

**EFFECTIVE AND REGIOSELECTIVE 5-IODINATION OF PYRIMIDINE BASES AND
CORRESPONDING NUCLEOSIDES BY AN INEXPENSIVE IODINE-SODIUM
NITRITE REAGENT**

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ABSTRACT

A new eco-friendly method for the regioselective 5-iodination of pyrimidine bases and the corresponding nucleosides at room temperature with iodine and sodium nitrite is developed. The method is simple and gives high yield in less reaction time under mild reaction conditions.

KEYWORDS

Iodination, Pyrimidine bases, Nucleosides, Iodine and Sodium nitrite.

INTRODUCTION

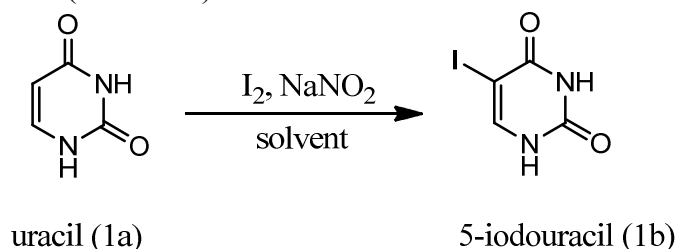
Pyrimidine derivatives substituted at the 5-position are of importance because of their biological activity and have attracted considerable attention in the field of human and animal medicinesⁱ. A number of 5-substituted pyrimidine nucleosides, especially 2'-deoxy derivatives, have been investigated extensively for the experimental and clinical treatment of neoplastic and viral diseasesⁱⁱ. They are not only used for the treatment of the diseases, but also used as diagnostic agents (radiopharmaceuticals) in advance technologies like SPECT (Single Positron Emission Computed Tomography) and PET (Positron Emission Tomography). 5-Iodo derivatives undergo high yield coupling with terminal alkynes to give 5-alkynyl nucleosides with antiviral activityⁱⁱⁱ and such products can be transformed into other 5-substituted compounds for automated DNA sequencing^{iv}.

Several methods have been reported for the iodination of pyrimidine bases and the corresponding nucleosides at the 5-position, such as I₂/HNO₃^v, NIS, ICl₃^{vi}, I₂/CAN^{vii}, I₂/mCPBA^{viii}, I₂-Pb(OAc)₄^{ix}, I₂-NaOH^x, I₂-bis(tetra-n-butyl ammonium)peroxydisulfate^{xi}, I₂-urea-H₂O₂^{xii}, I₂-H₂O₂-H₂O^{xiii}, I₂-dimethylaminopyridine^{xiv}, I₂-sodium percarbonate^{xv}. However, most of these methods have disadvantages such as use of toxic chemicals, high temperature, and long reaction time.

Considering the limitations of the reported methods and demand of 5-iodopyrimidines for the preparation of pharmaceuticals and bioactive compounds, we herein report an efficient and environmentally benign method for the 5-iodination of pyrimidine bases and the corresponding nucleosides using an eco-friendly, nontoxic, inexpensive, green reagent ($I_2/NaNO_2$). This combination was reported recently for the iodination of phenol by Konakahara^{xvi}. Sodium nitrite is a naturally occurring chemical, a food additive and has many medicinal applications. The main use of sodium nitrite is for the industrial production of organonitrogen compounds. It is used for conversion of amines to diazo compounds and used in the presence of halotrimethylsilane for the preparation of aryl halide. Low price of the reagent, simple work up procedure, low reaction temperature, eco-friendly nature of the reagent and high yield of the iodo product are the advantages of this method.

1. Results and Discussion:

For the iodination studies the reaction of uracil (1a) to 5-iodouracil (1b) with $I_2/NaNO_2$ was taken as a model reaction (Scheme 1).



Scheme 1. The reaction of uracil with $I_2/NaNO_2$

The reaction was carried out in the different solvents at room temperature (30°C) (Table 1).

Table 1. The reaction of uracil with $I_2/NaNO_2$ in different solvents.

Entry	Solvent	Time (h)	Yield of 1b (%) ^a
1	MeCN	1.5	90
2	MeOH	24	76
3	CH ₂ Cl ₂	24	71
4	THF	24	65

Reaction conditions: Uracil (112 mg, 1 mmol), Iodine (254 mg, 1 mmol), NaNO₂ (69 mg, 1 mmol), solvent - 1.2mL. Temp. 30°C, ^aIsolated yield.

Acetonitrile was the best solvent for the reaction. Decreasing the amount of solvent decreased the yield of 1b.

In order to elucidate the role of the NaNO₂, the reaction was conducted in acetonitrile in the absence of NaNO₂, when only a trace amount of 1b was obtained after 24h at room temperature. However, the reaction using NaNO₂ at room temperature in acetonitrile afforded the products in 90% yield in 1.5 h. Thus, in the absence of NaNO₂ the reaction was very slow; and even at 82°C (b.p. of acetonitrile) in acetonitrile the reaction gave negligible amount of 1b after 24h.

The amount of NaNO₂ also was important. The reaction was carried out using increasing quantity of NaNO₂ (Table 2). It was seen that minimum of one equivalent of NaNO₂ with

respect to iodine was essential for the reaction; increasing the amount of NaNO₂ further did not have any beneficial effect.

Table 2: Optimization of the amount of NaNO₂

NaNO ₂ (equiv)	Time (h)	Yield of 1b (%) ^a
0	24	-----
0.5	24	62
1.0	1.5	90
1.5	1.5	90

Reaction conditions: Uracil (112 mg, 1 mmol), iodine (254 mg, 1 mmol), acetonitrile (1.2 mL), Temp. 30°C,^aIsolated yield.

The reaction was carried out at different temperatures (Table 3). The best results were obtained at room temperature and increasing the temperature decreased the yield.

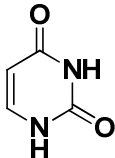
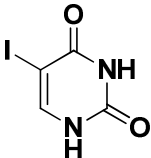
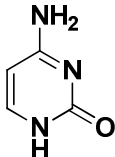
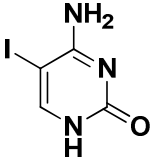
Table 3: Optimization of temperature

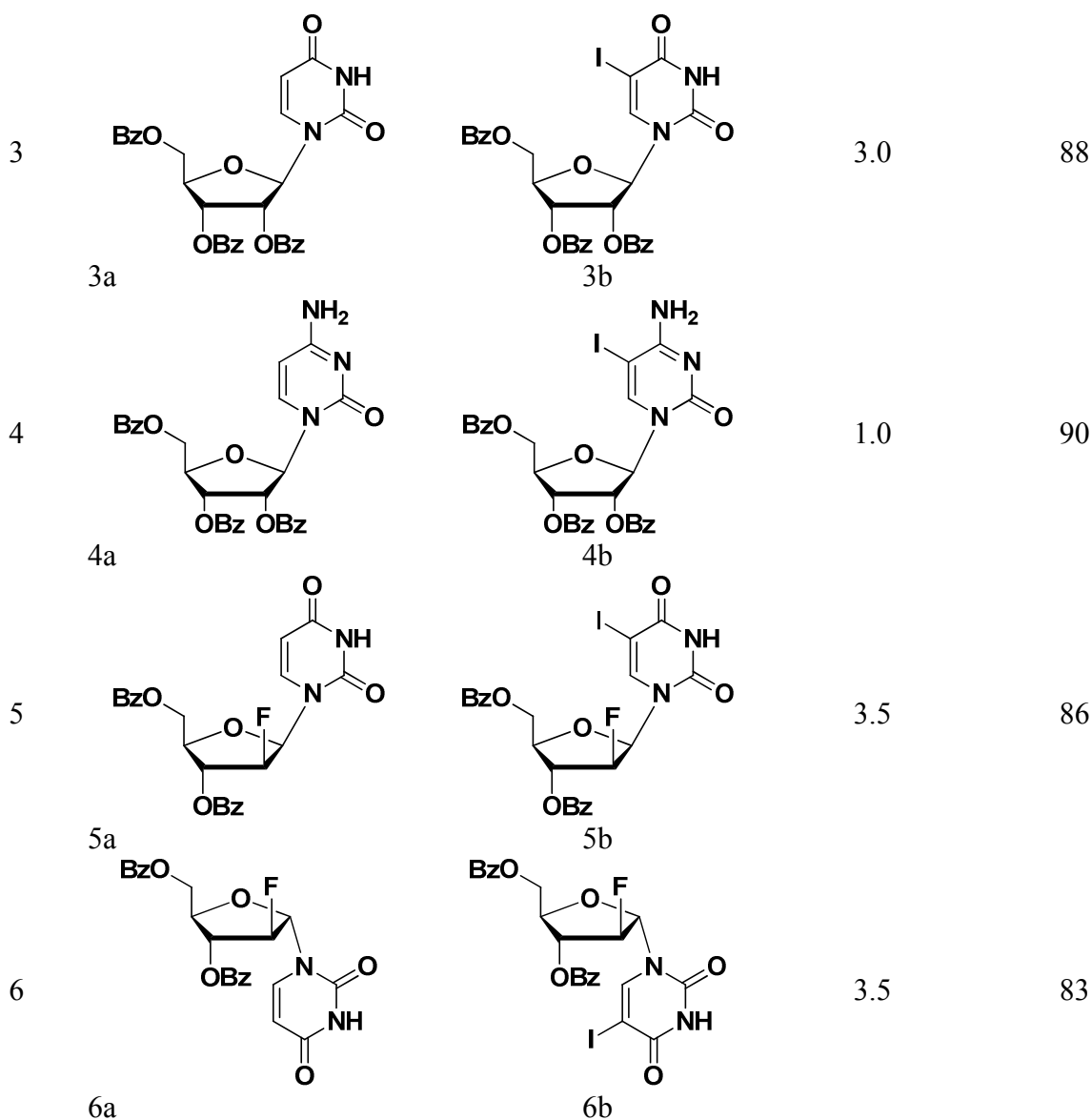
Entry	Temp. (°C)	Time (h)	Yield of 1b(%) ^a
1	30	1.5	90
2	50	1.5	74
3	80	1.5	62

Reaction conditions: Uracil (112 mg, 1 mmol), iodine (254 mg, 1 mmol), acetonitrile (1.2 mL), Temp. 30°C,^aIsolated yield.

Using the combination of I₂/NaNO₂ different pyrimidine bases and pyrimidine nucleosides were iodinated at the 5-position under the optimized conditions.

Table 4: Iodination of pyrimidine bases and pyrimidine nucleosides using I₂/NaNO₂

Entry	Substrate	Product	Time (h)	Yield of product (%) ^a
1			1.5	90
2			0.5	92



Reaction conditions: Substrate(1 mmol), iodine (254 mg, 1 mmol), sodium nitrite (1 mmol), acetonitrile (1.2 mL), Temp. 30°C, ^aIsolated yield.

5-iodo uracil (1b): white solid, mp 274-276°C, IR (KBr) cm^{-1} 3276 (NH), 1649 (C=O), 1601 (C=C), ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.87 (s, 1H, *H*-6), 11.14-11.39 (2 br s, 2H, exchangeable with D₂O, NH).

5-Iodo cytosine (2b): white solid, mp 249-252°C, IR (KBr) cm^{-1} 3446, 3269 (NH₂), 1646 (C=O), 1594 (C=C). ¹H NMR (300 MHz, DMSO-*d*₆): δ 6.48 (br s, 2H, D₂O exchangeable, NH₂), 7.76 (s, 1H, *H*-6), 10.76 (br s, 1H, exchangeable with D₂O, NH). ¹³C NMR (75 MHz, CDCl₃): δ 55.2, 149.4, 155.78, 164.44.

5-iodo-2',3',5'-tri-O-benzoyluridine(3b): white solid, mp 170-172°C, IR (KBr) cm^{-1} 3188 (NH), 3047, 1712, 1671 (COOR, CONHCO), 1605 (Ar), 1266 (C-O). ¹H NMR (300 MHz, CDCl₃): δ 4.68-4.85 (m, 3H, *H*-4', *H*-5a', *H*-5b'), 5.73-5.77 (t, *J* = 6.3, 6.0 Hz, 1H, *H*-3'), 5.88-5.91 (dd, *J* = 3.3, 3.3 Hz, 1H, *H*-2'), 6.35 (d, *J* = 6.0 Hz, 1H, *H*-1), 7.26-7.63 (m, 9H, Ar-*H*), 7.85-8.14 (m, 7H, *H*-6 and Ar-*H*), 9.18 (br s, 1H, NH).

5-iodo-2',3',5'-tri-O-benzoylcytidine (4b): white solid, mp 104-106°C, IR (KBr) cm^{-1} 3446, 3335 (NH₂), 3070 (Ar), 1727, 1642 (COOR, CONHCO), 1601 (C=C), 1266 (C-O). ¹H NMR (300 MHz, CDCl₃): δ 4.63-4.93 (m, 3H, *H-4'*, *H-5a'*, *H-5b'*), 5.72 (br s, 1H, NH), 5.77 (t, *J*=5.4 Hz, 1H, *H-3'*), 5.9-5.93 (t, *J*= 5.4, 5.1 Hz, 1H, *H-2'*), 6.37 (d, *J*=5.1 Hz, 1H, *H-1'*), 7.31-7.6 (m, 9H, Ar-*H*), 7.79 (s, 1H, *H-6*), 7.83-8.19 (m, 6H, Ar-*H*), 8.87 (br s, 1H, NH). ¹³C NMR (75 MHz, CDCl₃): δ 57.89, 63.96, 71.31, 74.65, 80.57, 88.93, 128.57, 128.75, 128.96, 129.35, 129.91, 130.05, 133.67, 133.74, 146.75, 154.29, 163.84, 165.38, 176.2.

1-(2-Deoxy-2-fluoro-3,5-di-O-benzoyl- β -D-arabinofuranosyl)-5-iodouracil (5b): white solid, mp 196-198°C, IR (KBr) cm^{-1} 3210 (NH), 3070, 1598 (Ar), 1716, 1686 (COOR, CONHCO), 1266 (C-O).

1-(2-Deoxy-2-fluoro-3,5-di-O-benzoyl- α -D-arabinofuranosyl)-5-iodouracil (6b): white solid, mp 148-150°C, IR (KBr) cm^{-1} 3210 (NH), 3062, 1601 (Ar), 1712, 1686 (COOR, CONHCO), 1266 (C-O). ¹H NMR (400 MHz, CDCl₃): δ 4.57-4.6 (dd, *J*= 5.6, 5.2 Hz, 1H, *H-5a'*), 4.65-4.7 (dd, *J*= 6.4, 6.4 Hz, 1H, *H-5b'*), 5.0-5.03 (t, *J*= 5.6, 5.2 Hz, 1H, *H-4'*), 5.4 (d, *J*= 48.4 Hz, 1H, *H-2'*), 5.73 (d, *J*=14.8 Hz, 1H, *H-3'*), 6.22 (d, *J*= 14.8 Hz, 1H, *H-1'*), 7.45-7.64 (m, 6H, Ar-*H*), 7.86 (s, 1H, *H-6*), 7.9-8.11 (m, 4H, Ar-*H*), 8.63 (bs, 1H, NH). ¹³C NMR (100 MHz, CDCl₃): δ 63.24, 68.36, 85.62, 91.94, 96.26, 98.14, 127.85, 128.55, 129.04, 129.25, 129.81, 129.87, 133.5, 134.29, 143.84, 149.35, 159.44, 164.67, 166.12

3. Conclusion:

Molecular iodine in the presence of sodium nitrite is the best iodinating reagent for C-5 iodination of pyrimidine bases and pyrimidine nucleosides at room temperature. The reaction is regioselective, the process is very simple and high yielding. The reaction is solvent sensitive and acetonitrile, which can be recovered, is the best solvent. Use of NaNO₂ as a mild, nontoxic, inexpensive, easily available, and efficient reagent for the iodination makes this protocol practical, environment-friendly and economically attractive. The reaction is simple, involves ambient conditions, high yielding.

4. Experimental

All commercial reagents were used as received without purification and all solvents were reagent grade. The reaction was monitored by TLC using 0.25 mm E-Merck silica gel 60 F₂₅₄ precoated plates, which were visualized with UV light. Melting points were taken in open capillaries and are uncorrected. The IR spectra were recorded on a PerkinElmer 257 spectrometer using KBr. ¹H and ¹³C NMR spectra were recorded on a 300/ 400MHz instrument using TMS as an internal standard.

4.1 General experimental procedure:

Procedure for iodination of Pyrimidine bases (1b and 2b)

A mixture of NaNO₂ (69 mg, 1 mmol) and I₂ (254mg, 1mmol) in acetonitrile (1.2 mL) was stirred at room temperature (30°C) for 0.5 h under nitrogen. To the stirred solution, substrate (1mmol) was added and the solution was stirred under ambient conditions for 0.5 to 1.5 h. The reaction was monitored by TLC. After completion of the reaction, cold water was added to the reaction mixture followed by 5% Na₂S₂O₃ to remove unreacted I₂. The colourless precipitate thus obtained was then filtered and washed with water. The crude 5-iodo product was purified by column chromatography using MeOH/CHCl₃ as mobile phase.

Procedure for iodination of Pyrimidine Nucleosides (3b to 6b)

A mixture of NaNO₂ (69 mg, 1mmol) and I₂ (254 mg, 1mmol) in acetonitrile (1.2 mL) was stirred at room temperature (30°C) for 0.5 h under nitrogen. To the stirred solution, substrate (1mmol) was slowly added and the solution stirred under ambient conditions for 1.0 to 3.5 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with CHCl₃ (10 mL) washed with 5% Na₂S₂O₃ (10 mL) to remove unreacted I₂. The organic layer was washed with water and dried over anhydrous Na₂SO₄. It was concentrated under reduced pressure on rota. The crude compound was purified by column chromatography over silica gel using pet. ether and ethyl acetate as mobile phase.

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