbutanal **1f** (267 µL, 2.00 mmol) was reacted with purified mCPBA (96%, 539 mg, 3.00 mmol). After aqueous work-up the organic layer was carefully evaporated in vacuo to afford **2f** (231 mg, 1.99 mmol, 99%) as a colourless liquid. R_f = 0.63 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.5 Hz, 6 H), 1.59−1.63 (m, 4 H), 4,88 (quint., J = 6.1 Hz, 1 H), 8.12 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.5, 26.4, 76.8, 161.1 ppm. GC-MS (CI, 1.5 keV) m/z [u] (%), 117.1 (3), 87.1 (6), 71.0 (100), 59.0 (65).

Heptan-3-yl formate (2g): According to general procedure A **1g** (311 µL, 2.00 mmol) was reacted with purified mCPBA (96%, 539 mg, 3.00 mmol). After aqueous work up the organic layer was carefully evaporated in vacuo to afford **2f** (243 mg, 1.69 mmol, 85%) as a colourless liquid. R_f = 0.53 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, J = 6.7 Hz, 3 H), 0.91 (t, J = 7.5 Hz, 3 H), 1.24−1.36 (m, 4 H), 1.54−1.65 (m, 4 H), 4,93 (quint., J = 6.2 Hz, 1 H), 8.11 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.5, 13.9, 22.5, 26.9, 27.4, 33.2, 75.7, 161.1 ppm. GC-MS (CI, 1.5 keV) m/z [u] (%), 145.3 (1), 115.1 (8), 99.1 (29), 87.1 (26), 69.0 (60), 57.1 (100).

17β-Hydroxy-androstan-3-one (6):[23] According to general procedure A **4** (79.0 mg, 248 µmol) in CH_2Cl_2 (620 µL) was treated with mCPBA (91%, 70.5 mg, 372 µmol). Aqueous work up and flash chromatography (silica, petroleum ether/ethylacetate 2:1 to 1:1) provided **6** (51.4 mg, 177 µmol, 71%) as a white solid. m.p. 173−176 °C. R_f = 0.32 (petroleum ether/ethyl acetate 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.70−0.74 (m, 1 H), 0.76 (s, 3 H), 0.84−0.99 (m, 2 H), 1.02 (s, 3 H), 1.08 (td, J = 12.9, 4.3 Hz, 1 H), 1.21−1.74 (m, 11 H), 1.82 (dt, J = 12.4, 3.3 Hz, 1 H), 2.00−2.11 (m, 3 H), 2.24−2.31 (m, 2 H), 2.33−2.44 (m, 1 H), 3.64 (t, J = 8.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.1, 11.5, 21.0, 23.4, 28.8, 30.5, 31.2, 35.4, 35.7, 36.6, 38.1, 38.5, 43.0, 44.7, 46.7, 50.8, 53.9, 81.8, 212.1 ppm. HRMS (CI): *m*/*z* calcd. $C_{19}H_{31}O_2$ $[M+H]^+$ 291.2319; found 291.2318.

2-Methyl-3-phenyloxiran-2-yl formate (9):[20] To a solution of α-methyl cinnamaldehyde **7** (98%, 568 µL, 4.00 mmol) in CH_2Cl_2 (10 mL) mCPBA (91%, 2.28 g, 12.0 mmol) was added. The reaction mixture was stirred at room temperature for 4 hours before it was diluted with CH_2Cl_2 (10 mL). The organic layer was washed with sat. $Na_2S_2O_3$ (5 mL), sat. $NaHCO_3$ (3 x 10 mL) and sat. NaCl (5 mL), dried (Na_2SO_4) and evaporated in vacuo. The crude product was purified by flash chromatography (silica, pentane/diethyl ether 9:1) to afford **9** (605 mg, 3.40 mmol, 85%) as a colourless liquid. R_f = 0.24 (pentane/diethyl ether 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53 (s, 3 H), 4.17 (s, 1 H), 7.33−7.42 (m, 5 H), 8.05 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4, 63.1, 85.2, 126.1, 128.4, 128.4, 133.0, 159.1 ppm. HRMS (CI): *m*/*z* calcd. $C_{10}H_{11}O_3$ $[M+H]^+$ 179.0703; found 179.0715.

1-Phenyl-1-hydroxy-acetone (10):[20] To a solution of **9** (250 mg, 1.42 mmol) in H_2O/THF (2:1, 3.6 mL) $NaHCO_3$ (237 mg, 2.82 mmol) was added. After vigorous stirring for 2 days the mixture was diluted with H_2O (15 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layer was dried (Na_2SO_4) and evaporated in vacuo to afford **10** (213 mg, 1.42 mmol, quant.) as colourless liquid. R_f = 0.51 (petroleum ether/ethyl acetate 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.08 (s, 3 H), 4.30 (bs, 1 H), 5.10 (s, 1 H), 7.32−7.42 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2, 80.1, 127.3, 128.7, 129.0, 137.9, 207.1 ppm. HRMS (CI): *m*/*z* calcd. $C_9H_{11}O_2$ $[M+H]^+$ 151.0754; found 151.0759.

(1R,3S,5R)-3-hydroxy-6,6-dimethylbicyclo[3.1.1]heptan-2-one (13):[24] To a solution of (−)-myrtenal **11** (155 µL, 1.00 mmol) in CH_2Cl_2 (2.5 mL) was added purified mCPBA (91%, 474 mg, 2.50 mmol) and the mixture was stirred at room temperature over night. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and subsequently washed with sat. $Na_2S_2O_3$, sat. $NaHCO_3$ (3x) and sat. NaCl before the organic layer was dried (Na_2SO_4) and evaporated in vacuo. Purification by flash chromatography (silica, petroleum ether/ethylacetate 9:1 to 4:1) afforded **12** (29.5 mg, 162 µmol, 16%) and **13** (95.6 mg, 620 µmol, 62%) as colourless liquids. Formate **12** was dissolved in H_2O/THF (2:1, 0.6 mL) and $NaHCO_3$ (27.2 mg, 364 µmol) was added. After vigorous stirring over night the mixture was diluted with H_2O (10 mL) and extracted with Et_2O (3 x 10 mL). The organic layer was dried (Na_2SO_4) and evaporated in vacuo to afford **13** (24.5 mg, 159 µmol, 16%) as colourless liquid. R_f = 0.22 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (s, 3 H), 1.37 (s, 3 H), 1.61 (dd, J = 15.5, 5.6 Hz, 1 H), 1.90 (dt, J = 14.3 Hz, 3.1 Hz, 1 H), 2.26 (tt, J = 5.5 Hz, 2.9 Hz, 1 H), 2.55 (ddt, J = 14.3 Hz, 9.5 Hz, 2.3 Hz, 1 H), 2.70 (td, J = 6.1 Hz, 2.3 Hz, 1 H), 2.73 (q, J = 5.6 Hz, 1 H), 3.21 (bs, 1 H), 4.17 (dd, J = 9.5 Hz, 3.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.2, 26.0, 28.0, 32.4, 40.4, 40.7, 57.6, 69.3, 213.7 ppm. HRMS (CI): *m*/*z* calcd. $C_9H_{15}O_2$ $[M+H]^+$ 155.1067; found 155.1075.

Phenylmethylene diformate (15):[20] To a solution of trans-cinnamaldehyde (189 µL, 1.50 mmol) in CH_2Cl_2 (3.75 mL) mCPBA (91%, 1.14 g, 6.00 mmol) was added. After stirring over night the mixture was diluted with CH_2Cl_2 (10 mL) and washed with sat. $Na_2S_2O_3$ (10 mL), sat. $NaHCO_3$ (3 x 10 mL) and sat. NaCl (10 mL). The organic layer was dried (Na_2SO_4) and evaporated in vacuo to afford **15** (199 mg, 1.10 mmol, 74%) as a colourless liquid. R_f = 0.26 (pentane/diethyl ether 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43−7.47 (m, 3 H), 7.55−7.57 (m, 2 H), 7.88 (s, 1 H), 8.15 (d, J = 1.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 88.5, 126.7, 128.8, 130.3, 134.1, 158.4 ppm. HRMS (CI): *m*/*z* calcd. $C_9H_9O_4$ $[M+H]^+$ 181.0495; found 181.0486.

(2*S*,3*S*)-3-((*N*-Boc)amino)-4-methoxy-2-methyl-4-oxobutanoic acid (19):[25] **18** (300 mg, 1.17 mmol) was dissolved in acetone (24 mL), cooled to −78 °C and ozone was passed through the solution until a blue color occured (2 min). The excess of ozone was removed by a flow of nitrogen before the mixture was warmed to 0 °C and Jones reagent (2.7 M CrO_3 in 4.3 M H_2SO_4) was added dropwise until an orange color persisted. After stirring at 0 °C for 20 minutes *i*PrOH was added until the solution turned green and the mixture was stirred for 15 minutes at 0 °C and 1 hour at room temperature. The mixture was filtrated through a pad of celite, the precipitate was rinsed with Et_2O and the organic layer was extracted with sat.

$NaHCO_3$ (3 x 10 mL). The combined aqueous layer was acidified with 6 N HCl (pH 2), extracted with Et_2O (3 x 15 mL) and the combined organic layer was dried (Na_2SO_4) and evaoporated in vacuo. After lyophylisation **19** (305 mg, 1.17 mmol, 94%, 96:4 dr, 99% ee) was obtained as a white solid. m.p. 86−89 °C. R_f = 0.48 (petroleum ether/ethyl acetate 1:1 + 1% HOAc). Major rotamer and diastereomer ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.02 (d, J = 7.2 Hz, 3 H), 1.38 (s, 9 H), 2.78 (qd, J = 7.6, 7.2 Hz, 1 H), 3.61 (s, 3 H), 4.29 (t, J = 8.7, 1 H), 7.29 (d, J = 9.2 Hz, 1 H), 12.41 (bs, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.3, 28.2, 40.4, 52.0, 55.1, 78.5, 155.6, 171.7, 174.9 ppm. Minor Rotamer (selected signals): ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.05 (m, 3 H), 1.34 (s, 9 H), 4.12 (t, J = 7.8 Hz, 1 H), 6.98 (m, 1 H), ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.9, 52.0, 56.3, 78.6, 171.4, 174.5 ppm. Minor diastereomer (selected signal) ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.37 (dd, J = 8.8 Hz, 5.7 Hz, 1 H) ppm. HRMS (CI): m/z calcd. $C_{11}H_{20}NO_6$ $[M+H]^+$ 262.1285; found 262.1283.

Supporting Information (see footnote on the first page of this article): Copies of NMR spectra and HPLC data of all new compounds.

Acknowledgement

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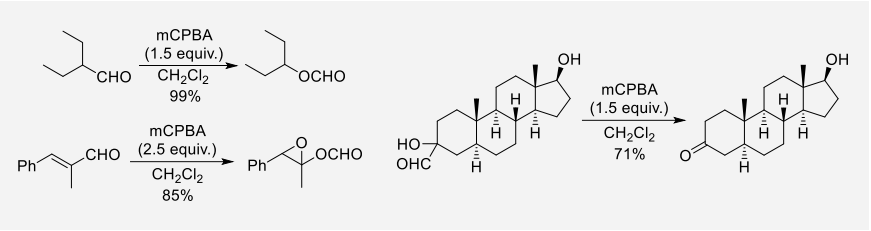
Entry for the Table of Contents

Baeyer Villiger oxidation



Purified mCPBA is an useful reagent for the oxidation of several classes of aldehydes. α-Branched aliphatic aldehydes undergo BV oxidation to give formates. α-Branched α,β-unsaturated aldehydes provide enolformates and/or the epoxides thereof, while α-hydroxylated aldehydes give rise to ketones.

Alexander Horn and Uli Kazmaier
Page No. – Page No.

Purified mCPBA, a useful reagent for the oxidation of aldehydes

Keywords: Bayer Villiger oxidation / Enolformates / Epoxides / α-Hydroxyketones / Peracids