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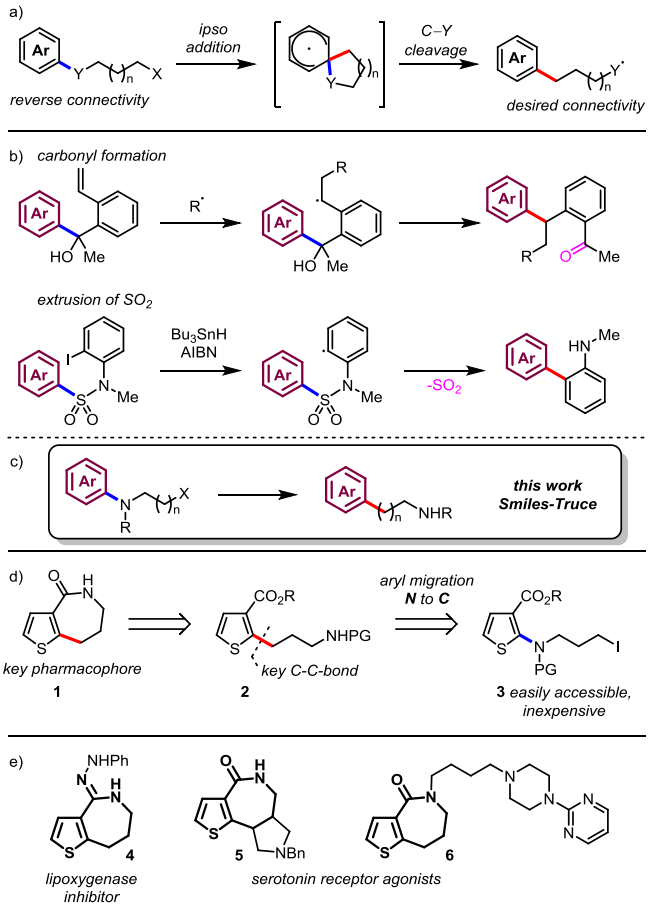
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Visible light mediated aryl migration by homolytic C–*N* cleavage of aryl amines

Dirk Alpers,[a] Kevin P. Cole,[b] and Corey R. J. Stephenson*[a]

Abstract: The photocatalytic preparation of aminoalkylated heteroarenes from haloalkylamides via a 1,4-aryl migration from nitrogen to carbon, conceptually analogous to a radical Smiles rearrangement, is reported. This method enables the substitution of amino groups in heteroaromatic compounds with aminoalkyl motifs under mild, iridium(III)-mediated photoredox conditions. It provides rapid access to thienoazepinone, a pharmacophore present in multiple drug candidates for potential treatment of different conditions, including inflammation and psychotic disorders.

The migration of remote aryl groups, such as the Smiles rearrangement, is a powerful tool for the synthesis of substituted aromatic and heteroaromatic structural motifs. Conceptually, it relies on the introduction of functional groups in an easily achieved, reverse connectivity and subsequent rearrangement into a desired product, bearing a difficult to construct connectivity (Scheme 1a). Due to groundbreaking developments in the field of transition metal and photoredox catalysis in recent years, radical-based protocols for the Smiles rearrangement have gained increased attention.[1] Formation of stable functional groups (e.g. carbonyls from benzylic alcohols) or extrusion of small molecules (e.g. CO_2 or SO_2) are often used as driving forces to facilitate efficient aryl transfer from carbon- or heteroatom-connected arenes[2-4] to carbon-centered radicals (Scheme 1b). For example, hydroxy- and amidoalkylated thiophenes were prepared by means of a radical Smiles rearrangements using arene sulfonamides and sulfonate esters under extrusion of SO_2.[3] However, these aromatic sulfonamides are often prepared from the corresponding aromatic amines through a three-step procedure consisting of diazotation, Sandmeyer-type chlorosulfonylation and sulfonamide/sulfonate ester formation.[5] In order to circumvent this step-intensive substrate synthesis, we questioned the possibility of a radical Smiles rearrangement through cleavage of an C_{Ar}–*N* bond to directly furnish the desired C–C bond, a transformation with only a small number of examples reported so far.[6] To thermodynamically enable desired reactivity, we intended to use



Scheme 1. a) Concept of radical aryl migration (X = radical precursor, Y = radical stabilizing group); b) Radical Smiles rearrangements driven by C=O formation (top, $R^{\bullet}$ = $N_3^{\bullet}$, $CF_3^{\bullet}$)[2a] and extrusion of SO_2 (bottom)[3h]; AIBN = Azobisisobutyronitrile; c) Radical aryl migration from *N* to C via Smiles-Truce rearrangement (this work); d) Retrosynthetic approach to thienoazepinone **1** with aryl migration from *N* to C as the key step; PG = protecting group; e) Examples for biologically active compounds containing the thienoazepinone pharmacophore.

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electron withdrawing *N*-protecting groups as well as alkyl halides as precursors for primary alkyl radicals to enhance the probability for a C–*N* cleavage in a Smiles-Truce like rearrangement (Scheme 1c). Potential products **2** of this reaction, using easily accessible 2-aminothiophenes **3** as starting materials, show great potential to serve as substrates for the synthesis of tetrahydrothienoazepinone **1**, which has received significant attention in drug development (Scheme 1d). Potential applications of this pharmacophore include the treatment of inflammations caused by proinflammatory cytokines through inhibition of nitric oxide synthase (NOS),[7] asthma

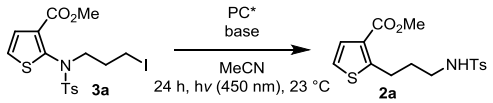
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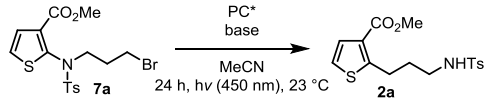
through inhibition of lipoxygenase (LOX)[8] or psychotic disorders through agonistic binding to serotonin receptors[9] (Scheme 1e).

An existing synthesis route to a thienoazepinone related to **1** involves the functionalization of a thiophene using numerous steps in order to forge two carbon-carbon bonds at C-2 and C-3 of the thiophene core.[10] Use of this route necessitates multiple telescoped steps due to the non-crystalline nature of the intermediates and utilizes chromatographic purifications, which are ill-suited for potential manufacturing applications. We hypothesized that the inexpensive 2-amino thiophene ester **3** could be used as a starting point to expedite the lactam preparation. The key transformation would entail the replacement of a C–N bond with a C–C bond in order to append the requisite three carbon linker (Scheme 1d).

Table 1. Optimization of Smiles-Truce rearrangement

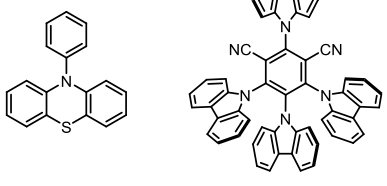


Entry	Catalyst (mol%)	Base (equiv)	annotations	Yield %[a]
1	**I** (1.0)	$^{i}Pr_2NEt$ (5.0)		>95 (87)
2	**II** (1.0)	$^{i}Pr_2NEt$ (5.0)		44
3	**III** (1.0)	$^{i}Pr_2NEt$ (5.0)		81
4	**IV** (10)	$^{i}Pr_2NEt$ (5.0)		29
5	**V** (5.0)	$^{i}Pr_2NEt$ (5.0)	370 nm	>95 (83)
6	**I** (0.01)	$^{i}Pr_2NEt$ (5.0)		67
7	**I** (1.0)	Et_3N (5.0)		54
8	**I** (1.0)	$^{i}Pr_2NEt$ (5.0)	under air	>95



9	**I** (1.0)	$^{i}Pr_2NEt$ (5.0)		0
10	**I** (1.0)	$^{i}Pr_2NEt$ (5.0)	1.0 equiv NaI	55
11	**I** (1.0)	$^{i}Pr_2NEt$ (5.0)	1.0 equiv NaI, 60 °C	>95
12	**I** (1.0)	$^{i}Pr_2NEt$ (5.0)	0.5 equiv NaI, 60 °C	>95
13	**I** (1.0)	$^{i}Pr_2NEt$ (5.0)	0.2 equiv NaI, 60 °C	16
14	**I** (1.0)	$^{i}Pr_2NEt$ (3.0)	0.5 equiv NaI, 60 °C[b]	>95 (95)

PC* = excited photocatalyst. All reactions were conducted on 0.1 mmol scale at 0.1 M in degassed MeCN unless otherwise noted. See Structures of catalysts **I**-**III** are given in the SI. [a] Determined by HPLC analysis; numbers in parentheses indicate isolated yield; [b] c = 0.2 M.



10-Phenylphenothiazine **IV** 4CzIPN **V**

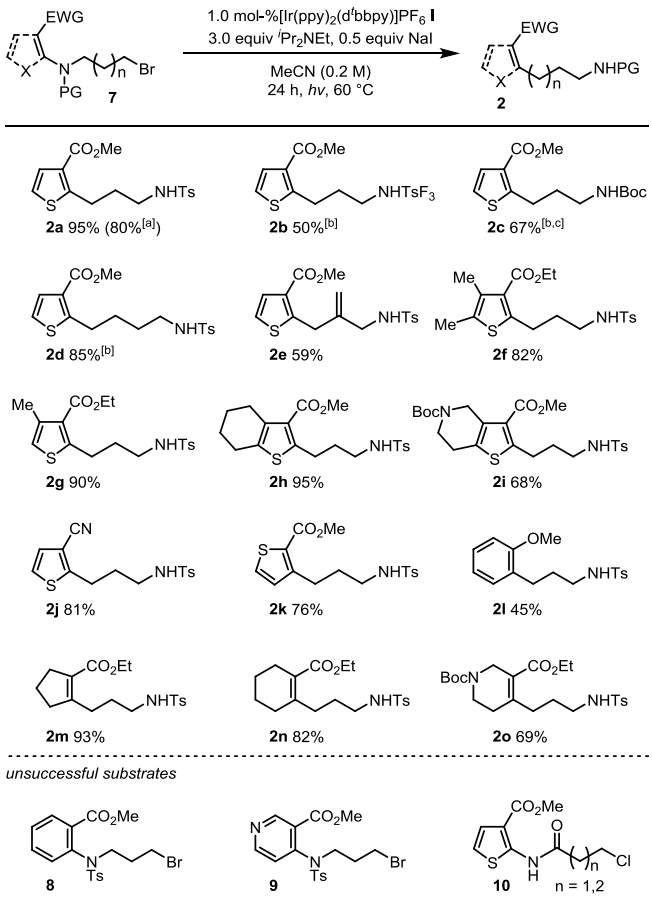
Alkyliodides have been shown to serve as viable sources for carbon centered radicals through Ir-mediated photocatalytic reduction.[11] Upon irradiation of alkyliodide **3a** with blue light in the presence of 1 mol% $[Ir(ppy)_2(d^tbbpy)]PF_6$ **I** ($E_{1/2}(M/M^-)$ = -1.51 V vs. SCE, ppy = 2-phenylpyridine, d^tbbpy = 4,4'-di-*tert*-butyl-2,2'-bypyridine)[12] and 5.0 equiv of $^{i}Pr_2NEt$ in MeCN, product **2a** was isolated in 87% yield after 3 h (Table 1, Entry 1). While $[Ru(bpy)_3](PF_6)_2$ **II** ($E_{1/2}(M/M^-)$ = -1.33 V vs. SCE, bpy = 2,2'-bipyridine)[13] only led to 44% conversion of **3a** (Entry 2), $[Ir(ppy)_3]$ **III** ($E_{1/2}(M^*/M^+)$ = -1.73 V vs. SCE)[14] provided **2a** in 81% yield (Entry 3). Utilization of the strong reductant 10-phenylphenothiazine **IV** ($E_{1/2}(P^*/P^+)$ = -2.1 V vs. SCE)[15] gave 29% of the rearrangement product, accompanied by several side products (Entry 4). Isophthalonitrile based photocatalyst 4-CzIPN **V** ($E_{1/2}(P/P^-)$ = -1.21 V vs. SCE)[16] furnished Smiles-product **2a** in 83% yield after purification, however complete removal of the catalyst by chromatography could not be achieved (Entry 5). The reaction proceeds well with loadings of Ir-catalyst **I** as low as 0.01 mol%, but complete conversion could not be achieved in this case within 24 h (Entry 6). When $^{i}Pr_2NEt$ was substituted with Et_3N, the triethylammonium salt of starting material **3a** was formed by nucleophilic substitution of the iodide to a notable extent, leading to a decreased yield (Entry 7, see SI for details). Notably, full conversion to **2a** was achieved when the reaction was conducted in non-degassed solvent (Entry 8).

Unactivated alkylbromides are generally inaccessible for mesolytic cleavage via visible light photoreduction due to a stronger C─Br bond, only UV light driven methods have been reported.[17] Irradiation of bromide **7a** in presence of catalyst **I** only provided undesired side products (Entry 9, see SI for details). To facilitate **2a** in a single step from **7a**, we added 1.0 equiv NaI to induce the *in situ* formation of alkyliodide **3a** and subsequently obtained **2a** in 55% yield (Entry 10). Elevation of the temperature to 60 °C led to full conversion within 24 h (Entry 11). Substoichiometric amounts of NaI were sufficient to lead to full conversion, however with 20 mol%, we observed the same decomposition products that were present in the reaction of bromide **7a** alone (Entries 12 and 13). Optimization of the process revealed that 3.0 equiv of $^{i}Pr_2NEt$ was the minimum amount required and the starting material concentration should not exceed 0.2 M. Under these conditions, product **2a** could be isolated in 95% yield (Entry 14). Notably the protocol could be scaled up to 1 g of starting material without significant reduction in yield (see Scheme 2). Additional data on the optimization is provided in the SI.

The optimized conditions of the Finkelstein/Smiles one-pot reaction were applied to a selection of different starting materials (Scheme 2). Variation of the *N*-protecting group showed the tosyl group to be most suitable for this reaction (**2a-c**). To prevent formation of side products, reactions with trifluorotosyl and Boc-protected substrates had to be run under diluted conditions (0.05 M). Product **2b** was isolated in 50% yield, while **2c** was achieved along with a putative spirocyclic thioaminal side product,

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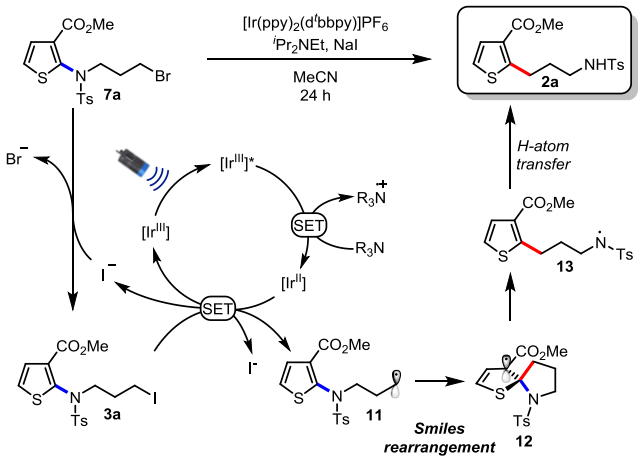
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Scheme 2. Substrate scope. All reactions were conducted on a 0.1 mmol scale in undegassed solvent. [a] 2.3 mmol (1.0 g) of starting material was used; [b] c = 0.05 M; [c] acidic aqueous workup procedure required, (see SI for details); EWG = electron withdrawing group, Ts = tosyl group, TsF_3 = 4-trifluoromethylbenzene sulfonyl group, Boc = *tert*-butyloxycarbonyl group.

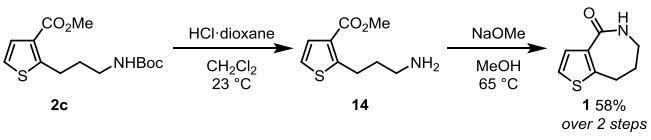
that could be transformed into the desired product by an acidic workup (see SI for details) to give **2c** in 67% yield. Introduction of a butenyl linker, thus requiring a 1,5-aryl shift to occur after radical formation, furnished product **2d** in 85% yield, also under diluted conditions. Formation of an allylic radical by reduction of an allyl halide led to alkenyl compound **2e** in 59% yield. Various alkyl substituents in 4- and 5-positions of the thiophene, including a Boc-protected amine, were well tolerated (**2f-i**), as was substitution of a nitrile group for the ester in the 3-position. The regioisomer of thiophene **3a** obtained by reversing substituents in the 2- and 3-positions afforded the expected product **2k** in 76% yield. This result suggests that the method is not limited to specific thiophene substitution patterns. Anisidine derivative **2l** was prepared in 45% yield, which represents an improvement over a previously reported tin-based method (30%),[6c] while acceptor substituted benzene and pyridine based compounds **8** and **9** were decomposed under the given conditions. Interestingly, non-aromatic electron poor cycloalkene derivatives worked well and provided aminoalkylated cyclopentene **2m**, cyclohexene **2n** and Boc-protected tetrahydropyridine **2o** in good to excellent yields. Chloroacylated aminothiophenes **10** either underwent fast elimination of HCl in the presence of a base (n = 1) or formed a pyrrolidinone via intramolecular nucleophilic substitution (n = 2).

A plausible mechanism for this aminoalkylation method is depicted in Scheme 3. Formation of primary alkyl radical **11** occurs via mesolytic cleavage of alkyliodide **3a** by the reduced form $[Ir^{II}(ppy)_2(d^tbbpy)]$ of the iridium photocatalyst **I**. Subsequent *ipso* addition to the the thiophene core breaks the aromaticity of the π-system but produces a tertiary radical **12** that is additionally stabilized by its electron withdrawing substituent. Homolytic cleavage of the C–N bond reestablishes the aromaticity of the thiophene and leads to *N*-centered radical **13**. The final product **2a** is presumably generated by H-atom transfer (HAT), whereby the amine base is the likely source of hydrogen-atom. Further mechanistic aspects are discussed in the SI.



Scheme 3. Proposed mechanism.

We finally investigated the conversion of alkylthiophenes **2** into the pharmaceutically important tetrahydrothienoazepinone **1**. Therefore, Boc-protected thiophene **2c** was treated with 5.0 equiv of HCl in 1,4-dioxane furnishing free amine **14** as the sole product after neutralization. Upon heating to 65 °C with 3.0 equiv of NaOMe in MeOH, cyclization to azepinone **1** was achieved with an overall yield of 58% over two steps starting from Boc-protected thiophene **2c**.



Scheme 4. Synthesis of tetrahydrothienoazepinone **1**.

In conclusion, we have developed a visible light mediated, scalable and mild protocol for the Smiles rearrangement of heteroarylamines and *N*-tosyl alkenylamides by means of a radical aryl migration featuring a C–*N*-cleavage. The products of this method can readily be transformed into pharmaceutically relevant fused lactams.

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Keywords: catalysis • heterocycles • photocatalysis • radical reactions • rearrangement

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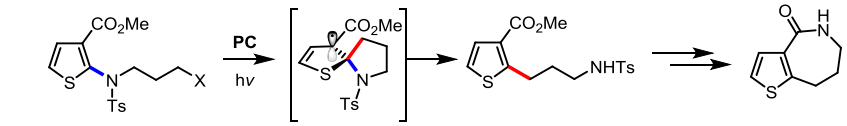
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COMMUNICATION



Visible light Smiles rearrangement *unusual C–N cleavage* *access to thienoazepinone pharmacophore*

Aminoalkylated heteroarenes are synthesized by radical Smiles rearrangement of haloalkylamides via a key C–N cleavage under mild, iridium (III)-mediated photoredox conditions. The method provides rapid access to the pharmaceutically relevant thienoazepinone scaffold.

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