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Carbohydrate Research 337 (2002) 613–619

CARBOHYDRATE RESEARCH

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Note

Direct regioselective 2-*O*-(*p*-toluenesulfonylation) of sucrose

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Received 4 December 2001; accepted 6 February 2002

Abstract

2-*O*-(*p*-Toluenesulfonyl)sucrose was regioselectively synthesized by direct *p*-toluenesulfonylation of sucrose using *N*-(*p*-toluenesulfonyl)imidazole in the presence of molecular sieves at 40 °C. The reactivities of the sucrose hydroxy groups toward this sulfonylation increased in the order as follows: OH-2 ≫ OH-1′ > OH-3′ > OH-6 > OH-6′. These results were diametrically opposite to the expected sulfonylation with *p*-toluenesulfonyl chloride in pyridine, for which the reactivity increased in the order as follows: OH-6′, OH-6 ≫ OH-1′ > OH-2. The desired 2-*O*-(*p*-toluenesulfonyl)sucrose was readily isolated by simple open reversed-phase column chromatography, followed by recrystallization, thus overcoming the main difficulties associated with regioselectivity, efficiency, and isolation techniques for the practical preparation.

Keywords: Sucrose; Regioselective sulfonylation; *p*-Toluenesulfonylation; Tosylation; Sulfonyl imidazole; Molecular sieves

Due to its availability in large quantities and the fact that it lends itself to biodegradation, sucrose and its derivatives are of interest as potentially useful substrates in the chemical and biological fields. To improve the function of these sucrose derivatives with new and attractive characteristics, structural modifications of sucrose have been extensively investigated. However, in spite of these efforts, direct regioselective chemical modification is often limited since sucrose has three primary hydroxy groups (C-6, C-1′, and C-6′ positions) and five secondary hydroxy groups (C-2, C-3, C-4, C-3′, and C-4′ positions). Selective protection and deprotection of the hydroxy groups is necessary for regioselective modification, and consequently, simple methods are required for the practical production of sucrose derivatives.

Within sucrose chemistry, sulfonylation has been extensively utilized to effectively functionalize the hydroxy groups. However, control of the specific positions and degrees of sulfonylation of sucrose are limited due to the various hydroxy groups. Starting with a report from 1950 describing the synthesis of tri-*O*-(*p*-toluenesulfonyl)sucrose using three molar equivalents of *p*-toluenesulfonyl chloride in pyridine,[1] regioselective sulfonylation of sucrose has been extensively investigated. Lemieux and Barrette[2] reported that *p*-toluenesulfonylation of sucrose using three molar equivalents of *p*-toluenesulfonyl chloride in pyridine resulted in a mixture of products containing penta-, tetra-, tri-, and di-*O*-(*p*-toluenesulfonyl)sucroses in the molar ratio of 0.05:0.33:1:1, respectively, and furthermore, 6,1′,6′-tri- and 6,6′-di-*O*-(*p*-toluenesulfonyl)sucroses were afforded in 29 and 12% yields, respectively. It was shown that by using two molar equivalents of *p*-toluenesulfonyl chloride in pyridine, 6,1′, 6′-tri- and 6,6′-di-*O*-(*p*-toluenesulfonyl)sucroses were obtained in 25 and 21% yields, respectively.[2] Jezo[3] reported that *p*-toluenesulfonylation with one molar equivalent of *p*-toluenesulfonyl chloride in pyridine afforded 6-mono-*O*-(*p*-toluenesulfonyl) and 6,6′-di-*O*-(*p*-toluenesulfonyl)sucroses in 66 and 8.9% yields, respectively. Ball et al.[4] reported that three molar equivalents of *p*-toluenesulfonylation of sucrose in pyridine at −20 °C gave 6,1′,6′-tri-*O*-(*p*-toluenesulfonyl)sucrose as the major and 2,6,6′-tri-*O*-(*p*-toluenesulfonyl)sucrose as the minor tri-*O*-(*p*-toluenesulfonyl) isomers. Ballard et al.[5] reported that four molar equivalents of *p*-toluenesulfonyl chloride in pyridine resulting in 6,1′,6′-tri-*O*-(*p*-toluenesulfonyl)sucrose in 33% yield and minor *O*-(*p*-toluenesulfonyl) isomers, which contained 2,6,1′,6′-tetra-*O*-(*p*-toluenesulfonyl)sucrose. Hough et al.[6] and Ball et al.[4] reported the use of

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0008-6215/02/$ - see front matter
PII: S0008-6215(02)00039-3

mesitylenesulfonyl chloride as an alternative for *p*-toluenesulfonyl chloride to effectively afford 6,1′,6′-tri-*O*-mesitylenesulfonylsucrose, and subsequently, 6,1′,6′-tri-*O*-mesitylenesulfonyl-2-*O*-(*p*-toluenesulfonyl)-sucrose was synthesized from 6,1′,6′-tri-*O*-mesitylenesulfonylsucrose in 55% yield by Ballard et al.[5] Consequently, Almquist et al.[7] successfully synthesized 6,1′,6′-tri-*O*-(2,4,6-triisopropylbenzenesulfonyl)sucrose in 54% yield by treatment of sucrose with 2,4,6-tri-isopropylbenzenesulfonyl chloride in pyridine. The reactivities of the hydroxy groups of sucrose among the preceding investigations on the sulfonylation of sucrose increased in the order as follows: OH-6, OH-6′ > OH-1′ > OH-2 > other secondary hydroxy groups.

Preparation of *O*-sulfonylsucrose has been extensively applied to functionalize the secondary hydroxy groups of sucrose. However, despite its wide usage, the sulfonylation of the secondary hydroxy group(s) of sucrose has yet to be fully developed as a direct regioselective reaction. Protection of the hydroxy groups at C-6, C-1′, and C-6′ has been used to selectively sulfonate the secondary hydroxy group(s). Khan et al.[8] has reported the synthesis of *ribo*-3′,4′- and *lyxo*-3′,4′-epoxysucroses using regioselective sulfonylation of protected sucroses. Furthermore, the *ribo*-3′,4′-epoxysucrose was used in the synthesis of 2,3′-anhydrosucrose.[9] In 1986, regioselective *p*-toluenesulfonylation of 6,1′,6′-tri-*O*-tritylsucrose[10] with one molar equivalent of *p*-toluenesulfonyl chloride in pyridine afforded 2-*O*-(*p*-toluenesulfonyl)-6,1′,6′-tri-*O*-tritylsucrose in 52% yield, followed by the preparation of the 2,3-*manno* epoxy derivative.[11]

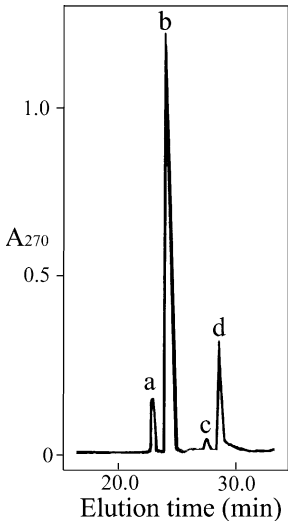
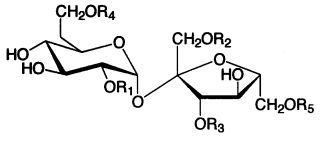


Fig. 1. Reversed-phase analytical HPLC chromatogram (Fuji Silysia Chromatorex-ODS DU0005MT column) of a mixture of *O*-(*p*-toluenesulfonyl)sucroses obtained by the reaction of sucrose with *N*-(*p*-toluensulfonyl)imidazole in the presence of 4A molecular sieves in DMF. Elution was done with 0:100 through 25:75 MeOH–H_2O for 10 min, 45:55 MeOH–H_2O for 30 min, and 100:0 MeOH–H_2O for 10 min; flow rate of 0.8 mL/min. Peak **a**: sulfonylsucrose **3**; peak **b**: sulfonylsucrose **1**; peak **c**: sulfonylsucrose **4** and **5**; peak **d**: sulfonylsucrose **2**.



	R_1	R_2	R_3	R_4	R_5
1	Ts	H	H	H	H
2	H	Ts	H	H	H
3	H	H	Ts	H	H
4	H	H	H	Ts	H
5	H	H	H	H	Ts

Fig. 2. Chemical structure of *O*-(*p*-toluenesulfonyl)sucroses.

N-(*p*-Toluenesulfonyl)imidazole[12] has been used in the saccharide chemistry for selective *p*-toluenesulfonylations.[13] In studies of synthesis of methyl 4,6-benzylidene-2-*O*-(*p*-toluenesulfonyl)-α-D-glucopyranoside[13a] and 2-*O*-(*p*-toluenesulfonyl)-heptakis[6-*O*-(*tert*-butyldimethylsilyl)]-β-cyclodextrin,[13b] protection of the C-6 hydroxy groups was needed for selective *p*-toluenesulfonylations of the C-2 hydroxy groups. Recently, well-designed reactions of the cyclodextrins with sulfonylimidazole reagents and molecular sieves in *N*,*N*-dimethylformamide (DMF) for the regioselective sulfonylation of the C-2 hydroxy group without protection of the C-6 hydroxy groups have been reported[14] and have proven to be especially useful since the mild non-alkaline reaction conditions do not induce the decomposition of the sulfonates, and since the reactions are independent of the type of sulfonyl group. Although the direct regioselective sulfonylation of the secondary hydroxy groups of sucrose has been a challenge within sucrose chemistry, this paper describes herein the direct regioselective sulfonylation of the C-2 hydroxy group of sucrose using *N*-(*p*-toluenesulfonyl)imidazole and molecular sieves.

1. Results and discussion

A mixture of sucrose, one molar equivalent of *N*-(*p*-toluenesulfonyl)imidazole, freshly activated powdered 4A molecular sieves (300% w/w, on the basis of sucrose) in DMF was stirred at 40 °C for 90 days. The reaction was monitored using reversed-phase HPLC until the starting material, *N*-(*p*-toluenesulfonyl)-imidazole, was determined to be exhausted. HPLC analysis of the final reaction mixture (Fig. 1), as compared to those of pure mono-*O*-(*p*-toluenesulfonyl)-sucroses **1**–**5** (Fig. 2), showed that 2-*O*-(*p*-toluenesulfonyl)sucrose (**1**) corresponds to the major HPLC signal (Fig. 1, peak **b**) in a 47% yield (Table 1, entry 1). Furthermore, 1′-*O*-(*p*-toluenesulfonyl)sucrose (**2**) and

Table 1
HPLC Yields of *O*-(*p*-toluenesulfonyl)sucroses in the sulfonylation of sucrose [a]

Entry no.	Reagent	Solvent	Temperature (°C)	Time	HPLC Yields of *p*-toluenesulfonylsucroses (%)			
					1	**2**	**3**	**4** and **5**
1	TsIm + MS	DMF	40	90 d	47	10	3.4	0.6 (**4**/**5** 1:0.47) [b]
2	TsIm + MS	DMF	60	15 d	30	6.6	2.1	0.5 (**4**/**5** 1:0.47) [b]
3	TsIm	DMF	40	20 d	0	0	0	0
4	TsIm + MS	DMSO	40	90 d	45	10	2.7	1.0 (**4**/**5** 1:0.5) [b]
5	TsIm	DMSO	40	30 d	0	0	0	0
6	TsCl + MS	DMF	40	7 d	0	0	0	0
7	TsCl	Pyridine	0	6 h	1.9	3.8	0	24 (**4**/**5** 1:1.7) [b]

[a] HPLC yields were determined on the basis of pure sulfonylsucroses **1**–**5**. The sulfonylations were carried out using *N*-(*p*-toluenesulfonyl)imidazole (TsIm), or *p*-toluenesulfonyl chloride (TsCl), with or without powdered 4A molecular sieves (MS) in *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), or anhydrous pyridine. For entries 3 and 5, anhydrous DMF or anhydrous DMSO was used.

[b] Ratio values, in parentheses, were determined by ^{1}H NMR analysis.

3′-*O*-(*p*-toluenesulfonyl)sucrose (**3**), which correspond to HPLC peaks **d** and **a** (Fig. 1), respectively, were afforded as minor mono-*O*-(*p*-toluenesulfonyl) isomers in 10 and 3.4% yields, respectively. The smallest HPLC signal (Fig. 1, peak **c**) was identified as a mixture of 6-*O*-(*p*-toluenesulfonyl)sucrose (**4**) and 6′-*O*-(*p*-toluenesulfonyl)sucrose (**5**) in a combined yield of 0.6%. It is important to note that the final ratio of the sulfonylsucroses **1**–**5**, as determined by HPLC analysis, was unchanged from the beginning of the reaction.

In the purification step, the molecular sieves were removed from the reaction mixture by filtration, and the filtrate was concentrated under reduced pressure, then dissolved in water. The aqueous solution was purified by chromatography using a simple open reversed-phase column to yield a mixture of sulfonylsucroses **1**–**5** in 56% yield. The 2-*O*-sulfonylsucrose (**1**) was isolated by recrystallization as a pure compound in 38% yield, based on sucrose, and therefore the main difficulties associated with the regioselectivity, efficiency, and isolation techniques for practical the preparation of 2-*O*-sulfonylsucrose (**1**) were successfully overcome. Reversed-phase preparative HPLC chromatography of the remaining sulfonylsucroses **2**–**5** provided pure sulfonylsucroses **2** and **3**, and a mixture of sulfonylsucroses **4** and **5**, which could not be further separated. Unreacted sucrose was detected, since the use of one molar equivalent of *N*-(*p*-toluenesulfonyl)imidazole resulted in the production of di- and multi-sulfonylsucroses.

Sulfonylsucroses **1**–**5** were fully characterized using FAB mass spectrometry and ^{1}H and ^{13}C NMR spectroscopy. The FAB mass spectra of sulfonylsucroses **1**–**5** exhibited molecular ions $[M + H]^+$ at m/z 497. The chemical shifts of the ^{1}H and ^{13}C NMR spectra of sulfonylsucroses **1**–**5** are shown in Tables 2 and 3. Spectral assignments of sulfonylsucroses **1**–**5** were performed using ^{1}H–^{1}H COSY, ^{1}H–^{13}C COSY, and DEPT techniques. For 2-*O*-sulfonylsucrose (**1**), the ^{1}H NMR signals for H-1, H-2, and H-3 protons shifted downfield by 5.36, 3.89, and 3.63 ppm, respectively, in comparison to the spectrum of sucrose. In particular, the H-2 proton exhibited a larger downfield shift than that of the H-1 and H-3 protons. It has been reported that the ^{13}C chemical shifts of the α-carbons of sulfonylated hydroxy groups show downfield shifts of 6–14 ppm, and upfield shifts of 2–3 ppm occur for β-carbons.[15] For 2-*O*-sulfonylsucrose (**1**), the ^{13}C chemical shift of the C-2 carbon demonstrated a downfield shift, whereas those of C-1 and C-3 carbons exhibited upfield shifts. These ^{1}H and ^{13}C NMR data indicate that the sulfonyl group of **1** is attached to the C-2 oxygen of the sucrose molecule. For sulfonylsucroses **2**–**5**, the signals for the H-1′ proton of **2**, H-3′ proton of **3**, H-6 proton of **4**, and H-6′ proton of **5** show large downfield shifts by 3.97–4.00, 4.90, 4.03–4.09, and 4.08–4.35 ppm, respectively, in comparison with the spectra for sucrose. Signals for the C-1′ carbon of **2**, the C-3′ carbon of **3**, the C-6 carbon of **4**, and the C-6′ carbon of **5** show large downfield shifts of 67.73, 83.03, 69.97, and 72.37 ppm, respectively, in comparison with the data for sucrose. Using these data, the minor sulfonylsucroses **2**–**5** were assigned as 1′-*O*-, 3′-*O*-, 6-*O*-, and 6′-*O*-(*p*-toluenesulfonyl)sucroses, respectively.

In an attempt to shorten the reaction time, *p*-toluenesulfonylation of sucrose using one molar equivalent of *N*-(*p*-toluenesulfonyl)imidazole was carried out in DMF at 60 °C in the presence of freshly activated powdered 4A molecular sieves. However, although the product ratio of sulfonylsucroses **1**–**5** was similar to that at 40 °C, the yields of sulfonylsucroses **1**–**5** decreased (Table 1, entry 2). In comparison, *p*-toluenesul-

fonylation of sucrose in dimethyl sulfoxide (DMSO) at 40 °C resulted in similar yields and product ratio of sulfonylsucroses **1**–**5** to those of DMF at 40 °C (Table 1, entry 4). However, due to its high boiling point, the use of DMSO introduces an additional complication during the final purification procedures. Among the reaction solvents used, DMF appears to be optimal for the *p*-toluenesulfonylation of the C-2 hydroxy group of sucrose. Interestingly, when the reaction was carried out without the molecular sieves in anhydrous DMF, the sulfonyl products were not afforded; furthermore, the starting sucrose and *N*-(*p*-toluenesulfonyl)imidazole were recovered (Table 1, entry 3), which indicate the necessity of the molecular sieves for the present *p*-toluenesulfonylation as well as the sulfonylation of cyclodextrins, as reported by Teranishi et al.[14a]. In case of reaction without the molecular sieves in anhydrous DMSO, *N*-(*p*-toluenesulfonyl)imidazole decomposed and resulted in no sulfonylsucroses (Table 1, entry 5). Although the quantity of molecular sieves did not seem to influence the regioselectivity of the sulfonylation, an increase in the amount of molecular sieves did decrease the reaction time required for sulfonylation. It was found that 4A molecular sieves (300% w/w, on the basis of sucrose) in sucrose–DMF solution (0.292 M) was suitable while maintaining effective stirring of the reaction mixture. It is important to note that using *p*-toluenesulfonyl chloride instead of *N*-(*p*-toluenesulfonyl)-imidazole in DMF, in the presence of molecular sieves, resulted in the decomposition of *p*-toluenesulfonyl chloride and therefore did not afford any sulfonylsucroses (Table 1, entry 6). Therefore, a combination of *N*-(*p*-

Table 2
^{1}H NMR chemical shifts (δ, ppm) and coupling constants (J, Hz) of *O*-(*p*-toluenesulfonyl)sucroses **1**–**5** [a]

H-No.	Sucrose	**1**	**2**	**3**	**4**	**5**
H-1	5.17 (d, 3.7)	5.36 (d, 3.7)	5.09 (d, 3.7)	5.17 (d, 3.7)	5.07 (d, 3.7)	4.91 (d, 3.7)
H-2	3.18 (dd, 3.7, 9.8)	3.89 (dd, 3.7, 9.8)	3.14 (dd, 3.7, 9.8)	3.18 (dd, 3.7, 9.7)	3.09 (dd, 3.7, 9.8)	3.08 (dd, 3.7, 9.2)
H-3	3.46 (t, 9.8)	3.63 (t, 9.8)	3.38 (t, 9.8)	3.37 (t, 9.7)	3.39 (t, 9.8)	3.38 (t, 9.2)
H-4	3.11 (t, 9.8)	3.13 (t, 9.8)	3.10 (t, 9.8)	3.16 (t, 9.7)	2.99 (t, 9.8)	2.97 (t, 9.2)
H-5	3.64 (m)	3.70 (m)	3.62 (m)	3.65 (m)	3.85 (m)	3.53 (m)
H-6	3.45–3.60 (m)	3.50–3.65 (m)	3.45–3.55 (m)	3.45–3.55 (m)	4.03 (dd, 4.9, 10.4) 4.09 (m)	3.40–3.60 (m)
H-1′	3.38 (d, 12.2) 3.41 (d, 12.2)	3.25 (d, 12.2) 3.34 (d, 12.2)	3.97 (d, 11.0) 4.00 (d, 11.0)	3.14 (d, 12.2) 3.29 (d, 12.2)	3.42–3.46	3.42–3.46
H-3′	3.87 (d, 7.9)	4.01 (d, 8.5)	3.79 (d, 8.5)	4.90 (d, 7.9)	3.83 (d, 7.9)	3.83 (d, 7.9)
H-4′	3.76 (t, 7.9)	3.71 (t, 8.5)	3.76 (t, 8.5)	4.05 (t, 7.9)	3.63 (t, 7.9)	3.70 (t, 7.9)
H-5′	3.55 (m)	3.58 (m)	3.48 (m)	3.64 (m)	3.52 (m)	3.70 (m)
H-6′	3.53 (m)	3.55–3.65 (m)	3.45–3.55 (m)	3.50–3.60 (m)	3.30–3.40 (m)	4.08 (m) 4.35 (dd, 7.9, 10.4)
$PhCH_3$		2.39 (s)	2.41 (s)	2.39 (s)	2.38 (s)	2.38 (s)
PhH		7.41 (d, 7.9)	7.48 (d, 7.9)	7.42 (d, 7.9)	7.42 (d, 7.9)	7.41 (d, 7.9)
PhH		7.78 (d, 7.9)	7.76 (d, 7.9)	7.79 (d, 7.9)	7.71 (d, 7.9)	7.72 (d, 7.9)

[a] In DMSO-d_6 containing 5% D_2O at 40 °C, referred to DMSO (2.49 ppm), letters and values in parentheses are multiplicities and coupling constants, respectively.

Table 3
^{13}C NMR chemical shifts (δ, ppm) of *O*-(*p*-toluenesulfonyl)sucroses **1**–**5** [a]

C-No.	Sucrose	**1**	**2**	**3**	**4**	**5**
C-1	91.88	89.40	91.78	91.67	91.80	91.67
C-2	71.63	79.95	71.05	71.33	71.38	71.51
C-3	72.87	69.46	72.57	72.95	72.67	72.83
C-4	69.95	69.74	69.74	69.57	69.44	70.36
C-5	72.90	72.53	72.85	73.01	69.87	72.91
C-6	60.62	60.02	60.39 or 61.64	60.41	69.97	61.13 or 61.68
C-1′	62.15	60.61	67.73	62.20	62.68	61.13 or 61.68
C-2′	104.15	104.42	101.19	102.64	104.12	104.33
C-3′	77.21	74.76	75.84	83.03	76.93	76.15
C-4′	74.43	73.75	72.96	71.86	74.49	74.18
C-5′	82.57	82.85	82.80	82.14	82.87	79.26
C-6′	62.20	62.22	60.39 or 61.64	61.41	62.02	72.37
$PhCH_3$		21.21	21.04	21.29	21.32	21.32
Ph-C		128.09	127.48	127.78	127.84	127.84
Ph-C		129.85	130.10	130.01	130.33	130.33
Ph-C		132.94	132.30	133.73	132.50 or 132.35	132.50 or 132.35
Ph-C		144.85	144.90	144.84	145.13	145.10

[a] In DMSO-d_6 containing 5% D_2O at 40 °C, referred to DMSO (39.50 ppm).

toluenesulfonyl)imidazole and molecular sieves are necessary for the regioselective *p*-toluenesulfonylation of the C-2 hydroxy group of sucrose.

The predominant *p*-toluenesulfonylation of the C-6 hydroxy group of sucrose using *p*-toluenesulfonyl chloride in pyridine has been previously described by Jezo.[3] In this present study, *p*-toluenesulfonylation under similar conditions as described by Jezo was carried out to yield mono-(*p*-toluenesulfonyl)sucroses **1** (1.9%), **2** (3.8%), and a mixture of **4** and **5** (24%) (Table 1, entry 7), on the basis of HPLC analysis of the reaction mixture. The ^1H NMR spectrum of the latter mixture of the mono-(*p*-toluenesulfonyl)sucroses **4** and **5**, obtained by an open reversed-phase column chromatography of the reaction mixture, indicated the ratio of **4** and **5** as 1:1.7. These results were not in agreement with those of Jezo and indicated that the reactivities of the hydroxy groups of sucrose toward sulfonylation by *p*-toluenesulfonyl chloride in pyridine increase in the order as follows: OH-6′ > OH-6 > OH-1′ > OH-2. The ^1H NMR spectrum of the mono-(*p*-toluenesulfonyl)sucrose mixture that was obtained by an open reversed-phase column chromatography of the reaction using *N*-(*p*-toluenesulfonyl)imidazole and molecular sieves (Table 1, entry 1), indicated the ratio of sulfonylsucroses **4** and **5** as 1:0.47. Thus, sulfonylation using *N*-(*p*-toluenesulfonyl)imidazole and molecular sieves exhibited sulfonylation reactivities as increasing in the order as follows: OH-2 ≫ OH-1′ > OH-3′ > OH-6 > OH-6′, which is diametrically opposite to the sulfonylation using *p*-toluenesulfonyl chloride in pyridine. The roles of the molecular sieves and the imidazole group in the *N*-(*p*-toluenesulfonyl)imidazole molecule are currently under investigation.

2. Conclusions

The combination of *N*-(*p*-toluenesulfonyl)imidazole and molecular sieves resulted in the practical regioselective 2-*O*-(*p*-toluenesulfonylation) of sucrose, with the reactivities of the hydroxy groups in the order as follows: OH-2 ≫ OH-1′ > OH-3′ > OH-6 > OH-6′. This order is diametrically opposite to the previously reported reactivities of the hydroxy groups in sucrose toward sulfonylation. The procedures for the production and purification of the 2-*O*-(*p*-toluenesulfonyl)sucrose (**1**) described herein are simple and useful, and consequently these procedures can be further utilized toward the controlled derivation of sucrose, thus overcoming the main difficulties associated with regioselectivity, efficiency, and isolation techniques. Detailed reaction mechanisms of the present sulfonylation, such as the roles of the molecular sieves and imidazole moiety of *N*-(*p*-toluenesulfonyl)imidazole, are currently under investigation.

3. Experimental

General methods. HPLC analysis and isolation were carried using a JASCO Gulliver HPLC system equipped with a MD-910 three-dimensional UV–Vis detector. A Fuji Silysia Chromatorex-ODS DU0005MT

column (4.6 × 150 mm) was used for the HPLC analysis. Preparative HPLC chromatography was performed using a Fuji Silysia Chromatorex-ODS BU0005MT column (20 × 250 mm). Preparative, open reversed-phase column chromatography was performed using Fuji Silysia Chromatorex-ODS DM1020T gel. Thin-layer chromatography (TLC) was performed on E. Merck Kieselgel 60 F254 glass plates coated with a 0.25 mm layer of silica gel (6:1, CH_3CN–H_2O). Compounds were visualized under a UV lamp or sprayed with *p*-anisaldehyde–H_2SO_4–EtOH solution. ^1H and ^{13}C NMR spectra of sucrose and its derivatives were recorded at 40 °C using a JEOL JNM-A500 spectrometer in DMSO-d_6. ^1H and ^{13}C NMR chemical shifts were assigned on the basis of ^1H–^1H COSY, DEPT ^{13}C NMR, and ^1H–^{13}C COSY experiments. Chemical shift values are reported in δ (ppm) relative to DMSO and coupling constants (*J*) are in Hz. FAB mass spectra (positive-ion) were measured using a JEOL DX-303 instrument with glycerol as a matrix. Melting point (mp) values were measured using a Yanagimoto Seisakusho apparatus and are uncorrected. Elemental analyses were measured using a Yanaco CHN-CORDER MT-3 instrument. IR spectra were measured using a JASCO FTIR-410 spectrometer as KBr pellets. Sucrose, powdered 4A molecular sieves, *p*-toluenesulfonyl chloride, DMF, DMSO, and anhydrous DMF were purchased from Nacalai Tesque, Inc. (Kyoto, Japan). Anhydrous DMSO and anhydrous pyridine were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). *N*-(*p*-Toluenesulfonyl)imidazole and DMSO-d_6 were purchased from Aldrich Chemical Co. (St. Louis, MO, USA).

General procedure for the reactions of sucrose with some sulfonyl reagents. In the cases with molecular sieves, freshly activated powdered molecular sieves 4A (1.5 g) was added to a solution of sucrose (0.50 g, 1.46 mmol) in DMF or DMSO (5.0 mL), followed by the addition of *N*-(*p*-toluenesulfonyl)imidazole (0.32 g, 1.46 mmol) or *p*-toluenesulfonyl chloride (0.28 g, 1.47 mmol) to the corresponding mixtures. The mixtures were stirred under conditions as listed in Table 1. In the case of pyridine (Table 1, entry 7), *p*-toluenesulfonyl chloride (0.28 g, 1.47 mmol) was added to a solution of sucrose (0.50 g, 1.46 mmol) in anhydrous pyridine (5.0 mL) at 0 °C. The reactions were monitored using HPLC analysis (0:100 through 25:75 MeOH–H_2O for 10 min, 45:55 MeOH–H_2O for 30 min, and 100:0 MeOH–H_2O for 10 min; flow rate of 0.8 mL/min). When the sulfonyl reagents were determined to be exhausted, HPLC analysis of the reaction mixture, using elution conditions as listed above, confirmed the yields of sulfonylsucroses **1**–**5**, in comparison with pure sulfonylsucroses **1**–**3** and a mixture of sulfonylsucroses **4** and **5**. After removing the molecular sieves by filtration, the filtrate was concentrated under reduced pressure, and the residue was then subjected to preparative, open reversed-phase column chromatography (15 × 120 mm; elution: H_2O to 35:65 MeOH–H_2O). The fractions containing the mono-*O*-(*p*-toluenesulfonyl)sucroses were concentrated, followed by ^1H NMR analyses (DMSO-d_6, 40 °C) to confirm the structure and ratio of the sulfonylsucroses.

2-O-(p-*Toluenesulfonyl)sucrose* (***1***), *1′*-O-(p-*toluenesulfonyl)sucrose* (***2***), *3′*-O-(p-*toluenesulfonyl)sucrose* (***3***), *6*-O-(p-*toluenesulfonyl)sucrose* (***4***), *and 6′*-O-(p-*toluenesulfonyl)sucrose* (***5***). To a solution of sucrose (10 g, 29.2 mmol) in DMF (100 mL) was added freshly activated powdered 4A molecular sieves (30 g), followed by the addition of *N*-(*p*-toluenesulfonyl)imidazole (6.48 g, 29.2 mmol). The mixture was stirred at 40 °C for 90 days. Molecular sieves were removed by filtration, and the resulting filtrate was concentrated under reduced pressure to dryness. The residue was subjected to preparative open reversed-phase column chromatography (45 × 150 mm; elution: H_2O to 35:65 MeOH–H_2O) to give a mixture of *O*-(*p*-toluenesulfonyl)sucroses **1**–**5** (8.10 g). The mixture was dissolved in MeOH (20 mL), poured into Et_2O (500 mL), and the resulting powder was filtrated to afford a solid containing sulfonylsucroses **1**–**5** (7.40 g). Based on HPLC analyses, the relative quantities of the regioisomers in the solid were: **1** (84%), **2** (10%), **3** (3.9%), **4** and **5** (1.5%). The solid (7.40 g) was recrystallized from CH_3CN (740 mL) to afford pure sulfonylsucrose **1** as colorless needles (5.48 g, 38% yield based on sucrose). A portion of the filtrate containing sulfonylsucroses **1**–**5** was purified by preparative HPLC chromatography (35:65 MeOH–H_2O) to give pure sulfonylsucroses **1**–**3** and a mixture of **4** and **5**.

Data for **1**: colorless needles; mp 156–157 °C; R_f 0.46 (6:1, CH_3CN–H_2O); IR (KBr) *v* 3398, 2929, 1598, 1358, and 1174 cm^{-1}; FABMS *m/z* 497 $[M+H]^+$; Anal. Calcd for $C_{19}H_{28}O_{13}S$: C, 45.96; H, 5.68. Found: C, 45.91; H, 5.73.

Data for **2**: colorless solid; R_f 0.46 (6:1, CH_3CN–H_2O); IR (KBr) *v* 3349, 2932, 1599, 1356, and 1174 cm^{-1}; FABMS *m/z* 497 $[M+H]^+$; Anal. Calcd for $C_{19}H_{28}O_{13}S$: C, 45.96; H, 5.68. Found: C, 45.74; H, 5.92.

Data for **3**: colorless solid; R_f 0.46 (6:1, CH_3CN–H_2O); IR (KBr) *v* 3356, 2932, 1598, 1357, and 1175 cm^{-1}; FABMS *m/z* 497 $[M+H]^+$; Anal. Calcd for $C_{19}H_{28}O_{13}S$: C, 45.96; H, 5.68. Found: C, 45.55; H, 5.97.

Data for the mixture of **4** and **5**: colorless solid; R_f 0.46 (6:1, CH_3CN–H_2O); IR (KBr) *v* 3397, 2928, 1598, 1356, and 1177 cm^{-1}; FABMS *m/z* 497 $[M+H]^+$; Anal. Calcd for $C_{19}H_{28}O_{13}S$: C, 45.96; H, 5.68. Found: C, 45.63; H, 5.86.

Acknowledgements

I am grateful for Assistance Programs by the Agriculture and Livestock Industries Corporation of Japan and Grant-in-Aid for Scientific Research on Priority Areas (A) (No. 13024241) and Grant-in-Aid for Scientific Research (C) (No. 11660106) from the Japanese Ministry of Education, Science, and Culture. The NMR instrument used in this research was installed at Cooperative Research Center of Mie University.

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