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A New Deprotection Method for Levulinyl Protecting Groups under Neutral Conditions

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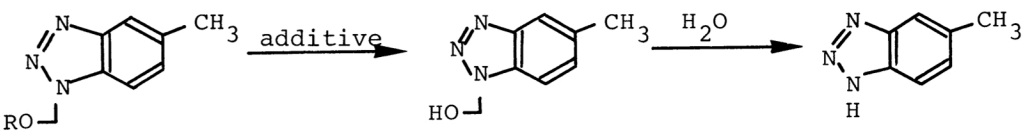
Sulfite ion-induced cleavage of the levulinyl group under neutral conditions provides a convenient and mild deprotection method especially for alkali labile and/or oxygen sensitive compounds.

Although it is well known that sodium bisulfite ($NaHSO_3$) forms reversible addition products with certain carbonyl compounds (e.g. 1),[1] few examples exploiting this behavior of the sulfite ion have been reported.[2]

$$C_6H_5\text{-}CHO + NaHSO_3 \rightleftharpoons C_6H_5\text{-}\underset{\underset{OH}{|}}{CH}\text{-}SO_3Na$$

1

In the course of studies on photographic developer-responsive organic compounds,[3] an urgent need to cleave levulinyl protecting groups without affecting groups such as methyl and phenyl esters prompted us to examine the characteristic affinity of sulfite ion to carbonyl functions. The levulinyl group has been used as a hydroxyl protecting group in carbohydrates,[4] nucleotides,[5] and steroids.[6] However, the reported cleavage conditions, a) $NaBH_4$ / aq. dioxane for 20 min,[7] b) excess NH_2NH_2 / boiling CH_3OH[8] or pyridine-AcOH,[4] c) NaH / THF,[9] are often unsuitable for the compounds containing additional electrophilic centres because of the irreversible reaction of these reagents. In this communication we wish to describe the first example of the cleavage of levulinyl groups induced by sulfite ion under essentially neutral conditions. The relative reactivity of sulfite compounds to carbonyl functions was estimated from the value of the pseudo-first order rate constants for reactions of the levulinate 2a in the presence of 10^2 times excess of sulfite compounds in Britton-Robinson buffer at pH = 7.0.[10]



2a R = $-COCH_2CH_2COCH_3$ 3 4
b R = $-COCH_3$

As listed in Table 1, the presence of sulfites (entries 1, 2, and 3) accelerated the cleavage reaction of 2a at a rate 10^4 times greater than in the case of

Table 1. The Pseudo-first Order Rate Constants for Cleavage Reactions of 2a and 2b[a)]

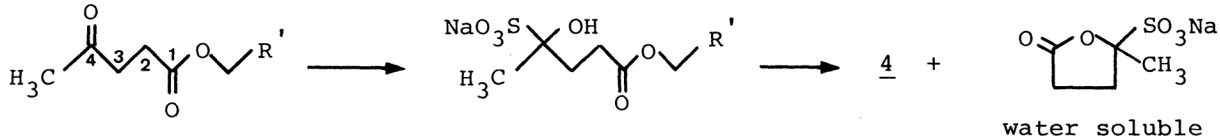
Entry	Compound	Additive	Rate constant k/s^{-1}	$t_{1/2}$
1	2a	$NaHSO_3$	1.83×10^{-3}	6 min
2	2a	Na_2SO_3	1.25×10^{-3}	9 min
3	2a	$Na_2S_2O_5$ b)	1.67×10^{-3}	7 min
4	2a	$Na_2S_2O_3$	7.08×10^{-5}	2.7 h
5	2a	$Na_2S_2O_6$	1.85×10^{-6}	104 h
6	2a	none	1.33×10^{-7}	62 d
7	2b	$NaHSO_3$	3.47×10^{-8}	230 d
8	2b	none	1.01×10^{-8}	2.2 y

a) 25 °C, 50 v/v% Acetonitrile/Britton-Robinson buffer (pH = 7.0). [2] = 5.64×10^{-4} M, [additive] = 5.64×10^{-2} M

b) $Na_2S_2O_5 + H_2O \longrightarrow 2NaHSO_3$

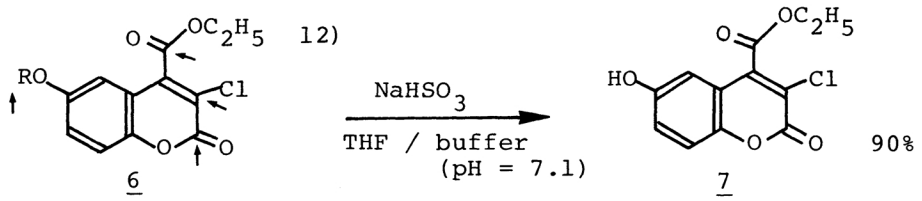
c) Obtained by extrapolation.

no additives (entries 6 and 8). The remarkable difference in the reactivity between levulinate 2a and acetate 2b (entries 1 and 7) are consistent with the assumed pathway shown in the Scheme below involving the initial attack of sulfite ion to the carbonyl carbon at the 4-position of 2a with the formation of the tetrahedral intermediate 5 and the subsequent intramolecular cyclization leading to cleavage of the ester function.



2a 5

A usefulness of this procedure was demonstrated in the selective cleavage of the levulinyl group of alkali labile compound 6 (mp 135-136 °C). Treatment of 6 with $NaHSO_3$ (2.5 equiv.) in THF / buffer (pH = 7.1) at room temperature for 2 h afforded ethyl 3-chloro-7-hydroxy-4-coumarincarboxylate 7 (mp 235-237 °C)[11)] in 90% yield.

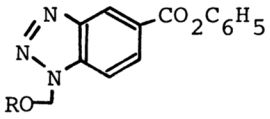
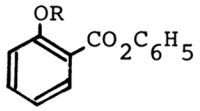
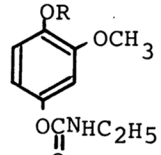
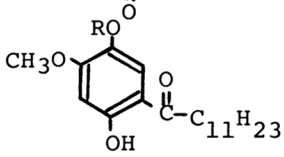
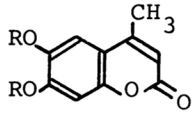
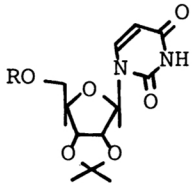
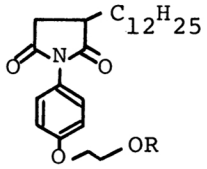
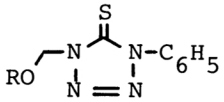


6 7

R = $-COCH_2CH_2COCH_3$

Moreover, a simpler procedure was developed by use of a mixture of Na_2SO_3 and $Na_2S_2O_5$ (4 to 1 molar ratio) in order to maintain neutrality of the reaction solution without pH control throughout the reactions.[13)] The successful protection[14)] and deprotection reactions listed in Table 2 also indicate a reasonable

Table 2. Results of the Selective Cleavage of Several Levulinates by Sulfite Compounds

Entry	Levulinate[a)]	Mp θ_m/°C	Conditions[b)]	Product	Yield/%[c)]
1		116-117	A: 1.5 equiv. 30 min, r.t.	triazole	95
2		54	A: 1.5 equiv. 30 min, r.t.	R = H	93
3		78-80	A: 3.0 equiv. 2 h, r.t.	R = H	85
4		55-56	B: 3.0 equiv. 3 h, 40 °C	R = H	95
5		103-105	B: 3.5 equiv. 2 h, 40 °C	R = H	82
6		amorphous	B: 2.0 equiv. 4 h, 40 °C	R = H	86
7		162-165	B: 1.5 equiv. 4 h, 40 °C	R = H	90
8		94-95	B: 1.5 equiv. 1 h, r.t.	R = H	90

a) R = $-COCH_2CH_2COCH_3$ b) All reactions were carried out by use of 0.2 M of substrate concentration in aqueous THF, CH_3CN, or C_2H_5OH; condition A (4 to 1 molar ratio of Na_2SO_3 and $Na_2S_2O_5$); condition B (10 to 1 molar ratio of Na_2SO_3 and $Na_2S_2O_5$).

c) The yields given are those of essentially pure products.

applicability for alkali labile and/or oxygen sensitive compounds. Thus, protected triazole (entry 1), phenols (entries 2 and 3), hydroquinones (entries 4 and 5), and udidine (entry 6) were smoothly deprotected by treatment of a mixture of Na_2SO_3 and $Na_2S_2O_5$ in aqueous organic solvent to regenerate the corresponding hydroxyl or secondary amino functions without affecting other functional groups.

A typical procedure is as follows: a solution of 2-(phenoxycarbonyl)phenyl levulinate (3.12 g, 10 mmol) in THF (25 cm^3) was added a solution of Na_2SO_3 and $Na_2S_2O_5$ (1.51 g, 12 mmol and 0.57 g, 3 mmol) in H_2O (25 cm^3). The reaction mixture was stirred vigorously for 30 min at room temperature, poured into water (100 cm^3) and extracted with ethyl acetate (3 x 50 cm^3). The extracts were washed with water (50 cm^3) and saturated brine (50 cm^3) and then dried over Na_2SO_4. The solvent was removed under reduced pressure to give crystals of phenyl salicinate (2.10 g).

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10) Accelerating effects of other additives (e.g. morpholine, sodium iodide, thiourea, and pyrazole) could not be observed under these conditions.
11) G. W. Holton, G. Parker, and A. Robertson, J. Chem. Soc., 1949, 2049.
12) The arrows in compound 6 designate possible positions cleaved by hydrolysis.
13) Sulfite ion did not accelerate cleavage reactions of levulinates below pH = 6.
14) All of levulinates were prepared with levulinic anhydride (1.5 equiv.) in the presence of pyridine (4.0 equiv.) and a catalytic amount of 4-dimethylamino-pyridine in anhydrous THF at room temperature for several hours.

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