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Novel Synthesis of α,β -Diketoesters from α,α' -Dioxo-type Oximes or Oxime Ethers *via* Zinc-Induced Deoximation

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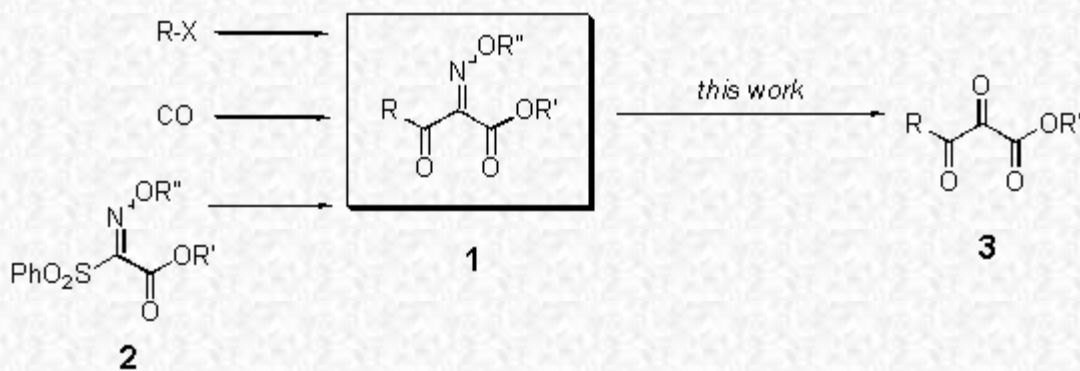
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Abstract

α,β -Diketoesters can be conveniently prepared from the corresponding α,α' -dioxo-type oximes or oxime ethers using a zinc/AcOH reduction system.



vic-Tricarbonyl compounds are a useful synthon for the preparation of the biologically active natural or unnatural compounds.^{1,2} It is well known that some important natural compounds such as Rapamycin and FK-506, contain this substructure.³ Recently, we have reported that the intermolecular cascade reaction based on radical one-carbon (C1) units composed of CO and sulfonyl oxime ethers⁴ proceeds smoothly to provide α,α' -dioxo-type oxime ethers, which would be precursors for *vic*-tricarbonyl compounds.⁵ When alkoxy-carbonyl attached oxime ether 2 is used, the compound 1 can be obtained in good yield. Alkyl radicals added to carbon monoxide and 2 in this order to form 1 with extrusion of phenylsulfonyl group (Chart 1).⁶ To our knowledge, there is one report on the deoximation of the type 1 compound 1 (R=*n*-octyl, R'=*t*-Bu, R''=H), which was reported by the Grasparski's group.⁷ They used 200 mol% TiCl₃/acetone for the reductive deoximation reaction. Unfortunately, the yield was very low (19%), which should need significant improvement. In pursuit for a better deoximation system of 1, we have examined a variety of deoximation

processes. In this paper, we describe the new, mild, and efficient method for deoxygenation of 1 leading to the a,b-diketoesters, which is based on the use of a zinc/AcOH system.

To a solution of ethyl 3-oxo-[2-(*O*-benzyl oxime)] hexanoate 1a (183.5 mg, 0.66 mmol) in AcOH (0.5 mL), zinc powder (385.0 mg, 5.89 mmol, purchased from Nakarai Tesque, Inc.) was added in one portion. After being stirred at room temperature for 1 h, the reaction mixture was diluted with Et₂O and filtered through NaHCO₃ to remove AcOH and remained zinc. The filtrate was evaporated to dryness to give a crude product. Purification by HPLC (GPC column, CHCl₃) provided the desired product, ethyl 2,3-dioxohexanoate 3a (81.7 mg, 72% yield) as a crystalline yellow.⁸

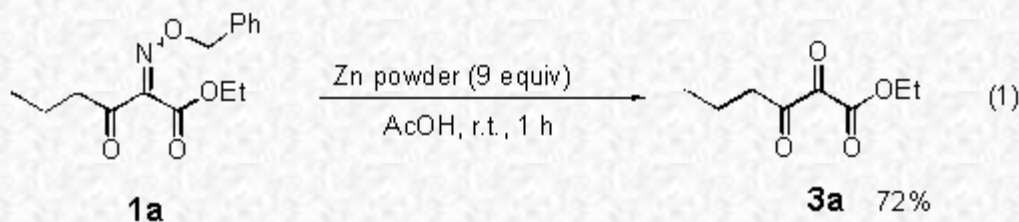


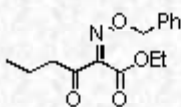
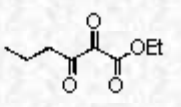
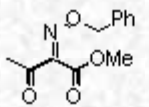
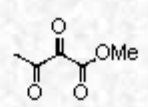
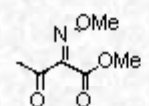
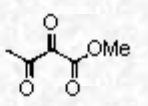
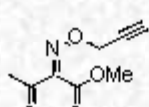
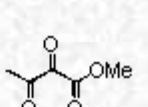
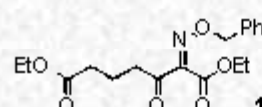
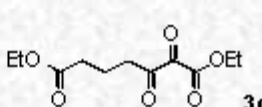
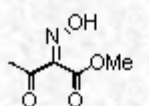
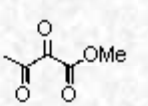
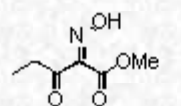
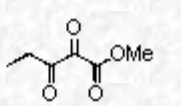
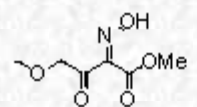
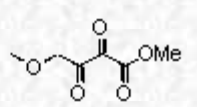
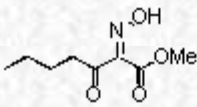
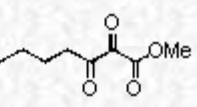
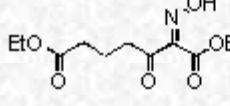
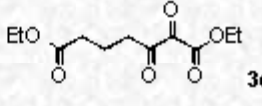
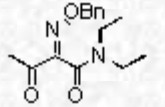
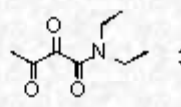
Table 1 demonstrates generality of this new deoxygenation method. R'' in oxime ether 1 bearing a functional group does not affect the deoxygenation reactions. Oximes can also be deoxygenated, although the yields were slightly lower than those for oxime ethers. The procedure can be applied to amide-type oxime ether 1k which provided the corresponding a,b-diketoamide 3g which was a kind of *vic*-tricarboxyl compounds (Entry 11).⁹ Zinc dust which was used instead of zinc powder provided the similar result.

In summary, we have shown that *vic*-tricarboxyl compounds are synthesized in good to moderate yields from a,a'-dioxo-type oximes or oxime ethers by using a zinc/AcOH reduction system. The mild reaction conditions as well as the use of conventional reagent are an attractive feature of this deoxygenation method.

Acknowledgement

I.R. thanks a Grant-in Aid for Scientific Research on Priority Areas (No. 283: Innovative Synthetic Reactions) from the Ministry of Education, Science, and Culture of Japan for financial support of this work. S.K. thanks the Korea Research Foundation (98-GH-12940) for financial support.

Table 1. Synthesis of *vic*-Tricarboxyl Compounds from a,a'-Dioxo-type Oximes and Oxime Ethers ^{a)}

Entry	Oximes or Oxime Ethers	Tricarbonyl compounds	Yield ^{b)} (%)
1			72
2			85(80) ^{c)}
3			86
4			78
5			75
6			72
7			55
8			49
9			57
10			40
11			54

a) Conditions: zinc powder (6-11 equiv), AcOH, r.t., 1 h. Products were isolated by either flash chromatography on silica gel (hexane/AcOEt = 19/1-4/1) or preparative HPLC chromatography (GPC column, CHCl₃).

b) Isolated yields except for entry 4 (¹H NMR yield).

c) Zinc dust (<10 micron) (Aldrich Chem. Co.) was used.

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8. The spectral data of compounds 3a-3g; 3a: mp 55-57 °C: ^1H NMR (400 MHz, CDCl_3) δ 1.00 (t, 3H, $J=7.25$ Hz, H-1), 1.44 (t, 3H, $J=7.09$ Hz, H-8), 1.77 (tq, 2H, $J=7.75, 7.25$ Hz, H-2), 3.02 (t-like, 2H, $J=7.75$ Hz, H-3), 4.49 (q, 2H, $J=7.09$ Hz, H-7); ^{13}C NMR (68 MHz, CDCl_3) δ 14.01 (C-1), 14.12 (C-8), 22.85 (C-2), 36.56 (C-3), 62.16 (C-7), 144.40 (C-4 or 5 or 6), 153.26 (C-4 or 5 or 6), 165.23 (C-4 or 5 or 6); IR (KBr) 2963, 1724 (some peaks may be superimposed), 1466, 1414, 1382, 1304, 1262, 1139 cm^{-1} ; EIHRMS m/z calcd for $\text{C}_8\text{H}_{12}\text{O}_4$ 172.0736, found 308.1778.

3b: mp 133-135 : ^1H NMR (400 MHz, CDCl_3) δ 2.81 (s, 3H, H-1), 4.00 (s, 3H, H-5); ^{13}C NMR (68 MHz, CDCl_3) δ 22.33 (C-1), 53.16 (C-5), 143.58 (C-2 or 3 or 4), 151.20 (C-2 or 3 or 4), 165.25 (C-2 or 3 or 4); IR (KBr) 1721, 1453, 1418, 1381, 1263, 1190, 1129 cm^{-1} ; EIHRMS m/z calcd for $\text{C}_5\text{H}_6\text{O}_4$ 130.0266, found 130.0235. This product was

previously reported, see: Schank, K.; Lick, C. *Synthesis* 1983, 392. 3c : ^1H NMR (270 MHz, CDCl_3) δ 1.25 (t, 3H, $J = 7.26$ Hz, H-1), 1.44 (t, 3H, $J = 7.26$ Hz, H-11), 2.10 (quint, 2H, $J = 7.59$ Hz, H-5), 2.42 (t, 2H, $J = 7.59$ Hz, H-4), 3.11 (t-like, 2H, $J = 7.59$ Hz, H-6), 4.13 (q, 2H, $J = 7.26$ Hz, H-2), 4.48 (q, 2H, $J = 7.26$ Hz, H-10); ^{13}C NMR (68 MHz, CDCl_3) δ 14.20 (C-1 or 11), 14.27 (C-1 or 11), 24.25 (C-5), 33.74 (C-4 or 6), 33.80 (C-4 or 6), 60.28 (C-2), 62.35 (C-10), 144.32 (C-7 or 8 or 9), 152.79 (C-7 or 8 or 9), 164.95 (C-7 or 8 or 9), 172.84 (C-3); IR (neat) 2982, 2939, 1735 (some peaks may be superimposed), 1448, 1414, 1375, 1304, 1254, 1130, 1024 cm^{-1} ; EIHRMS m/z calcd for $\text{C}_{11}\text{H}_{16}\text{O}_6$ 244.0947, found 452.2159. 3d : mp 78-80: ^1H NMR (270 MHz, CDCl_3) δ 1.33 (t, 3H, $J = 7.59$ Hz, H-1), 3.11 (q, 2H, $J = 7.59$ Hz, H-2), 4.02 (s, 3H, H-6); ^{13}C NMR (68 MHz, CDCl_3) δ 13.71 (C-1), 28.23 (C-2), 53.17 (C-6), 143.80 (C-3 or 4 or 5), 155.06 (C-3 or 4 or 5), 165.46 (C-3 or 4 or 5); IR (KBr) 2980, 2954, 1723 (some peaks may be superimposed), 1444, 1330, 1244, 1166, 1120 cm^{-1} ; EIHRMS m/z calcd for $\text{C}_6\text{H}_8\text{O}_4$ 144.0423, found $\text{C}_{17}\text{H}_{16}\text{O}_2$ 252.1161. 3e: mp 73-75: ^1H NMR (270 MHz, CDCl_3) δ 3.45 (s, 3H, H-1), 4.02 (s, 3H, H-6), 4.90 (s, 2H, H-2); ^{13}C NMR (68 MHz, CDCl_3) δ 52.81 (C-6), 59.09 (C-1), 72.45 (C-2), 143.85 (C-3 or 4 or 5), 151.30 (C-3 or 4 or 5), 164.64 (C-3 or 4 or 5); IR (KBr) 3412, 2987, 2932, 1717 (some peaks may be superimposed), 1444, 1367, 1271, 1253, 1165, 1139, 1108 cm^{-1} ; EIHRMS m/z calcd for $\text{C}_6\text{H}_8\text{O}_5$ 160.0372, found $\text{C}_{17}\text{H}_{17}\text{O}_4$ 285.1128. 3f : mp 41-43: ^1H NMR (270

MHz, CDCl₃) ?0.94 (t, 3H, $J = 7.26$ Hz, H-1), 1.42 (sex, 2H, $J = 7.26$ Hz, H-2), 1.70 (tt, 2H, $J = 7.92, 7.26$ Hz, H-3), 3.07 (t-like, 2H, $J = 7.92$ Hz, H-4), 4.02 (s, 1H, H-8); ¹³C NMR (68 MHz, CDCl₃) ?13.90 (C-1), 22.71 (C-2), 31.76 (C-3), 34.55 (C-4), 53.12 (C-8), 143.92 (C-5 or 6 or 7), 154.07 (C-5 or 6 or 7), 165.50 (C-5 or 6 or 7); IR (KBr) 2953, 2873, 1731 (some peaks may be superimposed), 1686, 1597, 1450, 1289, 1262, 1249, 1192 cm⁻¹; EIHRMS m/z calcd for C₈H₁₂O₄ 172.0736, found C₂₁H₂₄O₂ 308.1767. 3g: ¹H NMR (270 MHz, CDCl₃) ?1.11 (t, 3H, $J = 7.09$ Hz, H-6 or 6'), 1.30 (t, 3H, $J = 7.09$ Hz, H-6 or 6'), 2.52 (s, 3H, H-1), 3.14 (q, 2H, $J = 7.09$ Hz, H-5 or 5'), 3.60 (q, 2H, $J = 7.09$ Hz, H-5 or 5'); ¹³C NMR (68 MHz, CDCl₃) ?12.50 (C-6 or 6'), 13.72 (C-6 or 6'), 19.96 (C-1), 39.52 (C-5 or 5'), 42.84 (C-5 or 5'), 146.81 (C-2 or 3 or 4), 147.91 (C-2 or 3 or 4), 166.81 (C-2 or 3 or 4); IR (KBr) 1561, 1460, 1415, 1356, 1050, 1033, 696 cm⁻¹; EIHRMS m/z calcd for C₈H₁₃NO₃ 171.0895, found C₁₈H₂₈NO₃ 306.2078.

9. Attempted deoximation of biacylated oxime ether has met with a little success, resulting in the formation of a complex mixture.

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