Site-Selective Photobromination of *O*-Acetylated Carbohydrates in Benzotrifluoride

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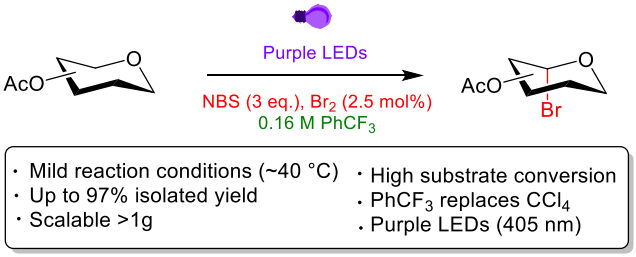
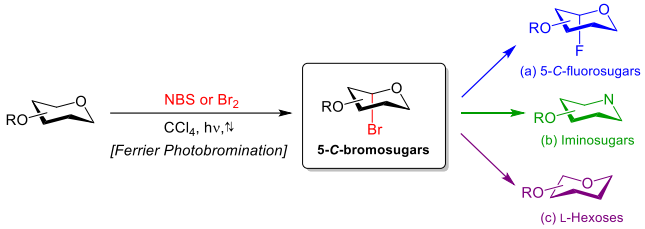
Supporting Information Placeholder



ABSTRACT: The Ferrier photobromination enables direct synthetic access to valuable 5-*C*-bromosugars but has limitations which restrict its broader use. The reaction is typically conducted in CCl_4 heated at reflux with irradiation by broad spectrum, energy inefficient heat lamps. Herein, we demonstrate that the reaction proceeds rapidly and efficiently with $PhCF_3$ as a safe and environmentally benign alternative to CCl_4 at mild temperatures (≤ 40 °C) inside a compact photoreactor fitted with purple LEDs.

Serendipitously discovered in 1977, the Ferrier photobromination enables the regio- and stereoselective installation of a bromine atom at C-1 and/or C-5 of carbohydrate derivatives.[1,2] The importance of this reaction has since been revealed through the synthetic applications of bromosugars.[3,4] 5-*C*-Bromosugars, in particular, are extremely useful building blocks for the preparation of biologically and medicinally significant compounds (Scheme 1). For example, direct nucleophilic substitution at C-5 of these compounds has yielded valuable substrates and inhibitors of glycosidase enzymes (e.g., 5-*C*-fluorosugars).[5,6] More recent applications of 5-*C*-bromosugars include the expeditious preparation of rare L-hexoses[7-10] and highly sought after nojirimycin-type iminosugars.[11]

Scheme 1. Accessible via the Ferrier photobromination, 5-*C*-bromosugars can be synthetically elaborated to (a) 5-*C*-fluorosugars, (b) nojirimycin-type iminosugars, and (c) rare L-hexoses.



A classical Ferrier photobromination entails heating an *O*-acylated substrate with *N*-bromosuccinimide (NBS) or Br_2 in CCl_4 at reflux. Concurrently, the reaction vessel is irradiated with a heat lamp to initiate and sustain bromine radical formation. Accordingly, the Ferrier photobromination mirrors the Wohl-Ziegler bromination of benzylic and allylic substrates across mechanistic and practical aspects. [12,13] The major limitation of these reactions, however, is their dependency on CCl_4 as solvent. CCl_4 is a hepatotoxic and ozone-depleting substance which was banned from commercial production and sale under the 1994 Montreal Protocol.[14] Unfortunately, while multiple sets of CCl_4-free conditions have been sourced for the Wohl-Ziegler bromination, a single, versatile substitute compatible with the Ferrier photobromination has yet to be identified. [15-22] It can also be considered that commercial heat lamps, which inherently

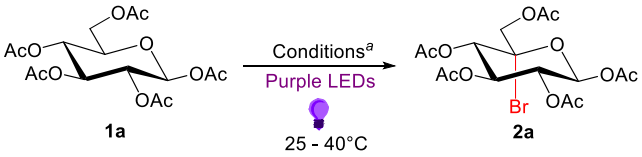
vary by their luminous flux (Φ_v) and emission wavelength (λ) range, introduce great concerns for reproducibility across studies.

We now report on a contemporary set of reaction conditions for the Ferrier photobromination which addresses these key issues. Firstly, we show that inexpensive $PhCF_3$ can be harnessed as a versatile, safe, and environmentally benign alternative to CCl_4 as the reaction solvent. Secondly, we demonstrate that when performed inside a compact photoreactor fitted with pur-ple light-emitting diodes (LEDs) of fixed Φ_v and ,λ Ferrier pho-tobrominations of *O*-acetylated substrates in $PhCF_3$ proceed swiftly and efficiently at a mild temperature. These conditions collectively enable the straightforward, scalable and reproduci-ble preparation of 5-*C*-bromosugars without the existing limita-tions.

Our studies commenced with the design and engineering of a compact photoreactor equipped with a cooling fan which main-tains an operating temperature between 25 - 40 °C, and temper-ature monitoring capability (details in Supporting Information, SI). This photoreactor was fitted with a suite of purple LEDs whose emission wavelength (λ = 405 nm) overlaps with λ_{max} of NBS in $PhCF_3$. With this technology in hand, we were able to ensure that all critical parameters (i.e., Φ_v, temperature and the distance between the reaction vessel and the light source) were conserved across all experiments performed in this study.

We then directed our attention towards finding a viable alternative to CCl_4. Commercially available 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose **1a** was selected as the substrate for our optimization experiments. Solvents which had found success as alternatives to CCl_4 in Wohl-Ziegler reactions were then screened.[22] Photolysis of **1a** with 3.0 equivalents of NBS in dry CH_3CN[17] (0.08 M) yielded only a trace amount of the known 5-*C*-bromide **2a**[11] after 2 h, as determined by nuclear magnetic resonance (NMR) spectroscopic analysis of the crude product mixture (Table 1, Entry 1). The same reaction performed in CH_2Cl_2 also resulted in limited conversion of **1a** to **2a** (11%; Entry 2). Strikingly, however, when anhydrous $PhCF_3$ was exploited as the solvent,[20] product formation improved considerably (76%; Entry 3). This result suggested that where CH_3CN and CH_2Cl_2 fail to do so, $PhCF_3$ is able to sufficiently and simultaneously stabilise bromine and glycosyl (C-5) radicals through key *p*-π and singly occupied molecular orbital (SOMO)-π interactions, respectively. [23,24]Adding CH_2Cl_2 as a co-solvent (20% *v*/*v*) to the reaction mixture proved detrimental to product formation (Entry 4), as was increasing the molar ratio of NBS to substrate (Entries 5 – 7). We next explored the influence of substrate concentration – the sensitivity of radical reactions to which is well established (Entries 8 – 10). [25] On increasing the reaction molarity from 0.08 M to 0.16 M, a measurable increase in conversion was noted (84%). This trend failed to continue at higher concentrations, however, in keeping with the propensity of radicals to self-quench under such conditions.

Table 1. Optimisation of photobromination conditions



Entry	Conditions	Added Br_2 (mol%)	% Conversion[b]
1	NBS (3.0 equiv.), CH_3CN (0.08 M)	0	Trace
2	NBS (3.0 equiv.), CH_2Cl_2 (0.08 M)	0	11
3	NBS (3.0 equiv.), $PhCF_3$ (0.08 M)	0	76
4	NBS (3.0 equiv.), $PhCF_3$/CH_2Cl_2 (4:1, 0.08 M)	0	9
5	NBS (4.0 equiv.), $PhCF_3$ (0.08 M)	0	78
6	NBS (5.0 equiv.), $PhCF_3$ (0.08 M)	0	65
7	NBS (8.0 equiv.), $PhCF_3$ (0.08 M)	0	35
8	NBS (3.0 equiv.), $PhCF_3$ (0.01 M)	0	36
9	NBS (3.0 equiv.), $PhCF_3$ (0.16 M)	0	84
10	NBS (3.0 equiv.), $PhCF_3$ (0.32 M)	0	82
11	NBS (3.0 equiv.), $PhCF_3$ (0.16 M)	1.25	38
12	NBS (3.0 equiv.), $PhCF_3$ (0.16 M)	2.5	96
13	NBS (3.0 equiv.), $PhCF_3$ (0.16 M)	5	49

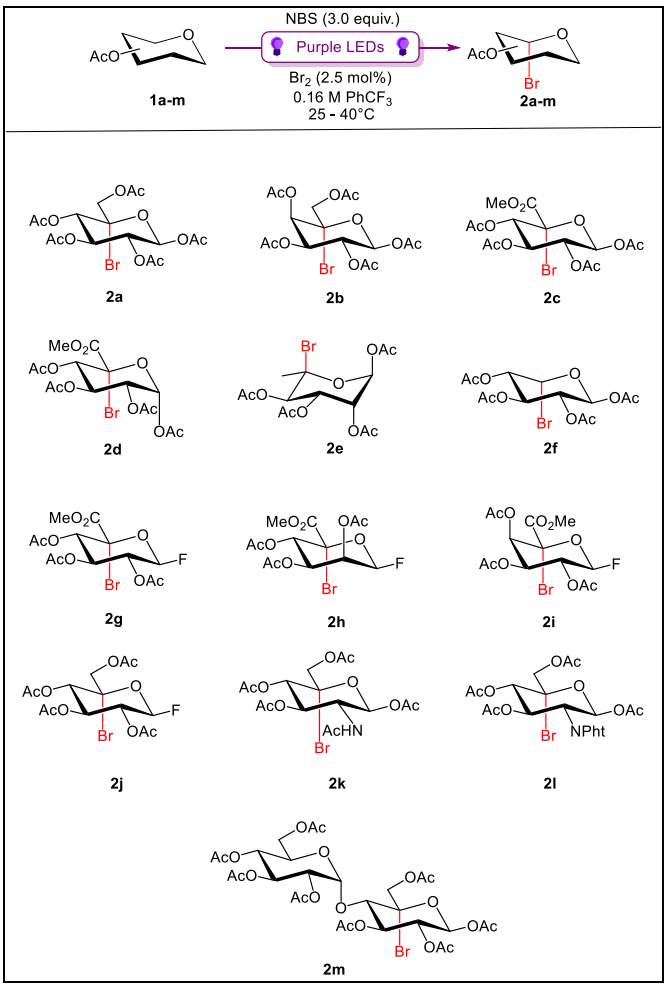
[a]All reactions were performed in anhydrous solvent and under $Ar_{(g)}$ with vigorous stirring. [b]Of **1a** to **2a**, determined by ^{1}H NMR spectroscopic analysis of the crude product mixture.

Finally, we considered the role of Br_2 as a radical propagating agent in this reaction. Across all trials, we observed an induction period which preceded the rapid *in situ* generation of Br_2. We therefore hypothesised that through the addition of catalytic Br_2 to the reaction mixture, the induction period may be bypassed to accelerate the formation of **2a** (Table 1; Entries 11 – 13). Indeed, a combination of 3.0 equivalents of NBS and 2.5 mol% Br_2 gratifyingly effected the rapid (2 h) and near quantitative conversion of **1a** to **2a**. Doubling the amount of Br_2 to 5 mol% had a detrimental effect on conversion (Entry 13).

With the optimized conditions in hand (Table 1, Entry 12), a substrate scoping study was performed. The structures of the isolated 5-*C*-bromide products are shown in Scheme 2 and their respective isolated yields are reported in Table 2. Substrate structures and details of their preparation are provided in the SI. On a 150 mg scale, photobromination of model substrate β-D-glucose pentaacetate **1a** under the optimised conditions provided 5-*C*-bromide **2a** in 84% isolated yield. Pleasingly, although a greater reaction time was required, the same reaction performed at gram-scale proceeded with similar efficiency (78%). The reaction of its C-4 epimer, β-D-galactose pentaacetate **1b**, also proceeded smoothly to deliver 5-*C*-bromide **2b** in high yield (82%). Compound **2b** is a building block for the synthesis of pharmacological chaperone and α-galactosidase inhibitor 1-deoxygalactonojirimycin (Migalastat).[11] Previously, however, **2b** was only accessible in 67% yield via a CCl_4-dependent Ferrier photobromination. Our protocol therefore provides an improved avenue to access this synthetically valuable 5-*C*-bromide.

D-Glucuronic acid derivatives **1c** and **1d** were then photobrominated. The reaction of β-anomer **1c** proceeded in appreciably higher yield (93%) than that of α-anomer **1d**, although the resulting 5-*C*-bromide of the latter substrate was still obtained in acceptable yield (**2d**: 60%) and purity. This difference in yield is readily traced to the configuration of the anomeric *O*-acetyl ester in both substrates. When disposed axially, electron withdrawing C-1 substituents temper the reactivity of C-5 radicals.[26] In line with our expectations, L-rhamnose derivative **1e** which bears an α-configured, axial OAc group and lacks a formal C-5 captodative centre failed to photobrominate under our conditions. However, while tetra-*O*-acetyl-β-D-xylopyranose **1f** also lacks an electron-withdrawing C-6 substituent, this substrate was successfully photobrominated to provide 5-*C*-bromide **2f** as a single (5*S*) diastereoisomer in 50% yield.

Scheme 2. Substrate scope explored for CCl_4-free Ferrier photobrominations.



In addition to their important roles as glycosyl donors,[27] glycosyl fluorides are useful synthons for the construction of rare L-hexoses.[28] Indeed, our group has shown that by engaging a β-fluorine-directing effect, these compounds can be accessed stereoselectively via the free radical reduction of 5-*C*-bromo-D-hexoses.[7,8] Thus, β-fluorides **1g** and **1h** which provide synthetic access to L-iduronic acid (L-IdoA)[8] and L-guluronic acid (L-GulA)[29] respectively, were photobrominated under the optimized reaction conditions. The corresponding 5-*C*-bromides were both obtained accordingly in excellent yields (**2g**: 89%; **2h**: 91%). D-Galacturonic acid derivative **2i** was also delivered unremarkably under these conditions at gram scale (95% yield; 97% on 150 mg scale). Pleasingly, our protocol also provides access to 5-*C*-bromide **2j** (73%) which is reported to be largely unreactive under CCl_4-dependent photobromination conditions (8%).[7]

Table 2. Comparison of isolated yields from this study with previous literature reports.

Entry	Substrate	Product	Established Product Utility	Yield (%)	Literature yield (%)
1	**1a**	**2a**	1-DNJ synthesis	84	56[11]
2	**1b**	**2b**	Migalastat synthesis	82	67[11]
3	**1c**	**2c**	α-L-Iduronidase inhibitor synthesis	93	70[30]
4	**1d**	**2d**	α-L-Iduronidase inhibitor synthesis	60	39[8]
5	**1e**	**2e**	N/A	0	N/A
6	**1f**	**2f**	*C*-glycoside synthesis[31]	50	46[32]
7	**1g**	**2g**	L-IdoA synthesis	89	44[8]
8	**1h**	**2h**	L-GulA synthesis	91	N/A
9	**1i**	**2i**	N/A	97	N/A
10	**1j**	**2j**	N/A	73	8[7]
11	**1k**	**2k**	N/A	0	N/A
12	**1l**	**2l**	Glycosidase enzyme substrate synthesis	39	66[33]
13	**1m**	**2m**	N/A	45	N/A[34]

Consistent with previous literature reports,[33] the Ferrier photobromination of GlcNAc derivative **1k** failed to deliver a measurable quantity of the desired 5-*C*-bromide **2k**. However, substrate **1l** whose C-2 *N*-phthalimido (Pht) group substituent is inert to radical substitution, was successfully photobrominated to afford the corresponding bromide[33] **2l** in moderate yield (39%; 62% based on recovered starting material). Finally, photobromination of disaccharide **1m** proceeded with high regio- and stereoselectivity to furnish 5-*C*-bromide **2m** in 45% yield (73% based on unrecovered starting material). Previously, **2m** was an un-isolated intermediate from photobromination of **1m** and was converted into the 5,6-alkene in low yield (12%).[34] Our new procedure thus represents a significant improvement on the classical photobromination for this substrate.

In summary, we have developed and implemented an improved set of reaction conditions for the Ferrier photobromination. We have shown in this study that $PhCF_3$ serves as a safe and environmentally benign alternative to hazardous CCl_4 with broad substrate combability. Purple LEDs demonstrate success in generating and sustaining bromine radical generation across the reaction time course, while providing a modern and energy-efficient substitute to commercial heat lamps. Together, these elements improve on the classical conditions of the Ferrier photobromination both in terms of product yield and accessibility.

In view of these advances, we greatly anticipate that this protocol will renew the interest of glycochemists in exploiting this reaction for the construction of valuable biomolecules.

ASSOCIATED CONTENT

Supporting Information

Specifications and photos of the compact photoreactor, UV absorbance spectrum of NBS in $PhCF_3$, experimental details, copies of ^{1}H, ^{13}C, ^{19}F NMR and 2D COSY and HSQC spectra (PDF).

The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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