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A GENERAL SYNTHETIC ROUTE OF 3,3-DISUBSTITUTED 3H-INDOLES AND REARRANGEMENT OF THEIR ACYL CHLORIDE ADDUCTS

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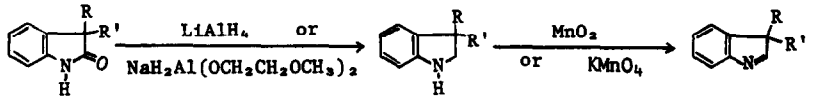
Of the known 3,3-disubstituted 3H-indole syntheses, the Brunner[2] and the Hoshino[3] method are representatives. In the former method which is the modification of the Fischer indole synthesis, it needs α-branched aldehyde which is not easy to prepare and does not succeed in the synthesis of 3,3-diaryl-3H-indole. Moreover, one of 3,3-two substituents tends to migrate sometimes to the 2 position in the course of synthesis[4b]. As for the Hoshino method which is founded on conversion of 3-alkylindolylmagnesium bromide to 3,3-dialkyl-3H-indole on treatment with alkyl halide, the purpose is not pursued when alkyl halide is bulky or replaced by aryl halide[4b]. Additionally, the reaction is apt to produce 1,3- and 2,3-disubstituted by-products[4a]. Thus, the applications of these methods are circumscribed within narrow bounds.

Improvement of such an unfavorable situation was required as the first step in our plan studying reactions of 3H-indoles. For this purpose, it was designed as a synthetic route to convert 3,3-disubstituted oxindole(I) to 3,3-disubstituted 3H-indole(III) through 3,3-disubstituted indoline(II). As a conclusion, this method was found to be able to be applied to syntheses of a wide variety of 3,3-disubstituted 3H-indole in pretty good yields, although it is a little roundabout way.



I II III Chart 1

Many procedures[5] have been reported for syntheses of 3,3-disubstituted oxindoles(I), but each is known to have its own fault which make wide application impossible. In this circumstance, the synthesis was improved by the following way: 3-Alkyloxindole was converted to 1-acetyl-3,3-dialkyloxindole by acetylation with boiling acetic anhydride followed by alkylation with sodium hydride and alkyl halide in refluxing THF. The product was saponified in ethanolic potassium hydroxide to transform to 3,3-dialkyloxindole(I): R,R'(m.p.,recrystallization solvent,% yield) of I[6] in Chart 2: Me,Me[5c](156-157°,EtOH,51); Me,Et(148-149°,benzene,60); Et,n-Pr(99-101°,n-hexane-benzene,65); Et,n-Bu(101-102.5°,n-hexane,52); Me,allyl(102-103°, n-hexane-benzene,59); Me,crotyl(74.5-75.5°,n-hexane-benzene,47); Me,benzyl(128-129°,n-hexane-benzene,86).

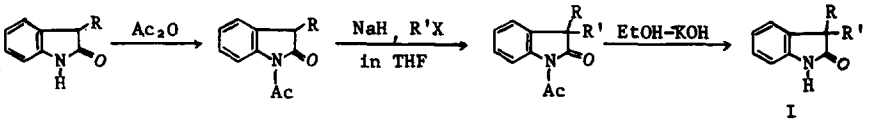
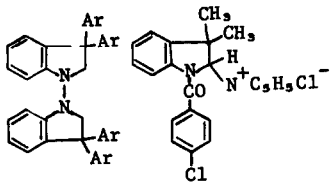


Chart2

3,3-Disubstituted oxindole(I) was reduced with lithium aluminum hydride or sodium dihydro-bis(2-methoxyethoxy)aluminate to 3,3-disubstituted indoline(II) in application of the known preparation method of 3,3-dimethylindoline[7]: R,R'(m.p.,recrystallization solvent, % yield) of II[6]in Chart 1: Me,Et(143-145° as N-p-nitrobenzoate,EtOH-acetone,57); Me,allyl(95-96° as N-p-nitrobenzoate,EtOH,94); Me,phenyl[8](139-140° as N-benzoate,EtOH,78); phenyl, phenyl[9](91-92°,EtOH,90); phenyl,benzyl[8](90-91°,n-hexane,63); p-tolyl,p-tolyl[9](117-118°, EtOH,60).

To convert the indolines(II) thus obtained to the 3H-indoles(III), various oxidizing agents were examined. As a result, the dehydrogenation method by refluxing with activated manganese dioxide in anhydrous toluene was generally recommended for the purpose: R,R'(m.p., recrystallization solvent,% yield) of III[6] in Chart 1: Me,Me[7](229-230°,EtOH,51); Me,allyl[4a] 144°,MeOH,51); Me,phenyl(>300°,benzene,76); phenyl,phenyl(93.5-94.5°,benzene,53); p-tolyl, p-tolyl(see reference 10, 50). Also, it was useful for dehydrogenation of 3,3-dialkyl-indoline to reflux with potassium permanganate[11] in acetone, for example yielding 3,3-dimethyl-3H-indole[7] in 50 % yield and 3-ethyl-3-methyl-3H-indole[4b] ,m.p.163-164°(EtOH) in 50 % yield. But this method was unfavorable for dehydrogenation of 3,3-diarylindoline because it resulted mainly in the formation of N,N'-bis(3,3-diarylindolinyl)(IV): Ar = phenyl,m.p. 170-171°(n-hexane-benzene),30% yield; Ar = p-tolyl,m.p.167-169°(n-hexane-benzene), 37 % yield[6].

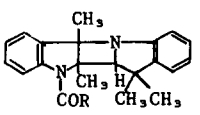


IV VIa

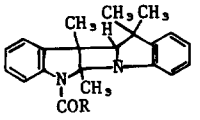
Leuchs[12] has reported that acyl chloride adds to 3,3-dimethyl-3H-indole to give 1-acyl-2-chloro-3,3-dimethylindoline(V) which, in turn, converts to 1-acyl-3,3-dimethylindolin-2-yl pyridinium chloride(VI) by reaction with pyridine. The pyridinium salt(VI) appealed to our interest by a preliminary experiment where it was found that the pyrolysis of VI gave an intermolecular condensation product of higher molecular weight rather than the Wagner-Meerwein rearrangement product. Therefore, this type reaction was examined in details. 3,3-Dimethyl-3H-indole was treated with equimole of p-chlorobenzoyl chloride in pyridine at room temperature to form 1-(p-chlorobenzoyl)-3,3-dimethylindolin-2-yl pyridinium chloride(VIa) through 1-(p-chlorobenzoyl)-2-chloro-3,3-dimethylindoline(Va). Without isolation of VIa, the pyridine solution was refluxed for 12 hrs. and the remaining residue after evaporation was washed with aqueous sodium carbonate and separated by silica-gel chromatography into two kinds of products. One was identical with 1-(p-chlorobenzoyl)-3,3-dimethylindolin-2-ol (VII), m.p. and a mixed m.p. with an authentic sample prepared by the Leuchs method[12] 127-128.5°. The other was further separated by repeated recrystallizations from ethanol into two compounds, colorless prisms of m.p. 204-206°($VIII_1$) and colorless prisms of m.p.133-135° ($VIII_2$), both of which have the same molecular formula, $C_{27}H_{25}ON_2Cl$(M^+ 428). Spectral data of them bear a close resemblance to each other suggesting that they are geometrically

isomeric: IR(nujol) 1670 cm^{-1}(>N-C=O); UV max(EtOH) 229.5(4.66), 261.5(4.28) and 287.4 nm(4.24); NMR($CDCl_3$) 5.94(1H,s,CH), 2.15(3H,s,CH_3), 1.81(3H,s,CH_3), 1.46(3H,s,CH_3) and 0.92 ppm (3H,s,CH_3) for $VIII_1$. IR(nujol) 1670 cm^{-1}(>N-C=O); UV max(EtOH) 225.0(4.56), 262.5(4.18) and 287.3 nm(4.11); NMR($CDCl_3$) 6.13(1H,s,CH), 2.15(3H,s,CH_3), 1.81(3H,s,CH_3), 1.48(3H,s,CH_3) and 0.92 ppm(3H,s,CH_3) for $VIII_2$. By taking all the data above-stated into consideration, A, B and C are proposed for the plane structure of $VIII_1$ and $VIII_2$ equal to each other.

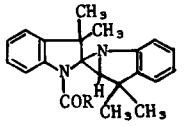
Of those, C was excluded because the signal of methine proton on aziridine ring should appear in higher field[13]. To get informations further on structure of $VIII_{1,2}$, $VIII_1$ was reduced with lithium aluminum hydride in ether and the products were separated into IX_1, X



A = $VIII_{1,2}$



B



C

R = p-ClC_6H_4

and II_a by alumina chromatography. X(m.p.111-112°) and II_a(in the form of N-3,5-dinitrobenzoate,m.p.135-136.5°) were identified as 2,3-dimethylindole[14] and 3,3-dimethylindoline[7]

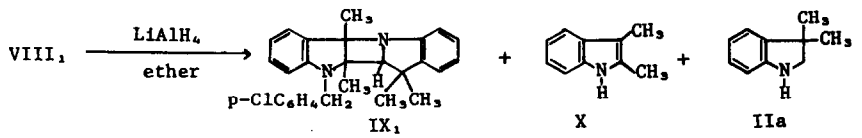


Chart 3

respectively by mixed m.p. determinations with authentic samples. The formations of these compounds by reductive fragmentation of $VIII_1$ offer an additional support to the structure, A or B, designated to $VIII_{1,2}$. IX_1 was proven to be a compound which was formed by reduction of the carbonyl group of $VIII_1$, $C_{27}H_{27}N_2Cl$, m.p.100-102°(MeOH), by spectral data: m/e 414 (M^+); IR absent (C=O); NMR($CDCl_3$) 5.45(1H,s,CH), 4.42,3.66(2H,AB q,15Hz,N-CH_2-), 2.21(3H,s,CH_3), 2.08(3H,s,CH_3), 1.38(3H,s,CH_3) and 0.89 ppm(3H,s,CH_3). Furthermore, the methine signal shifted to higher field by 0.49 ppm as a result of conversion from $VIII_1$ to IX_1, suggesting that the methine proton has been shielded very strongly by the carbonyl group in $VIII_1$. In this sense, A seems more favorable than B for the plane structure of $VIII_{1,2}$. Thus,it was made clear that $VIII_1$ and $VIII_2$ are geometrical isomers of 5(p-chlorobenzoyl)-5a,5b,6,11a-tetrahydro-5a,6,6,11a-tetramethylindolo[1,2:1',2']azetidino[3,4-b]indole, leaving the solution of a question, which corresponds to which form of end and exo, to future.

References and Footnotes

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