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An Electrocatalytic Newman−Kwart-type Rearrangement

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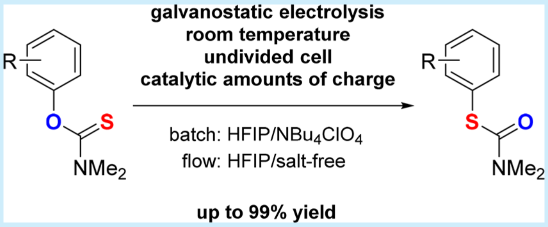
Supporting Information

ABSTRACT: An electrochemical approach toward rearrangement of *O*-aryl thiocarbamates to the corresponding *S*-aryl thiocarbamates is presented. The protocol requires only catalytic amounts of electric charge and allows for operation at room temperature. The electrolysis can be carried out with the simplest equipment, i.e., under galvanostatic conditions in an undivided cell. Furthermore, it is demonstrated that when the electrolysis is performed in a microflow reactor, almost quantitative yields can be achieved without using supporting electrolyte.



The thermally induced rearrangement of *O*-aryl thiocarbamates **2** to the corresponding *S*-aryl thiocarbamates **3**, commonly known as the Newman−Kwart rearrangement (NKR), represents the key reaction in the three-step transformation of phenols **1** to thiophenols **4** (see Figure 1).[1] In view of the good availability of various phenols, the readily achieved conversion of **1** to **2** as well as the facile cleavage of the rearrangement product **3**, the NKR route constitutes one of the most attractive possibilities for the generation of **4**.[2] The possibility for conversion of **3** into related sulfur containing compounds such as sulfones, sulfoxides, sulfonic acids, and thioethers further broadens the scope of the NKR.[3] Not surprisingly, the field of applications encompasses numerous examples from medicinal chemistry, materials, agrochemistry, ligand synthesis (including applications in homogeneous catalysis), supramolecular chemistry, etc.[1,2,4] Industrial applications, mostly carried out in flow reactors, have also been reported.[5−7]

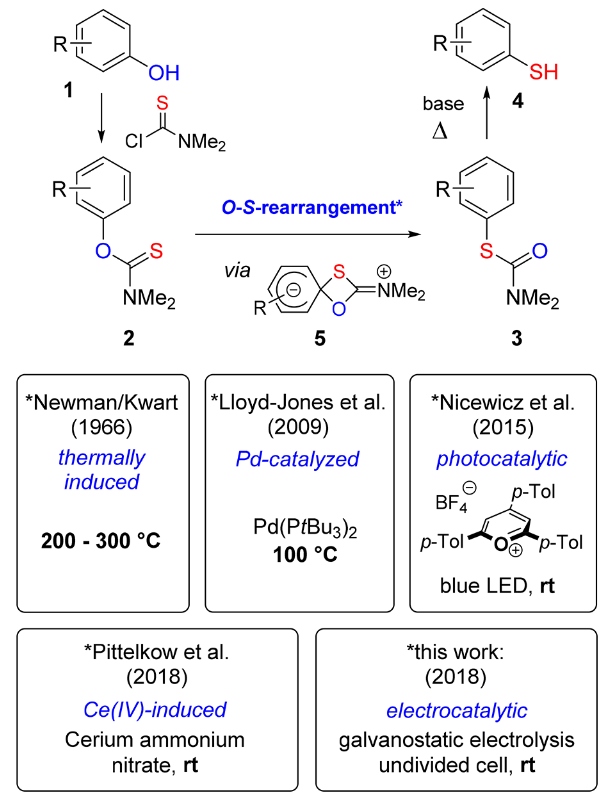


Figure 1. Conversion of phenols **1** to thiophenols **4** via Newman−Kwart rearrangement (NKR).

The NKR is generally assumed to proceed via intramolecular nucleophilic *ipso* substitution at the aromatic ring, passing through the highly strained spirocyclic intermediate **5** (see Figure 1).[8] The generation of this high-energy intermediate is favored in the presence of electron-withdrawing groups on the aromatic ring and typically requires temperatures >200 °C. In many cases, these harsh conditions lead to competing decomposition reactions, ultimately resulting in diminished yields, product charring and complicated separation procedures.[1] Since the appearance of the first reports in 1966,[9] a number of studies have therefore dealt with the development of protocols having milder reaction conditions. Important parts of this development are the exploration of the microwave-assisted NKR,[10] and of the use of a continuous flow reactor under supercritical conditions.[5,6] Other approaches are based on the use of catalysts in order to lower reaction temperatures. In some examples, the addition of catalytic amounts of $BF_3\cdot OEt_2$ helped to lower the reaction temperature and to improve the yields, whereby the catalytic effect did not turn out to be general.[11] A catalytic system with a broader scope was introduced in 2009 by Lloyd-Jones et al., who demonstrated that the use of palladium bis(tri-*tert*-butylphosphine) allows for conversion of several *para*-substituted substrates **2** to the corresponding NKR products at 100 °C.[12]

A subsequent report by Nicewicz et al. showed that the rearrangement can even be achieved at room temperature

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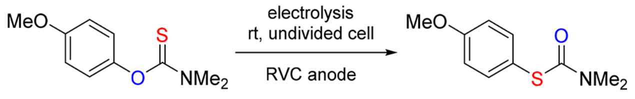
using a photochemical approach: Upon irradiation with blue LEDs in the presence of a pyrylium-based photoredox catalyst (see Figure 1), a number of substrates **2** having electron-donating groups in *ortho*- and/or *para*-position were successfully subjected to NKR.[13] Due to the inversion of the selectivity compared to the thermal rearrangement, the reaction was proposed to proceed via a cation radical $\mathbf{2}^{\bullet+}$, which rearranges in an intramolecular aromatic substitution. Just recently, Pittelkow et al. have demonstrated that a similar outcome can be achieved when the photocatalytic system is replaced by catalytic amounts of cerium ammonium nitrate and oxygen as terminal oxidant.[14] In parallel, we have explored the NKR under electrochemical conditions in our laboratory and developed a protocol where the transfer of catalytic amounts of charge triggers the rearrangement at room temperature.

We initiated our study with a screening of the electrolysis parameters using **2a** as test substrate under batch conditions (see Table 1). These experiments were carried out at rt in an undivided cell using a reticulated vitreous carbon (RVC) anode (an optimization of the anode material is described in the Supporting Information), a platinum wire cathode,[15] and 0.1 M NBu_4ClO_4 as supporting electrolyte. A particular importance can be ascribed to the choice of the solvent (entries 1–5). While employing MeOH, CH_3CN, or CH_2Cl_2 leads exclusively to negative results, the use of 2,2,2-trifluoroethanol (TFE) gives **3a** in 17% yield after passing a charge equivalent of 1 F per mole **2a**. A more promising outcome is obtained when 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) is employed under the same conditions, which leads to 80% yield after passing only 0.1 F at i = 10 mA (entry 5). The benign influence of HFIP may be explained by its ability to stabilize radical and ionic intermediates,[16] which is why this solvent turned out to be crucial in several previously reported electrosynthetic transformations.[17] Further advantages of HFIP are excellent electrochemical properties (high anodic stability and good conductivity) as well as the relatively low pK_a, which facilitates H_2 generation as a cathodic half-reaction.[18]

Table 1. Optimization of the Electrolysis Parameters[a]



2a **3a**

entry	solvent	Q mol^{-1} [F]	i [mA]	**3a**[b] [%]	TON$_e$[c]
1	MeOH	1	10	0	0
2	TFE	1	10	17	0.2
3	CH_3CN	1	10	0	0
4	CH_2Cl_2	1	10	0	0
5	HFIP	0.1	10	80	7.6
6	HFIP	0.1	20	54	5.1
7	HFIP	0.1	30	39	3.7
8	HFIP	0.1	5	81	7.8
9	HFIP[d]	0.05	10	79	15.2
10	HFIP[e]	0.05	10	22	4.2
11	HFIP[d]	0.3	10	95[f]	3.0

[a] Conditions: WE = RVC, CE = Pt wire, 0.1 M NBu_4ClO_4, HFIP (10 mL), **2a** (42.2 mg, 0.2 mmol, 0.02 M), stirring with 700 rpm (see the Supporting Information for more information), Ar atmosphere. [b] Yields determined via GC (external calibration). [c] TON$_e$ refers to the number of molecules **2a** converted to **3a** per transferred electron. [d] [**2a**] = 0.1 M. [e] [**2a**] = 0.2 M. [f] Isolated yield.

Due to the redox neutrality of the NKR and the fact that substoichiometric amounts of charge are sufficient for the conversion, we can conclude that the reaction is electrocatalyzed.[19] At this point, we define the parameter TON$_e$ as the number of molecules converted per transferred electron (TON$_e$ = 7.6, see entry 5) in order to characterize the efficiency of the reaction.[20] While the deviation from i = 10 mA does not lead to any improvements (entries 6–8), variation of the substrate concentration leads to a further optimization of TON$_e$ (compare entries 5, 9, and 10). Using the optimized values for i as well as for [**2a**] and applying an increased amount of charge in order to achieve higher conversion (0.3 F per mole **2a**), the product **3a** is obtained in 95% isolated yield (TON$_e$ = 3.0, entry 11). More details on the influence of passed charge, the electrode material, the water content, and the presence of oxygen are provided in the Supporting Information.

Using the optimized reaction conditions, the scope of the protocol was investigated (Figure 2). Electrolysis of substrates with alkoxy substituents in *ortho*- and/or *para*-position generally yields the corresponding NKR products **3** in ≥90% yield and with TON$_e$ values ranging from 3.0 to 4.6 (see **3a–c**). A comparison to the yields obtained from the thermal rearrangement of **2a–c** shows significant improvements (for details, see the Supporting Information). The influence of different *O*- and *N*-alkyl substitutions was also investigated, whereby no major influence of the alkyl chain lengths on the yields was found (**3d–f**).

Applying the standard conditions to sesamol-derived substrate **2g** leads to a clean NKR rearrangement, showing that acetal groups are not affected by the reaction conditions. Additional aryl substituents such as methyl, fluoro, and bromo are also tolerated and lead to yields between 70% and 90% (**3h–j**). We also found that the aliphatic alkoxy groups can be replaced by a thioether (**3k**), acetamido (**3l**), Boc-protected amino (**3m**) or a phenoxy group (**3n**), leading to slightly inferior results (68–85% yield). Good results were also obtained when the aryl substituent in **2** was replaced by a naphthyl group (**3o**, 72%). The presence of an allyl-, a vinyl-, or a dimethylamino substituent in the *para* position of the arene ring, however, leads to significantly decreased yields (35–54% after full conversion of **2p–r**). We note that apart from the desired product, no significant amounts of further low molecular compounds were detected by GC in these cases. We therefore assume that oligo- or polymerization reactions represent the competing pathways lowering the yields of **3p–r**. The conversion of methoxy hydroquinone-derived substrate **2s** under the standard conditions turned out to be similarly problematic, since **3s** was formed in only 32% yield (along with a number of unidentified low-molecular side products). The structure of **3s** was additionally confirmed via X-ray analysis of a single crystal (see Figure 2, top right).

Interestingly, the *p*-methyl-substituted substrate **2t** is only slowly converted under the standard conditions (12% conversion after passing 0.5 F, formation of byproducts). However, conducting the electrolysis at reflux temperature (bp of HFIP: 58 °C) under otherwise identical conditions gives **3t** in 70% yield (TON$_e$ = 0.8). The same conditions were also required in order to achieve rearrangement of estradiol derivative **2u** to the corresponding NKR product **3u**. In contrast, no conversion was observed upon electrolysis of the

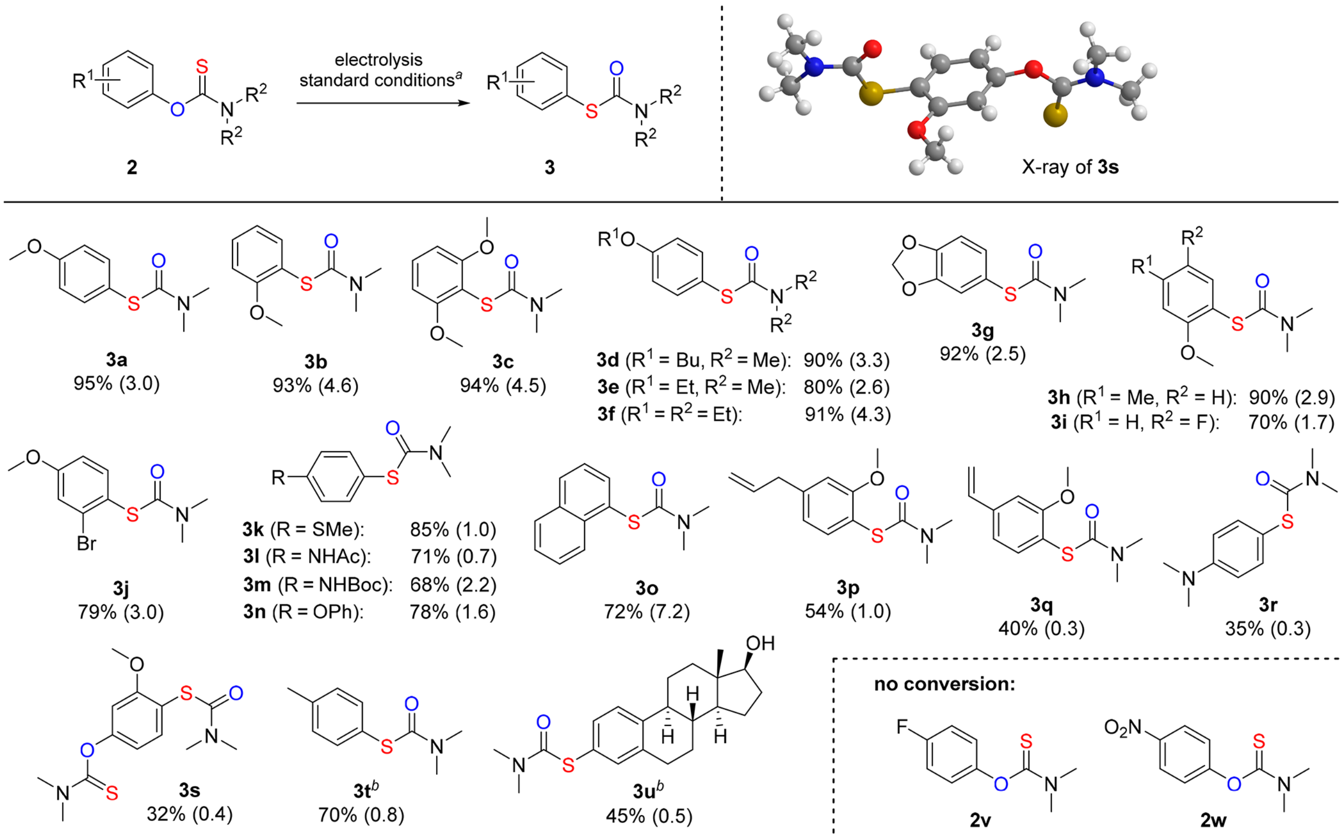
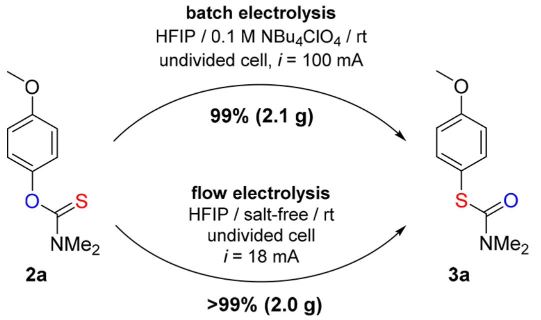


Figure 2. Scope of the electrocatalyzed NKR. Isolated yields, TON$_e$ in parentheses. [a]Standard conditions: Undivided cell, rt, WE: RVC, CE: Pt-wire, *i* = 10 mA, 10 mL HFIP (0.1 M Bu_4NClO_4), substrate, 1.0 mmol **2**, Ar atmosphere. [b]Electrolysis carried out under reflux conditions (bp of HFIP: 58 °C).

p-F- and *p*-NO_2-substituted *O*-aryl-thiocarbamates (**2v** and **2w**), neither at room temperature, nor under reflux conditions. Taken together, these results suggest that electron-donating groups are required to facilitate the electrocatalyzed NKR, which is in sharp contrast to the thermally induced NKR[1,2] and may be explained by formation of a radical cation intermediate $\mathbf{2}^{\bullet+}$ and subsequent rearrangement via intramolecular aromatic substitution (vide infra).

In order to investigate the scalability of the reaction, we increased the batch size for the conversion of **2a** to **3a** from 1 to 10 mmol (Scheme 1). The upscaling was achieved by increasing the electrolyte volume, the size of the electrode and the current (100 mA), while [**2a**] was maintained at 0.1 M. After passing 90 C (15 min), 2.1 g of **3a** were isolated (99% yield).

Scheme 1. Conversion of 2a to 3a on the Gram Scale



Next, we explored the possibility for further improvements under flow conditions. Generally, a decrease of the required supporting electrolyte load, an improvement of the mass transport and a more homogeneous potential distribution across the electrode surfaces can be expected when a microflow reactor with a parallel plate design is used.[21] We have therefore carried out studies using a sandwich-type microflow reactor (single pass) consisting of a glassy carbon working electrode and a platinum counter electrode, which are separated from each other by a Teflon spacer with a rectangular notch (3.0 × 0.3 cm) that together with the electrodes defines the reaction channel (for details, see the Supporting Information). It is worth noting that the conversion of **2a** to **3a** proceeds efficiently without added supporting electrolyte, which can be explained by the overlap of the diffusion layers in the microreactor.[22] Under these conditions, the electrochemically formed ionic intermediates provide sufficient ionic conductivity to close the electric circuit.

The optimization was carried out without supporting electrolyte by variation of the feed concentration [**2a**], the current density j, the flow rate $\dot{V}$, and the interelectrode distance l. We found that excellent results are obtained when a charge of 0.16 F per mole substrate is passed. The results along with the optimized parameters are summarized in Table 2 (all optimization steps are shown in the Supporting Information). Quantitative yield in **3a** was obtained with $\dot{V}$ = 1.0 mL min^{-1} and j = 19.9 mA cm^{-2}, whereby the product was obtained in analytical purity (^{1}H NMR and GC) after completed electrolysis and removal of the solvent (see Table 2, entry 1). We also found that the product forming rate PFR can be

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Table 2. **Electrocatalytic NKR of 2a to 3a under Flow Conditions: Optimized Product Yield, TON$_e$, and Product Forming Rate (PFR) along with the Corresponding Process Parameters at Q mol^{-1} = 0.16 F**[a]

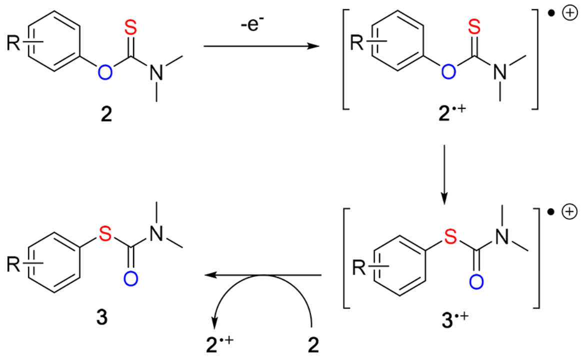
entry	[**2a**] [mM]	$\dot{V}$ [mL min^{-1}]	j [mA cm^{-2}]	**2a** [%][b]	**3a** [%][b]	TON$_e$	PFR [g h^{-1}]
1[c]	70	1.0	19.9	<1	>99	6.3	0.89
2[d]	100	1.1	31.3	2	98	6.2	1.37
3[d]	150	1.2	51.1	11	89	5.6	2.03

[a] Conditions: rt, undivided cell, WE = glassy carbon, CE = Pt, $A_{\text{electrode}}$ = 0.9 cm^2, l = 110 μm. [b] Isolated yields. [c] Batch size: 2.0 g **3a** [d] Batch size: 1.0 g **3a**.

improved when $\dot{V}$ and j are increased at constant Q mol^{-1} (Table 2, entries 2 and 3), whereby the conversion is simultaneously decreasing. Noteworthy, in a long-term experiment we did not observe any indication of electrode passivation after 24 h of electrolysis.

On the basis of our observations and in analogy to the findings by Nicewicz et al.,[13] we suggest the mechanism shown in Scheme 2. Both the benign influence of the HFIP solvent and the restriction of the scope to electron-rich substrates are strong indicators for the involvement of radical cation intermediates. The sequence is initiated by anodic generation of $\mathbf{2}^{\bullet+}$, followed by a rearrangement to $\mathbf{3}^{\bullet+}$, possibly via a spirocyclic intermediate similar to species **5**. Reduction of $\mathbf{3}^{\bullet+}$ either by discharge at the cathode or by reaction with another molecule **2** closes the catalytic cycle. The latter possibility, a radical chain mechanism, would explain why catalytic amounts of charge are sufficient for full conversion.

Scheme 2. Mechanistic Proposal for the Electrocatalytic Newman–Kwart-type Rearrangement



In conclusion, we have demonstrated that Newman–Kwart-type rearrangements can be carried out in a galvanostatic electrolysis by applying catalytic amounts of charge at ambient temperature without using catalysts. Our procedure is straightforward, scalable and applicable to a broad range of activated phenols. Compared to the heat-induced NKR, our protocol exhibits an inverted selectivity with respect to the aromatic substitution, preferring electron-rich arene moieties over electron-deficient ones. Further improvements were achieved by operation under flow conditions, which allows for omission of the supporting electrolyte and renders the product in analytical purity and quantitative yields after removal of the solvent. Our current efforts are focused on the expansion of the scope and on establishing the mechanistic details of the reaction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03257.

Experimental procedures, product characterization data (PDF)

Accession Codes

CCDC 1872953 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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