Journal of Carbohydrate Chemistry, 27:300–307, 2008

ISSN: 0732-8303 print / 1532-2327 online
DOI: 10.1080/07328300802107437

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Montmorillonite K-10 as a Reusable Catalyst for Fischer Type of Glycosylation under Microwave Irradiation

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Montmorillonite K10 catalyzed Fischer type glycosylation was studied for various monosacharides with different alcohols under microwave irradiation. The method was found to be efficient, economic, simple and time saving and the catalyst montmorillonite K-10 was reused three times without loss of catalytic activity and anomeric selectivity. With glycerol, the method gave products glycosylated at primary alcohols only.

Keywords Montmorillonite K10, Glycosylation, glycerol glucoside, microwave radiation

Due to immense biological importance of oligosacharides and glycoconjugates, many glycosylation strategies have been developed.[1–3] Among all the existing strategies for glycosylation of sugars, Fischer glycosylation procedure is the earliest and the simplest. In the classical Fischer glycosylation methodology, an unprotected carbohydrate is refluxed in an alcohol in presence of catalytic acid to give the corresponding glycoside. In spite of many limitations, Fischer glycosylation is utilized for synthesis of simple glycosides, such as, methyl, allyl, benzyl and p-methoxybenzyl glycosides.[4–7] In carbohydrate chemistry, methyl, allyl, benzyl and p-methoxybenzyl alcohols are used for temporary protection of the anomeric hydroxyl group, as glycosides of these alcohols can undergo easy deglycosylation.[8–10] Modification of Fischer glycosylation by replacing soluble acid with cation exchange resins, namely, Permutit Q, Duolite

Received March 20, 2008; accepted April 2, 2008.
The authors wish to thank the Director, NEIST, Jorhat for provision of facilities and DKR is thankful to the CSIR, New Delhi, for providing research fellowship.
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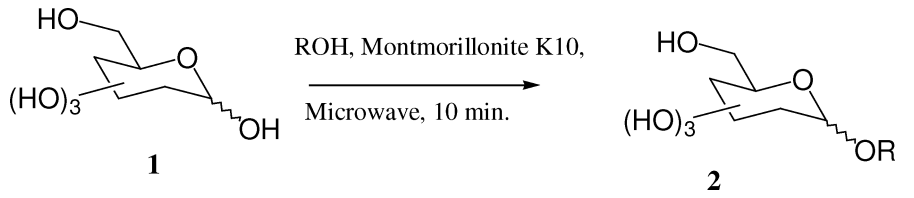
C-3 and C-3 Zeokarb H, has simplified the removal of the catalyst.[11] In one report, microwave was used for acceleration of Fischer glycosylation process catalyzed by Amberlite resin IRN 120 H^+.[12] Recently, sulfuric acid immobilized on silica was reported as a catalyst for Fischer type glycosylation.[13] In search of an inexpensive and environmentally benign and time saving method as part of our ongoing programme, we have developed an efficient and economic method of Fischer glycosylation catalysed by montmorillonite K-10 under microwave irradiation (Scheme 1).



Scheme 1.

In the initial experiments for testing the feasibility of montmorilloniteK1O as catalysts for Fischer glycosylation, a mixture of D-glucose (500 mg) and the clay (250 mg) was refluxed in anhydrous methanol (10 mL). The reaction was monitored by thin layer chromatography. The conversion was found to be almost complete in 5 hours. The reaction mixture was then cooled, filtered and the product was recrystallized from isopropanol. A mixture of both α and β anomer was obtained. To get the best α/β ratio, the reaction was studied in different reaction times (Table 1). Anomeric ratio was derived from the comparison of ^{1}H NMR peak at δ 4.70 ($J_{1,2} \approx 4.0$ Hz) and δ 4.27 $J_{1,2} \approx 8.5$ Hz). Improved α/β ratio was obtained in 10 hrs. Increase in reaction time beyond 10 hours improved α/β ratio slightly with increase in decomposition of the product.

We then studied the conversion under microwave radiation. D-glucose (500 mg) and montmorillonite K10 (250 mg) were mixed thoroughly in a mortar and the mixture was placed in a quartz reaction vessel of Prolabo Synthwave Microwave reactor. To it, 5 mL of methyl alcohol was added and

Table 1: Montmorillonite K10 catalyzed glycosylation of methanol with D-glucose under conventional reflux condition

Entry	Reaction time, hours	Yield,[a] %	α/β Ratio[b]
1	5	83	8.6/1
2	6	84	9.2/1
3	8	84	12.4/1
4	10	84	13.3/1
6	12	81	13.6/1
7	14	79	13.8/1
8	24	75	14.5/1

[a]Isolated yield. [b]The α/β ratio was determined by 300 MHz ^{1}H NMR spectroscopy.

Table 2: Montmorillonite K10 catalyzed glycosylation of methanol with D-glucose under microwave radiation

Entry	Reaction time, min	Yield,[a] %	α/β Ratio[b]
1	2	79	4.7/1
2	4	82	6.2/1
3	6	85	8.6/1
4	8	86	11.3/1
6	10	86	14.6/1
7	12	83	14.7/1
8	14	78	14.8/1
9	20	72	15.1/1

[a]Isolated yield. [b]The α/β ratio was determined by 300 MHz ^{1}H NMR spectroscopy.

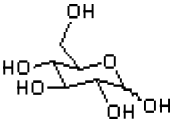
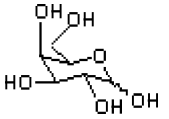
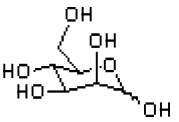
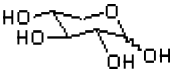
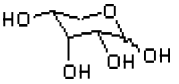
the mixture was allowed to react under microwave irradiation at a temperature of 90°C for 10 minutes. During the reaction, the temperature was not allowed to rise above 90°C by setting the programmer. The mixture was then allowed to cool, filtered and the product was recrystallized from isopropanol. To get improved α/β ratio, reaction was carried out for different time periods (Table 2). Optimum anomeric selectivity was found in 10 minutes. Further increase in reaction time increased the α/β ratio only slightly with increased decomposition.

After getting good result in microwave-assisted reaction between D-glucose and methanol, we generalized the reaction with a number of monosacharides and alcohols (Table 3). Very good yields and anomeric selectivity were obtained. After the reaction, the catalyst could be separated by filtration. After washing and activation at 110°C, the recycled catalyst was used again for glycosylation of D-glucose by benzyl alcohol. Over three times of recycle, comparable yields with same anomeric selectivity were obtained (Table 4).

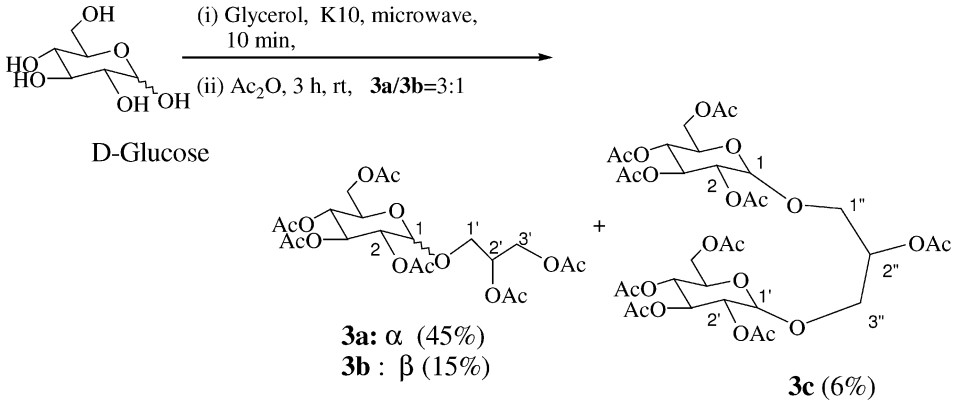
To study the utility of the method for alcohol containing both primary and secondary hydroxyl groups, we treated D-glucopyranose with glycerol in presence of montmorillonite K-10. *In situ* formed product was acetylated with acetic anhydride. Purification of the product by column chromatography gave l-(2,3,4,6-Tetraacetyl-α-D-glucopyranosyl)-2,3-diacetylglycerol **3a** (yield 45%), l-(2,3,4,6-Tetraacetyl-(β-D-glucopyranosyl)-2,3-diacetylglycerol **3b** (yield 15%) and 1,3-Bis (2,3,4,6-tetraacetyl-D-glucopyranosyl)-2-acetylglycerol **3c** (yield 6%) with mono- and di-glycosylated product in 5:1 ratio (Scheme 2). Anomeric ratio of the monoglycosylated products was determined to be 3:1. However, as in the glucosidase mediated method of glucosylation of glycerol[14] or similar to the glycerol glucoside isolated from marine blue-green alga,[15] and *Lilium japonicum*[16] no product glycosylated at secondary hydroxyl of glycerol was found to form in our reaction.

Thus, the use of montmorillonite K-10 for this Fischer type glycosylation method, has simplified its work up procedure. Only filtration was required to remove the catalyst. In addition, montmorillonite K-10 is stable, inexpensive,

Table 3: Microwave-assisted glycosylation catalyzed by Montmorillonite K10.

Entry	Sugar	Alcohol	Reaction time (min.)	Yields of Products[a] (%)	α/β Ratio[b]
01		CH_3OH	10	86	15/1
02		n-C_4H_9OH	10	82	10/1
03		$PhCH_2OH$	10	81	9/1
04			10	84	10/1
05		C_2H_5OH	10	77	13/1
06		n-$C_8H_{17}OH$	10	74	10/1
07		CH_3OH	10	84	11/1
08		$PhCH_2OH$	10	81	8/1
09			10	83	9/1
10		n-C_4H_9OH	10	80	10/1
11		CH_3OH	10	85	14/1
12		$PhCH_2OH$	10	82	9/1
13			10	84	9/1
14		C_2H_5OH	10	78	12/1
15		CH_3OH	10	87	14/1
16			10	85	11/1
17		$PhCH_2OH$	10	83	9/1
18		CH_3OH	10	85	15/1
19			10	85	12/1
20		$PhCH_2OH$	10	80	10/1

a. Isolated yield.
b. The α/β ratio was determined by 300 MHz ^1H NMR spectroscopy.



Scheme 2.

Table 4: Microwave assisted Glycosylation of benzyl alcohol with D-glucose catalysed be recycled montmorillonite K-10

Number of recycle Ratio[b](%)	Yield,[a]	α/β
1	79	9/1
2	78	9/1
3	76	9/1

[a]Isolated yield. [b]The α/β ratio was determined by 300 MHz ^{1}H NMR spectroscopy.

eco-friendly and found as reusable catalyst. Another advantage of the method is that it is very fast (only 10 minutes is required). As mentioned above, methyl, allyl and benzyl glycosides are very useful precursor for the synthesis of oligosacharides and other glycoconjugates.

In conclusion, we have developed an ecofriendly, inexpensive and fast method of Fischer glycosylation catalyzed by montmorillonite K-10 under microwave radiation. One notable advantage of the method is that the catalyst is reusable.

EXPERIMENTAL

General Methods

Melting points were recorded on a Buchi melting point apparatus with open capillary method and are unconnected. Specific rotations were recorded on a Perkin Elmer polarimeter model 343 at sodium light of wavelength 589 nm. IR spectra were recorded on a Perkin Elmer system 2000 FT-IR Spectrometer. All NMR spectra were recorded on a Bruker Avance DPX300 operated at 300 MHz. Chemical shifts are given in parts per million (ppm) and referenced to internal 0.03% TMS. Positive Electro-Spray Ionization mass spectra [(+)-ESIMS] were recorded on Bruker Esquire 3000 Iontrap Mass spectrometer. Elemental analysis was done on a Perkin Elmer Series II 2400 CHNS/O Micro Elemental Analyzer. Prolabo Synthwave Microwave reactor 402 with temperature programmer was used for reactions under microwave irradiation. Buchi rotary evaporator was used for distillation under reduced pressure. Silica gel G was used for TLC and silica gel (60–120 mesh) was used for column chromatography. All solvents used were distilled prior to use.

General Procedure for Glycosylation under Microwave Irradiation

Monosacharide (500 mg) and Montmorillonite K10 (250 mg) were mixed thoroughly in a mortar. The mixture was then placed in a quartz reaction vessel of Prolabo Synthwave Microwave reactor 402. To it, 5 mL of an alcohol was added and the mixture was allowed to react under microwave irradiation at a

temperature of 90°C for 10 minutes. During the reaction the temperature was not allowed to rise above 90°C by setting the programmer. The reaction mixture was then cooled and filtered. The residue was washed with methanol. The combined filtrate and washings were distilled under reduced pressure with a rotary evaporator to get the product. Product was crystallized from isopropanol and characterized by ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), ESIMS, IR spectroscopy and elemental analysis and direct comparison with that of authenticated compound.

Procedure for Reaction between D-Glucopyranose and Glycerol

D-glucopyranose (180 mg, 1 mmol), glycerol (920 mg, 10 mmol) and montmorillonite K-10 (90 mg) were mixed thoroughly in a morter and then the mixture was placed in a quartz reaction vessel of Prolabo Synthwave Microwave reactor 402. Then the mixture was allowed to react under microwave irradiation at a temperature of 90°C for 10 minutes. During the reaction, the temperature was not allowed to rise above 90°C by setting the programmer. After cooling the reaction mixture to room temperature, 5 mL of acetic anhydride was added to it and stirred for 3 hours. Chloroform (100 mL) was then added to it and filtered. Solid was washed with chloroform (10 mL). The combined filtrate and washings were washed with water (3 × 10 mL) and dried over anhydrous sodium sulfate. Solvent was distilled under reduced pressure to obtain a crude, which was chromatographed over a column of silica gel using ethyl acetate-hexane (1:3) to get two major product **3a** (227 mg, 45%) and **3b** (75 mg, 15%) and a minor product **3c** (48 mg, 6%).

*Spectral data of 1-(2,3,4,6-Tetraacetyl-α-D-glucopyranosyl)-2,3-diacetylglycerol **3a***

Gummy, $[\alpha]_D^{32}$+169.05° ($CHCl_3$, c 0.5); IR ($CHCl_3$)ν cm^{-1}: 2958, 2850, 1747, 1435, 1371, 1226, 1167, 1040, 957, 889, 768, 601; ^{1}H NMR (300 MHz) in $CDCl_3$: δ 5.43 (dt, 1H, $J_{1'b,2'} = J_{2'3'a} = 9.6$ Hz, $J_{1'a,2'} = 1.2$ Hz, H-2′), 5.17 (dd, 1H, $J_{3,4} = 10$ Hz, $J_{4,5} = 8.4$ Hz, H-4), 5.09 (d, 1H, $J_{1,2} = 3.2$ Hz, H-1), 5.04 (t, 1H, $J_{2,3} = J_{3,4} = 10$Hz, H-3), 4.84 (dd, 1H, $J_{2,3} = 10.0$Hz, $J_{1,2} = 3.2$ Hz, H-2) 4.32 (m, 1H, H-3′.a), 4.25 (m, 1H, H-3′b), 4.22 (dd, 1H, $J_{6a,6b} = 11$ Hz, $J_{5,6a} = 2.4$ Hz, H-6a), 4.12 (dd, 1H, $J_{6a,6b} = 11$ Hz, $J_{5,6b} = 4.8$ Hz, H-6b), 4.02(m, 1H, H-1′a), 3.81(m, 1H, H-1′b), 3.62 (ddd, 1H, $J_{4,5} = 8.4$ Hz, $J_{5,6a} = 2.4$ Hz, $J_{5,6b} = 4.8$ Hz, H-5) 2.09(s,3H, CH_3-CO), 2.08(s, 3H, CH_3-CO), 2.07(s,3H, CH_3-CO), 2.06(s, 3H, CH_3-CO), 2.03(s, 3H, CH_3-CO), 2.01(s, 3H, CH_3-CO); ^{13}C NMR (75 MHz) in $CDCl_3$: δ 169.96 (C=O), 169.95 (C=O),169.92 (C=O), 169.81 (C=O), 169.72 (C=O), 169.59 (C=O), 94.95 (C-1), 70.53 (C-2′), 69.24 (C-2), 68.61 (C-1′), 67.25 (C-3′), 65.85 (C-3), 65.73 (C-5), 62.59 (C-4), 61.82 (C-6), 21.80 (CH_3-CO), 20.75 (CH_3-CO), 20.73 (CH_3-CO), 20.65 (CH_3-CO), 20.55 (CH_3-CO), 21.41 (CH_3-CO); (+)-ESIMS for $C_{21}H_{30}O_{14}$ (M, 506): m/z 529.13 $[M+Na]^+$, 507.16 $[M+H]^+$, Anal, calcd. for $C_{21}H_{30}O_{14}$: C, 49.80%; H, 5.97%. Found C, 49.70%; H, 5.84%.

Spectral data of 1-(2,3,4,6-Tetraacetyl-β-D-glucopyranosyl)-2,3-diacetylglycerol ***3b***

mp 106–107°C (reported[16] 107–108°C); $[\alpha]_D^{32}$–35.1° ($CHCl_3$, c 0.5); IR ($CHCl_3$) νcm^1: 2952, 2856, 1741, 1435, 1366, 1226, 1161, 1045, 955, 888, 757, 607; ^1H NMR (300 MHz) in $CDCl_3$: δ 5.18 (m,1H, H-2′), 5.17 (dd, 1H, $J_{2,3}$ = 9.9 Hz, $J_{3,4}$ = 9.6 Hz, H-3), 5.07 (dd, 1H, $J_{2,3}$ =9.8 Hz, $J_{1,2}$ = 7.2 Hz, H-2), 4.98 (d, 1H, $J_{4,5}$ =9.2 Hz, $J_{3,4}$ = 9.6 Hz, H-4), 4.52 (d, 1H, J=7.2 Hz, H-1), 4.32 (m, 2H, H-3′), 4.25 (dd, 1H, $J_{6a,6b}$ = 12.3 Hz, $J_{5,6a}$ = 4.6 Hz, H-6a), 4.12 (dd, 1H, $J_{6a,6b}$ = 12.2 Hz, $J_{5,6b}$ = 2.6 Hz, H-6b), 3.92 (ddd, 1H, $J_{4,5}$ = 9.2 Hz, $J_{5,6a}$ = 4.7 Hz, $J_{5,6b}$ = 2.6 Hz, H-5), 3.68 (m, 2H, H-1′), 2.10(s, 3H, C*H*$_3$-CO), 2.09(s, 3H, C*H*$_3$-CO), 2.085 (s, 3H, C*H*$_3$-CO), 2.08(s, 3H, C*H*$_3$-CO), 2.03(s, 3H, C*H*$_3$-CO), 2.01(s, 3H, C*H*$_3$-CO). ^{13}C NMR (75 MHz) in $CDCl_3$: δ170.12 (C=O), 170.0 (C=O), 169.90 (C=O), 169.83 (C=O), 169.75 (C=O), 169.59 (CO), 95.57 (C-1), 72.96 (C-2), 71.88 (C-1′), 70.53 (C-3′), 70.52 (C-2′), 68.61 (C-4), 65.73 (C-3), 62.59 (C-5), 61.82 (C-6), 21.41 (C*H*$_3$-CO), 20.80 (C*H*$_3$-CO), 20.78 (C*H*$_3$-CO), 20.74 (C*H*$_3$-CO), 20.67 (C*H*$_3$-CO), 20.52 (C*H*$_3$-CO); (+)-ESIMS for $C_{21}H_{30}O_{14}$ (M, 506): m/z 531.15 $[M+2H+Na]^+$, 507.16 $[M+H]^+$, Anal, calcd. for $C_{21}H_{30}O_{14}$: C, 49.80%; H, 5.97%. Found C, 49.67%; H, 5.81%.

Spectral data of 1,3-Bis (2,3,4,6-tetraacetyl-D-glucopyranosyl)-2-acetylglycerol ***3c***

Gummy; $[\alpha]_D^{32}$+17.1° ($CHCl_3$, c 0.5); IR ($CHCl_3$)νcm^{-1}: 2980, 2850, 1715, 1410, 1250; ^1H NMR (300 MHz) in $CDCl_3$: δ 5.46 (m, 1H, H-2′), 5.30 (m, 1H), 5.22–5.01 (m, 5H), 4.33–4.08 (m, 8H), 3.85–3.54 (m, 4H), 2.13 (s, 3H, C*H*$_3$-CO), 2.085 (s, 3H, C*H*$_3$-CO), 2.10 (s, 3H, C*H*$_3$-CO), 2.096 (s, 3H, C*H*$_3$-CO), 2.08 (s, 3H, C*H*$_3$-CO), 2.06 (s, 3H, C*H*$_3$-CO), 2.03 (s, 3H, C*H*$_3$-CO), 2.02 (s, 3H, C*H*$_3$-CO), 2.01 (s, 3H, C*H*$_3$-CO); ^{13}C NMR (75 MHz) in $CDCl_3$: .δ 170, 169.95, 169.33, 169.50 (9 C=O), 100.10 (C-1, C-1′), 71.01 (C-1″ and C-3″), 70.80 (C-2″), 69.63, 69.15, 68.33, 68.12 (6>*C*HO-Ac), 64.07 (C-5, C-5.′), 61.40 (2-*C*H$_2$OAc, C-6, C-6′), 21.41, 20.85, 20.78, 20.71, 20.53 (9 *C*H$_3$-CO); (+)-ESIMS for $C_{33}H_{46}O_{22}$ (M, 794): m/z 817.24 $[M+Na]^+$, 795.26 $[M+H]^+$; Anal, calcd for $C_{33}H_{46}O_{22}$: C, 49.87%; H, 5.83%. Found : C, 49.99%; H, 5.70%.

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