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S_N2 substitution reaction of 2-*C*-acetoxymethyl glycals catalyzed by iodine: a novel synthesis of 2-*C*-*N*-arylamidomethyl glycals

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ABSTRACT

The reaction of 2-*C*-acetoxymethyl glycals with *N*-aryl amides such as *N*-aryltosyl amine, *p*-toluenesulfonamide, and *t*-butoxycarbonyl amine in the presence of a catalytic amount of iodine affords a novel class of 2-*C*-*N*-arylamidomethyl glycals through direct attack at the C-2 position bearing the acetyl group under mild reaction conditions. The use of iodine makes this method simple, convenient, and cost-effective. This is the first report on nucleophilic substitution of 2-*C*-acetoxymethyl glycals with *N*-aryl amides using molecular iodine as a catalyst.

Lewis acid catalyzed organic transformations are of great importance in organic synthesis because of their high reactivity, selectivity, and mild reaction conditions.[1] In particular, acid catalyzed nucleophilic substitution reactions are very useful for carbon–carbon[2] and carbon–heteroatom bond formation.[3,4] The allylic acetates are well-known carbon electrophiles capable of reacting with various nucleophiles and their ability to undergo nucleophilic substitution reactions contributes largely to their synthetic value.[5] Of various allylic acetates, glycals (1,5-anhydro-hex-1-enitols) are attractive chiral building blocks in organic synthesis.[6] In most cases, the glycals undergo allylic rearrangement with nucleophiles in the presence of acid catalysts.[7] However, 2-*C*-acetoxymethyl glycals behave differently depending upon the reactivity of nucleophiles. In the case of alcohols, they are known to undergo allylic rearrangement by preferential attack of nucleophile at anomeric carbon to give 2-*C*-methylene-*O*-aryl/alkyl glycosides.[8] In the case of thiols, they undergo nucleophilic substitution by direct attack of thiol at the C-2 position bearing the leaving group to furnish 2-*C*-arylthiomethyl glycals.[9]

Recently, molecular iodine catalyzed or mediated reactions have gained importance in organic synthesis because of its low cost and ready availability. The mild Lewis acidity associated with molecular iodine has enhanced its use in organic synthesis to perform several organic transformations using stoichiometric levels to catalytic amounts.[10] To the best of our knowledge, there are no reports on nucleophilic substitution of 2-*C*-acetoxymethyl glycals with aryl amides.

Following our interest on catalytic application of molecular iodine,[11] we herein report a novel strategy for the preparation of 2-C-*N*-arylamidomethyl glycals from 2-*C*-acetoxymethyl glycals and *N*-aryltosyl amines via nucleophilic substitution. Initially, we attempted the aminoglycosidation of 3,4,6-tri-*O*-benzyl-2-*C*-acetoxymethyl glycal (**1**) with aniline in the presence of 10 mol % of $InCl_3$ in acetonitrile. To our surprise, the reaction did not proceed even under reflux conditions. In this reaction, we anticipated the formation of sugar annulated tetrahydroquinolines from 3,4,6-tri-*O*-benzyl-2-*C*-acetoxymethyl glycal and aryl amine as has been described in our earlier work.[12] The above reaction also did not proceed with 5 mol % of iodine in acetonitrile. Next, we performed the reaction of 3,4,6-tri-*O*-benzyl-2-*C*-acetoxymethylglycal (**1**) with *N*-phenyltosyl amine (**2**) using 5 mol % of iodine in acetonitrile. Though, the reaction proceeded smoothly at 25 °C, the desired 2-*C*-*N*-phenyltosylaminomethyl glycal **3a** was obtained only in 70% yield. To improve the conversion, we carried out the above reaction in various solvents such as CH_2Cl_2 and THF. Of these, CH_2Cl_2 gave the best results. Therefore, the reaction was successful only with amides and not with amines due to their intrinsic basic nature and low reactivity. Under optimized conditions, treatment of 3,4,6-tri-*O*-benzyl-2-*C*-acetoxymethyl glycal (**1**) with *N*-phenyltosyl amine (**2**) in the presence of 5 mol % of iodine in CH_2Cl_2 at 25 °C gave the 2-*C*-*N*-phenyltosylaminomethyl glycal **3a** with high regioselectivity (Scheme 1).

This result provides the incentive to extend this method for other glycals and amides. Other glycals such as 3,4,6-tri-*O*-benzyl- and 3,4,6-tri-*O*-ethyl-2-*C*-acetoxymethyl glycals reacted smoothly with *N*-aryl sulfonamides to produce the corresponding 2-*C*-*N*-arylamidomethyl glycals in good yields (Table 1, entries b, c, f, g, and

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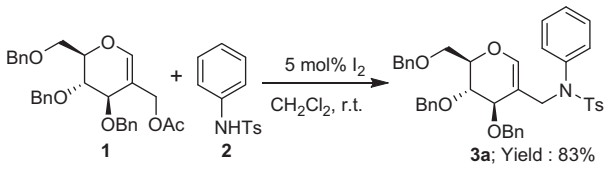


Scheme 1. S_N2 substitution of 2-*C*-acetoxymethyl glycal with *N*-phenyltosyl amine.

h). The structure of **3g** was thoroughly studied by NMR techniques. The characteristic NOEs of **3g** are shown in Figure 1.

Under similar conditions, 3,4,6-tri-*O*-benzyl-2-*C*-acetoxymethyl galactal also underwent a smooth nucleophilic substitution to produce 2-*C*-*N*-aryltosylaminomethyl galactal in good yields (entries d and e, Table 1).

The products were characterized by ^1H, ^{13}C NMR, IR spectra, and mass spectrometry. In the absence of catalyst, no reaction was observed even after an extended reaction time (12 h). As solvent, dichloromethane gave the best results. In all the cases, the reactions proceeded rapidly at 25 °C under mild conditions. The reactions were clean and no side products were detected under these conditions as determined from the NMR spectra of the crude

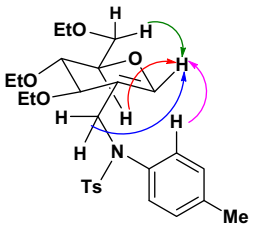
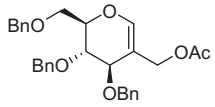
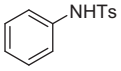
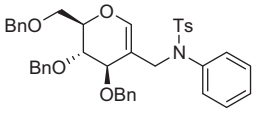
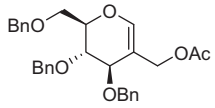
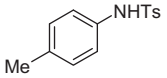
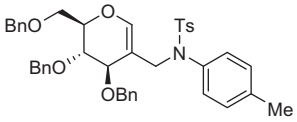
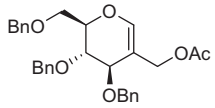
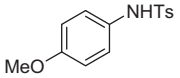
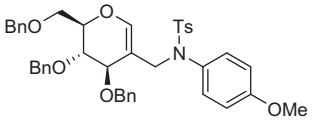
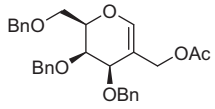
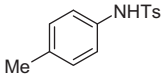
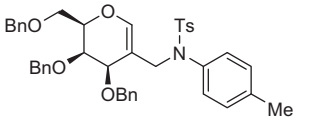
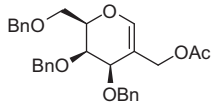
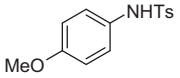
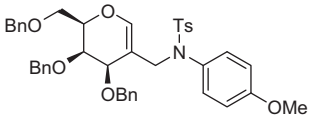
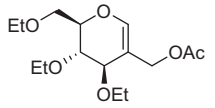
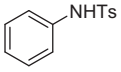
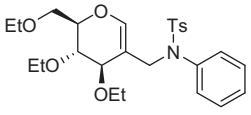
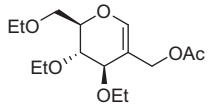
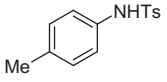
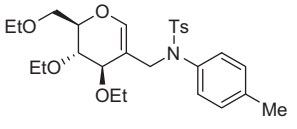
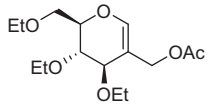
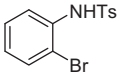
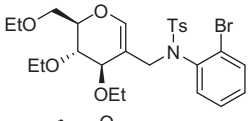
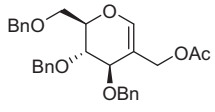
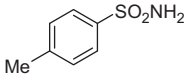
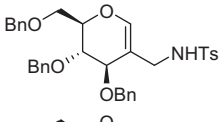
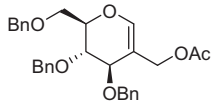
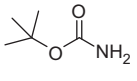
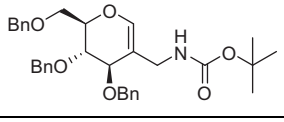
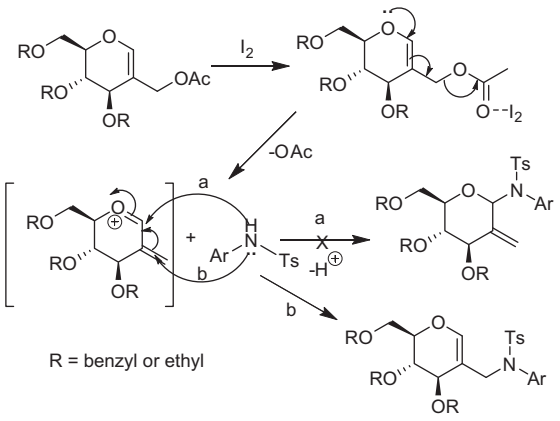


Figure 1. Characteristic NOE cross peaks of product **3g**.

Table 1
Iodine-catalyzed synthesis of 2-*C*-*N*-arylamidomethyl glycals

Entry	Substrate (**1**)	Nucleophile (**2**)	Product (**3**)[a]	Time (h)	Yield[b] (%)
a				3.0	83
b				3.5	86
c				4.3	81
d				3.2	89
e				4.0	75
f				3.5	86
g				3.0	83
h				3.5	80
i				5.1	73
j				4.6	65

[a] The products were characterized by NMR, IR, and mass spectroscopy.
[b] Yield refers to pure products after chromatography.



Scheme 2. A plausible reaction pathway.

products. The efficiency of various metal halides such as $FeCl_3$, $InCl_3$, $GaCl_3$, YCl_3, and $YbCl_3$ was studied for this transformation. Among them, 5 mol % of iodine was found to be superior to other catalysts tested. For instance, treatment of 3,4,6-tri-*O*-benzyl-2-*C*-acetoxymethyl glycal (**1**) with *N*-*p*-tolyltosyl amine (**2**) in the presence of 5 mol % of iodine and 5 mol % of $InCl_3$ gave the desired product **3b** in 86% and 75% yields, respectively.

The reaction likely proceeds via the activation of allylic acetate by molecular iodine thereby generating the oxocarbenium ion as shown in Scheme 2. Due to intrinsic low reactivity of oxocarbenium ion toward amide, the nucleophile is attacked preferentially at C-2-methylene position via path 'b' to give the desired 2-*C*-*N*-arylamidomethyl glycals (Scheme 2).

The scope and generality of this process are illustrated with respect to various 2-*C*-acetoxymethyl glycals and *N*-arylsulfonamides and the results are presented in Table 1.[13]

In summary, we have described a novel method for the synthesis of 2-*C*-*N*-arylamidomethyl glycals from 2-*C*-acetoxymethyl glycals and *N*-arylamides using a catalytic amount of molecular iodine under mild reaction conditions. This method provides various 2-*C*-*N*-arylamidomethyl glycals in good yields in short reaction times with high regioselectivity, which makes it a useful and attractive process.

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Supplementary data

Supplementary data (experimental procedures and compound characterization) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.106.

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13. **General procedure**: A mixture of 2-*C*-acetoxymethyl glycals (**1**, 1.0 mmol), *N*-arylamide (**2**, 1.1 mmol) in DCM (3 mL) and I_2 (12 mg, 5 mol %) was stirred at 25 °C for a specified time as required to complete the reaction (see Table 1). After complete conversion, as indicated by TLC, the mixture was quenched with 15% solution of sodium thiosulfate and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 60–120 mesh, ethyl acetate/hexane, 2:8) to afford the pure 2-*C*-*N*-arylamidomethyl glycals.