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Bromine As An Oxidant for Direct Conversion of Aldehydes to Esters

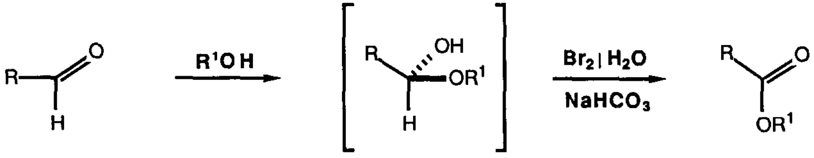
D.R. Williams*[a], F.D. Klingler[a,b], E.E. Allen[a], and F.W. Lichtenthaler*[b]

[a]Department of Chemistry, Indiana University, Bloomington, Indiana 47405
U.S.A.

[b]Institute für Organische Chemie, Technische Hochschule Darmstadt, D-6100 Darmstadt,
West Germany

Summary: Examples illustrate the direct conversion of aldehydes to esters using bromine in alcohol solvents with sodium bicarbonate buffer. The convenient and efficient one-pot procedure is compatible with secondary hydroxyl groups as well as a variety of O-protecting units such as MOM, MEM, $Ph_2{}^tBuSi$, benzyl, benzoyl, and isopropylidene functions.

More than one hundred years ago, carbohydrate chemists utilized bromine-water as a reagent for the conversion of aldoses (lactols) to the corresponding lactones.[1] This oxidation is considered one of the first examples of functional group selectivity for preparatively useful reactions in monosaccharide chemistry.[2] Today aldehydes are usually transformed into their corresponding esters using Jones' (acidic), and permanganate or silver oxide (basic) oxidations followed by esterifications. Convenient and general, single-step procedures are not widely utilized. Perhaps the cyanide-induced manganese dioxide oxidation of α,β-unsaturated aldehydes to their respective esters is most recognized.[3] Additionally, tributylstannyl alkoxides, derived from primary and secondary alcohols, react with N-bromosuccinimide in the presence of aldehydes to give good yields of esters.[4] These modern examples also mechanistically proceed through "hemiacetal" formation with subsequent C-H bond cleavage and collapse to the carbonyl.[5] Recently, the use of aqueous sodium hypochlorite in methanolic acetic acid has been shown to convert aldehydes to methyl esters, whereas secondary alcohols were oxidized to ketones.[6] Herein we wish to illustrate some examples featuring the use of bromine in alcohol solvents as a convenient and inexpensive technique for direct conversion of highly functionalized aldehydes 1 into a series of esters 2.



1 2

Our results are compiled in Table I, and yields are reported after isolation and purification.[7] Methyl, ethyl, and isopropyl esters are uniformly prepared in excellent yields, although our preliminary efforts indicate only moderate yields for the corresponding *tert*-butyl esters (25-50%). Reactions are buffered by the presence of sodium bicarbonate, thus permitting the coexistence of a number of functional groups without conflicting reactivity. For example, secondary alcohols are not oxidized to ketones under these conditions, and the acetal of entry 1 is unaffected. This latter observation may not be general as we can report only limited stability of tetrahydropyranyl ethers. However, a wide range of typical hydroxyl protecting units such as silyl ethers, various esters, acetonides, and the usual methylenedioxy blocking groups such as MOM, MEM, and SEM, all survive. In addition, activated benzylic sites are not prone to undergo bromination (entries 4, 5, and 8), and we find no evidence for competing α-bromination adjacent to electron-withdrawing groups (entries 2 and 9). Furthermore, the buffered conditions prevent acid-catalyzed elimination of β-alkoxy units to the corresponding α,β-unsaturated esters (entries 1, 3, 4, 6, and 8), and we have not observed α-epimerizations of established chirality (entries 1, 2, and 8). While epoxides (entry 4) and oxime ethers (entry 5) appear suitably resistant toward these electrophilic conditions, olefins, benzylidene acetals, and thioketals give rapid reactions. Only modest yields of esters were obtained in cases of electron-rich aromatic aldehydes (entry 11). However remaining starting aldehyde was recovered without evidence of ring bromination. Electron rich heteroaromatics, such as furfural, undergo competitive attack on the ring as expected based on literature precedents.

TABLE I

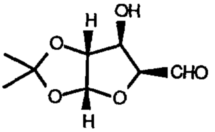
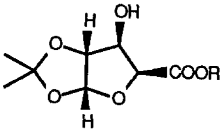
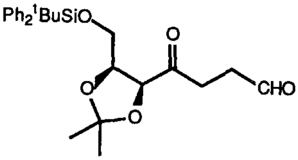
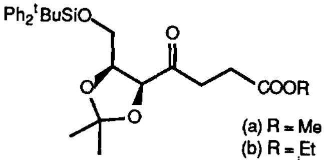
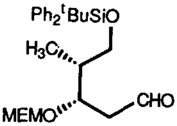
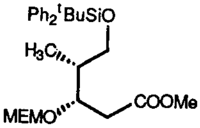
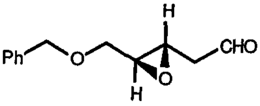
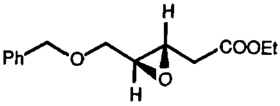
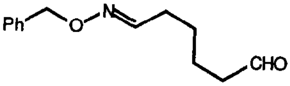
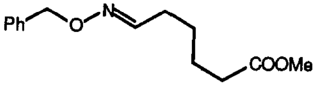
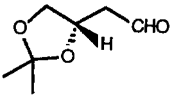
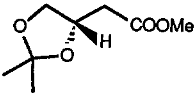
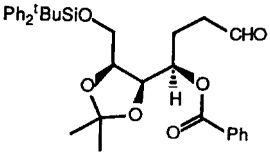
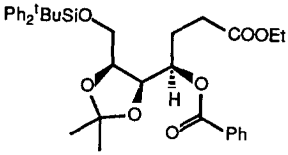
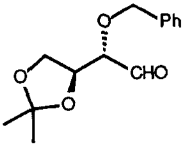
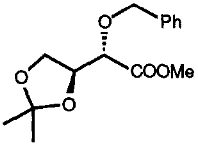
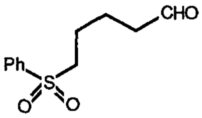
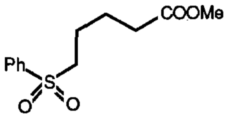
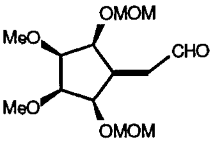
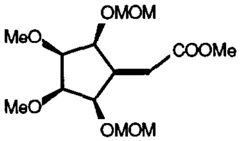
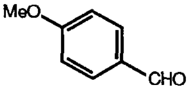
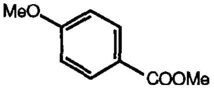
Entry	Aldehyde	Product	Yield (%)
1.		 (a) R = Me (b) R = Et (c) R = ^{i}Pr	94 91 80
2.		 (a) R = Me (b) R = Et (c) R = ^{i}Pr	95 85 70
3.			88
4.			71[a]
5.			91[a]
6.			90
7.			90

TABLE I (Continued)

8.			89
9.			98[a]
10.			70[a]
11.			50[a,b]

a) The aldehyde was added to a premixed solution of alcohol, water, sodium bicarbonate, and bromine.

b) Remaining material was starting aldehyde (24 hr).

General Procedure: Excess bromine (3 to 5 equiv), prepared as a 2.0 M stock solution in alcohol-water (9:1 by volume) was added to a 0.5 M solution of aldehyde in alcohol-water (9:1) buffered with sodium bicarbonate (20 equiv). Reactions were continuously monitored by thin-layer chromatography, and stirred at 22° C for generally 3 to 5 hours. Solid sodium thiosulfate was added to quench excess bromine, and dilution with water was followed by extraction with ether (3 times). Combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and the crude product was purified by flash chromatography on silica gel. Our reactions are not initiated by light, and rates are not substantially different when reactions are protected from ordinary lighting.

In summary, we have illustrated several examples of direct oxidations of aldehydes to esters with bromine in alcohol solvents in the presence of sodium bicarbonate. The technique affords yields which are often superior to the usual two-step processes for this transformation. Our method displays high potential for reliable extension to more complex substances, particularly enantiomerically pure building blocks obtained from sugars, as well as sugar dialdehydes derived from mono-and oligosaccarides by periodation.

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7. All products gave the expected characterizations as detailed by high-field ^{1}H-NMR, infrared, and high resolution mass spectrometry. Combustion analyses were obtained for entries 1,2, 3, 6, and 7.

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