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Ambient-Temperature Newman–Kwart Rearrangement Mediated by Organic Photoredox Catalysis

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Supporting Information

ABSTRACT: The Newman–Kwart rearrangement is perhaps the quintessential method for the synthesis of thiophenols from the corresponding phenol. However, the high thermal conditions required for the rearrangement of the requisite *O*-aryl carbamothioates often leads to decomposition. Herein, we present a general strategy for catalysis of *O*-aryl carbamothioates to *S*-aryl carbamothioates using catalytic quantities of a commercially available organic single-electron photooxidant. Importantly, this reaction is facilitated at ambient temperatures.

There are a number of strategies for formation of carbon–sulfur bonds on aromatic molecules,[1] one efficient method being the conversion of a phenol to a thiophenol known as the Newman–Kwart rearangement (NKR).[2,3] While the rearrangement of *O*,*O*-diaryl carbonothioates to *O*,*S*-diaryl carbonothioates had been reported in 1930 by Schonberg, it was not until 1966 that Newman and Karnes disclosed the thermal rearrangement of *O*-aryl carbamothioates to *S*-aryl carbamothioates, permitting the straightforward preparation of aryl thiols from the corresponding aryl phenols in good yields (Figure 1).[4,5] Earlier that same year, Kwart and Evans reported

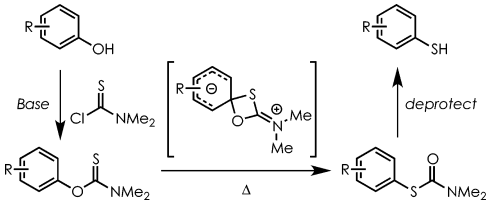

Figure 1. Thermal NKR of *O*-aryl carbamothioate to *S*-aryl carbamothioate.

a similar rearrangement in the vapor phase.[6] The NKR proceeds via *ipso* nucleophilic attack of the thiocarbonyl moiety onto the aryl ring, traversing through a spirocyclic transition state.[7] To access this highly strained intermediate, the NKR requires high temperatures regularly in excess of 200 °C, sometimes above 300 °C, to proceed. Nevertheless, the NKR is a widely used method for the synthesis of aryl thiols for a variety of applications.[8]

Unfortunately, the high temperatures required to enact the rearrangement often result in competitive decomposition pathways leading to diminished yields. Rigorous exclusion of moisture and oxygen is necessary to achieve optimal results. Particularly challenging are *O*-aryl carbamothioate substrates bearing electron-donating functionality, which require higher temperatures than more electron-deficient substrates due to an intrinsically higher barrier to nucleophilic attack of sulfur on the aromatic ring. Improvements upon the original procedures of Newman and Kwart have primarily focused on modified conditions to minimize deleterious side reactions, particularly the use of microwave heating (Figure 2).[9]

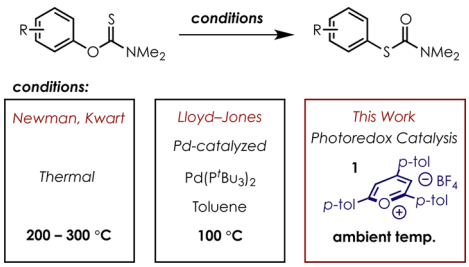

Figure 2. Development of conditions for *O*-aryl carbamothioate rearrangement.

Attempts to catalyze the NKR have also been reported in the literature, but are sparse. In Newman and Karnes' initial disclosure *O*-(pyridyl)carbamothioates rearranged at room temperature when prepared as their hydrochloride salts. Brooker et al. reported that boron trifluoride diethyl etherate significantly lowered the temperature necessary for NKR of a limited number of *ortho*-formyl substrates, but the catalytic effect did not prove general.[10] A more general method was published in 2009 by Lloyd-Jones, wherein catalytic loadings of palladium bis(tri-*tert*-butylphosphine) allowed for successful NKR of a number of *para*-substituted substrates in toluene at 100 °C.[11] The palladium-catalyzed method exhibits a similar electronic trend to the thermal NKR with shorter reaction times observed for substrates bearing electron-withdrawing functionality, increased reaction times and catalyst loadings necessary for substrates bearing electron-donating groups. An alternate strategy for aryl carbon–sulfur bond synthesis also makes use of palladium catalysis.[12−14] Hartwig and co-workers in particular have demonstrated the utility of Josiphos as a ligand for the palladium catalyzed coupling of aryl halides and pseudo-halides with a range of thiols, including triisopropylsilyl thiol which can be deprotected to give the corresponding free aryl thiol, or further elaborated to diaryl sulfides.[15,16]

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The need to prepare a variety of aryl thiol and aryl disulfide cocatalysts for use in our ongoing redox catalysis research program initially prompted our interest in the NKR.[17−20] We hypothesized that single electron oxidation of the *O*-aryl carbamothioate substrate should lower the barrier to nucleophilic attack of sulfur upon the aryl ring and accelerate rearrangement. Further examination of the NKR literature brought our attention to electrospray ionization mass spectrometry studies of *O*-aryl carbamothioates by Prabhakar and co-workers which indicated significant *O* to *S* aryl migration *in situ*.[21] The authors proposed that single-electron oxidation permitted the facile gas-phase rearrangement of the substrates. This further bolstered our confidence that the NKR could be amenable to cation radical acceleration in the solution phase.

We began our studies by irradiating solutions of *O*-(4-methoxyphenyl) dimethylcarbamothioate (**2a**) with 1.0 mol % 2,4,6-tri(*p*-tolyl)pyrylium tetrafluoroborate **1** using blue light emitting diodes (LEDs). After 24 h, formation of *S*-(4-methoxyphenyl) dimethylcarbamothioate (**3a**) was evident (^{1}H NMR), though appreciable amounts of **2a** remained (Table 1, entry 1). Additional solvents such as dichloromethane and acetonitrile were tested (entries 2 and 3, respectively), and complete conversion of **2a** was observed after 24 h. Ease of workup and purification led us to choose acetonitrile as the optimal solvent. No appreciable side products were observed by ^{1}H NMR analysis of the crude reaction mixture, and a silica plug eluted with 19:1 hexanes/ethyl acetate was sufficient to provide pure **3a**. Additional optimization using the less electron-rich 4-methyl-substituted **2b** displayed an intriguing concentration dependence, with more dilute conditions resulting in dramatic rate increases (entries 4−6). The parent *O*-phenyl dimethylcarbamothioate (**2c**) was sluggish to react even under appreciably dilute conditions (entry 7).

Table 1. Optimization of Photoredox-Mediated NKR

2 a, R = OMe
b, R = Me
c, R = H

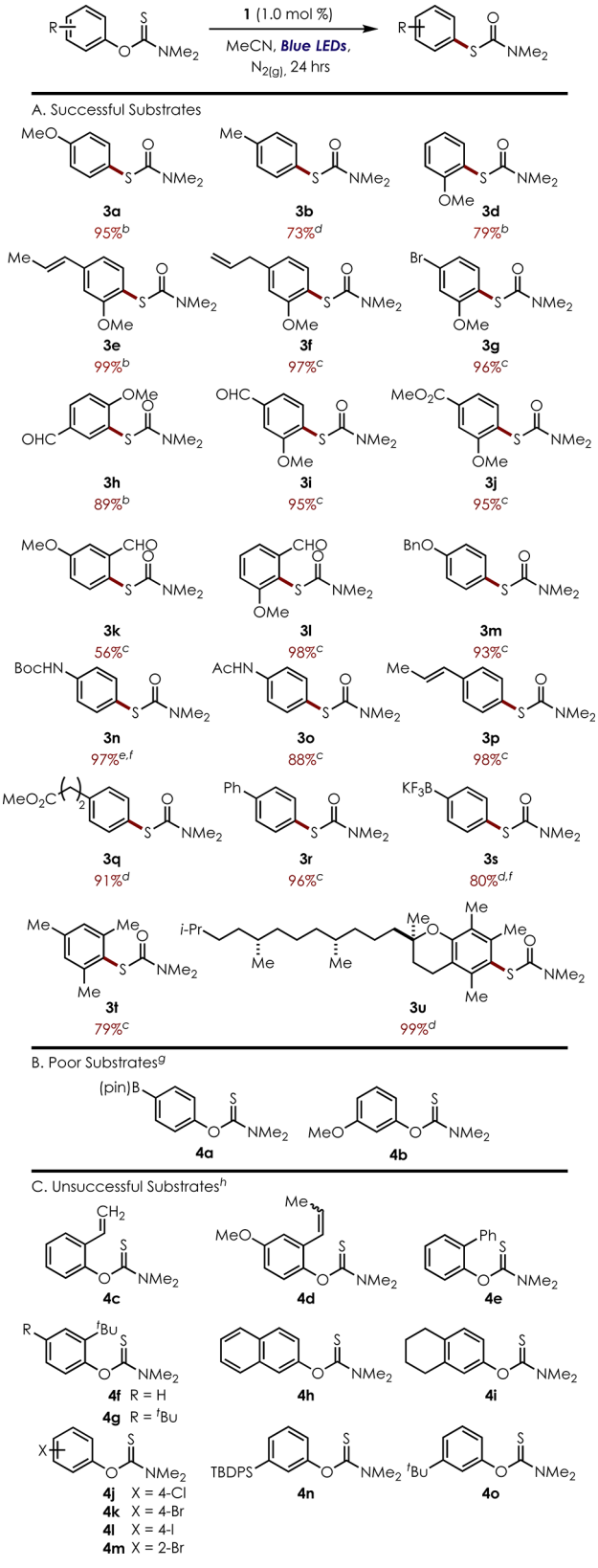
3

entry	substrate	solvent	conc [M]	3:2[a]
1	**2a**	$CHCl_3$	0.5	1:2
2	**2a**	DCM	0.5	>19:1
3	**2a**	MeCN	0.5	>19:1
4	**2b**	MeCN	0.5	1:9
5	**2b**	MeCN	0.12	1:3
6	**2b**	MeCN	0.06	>19:1
7	**2c**	MeCN	0.03	1:1

[a]Determined by analysis of crude ^{1}H NMR spectra of the reaction mixture.

Next, the scope of the reaction was investigated (Table 2A). Given the observed concentration dependence, an optimum concentration was sought that would afford 100% conversion within 24 h. In general, more dilute conditions were observed to accelerate rearrangement of all the substrates under examination. The *O*-(2-methoxyphenyl) dimethylcarbamothioate reacted competently to afford **3d** in good yield. Additional 2-methoxy-substituted substrates underwent smooth rearrangement providing the propenyl-substituted **3e**, allyl-substituted **3f**, bromo-substituted **3g**, *meta*- and *para*-formyl-

Table 2. Substrate Scope of Photoredox-Mediated NKR[a]



[a]Isolated yields, the average of two reactions at 100 mg scale of substrate. [b]0.5 substrate concentration. [c]0.12 M substrate concentration. [d]0.06 M substrate concentration. [e]0.03 M substrate concentration with 48 h irradiation. [f]5 mol% **1**. [g]<15% conversion, ^{1}H NMR [h]No product detectable, ^{1}H NMR.

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substituted **3h** and **3i**, respectively, and the 4-methylester-substituted **3j**, all in nearly quantitative yields. The *O*-(2-formyl-4-methoxyphenyl) dimethylcarbamothioate also rearranges smoothly to give **3k** in good isolated yield as does the *O*-(2-formyl-6-methoxyphenyl) dimethylcarbamothioate **3l**. Benzyl protecting groups are also tolerated (**3m**) in good yield as well as thermally sensitive Boc groups (**3n**). The corresponding dimethylcarbamothioate of acetaminophen readily undergoes the *O*−*S* rearrangement, giving the corresponding *S*-aryl dimethylcarbamothioate **3o** in excellent yield. Less electron-rich groups can also be present, as evidenced by 4-propenyl-substituted **3p**, dihydrocinnamyl methyl ester derivative **3q**, and biphenyl **3r** which all underwent rearrangement in good to excellent yields (88−98%). It is worthy of note that **3p** is produced as >19:1 ratio of *E*:*Z* isomers, despite beginning with a 1:9 *E*:*Z* ratio of the propenyl carbamothioate. Given this, it is notable that the allyl group of **3f** does not undergo any detectable isomerization to the propenyl product **3e**. We were also pleased to find that a potassium trifluoroborate salt substrate is capable of undergoing the redox-mediated NKR (**3s**), providing a handle for further elaboration using cross coupling techniques. Finally, sterically hindered substrates derived from mesitol and (±)-*α*-tocopherol also reacted efficiently, giving **3t** and **3u**, respectively.

Unfortunately, *O*-(2-naphthyl) dimethylcarbamothioate (**4i**) failed to give appreciable rearrangement, while the regioisomeric *O*-(1-naphthyl) dimethylcarbamothioate (**2v**) was a competent candidate providing **3v** in excellent yield (Figure 3).

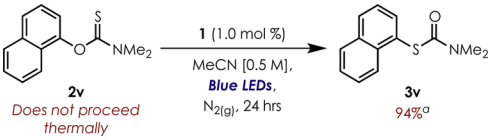

Figure 3. Photoredox-mediated rearrangement of **2v**.[22] [a]Isolated yield, the average of two reactions at 100 mg scale of substrate.

Intriguingly, the propensity toward rearrangement under thermal NKR conditions is reversed, with *O*-(2-naphthyl) dimethylcarbamothioate undergoing *O* to *S* aryl migration at 285 °C, while **2v** does not undergo rearrangement under thermal conditions.[22]

We chose *O*-(2,4,6-trimethylphenyl) dimethylcarbamothioate (**2t**) as a representative substrate to assess the suitability of this protocol using a flow apparatus (Figure 4). No

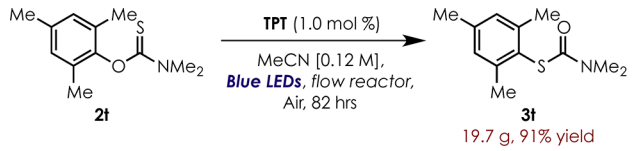

Figure 4. Large scale synthesis of **3t** using a flow reactor and commercially available triphenylpyrylium tetrafluoroborate (TPT).

precautions were taken to exclude moisture or oxygen and we employed commercially available triphenylpyrylium tetrafluoroborate as catalyst. Using the optimized conditions, 21.5 g of **2t** underwent smooth rearrangement to **3t** after 82 h. After chromatography, the desired product was isolated in a 91% yield providing 19.7 g of **3t**.

Despite the success of this system, there are substitution patterns for which rearrangement was not observed. Aryl boronate ester **4a** showed diminished reactivity, as did 3-methoxy-substituted **4b**, both achieving low conversion under the standard conditions (Table 2B). Substrates with alkenyl or aryl substitution *ortho* to the *O*-carbamothioate moiety also proved recalcitrant (**4c**−**4e**), regardless of the presence of an additional beneficial substituent (Table 2C). The rearrangement was also inhibited by sterically large *ortho* substituents (**4f**, **4g**). As previously discussed, 2-naphthyl-derived **4h** did not rearrange, nor did the 5,6,7,8-tetrahydronaphthyl analogue **4i**. Monosubstituted haloarenes also give little to no rearrangement, regardless of halide identity or position (**4j**−**4m**). Substrates bearing a single electron-donating substituent *meta* to the *O*-carbamothioate afforded trace amounts of rearranged product (**4n**, TBDPS = *tert*-butyldiphenylsilyl, **4o**), suggesting a strict electronic requirement for rearrangement (for example see **3a**, **3d** compared to **4b**).

Further analysis of **2a** and **3a** by cyclic voltammetry (CV) gave several irreversible oxidation waves (Figure 5). Qual-

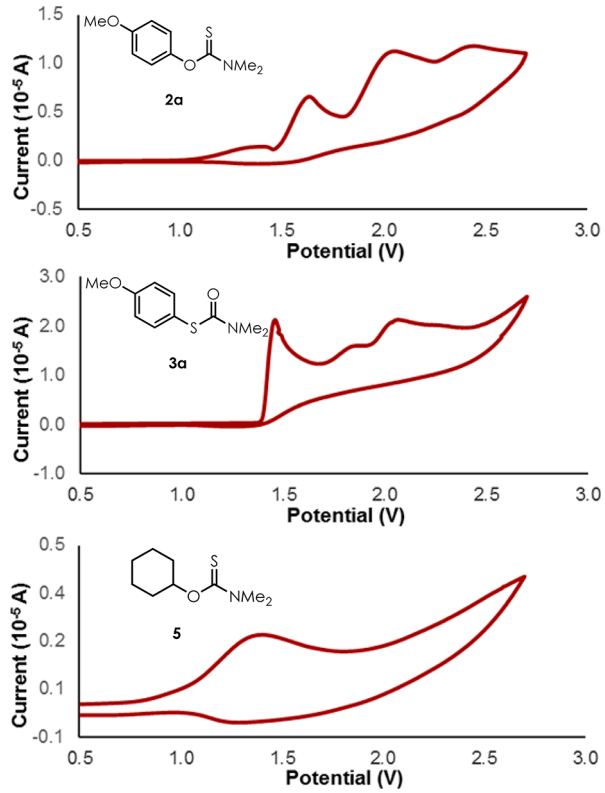

Figure 5. Cyclic voltammograms for **2a**, **3a**, and **5**. All values are in V vs SCE.

itatively, the traces for **2a** and **3a** appear similar except for an irreversible oxidation wave with $E_{p/2}$ = +1.1 V present in the CV trace for **2a** but absent for **3a**. For comparison, substrate **5** which cannot undergo rearrangement, exhibits an oxidation wave nearly identical to **2a** at +1.1 V. These data suggest that oxidation of the thiocarbonyl moiety, rather than the arene, is likely involved in the rearrangement. This is in agreement with previous work carried out in our laboratory on the cyclization of thioamides onto pendant alkenes.[20]

Given these observations, we propose the mechanism depicted in Scheme 1 for the redox-mediated NKR. Excitation of **1** by the blue LEDs followed by single electron oxidation of **2** by **1*** affords sulfur-centered cation radical **6** and the

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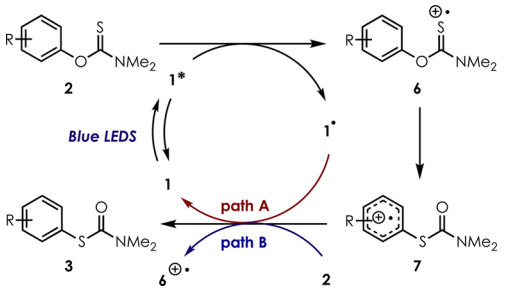
Scheme 1. Mechanistic Proposal for the Cation Radical-Accelerated NKR



persistent pyranyl radical **1**$^{\bullet}$. Rearrangement of **6** to give *S*-aryl dimethylcarbamothioate cation radical **6**. At this point two pathways are conceivable − cation radical **7** can undergo single electron transfer (SET) from **1**$^{\bullet}$ to generate the net rearranged product and ground state **1** (path A). Alternatively, or perhaps in conjunction with this reaction pathway, it is conceivable that a chain process could occur wherein SET from an additional equivalent of **2** to cation radical **7** forms adduct **3** and another equivalent of cation radical **6** (path B). Which mechanism is predominantly operative is the subject of continuing study.

In conclusion, we present a method for the ambient temperature NKR. This represents a dramatic reduction in reaction temperature relative to the traditional thermal NKR and even palladium-catalyzed methods. The transformation is enabled via organic redox catalysis using easily prepared, and even commercially available, triarylpyrylium salts. This reaction exhibits complementary reactivity relative to the thermal NKR, with more facile reactivity observed for more electron-rich substrates. Tolerance toward a number of functional and protecting groups was also demonstrated, in addition to amenability to scale-up of the reaction using flow chemistry. Studies to further elucidate the mechanism of the reaction, so as to expand the utility and substrate scope, are planned.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11800.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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