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A Simple One-Pot Preparation of Diazoacetoacetate Derivatives from Aldehydes

Marvis O. Erhunmwunse[†,‡] and Patrick G. Steel*[,†]

Department of Chemistry, University of Durham, Science Laboratories, South Road, Durham DH1 3LE, U.K., and Department of Chemistry, Faculty of Physical Sciences, University of Benin, PMB 1154 Benin City, Nigeria

p.g.steel@durham.ac.uk

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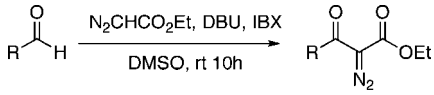
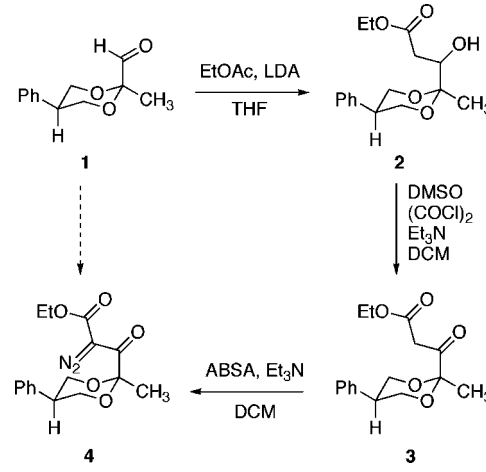


Diazoacetoacetate derivatives can be simply and efficiently prepared from aldehydes in a one-pot process involving initial DBU-promoted "aldol" condensation with ethyl diazoacetate followed by in situ oxidation with IBX. Aryl, alkyl, and unsaturated aldehydes are all viable substrates.

α-Diazocarbonyl compounds are useful intermediates in organic synthesis that undergo a broad spectrum of reactions catalyzed by various transition-metal salts.[1] In particular, diazoacetoacetate derivatives have been employed in cyclopropanation, ylide formation, and assorted X−H insertion reactions (X = C, N, O, Si, etc.). Such diazoacetoacetate derivatives not only provide for simpler methods than the parent diazoacetates but also result in increased functionality in the products. A major challenge in the use of such compounds is in their preparation. This is most commonly achieved by diazo transfer to a preformed β-dicarbonyl function.[2] An alternative, more convergent, process is to exploit the latent nucleophilicity of an α-diazoacetate and combine the associated anion with a suitable electrophile.[3,4] For example, a conceptually simple two-step sequence involves the addition of a metalated α-diazoester to an aldehyde followed by oxidation of the α-diazo-β-hydroxy carbonyl adducts.[5] While the nucleophilic addition of acyldiazomethanes to aldehydes and ketones is well precedented,[3,6,7] reports of the oxidation of the aldol products to diazodicarbonyl compounds are surprisingly rare and this sequence has not been widely utilized. In this paper, we describe how these two steps may be carried out in a single operation providing a simple, generic, one-pot method for the conversion of aldehydes to diazoacetoacetate derivatives.

SCHEME 1



As part of a wider program directed toward heterocycle synthesis through C−H insertion chemistry, we wished to transform aldehyde **1** into diazoacetoacetate **4**, Scheme 1. Although this can be achieved by classical diazo transfer, the preparation of the precursor β-ketoester **3** was rather protracted and inefficient. Consequently, we explored more direct routes involving condensation reactions of the anion of ethyl diazoacetate. While the reaction of the anion of ethyl diazoacetate with acid chlorides is precedented,[8] attempts to reproduce these with **1** afforded only complex mixtures, and we then turned to a more stepwise process involving condensation with an aldehyde and subsequent oxidation. Although initial attempts using lithio diazoacetates, generated through the action of LDA at −78 °C, provided the desired aldol product, it proved to be simpler and more efficient to follow the precedents established by Wang et al.[7] and use a substoichiometric amount of 1,8-diazobicyclo-[5.4.0]undec-7ene (DBU) as the base in acetonitrile at room temperature. This simple modification allowed the α-diazo-β-hydroxy carbonyl compound to be obtained in good yield (Table 1, entry 1). At this stage, all that remained was to oxidize this product to the diazodicarbonyl function. In view of the interest in diazocarbonyl compounds, it is rather surprising that relatively few oxidants have been reported for this transformation, presumably due to the fact that the diazo group itself can be easily oxidized.[9] In these cases, the reagents which have been

† University of Durham.
‡ University of Benin.

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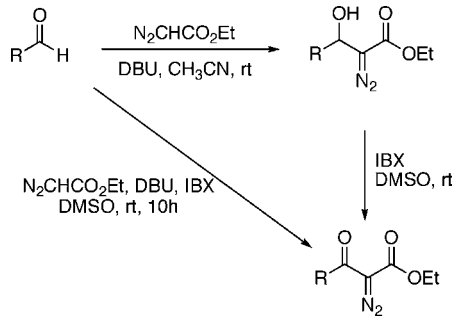
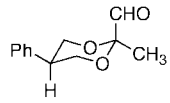
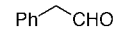
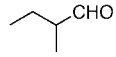
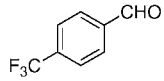
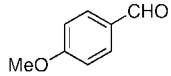
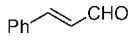
TABLE 1. Conversion of Aldehydes to Diazoacetoacetates



entry	Aldehyde	two-pot yield (%)[a,b]	one-pot yield (%)[a]
1		77 (86,90)	89
2		43 (67,64)	52
3		74 (95, 80)	74
4	PhCHO	78 (81,96)	80
5		93 (93, 100)	100
6		30 (32, 93)	50[c]
7		nd	60

[a] All yields refer to purified products following chromatography. [b] Yields of individual steps in parentheses. [c] Yield of 85% based on recovered starting material.

used for the oxidation of α-diazo-β-hydroxy compounds are limited to manganese dioxide,[10] barium permanganate,[11] and 2-iodoxybenzoic acid (IBX).[12] While initial attempts to use activated MnO_2 were successful giving over 80% yield of the desired diazoacetoacetate, the reaction was both slow and inefficient requiring large excesses of the oxidant. Much faster oxidation could be achieved using the Swern conditions, although at some cost to the yield (76%). Ultimately, a highly efficient (≥90%) and rapid oxidation was achieved using IBX in DMSO following the precedents established by Moody (Table 1). This two-step sequence proved to be general with a variety of aliphatic, aromatic, and heterocyclic aldehydes being converted in good yield to the corresponding diazoacetoacetate (Table 1). Moreover, the oxidation reaction is very clean requiring minimal purification, which in many cases simply involves the removal of excess IBX through an aqueous workup. The only limitation is that highly electron-rich and α,β-unsaturated aldehydes give only moderate conversions in the initial condensation step (Table 1, entries 6 and 7).

Since only a catalytic amount of DBU is required for the synthesis of the α-diazo-β-hydroxyl carbonyl intermediate and the presence of small quantities of DBU is not deleterious to the action of IBX, we speculated that this two-step procedure could have the potential to be conducted in a one-pot fashion. This requires a common solvent, and since IBX has limited solubility in acetonitrile we opted to explore the use of DMSO. Pleasingly, treatment of a DMSO solution of aldehyde **1** with ethyl diazoacetate and DBU for 8 h, followed by the addition of a solution of IBX (1.1−1.5 equiv) in DMSO, afforded the desired diazodicarbonyl compound **4** in good to excellent yields. Having established the compatability of all the reagents, we then examined the possibility of further telescoping the procedure by adding the oxidant at the outset of the reaction. Again this proved successful, providing the diazoacetoacetates in good yields that are equal to or greater than that obtained by the standard two-step protocol. Importantly, this one-pot procedure allows both electron-rich and α,β-unsaturated aldehydes to be converted to the desired diazoacetoacetates in moderate to good yields.

In conclusion, we have identified a simple, mild, and efficient one-pot process for the conversion of aldehydes to diazoacetoacetates.

Experimental Section

Representative Procedure for the Preparation of α-Diazo-β-hydroxyl Esters. Ethyl 2-Diazo-3-hydroxy-3-(2′-methyl-5′-phenyl-1′,3′-dioxan-2′-yl)propanoate (Table 1, Entry 1). To a solution of ethyl diazoacetate (0.65 mL, 6.17 mmol) in anhydrous CH_3CN (12 mL) at room temperature under nitrogen was added successively a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.08 mL, 0.52 mmol) in anhydrous CH_3CN (6 mL) and 2-methyl-5-phenyl-1,3-dioxane-2-carbaldehyde (1.06 g, 5.15 mmol) in anhydrous CH_3CN (12 mL) via cannula. After the mixture was stirred at room temperature for 15 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2 (3 × 20 mL). The solvent was removed in vacuo, and the crude product obtained was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 2/8) to afford the title diazoketol (Table 1, entry 1) (1.37 g, 86%) as a shiny yellow oil. ν_{max} (neat): 3520−3410, 2980, 2875, 2096, 1683, 1496, 1394, 1107, 1050, 870, 701 cm^{-1}. δ_H (500 MHz; $CDCl_3$): 7.41 (2H, d, *J* 7.6), 7.35 (2H, t, *J* 7.6), 7.27 (1H, t, *J* 7.6), 4.85 (1H, bs), 4.29−4.26 (2H, m), 4.25−4.19 (2H, m), 4.15 (2H, dd, *J* 11.7, 5.4), 2.94−2.90 (1H, m), 2.84 (1H, bs), 1.50 (3H, s), 1.28 (3H, t, *J* 7.0). δ_C (125 MHz; $CDCl_3$): 166.4, 140.0, 128.9, 127.8, 126.9, 100.4, 67.8, 65.1, 64.2, 60.8, 39.1, 17.6, 14.4. *m/z* (ES^+): 663 (2M + Na^+, 35), 417 (100), 343 (M + Na^+, 60). HRMS (ES^+): found 343.1262 ($C_{16}H_{20}O_5N_2Na$ requires 343.1264).

Representative Procedure for the Oxidation of α-Diazo-β-hydroxy Esters. Ethyl 2-Diazo-3-(2′-methyl-5′-phenyl-1′,3′-dioxan-2′-yl)-3-oxopropanoate (Table 1, Entry 1). Iodoxybenzoic acid (IBX) (0.34 g, 1.22 mmol) was dissolved in DMSO (5 mL) over 20 min at room temperature. To this was added a solution of the above alcohol (0.26 g, 0.81 mmol) in DMSO (4 mL) via cannula, and the solution was stirred for 4 h at room temperature. The reaction mixture was quenched with aqueous $NaHCO_3$ and then extracted with DCM (3 × 10 mL), the combined organic layers were copiously washed with aqueous $NaHCO_3$ (×3) and finally

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with water, and the mixture was then dried with $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 2/8) to afford the title diazoacetoacetate (Table 1, entry 1) (0.23 g, 90%) as a yellow solid. Mp: 60−62 °C. ν_{max} (neat): 2127, 1732, 1666, 1305, 1186, 1015, 856, 702, 629 cm^{-1}. δ_H (500 MHz; $CDCl_3$): 7.28−7.25 (2H, m), 7.23−7.19 (1H, m), 7.08 (2H, d, *J* 7.4), 4.31 (2H, q, *J* 7.4), 4.06 (2H, dd, *J* 11.9, 4.8), 3.91 (2H, t, *J* 11.9), 3.25−3.18 (1H, m), 1.53 (3H, s), 1.31 (3H, t, *J* 7.1). δ_C (125 MHz; $CDCl_3$): 188.6, 161.2, 136.7, 128.8, 127.61, 127.58, 100.5, 67.8, 62.0, 40.1, 25.0, 14.3. *m*/*z* (ES^+): 382 ($M + Na^+ + CH_3CN$, 20), 341 ($M + Na^+$, 100), 319 ($M + H^+$, 30). Anal. [Found: C, 60.8; H, 5.7; N, 7.3. $C_{16}H_{18}O_5N_2$ requires C, 60.4; H, 5.7; N, 8.0].

Representative Procedure for the One-Pot Synthesis of Diazodicarbonyl Compounds. Ethyl 2-Diazo-3-(2′-methyl-5′-phenyl-1′, 3′-dioxan-2′-yl)-3-oxopropanoate (Table 1, Entry 1). To a solution of ethyl diazoacetate (0.06 mL, 0.58 mmol) in DMSO (4 mL) at room temperature were added in succession DBU (0.007 mL, 0.05 mmol), 2-methyl-5-phenyl-1,3-dioxane-2-carbaldehyde (0.10 g, 0.49 mmol), and a solution of IBX (0.27 g, 0.97 mmol) in DMSO (5 mL). After being stirred for 10 h at room temperature, the reaction mixture was quenched with aqueous $NaHCO_3$ and then extracted with DCM (3 × 20 mL), the combined organic layers were copiously washed with aqueous $NaHCO_3$ (×3) and finally with water, and the mixture was then dried with $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether) afforded the title diazoacetoacetate (0.14 g, 89%) identical in all respects to that obtained above.

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Supporting Information Available: Experimental procedures, product characterization, and copies of NMR spectra for all new products. This information is available free of charge via the Internet at http://pubs.acs.org.

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