Synthesis of Glycosyl Fluorides by Photochemical Fluorination with Sulfur(VI) Hexafluoride

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ABSTRACT: This study describes a new convenient method for the photocatalytic generation of glycosyl fluorides using sulfur(VI) hexafluoride as an inexpensive and safe fluorinating agent and 4,4′-dimethoxybenzophenone as a readily available organic photocatalyst. This mild method was employed to generate 16 different glycosyl fluorides, including the substrates with acid and base labile functionalities, in yields of 43%−97%, and it was applied in continuous flow to accomplish fluorination on an 7.7 g scale and 93% yield.

Glycosyl fluorides have been of great importance to the synthesis of oligosaccharides and glycoconjugates, as well as studies of the enzymatic reactions. Its small molecular weight (MW), low toxicity, and simple methods for scavenging make the fluoride anion an ideal leaving group for the glycosylation reactions. The use of glycosyl fluorides is often advantageous, because of their high thermal and chemical stability, in particular, to water and chromatography. For example, Miller group has taken advantage of glycosyl fluoride stability in aqueous media to achieve selective and mild glycosylations in water. At the same time, the activation of glycosyl fluorides with Lewis acids that have high affinity to the F− anion may result in powerful glycosylative agents, which was recently highlighted by Montgomery and co-workers, who observed rapid glycosylations of various sterically hindered acceptors with tris(pentafluorophenyl)borane (BCF) catalysts. Many studies have focused on improving the synthesis of glycosyl fluorides; however, only few practical methods are available. The primary way to generate these species is based on deoxyfluorination of the anomeric position of sugars using (diethylamino)sulfur(IV) trifluoride (DAST). DAST exhibits a great reactivity profile; however, its high toxicity, corrosiveness and potential explosiveness pose limitations for its use, in particular, on a large scale. Other methods such as fluorination with corrosive and toxic HF/pyridine as the solvent or cosolvent (>50%) require a plastic or a metal vessel, special work-up conditions, and substrates that can survive an acidic environment.

While SF6 has been sporadically used to achieve fluorination, SF6 activation only recently was achieved under mild and catalytic reaction conditions. Thus, the recent study by Jamison and co-workers disclosed a photoredox activation of SF6 with Ir(III)-based catalysts resulting in deoxyfluorination of allylic alcohols (Scheme 1A). This study suggested that the reduction of SF6 leads to unidentified sulfur fluoride species (SF4−) that fluorinates the substrate. Subsequently, Rueping and co-workers (Scheme 1B) and Braun and Kemnitz described reductive activations of SF6 that resulted in the stoichiometric reagents that could be used for deoxyfluorination, and Wagenknecht described photoactivation of SF6 that resulted in SF5 group transfer. The reduction of SF6 to SF4− has been suggested to proceed via a photoactivation of SF6 to SF4− or SF4+. The reduction of SF6 to SF4− has been suggested to proceed via a photoactivation of SF6 to SF4− or SF4+.

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Scheme 1. Summary of Prior and Current Studies

A) Jamison et al. 2016

B) Rueping et al. 2017

C) This work

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Unlike many other fluorinating agents, SF₆ is an inexpensive and safe-to-handle gas produced on a large scale. The utilization of SF₆ represents an important challenge, because of its chemical inertness, and has great significance, because of its potency as a greenhouse gas.

Building on the aforementioned studies, this manuscript describes a mild, safe, and efficient fluorination of 16 protected carbohydrates with SF₆ using commercially available UV-A LED source (λₘₐₓ = 365 nm) and inexpensive 4,4′-dimethoxybenzophenone as the photocatalyst. Importantly, all of the substrates and products were found to be stable under the reaction conditions, which permitted to carry gram-scale fluorination reactions both in batch and continuous flow. Based on preliminary mechanistic studies, we propose that this reaction proceeds through the formation of SF₄ that is formed in trace quantities and either fluorinates the substrate or gets further reduced to S₂F₆ or elementary sulfur under the photochemical conditions.

Our studies commenced by subjecting the disarmed 2,3,4,6-tetra-O-acetyl-α-D-mannose 1a to the fluorination reaction condition previously developed by Jamison and co-workers (Table 1, entry 1). Excitingly, 1a showed no signs of decomposition under these conditions, and the reaction proceeded to 38% conversion of 2a after 20 h. However, the significant deceleration of the reaction progression after 12 h, and the high price and low availability of Ir(ppy)₂(dtbbpy)PF₆, prompted us to investigate more cost-effective organic photocatalysts, using commercially available LED light sources (Table 1, entries 2–13). Fluorescein derivative Eosin Y was able to activate SF₆ to form 2a in low conversions (Table 1, entry 2). A related dye, Rose Bengal, was also tested, but it did not show any catalytic activity (Table 1, entry 3). Next, we proceeded with testing the derivatives of thiazine because some of them have been used for the photoactivation of SF₆ with UV-A LED by Wagenknecht and co-workers (Table 1, entries 4 and 5). Both N-phenylphenoiazine and Methylene Blue demonstrated fair catalytic activity that was comparable with Ir(ppy)₂(dtbbpy)PF₆. Subsequently, we evaluated benzophenone (Table 1, entry 6), since this compound is often an indispensable catalyst for various photochemical transformations. Benzophenone was also found to promote the fluorination with both Blue and UV-A (λₘₐₓ = 365 nm) LEDs, although the yield was found to be higher with the UV-A LED. This is not surprising, because the n → π* band of benzophenone has a λₘₐₓ value of ~340 nm. It is known that additional substitution on benzophenones may increase the λₘₐₓ (cf. Figures SI 9–SI 11 in the Supporting Information), affect the lifetime of the triplet state, and increase the reduction potential of the benzophenone-derived ketyl radicals. Therefore, six other benzophenone derivatives (Table 1, entries 7–13) were tested. Among these six photocatalysts, Michler’s ketone, 4,4′-dimethoxybenzophenone, and 4-fluoro-4′-methoxybenzophenone showed enhanced catalytic activity with 4,4′-dimethoxybenzophenone providing the highest yield (60%; see Table 1, entry 12). Considering its low cost and high catalytic activity, we subsequently employed 4,4′-dimethoxybenzophenone (DMBP) as our default photocatalyst and proceeded to further optimize the reaction parameters, such as reaction stoichiometry, base, solvent, light intensity, irradiation surface, and reaction vessel (cf. Tables SI 2–SI 4). These optimizations permitted us to reduce the catalyst loading to 30 mol % and resulted in the enhanced formation of 2a (72% isolated yield, 95% BRSM, α:β = 13:1; see Table 1, entry 13).

With the optimized conditions in hand, the evaluation of the substrate scope was performed next (cf. Scheme 2, as well as Table SI 1 in the Supporting Information). First, we investigated the formation of other disarmed peracetylated...
Continuous Flow

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Scheme 3. Gram-Scale Fluorination in Batch and Continuous Flow

A. Gram scale synthesis in batch (1.0 g scale)

B. Gram scale synthesis in continuous flow (7.7 g scale, 100 psi, cycling time 120 h)

Figure 1. (A) Tentative reaction mechanism. (B) Catalyst decomposition products and side-products resulting from SF6. (C) Direct fluorination with sodium ketylute. (D) Light on/off control experiment.

The reaction did not proceed without a light source, which reinforces that light irradiation is required to initiate the first SET step between the excited DMBP and DIPEA. This also suggests that DIPEA cannot reduce SF6 by itself. Similarly, the reduction of SF6 did not happen in the absence of DIPEA, which indicates that the presence of this reagent is essential. Surprisingly, the omission of DMBP did not completely shut down the fluorination of 1g, and we observed some formation of 2g without a presence of a photocatalyst. Presumably, the open aldehyde form of 1g may participate in the SET process to activate SF6 but further mechanistic investigations are required for a better understanding of this phenomenon. To eliminate the possibility of the chain processes initiated by light, we performed the light on/off experiment depicted in Figure 1C. After the reaction was irradiated with UV-A light for 4 h, the light was turned off and the reaction vessel was covered with aluminum foil for 2 h, and no reaction progression happened in the absence of light. However, the
formation of 2g was resumed when the reaction was exposed to the light again. These results suggest that the photo-excitation of DMDB leads to the formation of its triplet state (DMBP*), and the observed catalyst decomposition products such as benzylic alcohol and pinacol adduct provide further evidence for this step (cf. Figure 1B).19 The resultant DMBP* species undergoes a known oxidation of DIPEA (E1/2(SCE) ∼ 0.8 V)15,18 to generate a ketyl radical (reduction of the [SF6]− to [SF5]−) arising from the reaction of the ketyl radical pregenerated from mildness, this method holds great potential for the large-scale reaction progression. We believe that, because of its safety and SF6, followed by further reactions with trace water.

In conclusion, we have developed a new convenient method for the photocatalytic generation of glycosyl fluorides using SF6 as an inexpensive and safe fluorinating agent and 4,4′-dimethoxybenzophenone as a readily available organic photocatalyst. This mild method was employed to generate 16 dimethoxybenzophenone as a readily available organic photo-

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/10.1021/acs.orglett.0c03915.

1H, 13C, and 19F NMR spectra of products; experimental information; description of the continuous flow experiments; and studies of the reaction mechanism (PDF)

Accession Codes

CCDC 2017701 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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