

# A Novel Aldol-type C-Glycosidation Reaction Promoted by Samarium Diiodide. Regioselective Generation of a Ulose-1-enolate from Phenyl 3,4,6-tri-*O*-benzyl-1-thio- $\beta$ -D-*arabino*-hexopyranosid-2-ulose.

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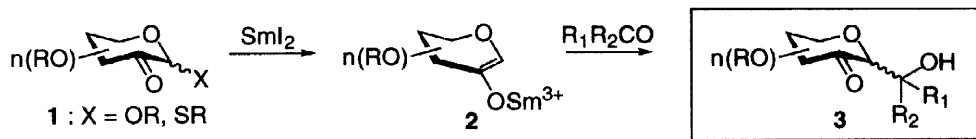
**Abstract:** A novel aldol-type C-glycosidation reaction promoted by samarium diiodide ( $\text{SmI}_2$ ) was developed. Treatment of phenyl 3,4,6-tri-*o*-benzyl-1-thio- $\beta$ -D-*arabino*-hexopyranosid-2-ulose (**6**) with  $\text{SmI}_2$  in THF regioselectively gave the corresponding 1-enolate, which was readily trapped with ketones or aldehydes to afford various C-glycosides in high yields. © 1998 Elsevier Science Ltd. All rights reserved.

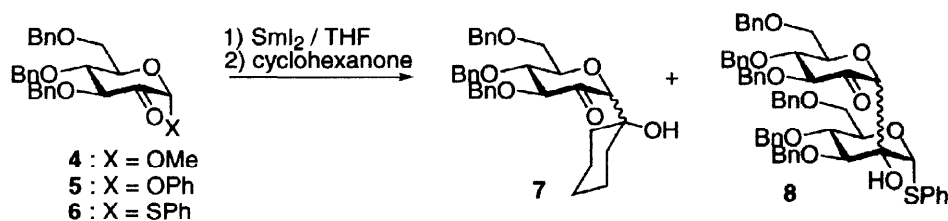
**Keywords:** aldol reactions; enolates; glycosidation; samarium diiodide

C-Glycosides are found in many natural products and are also important for providing hydrolytically stable mimetics of biologically active glycosidic compounds [1-5]. Accordingly, considerable effort [6-9] has been devoted to the synthesis of C-glycosides. Aldol-type reactions, which are some of the most effective methods for forming C-C bonds, have also been investigated for the formation of a C-glycosidic linkage; in these cases, 1-deoxy-*gluco*-2-uloses or 2-ulosyl-1-bromides [10,11] were used as precursors for generating 1-enolates [12-14]. However, the yields of C-glycosides were insufficient, and problems remained; the former gave undesirable enolization at the 3-position of uloses and in the latter case the precursors were significantly unstable. In this paper, we describe a samarium diiodide ( $\text{SmI}_2$ )-promoted efficient aldol-type C-glycosidation reaction using a stable 1-phenylthio-2-ulose derivative as a precursor for generating ulose-1-enolate.

$\text{SmI}_2$  [15] can reduce functional groups such as hydroxy, acetoxy, and alkoxy groups when a carbonyl group is present at the  $\alpha$ -position of these functional groups, and the generation of samarium enolates as intermediates is presumed to occur during the reaction course [16-18]. Accordingly, an aldol-type reaction may proceed if an electrophile is present in the reaction system. Therefore, we expected that a 1-enolate **2** would be generated regioselectively if 1-*O*- or 1-*S*-glycoside of 2-ulose **1** was treated with  $\text{SmI}_2$ , and that this could be added to a carbonyl group of ketones or aldehydes to give the corresponding C-glycoside **3** (Scheme 1). These precursors are significantly stable compared with ulose-1-bromides,

Scheme 1



**Table 1.**  $\text{SmI}_2$  promoted aldol-type *C*-glycosylation with cyclohexanone as an acceptor.

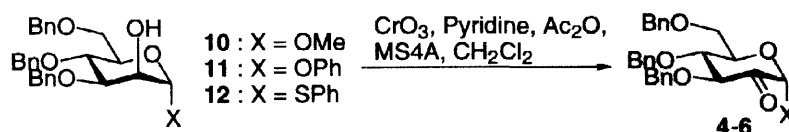
entry	X	$\text{SmI}_2$ (eq.)	additive	temp. (°C)	yield (%)	
					7 ( $\alpha$ : $\beta$ )	8
1	OMe	2.0	none	r.t.	0	0
2	OPh	2.0	none	r.t.	0	0
3	SPh	2.0	none	r.t.	19 (55/45)	19
4	SPh	2.0	none	0	59 (60/40)	11
5	SPh	2.0	none	-78	87 (79/21)	0
6	SPh	1.0	none	-78	52 (66/34)	24
7	SPh	2.0	HMPA	-78	0	21
8	SPh	2.0	TMEDA	-78	0	21

<sup>a</sup> Ratio of  $\alpha/\beta$ -diastereomer was determined by  $^1\text{H}$  NMR.

which have been used previously in similar reactions [10, 11].

We selected *O*-glycosides **4** and **5**, and *S*-glycoside **6**, as substrates for the reaction because they are stable and easy to prepare.<sup>1</sup> First, the reaction was carried out with cyclohexanone as an electrophilic acceptor (Table 1). A solution of the substrate **4**, **5**, or **6**, in THF was added dropwise to a stirred solution of  $\text{SmI}_2$  (2.0 equiv.) in THF at room temperature. Cyclohexanone (1.1 equiv.) was then added, and the mixture was stirred at room temperature (entries 1-3). *O*-Glycosides **4** and **5** did not react at all with cyclohexanone under these reaction conditions.<sup>2</sup> On the other hand, *S*-glycoside **6** reacted rapidly to give the desired-*C*-glycoside **7** in 19% yield as an anomeric mixture concomitant with the homocoupling product **8** in 19% yield. The ratio of  $\alpha/\beta$  anomers was determined to be 55/45 by the 500 MHz  $^1\text{H}$  NMR spectrum. The stereochemistry of the anomers was determined by difference NOE experiments for the  $\beta$ -anomer; correlations between H-1 and H-3 and between H-1 and H-5 was observed for the  $\beta$ -anomer but not for the  $\alpha$ -anomer. When the reaction with **6** was performed at -78 °C, the yield of *C*-glycoside **7** significantly increased to 87% (entry 5). Under these conditions, the stereoselectivity also improved, and the  $\alpha$ -anomer was

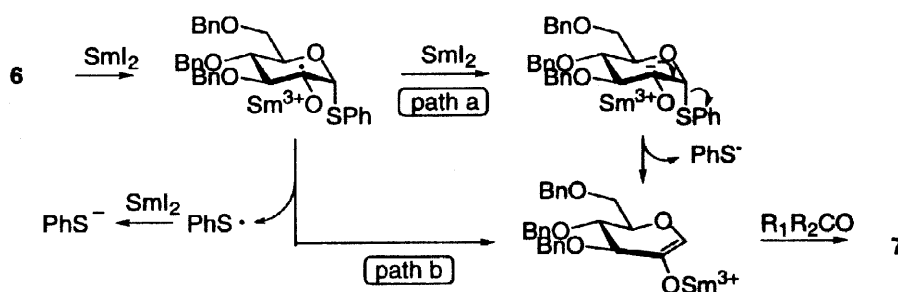
1. Substrates **4**, **5**, and **6** were prepared by oxidizing **10**, **11**, and **12** with  $\text{CrO}_3$ /pyridine/ $\text{Ac}_2\text{O}$  in  $\text{CH}_2\text{Cl}_2$ . Compounds **10**, **11**, and **12** were prepared as described previously [19, 20].



2. A dimerization (pinacol-type coupling) product was produced from both **4** and **5** when HMPA was added to the reaction system.

predominant ( $\alpha/\beta = 79/21$ ); the axial approach of cyclohexanone to the  $\alpha$ -face of the Sm(III) enolate may be favored by a stereoelectronic effect due to the pyranose ring oxygen. Reactions with **6** were also performed in the presence of an additive such as HMPA or TMEDA, which should enhance the ability of SmI<sub>2</sub> to transfer electrons. However, these reactions did not give **7** at all, and homocoupling product **8** was obtained as a sole product in both cases (entries 7 and 8). The reaction with 1.0 equiv. of SmI<sub>2</sub> gave **7** in the yield of 51% (entry 6). Therefore, 2.0 equiv. of SmI<sub>2</sub> was needed to complete the reaction. In addition, thiophenol, but not diphenyldisulfide, was isolated in 70% yield under the conditions in entry 5. It is possible that the reaction proceeds via a two-electron transfer mechanism; two electrons were transferred to the 2-carbonyl of **6** from two molecules of SmI<sub>2</sub> to generate the 1-samarium enolate via  $\beta$ -elimination of the 1-phenylthio group (path a, Scheme 2) or via homolytic cleavage (path b, Scheme 2).

Scheme 2



We next examined the reaction with several other carbonyl compounds as electrophilic acceptors. As shown in Table 2, all of the reactions proceeded effectively. However, when acetone was used as an acceptor,  $\alpha/\beta$ -selectivity was not observed at all (entry 1), and the

Table 2. SmI<sub>2</sub> Promoted aldol-type C-glycosylation with various acceptors.

entry	acceptor	product			
		R <sub>1</sub>	R <sub>2</sub>	yield (%)	$\alpha/\beta^a$
1	acetone	Me	Me	85	53/47
2	3-pentanone	Et	Et	88	>90/10
3	acetaldehyde	H	Me	75 (15) <sup>b</sup>	>90/10
4	cyclohexane-carboxaldehyde	H	$\alpha$ -C <sub>6</sub> H <sub>10</sub>	76 (24)	>90/10
5		H		73%	>90/10

<sup>a</sup>The ratio of  $\alpha/\beta$ -diastereomer was determined by <sup>1</sup>H NMR. <sup>b</sup> Number in parenthesis is yield of dehydrated products.

reaction with 3-pentanone gave the  $\alpha$ -C-glycoside selectively (entry 2). Reactions with acetaldehyde and cyclohexanecarboxaldehyde also gave the corresponding  $\alpha$ -C-glycosides selectively along with their dehydrated enone-products (entries 3 and 4). These  $\alpha$ -C-glycosides are the single diastereomers. Moreover, we applied this reaction to the synthesis of C-glycosidic disaccharide. Thus, similar  $\text{SmI}_2$ -promoted reaction of **6** with the 5-aldehyde derivative of xylofuranose [21] as an acceptor gave the corresponding  $\alpha$ -C-glycosidic disaccharide in 73% yield as a diastereomeric mixture at the carbon adjacent to the anomeric position (entry 5). To the best of our knowledge, there is no precedent for  $\text{SmI}_2$ -promoted aldol-type reaction using a phenylthio or an alkylthio group as a leaving group for generating enolates.

**Conclusion:** A stable precursor for generating ulose-1-enolate, i.e., phenyl 3,4,6-tri-*O*-benzyl-1-thio- $\beta$ -D-*arabino*-hexopyranosid-2-ulose (**6**), was developed and used effectively in a novel  $\text{SmI}_2$ -promoted aldol-type C-glycosidation reaction. Using this reaction, a variety of C-glycosides, including a C-glycosidic disaccharide, were readily prepared. This reaction is currently being applied to the synthesis of natural products.

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