Pergamon

Tetrahedron, Vol. 52, No. 16, pp. 5799-5804, 1996

0040-4020/96 $15.00 + 0.00

S0040-4020(96)00231-1

Nickel-Catalyzed Hydroxylation of 1,3-Dicarbonyl Compounds by Dimethyldioxirane

Waldemar Adam, Alexander K. Smerz*

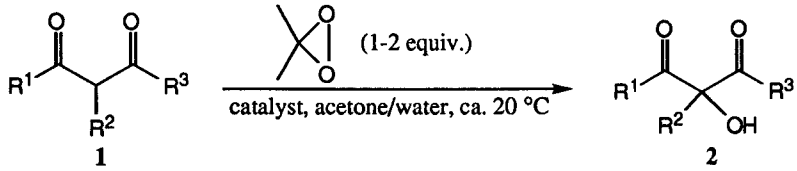
Institute of Organic Chemistry, University of Würzburg, Am Hubland, D-97074 Würzburg, Germany

Abstract: Various 1,3-dicarbonyl compounds were directly hydroxylated by dimethyldioxirane, a preparative useful extension of this oxidation is the efficient catalysis by Ni(II) salts through chelation.

Dimethyldioxirane has been well established as an extraordinary oxidizing agent during the last decade. Thus, it was shown that especially with isolated dimethyldioxirane (as acetone solution),[1] olefin epoxidations, C-H insertions and heteroatom oxidations can be performed selectively under mild conditions.[2] To explore the reactivity of this unique oxidizing agent, we have already reported on the oxidation of 1,3-dicarbonyl compounds with dimethyldioxirane (DMD); nevertheless, even though a high excess of DMD was used, the reaction was slow (3 days) and limited to reactive substrates.[3] Herein we describe the highly efficient nickel(II) catalysis in the oxidation of 2-alkylated 1,3-dicarbonyl substances to the corresponding hydroxy derivatives by DMD.

As shown in Table 1, the 2-hydroxy-1,3-dicarbonyl compounds **2** were the only products obtained in the oxidation of the various dicarbonyl substrates **1** by dimethyldioxirane (Scheme 1). The reactivity of the

Scheme 1: Oxidation of 1,3-Dicarbonyl Compounds with DMD



1 **2**

dicarbonyl substrates strongly depends on the substitution pattern; for instance, the order diketone > keto esters > diester was observed for the reactivity towards dimethyldioxirane. It is also apparent from Table 1 that cyclic substrates show a higher reactivity in their oxidation by DMD than the corresponding acyclic ones, e.g. the cyclic diester **1d** *versus* the acyclic ketoester **1e** (entries 7, 9). This reactivity order is in agreement with the general trend of decreasing enol content in the keto-enol equilibrium for 1,3-dicarbonyl compounds[4] since cyclic systems tend to enolize more readily than the analogous open chain ones.[5]

A limiting factor of this oxidation route was that the keto esters **1e**, **1g** and diesters **1f**, **1h** reacted only very sluggishly with DMD or not at all. To improve the reactivity, catalytic amounts (0.1 equiv.) of Ni(II) salts were employed, since this transition metal was successfully used as catalyst for the alkylations of 1,3-dicarbonyl substrates.[6] Indeed, even the diester **1f**, which in the absence of a catalyst was too sluggish to react, was successfully oxidized when 0.1 equiv. of nickel(II) acetate was used. The catalysis also proved to be effective for the slowly reacting substrates **1c-e**, whereas no acceleration was noted for the fast reacting compounds **1a** and **1b**. Furthermore, the Ni(II) catalyst was more effective than base or $^{n}Bu_4NF$, although the latter two

Table 1: Oxidation of 1,3-Dicarbonyl Compounds

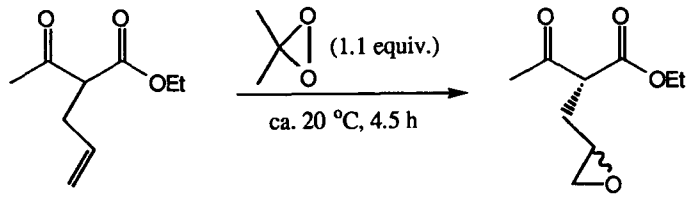
entry	starting material	R^1	R^2	R^3	catalyst (0.1 equiv.)	time [h]	conversion[a] [%]
1	**1a**	$-(CH_2)_4-$		Et	/	3	88
2	**1a**	$-(CH_2)_4-$		Et	$Ni(acac)_2$	3	90
3	**1b**	$-O-(CH_2)_2-$		Me	/	3.5	>95
4	**1b**	$-O-(CH_2)_2-$		Me	$Ni(acac)_2$	3.5	>95
5	**1c**	$-(CH_2)_3-$		OEt	/	3.5	75
6	**1c**	$-(CH_2)_3-$		OEt	$Ni(acac)_2$	3.5	>95
7	**1d**	$-O-(CH_2)_2-$		OEt	/	5	46
8	**1d**	$-O-(CH_2)_2-$		OEt	$Ni(OAc)_2$	5	84
9	**1e**	Me	CH_2Ph	OEt	/	4.25	11
10	**1e**	Me	CH_2Ph	OEt	$Ni(acac)_2$	4.25	78
11	**1f**	OEt	Me	OEt	/	120[b]	0
12	**1f**	OEt	Me	OEt	$Ni(OAc)_2$	12	47
13	**1g**	Me	H	OEt	/	24	35
14	**1g**	Me	H	OEt	$Ni(OAc)_2$	24	>95[c]
15	**1h**	OMe	H	OMe	/	24	15
16	**1h**	OMe	H	OMe	$Ni(OAc)_2$	16	>95

[a] Conversions were determined by ^1H NMR analysis of characteristic signals, the yields were >95%.
[b] The reaction mixture was still peroxidic. [c] The diketo ester hydrate **3g** is formed exclusively.

catalysts have been found to be expedient for similar oxidations.[7] Thus, when the oxidation of the derivative **1f** was performed under the same conditions (entry 12), but with $NaHCO_3$ or $^nBu_4NF$ as catalyst, only 5 and 28% conversions were obtained. It is also important to note that the selective monohydroxylation of substrate **1h** could be efficiently catalyzed by Ni(II), whereas the diketo ester hydrate **3g** was obtained when an excess of DMD (2.2 equiv.) was used in the nickel-catalyzed oxidation of the keto ester **1g**. In this case, the direct oxidation with DMD without the Ni(II) catalyst yielded the monohydroxylated product **2g**; therefore, entries 13 and 14 provide an exceptional example in which the presence of the catalyst also effects the extent of hydroxylation, i.e. mono- *versus* dihydroxylation.

To compare the reactivity of epoxidation *versus* hydroxylation, the known,[8] difunctionalized keto ester **1i** was oxidized with 1.1 equiv. dimethyldioxirane (Scheme 2). In the absence of Ni(II) catalyst the two

Scheme 2: Chemoselective Epoxidation of a Difunctionalized Keto Ester



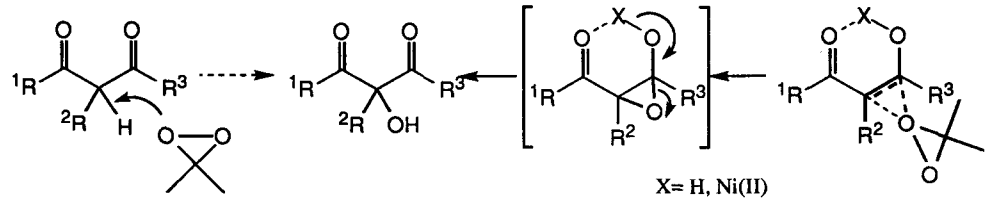
1i > 95%

diastereomeric epoxides were obtained chemoselectively in the DMD oxidation of **1i**, which shows that epoxidation is preferred over hydroxylation. When the catalytic procedure with Ni(II) was run, α-hydroxylation became competitive with epoxidation and a complex product mixture was obtained. While the Ni(II)-catalyzed

for this substrate is of little preparative value, it demonstrates once again that Ni(II) catalysis activates the difunctionalized substrate towards α-hydroxylation.

These data imply that the oxidation of 1,3-dicarbonyl substrates does not proceed by direct C-H bond insertion, which is currently subject of controversial discussion,[9] but instead by epoxidation of the enol form in the keto-enol equilibrium and subsequent ring-opening to the 2-hydroxylated 1,3-dicarbonyl products (Scheme 3). The proposed mechanism is supported by the facts that substrates with higher enol content react

Scheme 3: Proposed Mechanism for the Oxidation of 1,3-Dicarbonyl Compounds



very fast and more efficiently and that the reaction is catalyzed through Ni(II) chelating, which supplies a larger amount of enol form activated towards epoxidation. Decomplexation and ring-opening of the enol epoxides leads then to the product.

In the present report we have shown that Ni(II) serves as an effective catalyst for the hydroxylation of 1,3-dicarbonyl compounds by DMD. The usual methods for the oxidative α hydroxylation[10] require the prior or *in situ* generation of enolates by equimolar amounts of base; hence, the use of catalytic amounts of Ni(II) for the α hydroxylation of carbonyl substrates should be of preparative interest, as illustrated for the industrially relevant compounds **2d** and **2f**, which have been described in several recent patents.[11,12]

Experimental Section

General Aspects

^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 spectrometer by using $CDCl_3$ as internal standard. Potassium iodide-starch paper (Merck) was used for the peroxide tests. Dimethyldioxirane was prepared according to our described procedure, all starting materials were made according to literature-known procedures. Commercial compounds were used as received, solvents were purified and dried by reported standard methods.

General Procedure for the Nickel-catalyzed Oxidations of 1,3-Dicarbonyl Compounds by Dimethyldioxirane: 0.1 equivalent of the Ni(II) salt was dissolved in 3-6 mL H_2O and the starting material and dimethyldioxirane (0.05-0.10 M solution in acetone) were successively added at room temperature (ca. 20 °C). The solution was stirred at room temperature and the solvent was removed *in vacuo* (20 °C, 20 mbar). The aqueous residue was extracted with CH_2Cl_2 (3 x 15 ml), the organic phase was dried over $MgSO_4$ and the solvent was removed to yield the hydroxylated products.

For details of the uncatalyzed oxidations, which were performed for each substrate under the same conditions as described below but without Ni(II) salts, cf. Table 1.

2-Hydroxy-2-(1-oxopropyl)cyclohexanone (2a). According to the general procedure, the reaction of 20.0 mg (0.080 mmol) $Ni(OAc)_2 \cdot 4H_2O$ and 125 mg (0.81 mmol) 2-(1-oxopropyl)cyclohexanone with a 0.09 M solution of dimethyldioxirane (15.0 mL, 1.36 mmol) yielded after 3 h 122 mg **2a** (90%) as a light yellow needles, mp. 63-64°C. ^1H NMR (200 MHz, $CDCl_3$): δ 1.01 (t, J= 7.3 Hz, 3H), 1.54-2.02 (m, 4H), 2.25-2.34 (m, 4H), 2.66 (q, J=7.3 Hz, 2H), 4.85 (br.s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 7.3 (q), 21.5 (d), 27.1 (d), 30.6 (d), 38.6 (d), 39.1 (d), 85.2 (d), 208.9 (d), 209.8 (d); IR (CCl_4): 3420, 2900, 1780, 1690, 1440, 1360, 1220, 1200, 1005, 1080, 890 cm^{-1}. Anal Calcd for $C_9H_{14}O_3$ (170.2): C, 63.51; H, 8.29. Found: C, 63.19 ; H, 8.55.

3-Hydroxy-3-(1-oxoethyl)tetrahydrofuran-2-one[3] (2b). According to the general procedure, the reaction of 19.0 mg (0.070 mmol) $Ni(Acac)_2 \cdot 2H_2O$ and 89.7 mg (0.70 mmol) 3-(1-oxoethyl)tetrahydrofuran-2-one[13] with a 0.10 M solution of dimethyldioxirane (7.00 mL, 0.70 mmol) yielded after 3.5 h 100 mg **2b** (99%) as a colorless oil. ^1H NMR (250 MHz, $CDCl_3$): δ 2.26 (s, 3H), 2.32 (ddd, J_1= 13.5 Hz, J_2= 8.2 Hz, J_3= 7.8 Hz, 1H), 2.60 (ddd, J_1= 13.5 Hz, J_2= 7.2 Hz, J_3= 4.5 Hz, 1H), 4.28-4.46 (m, 2H), 4.53 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.9 (t), 34.2 (q), 66.5 (t), 81.5 (s), 175.0 (s), 205.4 (s).

Ethyl 1-Hydroxy-2-oxocyclopentanecarboxylate[3] (2c). According to the general procedure, the reaction of 19.0 mg (0.070 mmol) $Ni(Acac)_2 \cdot 2H_2O$ and 109 mg (0.70 mmol) methyl cyclopentan-2-onecarboxylate with a 0.10 M solution of dimethyldioxirane (7.00 mL, 0.70 mmol) yielded after 3.5 h 118 mg **2c** (98%) as a colorless oil. ^1H NMR (250 MHz, $CDCl_3$): δ 1.22 (t, J=7.1 Hz, 3H), 1.96-2.10 (m, 3H), 2.35-2.44 (m, 3H), 3.82 (s, 1H), 4.19 (q, J= 7.1 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 14.2 (q), 18.6 (t), 35.0 (t), 36.1 (t), 62.7 (t), 80.0 (s), 171.8 (s), 212.3 (s).

Ethyl 3-Hydroxy-2-oxotetrahydrofuran-3-carboxylate[7] (2d). According to the general procedure, the reaction of 16.0 mg (0.063 mmol) $Ni(Acac)_2 \cdot 2H_2O$ and 100 mg (0.63 mmol) ethyl 2-oxotetrahydrofuran-3-carboxylate with a 0.058 M solution of dimethyldioxirane (13.1 mL, 0.76 mmol) yielded after 5 h 92.0 mg **2d** (84%) as a colorless oil. ^1H NMR (250 MHz, $CDCl_3$): δ 1.30 (t, J=7.1 Hz, 3H), 2.40-2.55 (m, 1H), 2.73 (ddd, J_1= 13.5 Hz, J_2= 6.5 Hz, J_3= 4.9 Hz, 1H), 4.61 (q, J= 7.1 Hz, 3H), 4.42-4.50 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 13.9 (q), 34.1 (t), 63.5 (t), 66.0 (t), 75.6 (s), 169.8 (s), 173.4 (s).

Ethyl 2-Hydroxy-3-oxo-2-phenylmethylbutanoate[3] (2e). According to the general procedure, the reaction of 19.0 mg (0.070 mmol) $Ni(Acac)_2 \cdot 2H_2O$ and 154 mg (0.70 mmol) ethyl 3-oxo-2-phenylmethylbutanoate with a 0.067 M solution of dimethyldioxirane (10.5 mL, 0.70 mmol) yielded after 4.25 h at a conversion of 78% 153 mg **2e** (72%) as a colorless oil. ^1H NMR (250 MHz, $CDCl_3$): δ 1.28 (t, J= 7.2 Hz, 3H), 2.28 (s, 3H), AB system (δ_A= 3.18, δ_B= 3.42, $J_{A,B}$=14.1 Hz, 2H), 4.09 (s, 1H), 4.63 (q, J= 7.2 Hz, 2H), 7.21-7.27 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 10.1 (q), 25.0 (q), 40.6 (t), 62.8 (t), 84.1 (s), 127.1 (d), 128.1 (d), 130.1 (d), 134.6 (s), 170.5 (s), 204.0 (s).

Diethyl 2-Methyltartronate[12] (2f). According to the general procedure, the reaction of 14.0 mg (0.056 mmol) $Ni(OAc)_2 \cdot 4H_2O$ and 100 mg (0.56 mmol) ethyl 3-oxo-2-phenylmethylbutanoate with a 0.097 M solution of dimethyldioxirane (5.80 mL, 0.56 mmol) yielded after 12 h at a conversion of 47% 101 mg **2f** (46%) as a colorless oil. ^1H NMR (250 MHz, $CDCl_3$): δ 1.44 (t, J= 7.1 Hz, 6H), 1.59 (s, 3H), 3.82 (s, 1H), 4.12 (q, 4H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 13.9 (q), 21.5 (q), 62.3 (t), 75.9 (s), 170.1 (s).

Ethyl 2-Hydroxy-3-oxobutanoate[15] **(2g)**. A 0.079 M solution of dimethyldioxirane (17.2 mL, 1.36 mmol) in acetone was added to 80.0 mg (0.62 mmol) ethyl 3-oxobutanoate in 6.0 mL H_2O. After 24 h 84.0 mg **2g** (34%) were obtained at a conversion of 35%. Complete conversion to **2g** was achieved after 4 d with 6 equiv. of DMD. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, *J*=7.1 Hz, 3H), 2.33 (s, 3H), 4.26 (q, *J*=7.1 Hz), 2H), 4.77 (s, 1H), 5.3-5.9 (br.s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9 (q), 26.0 (q), 62.5 (t), 78.1 (d), 168.1 (s), 202.1 (s).

Ethyl 2,2-Dihydroxy-3-oxobutanoate[14] **(3g)**. According to the general procedure, the reaction of 15.0 mg (0.062 mmol) $Ni(OAc)_2 \cdot 4H_2O$ and 80.0 mg (0.62 mmol) ethyl 3-oxobutanoate with a 0.066 M solution of dimethyldioxirane (20.4 mL, 1.36 mmol) yielded after 24 h 80.0 mg **3g** (88%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, *J*=7.1 Hz, 3H), 2.28 (s, 3H), 4.31 (q, *J*=7.1 Hz, 2H), 4.4-5.5 (br.s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.6 (q,), 23.1 (q), 63.3 (t), 92.5 (s), 168.9 (s), 201.0 (s).

Dimethyltartronate[15] **(2h)**. According to the general procedure, the reaction of 15.0 mg (0.062 mmol) $Ni(OAc)_2 \cdot 4H_2O$ and 80 mg (0.61 mmol) dimethyl malonate with a 0.066 M solution of dimethyldioxirane (20.0 mL, 1.34 mmol) yielded after 24 h 71.0 mg **2h** (68%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.82 (s, 6H), 3.9-4.3 (br.s, 1H), 4.75 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 53.4 (q), 71.3 (d), 169.9 (s).

Ethyl 2-(2,3-Epoxypropyl)-3-oxobutanoate (2i). A 0.098 M solution of dimethyldioxirane (7.10 mL, 0.70 mmol) in acetone was added to 120 mg (0.70 mmol) ethyl 2-(1-oxoethyl)pent-4-enoate. The solution was stirred at room temperature for 4.5 h and the solvent was removed *in vacuo* (20 °C, 20 mbar) to yield 127 mg (98%) of a mixture of the two diastereomeric epoxides **2i** (d.r. 50 : 50) as a colorless oil. ^{1}H NMR (200MHz, $CDCl_3$): δ 1.25 (t, *J*=7.2 Hz, 3H), 1.26 (t, *J*=7.2 Hz, 3H), 1.75-1.96 (cm, 2H), 2.14-2.35 (cm, 2H), 2.25 (s, 3H), 2.26 (s, 3H), 2.48 (dd, J_1= 4.8 Hz, J_2= 2.6 Hz, 1H), 2.49 (dd, J_1= 4.8 Hz, J_2= 2.6 Hz, 1H), 2.71-2.78 (cm, 2H), 2.90-3.15 (cm, 2H), 3.59-3.69 (cm, 2H), 4.21 (q, *J*= 7.2 Hz, 2H), 4.22 (q, *J*= 7.2 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9 (q), 14.0 (q), 29.0 (q), 29.4 (q), 30.5 (t), 30.9 (t), 47.2 (t), 47.4 (t), 49.8 (d), 49.9 (d), 56.0 (d), 56.4 (d), 61.6 (t), 61.6 (t), 169.0 (s), 196.1 (s), 202.1 (s), 202.1 (s); IR (CCl_4): 2940, 2885, 1715, 1690, 1340, 1225, 1165, 1130, 890 cm^{-1}. Anal Calcd for $C_9H_{14}O_4$ (186.2): C, 58.05; H, 7.58. Found: C, 57.65; H, 7.34.

Acknowledgment: Financial support by the Deutsche Forschungsgemeinschaft (SFB 347 "Selektive Reaktionen Metall-aktivierter Moleküle") and the Fonds der Chemischen Industrie is gratefully acknowledged. We thank Dr. M. J. Richter for helpful discussions.

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(*Received in Germany* 12 *January* 1996; *accepted* 19 *February* 1996)