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Radical Dimerization of Glycosyl 2-Pyridylsulfones with Samarium (II) Iodide in the Presence of HMPA

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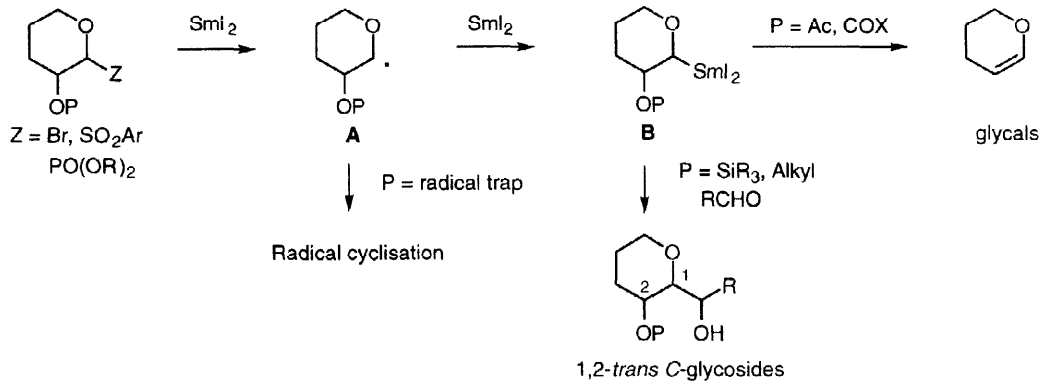
Abstract : Reduction of glycosyl 2-pyridylsulfones by samarium (II) iodide in the presence of HMPA leads to glycosyl dimers in up to 74% yield. This is rationalized by a free-radical mechanism.

Bimolecular radical reactions in the SmI_2-mediated production of radicals are not favored because, in these reducing reaction conditions, any radical reaction must occur significantly faster than the reduction of the radical to the corresponding organosamarium[1,2]. This behavior explains the absence of dimerization in the reduction of primary alkyl iodides (or bromides) to the corresponding alcanes[4,5]. SmI_2-promoted alkyl radical processes then mostly operate when an intramolecular trap of the radical is properly disposed as observed in cyclization reactions[1d].

The chemistry generated at the anomeric center of carbohydrates follows these general trends. Electron transfer into appropriate anomeric substituents (halogens[7], aryl sulfones[7-10], phosphates[11]) leads to an anomeric radical **A** (Scheme) either trapped by a suitably located unsaturation (5-exo[8] or 9-endo[7] radical cyclizations) or further reduced to an anomeric samarium (III) species **B**. With an oxygen at position 2 as found



Scheme

in neutral hexoses, the anomeric organosamarium will either suffer monomolecular elimination (2-OAc[7], 2-OCOR, -$OCNR_2$[9c]; glycal synthesis) or undergo C-C bond formation with carbonyl compounds[7,9] (2-O-alkyl

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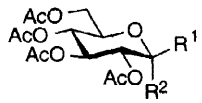
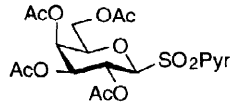
or silyl ether; *C*-glycoside synthesis) under Barbier procedures. Reduction of anomeric phenylsulfones by SmI_2 in THF necessitate the addition of HMPA to enhance the reducing power of SmI_2[7]. To facilitate radical cyclizations[8] as well as anionic Barbier procedures[9], we introduced the 2-pyridylsulfonyl substituent which undergoes fast reduction by SmI_2 without HMPA. We now report that, in the absence of competing intramolecular reactions, SmI_2-promoted reduction of anomeric 2-pyridylsulfones leads, via a radical process, to glycosyl dimers only in the presence of HMPA.

Fast addition of a THF solution of SmI_2 (0.1M, 2.4 equiv.) to a solution of β-D-glucopyranosyl-2-pyridylsulfone **1** in THF led, as expected, to the exclusive formation of glucal **7a** (Table, entry 1).



1 $R^1 = SO_2Pyr$, $R^2 = H$
2 $R^1 = SO_2Ph$, $R^2 = H$
3 $R^1 = H$, $R^2 = Br$



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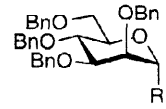
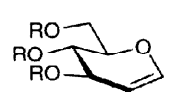


5 $R = SO_2Pyr$
6 $R = H$

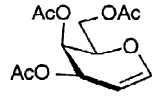
Pyr = 2-pyridyl

Entry	Substrates	Conditions[a]	HMPA (equiv.)	Products: Glycal (% yield)[b]	Dimers (% yield)[b]	**9**	**10** (% yield)[b]
1	**1**	A[a]	0	**7a** 92	-	-	-
2	**1**	A	8	**7a** 40	52	-	-
3	**1**	A	16	**7a** 20	74	-	-
4	**1**	A	32	**7a** 19	73	-	-
5	**2**	A	0	**7a** c	-	-	-
6	**2**	A	8	**7a** 92	-	-	-
7	**3**	A	0	**7a** 90	-	-	-
8	**3**	A	8	**7a** 94	-	-	-
9	**4**	A	0	**8** 94	-	-	-
10	**4**	A	8	**8** 35	50[d]	-	-
11	**5**	A	0	**7b** 24[e]	-		**6** 56[e]
12	**5**	A	8	**7b** 18[e]	49[d]		**6** 10[e]
13	**1**	B[a]	0	**7a** 31	-		34 (3.5)[f]
14	**1**	B	8	**7a** 96	-	-	-
15	**2**	B	0	**7a** 96	-	-	-
16	**3**	B	0	**7a** 65	-		27 (0.6)[f]

[a] To a solution of the substrate (1 mmol) in THF (40ml) with or without HMPA at room temperature was added a 0.1 M solution of SmI_2 (2.4 equiv.) in conditions A (dropwise addition in less than 10 s) or conditions B (seringe pump-driven addition in 2 h); [b] isolated yields by column chromatography; [c] no substancial reaction after 12 h at room temperature; [d] the isomeric composition of the dimeric mixture was not determined; [e] elimination and protonation of the anomeric organosamarium are known to compete for this substrate (see ref. 9a); [f] **9**:**10** ratio.



7a R = Ac
7b R = Bn



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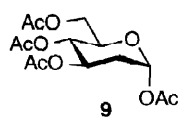

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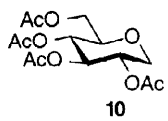

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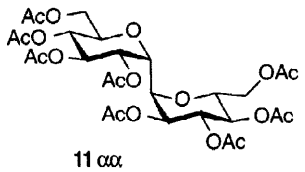
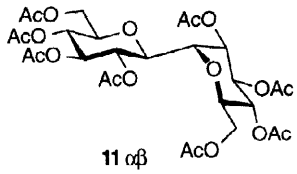
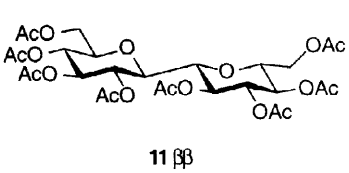


11 αα



11 αβ



11 ββ

In the presence of an increasing amount of HMPA, the reaction products partition between glucal **7a** and dimers **11**[12] (Table, entries 2-4) with a maximum production of dimers **11** (74%, entry 3) in the presence of 16 equiv. of HMPA to SmI_2. The three possible dimers **11**αα, **11**αβ and **11**ββ are formed in proportions (1.5:3.0:1.0, respectively)[13] independent of the quantity of HMPA. The galactosyl pyridylsulfone **4** or the mannosyl derivative **5** provided similarly about 50% isolated yields of dimers in the presence of 8 equiv. of HMPA to SmI_2 (Table, entries 9-12). The behavior of the anomeric pyridylsulfones is unique in that glucosyl phenylsulfone **2** or acetobromoglucose **3** led exclusively to elimination, under the same reaction conditions with or without HMPA[14] (Table, entries 5-8). HMPA only accelerates the rate of the elimination reaction.

Dimerization of glycosyl anomeric radicals were only observed under photolytic conditions, either from furanosyl[15] and pyranosyl[16] phenylsulfones (27% - 24% yield of dimers), or from glycosyl bromides and selenides[17] (irradiation in benzene in the presence of 1 equiv. of hexamethylditin, 32% yield of dimers). The efficiency of our dimerization results (74% of dimers) compares well with previous results and is, at first sight, surprising. HMPA, known to increase the reducing power of SmI_2[18], has been shown to enhance the rate of reduction of a primary alkyl radical to an organosamarium intermediate (second electron transfer)[19] up to 5-7 equiv. of HMPA to SmI_2. If this were the case, pyridylsulfone **1** and **4** should only provide the glycal. We rationalize dimer formation by a radical mechanism and consider that "anionic" couplings (anomeric anion-anomeric radical[20] or anomeric anion-anomeric pyridylsulfone[1b]) unreasonable because in both cases elimination of the anionic species to glycal should prevail. The dimer distribution (**11**αα, **11**αβ, **11**ββ ratio of 1.5:3.0:1.0) obtained from pyridylsulfone **1** are very similar to that obtained by photolysis[17a] or electrolysis[17b] of bromides or selenides[17] (1:2:1) which can also be taken as a typical stereochemical signature of a radical mechanism. The inescapable explanation is, when the availability of SmI_2 is not a limiting factor (fast addition mode), HMPA accelerates the first electron transfer more than the second one (formation of the anomeric organosamarium) so that the anomeric radical accumulates at a concentration high enough for dimerization to occur. This option is not available to phenylsulfone **2** and bromide **3** because, under the same conditions, the first electron transfer is still too slow.

This rationale was confirmed by a second series of experiments in which the SmI_2 solution was added slowly to the substrate (Table, entries 13-16). In the presence of 8 equiv. of HMPA to SmI_2, pyridylsulfone **1** furnished only glucal **7a** (Table, entry 14). Under these conditions, the anomeric radical is produced at a concentration too low for dimerization. Without HMPA, sulfone **1** and bromide **3** provided the same products **7a**, **9** and **10** in different ratios [**7a** : **9** + **10** ratio of ~1:1 (from **1**) or ~2:1 (from **3**)] whereas phenylsulfone **2** led only to elimination (Table, entries 13, 15 and 16). Glycal **7a** originates from the organosamarium whereas deoxy compounds **9** and **10** originate from the radical by either hydrogen transfer (→**10**) or 1,2-rearrangement and hydrogen transfer[21] (→**9**). We notice again different behavior of the three substrates which can provide a qualitative estimation of the relative rate for the first electron transfer onto anomeric substituents of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose which is in the $k(SO_2Pyr) > k(Br) > k(SO_2Ph)$ order.

In summary, the results described in this paper showed that (i) useful yields of glycosyl dimers can be obtained by reduction of glycosyl pyridylsulfones by the SmI_2/HMPA system under appropriate conditions, and (ii) proper experimental conditions should be chosen to perform glycal or *C*-glycoside synthesis (Barbier procedure) by reductive samariation of adapted anomeric substituents.

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