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A SUPERIOR SYNTHETIC METHOD FOR THE BROMINATION OF INDOLES AND BENZIMIDAZOLES.

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SUMMARY: Brominated indoles and benzimidazoles are formed in very high yields and with substantial regioselectivity by use of a reagent system consisting of N-bromosuccinimide (NBS) and silica gel in dichloromethane.

Brominated heterocyclic compounds have been key intermediates for the synthesis of biologically important molecules.[1] However, within the indole and benzimidazole[2] series there are few reports of bromination reactions and consequently there is no good, general method for the preparation of these brominated heterocycles, which is both high yielding and regioselective..

Brominations of indoles in protic media using N-bromosuccinimide (NBS) result in the formation of bromooxindoles[3,4] and bromoindolenines[5,6,7] rather than simple bromo-derivatives of the starting heterocycles. Although the latter compounds have sometimes been obtained from such reactions,[1,8,9] yields are generally poor. Brominations in aprotic media are more successful for synthesis of such compounds, but even so yields are not good. The reaction of skatole with NBS has been studied most extensively. This reaction initially yields 2-bromoskatole (isolated yield 45%)[5] and then upon further bromination 2,6-dibromoskatole (48%)[5,10]. A single report records the preparation of 2-bromoskatole (85%) from skatole using NBS in tetrachloromethane in the presence of benzoyl peroxide[11]. However, the reason for the improvement in yield in the presence of a radical initiator is not clear. Nor is it known if the reaction is general.

In this communication we wish to report a general bromination method which gives high yields and shows substantial regioselectivity in the bromination of indoles and benzimidazoles. The method was prompted by the development of successful silica-supported reagents for chlorination of aromatic compounds.[12] The silica serves to provide both a surface upon which the reaction can take place and acidic catalytic sites.[13]

The reactions are very convenient to carry out. In many cases simple removal of the silica by filtration and evaporation of the solvent provides the pure products in high yield. The degree of substitution is readily controlled by choice of stoicheiometry. Details of the results obtained with several indoles and benzimidazoles are given in the table.

Table

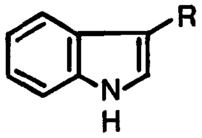
Synthesis of bromoindoles and bromobenzimidazoles.

Starting Material	Product	Mole ratio Starting Material : NBS	Reaction time[a]	Yields[b] (%)
1b	3b	1 : 1	25 min	90
1b	4b	1 : 2	20 min	95
1a	3a	1 : 1	30 min	96
1a	4a	1 : 2	35 min	77
2	5a	1 : 1	15 min	>98
2	5b	1 : 2	30 min	95
6a	6b	1 : 1	2 hrs	67
6a	6c	1 : 2	3 hrs	96(60)[c]
7a	7b	1 : 1	60 min	90

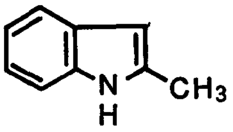
[a] Reaction mixtures were magnetically stirred at 20°C, under an atmosphere of nitrogen; in the cases of 2- and 3- methylindoles the reactions were also conducted in the dark.

[b] Yield of product obtained by washing the material from the silica with dichloromethane (indoles) or methanol(benzimidazoles) followed by removal of the solvent; in the benzimidazole cases the solid obtained was washed with water to remove NBS and then dried.

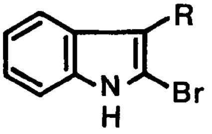
[c] The product obtained by the standard purification procedure described in footnote b contained some monobromo product; the yield in parentheses is that obtained following three recrystallizations to remove this impurity.



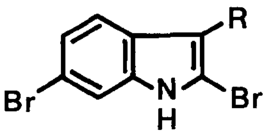
(1) (a) $R = CH_3$
(b) $R = CH_2CN$



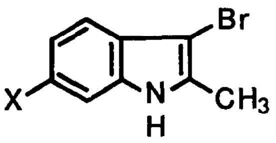
(2)



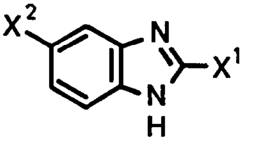
(3) (a) $R = CH_3$
(b) $R = CH_2CN$



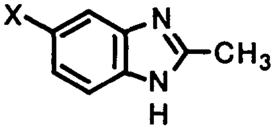
(4) (a) $R = CH_3$
(b) $R = CH_2CN$



(5) (a) $X = H$
(b) $X = Br$



(6) (a) $X^1 = X^2 = H$
(b) $X^1 = Br, X^2 = H$
(c) $X^1 = X^2 = Br$



(7) (a) $X = H$
(b) $X = Br$

The reactions are simply carried out by stirring a dichloromethane solution of the appropriate heterocycle under nitrogen with NBS and silica gel, in the dark in the cases of the methylindoles. The reaction product is then washed from the silica with the appropriate solvent (dichloromethane for indoles, methanol for benzimidazoles).

The indoles are obtained as essentially pure (by GC and tlc) off-while solids on removal of the dichloromethane. The methyl compounds darken rapidly on exposure to air and present difficulties for microanalysis but show the correct spectral properties for the pure products without need for further purification. Brominated indole-3-acetonitrile derivatives present no such problems and are relatively easily handled and characterized.

The procedure for extraction of benzimidazoles is only slightly more complex. Use of methanol to remove these compounds from the silica also elutes succinimide. Therefore, after removal of the solvent the residual solid is washed with water to remove the succinimide, and then dried. This generally provides analytically pure material.

This method for bromination of indoles and benzimidazoles is the most convenient and general method known. It enhances the ease with which the corresponding brominated heterocycles are obtained and should result in greater utilization of such compounds.

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13. B.D.H. silica gel (60-120 mesh) is used routinely for all reactions.

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