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A CONVENIENT CONVERSION OF INDOLES TO 3,3-DIBROMOOXINDOLES AND THEN TO ISATINS

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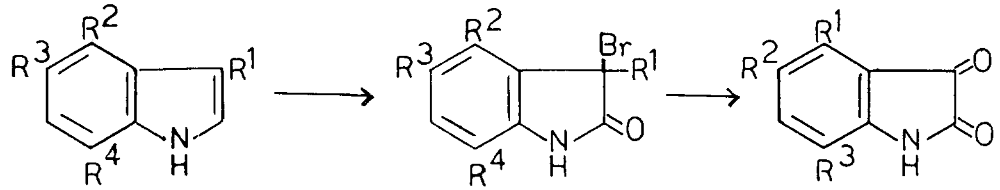
Abstract: 3-Bromoindoles, 3-unsubstituted indoles, or 3-formylindoles on treatment with NBS (2,3, or 4 molar equivalents, respectively) in t-butanol give 3,3-dibromooxindoles, and these readily yield the corresponding isatins on hydrolysis.

Recently we have been interested in the preparation of some isatins having a free NH group. The oxidation of indole to isatin has been achieved by the action of chromium trioxide in acetic acid[1], but the highest yields were obtained when an N-substituent was present[2].

While searching for novel mild conditions under which indoles unsubstituted in the 1- and 2-positions might be converted to isatins, we were impressed by the conversion of 3-alkyl(or aryl)-indoles into 3-bromo-3-alkyl(or aryl)-oxindoles with N-bromosuccinimide (NBS) in t-butanol[3]. It seemed possible that treatment of 3-bromoindoles with NBS in t-butanol would give 3,3-dibromooxindoles directly and these would be readily converted into the corresponding isatins. Some of our findings in investigations of this idea are presented.

Bromination of indole (1) with pyridinium perbromide gave 3-bromoindole (5) and this, on treatment with NBS (2 molar equivalents) in t-butanol gave 3,3-dibromooxindole (8) (Table), which was readily hydrolysed to isatin (12) (98% yield) with warm aqueous methanol. Similarly 5-bromoindole (2) was smoothly converted into 5-bromoisatin (13). Application of this procedure to 4,7-dimethoxyindole[4] (4) gave 3-bromo-4,7-dimethoxyindole (7) and then the expected 3,3,5-tribromo-4,7-dimethoxyoxindole (10) (45%) together with two other products. This example is one where the 3-bromoindole is markedly less stable than the indole. We considered that it might be possible to combine the initial 3-bromination and oxindole formation into a one-pot reaction by using NBS as the reagent for both reactions. This proved to be the case: 4,7-dimethoxyindole (3) with NBS (3 molar equivalents) in t-butanol gave (10) in 45% yield, and solvolysis of this gave the corresponding isatin (14), m.p. 269-270°C (ex chloroform) in 98% yield. This improved procedure has been applied to the one-pot conversion of 7-azaindole into 3,3-dibromo-7-azaoxindole.

Indole-3-carbaldehyde (4) with NBS (2 molar equivalents) in t-butanol gave 3-bromo- (11) and 3,3-dibromooxindole (8). Treatment of 6-azaindole-3-carboxaldehyde with NBS (4 molar equivalents) gave 3,3-dibromo-6-azaoxindole which yielded 7-azaisatin.



1 R^1=R^2=R^2=R^4=H
2 R^1=R^2=R^4=H, R^3=Br
3 R^1=R^3=H, R^2=R^4=OMe
4 R^1=CHO, R^2=R^3=R^4=H

5 R^1=Br, R^2=R^3=R^4=H
6 R^1=R^3=Br, R^2=R^4=H
7 R^1=Br, R^2=R^4=OMe
R^3=H

8 R^1=Br, R^2=R^3=R^3=H
9 R^1=R^3=Br, R^2=R^4=H
10 R^1=R^3=Br, R^2=R^4=OMe
11 R^1=R^2=R^3=R^4=H

12 R^1=R^2=R^3=H
13 R^1=R^3=H, R^2=Br
14 R^1=R^3=OMe, R^2=Br

Table Preparation of 3,3-Dibromooxindoles

Indole or 3-Bromoindole	Reaction Conditions[a] NBS (molar ratio)	Time (h)	3,3-Dibromo -oxindole	M.p. (°C) (Literature value)	Yield (%)
1	3	3.3	8	164-5 (165[6])	49
3	3	6	10	195-7[b,c]	45
4	2	3.3	8	163-5 (165[6])	43
			11	160-1 (161-2[7])	38
5	2	3.3	8	164-5 (165[6])	69
6	2	6.3	9	247-260[b] (250-260[6])	96
7	2	4	10	195-7[c]	23

a) The reaction mixture at room temperature. b) Decomposition occurs. c) Satisfactory elemental analysis data, and i.r. and ^{1}H n.m.r. spectra were obtained on all novel compounds.

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