



Original Research article

Solvent Free Stereoselective Iodoacetoxylation of Alkenes and Glycals using *N*-Iodosuccinimide and Acetic Anhydride



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KEYWORDS

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Stereoselective

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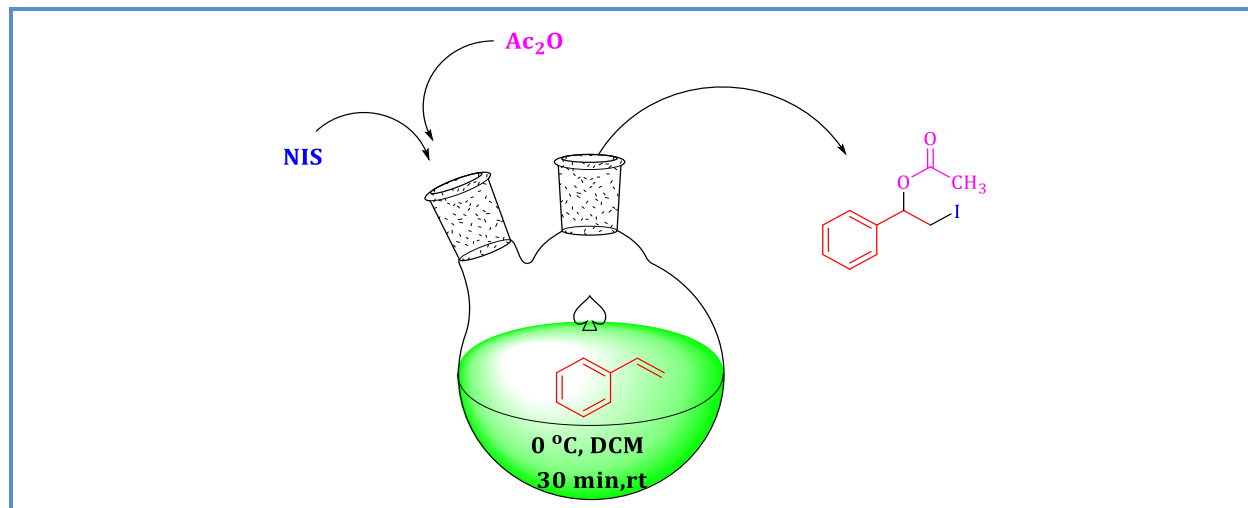
Iodoacetoxylation

ABSTRACT

The reactions of glycals with *N*-iodosuccinimide and acetic anhydride under solvent free conditions provide 2-deoxy-2-iodo- α -mannopyranosyl acetates with good stereoselectivity. The developed process is in accordance with principles of green chemistry and addresses the shortage of such methods for the regioselective iodo acetoxylation of alkenes.

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Graphical Abstract



Introduction

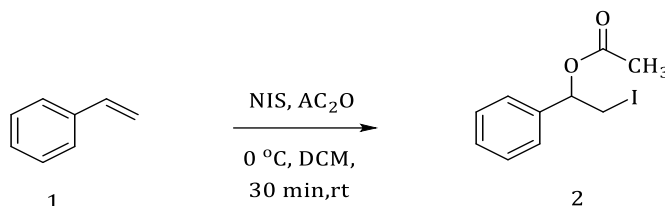
Green methodologies of synthetic organic chemistry have been the main centre of attention in the current research [1, 2]. Green chemical methods have focused on solvent free conditions as well as alternative strategies to reduce the *E* factor [3-5]. Stereo and regio-selective 1,2-additions across alkenic double bonds can be regarded as the area of interest for organic chemists [6]. Treatment of alkenes with iodine in presence of certain nucleophilic species leads to the formation of 2-functionalised iodo compounds [7]. The α -iodo acetates which are created through this transformation can serve as starting materials for the preparation of allyl acetates or α -iodo alcohols with subsequent formation of oxiranes [8]. Glycosyl acetates are ideal precursors for the construction of 2-deoxy glycosides, which occur as structural moieties of many bioactive natural products [9]. Reagents used for the acetoxyiodination of alkenes involve KIO₃ in glacial AcOH at 60 °C [10], or various heavy metal salts derived from silver (i), thallium (i), copper (ii), mercury (ii) or bismuth (iii), lead diacetate, all in the presence of I₂ [11].

Regioselective iodo acetoxylation of alkenes also involves the use of lead diacetate in iodine [12]. Iodoacetoxylation of glycals use Cerium (IV) ammonium nitrate, sodium iodide, and acetic acid [13] phosphonium salts of diacetoxyiodine (I) anions [14]. Due to the harsh reaction conditions employed and environmental problems involved with heavy metals, these methods have not found wide acceptance in reactions with multifunctional alkenes or in natural product synthesis. Accordingly, it was desirable to develop more selective methods for synthesis of iodo acetate stereoisomer.

Herein, we disclose regioselective synthesis of iodo acetoxylation of olefins in high yields under mild reaction conditions.

Results and Discussion

Initially we carried out reaction on styrene using acetic anhydride in dichloromethane (DCM) to obtain 96% iodo acetoxylated product in the presence of *N*-iodosuccinimide (NIS) (Scheme 1). The product was characterized by spectral analysis (¹H NMR, ¹³C NMR, IR, and MS) and compared to the reported literature indicating *trans*-2-iodoacetates [12].



Scheme 1. Iodo acetoxylation of styrene presence of *N*-iodosuccinimide

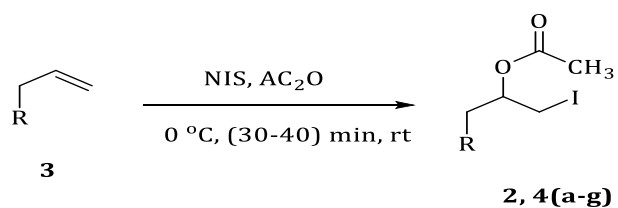
Furthermore, we start optimizing reaction condition *i.e.*, solvent and temperature. The reaction was studied in different solvents that included tetrahydrofuran (THF), methanol (MeOH), water, acetonitrile, 1,4-dioxane, dimethylformamide (DMF) *etc.* at room temperature (rt) (Table 1). The investigation was also extended for solvent free conditions and results were profound in terms of reaction time and yield (Table 1). After optimizing the solvent, we tried to carry out reaction at different temperatures. It was observed that reaction yields were high at 0 °C under solvent free conditions (Table 1).

Table 1. Effect of different solvents and temperature on the reaction of styrene with acetic anhydride in presence of NIS

Entry	Solvent	Time (min.)	Temperature (°C)	Yield ^a
1	water	60	20 -30	45
2	MeOH	60	20 -30	61
3	1,4-dioxane	65	20 -30	47
3	DME	50	20 -30	63
4	CH ₃ CN	40	20 -30	71
5	CHCl ₃	40	20 -30	55
9	DMF	40	20 -30	56
10	THF	35-40	20 -30	54
6	DCM	30-35	20 -30	78
7	DCM	30	0	91
8	DCM	30	>40	65
9	With solvent	30	0	96
10	With solvent	35	20 -30	88
11	With solvent	35-40	>60	85

^a Isolated yields formed from: styrene (1 mmol), acetic anhydride (1.5 mmol) and NIS (1.3 mmol)

Further reactions were carried out to validate the feasibility of the methodology using different alkenes and subjecting them to react with acetic anhydride (1.5 mmol) and NIS (1.3 mmol) under solvent free conditions (Scheme 2). The reactions proceeded smoothly with good to excellent yields under the optimized reaction conditions of temperature 0 °C for 30-40 minutes (Table 2).



Scheme 2. Reaction of different olefins with acetic anhydride in presence of NIS

Table 2. Reaction of different olefins with acetic anhydride in presence of NIS under solvent free conditions

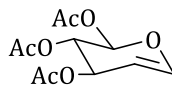
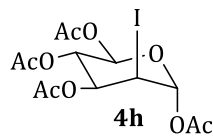
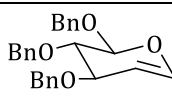
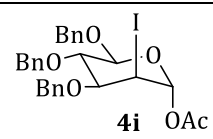
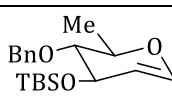
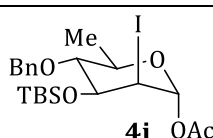
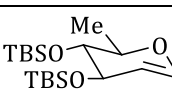
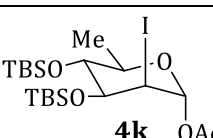
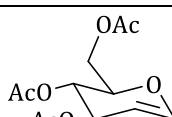
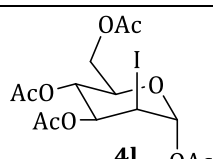
Entry	R	Product	Yield ^a
1			96
2			95
3			93
4			93
5			96
6			90
7			96
8			88

Reaction time: 30 min., temp.: 0 °C

^a Isolated yields.

We were interested in developing improved methods for the synthesis of 2-deoxy-2-iodoglycosyl acetates, dihydropyran type molecules which could be easily converted to 2 deoxy sugars by dehalogenation [15]. We decided to explore the reactions of glycols with acetic anhydride and NIS. To our considerable delight, we found that this reaction constitutes a very useful method for the synthesis of 2-deoxy-2-iodo- α -mannopyranosyl acetates. These reactions were typically performed by slow addition of NIS (1.3 mmol) to a solution of glycol (1 mmol) and acetic anhydride (1.5 mmol) under solvent free conditions at 0 °C. Total reaction times were generally 30-90 min. Products were isolated either by chromatography or by recrystallization. The reaction stereoselectivity was not highly temperature sensitive, although in most cases the best yields were obtained when the reactions were performed at temperatures ranging from -5 °C to ambient. As indicated by the examples presented in Table 3, a range of standard carbohydrate protecting groups (*e.g.* acetate esters, silyl and benzyl ethers) is fully compatible with this new iodoacetoxylation reaction. This method provides the β -isomer as the major product, in some cases; we have obtained up to 98:2 selectivity for the β -glycan iodo acetate isomer (4 h) in reactions performed at 0 °C.

Table 3. Iodoacetoxylation of glycols using NIS and acetic anhydride under solvent free conditions

Entry	Glycol	Product	Time(min)	Temp. (°C)	Selectivity
1		 4h	30	0	98:2
2		 4i	90	-5	96:4
3		 4j	30	-5 to 0	92:8
4		 4k	45	0 to 5	95:5
5		 4l	60	0	93:7

Conclusion

In summary, we have demonstrated that the reactions of glycols with acetic anhydride in the presence of NIS under solvent free conditions constitute an efficient, stereoselective method for the synthesis of 2-deoxy-2-iodomannopyranosyl acetates. In most cases, the selectivity of this new method is superior to those obtained by using other methods.

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[16] **General procedure (for model reaction):** In a round bottom flask containing appropriate amount of styrene (0.12 mL) and acetic anhydride (3 mL) and the contents stirred for 5 min. followed by the addition of NIS (292.5 mg) at 0 °C. The reaction mixture is allowed to stir at 0 °C for 30 minutes under solvent free conditions. On completion of the reaction, the contents were diluted with water, the organic layer separated and the aqueous portion extracted with DCM (3×50 mL). The combined organic layer was washed with water (2×10 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure at <40 °C. The crude reaction product was purified by column chromatography over silica gel (mesh 60–120) using hexane and ethyl acetate (19:1) as eluent to obtain products.

[17] **Spectral data for Iodoacetate 4l:** ¹H NMR (500 MHz, CDCl₃), d 6.43 (s, 1 H), 5.36 (broad s, 1 H), 4.83 (apparent t, *J* = 4.2 Hz, 1 H), 4.34 (m, 1 H), 4.23 (dd, *J* = 4.2, 0.7 Hz, 1 H), 4.18 (d, *J* = 6.8 Hz, 2 H), 2.12 (s, 3 H), 2.08 (s, 3 H), 2.02 (s, 3 H), 1.98 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃), 171.69, 170.8, 169.3, 168.0, 93.8, 69.81, 66.67, 62.3, 20.8, 20.7, 20.5, 18.8; IR (thin film), 1749, 1434, 1372, 1218, 1133, 1073, 1051, 994, 939 cm⁻¹.

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