Alcohol Etherification via Alkoxy Radicals Generated by Visible-Light Photoredox Catalysis

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ABSTRACT: A mechanistically divergent method is described that, employing a commercially available hypervalent iodine(III) reagent, generates alkoxy radicals from 1°, 2°, and 3° alcohols and allows their use in the functionalization of C(sp³)−H and C(sp²)−H bonds. This visible-light photoredox catalysis produces alkyl ethers via 1,5/6-hydrogen atom transfer or aryl ethers via 1,5-addition. This mild methodology provides a practical strategy for the synthesis of acetals, orthoesters, tetrahydrofurans, and chromanes.

Ethers constitute a common framework in many bioactive natural products, pharmaceuticals, and cosmetics. Moreover, ethers are broadly applied in industrial contexts as solvents, refrigerants, and more recently, lubricants and fuels. During the past decades, transition-metal catalysis became a heavily utilized tool for the synthesis of ethers, overcoming the functional group incompatibility observed for more classical methods. However, these cross-coupling reactions are limited to aryl halides and are typically conducted under high temperatures to achieve effective reductive elimination for palladium- and nickel-based systems or effective oxidative addition for copper-based processes (Scheme 1a). Photoredox catalysis has recently emerged as a powerful alternative that allows for direct C−O coupling using milder conditions. A recent application of this methodology is the room-temperature etherification developed by MacMillan and co-workers that allows for the formation of C−O bonds by employing dual photoredox and nickel catalysis. Nevertheless, this novel approach is limited to aryl bromides. We reasoned that alkoxy radicals generated from alcohols under photoredox catalysis, could be applied to avoid the use of halides as substrates in the construction of ethers. Photoredox catalysis has been employed to generate alkoxy radicals directly from alcohols via reductive quenching or by oxidative quenching in combination with stoichiometric oxidants or redox-active auxiliaries (Scheme 1b). Most commonly used alkoxy radical precursors from alcohols, such as nitrite esters, sulfenyl ethers, peroxides, hypohalites, N-alkoxypyridine-2-thiones, and N-alkoxyphthalimides, are sometimes challenging to synthesize, unstable, or toxic. On the other hand, hypervalent iodine(III) reagents (HIR) have been used for the direct generation of oxygen-centered radicals from alcohols under mild photoredox conditions via oxidative quenching (Scheme 1b), are commercially available, easy to handle, and nontoxic.
well-known 1,5-hydrogen atom transfer (1,5-HAT) for C(sp^2)−H remote functionalization\(^\text{13}\) and also the underexplored 1,5-addition to unsaturated functionalities for C(sp^3)−H functionalization. This strategy would provide access to a diverse set of oxacyclic frameworks in a redox-neutral fashion (Scheme 1c).

We began our investigations with benziodoxolone 2, derived from 4-phenylbutanol. First, we focused on the 1,5-HAT process as a model reaction. As shown in Table 1 (summary of key observations), we started screening for the optimal solvent in which benziodoxolone 2 would be converted into 2-phenyltetrahydrofuran 3 in the presence of photocatalyst fac-Ir(ppy)\(_3\). Among all the solvents investigated, acetonitrile showed the best result, giving the desired tetrahydrofuran 3 in 40% yield (NMR) after irradiation with blue LEDs for 16 h (entry 5). Subsequently, the etherification was optimized by varying reaction parameters and exploring various organic and transition-metal-based catalysts. None of these variations showed a notable increase in the reaction yield (see Supporting Information S11). However, the addition of base was essential for the etherification reaction given that no product was detected when the reaction was performed in their absence (entries 14 and 15). Finally, we explored the direct etherification of 4-phenyl butanol. Unfortunately, several studies showed that compound 2 cannot be formed using optimized conditions (see Supporting Information S12–14).

With the optimal conditions in hand, we next investigated the scope of the alkoxy benziodoxolone derivatives. All benziodoxolone derivatives were prepared using a modified method developed by Baker et al.,\(^\text{16}\) employing commercially available 1-acetoxy-1,2-benziodoxol-3(1H)-one and dibromomethane as the solvent. These conditions allowed us to reduce the required stoichiometry of the alcohol to only 1.5 equiv as compared to the solvolytic conditions reported by Baker\(^\text{16}\) (see Supporting Information S4). As shown in Scheme 2, double-

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**Table 1. Summary of the Optimization Conditions for the Photoredox-Catalyzed Etherification of Phenylbutoxy Benziodoxolone 2**

| entry | Ir(ppy)\(_3\) (mol %) | base | solvent | yield\(^\text{d}\) of 3 (%) |
|-------|---------------------|------|---------|---------------------|
| 1     | 5.0                 | DMF  | CH\(_3\)CN | 0                   |
| 2     | 5.0                 | DCE  | CH\(_3\)CN | 5                   |
| 3     | 5.0                 | THF  | CH\(_3\)CN | 5                   |
| 4     | 5.0                 | PhCF\(_3\) | 28          |
| 5     | 5.0                 | CH\(_3\)CN | 40          |
| 6     | 5.0                 | K\(_2\)HPO\(_4\) | CH\(_3\)CN | 42       |
| 7     | 5.0                 | Amberlite | CH\(_3\)CN | 46       |
| 8     | 5.0                 | pyridine | CH\(_3\)CN | 50       |
| 9     | 5.0                 | lutidine | CH\(_3\)CN | 35       |
| 10    | 5.0                 | DMAP  | CH\(_3\)CN | 32       |
| 11    | 2.0                 | pyridine | CH\(_3\)CN | 44       |
| 12    | 10.0                | pyridine | CH\(_3\)CN | 44       |
| 13    | 5.0                 | pyridine | CH\(_3\)CN | 52       |
| 14    | no catalyst         | pyridine | CH\(_3\)CN | 0        |
| 15    | 5.0                 | pyridine | CH\(_3\)CN | 0        |

\(^{d}\)Reaction conditions: 2 (0.1 mmol), Ir complex (2.0−10.0 mol %), base (1.0 equiv), and solvent (2 mL) under light irradiation using blue LED at rt for 16h under N\(_2\).

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**Scheme 2. Photocatalytic Etherification via 1,5-HAT\(^{14}\)**

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activated (benzylic and \(\alpha\)-heteroatom) C−H bonds produced the acetics 3a, 3b, and 3c in 75%, 92%, and 91% yield, respectively. These three examples illustrate that this \(\delta\)-C(sp\(^3\))−H etherification is not affected by the electronic nature and tolerates some steric bulk of the substituents on the arene. The use of only \(\alpha\)-heteroatom-activated C−H bonds allowed the formation of noncyclic acetal 3d with slightly decreased yield (52%). This result prompted us to question whether this methodology applies to the synthesis of nonsymmetric orthoesters, which are versatile synthetic intermediates known for their typically problematic synthesis.\(^\text{17}\) We were pleased to obtain orthoester 3e in 46% yield. The substrate used for the optimization of the reaction conditions, as well as the \(p\)-fluoro derivative, gave the corresponding tetrahydrofurans 3f and 3g in 48% (43% when scaled up to 1.0 mmol) and 51% yields, respectively. Finally, we examined the reactivity of secondary and tertiary alkoxy radicals, which are considered challenging due to rapid \(\beta\)-fragmentation based side reactions.\(^\text{18a}\) To our delight, both
secondary and tertiary alkoxy benziodoxolones yielded the desired tetrahydrofurans 3h−3k in good to excellent yields (56−97%). The different yields obtained for the various substrates investigated are effected by byproducts formations coupled to the characteristics of the benziodoxolone substrate (see Supporting Information S15).

In general, alkoxy radicals react via 1,5-HAT or β-fragmentation due to the formation of less energetic C-centered radicals acting as a thermodynamic driving force. However, when neither of these two paths is feasible, the resulting RO° has a propensity to add to unsaturated systems, as recently demonstrated by Dagousset and co-workers. Consequently, we decided to explore the possibility of applying our methodology to the synthesis of chromanes, which to the best of our knowledge has never been achieved using alkoxy radicals generated under photoredox catalysis.

When initially exploring the conditions identified as optimal for 1,5-HAT substrates, with substrates deemed suitable to undergo 1,5-addition, we observed that no base additive was needed to achieve full conversion. Subjecting 3-phenyl-1-propanol to these conditions a additive was needed to achieve full conversion. Subjecting 3-suitable to undergo 1,5-addition, we observed that no base for suitable 1,5-HAT substrates, with substrates deemed advantage: only alkoxy benziodoxolone derived from alcohol activity: only alkoxy benziodoxolone derived from alcohol

Unfortunately, the process takes place with poor regioselectivity: only alkoxy benziodoxolone derived from alcohol

Scheme 3. Photocatalytic Etherification via 1,5-Addition

![Scheme 3](image)

When initially exploring the conditions identified as optimal for 1,5-HAT substrates, with substrates deemed suitable to undergo 1,5-addition, we observed that no base additive was needed to achieve full conversion. Subjecting 3-phenyl-1-propanol to these conditions afforded 3m in a 55% yield after only 1 h. The scope of this novel photocatalyzed intramolecular aryl etherification was next investigated, and the results are summarized in Scheme 3.

Contrary to what we expected, electron-rich and electron-poor aromatic arenes produced the corresponding chromanes with similar yields (3m−3q, 56−54%). Remarkably, secondary and tertiary alcohols were also viable substrates affording the corresponding compounds 3r−3u in up to quantitative yield. Unfortunately, the process takes place with poor regioselectivity: only alkoxy benziodoxolone derived from alcohol.

Data

we propose that the reaction is initiated by single-electron reduction of benziodoxolone A (E_red = −1.07 V vs standard calomel electrode (SCE) in CH_3CN) by the photoexcited state of Ir^{III} (E_{1/2}^{III/IV} = −1.73 V vs SCE in CH_3CN), producing oxidized catalyst Ir^{IV}, 2-iodobenzoate, and the oxygen-centered radical B. Subsequently, B undergoes 1,5-HAT, forming the translocated carbon-centered benzylstabilized radical C. The Ir^{ppy}_3 catalyst is regenerated from Ir^{IV} by SET oxidation of carbon radical C to carbocation D. The oxidation potential of an alkyl-substituted benzylic radical such as C is E_{ox} = +0.35 V vs SCE in CH_3CN and the oxidation potential of oxidatively quenched Ir^{ppy}_3 is E_{ox} = +0.77 V vs SCE in CH_3CN, making the turnover event of the catalyst exergonic. Finally, carbocation D undergoes an intramolecular ring closure to form tetrahydrofuran E. It is worth mentioning that alkyl-substituted alcohols, such as decanol and 3-cyclohexylpropanol, with lower radical and carbocation...
stabilization capacity, were not suitable reaction partners in this transformation.

Regarding the formation of chromanes, the first step is the same as previously (the single electron reduction of the benziodoxolone). Next, the oxygen-centered radical B′ can either add to the ipso position of the aryl ring leading to the formation of carbon radical C′ or to the ortho position forming carbon radical C″. These cyclohexadienyl radicals, C′ and C″, can be oxidized (Eox= ca. 0.1 V vs SCE)24 to the corresponding carbocations D′ and D″, while reducing the IrIV back to IrIII. Finally, rearomatization produces the final chromane E′ in both cases. For carboxation D′ this rearrangement process is preceded by a rearrangement. The mixture of regioisomers obtained (Scheme 3) is most probably due to a competition between 1,5- and 1,6-addition as well as between carbon and oxygen migration in the rearrangement step of the spirocyclic intermediate. Given the regioselectivity ratios observed for the various aryl rings investigated, it is not possible to derive a qualitative rational for mechanistic pathway preferences. The regioisomer distribution observed in the formation of chromanes 3n−3q and 3t−3t′ does not suggest that there is a clear trend coupled to stereoelectronic effects; however, carbon migration is more likely to occur than oxygen migration for the electron-deficient derivatives 3o−3p.25a Accordingly, the regioisomeric ratio obtained for these compounds most probably reflect the 1,5- vs 1,6-addition preferences for these compounds. Chromane 3m was formed as a single regioisomer, which suggests that the reaction selectively progresses via the 1,6-addition pathway. However, similarly stabilized cationic spirocyclic compounds have been suggested to rearrange via oxygen migration involving a stepwise mechanism initiated with a C=O bond cleavage followed by a 1,4-addition.25b Taken together, the regioisomeric ratios observed for most substrates probably stems from competition between 1,5- and 1,6-addition. For very electron-rich systems, the picture might be more complicated.

In summary, two types of C–H bonds (Csp3 and Csp2) have been functionalized in the construction of cyclic ethers from alcohols by means of alkoxy radical generation at room temperature. This divergent protocol enabled by visible-light photoredox catalysis can proceed via 1,5-HAT giving rise to acetals, orthoesters, and tetrahydrofurans or via 1,5,6-addition producing chromanes. Notably, the use of commercially available, easy to handle, nontoxic HIR allowed the formation of alkoxy radicals from all types of alcohols (1°, 2°, and 3°). The operationally simple methodology and the mild photoredox reaction conditions provided a practical strategy that allowed for the synthesis of 21 alkyl and aryl ethers in 44% to 60% yields.
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