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A rapid and convenient synthesis of α and β forms of acetylated derivatives of sugars under microwave irradiation

Basanagoud S Patil & Vommina V Suresh Babu*

Department of Studies in Chemistry, Central College Campus, Bangalore University,
Dr. B. R. Ambedkar Veedhi, Bangalore 560 001, India.
Email: haricch@rediffmail.com

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In a novel method, the synthesis of α and β forms of penta as well as octa acetyl derivatives of several sugars under microwave irradiation with improved yields is described.

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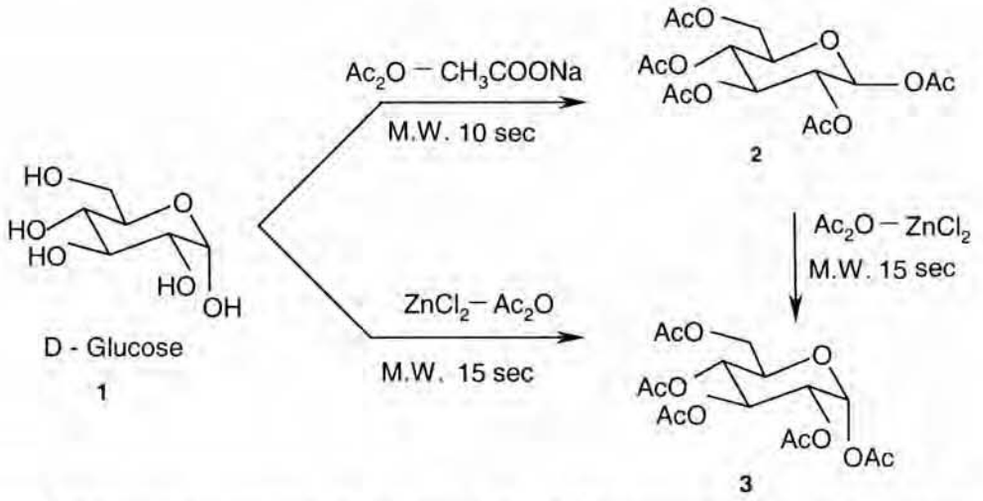
Acetylation is among one of the most important reactions employed in carbohydrate chemistry. The commonly used and well established protocol involve the use of acetic anhydride (Ac_2O) to carry out acetylation[1]. The hydroxyl groups at both the anomeric and non-anomeric carbon atoms can be readily acetylated. The reaction has to be carried out in presence of H_2SO_4[2] or pyridine[3]. But, the acetylation of D-glucose in presence of zinc chloride ($ZnCl_2$) gives the penta acetate 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranose. Similarly, the corresponding β-anomer can be obtained when the reaction is carried by the Libermann's method using sodium acetate (CH_3COONa)[4]. Further, the heating of β-anomer in presence of $Ac_2O/ZnCl_2$ results in its conversion to the corresponding α-anomer[5]. All these reactions, conventionally, have to be carried out using ten equivalents of Ac_2O on a boiling water bath for about 1-2 hr to isolate the penta acetate derivative in about 56 to 72% yield[6].

Microwave-assisted reactions have attracted much interest because of the simplicity in operation, greater selectivity and rapid synthesis of a variety of organic compounds[7-11]. The effects usually observed are 1) enhanced reaction rates, 2) formation of pure products in high yields and 3) cleaner reactions with easier work-up. Some of the microwave-assisted reactions reported in the carbohydrate synthesis include the reactions of phenols and alcohols with tri-*O*-acetyl-D-glucal[12], saponification of peracetylated glycosides using KOH impregnated onto alumina in dry media[13], *etc*. The direct acetylation of primary, secondary alcohols and phenols using zeolites HSZ-360[14] as well as microwave-mediated acetylation using Ac_2O in presence of iodine or montmorillonite k-10[15] have also been described. Acetylation of hydroxy, thiol and amino groups in solvent free conditions employing Ac_2O-pyridine over basic alumina under microwave-irradiation have been described recently[16].

We report herein the synthesis of α and β forms of penta- and octa-acetylated derivatives of sugars under microwave-irradiation (**Scheme I**). The reactions were carried out in a commercial, unmodified domestic LG make microwave oven (2450 MHz) at 60 % of its power. In a typical reaction[17], a mixture of D-glucose, Ac_2O (six equivalents) and CH_3COONa (two equivalents) in a conical flask was placed in a microwave oven and irradiated for 10 sec to yield β-anomer of 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose. The use of $ZnCl_2$ (0.25 equivalent) in place of CH_3COONa resulted in the isolation of the α-anomer. Also, the irradiation of β-anomer in presence of Ac_2O (six equivalents) –$ZnCl_2$ (0.25 equivalents) lead to its conversion to the α-anomer. In all the three cases, about 75 to 94 % of the product was isolated (**Table I**), which is about 20–30% increase in yield when compared with the literature yield[6]. In the case of the conventional and routinely employed procedure under thermal heating, the reaction mixture has to be heated to about 80-100°C for 1-2 hr. In the present protocol, the reaction was found to be complete in 10 sec in the case of α-anomer and 20 sec in the case of β-anomer (**Figure 1**).

The versatility of the procedure was further demonstrated by the preparation of acetate derivatives of another seven sugars (**Table I**). As tested for several times, the scale-up of this procedure in the



2: 1,2,3,4,6-penta-*O*-acetyl-*β*-D-glucopyranose; 3: 1,2,3,4,6-penta-*O*-acetyl-*α*-D-glucopyranose

Scheme I — Preparation of *α* and *β* forms of 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose

Table I — Conversion of sugars to the corresponding penta or octa acetyl derivatives under microwave irradiation*

Compd	Form	Method	Time (sec)	mp(°C) Observed	mp(°C) Reported[14]	$[\alpha]_D^{25}$ (c=1, $CHCl_3$)	Yield** (%)
penta-*O*-acetyl-D-gluco-	*α*	A	15	112	112-14	+102	79
pyranose	*β*	B	10	133	132-35	+4	94
	α	C	15	113	112-14	+102	88
penta-*O*-acetyl-D-galacto-	*α*	A	15	95	95	+106.5	78
pyranose	*β*	B	20	141	142	+25	92
	α	C	20	95	95	+106.6	86
penta-*O*-acetyl-D-fructo-	*α*	A	20	122	122-23	+47.3	76
pyranose	*β*	B	20	109	108-09	-120.9	91
	α	C	25	122	122-23	+47.4	83
penta-*O*-acetyl-D-manno-	*α*	A	20	65	64	+54.8	76
pyranose	*β*	B	20	117	117-18	-25.2	89
	α	C	25	66	64	+55	82
octa-*O*-acetyl-maltopyra-	*α*	A	30	124	125	+123	74
nose	*β*	B	25	160	159-60	+63	88
	α	C	25	125	125	+122.8	79
octa-*O*-acetyl-lactopyranose	*α*	A	25	152	152	+52.9	75
	β	B	25	89	90	-4.4	89
	α	C	30	151	152	+53	81
octa-*O*-acetyl-sucropyranose		B	35	69	69	+59.5	74

Method A: sugar, Ac_2O, $ZnCl_2$,; Method B: penta and octa-acetyl-*β*-D-sugars, Ac_2O and $ZnCl_2$, Method C: sugar, Ac_2O and CH_3COONa,. *All the compounds were satisfactorily characterized by ^1H NMR spectroscopy.**Isolated yield after crystallization

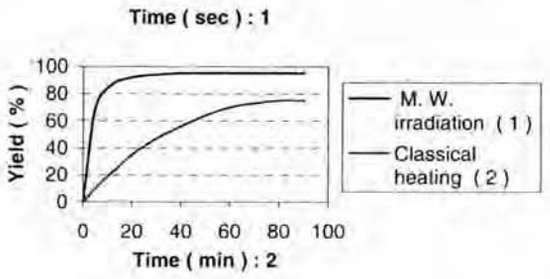


Figure 1

Table II — Conversion of D-glucose and D-galactose to the corresponding penta-*O*-acetyl-*β*-D-glucopyranose and penta-*O*-acetyl-*β*-D-galactopyranose under microwaveirradiation

Entry	Quantity of sugar in gms (mmole)	Acetic anhydride in millilitre (mmole, equivalent)	Time (sec)	Yield (%)
1	D-glucose			
	1(5.5)	3.15(33.3,6)	30	93
	1(5.5)	3.93(41.6,7.5)	20	94
	5(27.7)	15.7(66,6)	35	92
	5(27.7)	19.6(208,7.5)	25	94
	25(140)	79.3(840,6)	60	93
	25(140)	99.1(1050,7.5)	50	94
2	D-galactose			
	1(5.5)	3.15(33.3,6)	30	90
	1(5.5)	3.93(41.6,7.5)	20	92
	5(27.7)	15.7(166,6)	35	89
	5(27.7)	19.6(208,7.5)	30	92
	25(140)	79.3(840,6)	60	90
	25(140)	99.1(1050,7.5)	55	91

case of D-glucose and D-galactose up to about 150 mmole has not posed either any operational problems nor any noticeable decrease in purity as well as yield (**Table II**). However, in order to ensure the completion of the reaction, the duration of the irradiation time had to be increased to about one fourth of the time.

In summary, the present protocol can be employed not only for the synthesis of *β*- and *α*-anomers of acetylated sugar derivatives but also for the conversion of *α*-anomers to the corresponding *β*-anomers. Further, the acetylation can be carried out using only six equivalents of Ac_2O with substantial increase in the yield. As in the case of several microwave-assisted chemical syntheses of organic compounds, the present protocol is simple, rapid and efficient resulting in high yield without any side reactions. The scale-up of the protocol up to about 150 mmole has posed no practical difficulties.

Experimental Section

Melting points were determined using capillary method and are uncorrected. LG domestic microwave oven operating at 2450 MHz was used for the preparation of acetyl derivatives of sugars. Specific rotations were recorded on a Rudolf Research Autopol IV automatic polarimeter.

General procedure for the preparation of penta- and octa-*O*-acetyl derivatives of sugar

Method A. A mixture of anhydrous $ZnCl_2$ (0.25 mmole), Ac_2O (6 mmole) in a conical flask was exposed to microwave irradiation for 5 sec and then α-D-glucose (1 mmole) was added and continued the exposure to microwaves till the completion of the reaction. The resulting solution was poured onto 100 mL of ice-water under stirring. The separated solid was filtered, washed with water and recrystallized using ethanol to get the title compound.

Method B. A mixture of sugar (1 mmole), CH_3COONa (2 mmole) and Ac_2O (6 mmole) in a conical flask was exposed to microwave irradiation. After completion of the reaction, the resulting clear solution was worked up as described in the method A.

Method C. A mixture of anhydrous $ZnCl_2$ (0.25 mmole), Ac_2O (6 mmole) in a conical flask was exposed to microwave irradiation for 5 sec and then penta or octa-*O*-acetyl-*β*-sugar (1 mmole) was added and continued the exposure to microwaves till the reaction was complete. It was worked up as described in the method A.

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