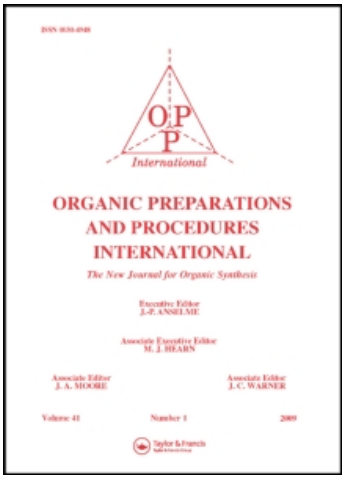


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# AN IMPROVED METHOD FOR THE SELECTIVE HYDROLYSIS OF 1-ACETYL-5-BROMO-4-CHLOROINDOXYL ACETATE TO 1-ACETYL-5-BROMO-4-CHLOROINDOXYL

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# AN IMPROVED METHOD FOR THE SELECTIVE HYDROLYSIS OF 1-ACETYL-5-BROMO-4-CHLOROINDOXYL ACETATE TO 1-ACETYL-5-BROMO-4-CHLOROINDOXYL

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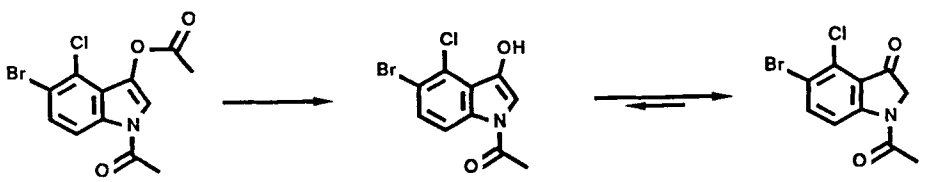
Derivatives of 5-bromo-4-chloroindoxyl have been found to be especially useful as staining indicators.[1] Commercially available 1-acetyl-5-bromo-4-chloroindoxyl acetate (1)[2] is hydrolyzed to 1-acetyl-5-bromo-4-chloroindoxyl (3), and is then derivatized to the appropriate substrate.




1 2 3

Literature procedures for this hydrolysis include the use of refluxing aqueous ethanol in the presence of sodium sulfite[3] and sodium in methanol.[4] The efficiency of the latter method is low (56% yield). The production of large amounts of blue dye via the former procedure, even when run under a nitrogen atmosphere, led to the development of the present procedure which affords high yields of 3 with minimal production of dye. Replacement of sodium sulfite with the more powerful anti-oxidant sodium hydrosulfite inhibits dye formation, and the use of one equivalent of sodium bicarbonate induces rapid hydrolysis. Excess sodium bicarbonate catalyzes indigo production and should be avoided.

## EXPERIMENTAL SECTION

1-Acetyl-5-bromo-4-chloroindoxyl (3).- A mixture of 3.51 g (10 mmol) of 1, 0.84 g (10 mmol) of sodium bicarbonate, and 3.50 g (20 mmol) of sodium hydrosulfite in 200 ml each of ethanol and water under a nitrogen atmosphere was heated at reflux until TLC monitoring indicated the reaction was complete (<15 min). Upon cooling and the addition of 100 ml of water, 3 was collected and washed with water. After drying in vacuo, 2.88 g (87%) of dull white to pale blue-green tinted solid was obtained. MS(FD): M+ 287/289

Anal. Calcd. for $C_{10}H_7BrClNO_2$: C,41.63; H,2.45; Br,27.69; Cl,12.29; N,4.85

Found: C,41.87; H,2.53; Br,27.66; Cl,12.33; N,4.86



## REFERENCES

1. a) J. P. Horwitz and J. V. Freisler, J. Med. Chem., 13, 1024 (1970).

2. Suppliers of 1-acetyl-5-bromo-4-chloroindoxyl acetate (5-bromo-4-chloro-3-indolyl-1,3-diacetate) include Research Organics, Inc., Fluka Chemical Corp., Vega Biotechnologies, Inc., BACHEM, Inc., ICN Pharmaceuticals, Inc., Sigma Chemical Co., Chemical Dynamics Corp., and Polysciences, Inc.

3. a) S. J. Holt, A. E. Kellie, D. G. O'Sullivan, and P. W. Sadler, J. Chem. Soc., 1217 (1958); b) D. Raileanu, O. Constantinescu-Simon, E. Mosanu, C. D. Nenitzescu, Rev. Roum. Chim., 67(12), 105 (1967); C. A., 68, 21775a; c) D. Nenitzescu and D. Raileanu, Chem. Ber., 91, 1141 (1958).

4. H. C. F. Su and K. C. Tsou, J. Am. Chem. Soc., 82, 1187 (1960).