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Simple and Efficient Method for the Preparation of 5-Bromoisatins

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Abstract: Isatin, *N*-methyl isatin and *N*-benzylisatin were smoothly monobrominated in the 5-position by treatment with pyridinium bromochromate (PBC) in acetic acid medium. In the similar conditions indigo underwent bromination and oxidation to give 5-bromoisatin in high yield.

Key words: Pyridinium bromochromate, Isatin, Oxidation, Regioselectivity

1. Introduction

Isatin (1H-indole-2,3-dione) is a versatile molecule with important applications in synthetic organic chemistry [1]. It was first prepared by Erdmann and Laurent through the oxidation of indigo by nitric acid and chromic acids [2, 3]. Some of it's derivatives, specifically 5-haloisatins, show a wide range of biological and pharmacological activity, such as antibacterial, antifungal, and anti-HIV [4]. Haloarenes have been extensively used in the aromatic bond formation reactions [5] such as Heck arylation, Suzuki, Buchwald, Negishi, Stille coupling reactions, etc., therefore 5-haloisatins through these coupling reactions can be used as precursor in the synthesis of a variety of active pharmaceutical ingredients [6]. They can be prepared by the Sandmeyer and similar methodologies from *p*-haloanilines [7], by the reaction of *N*-aryl nitrones with dichloroketene [8] or by direct halogenation of isatin [9]. Reagents that perform the bromination of isatin mainly in the 5-position consist of *N*-bromosuccinimide [10], *N*-bromocaprolactam [11] and *N*-bromosaccharin [12]. However, while these methods can generate the desired product, they have some disadvantages such as low yield of product and long reaction time.

2. Experimental

Pyridinium bromochromate, *N*-methyl isatin and *N*-benzylisatin were prepared according to the litreture

[13, 14]. Other starting materials and solvents were purchased from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR: Bruker DRX-500 spectrometer; all ^{1}H NMR spectra were recorded at 500 MHz and ^{13}C NMR were recorded at 125 MHz in $CDCl_3$ or DMSO-d_6. Melting points were recorded on Electro Thermal 9100.

2.1. General Procedure for the Bromination of Isatins (1a-c)

To a suspension of PBC (3.12 g, 12 mmol) in glacial acetic acid (25 mL) was added the substrate (10 mmol) dissolved in a small amount of acetic acid. The reaction mixture was heated at 90 °C on a water bath for 20 min. After completion of the reaction, cold water (100 mL) was added to the mixture and extracted by ether (3×20 mL). The combined ethereal extract was washed with aqueous $NaHCO_3$ and water and then dried with Na_2SO_4. The solvent was evaporated at reduced pressure and the crude product recrystallized from ethanol or carbon tetrachloride to give **2a-c**.

2.2. Reaction of PBC with indigo

A mixture of indigo (0.78 g, 3 mmol) and PBC (4.68 g, 18 mmol) in glacial acetic acid (25 mL) was heated on a water bath for 5 min. The reaction mixture was poured into cold water (100 mL) and extracted by ether (3×20 mL). The combined ethereal extract was washed with aqueous $NaHCO_3$, water and dried (Na_2SO_4). The solvent was evaporated at reduced pressure and the crude product recrystallized from ethanol to give 5-bromoisatin (**2a**) (1.21 g, 89%).

2a: Mp 249-250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ = 6.88 (d, *J* = 8.3 Hz, 1 H), 7.66 (d, *J* =1.9 Hz, 1 H), 7.74 (dd, *J* = 8.3 and 1.9 Hz, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 115.13, 115.15, 120.44, 127.76, 140.89, 150.43, 159.84, 184.05.

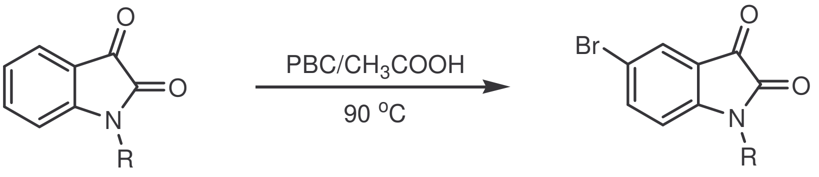
2b: Mp 162-164 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.22 (s, 3 H), 6.79 (d, *J* = 8.3 Hz, 1 H), 7.65 (br s, 1 H), 7.69 (br d, *J* = 8.3 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 26.33, 111.62, 116.63, 118.62, 128.01, 140.57, 150.16, 157.49, 182.11.

2c: Mp 151-152 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.90 (s, 2 H), 6.65 (d, *J* = 8.4 Hz, 1 H), 7.25-7.35 (m, 5H), 7.56 (dd, *J* = 8.4 and 1.9 Hz, 1 H), 7.69 (d, *J* = 1.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 44.20, 112.67, 116.75, 118.91, 127.38, 128.15, 128.35, 129.15, 134.06, 140.45, 149.41, 157.53, 182.00.

3. Results and Discussion

Pyridinium bromochromate (PBC) is an inexpensive and easily prepared oxidizing and brominating agent whereby several synthetically useful organic transformations such as oxidation of oximes [15], diols [16], alpha-amino acids [17] and brominating of hydroxyl aromatics [13] have been performed. In this work we wish to report our results on the synthesis of 5-bromoisatins by using PBC.It was observed that when a mixture of isatin and PBC in acetic acid was heated on a water-bath with constant stirring, 5-bromoisatin was produced as a sole-product. Similarly *N*-methylisatin and *N*-benzylisatin underwent bromination only in the 5-position (Table 1).

The regioselectivity of this reaction was established by ^{1}H NMR of crude products and also by thin layer chromatography. The reactions were completed in less than 20 min and the products were identified by their spectroscopic data and by comparing their melting points with those that were reported in the literature [8, 14].



1a-c **2a-c**

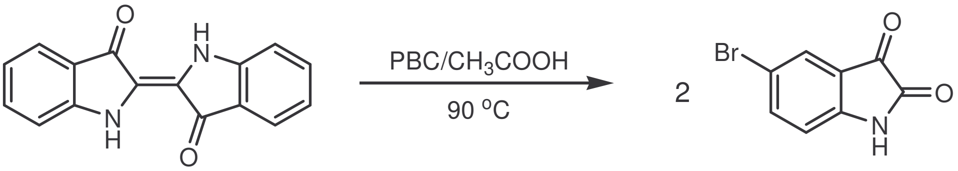
Scheme 1 Synthesis of 5-bromoisatin from indigo by using PBC

Table 1. Bromination of isatins with PBC

Product	R	Yield (%)[a]
2a	H	66
2b	CH_3	63
2c	$PhCH_2$	65

[a] Yields refer to isolated products

Also It was found that with the utilization of both brominating and oxidizing properties of PBC, indigo can undergo bromination and oxidation by this reagent in acetic acid to give 5-bromoisatin in 89% isolated yield. The reaction was completed in less than 5 minutes and the product was isolated by a simple work up procedure (Scheme 1). The advantage of using this reagent over other brominating reagents is illustrated in Table 2. As shown in Table 2, the bromination of isatin or especially indigo with PBC is a simple and efficient method. Higher yields and shorter reaction times are important features of this method.



Scheme 1 Synthesis of 5-bromoisatin from indigo by using PBC

Table 2 Comparison of PBC with other reagents for the preparation of 5-bromoisatin

Reagent	Time	Yield (%)[a]	Ref.
N-bromocaprolactam	overnight	77	11
N-bromosaccharine/SiO_2	12 h	58	12
PBC[a]	20 min	66	present work
PBC[b]	5 min	89	present work

[a] From isatin; [b] From indigo

4. Conclusion

In summary, we report a simple and an efficient method for the synthesis of 5-bromoisatins using PBC in acetic acid medium. The high rate of reaction, the simple procedure, regioselectivity and relatively good yields make this method a useful addition to the array of procedures for the synthesis of 5-bromoisatins.

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5. References

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