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Mild and Efficient Synthesis of Aryliodonium Ylides of 2,6-Dimethylpyrimidin-4-ol

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ABSTRACT: *Mild and efficient synthesis of new synthetically useful aryliodonium ylides of 2,6-dimethylpyrimidin-4-ol (***3a–d***) using (dichloroiodo)arenes in aqueous medium is reported. Antibacterial activity of these ylides* **3a–d** *against* Escherichia coli *and* Bacillus Licheniformis *is also described.*
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INTRODUCTION

In recent years, considerable attention has been devoted to the use of hypervalent iodine reagents in organic synthesis for various synthetically useful transformations due to their low toxicity, ready availability, and ease of handling [1]. As an important class of this family, zwitterionic iodonium compound (iodonium ylide) represents a molecule with a positive charge at iodine compensated by an internal negative charge that is localized formally at an α-carbon atom or nitrogen atom (1,2-dipole) or, in some instances, delocalized to a neighboring oxygen or nitrogen (1,4-zwitterionic structure) [2]. Iodonium ylides can be used for the synthesis of new reagents and in fine organic synthesis due to considerable synthetic potential [1].

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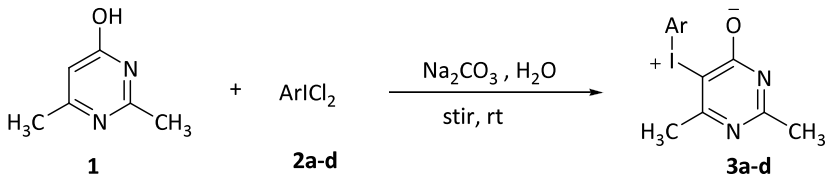
As a privileged scaffold, pyrimidine is a ubiquitous subunit in many natural products with remarkable biological activities and unique physical properties. Pyrimidine derivatives have proved to be of great importance in exhibiting therapeutic applications [3]. A large number of pyrimidine nucleosides are clinically useful for the control of retroviral infections [4–7]. One of the important class of antiherpetic nucleosides is a series of 5-substituted uracil nucleosides such as (*E*)-5-(2-bromovinyl)-2′-deoxyuridine [8] showed specific antivaricella zoster virus activity. In view of effect of 5-substitution on the activity of thiouracil, synthesis and antithyroid activity of several 5-substituted pyrimidine derivatives have been reported [9]. In addition, 5-alkyl or 5-aryl-substituted pyrimidine derivatives are useful intermediates in the synthesis of nucleosides [10]. Also, many 5-substituted pyrimidines have shown inhibitory activity against *Streptococcus faecalis* R growth [11] and some are evaluated as inhibitors of enzymes involved in the pyrimidine catabolism like dihydrouracil dehydrogenase and uridine phosphorylase [12]. Further, 5-iodo substituted pyrimidine analogues are known for their antimicrobial [13] and antiviral activity [14,15].

In view of the synthetic utility of iodonium ylides and biological properties associated with pyrimidine derivatives, in particular 5-substituted pyrimidines, we wish to synthesize pyrimidine analogues substituted at C-5 position. Thus, as a general approach for the synthesis of subsequent analogues, our attention was focused on the report of Habib and Kappe regarding the synthesis of iodonium ylides [16a]. In the present communication, we report herein mild and efficient synthesis



Ar = **a**, C_6H_5; **b**, 4-BrC_6H_4; **c**, 4-ClC_6H_4; **d**, 3-$MeOCOC_6H_4$

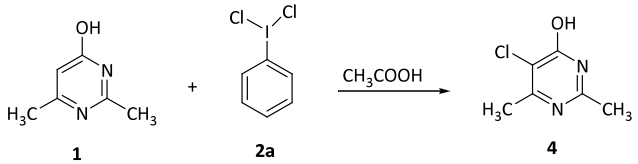
SCHEME 1 Synthesis of aryliodonium ylides **3a–d**.

of new synthetically useful aryliodonium ylides (**3a–d**) of 2,6-dimethylpyrimidin-4-ol (**1**) using (dichloroiodo)arenes in aqueous medium. Reaction provides easy accessibility of the aryliodonium ylides **3a–d** in excellent yields under mild conditions.

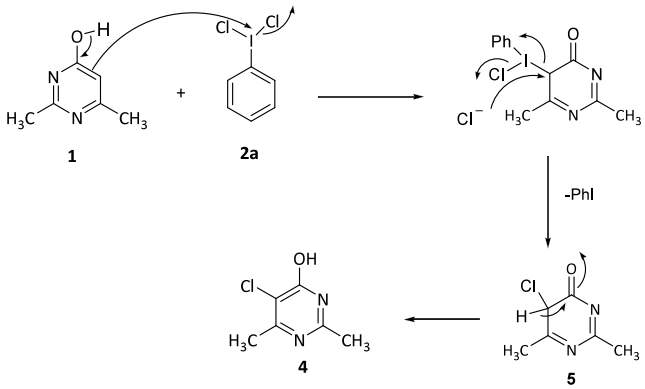
RESULTS AND DISCUSSION

Accordingly, 2,6-dimethylpyrimidin-4-ol (**1**) was treated with (dichloroiodo)benzene (**2a**) in water at room temperature, followed by addition of sodium carbonate. The reaction afforded phenyliodonium ylide **3a** in 76% yield. Encouraged by this observation, 4-hydroxypyrimidine **1** was treated with other (dichloroiodo)arenes (**2b–d**) (Scheme 1). The reaction afforded corresponding iodsonium ylides **3b–d** in good yields thereby establishing the generality of the method. The structures of compounds **3a–d** were confirmed by their spectral as well as elemental analysis. These results were highly promising, as the presence of the iodo substituent at C-5 in compounds **3** opens up a broad range of opportunities to introduce diverse substituents at C-5. The probable mechanism for the formation of iodonium ylides might involve the attack of iodosoarene, generated in situ from (dichloroiodo)arene, on C-5 of compound **1** leading to the formation of intermediate which subsequently rearrange to give ylide **3** [16a].

In another experiment, we attempted the reaction of 2,6-dimethylpyrimidin-4-ol (**1**) with (dichloroiodo)benzene (**2a**) in acetic acid. The reaction led to the nuclear chlorination with the formation of 5-chloro-2,6-dimethyl-4-hydroxypyrimidine (**4**) in 73% yield (Scheme 2). Structure of compound **4** was confirmed by the spectral and elemental data.



SCHEME 2 Reaction of compound **1** with (dichloroiodo)-benzene in acetic acid.



SCHEME 3 Probable mechanism for the formation of compound **4**.

It is worthwhile to mention that reaction of nucleic bases under similar conditions has been reported to yield C-5 chlorinated product [16b]. The probable mechanism for the formation of **4** might involve the electrophilic attack of (dichloroiodo)benzene (**2a**) at C-5 position of compound **1**, followed by nucleophilic attack of "Cl^- (chloride ion)" leading to reductive elimination of iodobenzene to give intermediate **5** which subsequently rearrange to give compound **4** (Scheme 3).

The compounds **3a–d** and **4** were also screened for their antibacterial activity against *Escherichia coli* and *Bacillus licheniformis*. Results of the antibacterial testing are summarized in Table 1. Results revealed that ylide **3c** is comparable or even more potent than the commercial antibiotic, streptomycin, against *E. coli* whereas compound **3d** showed promising results against *B. licheniformis*. However, the parent compound **1** neither shows activity against *E. coli* nor against *B. licheniformis*. These observations led to the conclusion that the presence of iodine atom at C-5 position might have a positive impact on the antibacterial activity.

CONCLUSION

A mild and efficient synthesis of new synthetically useful aryliodonium ylides (**3a–d**) using

TABLE 1 Antibacterial Activity of Aryliodonium Ylides **3a–d** and 5-Chloro-4-Hydroxy-2,6-Dimethylpyrimidine (**4**)

		Diameter of Zone Inhibition	
Compound	*Conc.* (μg/mL)	*Escherichia coli*	*Bacillus Licheniformis*
1	50	Nil	Nil
	100	Nil	Nil
	250	Nil	Nil
	500	Nil	Nil
3a	50	Nil	Nil
	100	Nil	Nil
	250	Nil	Nil
	500	Nil	1 mm
3b	50	Nil	Nil
	100	Nil	Nil
	250	Nil	Nil
	500	Nil	1 mm
3c	50	4 mm	Nil
	100	6 mm	2 mm
	250	8 mm	4 mm
	500	12 mm	6 mm
3d	50	Nil	Nil
	100	Nil	2 mm
	250	Nil	4 mm
	500	Nil	9 mm
4	50	Nil	Nil
	100	Nil	Nil
	250	Nil	Nil
	500	Nil	Nil
Streptomycin	50	4 mm	3 mm
	100	6 mm	6 mm
	250	8 mm	8 mm
	500	10 mm	10 mm

(dichloro)iodo arenes in aqueous medium is described. Aryliodonium ylides (**3a–d**), obtained from the present study, can be utilized in organic synthesis as useful synthetic precursors to synthesize variety of pyrimidine derivatives, such as, *o*-iodoaryloxy ethers, 5-aryl/hetryl pyrimidines, and so forth. Furthermore, ylides **3c** and **3d** showed significant antibacterial activity as compared to the commercial antibiotic, streptomycin.

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. Infrared (IR) spectra were recorded on Perkin-Elmer IR spectrophotometer. The ^{1}H NMR spectra were recorded on BRUKER 400 MHz instrument. The chemical shifts are expressed in ppm units (δ) downfield from an internal TMS standard. Elemental analyses were performed on Perkin-Elmer 2400 instrument and mass spectra were recorded on Kratos MS-50 mass spectrometer. 2,6-Dimethylpyrimidin-4-ol (**1**) needed for study was prepared from ethyl acetoacetate and acetamidine hydrochlride by following the literature procedure [17]. (Dichloroiodo)arenes **2a-d**, needed for the present study, were prepared according to the procedures reported in the literature [18,19]. The antibacterial activities of the newly synthesized compounds were evaluated by Agar Well Diffusion Assay technique [20].

*Synthesis of Aryliodonium Ylides (**3a–d**)*

General Procedure. To a solution of 2,6-dimethylpyrimidin-4-ol (**1**, 10 mmol) in water, was added (dichloroiodo)arenes (**2a–d**, 11 mmol), followed by sodium carbonate (10 mmol). The resulting mixture was stirred for 6–7 h. Solid was filtered and washed with water and dried to give pure ylide (**3a–d)**.

*Characterization Data of the Ylides (**3a–d**)*

3a: mp 224°C; yield 76%; ^{1}H NMR (DMSO, δ): 2.58 (s, 3H, $-CH_3$), 2.59 (s, 3H, $-CH_3$), 7.32–7.42 (m, 2H), 7.42–7.51 (m, 1H), 7.58–7.63 (m, 2H); Elemental analysis: $C_{12}H_{11}N_2OI$ Found (C, 44.15; H, 3.35; N, 8.53%); Requires (C, 44.19; H, 3.40; N, 8.59%); Mass, m/z: 326 (M^+).

3b: mp 225°C; yield 78%; ^{1}H NMR (DMSO, δ): 2.57 (s, 3H, $-CH_3$), 2.61 (s, 3H, $-CH_3$), 7.34–7.37 (d, 2H, J = 8.4 Hz), 7.82–7.85 (d, 2H, J = 8.4 Hz); Elemental analysis: $C_{12}H_{10}N_2OBrI$ Found (C, 35.52; H, 2.45; N, 6.89%); Requires (C, 35.58; H, 2.49; N, 6.92%); Mass, m/z: 405 (M^+).

3c: mp 234°C; yield 79%; ^{1}H NMR (DMSO, δ): 2.55 (s, 3H, $-CH_3$), 2.58 (s, 3H, $-CH_3$), 7.24–7.26 (d, 2H, J = 8.2 Hz), 7.73–7.75 (d, 2H, J = 8.2 Hz); Elemental analysis: $C_{12}H_{10}N_2OClI$ Found (C, 39.95; H, 2.85; N, 7.77%); Requires (C, 39.97; H, 2.80; N, 7.77%); Mass, m/z: 360 (M^+).

3d: mp 230°C; yield 70%; ^{1}H NMR (DMSO, δ): 2.58 (s, 3H, $-CH_3$), 2.64 (s, 3H, $-CH_3$), 3.88 (s, 3H, $-OCH_3$), 7.45–7.53 (m, 1H), 7.77–7.88 (m, 2H), 7.87–7.99 (m, 1H); Elemental analysis: $C_{14}H_{13}N_2O_3I$ Found (C, 43.75; H, 3.39; N, 7.28%); Requires (C, 43.77; H, 3.41; N, 7.29%); m/z: 384 (M^+).

*Synthesis of 5-Chloro-2,6-dimethylpyrimidin-4-ol (**4**)*

(Dichloroiodo) benzene (**2a**, 3 mmol) was added to a stirred solution of of 4-hydroxy-2,6-dimethyl pyrimidine (**1**, 2.5 mmol) in acetic acid (15 mL) at 80°C. Stirring was continued at 80°C for 1 h. The resulting mixture was evaporated in vacuo. Repeated addition and evaporation of methanol-water and then with methanol, resulted solid product. This solid was

dissolved in minimum volume of hot chloroform and then methanol was added and the mixture was cooled. Solid separated out was filtered and dried to give pure **4**.

4: mp 201°C; yield 73%; ^{1}H NMR (DMSO, δ): 2.67 (s, 3H, $-CH_3$), 2.69 (s, 3H, $-CH_3$); Elemental analysis: $C_6H_7N_2OCl$ Found (C, 45.42; H, 4.41; N, 17.63%); Requires (C, 45.44; H, 4.45; N, 17.66%); m/z: 158 [M^+]

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