

Photosynthesis

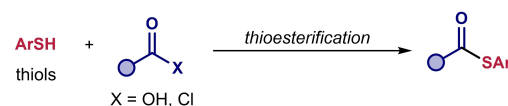
Photochemical Synthesis of Thioesters from Aryl Halides and Carboxylic Acids

Shuo Wu and Paolo Melchiorre*

Abstract: Thioesters are important in synthesis, materials science, and biology, and their preparation traditionally relies on the use of disagreeable thiols. Here, we report a thiol-free protocol that stitches together widespread carboxylic acids and aryl halides, producing a diverse array of thioesters. Crucial to this strategy is the discovery that tetramethylthiourea can serve as both a sulfur source and, upon direct excitation by purple light, as a strong reductant, suitable for activating aryl halides via single-electron transfer. Coupling of the resulting aryl radicals provides an isothiuronium ion intermediate, which can be attacked by carboxylic acids via a polar pathway, affording the thioester products under mild conditions.

The importance of thioesters extends beyond applications in synthetic chemistry to encompass fields such as materials and biology.^[1] Thioesters are also typical motifs in various natural products.^[2] Therefore, there is a need to develop efficient methods for their preparation from readily available substrates and under mild conditions. The vast majority of available protocols rely on thiols,^[3–4] characterized by undesirable traits like unpleasant odor, limited commercial variety, and air instability (Figure 1a). Classic methods include the thioesterification of carboxylic acids with thiols in the presence of harsh dehydrating reagents^[3] or the reaction of thiols with pre-activated acylating compounds^[4] (e.g., acyl chlorides and carboxylic anhydrides). Transition-metal catalysis also enables efficient thioester synthesis via carbonylative coupling reactions involving thiols,^[5] which generally require elevated temperatures and specific ligands to overcome the high coordinating ability of thiols to transition metals.^[6]

a) Traditional pathways for thioesters' synthesis



b) Thiol-free synthesis of thioesters (this work)

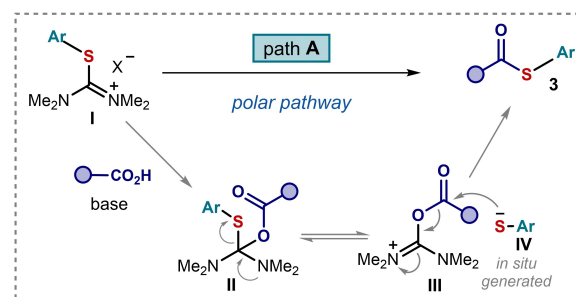
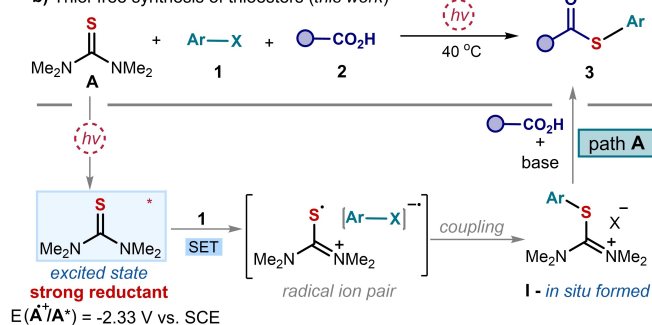


Figure 1. (a) Traditional methods for synthesizing thioesters using thiols. (b) A new thiol-free strategy that uses the dual nature of tetramethylthiourea **A**, which serves as both sulfur source and potent photoreductant for aryl radical formation under purple light excitation (405 nm). The aryl radicals are generated via SET reduction of halides **1** from the excited state of **A**, leading to the formation of isothiuronium salts **I**.^[10] A polar deoxythiolation pathway (*path A* in the lower panel) involving carboxylic acids **2** then leads to thioesters **3**; SET: single-electron transfer.

Clearly, the identification of mild new strategies for thioester synthesis that do not rely on thiols^[7] but solely on widely accessible, inexpensive, and stable chemicals would be highly valuable. Here, we introduce a new protocol based on readily available 1,1,3,3-tetramethylthiourea **A** as the sulfur source, which uses purple light to stitch together widely available aryl halides **1** and carboxylic acids **2**, thus affording thioesters **3** (Figure 1b). This study was inspired by our recent finding that isothiuronium salt **I** can be readily prepared upon trapping aryl radicals, generated from **1**, with tetramethylthiourea **A**.^[8] Considering the electrophilic nature of such intermediates **I**, we surmised that nucleophilic

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addition of carboxylic acids **2** would lead to intermediate **II**, which is in equilibrium with the isouronium salt **III** upon extrusion of thiolate **IV** (*path A*, lower panel of Figure 1b). The transiently formed **IV** would eventually reattack intermediate **III**, following a deoxythiolation polar pathway that leads to the formation of the desired thioesters **3**. A few reports on the reactivity of preformed stoichiometric isothiuronium salts further supported the feasibility of this plan.^[9]

Importantly, and in contrast to our previous study,^[8] we discovered that tetramethylthiourea **A** does not act solely as a sulfur source and aryl radical trap. **A** can be directly excited upon absorption of purple light (405 nm) to acquire strong reducing power, useful for activating aryl halides **1** via single-electron transfer (SET). Therefore, in this protocol, we could avoid the use of an external photoredox catalyst for the generation of aryl radicals, which was instead required in our previous method.^[8]

We started out our investigations using 1,1,3,3-tetramethylthiourea **A** as the sulfur source, 4-chlorobenzonitrile **1a** as the radical precursor ($E(1a/1a^{\bullet-}) = -2.2$ V vs. Ag/AgCl), and cyclohexanecarboxylic acid **2a** as the nucleo-

phile (Figure 2a). The reaction was conducted in DMSO as the solvent under irradiation by a purple light-emitting diode (LED, $\lambda_{\max} = 405$ nm) and employing DIPEA (*N,N*-diisopropylethylamine) for deprotonation of acid **2a**. Surprisingly, we observed that the photochemical reaction proceeded smoothly, yielding the thioester product **3a** in 83% yield (entry 1 in the table in Figure 2a), without the need for any external photoredox catalysts, which we initially believed were essential for generating aryl radicals upon SET reduction of **1a**. We then tested other bases and solvents, which offered product **3a** with comparable yet slightly lower efficiency (entries 2–4). However, using different sulfur sources **B–E** (entry 5) or blue light illumination (465 nm) failed to produce **3a** (entry 6). Reactivity was completely inhibited by adding TEMPO as the radical scavenger (entry 7), consistent with the involvement of a radical pathway. Control experiments indicated that both purple light illumination and the presence of a base were essential for reactivity (entries 8–10).

We then conducted mechanistic studies to elucidate why light could trigger the process. Spectroscopic analyses of the substrates (Figure 2b) excluded the possibility of ground-

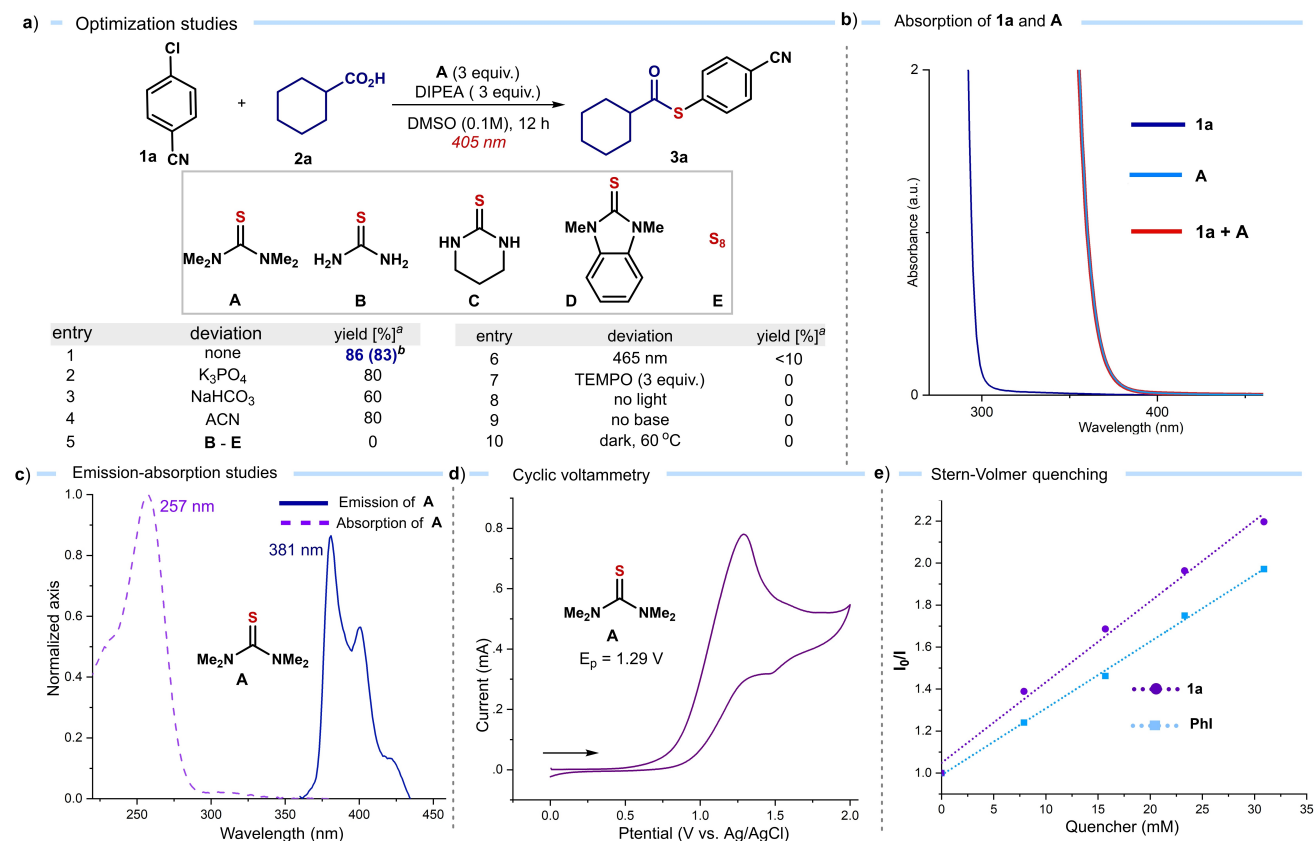


Figure 2. (a) Optimization and control experiments. Reactions performed on a 0.2 mmol scale for 12 h using 1 equiv. of **2a**, 3 equiv. of **1a**, and 3 equiv. of **A** under illumination by a purple LED (EvoluChem) at 405 nm. (b) Absorption spectra recorded for 1,1,3,3-tetramethylthiourea **A**, 4-chlorobenzonitrile (**1a**) and a mixture of **A** and **1a** in DMSO (0.3 M). (c) Emission of the excited tetramethylthiourea **A** in CH₃CN upon irradiation at 350 nm. A 0–0 transition energy ($E_{0,0}$) was determined to be 3.54 eV referring to the tail of absorption spectrum at 350 nm. (d) Cyclic voltammetry measurement of tetramethylthiourea **A** carried out in CH₃CN vs. Ag/AgCl. (e) Stern–Volmer luminescence quenching studies of tetramethylthiourea **A** ($0.95 \cdot 10^{-4}$ M in CH₃CN) with increasing amounts of 4-chlorobenzonitrile **1a** and iodobenzene **1g** (excitation at 350 nm; emission was acquired from 360 nm to 440 nm).^[a]Yield determined by ¹H NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene as the internal standard.^[b]Yield of the isolated product **3a**.

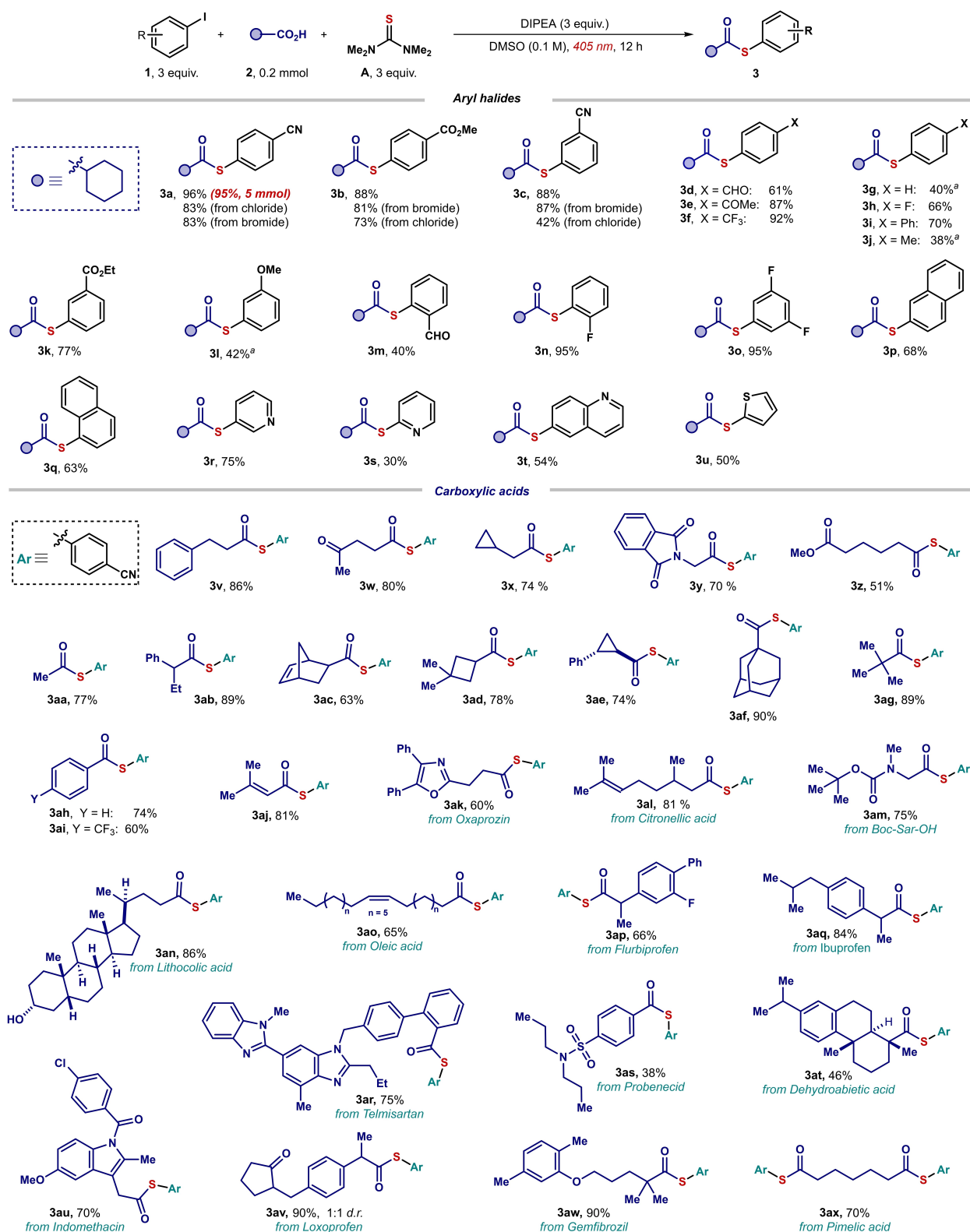


Figure 3. Photochemical synthesis of thioesters **3** from aryl halides **1** and carboxylic acids **2**. Reactions performed on a 0.2 mmol scale at 40 °C using 3 equiv. of **1** and 3 equiv. of thiourea **A** under illumination by a purple LED (EvoluChem) at 405 nm. Yields refer to isolated products **3** after purification. Aryl iodides were used as radical precursors unless otherwise stated. ^a24 h reaction time.

state aggregation (e.g., no electron donor-acceptor complexes were detected),^[11] as evidenced by the absence of any

bathochromic shift in the UV/Vis spectroscopic profile of **1a**, **A**, and their mixture. We then focused on the photo-

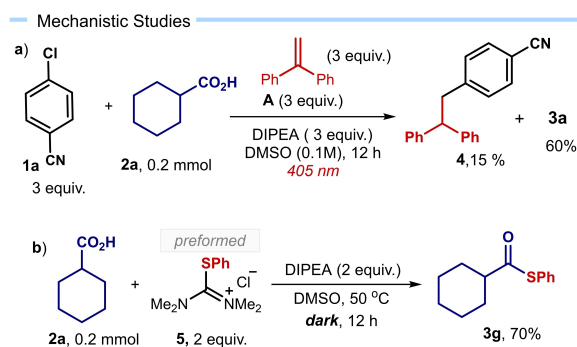


Figure 4. Mechanistic investigations: (a) capture of the aryl radical by 1,1-diphenylethylene; (b) thioetherification from preformed phenyl isothiuronium salt **5**.

physical behavior of tetramethylthiourea **A**, the sole absorbing species at 405 nm, the wavelength of irradiation used in this study. Upon irradiation at 350 nm of a CH₃CN solution of 1,1,3,3-tetramethylthiourea **A**, we detected emission, confirming that **A** could access an electronically excited state (Figure 2c). The 0–0 transition energy ($E_{0,0}$) was determined to be 3.54 eV, referring to the tail of the absorption spectrum at 350 nm. Next, the ground-state redox property of **A** was determined by cyclic voltammetry (Figure 2d). An irreversible oxidation peak was found at +1.29 V vs Ag/AgCl in CH₃CN. Applying the Rehm–Weller formalism,^[12] the redox potential of the excited **A** ($E(\mathbf{A}^{*+}/\mathbf{A}^*)$) was estimated as –2.33 V vs SCE. This confirmed that **A** acquires a strongly reducing power upon excitation. Stern–Volmer quenching studies (Figure 2e) revealed that the fluorescence of excited tetramethylthiourea **A**, induced by a laser at 350 nm, was effectively quenched by 4-chlorobenzonitrile **1a** [$E_{\text{red}} = -2.1$ V vs. Ag/AgCl] and iodobenzene [$E_{\text{red}} = -2.3$ V vs. Ag/AgCl],^[13] respectively. This observation supported the ability of the excited **A** to activate aryl halides **1** through an SET mechanism.

Under the optimal conditions outlined in entry 1 of Figure 2a, we explored the scope of the photochemical thioesterification (Figure 3). Initially, we demonstrated the process's efficiency on a preparative scale (5 mmol scale), yielding 1.2 g of product **3a** (95 % yield). We then investigated the reactivity of various aryl halides **1** as radical precursors using cyclohexanecarboxylic acid **2a** as the nucleophile. Notably, in addition to iodides, aryl bromides and chlorides, which are more challenging to activate by SET, were suitable substrates, yielding the corresponding thioesters **3a–c** in good yields. Aryl iodides with diverse substituents at various positions on the phenyl ring were well-tolerated, affording products **3d–3o** in good yields. The protocol exhibited tolerance towards sensitive functional groups, including aldehydes (products **3d**, **3m**), a ketone (product **3e**), and esters (products **3b**, **3k**), highlighting the mild conditions of the reaction. However, the method showed lower efficiency with electron-neutral and electron-rich aryl iodides (products **3g**, **3j**, and **3l**), consistent with a difficult activation of these substrates by excited **A**. A complete list of unreactive or poorly reactive substrates is

reported in Figure S3 of the Supporting Information. The reaction was also compatible with substrates containing polycyclic aromatic structures (products **3p–3q**) and valuable heterocyclic frameworks, including pyridines, quinoline, and thiophene (products **3r–3u**).

Next, we explored the scope of widely available carboxylic acids **2** using 4-iodobenzonitrile as the radical precursor. Primary carboxylic acids, bearing various functional groups such as carbonyl (product **3w**), cyclopropane (**3x**), phthalimide (**3y**), and ester (**3z**) moieties, were tolerated well. Thioesterification of simple acetic acid was straightforwardly achieved affording adduct **3aa**. A diverse array of secondary (**3ab–ae**) and tertiary (**3af–ag**) alkyl carboxylic acids, as well as aromatic acids (**3ah–ai**) and acrylic acid (**3aj**), were compatible with this photochemical transformation. Notably, pharmaceutical agents and natural products bearing a carboxylic acid functionality, such as *Oxaprozin* (product **3ak**), *Citronellic acid* (**3al**), protected *sarcosine* (**3am**), *Lithocolic acid* (**3an**), *Oleic acid* (**3ao**), *Flurbiprofen* (**3ap**), *Ibuprofen* (**3aq**), *Telmisartan* (**3ar**), *Probenecid* (**3as**), *Dehydroabiatic acid* (**3at**), *Indomethacin* (**3au**), *Loxoprofen* (**3av**), and *Gemfibrozil* (**3aw**) were efficiently functionalized. The dithioester **3ax** was also obtained from a diacid (*Pimelic acid*).

Finally, we carried out further investigations to elucidate the mechanism. When conducting the model reaction in the presence of 1,1-diphenylethylene (3 equiv.), an established radical trap, adduct **4** was isolated in 15 % yield, consistent with the formation of the aryl radical from **1a** (Figure 4a), while thioester **3a** remained the major product. Subsequently, we conducted an experiment reacting the preformed isothiuronium ion **5**, carboxylic acid **2a**, and DIPEA under dark conditions (Figure 4b). This experiment resulted in the formation of thioester **3g**, confirming that the polar *path A* depicted in the lower panel of Figure 1b is indeed operational. Additionally, we determined the quantum yield (Φ) of the overall photochemical process between **1a** and **2a**, which stood at a low value of 0.067, indicating that a radical chain mechanism is unlikely.^[10]

In summary, we have reported a novel photochemical method for synthesizing thioesters from readily available aryl halides and carboxylic acids. This thiol-free protocol hinges on the direct excitation of 1,1,3,3-tetramethylthiourea **A** and its multifaceted ability to act as the sulfur source, generate aryl radicals upon SET activation of halides, and trap them to produce reactive isothiuronium ions. A synthetic advantage of this method is its mild conditions, which enable remarkable tolerance for functional groups, facilitating late-stage modifications of biorelevant compounds.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Thioesters · 1,1,3,3-tetramethylthiourea · photochemistry · radicals · aryl halides

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- [11] In Figure , we display the formation of isothiuronium salts **I** resulting from SET activation of aryl halides **1** by the excited tetramethylthiourea **A**, leading to a radical ion pair. Halide cleavage within this pair triggers aryl radical formation, which then recombines with the sulfur radical within the solvent cage, yielding intermediate **I**. In an alternative scenario, the aryl radical may exit the solvent cage and be intercepted by ground-state tetramethylthiourea **A** following a radical chain manifold. Mechanistic studies discussed in the final section of this paper, including quantum yield determination, suggest the former pathway as more probable.
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