A NOVEL SYNTHESIS OF INDOLE DERIVATIVES

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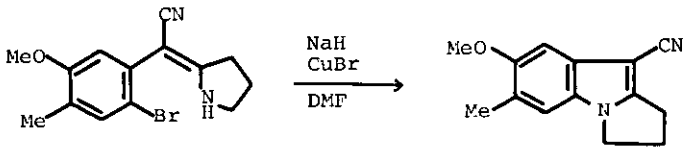
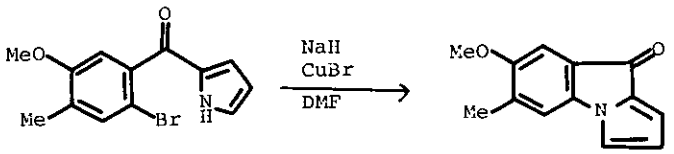
Abstract —— 1-Acetyl-2,3-dihydro-5,6-dimethoxy-1H-indole (13) was synthesized by cyclization of N-(2-bromo-4,5-dimethoxyphenethyl)-acetamide (6) using sodium hydride and cuprous halide in dimethylformamide. Indoles (14, 15 and 16) were prepared in a similar manner from the corresponding amides (8 and 10) and the carbamate (12). Under similar reaction conditions, phenylacetamides (20 and 21) afforded the oxindoles (22 and 23).

Recently several reports have appeared in which indoles were synthesized using reactions catalyzed by organometallic compounds such as nickel and palladium complexes[1]. Previously, in the course of synthetic approaches to the mitomycins, we developed a new intramolecular nucleophilic aromatic substitution reaction using sodium hydride and cuprous bromide in dimethylformamide. The aryl halides (1) and (3) were thus converted to pyrrolo[1,2-a]indoles (2)[2a] and (4)[2b] respectively in good yields. We have further extended this reaction for the synthesis of indoles and here wish to report the results.

Scheme 1



(1) (2)



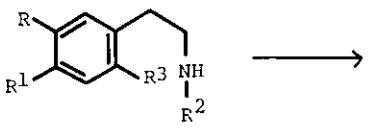
(3) (4)

As a typical example, one mole equivalent of cuprous iodide was added to a solution of N-(2-bromo-4,5-dimethoxyphenethyl)acetamide (6) [prepared by bromination of amide (5)[3]] in dimethylformamide containing two mole equivalents of sodium hydride. This mixture was heated at 80°C for 12 h and then quenched with excess ammonium chloride. After the usual work-up and chromatography of the crude product on a short column of silica gel, 1-acetyl-2,3-dihydro-5,6-dimethoxy-1H-indole (13) was obtained as colorless needles, m.p. 173 ∿ 174°C, in 74.0 % yield. The melting point and spectral data of this compound are in agreement with those reported in the literature[4].

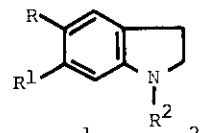
The use of cuprous bromide or cuprous chloride instead of cuprous iodide led to lower yields of the product, 58.9 and 57.9 % respectively. The above indoline (13) was converted, in excellent yield, to the indole (17), m.p. 155 ∿ 156°C (lit.[5], m.p. 154 ∿ 155°C), by oxidation with manganese dioxide in methylene chloride followed by alkaline hydrolysis.

In a similar manner, bromoacetamides (8) and (10), obtained by bromination of acetamides (7)[6] and (9)[7], afforded indolines (14), m.p. 137 ∿ 138°C (lit.[8], m.p. 135 ∿ 136°C), and (15), m.p. 117 ∿ 118°C, in 51.6 % and 53.0 % yields respectively. Moreover, in order to examine the utility of carbamates in place of acetamides, methyl 2-bromo-4,5-dimethoxyphenethylcarbamate (12), produced by bromination of the urethane (11)[9], was submitted to this cyclization procedure and was found to afford 2,3-dihydro-5,6-dimethoxy-1-methoxycarbonyl-1H-indole (16) as colorless needles, m.p. 134 ∿ 135°C, in 65.7 % yield.

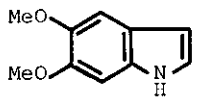
Scheme 2



(5) R=R^1=MeO, R^2=Ac, R^3=H
(6) R=R^1=MeO, R^2=Ac, R^3=Br
(7) R=MeO, R^1=H, R^2=Ac, R^3=H
(8) R=MeO, R^1=H, R^2=Ac, R^3=Br
(9) R+R^1=OCH$_2$O, R^2=Ac, R^3=H
(10) R+R^1=OCH$_2$O, R^2=Ac, R^3=Br
(11) R=R^1=MeO, R^2=CO$_2$Me, R^3=H
(12) R=R^1=MeO, R^2=CO$_2$Me, R^3=Br



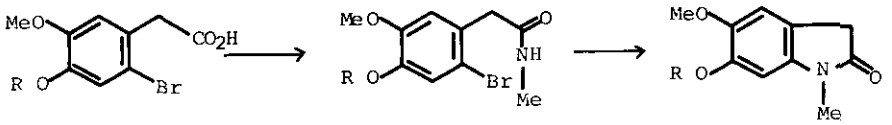
(13) R=R^1=MeO, R^2=Ac
(14) R=MeO, R^1=H, R^2=Ac
(15) R+R^1=OCH$_2$O, R^2=Ac
(16) R=R^1=MeO, R^2=CO$_2$Me



(17)

Subsequently, attempts to synthesize oxindoles were carried out as follows. Treatment of N-methyl-2-bromo-4,5-dimethoxyphenylacetamide (20) and its 4-benzyloxy analog (21) [obtained from the corresponding carboxylic acids (18)[10] and (19)[11]] with sodium hydride and cuprous bromide in dimethylformamide at room temperature for 10 h gave the oxindoles (22) and (23), in 63.4 % and 72.5 % yields respectively. This reaction provides a useful method for the synthesis of indole derivatives because the starting materials are easily prepared from commercially available compounds, and it is possible to synthesize indoles with electron-donating substituents at definite positions.

Scheme 3



(18) R = Me
(19) R = $PhCH_2$

(20) R = Me
(21) R = $PhCH_2$

(22) R = Me
(23) R = $PhCH_2$

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