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Convenient synthesis of glycosyl bromide from 1-*O*-acetyl sugars by photo-irradiative phase-vanishing reaction of molecular bromine

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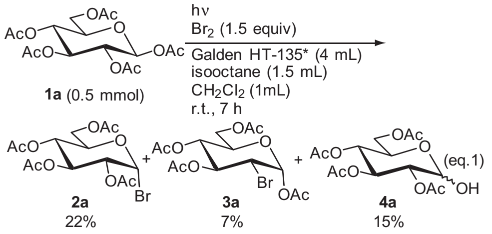
ABSTRACT

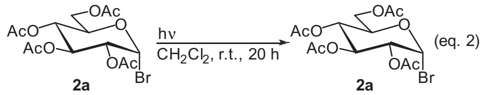
The synthesis of glycosyl bromides from 1-*O*-acetyl sugars using a photo-irradiative phase-vanishing method involving molecular bromine was achieved. A bottom phase of molecular bromine was overlaid first with perfluorohexanes (FC-72), followed by overlaying with ethyl acetate containing a 1-*O*-acetyl sugar. Upon irradiation, the bromine layer gradually disappeared, leaving two phases. Glycosyl bromide was obtained in good yield from the ethyl acetate phase.

The carbohydrate moiety can be important for the biological activity and recognition of the cellular targets.[1] Therefore, complex carbohydrate syntheses have been attempted, but have been challenging.[2] Synthesis of the carbohydrate moiety often is conducted under the reaction conditions using excess reagent. For example, the synthesis of glycosyl bromide, which is a useful *O*-glycosyl donor[3] and *C*-glycosyl precursor[4] has been prepared from peracetylated saccharides and an acetic acid solution of HBr[5] or BiBr$_3$–Me$_3$SiBr[6] or the free saccharides with AcBr,[7,8] AcBr–AcOH,[9,10] or Ac$_2$O–HBr–AcOH.[11,12] Recently, Hunsen and co-workers reported the one-pot preparation of glycosyl bromide from acetyl bromide, MeOH, and excess acetic acid.[13] However, environmentally friendly ('green') syntheses, which do not require heavy metals, are gaining favor for atom economy reactions. Additionally, the removal of excess HBr and/or acetic acid is tedious. Recently, Ryu's group developed a method that controls the amount of HBr generated, involving the treatment with molecular bromide and isoocatane by a photo-irradiative phase-vanishing method (Scheme 1).[14] Phase-vanishing method is established in the field of fluorous chemistry[15] and is employed in a fluorous triphasic system to control exothermic reactions by diffusion-based transport of bottom reagents via the middle fluorous phase to the top substrates.[16] This method was applied to the synthesis of the glycosyl bromides. In this Letter, the synthesis of glycosyl bromides by a photo-irradiative phase-vanishing method is described.

First, the synthesis of glycosyl bromide was conducted using a mixture of CH$_2$Cl$_2$ and isooctane to dissolve the 1-*O*-acetyl sugar in the organic phase, and the fluorous polyether, Galden HT-135 as fluorous phases. Ultraviolet (UV) irradiation at 352 nm using a 15 W black light at room temperature for 7 h gave glycosyl bromide **2a** in 22% yield, together with byproducts **3a** (7%) and **4a** (15%) (eq. 1). To determine the resistance of glycosyl bromide to photodecomposition, the glycosyl bromide **2a** was exposed to UV irradiation at room temperature for 20 h (eq. 2). No degradation of **2a** was occurred.



*Galden HT-135: CF$_3$[OCF(CF$_3$)CF$_2$)$_m$(OCF$_2$)$_n$]OCF$_3$



recovery ca. 100%
(determined by ^{1}H NMR analysis)

Next, the synthesis of glycosy bromide using the phase-vanishing method in various solvents was investigated (Table 1). The combination of AcOEt and perfluorohexanes (C$_6$F$_{14}$) as solvents was effective in producing a high yield of **2a** (run 10). Generally, perfluorohexane is miscible with organic solvents, compared with Galden HT-135.[17] Therefore, it would be expected that both bromine and AcOEt easily diffused through the perfluorohexane phase to generate HBr effectively. Consequently, this system was afforded the desired

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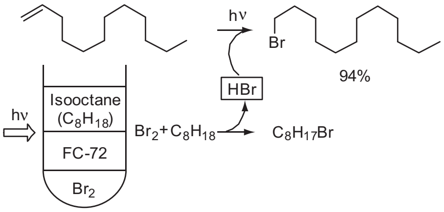
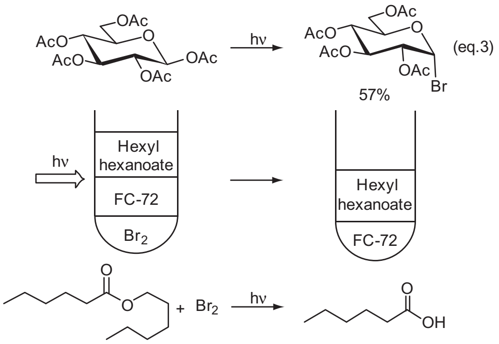


Scheme 1. Photo-irradiactive phase-vanishing generation of HBr and addition to 1-dodecence.[5]

glycosyl bromide in good yield. Higher concentrations were the most effective (runs 9, 10, and 12). Note that both the black light and fluorous phase are essential for the synthesis of glycosyl bromide from the 1-*O*-acetyl sugar and molecular bromide (run 13 and 14).

Having the optimized reaction conditions, a series of carbohydrate derivatives were examined in the goal of obtaining the corresponding glycosyl bromides (Table 2). Galactose derivative **1b** gave the corresponding glycosyl bromide **2b** in excellent yield (run 1). Mannose derivative **1c** afforded the product **2c** in moderate yield along with 1-OH derivative **4c**, which was hydrolyzed during isolation on silica gel (run 2). 2-Azide-glucose derivative **1d** gave the corresponding glycosyl bromide **2d** (84%). *N*-Troc glucosamine derivative **1e** gave the corresponding glycosyl bromide in moderate yield. This reaction was complex, compared with other 1-*O*-acetyl sugars from ^{1}H NMR analysis of crude reaction mixture. The minor products corresponding to **1e** were not identified. Glucuronate derivative **1f** afforded the corresponding glycosyl bromide **2f** (run 5). These results can be explained by an ionic mechanism with HBr generated in situ. A previous study reported that the treatment of glucuronate derivative **1f** under the favorable radical conditions gave 5-bromo glucuronate derivative.[18]



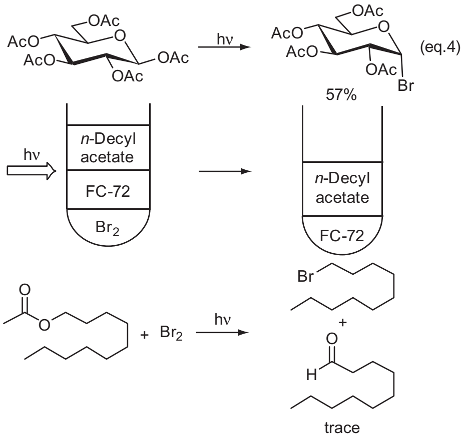
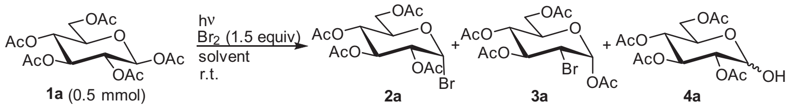


Table 1

Optimization of solvents for synthesis of glycosyl bromide by phase-vanishing method



	Solvent		Yields[a] [%]				
Run	Fluorous	Organic	Time	**2a**	**1a**	**3a**	**4a**
1	Galden HT-135	DMF	24	0	93		
2	Galden HT-135	CH_2Cl_2	24	62	0		
3	C_6F_{14}	CH_2Cl_2	24	69	0		
4	Galden HT-135	THF	24	0	32		
5	Galden HT-135	CH_3CN	24	0	23	22	27
6	Galden HT-135	1,4-Dioxane	24	12	4	Trace	7
7	Galden HT-135	Acetone	24	0			
8	Galden HT-135	AcOEt	24	59	0		
9	C_6F_{14}	AcOEt	24	85 (82)[b]	0		
10[c]	C_6F_{14}	AcOEt	23	93 (91)[b]	0		
11[c]	C_6F_{14}	AcOEt/CH_2Cl_2 = 9/2	23	88 (85)[b]	0		
12[d]	C_6F_{14}	AcOEt	19	90 (86)[b]	0		
13[e]	C_6F_{14}	AcOEt	19	8[b]	68 (α/β = 59/9)[f]		
14[g]	—	AcOEt	19	5	56 (α/β = 7/1)[f]		

[a] NMR yield.

[b] Isolated yield by chromatography on SiO_2.

[c] 1 mmol of **1** was used.

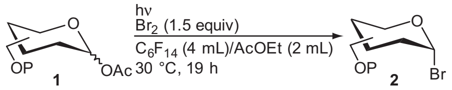
[d] 0.8 mmol of **1** was used.

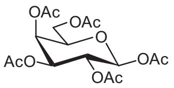
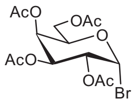
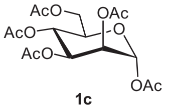
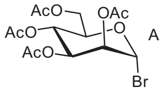
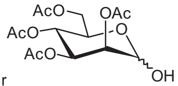
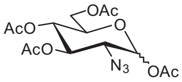
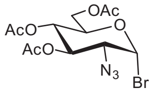
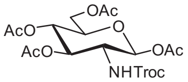
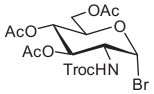
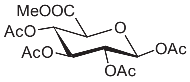
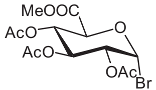
[e] The reaction was carried out in the dark.

[f] Determined by ^{1}H NMR.

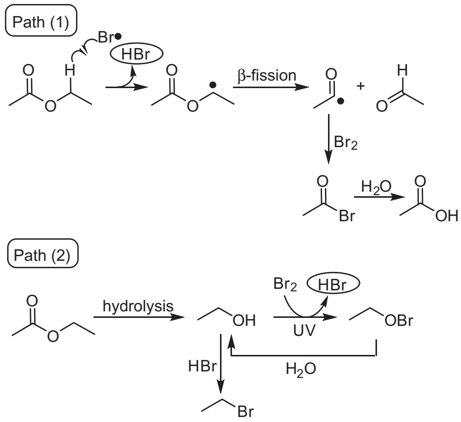
[g] Bromine was directly added to a solution of **1** in AcOEt.

Table 2
Synthesis of glycosyl bromides by phase-vanishing method



Run	Substrate	Product yield[a](NMR yield)[b]
1	 **1b**	 **2b** 91%(quant)
2	 **1c**	 **2c** 67%(86%)  **4c** 28%
3	 **1d** (α/β =69/31)[c]	 **2d** 84%(85%)
4	 **1e**	 **2e** 60%(63%)
5	 **1f**	 **2f** 89%(90%)

[a] Isolated yield by chromatography on SiO_2.
[b] Determined by ^{1}H NMR of crude reaction mixture.
[c] Determined by ^{1}H NMR.



Scheme 2. Two possible processes of HBr generation.

The generation of HBr also was investigated. The use of hexyl hexanoate as a solvent resulted in the partial formation of hexanoic acid (eq. 3). Unfortunately, we could not detect another part of hexyl hexanoate. To pursue another part of ester, *n*-decyl acetate was used as a solvent, which was partially converted into *n*-decyl bromide and a trace amount of *n*-decyl aldehyde (eq. 4).[19] These results suggest that HBr was generated through two paths (Scheme 2): (1) a bromide radical generated from molecular bromine under irradiative homolysis abstracted a hydrogen from ethyl acetate to give HBr[20] or (2) a bromine radical abstracted a hydrogen from ethanol, forming hydrolyzed ethyl acetate, to give HBr.[21] The HBr generated in situ reacted with the 1-*O*-acetyl sugar to give the corresponding glycosyl bromide.

In summary, a synthesis of glycosyl bromides by photo-irradiative phase-vanishing method was developed. Fluorous phase is essential to be reacted with molecular bromine and AcOEt predominantly. In this reaction, HBr generated from molecular bromine and ethyl acetate under UV irradiation at 352 nm reacted with a monosaccharide to give glycosyl bromide in high yield. This method is simple and environmentally friendly, limiting the amount of HBr generated.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.088.

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