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Convenient Synthesis of 3-Glycosylated Isocoumarins

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Abstract: A new route for the synthesis of 3-substituted and 8-hydroxy-3-substituted isocoumarins has been developed by using modified Julia olefination for initial C-C bond formation between aldehydes and benzylic-sulfones. Palladium-catalyzed Meinwald rearrangement was used as a key step for the obtainment of ketone intermediates, which on base promoted intramolecular cyclization afforded the desired isocoumarins. The developed method has paved the way for hitherto unknown 3-glycosyl isocoumarins in general and 3-glucosyl isocoumarins in particular wherein the glucosyl moiety is attached to the pyrone ring of isocoumarin framework, for the first time.

Introduction

Dapagliflozin **1** has emerged as a potent and selective Sodium-Dependent Glucose Cotransporter 2 (SGLT2) inhibitor, which reduces blood glucose levels in a dose-dependent manner for the treatment of type 2 diabetes through blocking glucose reabsorption in the kidneys.[1a-c] Structurally **1** is a *C*-aryl glucoside, in which the *gluco*-configured pyranosyl unit is directly attached to the aromatic ring. The success of dapagliflozin has inspired further variation of the ring A of the aglycone part. The ring A has been replaced with other heteroaryl rings like pyridine, pyrrole, pyrazine and thiophene.[2a-b] Given the fact that nature presents several *O*- or *C*- linked glycosides of the flavones,[3a-b] isoflavones,[3c] coumarins[3d] and isocoumarins[3e-g] as valuable natural products, we became interested in 3-glucosylated isocoumarins **2** and **3** in particular as new potential structural motif, worthy of synthesis and biological evaluation. The hydroxyl group at the 8th position of the isocoumarin framework has been found to be essential for diverse biological properties represented by important natural products like Thunberginol A and B.[4a-b] The *C*-glucosylated flavones, isoflavones and coumarins represented by **4**, **5** and **6** respectively carry the glucosyl residue in the aromatic ring (Figure 1). Interestingly, *C*-linked coumarins **7**[5a-d] and isocoumarins **8** wherein the glycosyl unit is attached to the pyrone ring are rare in nature and very limited reports are available for the synthesis of this class of compounds. To the best of our knowledge, only one isolated report exists in the literature for *C*-glycosides of isocoumarin, wherein the *C*-3 position contains a glycosyl residue.[6] The absence of a convenient synthetic route for the access to *C*-3 glycosyl isocoumarins **8** in general and the need of our targeted compounds **2** and **3** in particular, motivated us to develop a new synthetic route. The results of these studies are presented herein.

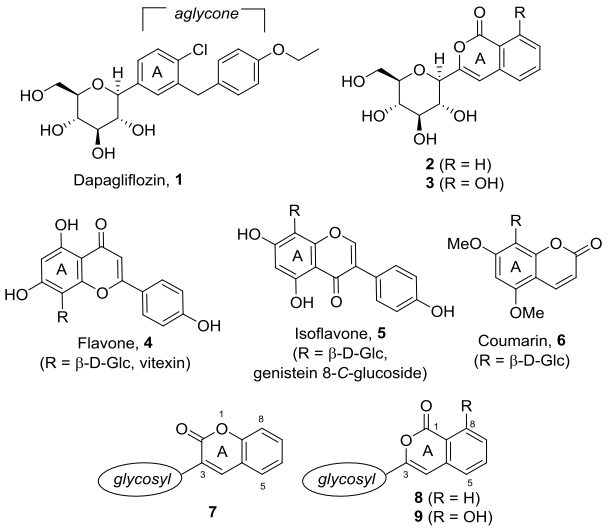

Figure 1. Structures of important aryl and heteroaryl glycosides

Results and Discussion

The new method reported by us for the synthesis of 3-aryl isocoumarins[7] wherein α-aryl aminonitriles **10** were conveniently used as acyl anion equivalents for the requisite C-C bond formation, has a drawback for the synthesis of **8** and **9** because alkylated α-alkyl aminonitriles **11a** requires strongly acidic conditions in most cases[8a-f] in contrast to alkylated α-aryl aminonitriles **10a**, for the release of carbonyl functionality (Figure 2). For the sugar based α- aminonitriles **12**, if availed and used, the situation with alkylated glycosyl aminonitriles **12a** would be even more detrimental, given the sensitive functionalities and protections present on the glycosyl part.

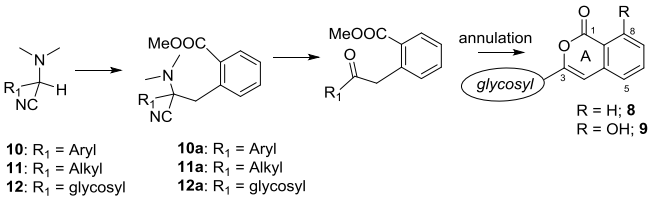

Figure 2. Limitations of acyl anion chemistry for the synthesis of 3-glycosyl isocoumarins **8** and **9**.

In this context, a new synthetic scheme was envisaged for the synthesis of 3-glycosyl-isocoumarins **8**, which invoked the use of modified Julia olefination[9] for the initial C-C bond formation between the functionalized aldehydes **13** derived from the carbohydrate domain and sulfone **14a** (Figure 3).

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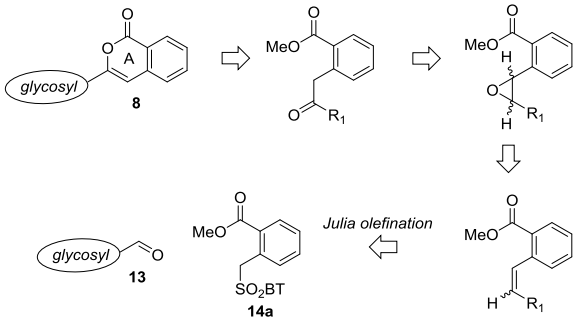
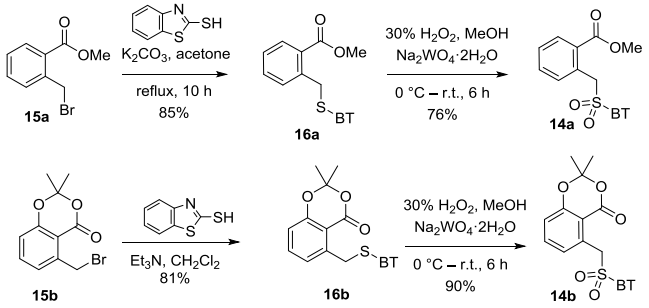


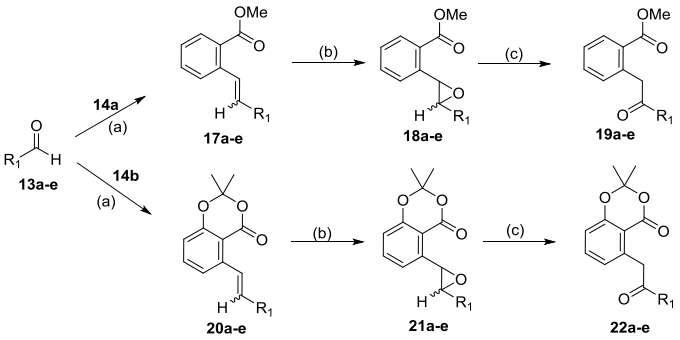
Figure 3. Proposed disconnection for 3-glycosyl isocoumarins **8**.

The sulfones **14a**[10] and **14b** required for the synthesis of 3-glycosyl isocoumarins **8** and 8-hydroxy-3-glycosyl isocoumarins **9** respectively were easily synthesized from the corresponding bromides **15a-b** as described in scheme 1. The reaction sequence involved nucleophilic substitution of the bromides **15a-b** with 2-mercaptobenzothiazole in presence of a base for the formation of sulfides **16a-b**, followed by oxidation of the sulfides with 30% H_2O_2 in the presence of sodium tungstate at 0 °C in MeOH. Both the sulfones (**14a** and **14b**) were obtained as white crystalline solids.



Scheme 1. Synthesis of sulfones **14a** and **14b**.

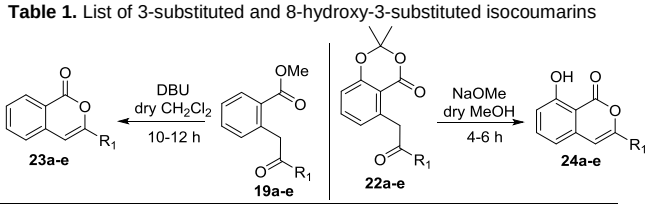
Before commencing olefination of glycosyl aldehydes **13** with sulfone **14a**, a model study with simple commercially available aliphatic aldehydes **13a** and **13b** was undertaken. The alkene products **17a** and **17b** were obtained as *E*/*Z* mixture which was evident from the NMR spectroscopy. Similarly other aldehydes **13c**-**e**[11] with additional functionalities such as ether, ester and *N*-*tert*-butoxy carbonyl (Boc) functionalities also underwent clean reaction with the sulfone **14a** affording the corresponding alkenes **17c-e** in good yields. The olefins **17c** and **17d** were formed as *E*/*Z* mixture whereas olefin **17e** was obtained exclusively as *E* isomer (Scheme 2). The olefins **17a**-**e** on treatment with *m*-CPBA underwent epoxidaton[12] furnishing the mixture of epoxides **18a**-**e**. These epoxides underwent clean regioselective Meinwald type rearrangement upon treatment with tributylphosphine in presence of $Pd(OAc)_2$[13] affording the corresponding keto esters **19a**-**e** as desired in the projected synthetic scheme.



Scheme 2. Synthesis of ketones **19a**-**e** and **22a**-**e**. Reagents and conditions: (a) NaH, DMF, 0 ºC to r.t. 2-4 h, (63-74%). (b) *m*-CPBA, CH_2Cl_2, H_2O, p^H = 7, 12-14 h, (66-92%). (c) $Pd(OAc)_2$, PBu_3, dry *t*-BuOH, 3-4 h (67-97%).

Similarly, for the synthesis of 8-hydroxy-3-substituted isocoumarins the same reaction sequence was deployed using **14b** as the starting sulfone for arriving at keto lactones **22a-e** (Scheme 2).The Keto esters **19a**-**e** on treatment with DBU in dry CH_2Cl_2 afforded the corresponding 3-substituted isocoumarins **23a**-**e** in good yields (Table 1). However, the keto lactones **22a-e** failed to undergo cyclization under same condition. This was probably due to the unsuitable disposition of the lactone carbonyl group because of the locked conformation resulting from the isopropylidene protection. The cyclization, however, could be easily achieved with the use of NaOMe as a base resulting in the formation of 8-hydroxy-3-substituted isocoumarins **24a-e** in good yields (Table 1).

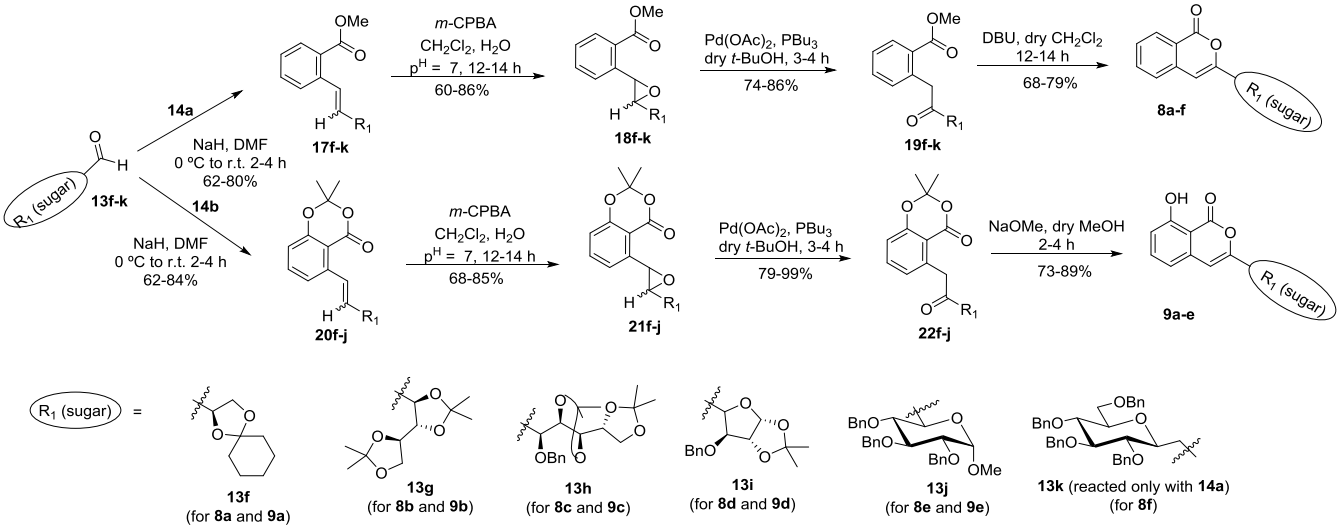
Table 1. List of 3-substituted and 8-hydroxy-3-substituted isocoumarins



S. No.	R_1 in R_1-CHO **13**	**23a-e** (% yield)[a]	**24a-e** (% yield)[a]
1	**13a**	**23a** (83)	**24a** (74)
2	**13b**	**23b** (91)	**24b** (68)
3	**13c**	**23c** (76)	**24c** (92)
4	**13d**	**23d** (84)	**24d** (82)
5	**13e**	**23e** (89)	**24e** (83)

[a] for the annulation step

With the successful model studies, efforts were now directed towards the extending the reaction of sulfones **14a** and **14b** with more functionalized aldehydes derived from the carbohydrate domain.

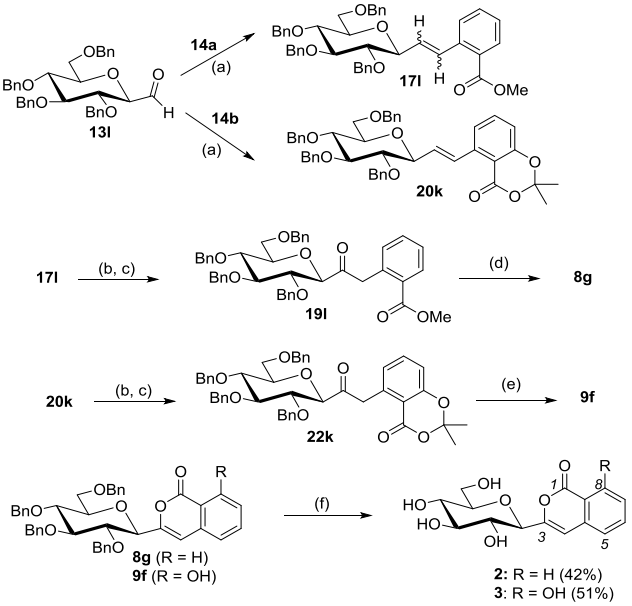


Scheme 3. Synthesis of 3-glycosyl and 8-hydroxy-3-glycosyl isocoumarins.

Towards this objective, we chose aldehydes **13f-k**[14] as representative examples and prepared them according to the literature known protocols. The choice of these aldehydes was purely dictated by the ready availability of starting materials and the convenience of synthetic methods used to prepare them. All these aldehydes **13f-k** successfully reacted with the sulfones **14a** and **14b** under the optimized conditions to afford the corresponding olefins **17f-k** and **20f-j** respectively with *E* isomer as the major product (Scheme 3). These olefins were converted to the corresponding 3-glycosylated isocoumarins **8a**-**f** and 8-hydroxy-3-glycosylated isocoumarins **9a**-**e** respectively by a sequence of reactions described in scheme 3. In case of isocoumarin **8b,** it was observed that the epoxy ester **18g** directly annulated to **8b** without the intermediacy of keto ester **19g**.

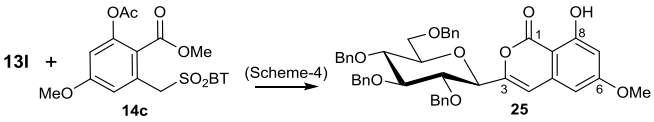
With the obtainment of 3-glycosyl (**8a**-**f**) and 8-hydroxy-3-glycosyl isocoumarins (**9a**-**e**), the developed route was now utilized for the synthesis of targeted 3-glucosylated isocoumarins **2** and **3**. The β-*C*-glucopyranosyl aldehyde **13l**[15] was subjected to olefination with sulfones **14a** and **14b** to obtain the corresponding olefins **17l** (as *E*/*Z* mixture) and **20k** (as *E* isomer) respectively in good yields. (Scheme 4). These olefins on epoxidation followed by palladium catalyzed rearrangement gave ketones **19l** and **22k** respectively. Base promoted intramolecular cyclization of **19l** and **22k** resulted in corresponding isocoumarins **8g** and **9f** respectively. Finally for the synthesis of the targeted isocoumarins **2** and **3** in particular, the removal of benzyl ether protection in **8g** and **9f** was attempted under hydrogenation condition. Although catalytic hydrogenation under balloon pressure in the presence of Pd/C in dry THF did remove the benzyl ether protections, it also reduced the C3-C4 double bond of the isocoumarin ring. The ^{1}H-NMR spectrum of the homogenous product obtained during hydrogenation reaction (TLC, R_f = 0.1, 10% MeOH: EtOAc) revealed it to be an inseparable mixture of desired compound along with 3,4-dihydroisocoumarin compound. The selective removal of benzyl ether protection, however could be achieved with the use of BBr_3. (Scheme 4).

Further, to demonstrate the generality of the developed route, another sulfone **14c**, [16] containing oxygenation pattern present in natural orsellinic acid, was synthesized and used for reaction with β-*C*-glucopyranosyl aldehyde **13l**. The expected isocoumarin **25** was obtained there by demonstrating the usefulness of the developed method (Scheme 5).



Scheme 4. Synthesis of 3-glucosyl (**2**) and 8-hydroxy-3-glucosyl isocoumarins (**3**). Reagents and conditions: (a) NaH, DMF, 0 ºC to r.t. 2-4 h, (60% for **17l** and **20k**). (b) *m*-CPBA, CH_2Cl_2, H_2O, p^H = 7, 12-14 h, (81% for **18l**, 84% for **21k**). (c) $Pd(OAc)_2$, PBu_3, dry *t*-BuOH, 3-4 h (81% for **19l** , 98% for **22k**). (d)

DBU, dry CH_2Cl_2, 12-14 h (75%). (e) NaOMe, dry MeOH, 2-4 h, (80%) (f) BBr_3, dry CH_2Cl_2, -78 °C, 12 h.



Scheme 5. Synthesis of isocoumarin **25**.

The synthesis of **2** and **3** constitutes the first report in the literature for *C*-anomerically linked glucosyl unit to the pyrone ring of the isocoumarin at C-3 position.

Conclusions

Synthesis of 3-glycosyl and 8-hydroxy-3-glycosyl-substituted isocoumarins has been achieved for the first time. The synthetic scheme banks on the convenience of C-C bond formation through Julia olefination reaction and subsequent Meinwald rearrangement for acquiring the requisite carbon framework. The developed methodology has large substrate scope and wide functional group compatibility during the implementation of the synthetic scheme.

Experimental Section

General Procedure for Julia olefination of sulfones with aldehydes (Procedure A): To a suspension of NaH (2 equiv.) in dry DMF (2 ml per 100 mg of the aldehyde), a solution of sulfones **14a** or **14b** (1 equiv.) was added at 0 °C. The solution turned to reddish orange color which indicates the formation of carbanion. After 10 minutes, a solution of aldehydes **13a-l** (1 equiv.) in dry DMF (1 ml per 100 mg of the aldehyde) was added to the reaction mixture. The disappearance of reddish orange color was observed. The reaction mixture was allowed to attain room temperature and maintained for further 2.5 h. After the complete consumption of starting material, the reaction mixture was quenched with saturated ammonium chloride solution (10 mL) followed by water addition (10 mL) and extracted with ethyl acetate (3×15 mL). The combined organic layer was washed with 20% aqueous cold solution of NaOH (3×15 mL) to remove by-product 2-hydroxybenzothiazole followed by water (10 mL) and brine (10 mL). The collected organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated and subjected to purification by silica gel column chromatography to yield the corresponding alkenes **17a-m** or **20a-k** respectively as diasteromeric mixture.

General Procedure for epoxidation (Procedure B): To a solution of alkenes **17a-m** or **20a-k** (1 equiv.) in CH_2Cl_2/ phosphate buffer (pH 7, the buffer was prepared by adding 1.56g of $NaH_2PO_4.2H_2O$ in 10 mL (1 M) and 1.42g of anhydrous Na_2HPO_4 in 10 mL (1 M), (1:1, 8 mL) was added portion wise *m*-CPBA (3 equiv.) at 0 °C. After stirring at rt for 12 h, the organic phase was separated and the aqueous phase was washed with dichloromethane (2 × 50 mL). The combined organic phases were washed with saturated sodium thiosulfate and saturated sodium bicarbonate solutions. The collected organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated and subjected to purification by silica gel column chromatography to obtain the corresponding epoxides **18a-m** or **21a-k** respectively as diasteromeric mixture.

General Procedure for epoxides to ketones rearrangement (Procedure C): To a solution of epoxides **18a-m** or **21-a-k** (1 equiv.) and palladium acetate (0.3 equiv.) in degassed anhydrous *t*BuOH was added tributylphosphine (1.3 equiv.) under nitrogen atmosphere at room temperature. The reaction mixture was stirred at reflux for 4 h (monitored by TLC). The solvent was removed under reduced pressure and purified by column chromatography to yield keto esters **19a-m** or keto lactones **22a-k** respectively.

General Procedure for synthesis of 3-substituted isocoumarins (Procedure D): To a solution of aryl ketones **19a-m** (1 equiv.) in dry CH_2Cl_2 (4 mL), DBU (2 equiv.) was added under inert atmosphere. The reaction mixture was stirred for 12 h. Then 20 mL DCM was added to the reaction mixture. The mixture was washed with 5% hydrochloric acid (20 mL). After that, the organic layer was washed with 20 mL water and finally dried over Na_2SO_4. The organic layer was concentrated under reduced pressure and the obtained residue was purified by column chromatography over silica gel to yield the corresponding 3-substituted isocoumarins **23a-e**, **8a-g** and **25**.

General Procedure for synthesis of 8-hydroxy-3-substituted isocoumarins (**Procedure E**): To a solution of the aryl ketones **22a-k** (1 equiv.) in dry MeOH (3 mL), NaOMe (1.1 equiv.) was added under inert atmosphere. The reaction mixture was stirred for 6 h under inert atmosphere at room temperature. Then the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to obtain the corresponding 8-hydroxy-3-substituted isocoumarins **24a-e**, **9-f**.

General procedure Debenzylation reaction (**Procedure F**): To a solution of isocoumarins **8g** or **9f** (1 equiv.) in dry CH_2Cl_2 (6 mL) was added BBr_3 (1.0 M in CH_2Cl_2, 8 equiv.) at −78 °C under nitrogen atmosphere and was stirred at same temperature for 12 h.The progress of the reaction was monitored by TLC, after complete consumption of starting material the reaction mixture was quenched with MeOH (2 mL) at −78 °C. The mixture was evaporated in vacuo. The residue was diluted with EtOAc and the organic solution was washed with brine solution (10 mL). The organic layer was dried over anhydrous sodium sulphate and then filtered. The filtrate was concentrated under vacuum and subjected to purification by silica gel column chromatography to yield the corresponding isocoumarins **2** and **3**.

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Keywords: Glucosyl isocoumarins • Julia olefination • Epoxidation • Cyclization • Rearrangement

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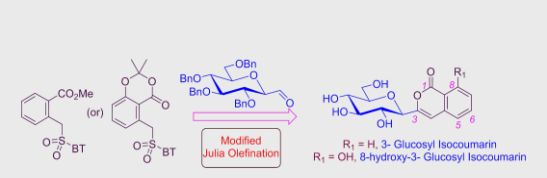
[16] See in supporting information for the detailed procedure of synthesis of sulfone **14c**.

Entry for the Table of Contents

Layout 2:

COMMUNICATION



3-substituted and 8-hydroxy-3-substituted isocoumarins are synthesized using modified Julia olefination for the initial carbon-carbon bond formation reaction. Palladium catalyzed Meinwald rearrangement of epoxides to ketones is used as key step in this study. A variety of aldehydes derived from carbohydrates reacted successfully for the synthesis of both 3-glycosyl in general and 3-glucosyl substituted isocoumarins in particular.

3-Glycosyl Isocoumarins*

*Kasireddy Sudarshan, Indrapal Singh Aidhen**

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Convenient Synthesis of 3-Glycosylated Isocoumarins