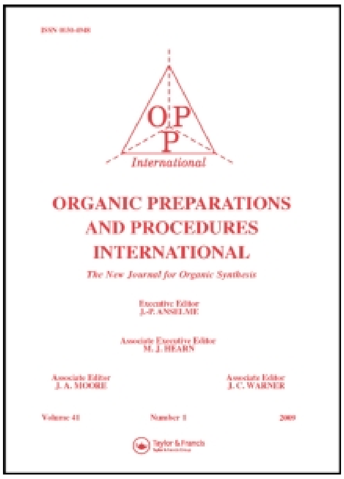

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AN IMPROVED OZONOLYTIC APPROACH TO 6-OXOHEPTANAL

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on a steam-bath for about 3 hrs. Then about 5 ml of 6N sodium hydroxide solution and a boiling chip were added to the reaction mixture which was boiledgently on the steam-bath for another 10 min. The reaction mixture was then poured onto crushed ice and the resulting 6-hydroxy-4,8,9,10-tetraaryl-1,3-diazaadamantane was collected and crystallized from chloroform.

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AN IMPROVED OZONOLYTIC APPROACH TO 6-OXOHEPTANAL

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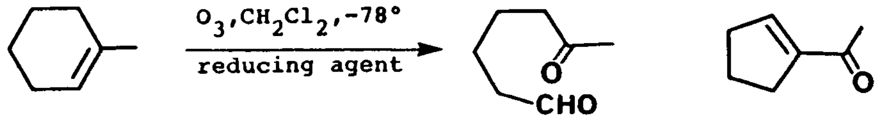
As part of a program aimed at the construction of macrocyclic lactone and medium-sized carbocyclic rings,[1] we required access to 6-oxoheptanal (1). The most direct literature approaches to 1 involve the ozonolysis of 1-methylcyclohexene (2) followed by the use of various reductive work-up procedures.[2,3] However, a number of these reports provide no experimental details and the yields of 1 (or products derived from crude 1) are often poor or notreported. In contrast, McMurry reported the isolation of 1 in 82% yield by the ozonolysis of 2 in CH_2Cl_2 at -78°, followed by reductive work-up using anhydrous Me_2S.[3] However, in our hands this reaction proved problematic, and none of the desired product could be detected in the crude reaction product. The major component (40% by GC) was the intramolecular aldol condensation product 1-acetylcyclopentene (3). Similar problems with this reaction have been encountered by another group,[4] while numerous reports lend credence to the ease of such an intramolecular aldol condensation.[5] Since the sensitive ketoaldehyde 1 was not surviving the work-up and product isolation conditions in this reaction, milder alternate procedures were sought.



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Contrary to expectation,[6] ozonolysis of 2 in CH_2Cl_2 at -78° followed by evaporation of the solvent and hydrogenolytic work-up afforded only 5% of 1, together with about 10% of 1-acetylcyclopentene (3).[7] We then turned our attention to the use of polymer-supported triphenylphosphine as the reducing agent. The use of triphenylphosphine for the reduction of ozonides is well established.[8] However, to our knowledge, only one report has appeared concerning the use of polymer-supported triphenylphosphine for such reductions.[9] When the ozonide derived from 2 was treated with polymer-supported triphenylphosphine, and the resulting polymer-supported triphenylphosphine oxide was removed by simple filtration under nitrogen, essentially pure ketoaldehyde 1 was isolated in 83% yield after solvent evaporation. No traces of the undesired 3 were evident. Although polymer-supported triphenylphosphine is quite expensive, it can be easily regenerated from the readily recovered phosphine oxide and reused.[10] This approach to 6-oxoheptanal appears much less capricious than those described in the literature, and can be used to generate gram quantities of 1 in a clean and efficient manner. Given the demonstrated importance of this sensitive ketoaldehyde as a synthetic intermediate,[11] this improved method of preparation should prove of widespread utility.

EXPERIMENTAL SECTION

^1H NMR spectra were obtained at 60 MHz on a Varian EM-360A NMR spectrometer using TMS as an internal reference. Mass spectra were recorded on a Hewlett Packard 5995 GC-MS instrument in electron impact ionization mode; only selected ions are reported here. Ozone (2% in oxygen) was generated using a Welsbach Laboratory Ozonator (Model T-408). Commercial (Aldrich Chemical Co.) polymer-supported triphenylphosphine was employed; this reagent consisted of a cross-linked (2% DVB) polystyrene support containing 3.06 mmol triphenylphosphine/gram polymer. Dichloromethane was dried using a standard literature procedure [ref. 12].

6-Oxoheptanal (1).- A stream of ozone (2% in oxygen) was bubbled through a solution of 1-methylcyclohexene (2) (1.165 g, 12.1 mmol) in anhydrous CH_2Cl_2 (50 mL) at -78° until a blue color persisted. Excess ozone was removed by bubbling nitrogen through the solution. Polymer-supported triphenylphosphine (4.013 g, containing 12.3 mmol Ph_3P) was then added at -78°, the cooling bath was removed, and the solution was allowed to warm to room temperature over 2 hrs. The resulting polymer-supported triphenylphosphine oxide was removed by filtration under nitrogen, and the solvent was evaporated in vacuo at room temperature to afford 1.1 g (83%) of essentially pure 6-oxoheptanal (1) as a colorless liquid. ^1H NMR ($CDCl_3$): δ 1.57 (m, 4, C-3 and C-4 protons), 2.10 (s, 3, $-COC\underline{H}_3$), 2.43 (m, 4, $C\underline{H}_2CHO$ and $C\underline{H}_2CO-$), 9.60 (br. s, 1, $-C\underline{H}O$). MS: m/z (relative intensity): 128 (M^+, 0.4%), 100 (2.5), 85 (4), 84 (5), 71 (11), 70 (11), 58 (24), 43 (100).

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