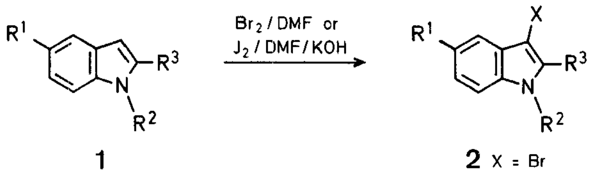
High Yield Selective Bromination and Iodination of Indoles in *N*,*N*-Dimethylformamide

Vittorio Bocchi, Gerardo Palla*

Istituto di Chimica Organica dell'Università, Via M. D'Azeglio 85, I-43100 Parma, Italy

Although the brominations of simple indoles have been extensively studied[1,2], selective brominations giving satisfactory yields have only been obtained with special reagents such as pyridinium perbromide and dioxan perbromide[3], 2,4,4,6-tetrabromocyclohexane-2,5-dienone[4], alkyl bromides in dimethyl sulphoxide[5].

In this paper, we report the synthesis of 3-bromo- (**2**) and 3-iodoindoles (**3**) by addition of a solution of the halogen in dimethylformamide to the 3-unsubstituted indoles (**1**) dissolved in dimethylformamide. The reaction is performed at room temperature and the yields are almost quantitative (Table).

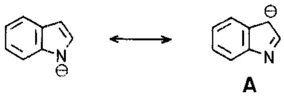


1

2 X = Br
3 X = J

The reaction requires about 1 mol of halogen per mol of indole and is carried out by dropping the freshly prepared halogen solution into the dimethylformamide solution of the substrate under stirring. The reaction is similar to a titration and the end point is perfectly detectable when the substrate (**1**) solution is colourless (appearance of halogen colour).

We think that the mildly basic characteristics of the dimethylformamide play an essential role, favouring the high yield by trapping the halogenic acid produced during the reaction. The reaction with iodine, less reactive than bromine, requires an activation of the indole substrate by addition of potassium hydroxide pellets, that probably produce the reactive anionic species **A**.



A

We found that, if the species **A** is not generatable (*N*-methylindole **1**; $R^2 = CH_3$), the reaction is very slow and requires harsher conditions to reach the complete conversion.

Bromination of Indoles 1; General Procedure for 2:

A solution of bromine (4.05 mmol) in dimethylformamide (20 ml) is dropped within a few minutes into a dimethylformamide solution (20 ml) of the indole **1** (4.0 mmol) at room temperature under stirring. The reaction mixture is then poured into ice and water (200 ml) containing ammonia (0.5%) and sodium metabisulphite (0.1%). The white precipitate is filtered, washed with cold water, dried, and weighed [for indole: yield: 0.78 g (96%); m.p. 65 °C]. Crystallisation can be carried out from hexane/ethyl acetate (4/1, v/v) or from ethanol/water. If the product is an oil, the recovery from the water emulsion is made by solvent extraction with hexane and ethyl acetate (1/1, v/v); before drying, the organic phase must be washed with cold water.

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Table. Selective Bromination and Iodination of Indoles **1**

Product[a] No.	R^1	R^2	R^3	X	Yield [%][b]	m.p. [°C][c]	Molecular formula[d] or Lit. m.p. [°C]	^{1}H-N.M.R. (DMSO-d_6/TMS$_{int}$)[e] δ [ppm]	M.S. (70 eV) *m/e* (rel. intensity %)
2a	H	H	H	Br	96	65° (dec)	66°[3] (dec)	6.8–7.7 (m, 5 H_{arom}); 11.5 (br. s, 1 H, NH)	197/195 (M^+, 72); 116 (100); 89 (48)
2b	H	H	CH_3	Br	96	90° (dec)	90–91°[7] (dec)	2.43 (s, 3 H); 6.8–7.6 (m, 4 H_{arom}); 11.4 (s, 1 H, NH)	211/209 (M^+, 90); 130 (100); 103 (24)
2c	H	CH_3	H	Br	94	oil[f]	C_9H_8BrN (210.1)	3.70 (s, 3 H); 6.8–7.6 (m, 5 H_{arom})	211/209 (M^+, 100); 196/194 (10); 130 (38)
2d	Cl	H	H	Br	94	89° (dec)	C_8H_5BrClN (230.5)	6.7–7.7 (m, 5 H_{arom}); 11.7 (br. s, 1 H, NH)	233/231/229 (M^+, 24/100/79); 196/194 (5/5); 152/150 (29/86); 125/123 (10/29)
2e	H_3CO	H	H	Br	98	79° (dec)	C_9H_8BrNO (226.1)	3.76 (s, 3 H); 6.6–7.6 (m, 4 H_{arom}); 11.1 (br. s, 1 H, NH)	227/225 (M^+, 100); 212/210 (67); 184/182 (39); 146 (9); 103 (31)
2f	H	H	C_6H_5	Br	95	78–79°	$C_{14}H_{10}BrN$ (272.2)	7.0–8.1 (m, 9 H_{arom}); 11.8 (s, 1 H, NH)	273/271 (M^+, 100); 191 (27); 165 (58)
3a	H	H	H	J	93	76° (dec)	75°[6] (dec)	6.8–7.7 (m, 5 H_{arom}); 11.6 (br. s, 1 H, NH)	243 (M^+, 100); 116 (73); 89 (40)
3b	H	H	CH_3	J	95	81° (dec)	81.5°[6] (dec)	2.40 (s, 3 H); 6.8–7.5 (m, 4 H_{arom}); 11.5 (s, 1 H, NH)	257 (M^+, 100); 130 (52); 103 (19)
3c	H	CH_3	H	J	98	oil[f]	C_9H_8JN (257.1)	3.67 (s, 3 H); 6.8–7.7 (m, 5 H_{arom})	257 (M^+, 100); 242 (5); 130 (27)
3d	Cl	H	H	J	95	93–95° (dec)	C_8H_5ClJN (277.5)	6.8–7.7 (m, 4 H_{arom}); 11.7 (br. s, 1 H, NH)	279/277 (M^+, 33/100); 242 (2); 152/150 (21/65); 125/123 (10/29)
3e	H_3CO	H	H	J	97	88–90° (dec)	C_9H_8JNO (273.1)	3.73 (s, 3 H); 6.6–7.6 (m, 4 H_{arom}); 11.2 (br. s, 1 H, NH)	273 (M^+, 100); 258 (67); 230 (39); 146 (15); 103 (27)
3f	H	H	C_6H_5	J	95	70–71°	$C_{14}H_{10}JN$ (319.2)	7.0–8.1 (m, 9 H_{arom}); 12.05 (s, 1 H, NH)	319 (M^+, 100); 191 (17); 165 (39)

[a] The secondary products are trace amounts of oxindoles for indole, 2-methylindole, 5-methoxy- and 5-chloroindole, and traces of dihaloderivatives for *N*-methyl- and 2-phenylindole.

[b] Yields of isolated products with purity ⩾98%, determined by H.P.L.C. [conditions: C-18 reverse phase, methanol/water (80/20, v/v) as eluent, U.V. detection at 280 nm].

[c] M.p. after recrystallisation from hexane/ethyl acetate (4/1, v/v).

[d] Satisfactory microanalyses obtained for all products: C ±0.30, H ±0.39, N ±0.42.

[e] The comparison with spectra of starting indoles showed the disappearance of the indole-3-hydrogen.

[f] Compounds **2c** and **3c** decompose without boiling at 91–93° (**2c**) and 175–178° (**3c**).

Iodination of Indoles 1; General Procedure for 3:

The procedure differs from bromination only in that it is necessary to add potassium hydroxide pellets (10 mmol) to the reaction medium. A particular case is given by the iodination of the *N*-methylindole: the reaction must be carried out adding, at the beginning, solid iodine (8 mmol) to the substrate (4 mmol) dissolved in dimethylformamide (10 ml); in the presence of potassium hydroxide pellets (15 mmol) under stirring at room temperature the reaction is complete within a few minutes.

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