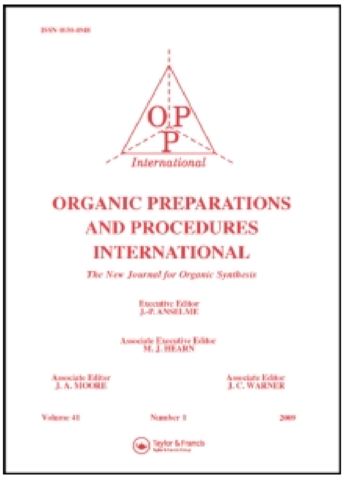

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A CONVENIENT N-ACETYLATION OF INDOLES

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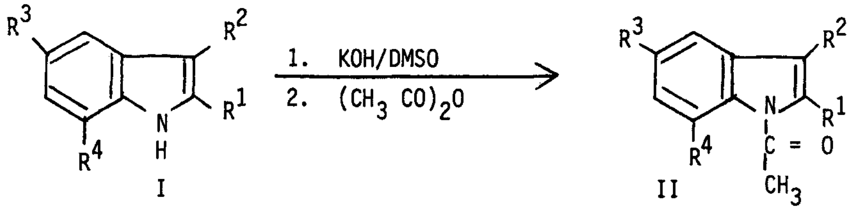
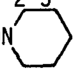
We now report a rapid and efficient method for the selective N-acetylation of indoles under mild conditions. Thus, treatment of I with powdered potassium hydroxide in dimethyl sulfoxide at room temperature generates the indolyl potassium anion[1] which on addition of acetic anhydride affords the N-acetylindole (II) in good yield. Our results are summarized in the Table.



This method provides a very attractive alternative to earlier indole acylation methods,[2] some of which give a mixture of N- and C-acylation product, and to the more recent methods[3-5] for selective N-acylation that require elevated temperatures and/or extended reaction times. Our method seems to be applicable to any indole capable of forming the corresponding indolyl anion under these conditions and cleanly affords N-acylation product (II). The only other material present in the reaction product is unchanged indole which can be removed by crystallization or chromatography. Attempts to drive the reaction to completion by using a large excess of reagents were not successful and the

Table

N-Acetylation of Indoles with Potassium Hydroxide/Acetic Anhydride in Dimethyl Sulfoxide

No.	Substrate[a] R^1	R^2	R^3	R^4	Yield[b] (%)	mp. or bp./torr
Ia	H	H	H	H	65	97.5-101°/0.15 (Ref.[9] 152-153°/14)
Ib	CH_3	H	H	H	36[c]	42-42.5°
Ic	H	CH_3	H	H	54[d]	60-62.5°(Ref.[11] 66-67°)
Id	CH_3	CH_3	H	H	43	68-70°(Ref.[4] 68-70°)
Ie	H	H	H	CH_3	51[e]	75-75.5°
If[12]	$-CH_2CH_2CH_2CH_2-$		H	H	61	75-75.5°(Ref.[13] 77-78°)
Ig	C_6H_5	C_6H_5	H	H	61[f]	139-140°(Ref.[14] 138°)
Ih	H	H	Br	H	80	109-109.5°(Ref.[5] 101-102°)
Ii	H	H	NO_2	H	80	178.5-180°(Ref.[3] 178-180°)
Ij[15]	H	$COCO_2C_2H_5$	H	H	54	94-95°[g]
Ik[16]	H	CH_2CON	H	H	62	132.5-134°[h]

a) Commercial materials unless otherwise noted. b) Yields refer to recrystallized (95% ethanol) or distilled product. In some cases additional product and recovered I was obtained by dry column chromatography or preparative T.L.C. of the recrystallization mother liquors. All products exhibited satisfactory I.R., U.V., and ^{1}H-N.M.R. spectra. c) The product decomposes at room temperature; 38% of 2-methylindole was recovered after a reaction time of 5 min. This compound has been prepared previously but physical properties were not recorded.[10] d) Recovered 3-methylindole: 15%. e) Recovered 7-methylindole: 10%; Calcd. for $C_{11}H_{11}NO$ (173.1): C,76.28; H,6.40; N,8.09; found: 76.05; 6.32; 8.26. f) Recovered 2,3-diphenylindole: 12%. g) calcd. for $C_{14}H_{13}NO_4$ (259.1): C,64.86; H,5.05; N,5.40; found: 64.96; 5.10; 5.44. h) Calcd. for $C_{17}H_{20}N_2O_2$ (284.1): C,71.81; H,7.09; N,9.85; found: 71.92; 6.87; 9.99.

1.00g (0.005 mol) of 5-bromoindole (Ih) in one portion. The mixture was stirred an additional 5 min and then 1.0 ml (0.011 mol) of acetic anhydride was added in one portion. The resulting viscous solution was stirred for an additional 30 min at room temperature. The reaction was worked up by pouring onto ice-water, extracting with ether (3x), washing the ether extract with water (5x) and brine (1x), drying over sodium sulfate, and concentrating *in vacuo* to afford the crude product. Crystallization from 95% ethanol gave, in several crops, 0.97g (80%) of N-acetyl-5-bromoindole (IIh) as colorless needles, m.p. 109-109.5°, lit.[5] 101-102°.

'H-N.M.R. ($CDCl_3$): δ=2.54 (S,3H), 6.43 (d,1H,J=4 Hz), 7.22-7.44 (m,2H), 7.58 (d,1H,J=2HZ) and 8.17 (d,1H,J=9HZ) ppm.

I.R. ($CHCl_3$) ν max: 1710 cm^{-1}, no N-H.

U.V. (95% EtOH) λ max: 244,286,295,304 nm.

N-Acetylindole (IIa).-

The above procedure was followed using 40 ml of dimethyl sulfoxide, 1.91g (0.034 mol) of potassium hydroxide, 2.00g (0.017 mol) of indole (Ia), and 3.3 ml (0.035 mol) of acetic anhydride to afford, after workup, a golden oil. Distillation gave a mixture of N-acetylindole (IIa) and Ia as a colorless oil; yield: 1.94g; bp. 97.5-101°/0.15 torr. Analysis by G.L.C. showed IIa:Ia in the ratio 79:21 (1.5% OV-101 on 100-120 chromosorb G; 5'X1/8"; 110°). These could be separated by dry column chromatography or preparative T.L.C. The pot residue was subjected to preparative T.L.C. (silica gel, benzene) to afford an additional 0.23g of pure IIa. Total yield of IIa: 1.77g (65%). The product was identical with a commercial sample of IIa (K & K Laboratories).

gen was added 0.57g (0.010 mol) of powdered potassium hydroxide. The mixture was mechanically stirred for 5 min and to it was then added

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optimum conditions appear to involve using two equivalents each of potassium hydroxide and acetic anhydride. Presumably, the equal excess of each reagent results in self-neutralization during workup and precludes the possibility of base-catalyzed hydrolysis of the labile II. For example, Bergman and his group have reported that N-acetylindole is hydrolyzed to indole by treatment with 0.1 M sodium hydroxide in aqueous ethanol at 25° for 30 minutes.[5] However, control experiments demonstrate that recovered I does not arise from II by hydrolysis during workup.

As seen by examples in the Table, our N-acetylation method is general for a variety of alkyl- and aryl-substituted indoles and leaves untouched the ester function in Ij and the amide function in Ik. The method should be applicable to the synthesis of other N-acylindoles, and we have prepared N-propionylindole and N-benzoylindole in yields of 42% (34% recovered I) and 22% (75% recovered I), respectively, under these same reaction conditions.

The absence of C-acetylation product (i.e., I, $R^2 = COCH_3$) is not surprising[1] since it is well established that dimethyl sulfoxide strongly solvates potassium cation,[6] elevating the reactivity of the indolyl anion and giving exclusive N-acetylation (the site of highest charge density).

We have avoided using carboxylic acid chlorides in this reaction (apart from one spectacularly unsuccessful attempt) because of the reported violence of their reaction with dimethyl sulfoxide.[7,8]

EXPERIMENTAL

General Procedure. N-Acetyl-5-bromoindole(IIh).- To 20 ml of dry dimethyl sulfoxide (distilled from CaH_2) at room temperature under nitro-

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