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Sulfite formation versus chlorination of benzyl alcohols with thionyl chloride

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ABSTRACT

Recently, we have reported the photolytic decay of a library of para-substituted dibenzylic sulfites in a Srinivasan-Griffin-Rayonet photochemical reactor. In an attempt to synthesize the complete library for that study we discovered that bis(p-methoxybenzyl) sulfite and bis(p-phenoxybenzyl) sulfite could not be formed and only their corresponding benzyl chlorides were synthesized. Thus, sulfite formation versus chlorination of a range of para-substituted benzyl alcohols with thionyl chloride was investigated. Sulfite formation was observed to be parabolically related to Swain and Lupton's Field 3-values while chloride formation was found to be linearly related to Swain and Lupton's Field \Re -values.

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Organosulfite is a rarely used functionality. Three most commonly studied compounds containing this structural moiety are dimethyl sulfite, diethyl sulfite, and propargite. Dimethyl sulfite is commonly used as an additive in some polymers as a means to prevent oxidation.^{1–3} Recently, much effort has been done on its potential use as an electrolyte solvent for battery applications.^{4–6} In addition to being an antioxidant,^{5,6} diethyl sulfite has found use within the grain storage industry as an antifungal agent.⁷ Unlike both dimethyl and diethyl sulfites, propargite is an unsymmetrical sulfite. It is a commonly used acaricide pesticide^{8–10} and is conventionally known as Omite[®]. In addition to the killing of mites, it is also highly toxic to plankton,¹¹ fish,¹² and amphibians.¹³ In the above examples, the synthesis of the sulfite moiety is accomplished by the reaction of an alcohol with thionyl chloride.

Chlorination with thionyl chloride is a technique that is covered in most undergraduate organic chemistry textbooks (Fig. 1) and is even performed in some undergraduate teaching laboratory settings. Less commonly taught, however, is that sulfite formation is also possible with the use of the same reagent but at different reactant equivalences (Fig. 1).

Recently, we synthesized a library of bis(benzyl) sulfites to study their photolytic decay profiles.¹⁴ In the course of this investigation, we observed that the rate of photolytic decomposition was parabolically related to Swain and Lupton's Field (8-) values, regardless of



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Scheme 1. Possible mechanism for the formation of benzyl chlorides opposed to bis(benzyl) sulfites.

Table 2

Table 1 Product % ratios determined by 1 H NMR, using 2:1 benzyl alcohols and thionyl chloride at different reaction times

X-Ph-CH ₂ OH	$R \times n$ times (min)	% chloride	% sulfite	% alcohol
Н	5	11.2	55.3	33.5
	60	10.8	54.6	34.6
	120	12.3	54.9	32.8
	180	11.5	56.2	32.3
	240	9.9	57.3	32.8
	300	12.1	53.1	34.8
NO ₂	5	34.0	15.4	50.6
	60	32.2	17.1	50.7
	120	32.8	16.2	51.0
	180	36.2	15.0	48.8
	240	34.8	13.8	51.4
	300	33.4	16.0	50.6
Cl	5	7.3	67.5	25.2
	60	5.1	66.9	28.0
	120	6.8	68.8	24.4
	180	8.2	68.1	23.7
	240	8.5	64.2	27.3
	300	7.0	67.1	25.9

the solvent employed. Interestingly, neither bis(*p*-methoxybenzyl) sulfite nor bis(*p*-phenoxybenzyl) sulfite could be synthesized in great enough quantity to further study, regardless of the reaction temperature, solvent, time, or base used. We proposed a possible mechanism for the formation of benzyl chlorides as opposed to bis(benzyl) sulfites (Scheme 1),¹⁴ suggesting that electron donation from the ether oxygen led to the displacement of SO₂ prior to the attack of another equivalent of benzyl alcohol. Interestingly, the amounts of sulfite and chloride products formed from the other benzyl alcohols used were dependent on the substituent at the *para*-position. Herein, we report the results of our investigation of relative sulfite formation versus chlorination upon treatment of *para*-substituted benzyl alcohols with thionyl chloride.

The reported general procedure for the synthesis of sulfites from benzyl alcohols involves reacting benzyl alcohol with thionyl chloride and pyridine in a ratio of 2:1:2 for 5 h in dichloromethane.¹⁵ Subsequent quenching with distilled water, washing twice with brine, drying on MgSO₄, concentrating under reduced pressure, and purification by column chromatography with 5:1 hexanes/ethyl acetate allowed for the isolation of unreacted starting materials, benzyl chlorides, and bis(benzyl) sulfites. We began by evaluating the reaction rate, using ¹H NMR to measure product distribution for reactions with a 2:1 ratio of benzyl alcohol/thionyl chloride at 5-300 min (Table 1). We were surprised and elated to observe that in all cases the reaction was complete within 5 min. We repeated this with 4-nitro- and 4-chlorobenzyl alcohols and again observed completion of the reaction within 5 min. Importantly, the ratios of chloride to sulfite to unreacted alcohol did not change over time, indicating the stability of the products in solution. Thus, all subsequent reactions were run for ≥ 5 min.

In order to ascertain the effect of the *para* substituent on the ratio of products, we examined the reactions of eleven different benzyl alcohols with thionyl chloride at five different ratios, 5:1, 2:1, 1:1, 1:2, and 1:5, respectively (Table 2). [All benzyl alcohols

Product % ratios determined by 1 H NMR, using various benzyl alcohols (BA) at 5:1, 2:1, 1:1, 1:2, 1:5 ratios of BA/SOCl₂

X-Ph-CH ₂ OH	BA/SOCl ₂	% chloride	% sulfite	% alcohol
Н	5:1	0	23.4	76.6
	2:1	11.2	55.3	33.5
	1:1	80.4	12.6	7.0
	1:2	100	0	0
Ме	1:5	100	0	0
	5:1	0	5.9	94.1
	2:1	32.7	39.8	27.5
	1:1	81.7	0	18.3
	1:2	100	0	0
	1:5	100	0	0
tBu	5:1	6.4	10.4	83.2
	2:1	27.0	60.1	12.9
	1:1	74.4	0	25.6
	1:2	100	0	0
	1:5	100	0	0
Ph	5:1	0	14.0	86.0
	2:1	26.3	29.2	44.5
	1:1	66.1	0	33.9
	1:2	100	0	0
	1:5	100	0	0
ОМе	5:1	19.1	0	80.9
	2:1	48.6	0	51.4
	1:1	88.1	0	11.9
	1:2	100	0	0
	1:5	100	0	0
OPh	5:1	16.5	4.6	78.9
	2:1	40.2	6.4	53.4
	1:1	66.1	0	33.9
	1:2	100	0	0
	1:5	100	0	0
Cl	5:1	0	22.1	77.9
	2:1	34.0	15.4	50.6
	1:1	64.8	4.5	30.7
	1:2	98.8	1.2	0
	1:5	100	0	0
Br	5:1	0	10.7	89.3
	2:1	35.6	30.1	34.3
	1:1	90.2	0	9.8
	1:2	100	0	0
	1:5	100	0	0
CF ₃	5:1 2:1 1:1 1:2 1:5	0 0 5.8 100	16.9 12.5 11.6 8.8 0	83.1 87.5 88.4 85.4 0
CN	5:1	0	14.8	85.1
	2:1	0	39.1	60.9
	1:1	0	6.3	93.7
	1:2	6.2	17.5	76.2
	1:5	100	0	0
NO ₂	5:1	0	13.7	86.3
	2:1	7.3	67.5	25.2
	1:1	59	17.7	23.3
	1:2	87.0	0	13.0
	1:5	100	0	0

used were obtained from commercial sources with the exception of 4-cyanobenzyl alcohol which was initially reduced from its

Table 3

Product % ratios determined by ¹H-NMR, using 2:1 benzyl alcohols and thionyl chloride compared to Swain and Lupton's \Re - and ϑ -values

X-Ph-CH ₂ OH	F	% sulfite	R	% chloride
tBu	-0.02	60.1	-0.18	27.0
Н	0	55.3	0	11.2
Me	0.01	39.8	-0.18	32.7
Ph	0.12	29.2	-0.13	26.3
OMe	0.29	0	-0.56	48.6
OPh	0.37	6.4	-0.40	40.2
CF ₃	0.38	12.5	0.16	0
Cl	0.42	15.4	-0.19	34
Br	0.45	30.1	-0.22	35.6
CN	0.51	39.1	0.15	0
NO ₂	0.65	67.5	0.13	7.3



Figure 2. Percent sulfite formation determined by ¹H NMR, using 2:1 benzyl alcohols and thionyl chloride versus Swain and Lupton's \mathcal{F} -values.

corresponding acid as previously reported.¹⁶] Significant variability in product distribution was observed at all ratios except 1:5, in which case only benzyl chlorides were generated. For example, the reaction of 4-cyanobenzyl alcohol with thionyl chloride in a ratio of 2:1 gave a product mixture consisting of 0% chloride and 39% sulfite, while the same reaction with 4-*tert*-butylbenzyl alcohol afforded a product mixture consisting of 27% chloride and 60% sulfite.

Though there appeared to be no correlation of our results for these reactions (2:1 ratio of benzyl alcohol to thionyl chloride) to Hammett's constant,¹⁷ we did observe that the sulfite product predominated when the *para*-substituent had a Swain and Lupton's *s*-value¹⁸ either on the high or low end (Table 3).

Overall, percent sulfite formation is parabolically related to Swain and Lupton's *3*-values (Fig. 2). Mechanistically, a lack of correlation with Hammett's constant for the production of sulfite can be rationalized, since an additional atom separates the site of reaction from the aromatic ring. We have observed this parabolic phenomenon with Swain and Lupton's *3*-value in previous studies, particularly with the analogous dibenzylic dialkoxy disulfides which underwent both thermolytic and photolytic decomposition at rates that parabolically correlated to *s*-values.^{19,20} in addition to the aforementioned bis(benzyl) sulfites photolytic decomposition study.¹⁴ It can be rationalized that a substituent with a high 5-value, such as nitro, withdraws the electron cloud toward it and away from the sulfonyl chloride moiety, hence making it more prone to nucleophilic attack by another benzyl alcohol (Scheme 2). As the magnitude of the *s*-value decreases, this polarization difference decreases, 'bottoming-out' with methoxy at an &-value of 0.29. Substituents with \mathcal{F} -values lower than methoxy, such as *t*-Bu, Me, etc. that do not possess a lone pair of electrons (vide supra), can donate electron density toward the reacting sulfur site. As a result, the benzylic oxygen can donate a pair of electrons to the sulfur displacing chloride, which would thus allow for the subsequent attack by another benzyl alcohol (Scheme 2).

While this rationale accounts for the product distribution of sulfite, it is not consistent with that of chloride. We observed only a loose association of the amount of chloride product formed with Hammett's constants and none with Swain and Lupton's \mathcal{F} -values, but we did observe a linear correlation with Swain and Lupton's Resonance (\Re -) values.¹⁸ It logically follows that the chloride product distribution is more strongly related to a resonance effect than an overall field effect because product formation results from nucleophilic attack directly on the benzylic carbon. Substituents



Scheme 2. Possible rationale for the formation of bis(benzyl) sulfites at high and low Swain and Lupton's 3-values.



Figure 3. Percent chloride formation determined by ^1H NMR, using 2:1 benzyl alcohols and thionyl chloride versus Swain and Lupton's $\ensuremath{\Re}\xspace$ -values.

with a more negative \Re -value, such as methoxy (-0.56), more strongly donate electron density into the aromatic ring, liberating SO₂, and increasing the formation of the quino-type intermediate (Scheme 1). Substituents with positive \Re -values do not promote such a mechanism and are thus associated with virtually no chloride formation. Indeed, both cyano- and trifluoromethyl benzyl alcohols produced no detectable benzyl chlorides when the reactions were performed at 2:1 ratios of benzyl alcohol to thionyl chloride (Table 2). We lastly augmented the ratio of the *para*substituted benzyl alcohol and thionyl chloride by running at 5:1, 2:1 (vide supra) 1:1, 1:2, and 1:5 benzyl alcohol to thionyl chloride (Table 2). Unsurprisingly, as the amount of SOCl₂ increases compared to benzyl alcohol, the amount of the corresponding benzyl chloride increases and reaches 100% even with benzyl alcohol containing substituents with positive \Re -values (Fig. 3).

In summary, we have examined the chlorination versus sulfite formation of a range of *para*-substituted benzyl alcohols when reacted with thionyl chloride. The sulfite formation is parabolically related to Swain and Lupton's Field \mathscr{F} -values where the extremes (i.e. NO₂: \mathscr{F} -value = 0.65 and *t*Bu: \mathscr{F} -value = -0.02) predominately produce sulfite when reacted in a 2:1 ratio of benzyl alcohol to thionyl chloride. Chloride formation is linearly related to Swain and Lupton's Field \mathscr{R} -values where the electron donating methoxy-substituted benzyl alcohol yields the highest percentage of chloride formation as opposed to the cyano- and trifluoromethylsubstituted benzyl alcohols, which afford none when run at the 2:1 ratio of benzyl alcohol to thionyl chloride. Finally, we were able to show that this reaction does not require the previously reported 5 hours, but is in fact completed after only 5 min.

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