A regioselective and common synthetic method of dihalogenoindoles and its application for the total syntheses of marine alkaloids, 4,6-dibromo-,4,6-dibromo-2-methyl-, and 3,4,5-tribromoindole

A REGIOSELECTIVE AND COMMON SYNTHETIC METHOD OF DIHALOGENOINDOLES AND ITS APPLICATION FOR THE TOTAL SYNTHESES OF MARINE ALKALOIDS, 4,6-DIBROMO-, 4,6-DIBROMO-2-METHYL-, AND 3,4,5-TRIBROMOINDOLE[1]

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Abstract ——— A regioselective and common synthetic method for indoles carrying two different kinds of halogens was developed and applied successfully to the total syntheses of marine alkaloids, 4,6-dibromo- and 3,4,5-tribromoindole. The first total synthesis of 4,6-dibromo-2-methylindole is also reported.

In the previous papers,[2] we have already established the regioselective synthetic methods for both 4-[2a] and 7-substituted indoles.[2b] Application of these methods for 5- and/or 6-substituted indoles is expected to produce regioselectively polysubstituted indoles. Considering indoles, having two different kinds of substituents only at the benzene nucleus, there exist theoretically six types such as 4,5-, 4,6-, 4,7-, 5,6-, 5,7-, and 6,7-disubstituted indoles. Among them, syntheses of 5,6-disubstituted type indoles were so far extensively studied.[3] Therefore, we attempted to obtain indoles of the rest five types based on the above synthetic strategy.

First of all, we confined our attention to halogen because recently many halogen containing polysubstituted indoles were isolated as marine alkaloids[4] and they elicited considerable interests from synthetic organic chemists due to their interesting biological activity[4] and challengeable structures.[4b] In this communication, we report a regioselective and common synthetic method suitable for indoles having two different kinds of halogens. Utilizing the method, total syntheses of marine alkaloids, 4,6-dibromo-[4c] (1a), 4,6-dibromo-2-methyl-[4c] (2a), and 3,4,6-tribromoindole[4d] (3a) were accomplished.

I. Syntheses of 4,5-Dihalogenated Indoles

5-Iodo-[2b,5a] (4a), 5-bromo-[5b] (4b), and 5-chloro-3-indolecarboxaldehyde[5c] (4c) were

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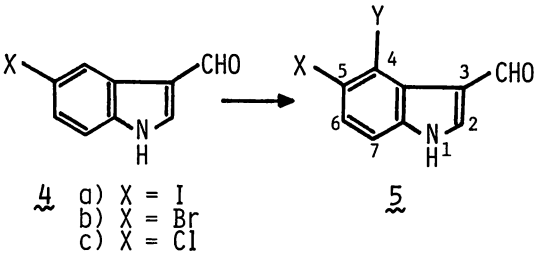

4 a) X = I
b) X = Br
c) X = Cl

5

5,10	X	Y
aa	I	I
ab	I	Br
ac	I	Cl

5,10	X	Y
ba	Br	I
bb	Br	Br
bc	Br	Cl

5,10	X	Y
ca	Cl	I
cb	Cl	Br
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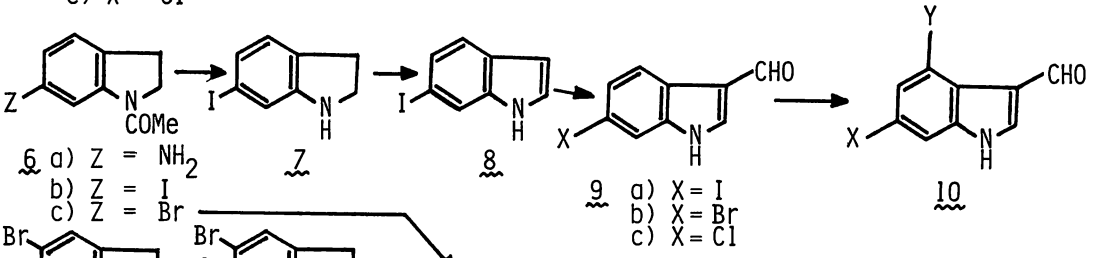

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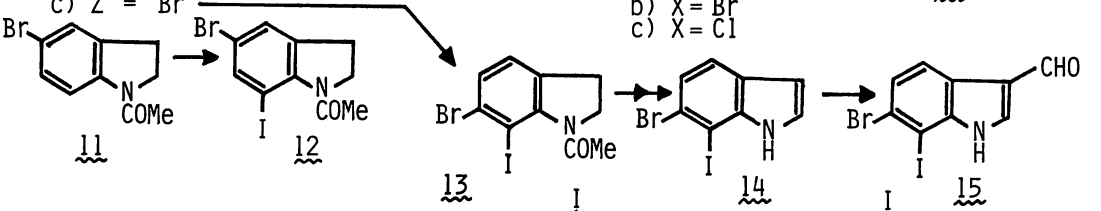
b) Z = I
c) Z = Br

7 8

9 a) X = I
b) X = Br
c) X = Cl

10



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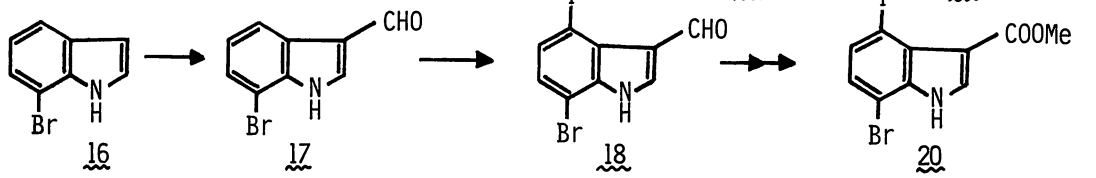

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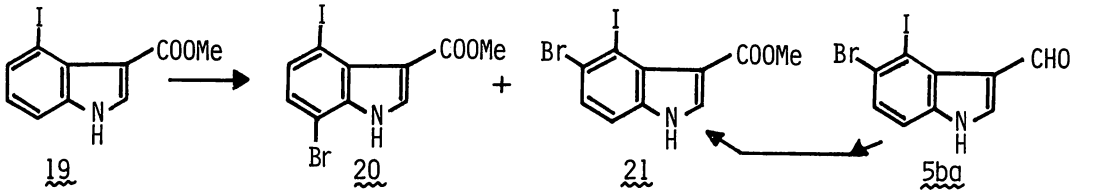
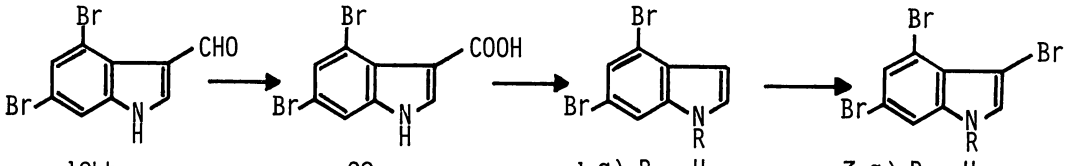
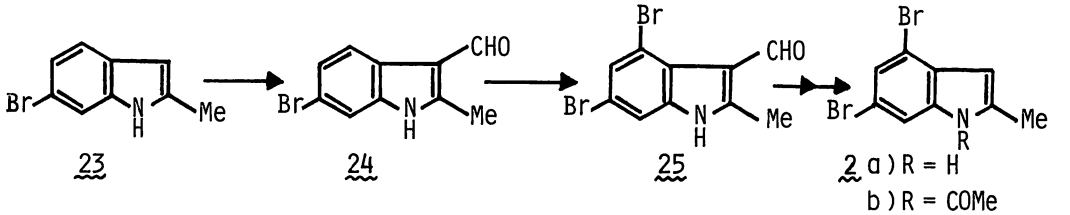


19 20 + 21 5ba



10bb 22 1 a) R = H
b) R = COMe
3 a) R = H
b) R = COMe



23 24 25 2 a) R = H
b) R = COMe

prepared by the usual method starting from 2,3-dihydroindole.[6] Thallation of 4a-c with thallium tris-trifluoroacetate (TTFA) in trifluoroacetic acid (TFA) and subsequent treatments with either aqueous potassium iodide (KI), cupric bromide ($CuBr_2$), or cupric chloride ($CuCl_2$) afforded the following 4,5-dihalogeno-3-indolecarboxaldehydes in yields described in the parenthesis: 4,5-diiodo- (5aa, mp 238-239°C, 57%), 4-bromo-5-iodo- (5ab, mp 246-247°C, 72%), 4-chloro-5-iodo- (5ac, mp 248-250°C, 51%), 5-bromo-4-iodo- (5ba, mp 232-233°C, 58%), 4,5-dibromo- (5bb, mp 234-234.5°C, 52%), 5-bromo-4-chloro- (5bc, mp 248-248.5°C, 62%), 5-chloro-4-iodo- (5ca, mp 234-235°C, 49%), 4-bromo-5-chloro- (5cb, mp 242.5-244°C, 68%), and 4,5-dichloro-3-indolecarboxaldehyde (5cc, mp 244-245°C, 43%).

II. Syntheses of 4,6-Dihalogenated Type Indoles

Sandmeyer reaction of 1-acetyl-6-amino-2,3-dihydroindole[7] (6a) with aqueous KI gave a 55% yield of 1-acetyl-2,3-dihydro-6-iodoindole (6b, mp 131-132°C). Alkaline hydrolysis of 6b afforded 2,3-dihydro-6-iodoindole (7, mp 92.5°C) in 96% yield. Salcomine catalyzed oxidation[6] of 7 with dioxygen produced 6-iodoindole (8, mp 111-111.5°C) in 81% yield. Vilsmeier reaction of 8 with phosphorus oxychloride ($POCl_3$) and N,N-dimethylformamide (DMF) afforded 6-iodo-3-indolecarboxaldehyde (9a, mp 216°C) in 87% yield. According to the similar synthetic route, 6-bromo-[8a] (9b) and 6-chloro-3-indolecarboxaldehyde[8b] (9c) were also prepared from 2,3-dihydroindole. Thallation of 9a-c with TTFA in TFA and subsequent treatments with either aqueous KI, $CuBr_2$, or $CuCl_2$ were found to produce the following 4,6-dihalogenated 3-indolecarboxaldehydes: 4,6-diiodo- (10aa, mp 280.5-283°C, 67%), 4-bromo-6-iodo- (10ab, mp 273-276°C, 54%), 4-chloro-6-iodo- (10ac, mp 273-274.5°C, 49%), 6-bromo-4-iodo- (10ba, mp 234-235°C, 61%), 4,6-dibromo- (10bb, mp 236-236.5°C, 63%), 6-bromo-4-chloro- (10bc, mp219-220°C, 52%), 6-chloro-4-iodo- (10ca, mp 232-232.5°C, 64%), 4-bromo-6-chloro- (10cb, mp 218.5-219°C, 59%), and 4,6-dichloro-3-indolecarboxaldehyde (10cc, mp 216-217°C, 65%). Thus, we could produce regioselectively all compounds belonging to 4,5- and 4,6-disubstituted indoles except for fluorine containing compounds.

III. Syntheses of 5,7-, 6,7-, and 4,7-Dihalogenated Type Indoles

1-Acetyl-5-bromo-2,3-dihydro-7-iodoindole (12, mp 165-166°C) was prepared in 65% yield by the thallation of 1-acetyl-5-bromo-2,3-dihydroindole[9] (11) with TTFA in TFA, followed by the treatment with aqueous KI. Similarly, 1-acetyl-6-bromo-2,3-dihydroindole (6c, mp 138-138.5°C), prepared in 64% yield by the Sandmeyer reaction of 6a,[7] was converted successfully to 1-acetyl-6-bromo-2,3-dihydro-7-iodoindole (13,

mp 164.5-166°C) in 45% yield. Alkaline hydrolysis of 13 and subsequent salcomine catalyzed oxidation[6] with dioxygen afforded 6-bromo-7-iodoindole (14, mp 108-108.5° C) in 76% yield. Vilsmeier reaction of 14 with $POCl_3$ and DMF gave a 94% yield of 6-bromo-7-iodo-3-indolecarboxaldehyde (15, mp 235-236.5°C). 7-Bromo-3-indolecarboxaldehyde (17, mp 175-176°C), prepared in 93% yield from 7-bromoindole[2b] (16) by the Vilsmeier reaction as described above, was also readily thallated with TTFA in TFA and subsequent iodination with aqueous KI produced 7-bromo-4-iodo-3-indolecarboxaldehyde (18, mp 248-249°C) in 95% yield. The success for obtaining above three compounds (12, 13, and 18) clearly demonstrated that our thallation-halogenation method[2] could be applicable for the preparation of the rest 5,7-, 6,7-, and 4,7-dihalogenated type indoles.

IV. Short Step Syntheses of 4,7- and 5,7-Dihalogenated Indoles

Since regioselective and reliable synthetic method for every dihalogenated type indoles is established, we next examined to develop a short step approach to 4,7- and 5,7-dihalogenated type indoles. Thus, methyl 4-iodo-3-indolecarboxylate[10] (19) was found to produce methyl 7-bromo-4-iodo- (20, mp 187-188°C) and 5-bromo-4-iodo-3-indolecarboxylate (21, mp 142-143°C) in 9% and 65% yields, respectively, by the reaction with bromine in acetic acid. The structures of 20 and 21 were unequivocally proved by the direct comparisons with the authentic samples, which were prepared in 57% and 44% yields, respectively, from 18 and 5ba by the oxidation with sodium chlorite,[10b,11] followed by methylation of the resulted 3-indolecarboxylic acids with ethereal diazomethane. On the other hand, bromination of readily available 1-acetyl-2,3-dihydro-7-iodoindole[2b] in acetic acid proceeded regioselectively to give 12 in 78% yield.

V. Total Syntheses of Marine Alkaloids, 4,6-Dibromo-, 4,6-Dibromo-2-methyl-, and 3,4,6-Tribromoindole

Oxidation of 4,6-dibromo-3-indolecarboxaldehyde (10bb) with sodium chlorite[11] gave 4,6-dibromo-3-indolecarboxylic acid (22, mp 108°C) in 89% yield. Decarboxylation of 22 was easily carried out in refluxing pyridine[10b] to give 4,6-dibromoindole[12] (1a, mp 59.5°C) in 92% yield. Treatment of 1a with N-bromosuccinimide produced 3,4,6-tribromoindole [3a, mp 89-90°C (dec.)] in 71% yield. Acetylation of 1a and 3a with acetic anhydride and pyridine afforded 1-acetyl-4,6-dibromo- (1b, mp 108-108.5°C) and 1-acetyl-3,4,6-tribromoindole[12] (3b, mp 240-242°C) in 89% and 92% yields, respectively. Spectral data of 1a, 3a, 1b, and 3b were identical with those of the natural marine alkaloids[4c,d] and their acetyl derivatives.

2-Methyl-4,6-dibromoindole (2a) was prepared as follows. Starting from 2-methylindole, 6-bromo-2-methylindole[13] (23, mp 134.5-135°C) was obtained in 25% overall yield by the similar reaction sequences applied for the preparation of 6c. Vilsmeier reaction of 23 with $POCl_3$ and DMF afforded a 88% yield of 6-bromo-2-methyl-3-indolecarboxaldehyde (24, mp 253-253.5°C). Thallation of 24 with TTFA in TFA and subsequent treatment with $CuBr_2$ produced 4,6-dibromo-2-methyl-3-indolecarboxaldehyde (25, mp 250-250.5°C) in 57% yield. Oxidation of 25 with sodium chlorite,[10b,11] followed by the treatment with refluxing pyridine[10b] afforded 2a (mp 96-97°C) in 63% yield. Acetylation of 2a with acetic anhydride and pyridine produced 1-acetyl-4,6-dibromo-2-methylindole (2b, mp 146-146.5°C) in 91% yield. Spectral data of 2a and 2b were identical with those of the natural alkaloid[4c] and its acetyl derivative.[4c] Thus, the first synthesis of 2a was accomplished.

Biological evaluations of compounds described in this report and syntheses of indoles having more than two halogens or substituents at the benzene part are currently in progress.

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