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A mild, efficient method for the oxidation of α-diazo-β-hydroxyesters to α-diazo-β-ketoesters

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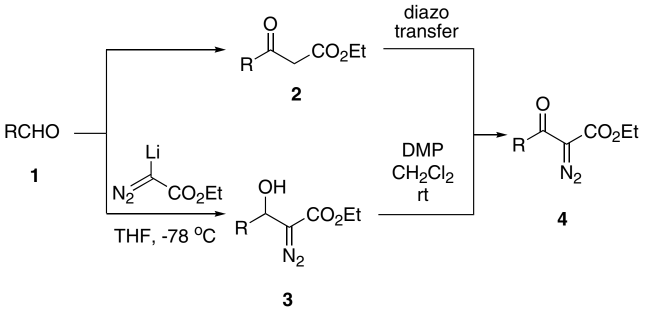
Abstract

A wide variety of α-diazo-β-ketoesters can be prepared in good overall yields via a two-step sequence involving addition of ethyl lithiodiazoacetate to aliphatic, aromatic, and conjugated aldehydes followed by mild oxidation with the Dess–Martin periodinane.

Keywords: Ethyl diazoacetate; Dess–Martin periodinane; Oxidation

In the course of some natural product syntheses currently ongoing in these labs, we needed to convert an aldehyde **1** into an α-diazo-β-ketoester **4** and two reasonable sequences seemed possible (Scheme 1). The most common methodology for this transformation would involve first homologating **1** to the corresponding β-ketoester **2**, followed by a Regitz diazo transfer step to produce **4**.[1] Alternatively, a potentially more attractive route would be to initially add ethyl lithiodiazoacetate to aldehyde **1** to produce an α-diazo-β-hydroxyester **3**, which would be oxidized to the desired diazo compound **4**. Although the addition of metallated ethyl diazoacetate to aldehydes is well precedented,[2] examples of the oxidation of adducts **3** to the corresponding ketones **4** are rare. In the few extant cases, the β-hydroxy-α-diazoesters **3** are derived only from aromatic or conjugated aldehydes. Moreover, the only reagents which have been used for alcohol oxidation in these few examples are limited to manganese dioxide,[3] IBX,[4] or barium permanganate.[5]



Scheme 1.

Since we were particularly interested in effecting this sequence starting with aliphatic aldehydes, and also required a mild oxidant for the second step which is compatible with sensitive functionality, we have explored this methodology further, particularly with regard to the oxidation process. Since there was good literature precedent that α-diazo-β-ketoesters are stable toward Dess–Martin periodinane (DMP),[6] we chose to investigate this reagent for oxidation of substrates like **3**.

As listed in Table 1, several α-diazo-β-hydroxyesters **3** were prepared from a variety of aliphatic, aromatic, and unsaturated aldehydes and ethyl lithiodiazoacetate in THF using the experimental procedure of Padwa et al.[2b] It was found that exposure of these compounds to Dess–Martin periodinane in methylene chloride at room temperature indeed led to the formation of the corresponding α-diazo-β-ketoesters **4**. An interesting observation was that addition of excess pyridine (∼12 equiv) to the oxidation

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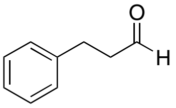
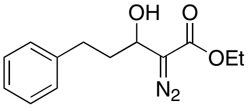
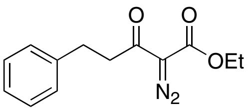
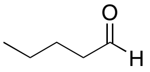
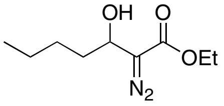
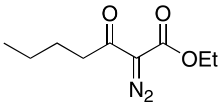
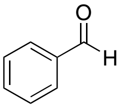
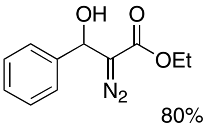
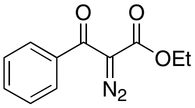
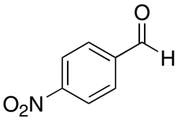
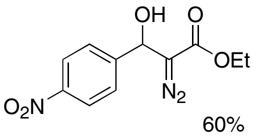
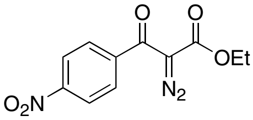
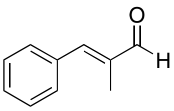
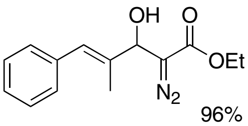
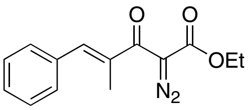
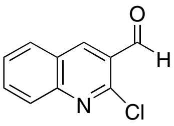
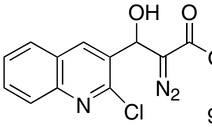
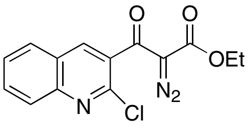
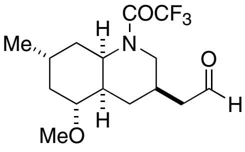
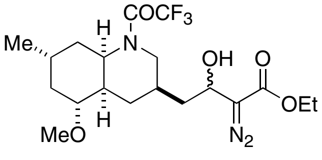
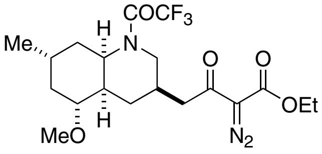
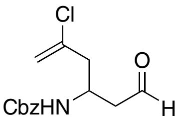
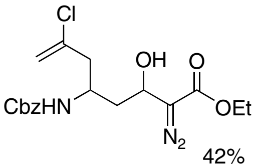
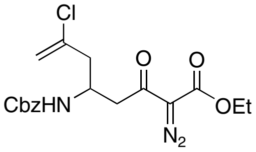
Table 1
Preparation of representative α-diazo-β-ketoesters

Entry	Aldehyde substrate	α-Diazo-β-hydroxyester **3**	α-Diazo-β-ketoester **4**
a		 85%	 88%[a]
b		 62%	 64%[a]
c		 80%	 78%[a]
d		 60%	 98%
e		 96%	 78%
f		 97%	 92%
g		 78%	 78%
h		 42%	 94%[a]

[a] ~12 equiv pyridine added to reaction mixture.

reaction resulted in higher product yields in a few cases. This improvement may be due to the pyridine minimizing decomposition of the diazo compounds by adventitious acid.[7] A number of examples of this oxidation are listed in the table along with the isolated yields of diazoketones **4**. Thus, Dess–Martin periodinane appears to be a general, superior oxidant for conversion of all types of α-diazo-β-hydroxyesters to α-diazo-β-ketoesters and thereby expands the scope of this two-step procedure for synthesizing the latter class of compounds.

General procedure for oxidation of α-diazo-β-hydroxyesters **3** *to α-diazo-β-ketoesters* **4**: To a solution of alcohol **3** (0.51 mmol) in CH_2Cl_2 (7.5 mL) was added DMP (0.76 mmol). The heterogeneous mixture was stirred at rt until the complete consumption of the starting material was observed by TLC (~1–3 h). The reaction mixture was diluted with a 1:1 mixture of $NaHCO_{3(aq)}$ and $Na_2S_2O_{3(aq)}$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo. The resulting crude residue was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexanes. Isolated yields of products **4** are shown in Table 1.

Acknowledgment

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