Pergamon

Tetrahedron Letters 42 (2001) 8793–8796

TETRAHEDRON LETTERS

Oxoammonium salts. Part 8: Oxidations in base: oxidation of O-1 unprotected monosaccharides to lactones using 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate†

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Received 1 August 2001; accepted 16 October 2001

Abstract—The oxidant, 4-acetylamino-2,2,6,6-tetramethylpiperidine-oxoammonium tetrafluoroborate in pyridine/CH_2Cl_2, is reported to be an excellent reagent for the conversion of hemiacetals to lactones. Specifically, the conversion of 1-O unprotected sugars to their corresponding aldonolactones is achieved in high yields. The basic reaction conditions partially overcome some disadvantages reported for oxoammonium-type oxidants, namely the inability to run the reaction in the presence of acid-labile groups and in the presence of β-oxygens. © 2001 Elsevier Science Ltd. All rights reserved.

We described in a previous paper,[1b] the oxidations of alcohols to the corresponding aldehydes or ketones with an oxoammonium salt, specifically 4-acetylamino-2,2,6,6-tetramethylpiperidineoxo-ammonium perchlorate. However, there are limitations to that method: most seriously, the perchlorate salt turned out to be explosive.[2] Secondly, a limitation noted by us and others was that a β-oxygen or β-nitrogen inhibited the reaction.[3] For instance, the oxidation of 2-phenoxyethanol proceeded to only 7% conversion over 72 h.[1b] Thirdly, the oxidations were carried out in a mildly acidic medium (CH_2Cl_2/silica gel catalysis), meaning that the method was not applicable to substrates carrying acid labile protecting groups such as most silyl and acetal groups. Lastly, trisubstituted double bonds reacted appreciably with the oxidant to form unidentified side products.[1b]

In this paper, we will describe a method overcoming some of these limitations, thereby expanding the applicability of the mild, heavy metal-free, convenient and clean oxoammonium oxidant. We will demonstrate that the method is an excellent, high yielding and simple way to prepare aldonolactones from their corresponding O-1 unprotected aldose derivatives. Aldonolactones are key intermediates in the synthesis of a number of sugar derivatives of current interest. They have been synthesized using oxidants such as $AgCO_3$ on Celite, PCC, or involved multi-step procedures with photochemical key steps, Swern or Dess–Martin oxidations.[8–13]

The explosion hazard of the perchlorate salt can be eliminated by using the tetrafluoroborate salt which possesses identical oxidizing properties.[1b,2,4] The key to overcoming some of the limitations posed by the original reaction conditions and the choice of substrates was performing the oxidation in the presence of base. Reaction of a hemiacetal with 2 equiv. of oxoammonium salt in CH_2Cl_2 in the presence of 2 equiv. of pyridine at room temperature furnishes the corresponding lactones overnight in excellent yields (see Table 1). We are not aware of any report describing the use of oxammonium salts as stoichiometric oxidants in the presence of base. Endo and co-worker, however, demonstrated the oxidation of simple cyclic five- and six-membered hemiacetals, formed in situ by oxidation of 1,ω-diols, to the corresponding lactones using an oxoammonium chloride (in the absence of base).[5]

The use of base changes the course of the reaction compared to that of the acidic counterpart. 2 Equiv. of oxidant are used (instead of one under acidic conditions) and the oxidant is reduced to a nitroxide (and not a hydroxyl amine). Thus, its mechanism appears to be similar to nitroxide catalyzed oxidations using ClO^- as terminal oxidant.[6] Scheme 1 shows the overall reaction scheme.

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† For Parts 6 and 7, see: Ref. 1.

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01950-5

Table 1.

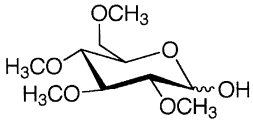
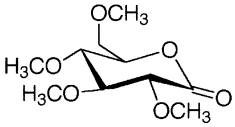
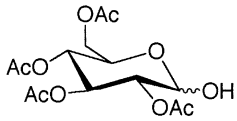
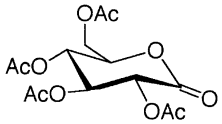
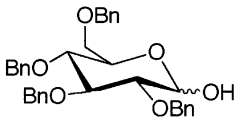
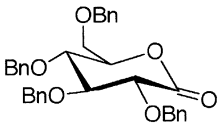
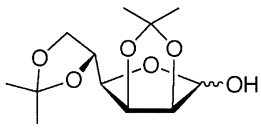
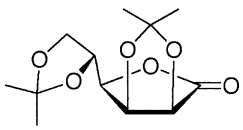
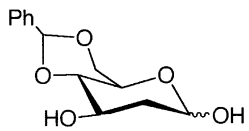
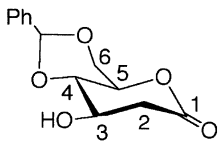
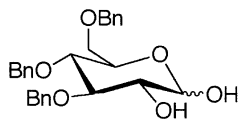
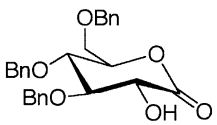
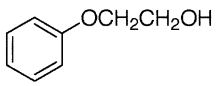
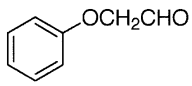
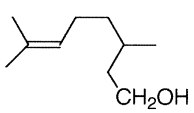
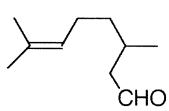
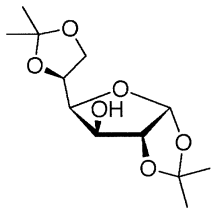
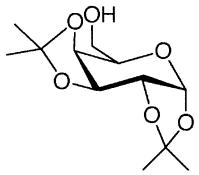
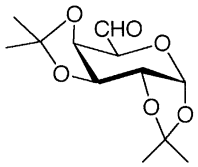
Entry	Substrate	Product[a]	Isolated yield (%)	Ref.
1	 2,3,4,6-Tetra-*O*-methyl-D-glucopyranose[e]		95	8
2	 2,3,4,6-Tetra-*O*-acetyl-D-glucopyranose[e]		94	9
3	 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose[e]		97	10
4	 2,3,5,6-Diisopropylidene-D-mannofuranose[e]		94	11
5	 4,6-Benzylidene-2-deoxy-D-glucopyranose[e]		91	12[f]
6	 3,4,6-Tri-*O*-benzyl-D-glucopyranose[e]		80	13
7	TBMS-O-$(CH_2)_4CH_2OH$	TBMS-O-$(CH_2)_4CHO$	97	14
8		 +aldol product	[d]	
9			Incomplete (~90%) conversion[b,c,d]	

Table 1. (*Continued*)

Entry	Substrate	Product[a]	Isolated yield (%)	Ref.
10	 1,2,5,6-Diisopropylidene-α-D-glucofuranose	–	No reaction after 24 h	
11	 1,2,3,4-Diisopropylidene-α-D-galactopyranose		Product in complex mixture[b,c,d]	

[a] General procedure: About 2 mmol of substrate was dissolved in CH_2Cl_2 (20 mL) and 2.05 equiv. of pyridine was added, followed by 2.05 equiv. of 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate. The mixture was stirred overnight, filtered to remove the precipitated pyridinium tetrafluoroborate, and evaporated to dryness under reduced pressure. The residue was suspended in dry diethyl ether. Filtration of the suspension recovers almost all of the nitroxide. The filtrate was concentrated to a small volume and passed over a short (~5×1 cm) column of silica gel. Using diethyl ether as eluent, the product eluted ahead of the orange nitroxide band in all cases investigated. Evaporation of the main fraction yielded product which was identified by ^1H and ^{13}C NMR. The purity of the compounds was assessed by ^1H NMR or GC (GC-MS).

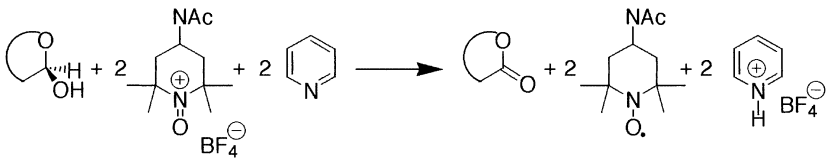
[b] By ^1H NMR.

[c] By GC.

[d] By GC–MS.

[e] Mixture of the α- and β-epimers.

[f] Compound data for the product, 4,6-benzylidene-2-deoxy-γ-gluconolactone have not been reported in Ref. 12: white crystal; mp 156–157°C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54–7.44 (m, 5H, phenyl), 5.64 (s, 1H, H7), 4.49 (dd, 1H, H6), 4.29 (m, 1H, H3), 4.14 (m, 1H, H5), 3.87 (t, 1H, H6), 3.78 (broad t, 1H, H4), 3.24 (dd, 1H, H2), 2.72 (dd, 1H, H2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168 (C1), 136.4, 129.6, 128.5, 126.3 (phenyl), 102.1 (C7), 80.7 (C4), 68.1, 68.0, 66.5 (C3, C5, C6), 37.7 (C2).



Scheme 1.

Since sugar derivatives are the quintessential β-oxygenated compounds, they are ideal substrates to test the superiority of our novel methodology over our originally reported protocols. In addition, we have also tested our new method with compounds that did not undergo satisfactory reactions in our original work.[7] The results are listed in Table 1. All of the products are known.

Several conclusions can be drawn from the data compiled in Table 1. Fully or partially protected sugar acetals can be oxidized to the corresponding lactones in high yields with utmost simplicity (entries 1–6). Thus, β-oxygens do not inhibit the *hemiacetal* reactions. Such sugar hemiacetals are not oxidized under the original acidic oxidation conditions (as demonstrated by a failed oxidation attempt of the glucose derivative of entry 1).[1b,15] Hence, this oxidation method represents a good alternative to other methods for the synthesis of aldolactones.[8–13] Some features of this oxidation are noteworthy. Isolated secondary hydroxyl groups in the sugar ring are not (or very slowly) oxidized and do not interfere with (fast) hemiacetal oxidations (entries 5, 6, 10). Sugars carrying acid-labile protecting groups can be oxidized without inadvertent deprotection (entries 4, 5). As well, and in direct contrast to our earlier paper,[1b] the TBDMS group is stable under the basic oxidation conditions (entry 7).

Entries 8–11 delineate the limits of the reaction: compounds such as phenoxyethanol oxidize readily but undergo an aldol condensation (entry 8). Hence, the reaction conditions are too basic for carbonyls undergoing facile aldolization. Unlike using the acidic protocol,[1b] trisubstituted olefins are not (or are very slowly) attacked by the oxidant under basic conditions. For instance, the oxidation of citronellol produces the corresponding aldehyde, but the reaction is retarded and up to 10% of the starting material remained in the reaction mixture after 24 h reaction time (entry 9). The oxidation of a primary hydroxyl groups in sugars takes place, albeit slowly, but does not give a clean product (entry 11). The effect of β-oxygens on the oxidation cannot be clearly delineated.

In conclusion, we have demonstrated the applicability of an oxoammonium salt as an oxidant for the mild and high yielding conversion of sugar hemiacetals to their corresponding lactones under mildly basic conditions. This oxidation method was particularly successfully applied to the synthesis of aldolactones by oxidation of O-1 unprotected sugars.

References

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15. This implies that, using the acidic conditions, other oxidizable portions can be oxidized without protection of the hemiacetal functionality.