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

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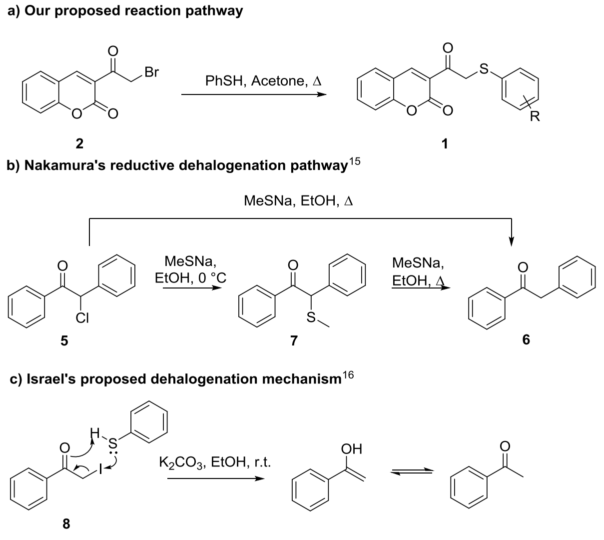
ABSTRACT

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

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