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OXIDATION OF INDOLES WITH PYRIDINIUM BROMIDE PERBROMIDE A SIMPLE AND EFFICIENT SYNTHESIS OF 7-AZAOXINDOLES

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Abstract: Indoles and azaindoles on treatment with pyridinium bromide perbromide (PBPB) in t-butanol give 3,3-dibromooxindoles which, upon further reduction, yield the corresponding oxindoles.

Indoles and oxindoles continue to pose a synthetic challenge to chemists because of their interesting and varied biological properties[1,2]. Although much has been done in the area of indoles and their derivatives, a limited amount of work has been reported with azaindoles. Because of their potentially interesting biological properties, we were interested in the synthesis and biological evaluation of azaindoles, in particular 7-azaoxindoles.

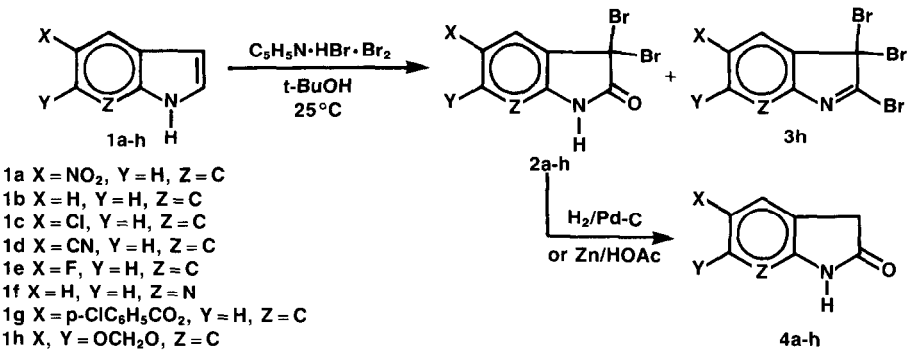
To our knowledge, there are only two reported syntheses of 7-azaoxindoles[3,4], both of which have serious synthetic drawbacks due to either the nature of the reagents used or poor yields. The classical method of Kagi[3], for example, has as a key step the reaction of 2-aminonicotinic acid chloride with a large excess of diazomethane, thus making it unattractive for large scale work. The second method of Robison[4] requires sealed tube hydrolysis of a key intermediate, 2-chloro-5-cyanopyridine, as well as several sublimations in order to obtain pure product, and proceeds in very poor yield. Because of these drawbacks a general method which would efficiently convert the readily available parent indoles and azaindoles to the corresponding oxindoles and their derivatives appeared to be of great synthetic value.

Because 7-azaindole is readily available, we were prompted to search for an oxidative method which would efficiently convert 7-azaindole to the corresponding 7-azaoxindole. Detailed bromination reactions of indoles with NBS or bromine in different solvent systems, their substitution, oxidation and derivatization have been reported[5,6,7,8,9,10,11]. In general, it is now well established that halogenation (bromination) of the indole nucleus in aqueous media favors oxidation whereas halogenation in non-aqueous media favors bromination, and that the two reactions are usually competitive, with neither one yielding exclusively one product. A recent exception to this rule might be a method reported by Smith *et al,*[12] which employs a reagent system consisting of NBS and silica gel. Very good yields of monobrominated indoles and benzoimidazoles with a high degree of regioselectivity were obtained.

Despite numerous reports of oxidation/bromination of indoles, little work has been done with corresponding azaindoles. In work recently reported by Parrick, *et al,*[13] in which indoles were converted to isatins via 3,3-dibromooxindole intermediates using NBS in t-butanol, the synthesis of 3,3-dibromo-7-azaoxindole was mentioned However, no yield or physical data was reported. We found that reaction of 7-azaindole with NBS in t-butanol or acetic acid gave variable results however, and thus studied other oxidizing agents

We next turned to a mild and selective brominating agent[14] pyridinium bromide perbromide (PBPB), which has been used extensively for bromination of ketones[15], aromatic amines[16] and olefins[17]. Use of PBPB as a brominating agent and pyridine as a solvent at low temperature was also reported to be ideal for the synthesis of 3-bromoindole[18].

Scheme 1:



1a-h

1a X = NO_2, Y = H, Z = C
1b X = H, Y = H, Z = C
1c X = Cl, Y = H, Z = C
1d X = CN, Y = H, Z = C
1e X = F, Y = H, Z = C
1f X = H, Y = H, Z = N
1g X = p-$ClC_6H_5CO_2$, Y = H, Z = C
1h X, Y = OCH_2O, Z = C

2a-h

3h

4a-h

Thus, reaction of 7-azaindole with PBPB in t-butanol proceeds in excellent yield to give 3,3-dibromo-7-azaoxindole **2f** which, after hydrogenation over 10% Pd-C in ethanol, yields 7-azaoxindole **4f** in 75% isolated yield (Scheme 1). This represents a significant improvement over previous methods[3,4]. We have also examined oxidation of several other indoles (Scheme I, Table I) and found that PBPB oxidation/bromination works equally well when strong electron withdrawing groups are present in the C-5 position (e.g., **1a**). However, the reaction proceeds in a less satisfactory manner when electron donating substituents are present. With these compounds, in addition to the desired oxidation product, at least two less polar by-products are found which are presumed to be unstable 3-bromoindole or tribromo indole derivatives. In most cases, the major by-product was found to be the very unstable tribromo indolenine derivative which was extremely difficult to characterize, with the exception of the indolenine derived from 5,6-methylenedioxyindole. In this case, tribromo indolenine intermediate **3h** is obtained as a single major product (80%) which is a reasonably stable orange crystalline material (mp = 88-89°C) whose structure was confirmed by x-ray analysis. As with the 3,3-dibromo-7-azaoxindole, other 3,3-dibromooxindole derivatives (Table I) can be either hydrogenated (H_2/Pd-C) or reduced with zinc in acetic acid (depending on C-5 substitution) to provide the corresponding oxindoles **4** in very good yield. For example, compound **2c**, upon treatment with 10 equivalents of zinc dust in HOAc at room temperature, provides 5-chlorooxindole **4c** in nearly quantitative yield (mp = 196-198°C, Lit[18,19] mp = 195-196°C)

Table 1
PREPARATION OF 3,3-DIBROMOOXINDOLES

Indole	Reaction Conditions[c] Molar Ratio[b] of Indole/PBPB	Time(h)	3,3-Dibromo-oxindoles	mp°C (Literature Value)	Yield (%)[c]
1a	1:3.5	4.0	2a	205-207[d]	88
1b	1:3	20.0	2b	165-167(164-165)[13]	20
1c	1:3	3.5	2c	203-205[d]	60
1d	1:3	4.0	2d	223-225[d]	65
1e	1:3	20.0	2e	171-173[d]	48
1f	1:4	5.5	2f	198-200[d]	86
1g	1:3	18.0	2g	250 dec[d]	38
1h	1:3	2.5	2h	—	0[e]

[a] All reactions were carried out at room temperature above the freezing point of t-butanol.
[b] With the exception of 1f, all PBPB was added over an initial period of 0.5 hr.
[c] Isolated yields by silica gel column chromatography (20% EtOAc/CH_2Cl_2 or 30% EtOAc/hexane used as eluant). Two other by-products were also observed: unstable tribromo indolenines and 3-bromoindoles.
[d] Satisfactory elemental analysis data, mass spectra, i.r. and ^1H n.m.r. spectra. were obtained on all new compounds.
[e] 3h was obtained as a single major product.

In conclusion, oxidation of 7-azaindole to the 3,3-dibromo-7-azaoxindole with PBPB followed by hydrogenation provides an efficient and convenient synthesis of 7-azaoxindole. This method is applicable to other substituted indoles and complements previously reported methods. Although this reaction is limited to indoles bearing electron withdrawing substituents, this difficulty can be ultimately circumvented by subsequent conversions (e.g. reduction of a nitro group to an amine). The ready availability of PBPB and the convenience under which these oxidation reactions are carried out should find extended use of this reagent with related heterocycles

Typical Experimental Procedure: Synthesis of 7-Azaoxindole

To a stirred solution of 7-azaindole (Aldrich; 2.0 g, 0.0164 mole) in 120 ml of undistilled t-butanol (Fisher) was added in portions 16.2 g (0.05 mole) of 90%-PBPB (Aldrich) over a period of 0.5 hr. The reaction mixture was allowed to stir at room temperature with occasional warming (to prevent t-BuOH from freezing) over a period of 3 hr. TLC analysis EtOAc/CH_2Cl_2 (20:80) after this time indicated nearly complete consumption of starting azaindole and formation of a major less polar product. An additional equivalent of PBPB (5.4 g) was added and the reaction mixture was stirred for an additional 2.5 hr. t-Butanol was removed *in vacuo* and the resulting residue dissolved in EtOAc/water (500 ml/500 ml). The organic layer was separated and the aqueous layer was extracted with an additional 300 ml of EtOAc. The combined EtOAc extracts were washed with water (2x), brine, dried (Na_2SO_4) and concentrated *in vacuo* to give 4.9 g of light brown-tan solid contaminated by a small amount of baseline material. Trituration of the crude product with methlyene chloride gave 4.25 g (86%) of pure 3,3-dibromo-7-azaoxindole **2f** as a white solid. Recrystallization from toluene gave 3.7 g of light tan crystalline product mp 194-196°C dec. Hydrogenation of **2f** (1.38 g, 0.0047 mole) over 10% Pd-C (1 0 gram) in 140 ml of anhydrous ethanol at 30 psi afforded after purification through a short silica gel column (10% CH_3OH/CH_2Cl_2) 0.48 g (75%) of 7-azaoxindole **4f** as a white-pink solid. Recrystallization from toluene gave light pink needles mp 178-179°C; Lit[3,4] mp = 175°C.

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