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Unexpected transformations of 3-(bromoacetyl)coumarin provides new evidence for the mechanism of thiol mediated dehalogenation of α-halocarbonyls

Faith N. Magwenzi,[a] Setshaba D. Khanye,[b] Clinton G. L. Veale[a,]*

[a]*Faculty of Pharmacy, Rhodes University, Grahamstown, 6140, South Africa*
[b]*Department of Chemistry, Rhodes University, Grahamstown, 6140, South Africa*

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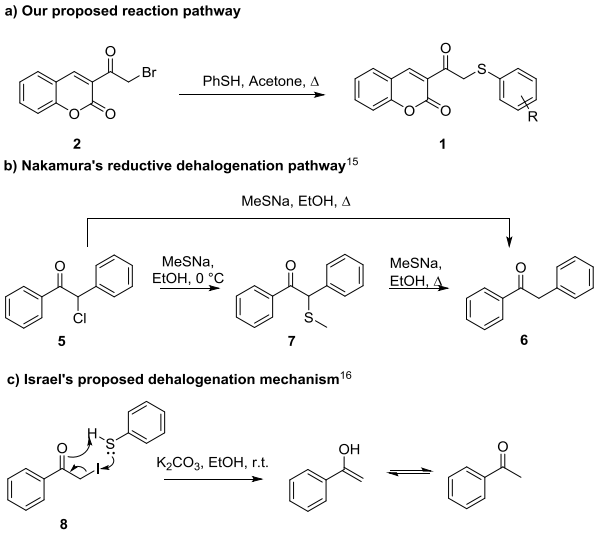
ABSTRACT

The mechanism for the thiol mediated dehalogenation of α-halogenated carbonyls has remained an unresolved problem, despite its ongoing application in synthetic organic chemistry. Nakamura and co-workers first proposed that net dehalogenation occurs *via* sequential nucleophilic substitutions, while Israel and co-workers concluded that the rate at which dehalogenation occurred suggested that dehalogenation proceeds in a single concerted step. In this study, we investigated the debromination and nucleophilic substitution of 3-(bromoacetyl)coumarin with a variety of thiophenols, whose electron donating or withdrawing natures resulted in large variations in the degree of nucleophilic substitution and dehalogenation products, respectively. Results from these experiments, in addition to an unexpected formation of thioether containing dibenzo[*b*,*d*]pyran-6-ones from a Robinson annulation, has provided new evidence for this disputed mechanism.

The unique chemical characteristics of both synthetic and naturally occurring coumarin derivatives has resulted in extensive investigation regarding their potential applications as agrochemicals, pharmaceuticals, fluorescent dyes and cosmetics.[1–5] Accordingly, we were interested in incorporating this scaffold into our antimalarial ethanone-α-thioether programme.[6] We reasoned that coumaryl-3-ethanone-α-thioethers (**1**) could be prepared through the apparently facile nucleophilic substitution of 3-(bromoacetyl) coumarin (**2**) with an appropriate thiophenol in acetone (Scheme 1a). A similar transformation has previously been reported using ethanol as a solvent,[7] which we opted to avoid due to our experience where excess ethanol could possibly compete as a nucleophile. However, we did not anticipate significant challenges in generating a small library of compounds. Our first attempt at this reaction (Table 1, entry a1) with unsubstituted thiophenol (**3a**) resulted in low conversion to the corresponding thioether **1a**, while unexpectedly a significant amount of compound **2** underwent a net reductive dehalogenation, forming 3-acetylcoumarin (**4**) with very little detectable α-bromoketone remaining.

Chemoselective reductive dehalogenation of organo-halide compounds has persistently evoked the interest of synthetic organic chemists, not only for environmental applications, but also for the controlled manipulation of chemical scaffolds.[8] Consequently, the selective reduction of α-haloketones has also proven to be a synthetic transformation of general utility which routinely recurs in the literature.[9–13] While, thiol assisted reductive dehalogenation of α-haloketones is not an unknown phenomenon,[14] we noted that this transformation is still not entirely understood.



Scheme 1. (a) Our proposed scheme for the synthesis of various thioethers. (b) Reductive dehalogenation pathway as described by Nakamura and co-workers (c) Reductive dehalogenation mechanism proposed by Israel and co-workers

* Corresponding author. Tel.: +27-46-603-8096; fax: +27-603-7506; e-mail: c.veale@ru.ac.za

Nakamura and co-workers[15] noted that heating α-chlorodeoxybenzoin (**5**) with excess sodium methanethiolate in ethanol unexpectedly formed deoxybenzoin (**6**) in near quantitative yield, while repeating the reaction at 0 °C gave rise to α-(methylthio)deoxybenzoin (**7**, Scheme 1b). Furthermore, they determined that compound **6** could also be formed upon heating **7** with additional methanethiolate, leading to the reasonable conclusion that the mechanism for net reductive dehalogenation of **5** occurs first by thioether formation, followed by a second nucleophilic attack by excess thiolate on the thioether sulfur. They further observed that displacement of methanethiolate was slower using thiophenol, which they reasoned was due to the lower nucleophilicity of thiophenol. Israel and co-workers[16] also reported a rapid and unexpected reductive dehalogenation of 14-iodo-*N*-(trifluoroacetyl)-daunorubicin in the presence of alkanethiols or thiophenol (2 eq.) with K_2CO_3 in ethanol at room temperature. They further demonstrated the same phenomenon occurred in quantitative yields with α-iodoacetophenone (**8**), while repetition with either α-bromo or chloro acetophenones resulted in formation of the corresponding thioethers. They concluded from their study, that the respective halogen reactivity influences the course of the reaction toward either substitution or dehalogenation. Furthermore, they hypothesized that the rate at which dehalogenation occurred precluded the pathway proposed by Nakamura and co-workers leading them to offer an alternative mechanistic explanation, in which dehalogenation occurs in a single discreet step (Scheme 1c).

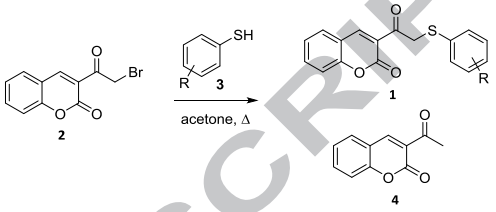
We reasoned that apart from halogen reactivity, the primary differences between the mechanisms of Nakamura and Israel lie in the relative ability of the thiol to act as a nucleophile, therefore requiring two equivalents of thiophenol (Nakamura) or a proton donor, leading to enol formation, requiring one thiophenol equivalent (Israel). Hudson and Klopman had previously demonstrated that electron withdrawing and donating groups decrease and increase nucleophilicity of thiophenols, respectively.[17] Accordingly, we embarked on an exploratory study to further understand the role that the electronic environment of thiophenol would have on the reductive dehalogenation of **2**.

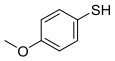
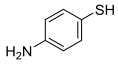
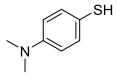
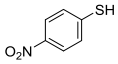
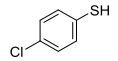
Our first group of experiments (Table 1, entries b1–e1) focused on increasing the electron density on the thiophenol sulfur using electron donating substituents. Initially, a negligible influence on conversion was observed using the weakly electron donating *para*-methyl group (Entry b1), while thiophenols containing *para*-methoxy, amino and dimethylamino moieties (Entries c1–e1), which are able to donate electron density through resonance, reversed this trend. In particular, the increased nucleophilicity of the *para*-amino and dimethylamino thiophenols resulted in satisfying conversion to the respective thioethers (**1d** and **1e**), coupled with low levels of dehalogenation.

Accordingly, we then turned our attention to the influence that electron withdrawing groups, and the consequent reduction in sulfur electron density, might have on the relative conversion of **2**. In contrast to entries d1 and e1, the presence of a strongly electron withdrawing *para*-nitro group (Entry f1) resulted in significant conversion to **4**, with no trace of the starting α-bromoketone and only a small quantity of thioether **1f**. Similarly, *para*-chloro thiophenol (Entry g1) resulted in significant dehalogenation, with no detectable thioether **1g**. Interestingly, however, was the presence of a low yet still appreciable quantity of unreacted starting material **2**, indicating, that the capacity for reductive dehalogenation did not necessitate an increase in nucleophilic character. The reaction, with *meta*-chloro thiophenol (Entry h1) resulted in a similar degree of dehalogenation, this time with the formation of a small amount of thioether **1h**, while *ortho*-chloro thiophenol (Entry i1) resulted in complete dehalogenation.

In order to gain further mechanistic insight, several experiments were repeated with lower thiophenol equivalents (1.2 eq. entries a2–d2, f2 and h2). Here we generally observed similar levels of dehalogenation, and in instances where lower dehalogenation was seen, this corresponded with a greater proportion of α-bromoketone remaining rather than thioether formation. Of greatest significance in this series was entry d2 where dehalogenation increased in the presence of lower equivalents of *para*-amino thiophenol. Importantly, no reaction was observed when no thiophenol was added (Entry j).

Table 1.[a]



Entry	Thiophenol	**1**[b]	**2**[b]	**4**[b]
a1[c]		21	2	77
a2[d]		3	23	74
b1		17	3	80
b2		15	9	76
c1		46	0	54
c2		9	35	56
d1		88	0	12
d2		48	0	52
e1		85	5	10
e2		NA	NA	NA
f1		6	0	94
f2		5	22	73
g1		0	12	88
g2		NA	NA	NA
h1		14	1	85
h2		17	7	76
i1		0	0	100
i2		NA	NA	NA
j	None	0	100	0

[a]Reagents and conditions: Compound **2** (100 mg, 0.374 mmol, 1 eq.), acetone (10 mL), thiophenol (2 or 1.2 eq.), reflux, 5 h. [b]Percent conversion determined by ^{1}H NMR integrals. [c]Thiophenol (2 eq.). [d]Thiophenol (1.2 eq.).

Overall a general pattern was observed, where strongly electron withdrawing substituents on the thiophenol ring resulted in greater reductive dehalogenation compared to strongly electron donating substituents. In the context of Nakamura's nucleophilic displacement theory which cited the lower nucleophilicity of thiophenol as a factor contributing to decreased dehalogenation, one would expect that stronger nucleophiles such as **3d** and **3e** would display superior dehalogenation, while conversely, *para*-nitro thiophenol possessing far less electron density at the sulfur, should not dehalogenate to such an extent. Furthermore, this mechanism requires a second equivalent of thiophenol to complete dehalogenation. Therefore, in experiments conducted with 1.2 eq. of thiophenol a greater proportion of thioether would be expected in the reaction mixture, having been unable to undergo the second nucleophilic attack. However, our results indicated that similar levels of dehalogenation were achievable with fewer equivalents of thiophenol, a result more congruent

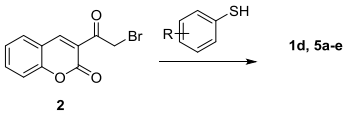
with the proposed mechanism of Israel and co-workers, and as mentioned, lower levels of dehalogenation did not correspond with increased thioether being present, but rather, the presence of unreacted starting material. Finally, in the case of entry d2, lowered equivalents of a demonstrably good nucleophile resulted in increased dehalogenation, further suggesting that the dehalogenation and substitution mechanisms are unrelated in this system.

Having struggled to initiate bromine substitution with several thiophenols, we were curious as to the effect that stoichiometric quantities of K_2CO_3 would have on this reaction, possibly allowing the desired nucleophilic displacement to outcompete dehalogenation (Scheme 2). We first attempted this modified reaction with the best performing nucleophile from the previous study, *para*-amino thiophenol. Here the addition of K_2CO_3 resulted in complete conversion to thioether **1d**, seemingly suppressing the small levels of dehalogenation observed in the absence of base. Accordingly, this reaction was repeated using several thiophenols (**3a, f–i**) which had displayed limited capacity as nucleophiles.

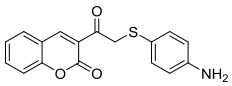
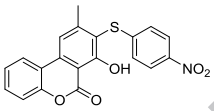
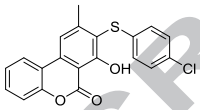
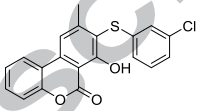
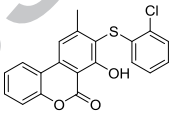
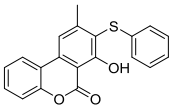
^{1}H NMR analysis of the crude reaction mixtures offered no clear evidence as to the presence of the α-bromoketone, nor the substitution and dehalogenation products. However, purification of the respective crude mixtures, led to the isolation of a series of unreported C-8 thiophenol functionalised dibenzo[*b,d*]pyran-6-ones in low yields (**5a–e,** Table 2). Related dibenzo[*b,d*]pyran-6-one scaffolds are found in several pharmaceutically interesting natural products,[18] find important applications in physical chemistry,[19] and have been the subject of a number of recent synthetic procedures.[20–24]

Koelsch and Sundet previously reported the formation of 7-hydroxy-9-coumarinyl-6*H*-benzo[*c*]chromen-6-one *via* a Michael type condensation between two subunits of **4** when heated at reflux in an ethanol solution containing piperidine.[25] This allowed us to propose a mechanism for the formation of **5a–e** as depicted in Scheme 2. Firstly, the addition of base facilitates nucleophilic substitution of the bromine atom, leading to the formation of an α-thiocarbonyl (**1**). Subsequent Robinson annulation between the α,β-unsaturated system of the 3-acylcoumarin and an enolate formed from acetone gives compound **6**. The electrophilicity of the α,β-unsaturated system is enhanced through chelation between the potassium cations and the 1,3-dicarbonyl system. Following addition of acetone, the strong electron withdrawing nature of the thiophenol moiety renders the adjacent methine protons slightly acidic, thereby facilitating deprotonation and subsequent enolate formation. The resultant enolate is then free to nucleophilically attack the carbonyl leading to cyclisation. This is followed by dehydration to complete the Robinson annulation, and subsequent aromatisation results in the formation of phenol, as reported by Koelsch and Sundet, to yield compound **5**. This final aromatisation step was described by Koelsch and Sundet as a spontaneous intramolecular aldolization and dehydrogenation, in addition to the dehydration step. While the mechanism involved here is currently uncertain, it is likely an air facilitated oxidation. Moriuchi and co-workers.[26] have explored a vanadium catalysed oxidative aromatisation of 2-cyclohexenones in the presence of atmospheric oxygen and a source of bromide. They also showed that this reaction could occur in low yield without the catalyst, which may provide a clue as to what is occurring here.

Table 2.[a] Yields of **1d** and **5 a-e**



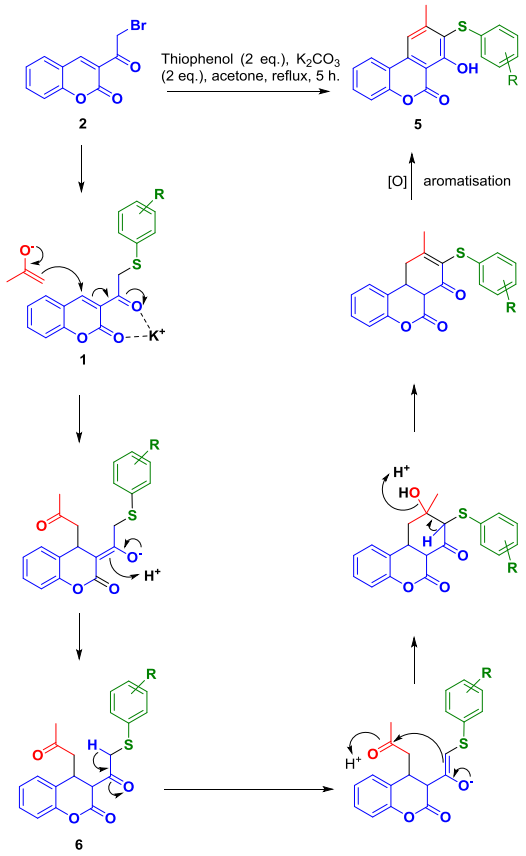
2

Compound	Structure	Yield[b] (%)
1d		quant.
5a		10
5b		4
5c		13
5d		12
5e		13

[a]Reagents and conditions: Compound **2** (100 mg, 0.374 mmol, 1 eq.), acetone (10 mL), thiophenol (2 eq.), K_2CO_3 (2 eq.) reflux, 5 h. [b]Isolated yields.

Three further control experiments were conducted, where 1) thiophenol was omitted, 2) TEA replaced K_2CO_3 and 3) the reaction was performed with methyl ketone **4** instead of **2**. Interestingly, in our hands, we did not observe the formation of the corresponding dibenzo[*b,d*]pyran-6-one in any of these reactions. We believe these observations tentatively support the notion that potassium chelation enhances the electrophilicity of the α,β-unsaturated system and that the electron withdrawing nature of the thiophenol facilitates the second enolate formation. Additionally, we did not observe cyclization in the presence of *para*-amino thiophenol, which we hypothesize is due to its electron donating capabilities which hinders methine deprotonation. While this transformation is potentially useful it also provides additional insight into the mechanism of debromination observed here.

The study described herein, was used to further develop the understanding of the thiol mediated dehalogenation of α-bromo carbonyls. A previous related study conducted by Israel and co-workers proposed that removal of iodine from an α-iodocarbonyl preferentially occurs in a single step, which does not require a strongly nucleophilic thiol species. However, this mechanism is incongruent with the observations of Nakamura and co-workers , and more recently Liu and co-workers,[14] who both showed that removal of chlorine from α-chlorocarbonyls occurs first by nucleophilic substitution. These seemingly contrasting mechanisms can be plausibly explained in the context of Pearson's hard and soft acid base theory.[27] The thiophenol sulfur is considered a 'soft' base which would preferably interact with the soft iodine, facilitating single step dehalogenation, whereas, sulfur is less likely to interact with the harder chlorine, therefore preferentially resulting in nucleophilic substitution as the initial step.



Scheme 2. Proposed reaction pathway for the formation of compounds **5a-e**

Evidence obtained in this study demonstrated that a mixture of substitution and debromination products were obtained in varying degrees depending on the electronic environment of the respective thiophenol, and that dehalogenation was not related to thiol nucleophilicity. Of particular importance was the observation that similar levels of dehalogenation were observed with lowered equivalents of the least nucleophilic thiophenols.

This suggests that the mechanism of debromination observed here mirrors that of Israel's de-iodination, whereby soft sulfur interacts with the relatively soft bromine. Additionally, strong electron withdrawing groups present on the reductive thiophenols decreases the pKa, thereby facilitating proton donation and enol formation, ultimately resulting in dehalogenation. Equally, an increase of thiol nucleophilicity either through electron donating groups, or the introduction of base, favours nucleophilic displacement of bromine, rather than dehalogenation.

In conclusion, we have gained new insight into an unresolved problem in chemistry, relating to the mechanism of thiol induced dehalogenation of α-haloketones. We observed significant changes in the degrees of dehalogenation and/or nucleophilic substitution of α-bromoketone **2** in the presence of variably substituted thiophenols. Furthermore, similar levels of dehalogenation were observed with lowered equivalents of thiophenol. These reactants were chosen to influence their respective electronic environments and as such provided evidence that the mechanisms of nucleophilic substitution and dehalogenation are not necessarily related, but can rather be influenced by subtle variations in the electronic environments of the respective reactants. This explanation also provides a feasible explanation for the differences observed by Nakamura and Israel, respectively. With respect to 3-(bromoacetyl) coumarin, reductive dehalogenation occurs in a single step in the presence of softer bases rather than requiring an initial nucleophilic substitution. Finally, the addition of stoichiometric quantities of K_2CO_3, resulted in small, yet isolatable quantity of new thiophenol containing dibenzo[*b*,*d*]pyran-6-ones.

Acknowledgments

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Supplementary data

Supplementary data relating to experimental procedures and spectral data can be found in the online version.

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Highlights

- **This work provides new insight into the disputed mechanism of thiol mediated dehalogenation of α-halogenated carbonyls**
- **Dehalogenation can be manipulated by alteration of thiophenol substitution**
- **A new synthesis of unknown thiolated benzopyranones has been discovered**

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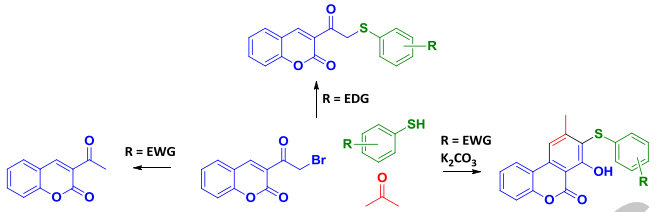

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