Photocatalysis

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A Visible-Light-Mediated Radical Smiles Rearrangement and its Application to the Synthesis of a Difluoro-Substituted Spirocyclic ORL-1 Antagonist

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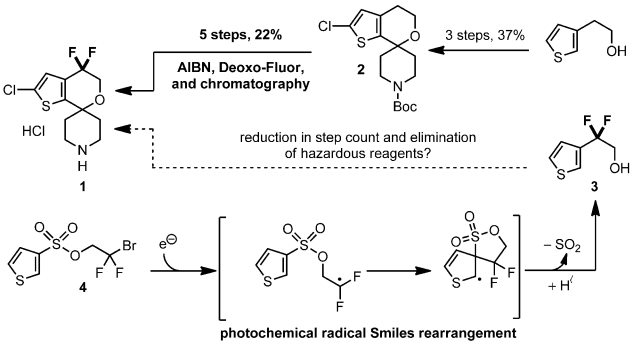
Abstract: *A visible-light-mediated radical Smiles rearrangement has been developed to address the challenging synthesis of the gem-difluoro group present in an opioid receptor-like 1 (ORL-1) antagonist that is currently in development for the treatment of depression and/or obesity. This method enables the direct and efficient introduction of the difluoroethanol motif into a range of aryl and heteroaryl systems, representing a new disconnection for the synthesis of this versatile moiety. When applied to the target compound, the photochemical step could be conducted on 15 g scale using industrially relevant $[Ru(bpy)_3Cl_2]$ catalyst loadings of 0.01 mol%. This transformation is part of an overall five-step route to the antagonist that compares favorably to the current synthetic sequence and demonstrates, in this specific case, a clear strategic benefit of photocatalysis.*



Scheme 1. Previously reported route towards **1** and the proposed photochemical radical Smiles rearrangement. AIBN = azobis(isobutyronitrile).

In recent years, there has been an exponential increase in the number of transformations mediated by visible-light photocatalysis;[1] however, there remain to be only few reports detailing its application to agrochemical or pharmaceutical synthesis.[2] Key to the expansion of this mode of catalysis is the demonstration of a strategic benefit when compared to other routes, most likely showcased by the ability of photocatalysis to provide new synthetic disconnections. We aimed to test the potential advantage of photocatalysis in the synthesis of difluoro-substituted spirocyclic thiophene **1**,[3] a building block in the synthesis of an opioid receptor-like 1 (ORL-1) antagonist that is currently in development for the treatment of depression and/or obesity (Scheme 1).[4] A production campaign demonstrated rapid access to the carbocyclic framework **2** in good yield and on multi-kilogram scale. However, the benzylic fluorination of **2** proved to be a challenge, requiring four synthetic steps in an overall 25% yield. Furthermore, this sequence included an AIBN initiated radical bromination, utilized 2.6 equivalents of Deoxo-Fluor as the fluoride source,[5] and required chromatographic purification. Benzylic fluorination remains a general problem, with classical methods including nucleophilic or electrophilic fluorination of pre-functionalized substrates.[6] Direct benzylic C–H fluorination strategies, typically employing either transition metals[7] or non-metal promoters,[8] have recently been reported. Chen and co-workers have shown that visible-light photocatalysis is a potentially viable method;[9] however, their method requires the use of 3.0 equivalents of Selectfluor II. An appealing strategy to address the high step count, low yield, and the use of specialized fluorinating reagents for the fluorination sequence would be to start from pre-fluorinated thiophene **3**.

This route could make use of ethyl bromodifluoroacetate as an inexpensive, readily available source of the requisite benzylic *gem*-difluoromethyl group,[10] diverting the key step from C–F to C–C bond formation. C–H[11] or directed coupling strategies[12] as well as radical arylation methods[13] are well documented (Scheme 2), but proved poorly selective in the context of **1**. Specifically, employing coupling conditions originally introduced by Kobayashi and co-workers,[14] treatment of 4-bromo-2-chlorothiophene with superstoichiometric amounts of copper and ethyl bromodifluoroacetate led primarily to functionalization at the five position.[15] Radical arylation is generally limited to the 5-position of the heteroaromatic compound; in our system, with both the 2- and 5-positions blocked, the desired product was not obtained.[16] Given the need for selectivity and step efficiency, we surveyed methods that would lead directly and regiospecifically to the difluoromethyl group. The Smiles rearrangement is an intramolecular nucleophilic substitution reaction that occurs exclusively at the *ipso* position of an activated aromatic leaving group, typically a sulfonate.[17] Radical versions of the Smiles rearrangement have also been demonstrated[18] and

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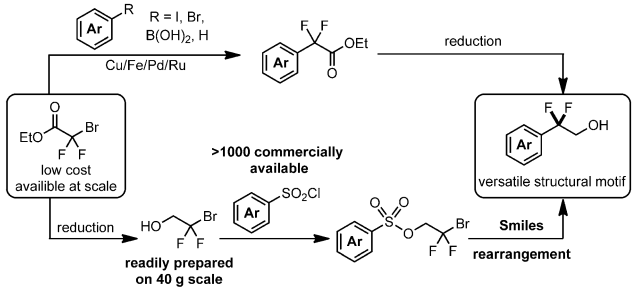
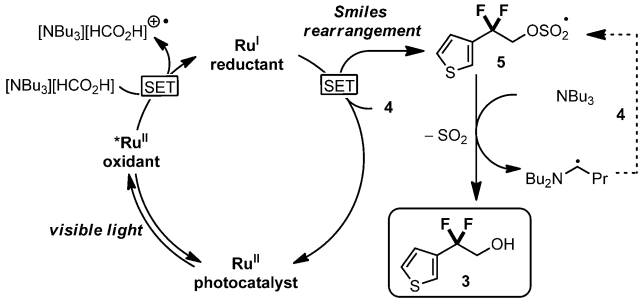


Scheme 2. Approaches to the difluoroethanol motif.

can proceed without the requirement for a strongly electron-withdrawing group adjacent to the sulfonate. Tada et al. have developed an AIBN initiated (50 mol%) rearrangement using stoichiometric Bu_3SnH, conditions we did not deem to be applicable in our setting.[19] Given the extensive literature detailing visible-light-mediated reductive dehalogenation,[1a,20] we were confident of developing a radical Smiles rearrangement from a difluorobromo sulfonate such as **4** (Scheme 1). Furthermore, given the wide availability of sulfonyl chlorides (>1000 commercially available) and the ready access to bromodifluoroethanol,[16] we envisioned this as a general method for the synthesis of the difluoroethanol motif (Scheme 2).

Our envisioned reaction mechanistically proceeds by quenching of the excited state of a photocatalyst such as $[Ru(bpy)_3]^{2+}$ ($E_{1/2}^{II*/I} = +0.77$ V vs. SCE; bpy = bipyridine) by a suitable electron donor, such as $[NBu_3][HCO_2H]$, to generate the strongly reducing Ru^I species ($E_{1/2}^{II/I} = -1.33$ V vs. SCE; Scheme 3).[21] Single-electron reduction of thiophene **4** provides the desired difluoromethyl radical and regenerates the Ru^{II} photocatalyst. The newly formed radical may then undergo intramolecular *ipso* addition/elimination with the sulfonate group (Scheme 1) to give **5**, with subsequent H atom abstraction followed by polar extrusion of SO_2 leading to the desired product.

At this juncture, we cannot rule out the possibility of radical chain processes contributing to the formation of the product, especially given the low photocatalyst loading and the short reactions times for **6** (see below).[22] These conditions (0.01 mol% initiator, 1 h) are in contrast to those of the classical chain process using Bu_3SnH, which requires

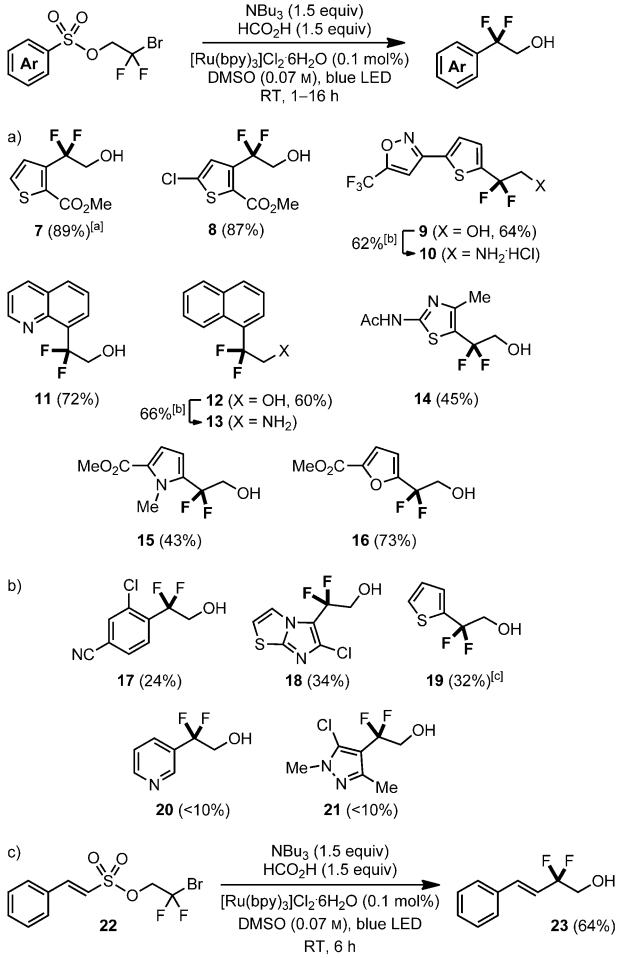


Scheme 3. Mechanistic proposal for the photocatalyzed radical Smiles rearrangement.

Table 1: Optimization of the reaction conditions.

Entry	Electron/H atom source	Solvent	Cat. [mol%]	**6** [%][a]	**7** [%][a]
1[b]	iPr_2NEt[c]	DMA	1.0	43	36
2	iPr_2NEt[c]	DMSO	1.0	28	53
3	iPr_2NEt,[c] HCO_2H[c]	DMSO	1.0	<2	67
4	NBu_3,[c] HCO_2H[c]	DMSO	1.0	<2	86
5[d,e]	NBu_3,[f] HCO_2H[f]	DMSO	1.0	<2	95
6[d,e]	**NBu_3,[f] HCO_2H[f]**	**DMSO**	**0.01**	**<2**	**94 (89)**[g]
7	NBu_3,[f] HCO_2H[f]	DMSO	–	>98	<2

All reactions were performed at 0.14 M with 1.0 mol% of the photocatalyst without degassing unless otherwise stated. [a] Yield determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture using $PhCF_3$ as the internal standard. [b] Reaction degassed by freeze–pump–thaw cycles. [c] 2.5 equiv. [d] 0.07 M. [e] 1 h. [f] 1.5 equiv. [g] Yield of isolated product. DMA = dimethylacetamide, DMSO = dimethyl sulfoxide.



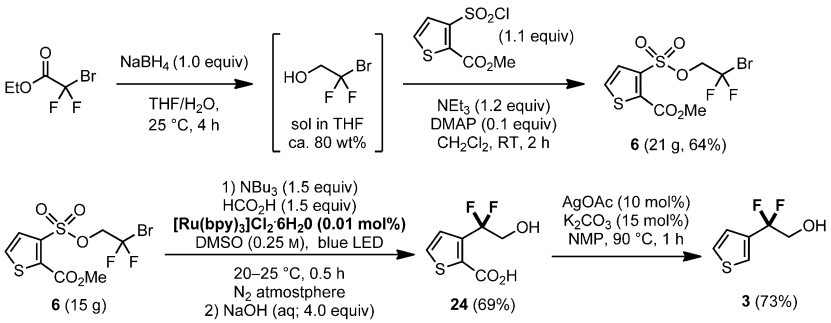
Scheme 4. Substrate scope. [a] $[Ru(bpy)_3]Cl_2$ (0.01 mol%). [b] Tf_2O (1.1 equiv), pyridine (1.6 equiv), MeCN, 0°C to RT; then NH_4OH (10 equiv), 50°C. [c] Yield determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture with $PhCF_3$ as the internal standard.

a significantly larger amount of initiator (AIBN, 50 mol%), longer reaction times (22 h), and elevated temperature (80 °C).[19] In our system, propagation may occur following H atom abstraction from NBu_3 by **5** to give an α-aminoalkyl radical, which has previously been shown to be a competent reductant of C–Br bonds.[22b,23]

Initial studies on employing sulfonate **4** yielded no observable rearrangement product, providing only moderate consumption of starting material amongst a complex mixture.[16] Considering the structural features required for an efficient radical Smiles rearrangement[19] as well as both the cost and availability of sulfonyl chlorides,[24] we continued our investigations with thiophene **6**.[25] Employing conditions similar to those previously developed for the reduction of activated alkyl bromides[20a] gave a promising 36% yield (Table 1, entry 1). Switching to DMSO as the solvent gave an improved yield of 53% without the need for degassing.[26] The addition of formic acid, a known H atom source,[20a] led to full consumption of the starting material (entry 3), and following a switch to NBu_3 as the electron/H atom source,[20b] the desired product **7** was formed in 86% yield (entry 4). Increased dilution gave full starting material consumption within one hour (entry 5), even with a 100-fold reduced catalyst loading (entry 6). A reaction conducted in the absence of photocatalyst returned unreacted **6** (entry 7).

We next applied our optimized procedure to a range of other aromatic and heteroaromatic substrates (Scheme 4). Good yields were obtained for an alternative thiophene with application to the synthesis of **1** (**8**, 87%) as well as a more complex thiophene substrate (**9**, 64%). Extended aromatic systems reacted efficiently, presumably owing to a lower penalty associated with dearomatization upon radical *ipso* addition (**11** and **12**, 72% and 60%). Other heterocyclic systems typically found in pharmaceutical targets, such as thiazole **14**, pyrrole **15**, and furan **16**, could be obtained in moderate to good yield (45%, 43%, and 73%, respectively). We also explored the limits of this method and found that benzene-derived substrates or heterocycles lacking radical-stabilizing groups provided low to moderate yields (**17**–**21**, < 10–34%).[27] Whereas the difluoroethanol motif is featured in a number of biologically active compounds such as Abediterol,[28] it is also used as a precursor to the more common difluoroethylamine group.[29] Access to this motif by a two-step triflation–amination sequence was demonstrated on representative Smiles products **9** and **12**, providing the corresponding amines in good yield (**10** and **13**). Finally, we also applied the Smiles rearrangement to a single example of a vinyl sulfonate (64% yield; Scheme 4c)[18b] to afford the vinyl difluoroethanol motif[30] featured in the prostaglandin analogue Tafluprost.

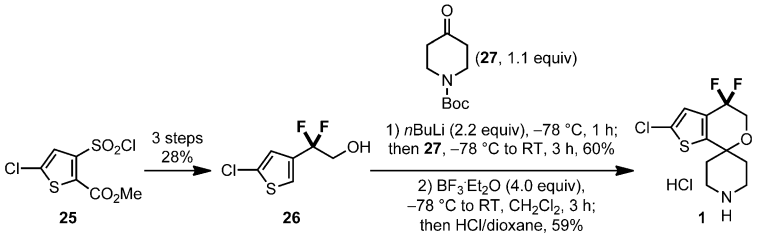
Following the establishment of this procedure as a general method, we returned to target compound **1**. The starting material **6** could be readily obtained on > 20 g scale and was isolated by crystallization in 64% yield (Scheme 5). Whereas the low catalyst loading and fast reaction time associated with the radical Smiles rearrangement of **6** are ideal from a synthetic perspective, the dilute reaction conditions limited the assessment of this reaction on larger scale. Conducting the reaction at increased concentrations (0.26 M) led to competitive formation of the sulfonic acid, resulting in consistently lower yields (70–75% by ^{19}F NMR spectroscopy). This issue could be mitigated by a two-step, one-pot photocatalyzed Smiles rearrangement/ester hydrolysis sequence on 15 g scale with industrially relevant catalyst loadings (0.01 mol%), yielding 69% of the thiophenecarboxylic acid **24** without purification. The silver-catalyzed decarboxylation[31] proceeded to give thiophene difluoroethanol **3** in 73% yield following distillation (Scheme 5).



Scheme 5. Application to the synthesis of **3**. DMAP = dimethylaminopyridine, NMP = *N*-methylpyrrolidone.

Efforts to realize the subsequent transformation of **3** into spirocyclic thiophene **1** proved challenging, potentially owing to the decreased nucleophilicity of the hydroxy group, which is now proximal to a difluoromethyl substituent.

We progressed by investigating the possibility of eliminating the downstream chlorination step by repeating the three-step sequence with the corresponding chlorinated sulfonyl chloride, providing the target thiophene **26** in 28% overall yield.[32] **26** could be converted into the required spirocyclic material **1** by lithiation, addition to *N*-Boc-4-piperidinone **27** in 60% yield, followed by concurrent spirocyclization/Boc deprotection in 59% yield (Scheme 6). This unoptimized five-step sequence addresses many of the undesirable features of the current synthetic route. Most importantly, the challenging benzylic fluorination can be



Scheme 6. Synthesis of spirocyclic thiophene **1**.

accomplished by switching this key transformation to a C–C rather than a C–F bond formation. This allows the use of ethyl bromodifluoroacetate to introduce the *gem*-difluoro group, directly and regiospecifically accessing the difluoroethanol motif under mild conditions using low catalyst loadings.

In conclusion, we have developed a visible-light-mediated radical Smiles rearrangement that addresses a current and pressing challenge associated with the synthesis of a key starting material for an ORL-1 antagonist. The method is general for other aromatic and heteroaromatic substrates, allowing rapid and efficient access to the benzylic difluoroethanol motif from widely available sulfonyl chlorides. Preliminary assessment of this method with regards to the target compound has been demonstrated on significant scale (15 g) and proceeds with short reaction times (as low as 0.5 h) and industrially relevant catalyst loadings (0.01 mol%). Furthermore, employing ethyl bromodifluoroacetate as a source of the benzylic difluoro group rather than a route using AIBN and Deoxo-Fluor is highly desirable. Importantly, this study demonstrates the viability of photocatalysis to provide a strategic advantage in process development by enabling a new retrosynthetic disconnection and greater route flexibility. Ongoing research is aimed at assessing the wider utility of the photochemical Smiles rearrangement and application to the target on greater scale.

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