SiO_2 MEDIATED REACTION OF ISATIN WITH *N*-HALOSACCHARINS: A REGIOSPECIFIC PREPARATION OF 5-HALOISATINS

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Abstract: *N*-halosaccharins (5 mmol) react smoothly at room temperature with isatin (5 mmol) in the presence of SiO_2 (5 g) to produce specifically the 5-halo derivative. Using this procedure, 5-chloroisatin was obtained in 48 % purified yield (72 h), 5-bromoisatin in 58 % (12 h) and 5-iodoisatin in 80 % (8 h).

Introduction

Surface mediated reactions are of great utility in organic synthesis, and in many cases the products are obtained in better yields and improved selectivities than in a homogeneous media in solution (1). *N*-halosuccinimides proved to be efficient reagents for the halogenation of heteroaromatics in mild homogeneous or heterogeneous conditions (2).

Isatin (1*H*-indole-2,3-dione, 1) is a versatile molecule with many applications in synthetic organic chemistry (3). Furthermore, some derivatives have important biological and pharmacological properties (3b). Several reagents (4) are described in the literature to perform the halogenation of isatin mainly in the 5-position and among them *N*-haloamides and *N*-haloimides (4a, 4b). These reagents are a suitable synthetic alternative to the highly toxic and corrosive Cl_2 and Br_2, which can also lead to other products, just as when the bromination of isatin is performed with bromine in an alcoholic media, and 5,7-dibromo-3,3-dialkoxyoxindole is then obtained (5).

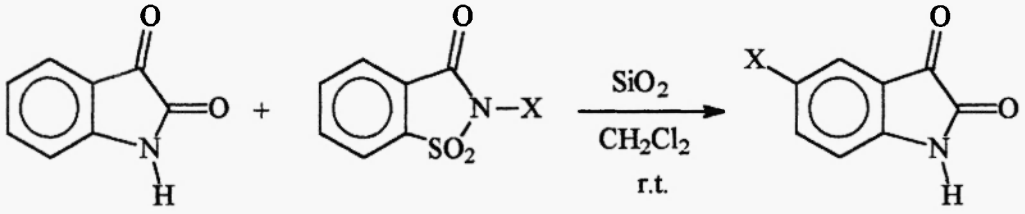
We communicate here our results on the SiO_2 mediated reaction of isatin with *N*-halosaccharins (NXSac), reagents more electrophilic (6) but much less employed than the structural analogs *N*-halosuccinimides in synthetic organic chemistry

Results

N-halosaccharins react smoothly with isatin in the presence of SiO_2 to produce especificaly the 5-halo derivatives **2** in moderate to good yields (Scheme and Table 1). The reaction was performed stirring together at room temperature a suspension of SiO_2 (5 g), isatin (5 mmol) and NXSac (5 mmol) in CH_2Cl_2. After work up, the product was recrystallized from aqueous etanol.

In all the reactions the purity of the products (> 95 %) was confirmed by analytical methods (^{13}C NMR and high-resolution gas chromatography). The products were characterized by analytical data and by coelution with authentic samples in a high-resolution gas chromatograph. No products derived from N-halogenation of isatin (7) or in the 7-position were detected by the analytical techniques employed (^1H and ^{13}C NMR and high-resolution gas chromatography).

The same reaction performed with NCSac in the absence of SiO_2 produced 5-chloroisatin in low yield along with some unidentified products and unreacted isatin after more than 75 h.



1 **NXSac** **2**

Scheme.

2	**t (h)**	**Yield (%)**[a]
X = Cl	72	48
X = Br	12	58
X = I	8	80

[a] Yield of pure product based on isatin.

Table 1. Yields of **2** from the SiO_2 mediated reaction of isatin with NXSac.

In summary, we present here a convenient regiospecific preparation of 5-haloisatins, important precursors of antimicrobial compounds (8). Furthermore, the reaction conditions are mild, there is no need of special techniques or harzadous reagents and the isolation of the product is very easy.

Experimental

NCSac (9), NBSac (9) and NISac (6) were prepared as described in the literature. SiO_2 (Aldrich, 270-70 MESH, 60 Å) was activated by heating for 1.5 min in a domestic microwave oven at highest power (10). Isatin (Aldrich, Gold label) and other chemicals were used without further purification. ^1H and ^{13}C NMR were acquired on a Bruker AC-200 (200 MHz and 50 MHz, respectively) spectrometer in $CDCl_3$ / DMSO-d_6 solutions with TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer (KBr film). Analyses by high-resolution gas chromatography were performed on a HP-5890-II gas chromatograph with FID by using a 25 m (length), 0.53 mm (ID) and 0.50 μm (phase thickness) RTX-5 silica capillary column (Restek Corporation) and He (flow rate 50 cm / s) as carrier gas (split 1 : 20). Analysis conditions: injector: 220 °C, detector: 280 °C, oven temperature program: 70 °C (2 min) // 8 °C/min // 150 °C // 25 °C/min // 250 °C (5 min).

General procedure for the halogenation of isatin: a suspension of isatin (5 mmol), NXSac (5 mmol) and SiO_2 (5 g) in CH_2Cl_2 (25 mL) was stirred at r.t. for the time show in Table 1. The SiO_2 was filtered off, washed with MeOH and the organic solvents rotaevaporated. The residue was recrystallized from aqueous EtOH to produce pure 5-haloisatin. The physical data of the products are shown in Table 2.

2	ν (cm^{-1}, KBr)	δ_H (ppm, $CDCl_3$ / DMSO-d_6)	δ_C (ppm, $CDCl_3$ / DMSO-d_6)	t_R (min)
X = Cl	3183, 3103, 3080, 2999, 1752, 1710, 1618, 1472, 1451, 847, 749, 701, 657	6.91 (d, *J* 9.0 Hz, 1H), 7.50 (m, 2H), 10.99 (broad s, 1H, NH)	109.2 (CH), 113.8 (C), 120.0 (CH), 123.6 (C-Cl), 133.0 (CH), 144.6 (C), 154.4 [C(O)N], 178.9 [C(O)]	14.5
X = Br	3092, 3067, 3045, 2989, 1745, 1704, 1614, 1466, 1448, 843, 749, 720, 686	6.87 (d, *J* 8.1 Hz, 1H), 7.52 (m, 2H), 11.03 (broad s, 1H, NH)	113.8 (CH), 115.0 (C), 117.1 (C-Br), 126.9 (CH), 139.8 (CH), 149.2 (C), 158.3 [C(O)N], 182.9 [C(O)]	15.4
X = I	3240, 3092, 3065, 2995, 1745, 1735, 1606, 1460, 1448, 834, 745, 730, 670	6.70 (d, *J* 8.2 Hz, 1H), 7.70 (m, 2H), 11.10 (broad s, 1H, NH)	88.5 (C-I), 113.1 (CH), 119.5 (C), 133.0 (CH), 146.2 (CH), 152.1 (C), 160.2 [(C(O)N], 183.5 [C(O)]	-[a]

[a] Decomposes during high-resolution gas chromatography analysis.

Table 2. Physical data of 5-haloisatins.

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