OL | Organic Letters

Letter

Cite This: *Org. Lett.* 2020, 22, 274–278

pubs.acs.org/OrgLett

Iron(II)/Persulfate Mediated Newman–Kwart Rearrangement

Thibault Gendron,[†,‡,⊥] Raul Pereira,[§,∥,⊥] Hafsa Y. Abdi,[‡] Timothy H. Witney,*[,§,∥] and Erik Årstad*[,†,‡]

[†]Centre for Radiopharmaceutical Chemistry, University College London, 5 Gower Place, London WC1E 6BS, United Kingdom

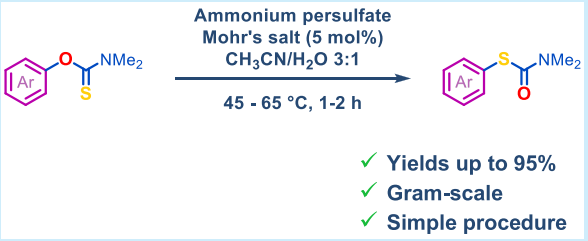
[‡]Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, United Kingdom

[§]Centre for Advanced Biomedical Imaging, University College London, 72 Huntley Street, London WC1E 6DD, United Kingdom

[∥]Department of Imaging Chemistry and Biology, School of Biomedical Engineering & Imaging Sciences, King's College London, St. Thomas' Hospital, London SE1 7EH, United Kingdom

Supporting Information

ABSTRACT: Herein, we report that iron(II)/ammonium persulfate in aqueous acetonitrile mediates the Newman–Kwart rearrangement of *O*-aryl carbamothioates. Electron-rich substrates react rapidly under moderate heating to afford the rearranged products in excellent yields. The mild conditions, rapid reaction rates, and suitability for scale up offers immediate practical benefits to access functionalized thiophenols.



The Newman–Kwart rearrangement (NKR)—the transformation of *O*-aryl carbamothioates to the corresponding *S*-aryl carbamothioates—gives access to thiophenols from their more readily available phenol counterparts.[1,2] The three-step sequence, which involves phenol protection with thiocarbamoyl chloride, NKR, and deprotection of the resulting carbamothioate, is appealing, as it avoids the need for highly reactive reagents or handling of foul-smelling chemicals. The NKR is therefore a synthetically important reaction with widespread applications.[3−6] The high activation barrier (ca. 35–43 kcal·mol^{-1})[7] of the reaction has been a long-standing limitation, as thermal activation requires temperatures of 150 °C for electron-deficient substrates to >300 °C for nonactivated arenes (Figure 1).[7] At such high temperatures, compound volatility, decomposition, and charring become problematic. In practice, the thermal reaction is therefore limited to activated, thermally stable, and nonvolatile substrates. Renewed interest in the NKR has led to the discovery of several catalytic systems that favor electron-rich substrates, including a photoredox catalytic system[8] and, very recently, an electrochemical method,[9] as well as a chemical reaction involving single-electron oxidation of *O*-aryl carbamothioates with ceric ammonium nitrate (CAN) in dimethyl sulfoxide (DMSO).[10] The latter method makes the NKR with electron-rich substrates widely accessible, as it overcomes the need for specialist equipment. However, the use of DMSO as the solvent, and the need for high substrate dilution, practically limits applications to small-scale reactions.

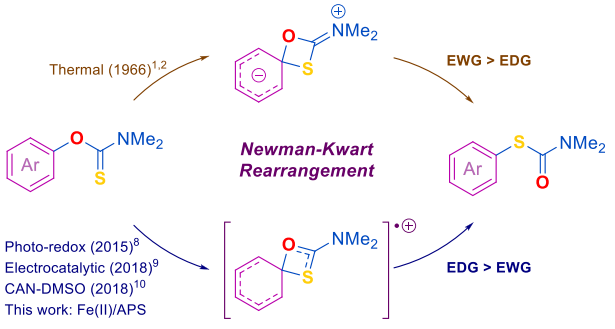


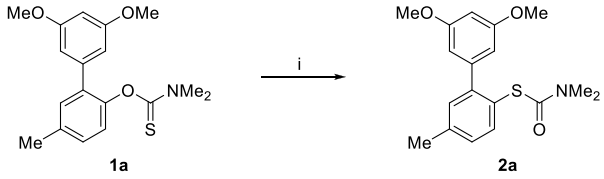
Figure 1. Newman–Kwart Rearrangement (NKR). Abbreviation: APS, ammonium persulfate; EWG, electron-withdrawing groups; EDG, electron-donating groups.

As a part of our ongoing research program, we needed a robust scalable method to access *S*-(3′,5′-dimethoxy-5-methyl-[1,1′-biphenyl]-2-yl) dimethylcarbamothioate **2a** from the corresponding *O*-aryl carbamothioate **1a** (Scheme 1).[11] Although successful on small scale, the thermal NKR proved operationally challenging to scale to multigram quantities, as inconsistent heating resulted in variable yields. Attempted Pd-catalyzed NKR only afforded trace amounts of product **2a** in agreement with the previously reported scope.[12] Inspired by the work of Anderson and Kochi on radical decarboxylation of carboxylic acids,[13] we attempted to use silver nitrate and ammonium persulfate (APS) as a single electron oxidant to mediate this transformation. Gratifyingly, under these conditions (35 mol % $AgNO_3$, 1 equiv of APS, CH_3CN/H_2O, 85 °C) **1a** rearranged to target product **2a** in 78% yield (Scheme 1). In a bid to develop a practical and scalable method, we investigated the effect of the different

Received: November 28, 2019
Published: December 18, 2019

DOI: 10.1021/acs.orglett.9b04280
Org. Lett. 2020, 22, 274–278

Scheme 1. Preliminary Results[a]



[a]Conditions: silver nitrate (35 mol %), ammonium persulfate (1.3 equiv), CH_3CN/H_2O 3:1, 85 °C, 90 min, 78% yield.

reagents and reaction parameters using *O*-(4-methoxyphenyl) dimethylcarbamothioate **1b** as a model compound (Table 1). When subjected to the aforementioned conditions, **1b** was fully converted to **2b** (Table 1, entry 1). Control experiments proved that APS is essential for the reaction to proceed (Table 1, entry 2). In the absence of silver, we observed large variations in yields depending on the source of APS. Subsequent analysis by inductively coupled plasma mass spectrometry (ICP-MS) revealed high levels of iron in the batch of APS that most effectively mediated transformation of **1b** to **2b** (see Supporting Information). As iron is known to accelerate the decomposition of APS in a similar manner to silver,[13,14] we hypothesized that the iron impurity played a key role in the reaction. Gratifyingly, replacing silver nitrate with catalytic amounts (5 mol %) of Mohr's salt ($(NH_4)_2Fe(SO_4)_2{\cdot}6H_2O$) afforded **2b** in 95% yield (Table 1, entry 4). Lowering the reaction temperature from 85 to 45 °C still gave full conversion within 1 h and afforded **2b** in 91% isolated yield (Table 1, entry 5). As described in the previously reported non-thermal NKR protocols,[8−10] the reaction proved less efficient at high concentrations. At a concentration up to 0.17 M (Table 1, entry 7), the rate of transformation appeared to be unaffected; however, at 0.25 M the yield dropped to 10% under otherwise identical conditions (Table 1, entry 6). Finally, the use of water as cosolvent proved crucial for the formation of the target product. Indeed, when acetonitrile was used as the sole reaction solvent, starting material **1b** was converted quantitatively to the corresponding carbamate **3b** (Table 1, entry 8).

With optimized conditions in hand (5 mol % Mohr's salt, 1 equiv of APS, CH_3CN/H_2O 3:1), we explored the scope of this novel NKR reaction (Figure 2). Substrates substituted

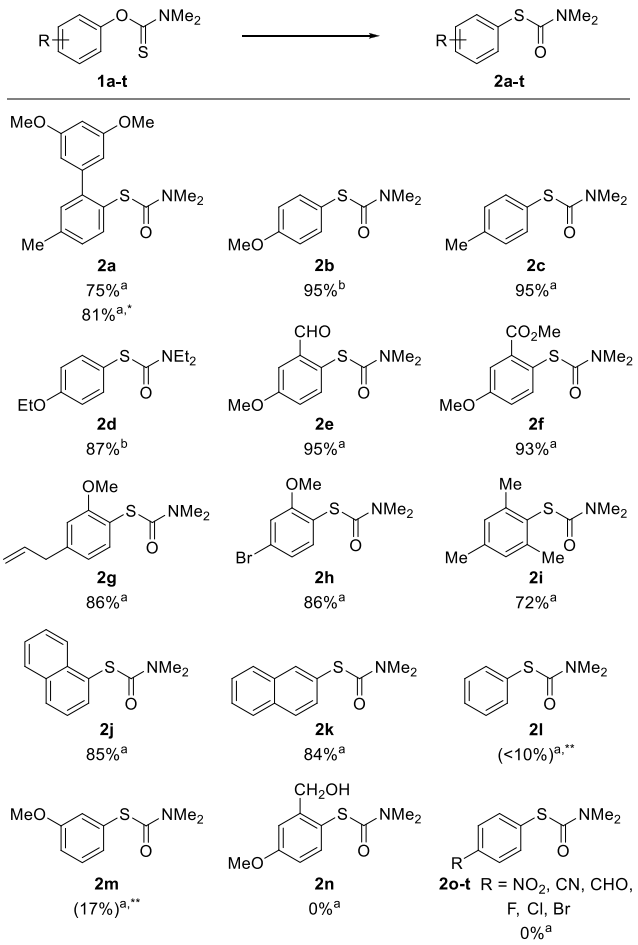
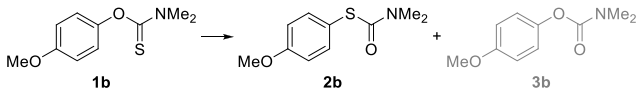


Figure 2. Scope study. Conditions: [a]**1** (1 mmol), Mohr's salt (5 mol %), APS (1 equiv), CH_3CN/H_2O 3:1, 65 °C, 2 h; [b]**1** (1 mmol), Mohr's salt (5 mol %), APS (1 equiv), CH_3CN/H_2O 3:1, 45 °C, 1 h. *Scale-up to 10 mmol. **Conversion determined by ^{1}H NMR.

with electron-donating groups (EDG) in the *para*-position afforded rearranged products **2a−f** in nearly quantitative yields. Additional electron-withdrawing groups (EWG) were well tolerated, as exemplified with the formation of aldehyde and ester substituted products **2e** and **2f** in 95% and 93% yields, respectively. Steric hindrance had little-to-no influence

Table 1. Optimization of the Novel NKR Protocol

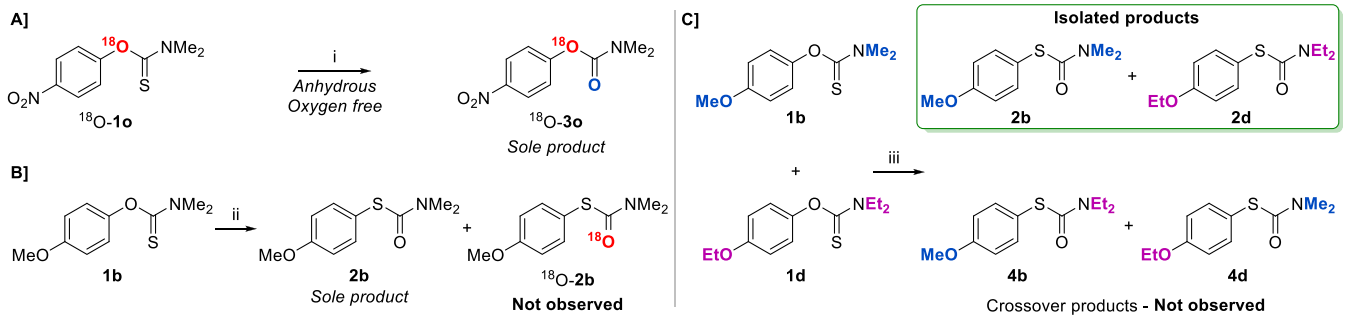


no.	equiv of APS	metal (mol %)	solvents	temp (°C)	concn (M)	conv (%)[a]
1	1.3	Ag (35)[b]	CH_3CN/H_2O 3:1	85	0.083	>95
2	0	Ag (35)[b]	CH_3CN/H_2O 3:1	85	0.083	<5
3	1	–	CH_3CN/H_2O 3:1	85	0.083	10−95[d]
4	1	Fe (5)[c]	CH_3CN/H_2O 3:1	85	0.083	>95
5	1	Fe (5)[c]	CH_3CN/H_2O 3:1	45	0.083	>95 (91)
6	1	Fe (5)[c]	CH_3CN/H_2O 3:1	45	0.25	10
7	1	Fe (5)[c]	CH_3CN/H_2O 3:1	45	0.17	>95
8	1	Fe (5)[c]	CH_3CN	65	0.083	>95[e] (**3b** 84%)

[a]As determined by ^{1}H NMR, isolated yields are given in brackets. [b]As silver nitrate. [c]As Mohr's salt. [d]Depending on the source of APS. [e]Reaction was heated for 4 h, conversion to **3b**.

DOI: 10.1021/acs.orglett.9b04280
Org. Lett. 2020, 22, 274−278

Scheme 2. Isotopic Labeling Experiments (A, B) and Crossover Experiment (C)[a]



[a]Conditions: (i) Mohr's salt (5 mol %), APS (2 equiv), anhydrous degassed CH_3CN, 65 °C, 3 h; (ii) Mohr's salt (5 mol %), APS (1 equiv), $CH_3CN/[^{18}O]H_2O$ 3:1, 45 °C, 1 h; (iii) Mohr's salt (5 mol %), APS (1 equiv), CH_3CN/H_2O 3:1, 45 °C, 1 h.

on the rearrangement, as *ortho*-substituted products **2a** and **2f–i** were obtained in good-to-excellent yields. The reaction displayed good functional group tolerance, as aldehyde, ester, allyl, and bromo substituents in products **2e–h** remained intact through the procedure; notably, oxidation of aldehyde **2e** was not observed. However, rearrangement of benzylic alcohol **2n** was problematic, as oxidation of the alcohol resulted in the formation of a complex mixture of products. *S*-(Naphthalene-1-yl) dimethyl-carbamothioate **2j** and its 2-regioisomer **2k** were obtained in 85% and 84% isolated yields, respectively. This result is of note, as the CAN[10] and photoredox[8] methods allow access to the 1-napthalene but not the 2-napthalene derivative. Formation of electron-neutral **2l** and moderately electron-deficient *meta*-methoxy substituted **2m** was observed, albeit in moderate conversions (<10% and 17%, respectively). Attempted reactions with electron-deficient substrates proved troublesome; nitro- **1o**, nitrile- **1p**, aldehyde- **1q**, and halide- **1r–t** substituted *O*-aryl carbamothioate failed to rearrange. In most cases, NMR analysis of the reaction mixture showed that the starting materials were transformed to the corresponding *O*-aryl carbamates instead of the expected *S*-aryl carbamothioate (see Supporting Information, Figures S5 and S6). Formation of carbamates has previously been reported for the CAN-DMSO mediated NKR reaction.[10]

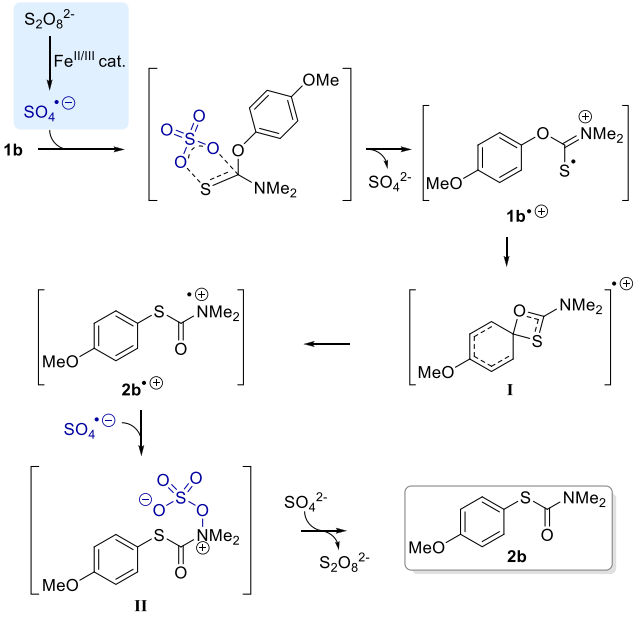
To gain a better understanding of this side reaction, isotopically labeled $[^{18}O]$*O*-aryl carbamothioate ^{18}O-**2o** was subjected to the reaction conditions with strict exclusion of water and oxygen (Scheme 2A). Carbamate ^{18}O-**3j** was isolated in 60% yield. Tandem mass spectrometry (MS/MS) confirmed the position of the $[^{18}O]$oxygen on the molecule as shown on Scheme 2A (see Supporting Information). In the absence of any other source of oxygen, this demonstrates that the extra oxygen added on the carbamate is likely to come from the persulfate. Furthermore, subjecting **1b** to the standard reaction conditions while replacing H_2O with $[^{18}O]H_2O$ did not lead to any isotopic exchange on the rearranged product, thus suggesting that water is not actively participating in the reaction (Scheme 2B). Overall, the results of this scope study are in line with the work previously published on oxidative NKR: the reaction proceeded rapidly with electron-rich ring systems and nonactivated systems reacted more sluggishly, while electron-deficient substrates failed to react, or underwent a side-reaction to give the corresponding *O*-carbamates.

To elucidate the rearrangement mechanism itself, we first focused our attention on the reaction kinetics. ^{1}H NMR reaction monitoring of the *para*-methoxy derivative **1b** led to a sigmoidal kinetic profile (see Supporting Information, Figure S8). After an induction period of about 35 min, **1b** was quantitatively rearranged to product **2b** within 20 min on a 0.5 mmol scale (zero-order linear approximation $k \approx 5$ mmol·L^{-1}·min^{-1}). Although not uncommon, sigmoidal kinetic profiles are difficult to interpret; unravelling which mechanisms are responsible for the induction period and then for reaction lift-off is challenging and outside of the scope of the present study. We subsequently investigated whether the reaction was inter- or intramolecular through a crossover experiment between the *para*-methoxy derivative **1b** and its ethyl analogue **1d** (Scheme 2C). Should the reaction be intermolecular, an interchange of substituents would occur, giving rise to crossover rearranged products **4b** and **4d**. NMR analysis of the crude reaction mixture showed exclusive formation of the two noncrossover rearranged products **2b** and **2d**, in equal amounts. The absence of crossover products confirms that the reaction proceeds through an intramolecular mechanism.

The observed reactivity points to a radical-cation transition state as reported for other nonthermal NKR.[8−10] Indeed, iron(II)/(III) salts and oxides are known to decompose aqueous APS to sulfate radical anions $SO_4^{-\bullet}$ in a Fenton-like process.[15] Consistent with this, a dark orange-brown residue was observed in the product mixtures. Blocking of the reaction with 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), an established radical trap, provided further evidence of a radical reaction mechanism. On the basis of these observations, we propose the mechanism depicted in Scheme 3. A Fenton-like process generates sulfate radical anion $SO_4^{-\bullet}$ (Scheme 3, blue box), which, in turn, reacts by abstracting an electron from the sulfur atom in **1b**, forming radical cation **1b**$^{+\bullet}$. Subsequent intramolecular (*vide supra*) rearrangement of **1b**$^{+\bullet}$ leads to the formation of a putative four-center intermediate **I**, as previously described.[16] Heterolytic cleavage of the O_{Aryl} bond gives radical cation **2b**$^{+\bullet}$, which after single-electron reduction affords product **2b**. The exact nature of the reduction step is unclear; **2b**$^{+\bullet}$ could potentially abstract an electron from **1b**. However, experimental observations suggest that **1b** alone cannot sustain a radical chain reaction. It is therefore more likely that single electron reduction is mediated by the persulfate system, possibly by combination of the sulfate radical anion $SO_4^{-\bullet}$ with **2b**$^{+\bullet}$ to give intermediate **II**. Nucleophilic attack by sulfate would then liberate the product **2b** and regenerate the peroxide.[17] The high reactivity of the APS/Fe(II) system may

DOI: 10.1021/acs.orglett.9b04280
Org. Lett. 2020, 22, 274−278

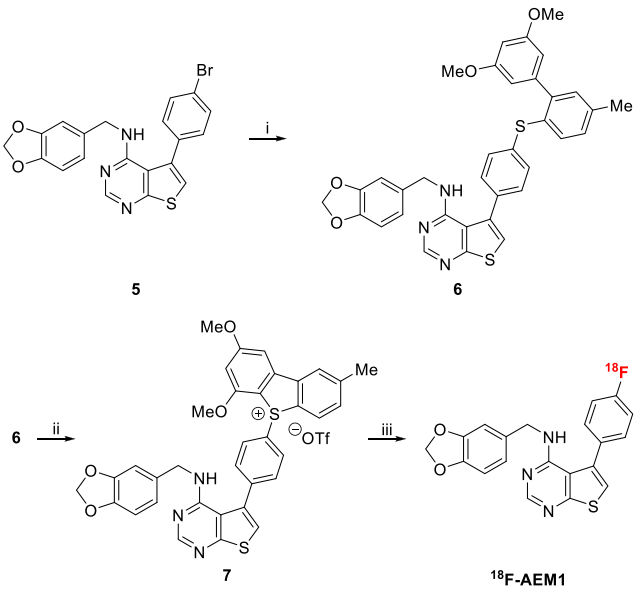
Scheme 3. Proposed Mechanism



reflect the ability of sulfate to stabilize single electron transfer through cyclic transition states.[18]

Finally, we employed the novel strategy for the synthesis of ^{18}F-AEM1,[19] a putative radiotracer for imaging of cancer drug resistance with positron emission tomography (Scheme 4). On a 3 g scale (10 mmol), **1a** rearranged to give biaryl building block **2a** in 81% yield. Coupling with the aryl bromide **5** gave the corresponding biaryl thioether **6** in 56% yield, which upon treatment with aqueous calcium hypochlorite[11] afforded the dibenzothiophene sulfonium salt **7** in 72% yield. Labeling with [^{18}F]fluoride (2.5 mg, DMSO, 125 °C, 25 min) under nonoptimized conditions afforded ^{18}F-AEM1 in 15 ± 4% (n = 4) decay-corrected radiochemical yield (d.c. RCY).

Scheme 4. Application to the Labeling of ^{18}F-AEM1[a]



[a]Conditions: (i) **2a**, *t*BuOK, $Pd_2(dba)_3$, DPEPhos, toluene, reflux, 56% yield; (ii) $Ca(OCl)_2$, acetate buffer pH 4, acetonitrile, 3 °C, 15 min, 72% yield; (iii) $^{18}F^-$, $K_{222}/KHCO_3$, DMSO, 125 °C, 25 min, 15 ± 4% d.c. RCY (n = 4).

Very recently, Ritter and Alcarazo independently reported late-stage, site-selective aromatic C−H insertion of aryl dibenzothiophenium salts.[20,21] Although synthetically more demanding, the ring-closing route exemplified with **2a** above is highly complementary in that it gives access to complex heteroatom-rich molecules such as ^{18}F-AEM1 and allows the point of functionalization to be chosen at will.

In conclusion, we report that catalytic amounts of Fe(II) in the presence of APS mediates conversion of electron-rich and electron-neutral *O*-aryl carbamothioates to the corresponding *S*-aryl carbamothioates under mild conditions. The reaction has a similar scope to the previously reported methods for cation-radical mediated NKR, but offers clear practical advantages in that it circumvents the need for specialist equipment and proceeds with shorter reaction times and at higher substrate concentration, and the use of a volatile solvent makes it well suited for scale up. The practicability of the APS/Fe(II) system may prove beneficial for radical-driven reactions beyond the NKR.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04280.

Experimental procedures, spectral and analytical data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: e.arstad@ucl.ac.uk.
*E-mail: tim.witney@kcl.ac.uk.

ORCID

Thibault Gendron: 0000-0002-2162-3704
Raul Pereira: 0000-0001-5696-2266
Hafsa Y. Abdi: 0000-0003-3750-8265
Timothy H. Witney: 0000-0002-9475-2873
Erik Årstad: 0000-0002-3240-2106

Author Contributions

⊥T.G. and R.P. contributed equally.

Author Contributions

*T.W. and E.A. jointly supervised this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr Laure Benhamou (Department of Chemistry, University College London) and Dr. Julie Charpentier (Givaudan) for helpful discussions. We thank the mass spectrometry facility at King's College London for assistance with the HRMS, ICP-MS and MS/MS experiments. The research leading to these results was funded by the European Union's Seventh Framework Programme (FP7/2007-2013) under Grant Agreement No. 602102 (EPITARGET) (E.A.), a Wellcome Trust and Royal Society Sir Henry Dale Fellowship (107610/Z/15/Z) to (T.H.W.), CRUK & EPSRC Comprehensive Cancer Imaging Centre at KCL,

DOI: 10.1021/acs.orglett.9b04280
Org. Lett. 2020, 22, 274−278

UCL & Imperial jointly funded by Cancer Research UK and the Engineering and Physical Sciences Research Council (EPSRC; C1519/A16463; C2536/A10337) (T.G.), and the UCL MSci in Chemistry (H.Y.A.). This work was undertaken at UCLH/UCL, which is funded in part by the Department of Health's NIHR Biomedical Research Centres funding scheme.

REFERENCES

(1) Kwart, H.; Evans, E. R. The Vapor Phase Rearrangement of Thioncarbonates and Thioncarbamates. *J. Org. Chem.* **1966**, *31* (2), 410−413.
(2) Newman, M. S.; Karnes, H. A. The Conversion of Phenols to Thiophenols via Dialkylthiocarbamates. *J. Org. Chem.* **1966**, *31* (12), 3980−3984.
(3) Porter, D. W.; Bradley, M.; Brown, Z.; Canova, R.; Charlton, S.; Cox, B.; Hunt, P.; Kolarik, D.; Lewis, S.; O'Connor, D.; et al. The Discovery of Potent, Orally Bioavailable Pyrazolo and Triazolopyrimidine CXCR2 Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **2014**, *24* (1), 72−76.
(4) Sørensen, A.; Rasmussen, B.; Agarwal, S.; Schau-Magnussen, M.; Sølling, T. I.; Pittelkow, M. Conversion of Phenols into Selenophenols: Seleno Newman-Kwart Rearrangement. *Angew. Chem., Int. Ed.* **2013**, *52* (47), 12346−12349.
(5) Otto, S. Selection and Amplification of Hosts From Dynamic Combinatorial Libraries of Macrocyclic Disulfides. *Science* **2002**, *297* (5581), 590−593.
(6) Błaszczyk, A.; Chadim, M.; von Hänisch, C.; Mayor, M. Synthesis of Macrocyclic Molecular Rods as Potential Electronic Devices. *Eur. J. Org. Chem.* **2006**, *2006*, 3809−3825.
(7) Lloyd-Jones, G.; Moseley, J.; Renny, J. Mechanism and Application of the Newman-Kwart O→S Rearrangement of O-Aryl Thiocarbamates. *Synthesis* **2008**, *2008* (5), 661−689.
(8) Perkowski, A. J.; Cruz, C. L.; Nicewicz, D. A. Ambient-Temperature Newman−Kwart Rearrangement Mediated by Organic Photoredox Catalysis. *J. Am. Chem. Soc.* **2015**, *137* (50), 15684−15687.
(9) Broese, T.; Roesel, A. F.; Prudlik, A.; Francke, R. An Electrocatalytic Newman−Kwart-Type Rearrangement. *Org. Lett.* **2018**, *20* (23), 7483−7487.
(10) Pedersen, S. K.; Ulfkjær, A.; Newman, M. N.; Yogarasa, S.; Petersen, A. U.; Sølling, T. I.; Pittelkow, M. Inverting the Selectivity of the Newman−Kwart Rearrangement via One Electron Oxidation at Room Temperature. *J. Org. Chem.* **2018**, *83* (19), 12000−12006.
(11) Gendron, T.; Sander, K.; Cybulska, K.; Benhamou, L.; Sin, P. K. B.; Khan, A.; Wood, M.; Porter, M. J.; Årstad, E. Ring-Closing Synthesis of Dibenzothiophene Sulfonium Salts and Their Use as Leaving Groups for Aromatic ^{18}F-Fluorination. *J. Am. Chem. Soc.* **2018**, *140* (35), 11125−11132.
(12) Harvey, J. N.; Jover, J.; Lloyd-Jones, G. C.; Moseley, J. D.; Murray, P.; Renny, J. S. The Newman-Kwart Rearrangement of O-Aryl Thiocarbamates: Substantial Reduction in Reaction Temperatures through Palladium Catalysis. *Angew. Chem., Int. Ed.* **2009**, *48* (41), 7612−7615.
(13) Anderson, J. M.; Kochi, J. K. Silver(I)-Catalyzed Oxidative Decarboxylation of Acids by Peroxydisulfate. Role of Silver(II). *J. Am. Chem. Soc.* **1970**, *92* (6), 1651−1659.
(14) House, D. A. Kinetics and Mechanism of Oxidations by Peroxydisulfate. *Chem. Rev.* **1962**, *62* (3), 185−203.
(15) Wacławek, S.; Lutze, H. V.; Grübel, K.; Padil, V. V. T.; Černík, M.; Dionysiou; Dionysios, D. Chemistry of Persulfates in Water and Wastewater Treatment: A Review. *Chem. Eng. J.* **2017**, *330*, 44−62.
(16) Cruz, C. L.; Nicewicz, D. A. Mechanistic Investigations into the Cation Radical Newman−Kwart Rearrangement. *ACS Catal.* **2019**, *9* (5), 3926−3935.
(17) The proposed mechanism implies that substoichiometric amounts of APS should mediate the NKR; However, APS is not truly catalytic in this reaction as 1 equiv is required for optimal yields. The stoichiometry of the reaction suggests that the iron catalyst only generates one sulfate radical anion per persulfate that is cleaved. We can only speculate that the second sulfate radical is consumed in a nonproductive redox cycle of iron(II/III).
(18) Tanwar, L.; Börgel, J.; Ritter, T. Synthesis of Benzylic Alcohols by C−H Oxidation. *J. Am. Chem. Soc.* **2019**, *141* (45), 17983−17988.
(19) Bollong, M. J.; Yun, H.; Sherwood, L.; Woods, A. K.; Lairson, L. L.; Schultz, P. G. A Small Molecule Inhibits Deregulated NRF2 Transcriptional Activity in Cancer. *ACS Chem. Biol.* **2015**, *10* (10), 2193−2198.
(20) Ritter, T.; Xu, P.; Zhao, D.; Berger, F.; Hamad, A.; Rickmeier, J.; Petzold, R.; Kondratiuk, M.; Bohdan, K. Site-Selective Late-Stage Aromatic ^{18}F-Fluorination via Aryl Sulfonium Salts. *Angew. Chem., Int. Ed.* **2019**, DOI: 10.1002/anie.201912567.
(21) Kafuta, K.; Korzun, A.; Böhm, M.; Golz, C.; Alcarazo, M. Synthesis, Structure and Reactivity of 5-(Aryl)Dibenzothiophenium Triflates. *Angew. Chem., Int. Ed.* **2019**, DOI: 10.1002/anie.201912383.

DOI: 10.1021/acs.orglett.9b04280
Org. Lett. 2020, 22, 274−278