# Iron(II)/Persulfate Mediated Newman-Kwart Rearrangement

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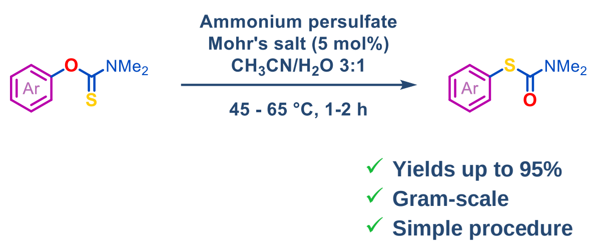
*Supporting Information Placeholder*




**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 non-activated arenes (Figure 1).[7] At such high temperatures, compound volatility, decomposition and charring becomes problematic. In practice, the thermal reaction is therefore limited to activated, thermally stable and non-volatile substrates. Renewed interest in the NKR has led to the discoveries of several catalytic systems that favors electron rich substrates, including a photo-redox catalytic system,[8] and very recently an electrochemical method,[9] and a chemical reaction involving single-electron oxidation of *O*-aryl carbamothioates with ceric-ammonium nitrate (CAN) in dimethylsulfoxide (DMSO).[10] The latter method makes the NKR with electron-rich substrates widely accessible as it overcomes the need for specialist equipment.

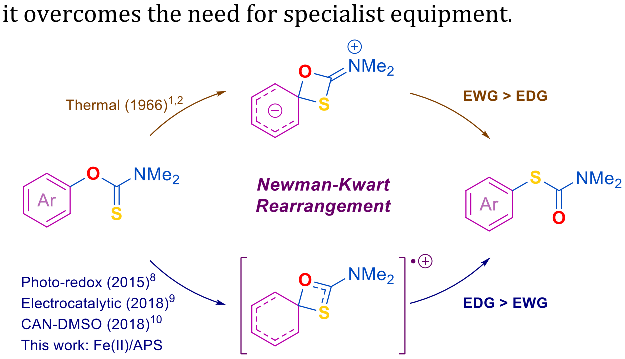
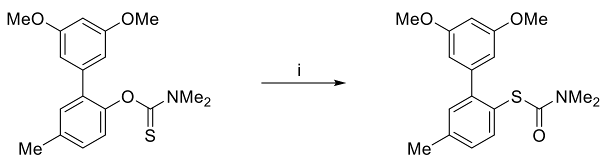



**Figure 1.** The Newman-Kwart Rearrangement (NKR). Abbreviation: APS: ammonium persulfate; EWG: electron-withdrawing groups; EDG: electron-donating groups.

However, the use of DMSO as the solvent, and the need for high substrate dilution, practically limits applications to small-scale reactions. 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 multi-gram quantities as inconsistent heating resulted in variable yields.

**Scheme 1. Preliminary results.**

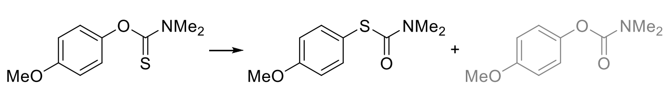


1a 2a

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

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. 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 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 °C to 45 °C still gave full conversion within an hour and afforded **2b** in 91% isolated yield (Table 1, entry 5).

**Table 1. Optimization of the novel NKR protocol.**



1b 2b 3b

| No | Equiv. of APS | Metal (mol%) | Solvents | Temp (°C) | Conc. (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[d] (**3b** 84%) |

[a]As determined by $^1H$ 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 four hours, conversion to **3b**.

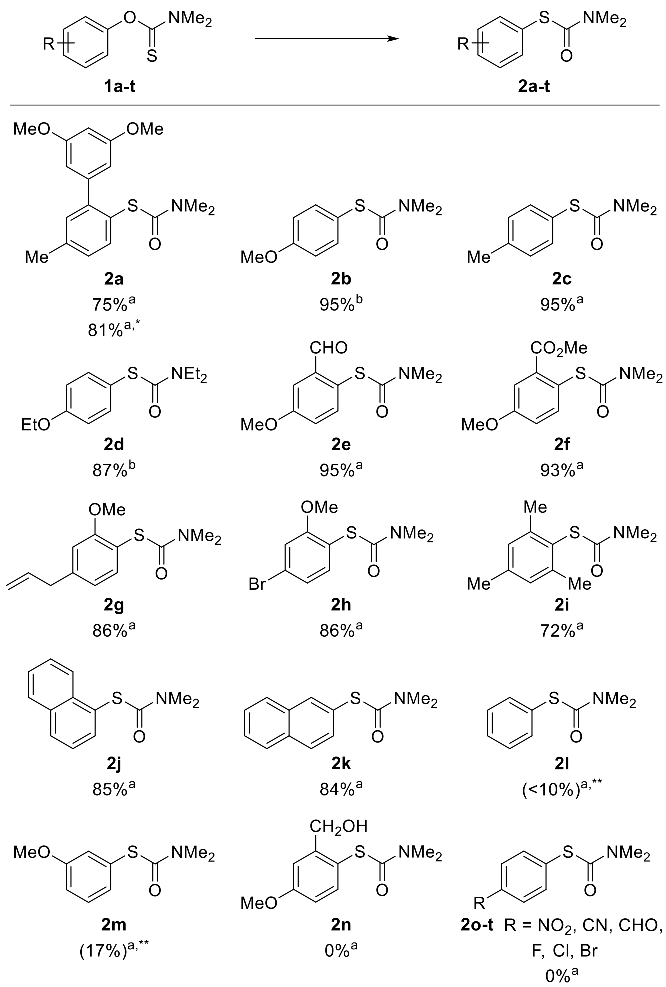
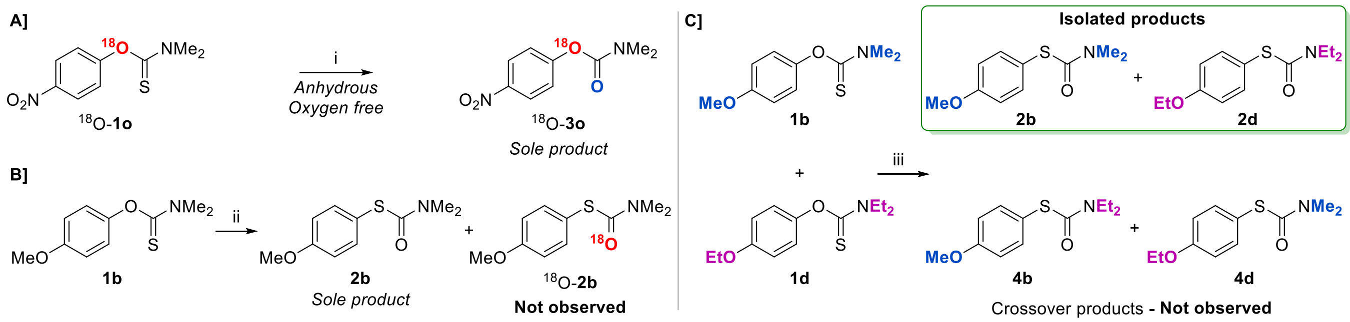



**Figure 2.** Scope study. Conditions: [a]**1** (1 mmol), Mohr's salt (5 mol%), APS (1 equiv.), $CH_3CN/H_2O$ 3:1, 65 °C, 2 h; [b]**1** (1 mmol), Mohr's salt (5 mol%), APS (1 equiv.), $CH_3CN/H_2O$ 3:1, 45 °C, 1 h; *Scale-up to 10 mmol; **Conversion determined by $^1$H NMR.

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 co-solvent 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. APS, $CH_3CN/H_2O$ 3:1), we explored the scope of this novel NKR reaction (Figure 2). Substrates substituted with electron donating groups (EDG) in *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 on the rearrangement, as *ortho*-substituted products **2a** and **2f-i** were obtained in good to excellent yields. The reaction displayed a 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.

**Scheme 2. Isotopic labeling experiments (A, B) and crossover experiment (C).**




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.

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** as well as its 2-regioisomer **2k** were obtained in 85% and 84% isolated yields, respectively. This result is of note as the CAN,[10] photoredox[8] and electrocatyltic[9] 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 modest 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, Figure S5 and S6). Formation of carbamates has previously been reported for the CAN-DMSO mediated NKR reaction.[10]

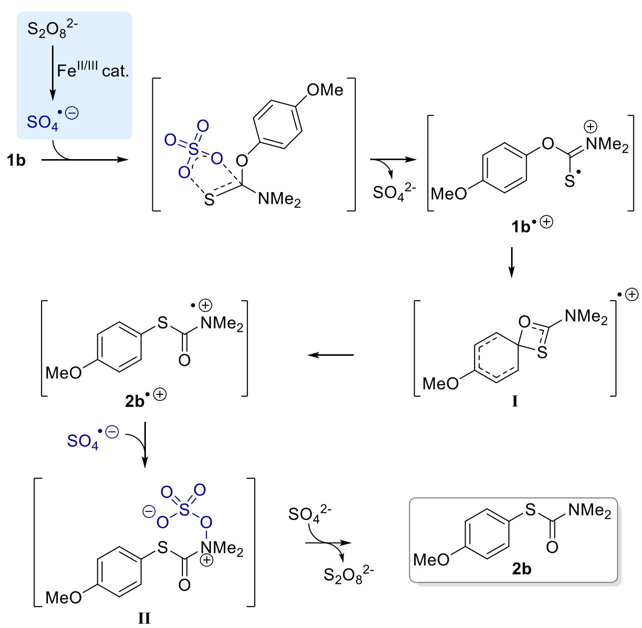
To get a better understanding of this side reaction, isotopically labeled [$^{18}$O]*O*-aryl carbamothioate $^{18}$O-**2o** was subjected to the reaction conditions with strict exclusion of water and oxygen (Scheme 2A). Carbamate $^{18}$O-**3j** was isolated in 60% yield. Tandem mass spectrometry (MS/MS) 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 whilst 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 works previously published on oxidative NKR: the reaction proceeded rapidly with electron rich ring systems, non-activated 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 non-crossover rearranged products **2b** and **2d**, in equal amounts. The absence of cross-over products confirms that the reaction proceeds through an intramolecular mechanism.

The observed reactivity points to a radical-cation transition state as reported for other non-thermal 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, react by abstracting an electron from the sulfur atom in **1b**, forming radical cation **1b**$^{+\bullet}$.

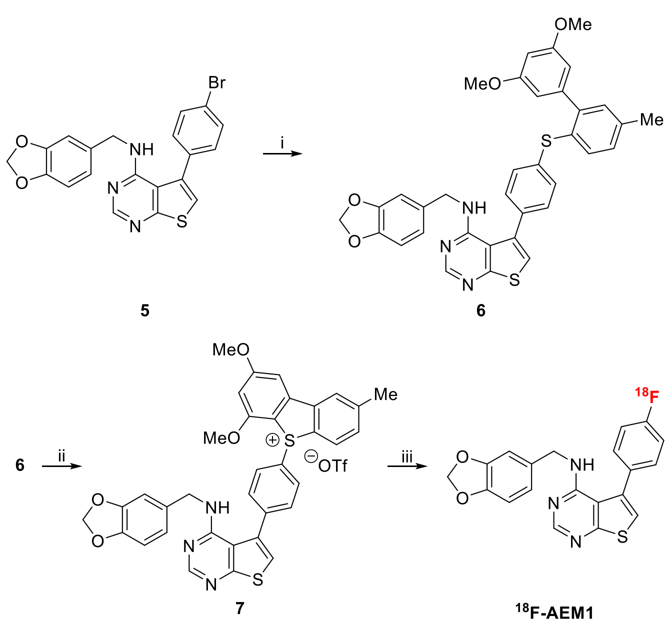
**Scheme 3. Proposed mechanism.**



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 $O_{\mathrm{Aryl}}$ 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 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 non-optimized conditions afforded $^{18}$F-AEM1 in 15 ± 4% ($n$ = 4) decay-corrected radiochemical yield (d.c. RCY). 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.

**Scheme 4. Application to the labeling of $^{18}$F-AEM1.**




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).

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, 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

Experimental procedures, spectral and analytical data. The Supporting Information is available free of charge on the ACS Publications website.

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### Author Contributions

All authors have given approval to the final version of the manuscript. ‡These authors contributed equally. * TW and EA jointly supervised this work.

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