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THE OXIDATION OF ALDEHYDE BISULFITE ADDUCTS TO CARBOXYLIC ACIDS AND THEIR DERIVATIVES WITH DIMETHYLSULFOXIDE AND ACETIC ANHYDRIDE

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Summary: Bisulfite adducts which are readily formed from aldehydes are conveniently oxidized to carboxylic acids and derivatives by the action of DMSO/Ac_2O followed by quenching with water, an alcohol or an amine.

During the course of a study on the synthesis of medicinally important hydratropic acids we had occasion to examine the oxidation of aldehyde 1 to acid 3. Although this transformation should be straightforward based on oxidation potential it is often encumbered with low yields. Highly enolizable aldehydes such as 1 are particularly prone to carbon-carbon bond cleavage giving diminished yields of desired acid.[1] An examination of conventional methodologies employing permanganate[2] or chromium based reagents[3] generally gave mediocre yields. Some of the newer procedures such as those based on hypochlorite[4] or the Sharpless $RuCl_3/NaIO_4$ method[5] were similarly unsuccessful. An attempt to carry out the reaction electrochemically gave the acid in an exiguous 19% yield.[6] In all cases over-oxidation to ketone 4 was extensive. Silver oxide[7] is reported to work well but presents a considerable economic problem upon scale-up.

Due to the economic constraints and the general problem of over-oxidation we explored, as an alternative, the possible oxidation of aldehydes through their bisulfite adducts in analogy to Corey's oxidation of cyanohydrins with manganese dioxide.[8] We now report the successful new oxidation wherein the preformed bisulfite[9] adduct is treated with DMSO and Ac_2O[10] at rt for 24 hr. Basic hydrolysis of the reaction mixture followed by extractive work-up gives the carboxylic acid in excellent yield without the problem of over-oxidation to ketone 4. Preliminary results for a series of aldehydes are shown in Table I. The yields are in general quite good especially in light of the general tendency for over-oxidation of these substrates. Even though we have not carried out an extensive survey, the reaction should be compatible with most aldehydes.

Scheme I

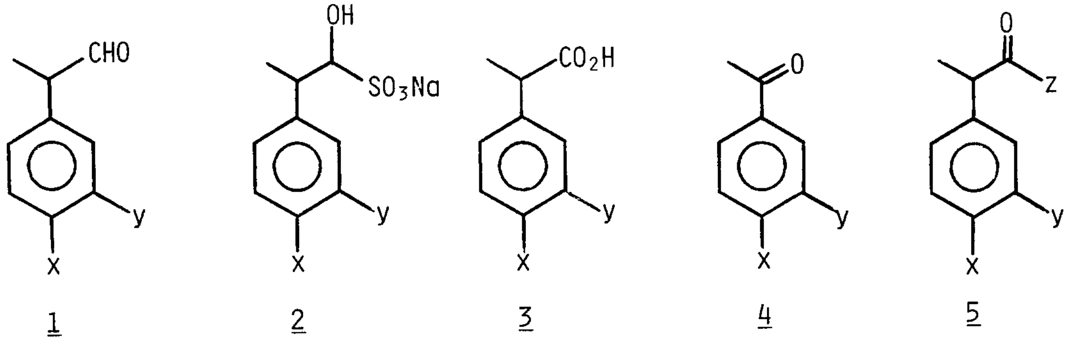
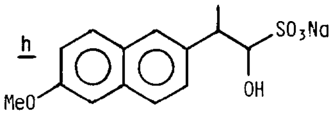


Table I: Results for oxidation of adducts 3.

Entry	Bisulfite adduct 2		Yield*	Entry	Bisulfite adduct 2		Yield*
	X	Y	acid 3		X	Y	acid 3
a	Ph	F	90	e	OPh	H	76
b	OMe	H	76	f	$(CH_3)_2CHCH_2$	H	81
c	Cl	H	67	g	F	H	76
d	Ph	H	84	h			76

*Yields are for chromatographically pure material and are not optimized.

The pathway illustrated in Scheme II provides a useful heuristic which is compatible with the observed results. The hydroxyl of the bisulfite adduct 6 is initially oxidized by DMSO and Ac_2O to give the α-ketosulfonate salt 7 which is hydrolyzed to form acid 8. On the basis of this mechanistic rationale it was expected that if nucleophiles other than water were substituted during the workup procedure it should be possible to prepare esters and amides directly. In fact, quenching the reaction with NaOMe/MeOH cleanly gave the methyl ester

5 (Z=OMe). Moreover, extension of this methodology to the synthesis of amides also proved facile. When the intermediate ketosulfonate was treated with ammonia we obtained a 91% yield of amide 5 ($Z=NH_2$). From Table II it is clear that primary and secondary amides may also be may also be prepared in this manner.

Scheme II

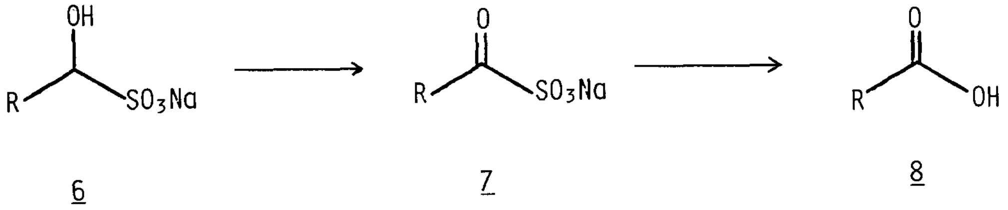


Table II: Yield of acid derivatives 5.

	Quenching Nucleophiles			
Bisulfite Adduct	Methanol	Ammonia	Piperidine	Benzyl Amine
3a	90%*	91%	85%	82%

*All yields in the table are for isolated chromatographically pure material.

Sample Experimental Procedure:

A mixture of 1.50g (4.50 mmole) of bisulfite adduct 2a, 6.5ml dimethylsulfoxide (DMSO), and 3.1 ml acetic anhydride (Ac_2O) was stirred at room temperature for 24hr. At this point the bisulfite adduct had all dissolved. Ammonia gas was then bubbled into the solution (exothermic) for 3 min. The mixture was stirred at room temp. for 1/2 hr, poured into water and extracted with methyl t-butyl ether (MTBE). The ether layers dried over $MgSO_4$ and concentrated to afford the amide as a white solid in 91% yield after silica gel chromatography. Other amides are prepared by adding an excess of the desired amine to the intermediate sulfonate. Acids are prepared by quenching the reaction with aqueous K_2CO_3, followed by acidification and MTBE extraction.

In conclusion we have developed an alternative procedure for the high yield oxidation of aldehydes which gives acids, esters and amides directly. The procedure is particularly useful in cases where over-oxidation presents a major problem as in the oxidation of the highly enolizable hydratropic aldehydes.

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[9] Bisulfite adducts were easily prepared by the addition of an aqueous solution of $NaHSO_3$ to a methanolic or ethanolic solution of the aldehyde followed by filtration of the precipitated adduct.

[10] For a review of DMSO based oxidations see: A. J. Mancuso and D. Swern Synthesis, 165 (1981).

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