Zinc-Induced Deoximation of α,α'-Dioxo-Type Oximes and Oxime Ethers Leading to α,β-Diketo Esters

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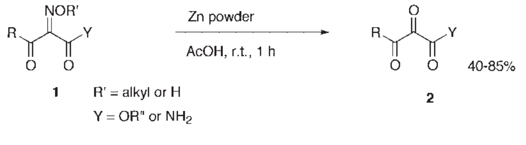
The deoximation of a variety of α,α'-dioxo-type oximes and oxime ethers was achieved under mild conditions using zinc/AcOH, which gave good yields of α,β-diketo esters.

vic-Tricarbonyl compounds represent a useful synthon for the preparation of biologically active natural and unnatural compounds.[1,2] It is also known that some important natural compounds, such as rapamycin and FK-506, contain the *vic*-tricarbonyl substructure. Recently, we have reported that an intermolecular radical cascade reaction, which employs multiple radical one-carbon (C1) units,[3] such as CO and sulfonyl oxime ethers,[4,5] can be successfully achieved. With this strategy in hand, α,α'-dioxo-type oxime ethers **1** can be prepared conveniently, which represent potential precursors for *vic*-tricarbonyl compounds. The deoximation of **1** having an adjacent acyl functionality was found to be particularly difficult, with HCl–HCHOaq, which can affect the deoximation of the usual oxime ethers.[4] A literature survey showed that there was one group that achieved the deoximation of a bis-acylated oxime using 200 mol% $TiCl_3$/acetone.[6] However, the reported yield of 19% of the corresponding *vic*-tricarbonyl compound, as well as the procedure requiring pH control, is obviously in need of a significant improvement. In this paper, we describe a useful method for the deoximation of **1**, leading to α,β-diketo esters **2**, which employs a system simply comprised of zinc powder and AcOH (Eq. 1). We found that the procedure is applicable to both oximes and oxime ethers, and that the preparation of an α,β-diketo amide by this procedure is also possible.



(1)

Using methyl 2-(benzyloxyimino)-3-oxobutanoate (**1a**) as a model compound, we attempted its deoximation under a variety of reaction conditions. Attempted oxidative deoximation using ozone, KIO_4, Oxone ($2KHSO_5/KHSO_4/K_2SO_4$), $Cu(NO_3)_2$, and $Mn(OAc)_3$[7] were all unsuccessful. An attempted reductive cleavage of **1a** with Raney Ni at room temperature[8] resulted in the recovery of **1a**. On the other hand, a treatment of **1a** with 3 mol% of fresh 10% Pd on C under an atmosphere of hydrogen in EtOH/AcOH/H_2O (15:2:10) at room temperature underwent simple debenzylation to give an oxime in 93% yield. Interestingly, a stoichiometric use of Pd/C gave a moderate yield of **2a**.

Consequently, we were pleased to find that a quite inexpensive and familiar reduction system solved the problem. Reductive deoximation induced by zinc in acetic acid proved to be useful to convert **1** to **2**. Thus, when ethyl 2-(benzyloxyimino)-3-oxohexanoate (**1b**) was treated with an excess amount of zinc powder in acetic acid, the desired product, ethyl 2,3-dioxohexanoate (**2b**), was prepared in 72% yield after purification by HPLC (Table 1, run 3). Each isolated product showed clear ^{1}H and ^{13}C NMR spectra, which can support the *vic*-tricarbonyl structure, whereas the IR spectra, which showed weak absorption at 3412 cm^{-1}, as in the case of **2b**, do not necessarily exclude the possibility of water-inclusion in each case.[2] Irrespective of the shapes of zinc being a powder or a dust, this deoximation gave identical results (runs 1 and 2). Some other results are summarized in Table 1. Besides benzyl oxime ethers, methyl and 2-propynyl oxime ethers underwent smooth deoximation reaction (runs 4 and 5). Oximes can also be deoximated to give corresponding *vic*-tricarbonyl compounds, although the yields were rather modest compared with the corresponding oxime ethers (runs 7–11). The procedure can be applied to the amide-type oxime ether **1k**, which provided the corresponding α,α'-diketo amide **2g** (run 12).

In summary, we have shown that *vic*-tricarbonyl compounds can be prepared conveniently from α,α'-dioxo-type oximes or oxime ethers as precursors by using a zinc–AcOH system. The mild reaction conditions, a simple reaction procedure, and the use of conventional reagents are attractive features of this deoximation method.

Experimental

^{1}H NMR spectra were recorded with a JEOL FT-NMR JNM-EX 270 (270 MHz) spectrometer and a JNM-EX 400 (400 MHz) spectrometer. ^{13}C NMR spectra were recorded with a JEOL JNM-EX 270 (68 MHz) spectrometer. Infrared spectra were recorded with a JASCO FT/IR-410 spectrometer. The products were purified by flash chromatography on silica gel (Fuji Silysia BW-300) or by recycling preparative HPLC (JAI, LC-908). Both zinc powder and zinc dust were purchased from Nakarai Tesque and Aldrich, respectively. For all instances, except for **2a**, EIMS spectra showed unidentified prominent peaks corresponding to 2M-36.

Preparation of Ethyl 2,3-Dioxohexanoate (2b). To a solution of ethyl 2-(benzyloxyimino)-3-oxohexanoate (**1b**) (183.5 mg, 0.66 mmol) in AcOH (0.5 mL), zinc powder (385 mg, 5.89 mmol) was added in one portion. After stirring at room temperature for 1 h, the reaction mixture was diluted with Et_2O and filtered through $NaHCO_3$ to remove AcOH and the remaining zinc. The filtrate was evaporated to dryness to give a crude product. Purification by HPLC ($CHCl_3$) provided the desired product **2b**

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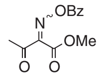
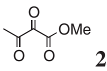
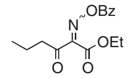
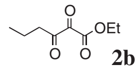
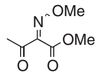
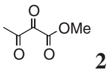
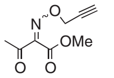
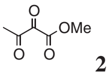
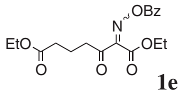
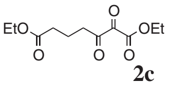
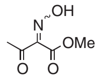
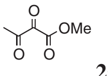
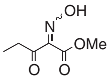
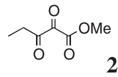
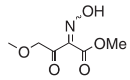
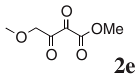
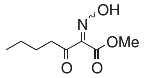
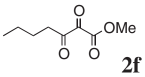
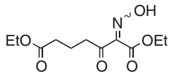
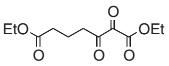
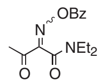
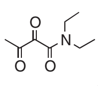
Table 1. Zn-Induced Deoximation of **1** Leading to *vic*-Tricarbonyl Compounds **2**[a)]

Run	Oximes or oxime ethers	Tricarbonyl compounds	Yield[b)]/%
1	 **1a**	 **2a**	85
2[c)]			80
3	 **1b**	 **2b**	72
4	 **1c**	 **2a**	86
5	 **1d**	 **2a**	78
6	 **1e**	 **2c**	75
7	 **1f**	 **2a**	72
8	 **1g**	 **2d**	55
9	 **1h**	 **2e**	49
10	 **1i**	 **2f**	57
11	 **1j**	 **2c**	40
12	 **1k**	 **2g**	54

a) Conditions: zinc powder (6–11 equiv), AcOH, r.t., 1 h. b) Products were isolated by either flash chromatography on silica gel (hexane/AcOEt = 19/1–4/1) or preparative HPLC ($CHCl_3$). c) Zinc dust (<10 micron) was used.

(81.7 mg, 72% yield) as yellow crystals: mp 55–57 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, 3H, $J = 7.25$ Hz), 1.44 (t, 3H, $J = 7.09$ Hz), 1.77 (tq, 2H, $J = 7.75$, 7.25 Hz), 3.02 (t-like, 2H, $J = 7.75$ Hz), 4.49 (q, 2H, $J = 7.09$ Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.01, 14.12, 22.85, 36.56, 62.16, 144.40, 153.26, 165.23; IR (KBr) 2963, 1724, 1466, 1414, 1382, 1304, 1262, 1139 cm^{-1}.

Methyl 2,3-Dioxobutanoate (2a):[9] Yellow crystals: mp 133–135 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (s, 3H), 4.00 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 22.33, 53.16, 143.58, 151.20, 165.25; IR (KBr) 1721, 1453, 1418, 1381, 1263, 1190, 1129 cm^{-1}; EIHRMS m/z calcd for $C_5H_6O_4$ 130.0266, found 130.0235.

Diethyl 2,3-Dioxopimelate (2c): Yellow oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25 (t, 3H, $J = 7.26$ Hz), 1.44 (t, 3H, $J = 7.26$ Hz), 2.10 (quint, 2H, $J = 7.59$ Hz), 2.42 (t, 2H, $J = 7.59$ Hz), 3.11 (t-like, 2H, $J = 7.59$ Hz), 4.13 (q, 2H, $J = 7.26$ Hz), 4.48 (q, 2H, $J = 7.26$ Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.20, 14.27, 24.25, 33.74, 33.80, 60.28, 62.35, 144.32, 152.79, 164.95, 172.84; IR (neat) 3412, 2982, 2939, 1735, 1448, 1414, 1375, 1304, 1254, 1130, 1024 cm^{-1}.

Methyl 2,3-Dioxopentanoate (2d): Light yellow crystals: mp 78–80 °C: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.33 (t, 3H, $J = 7.59$ Hz), 3.11 (q, 2H, $J = 7.59$ Hz), 4.02 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.71, 28.23, 53.17, 143.80, 155.06, 165.46; IR (KBr) 3425, 2980, 2954, 1723, 1444, 1330, 1244, 1166, 1120 cm^{-1}.

Methyl 4-Methoxy-2,3-dioxobutanoate (2e): Yellow crystals: mp 73–75 °C: ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.45 (s, 3H), 4.02 (s, 3H), 4.90 (s, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 52.81, 59.09, 72.45, 143.85, 151.30, 164.64; IR (KBr) 3412, 2987, 2932, 1717, 1444, 1367, 1271, 1253, 1165, 1139, 1108 cm^{-1}.

Methyl 2,3-Dioxoheptanoate (2f): Light yellow crystals: mp 41–43 °C: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.94 (t, 3H, $J = 7.26$ Hz), 1.42 (sex, 2H, $J = 7.26$ Hz), 1.70 (tt, 2H, $J = 7.92$, 7.26 Hz), 3.07 (t-like, 2H, $J = 7.92$ Hz), 4.02 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.90, 22.71, 31.76, 34.55, 53.12, 143.92, 154.07, 165.50; IR (KBr) 2953, 2873, 1731, 1686, 1597, 1450, 1289, 1262, 1249, 1192 cm^{-1}.

***N*,*N*-Diethyl 2,3-Dioxobutanamide (2g):** Yellow crystals: decomposed at 70 °C to form a white solid which did not melt at 300 °C: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.11 (t, 3H, $J = 7.09$ Hz), 1.30 (t, 3H, $J = 7.09$ Hz), 2.52 (s, 3H), 3.14 (q, 2H, $J = 7.09$ Hz), 3.60 (q, 2H, $J = 7.09$ Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 12.50, 13.72, 19.96, 39.52, 42.84, 146.81, 147.91, 166.81; IR (KBr) 3425, 1561, 1460, 1415, 1356, 1050, 1033, 696 cm^{-1}.

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