A Regioselective Synthesis Method of Tri- and Tetrahalogenoindoles and Its Application for the Total Syntheses of Marine Alkaloids

A REGIOSELECTIVE SYNTHESIS METHOD OF TRI- AND TETRAHALOGENOINDOLES AND ITS APPLICATION FOR THE TOTAL SYNTHESES OF MARINE ALKALOIDS[1]

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Abstract ——— Various novel tri- and tetrahalogenoindole derivatives are produced based on the regioselective thallation-halogenation method. Syntheses of 2,3,4,7-tetrahalogenated type indoles, which are believed to be marine alkaloids, are achieved for the first time.

Many tri- and tetrahalogenated indole derivatives are reported as marine alkaloids,[2] and they have recently attracted much attention due to their potent biological activities. However, their total syntheses still remain as challenging problems, because the introduction of suitable halogens onto the indole nucleus is quite difficult. We have sofar elaborated the regioselective thallation-halogenation method[3] and reported the preparation of mono-[3a] and dihalogenated indoles.[3b] In this report, we wish to describe a preparation method of tri- and tetrahalogenated indoles and its application for the first syntheses of 2,3,4,7-tetrahalogenated indoles,[2f] which are believed to be marine alkaloids.[2f]

I. Preparation of Tribromoindole Derivatives

Indoles carrying three halogens on the benzene part are divided into four types depending on the substitution pattern, such as 4,5,6-, 4,5,7-, 4,6,7-, and 5,6,7-trisubstituted compounds. We now succeeded in the synthesis of every substitution type of indoles using bromine as a representative halogen. First, 4,5,6-tribromoindole derivatives were prepared as follows (Chart 1). Bromination of 1-acetyl-5-amino-2,3-dihydroindole (1) with bromine in acetic acid (AcOH) afforded 1-acetyl-5-amino-4,6-dibromo-2,3-dihydroindole (2, mp 208-210°C) in 42% yield. Subsequent reaction of 2 with sodium nitrite and aqueous hydrobromic acid (HBr), followed by the treatment with cuprous bromide in aqueous HBr, produced 1-acetyl-2,3-

dihydro-4,5,6-tribromoindole (3, mp 192.5-194°C) in 81% yield. Alkaline hydrolysis of 3 with 40% sodium hydroxide in methanol (MeOH) produced 2,3-dihydro-4,5,6-tribromoindole (4, mp 110-111°C) in 96% yield. Oxidation of 4 with dioxygen in MeOH in the presence of salcomine[4] yielded the desired 4,5,6-tribromoindole (5, mp 127-128°C) in 86% yield. Similarly, the above mentioned series of reactions were successfully applied to 1-acetyl-6-amino-2,3-dihydroindole (6) culminating in the formation of 5,6,7-tribromoindole derivatives. Thus, 1-acetyl-6-amino-5,7-dibromo-2,3-dihydro- (7, mp 138-139°C), 1-acetyl-2,3-dihydro-5,6,7-tribromo- (8, mp 173-174°C), 2,3-dihydro-5,6,7-tribromo- (9, mp 56.5-57°C), and 5,6,7-tribromoindole (10, mp 134-135°C) were obtained in 48%, 78%, 95%, and 83% yields, respectively.

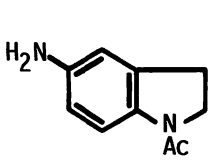
Vilsmeier-Haack reaction of 5 and 10 using phosphorus oxychloride and N,N-dimethylformamide (DMF) produced 4,5,6-tribromo- (11, mp 278.5-280°C) and 5,6,7-tribromoindole-3-carboxaldehyde (12, mp 282-282.5°C) in 86% and 87% yields, respectively. The compound (11) was alternatively prepared in 69% yield by the thallation of 5,6-dibromoindole-3-carboxaldehyde[5] (13, mp 298-300°C) with thallium tris(trifluoroacetate) (TTFA, 2.0 mol eq.) in trifluoroacetic acid (TFA) at refluxing temperature, followed by the treatment with cupric bromide ($CuBr_2$, 3.6 mol eq.) in DMF. The same regioselective thallation-bromination method as described above was applied to 5,7-dibromoindole-3-carboxaldehyde[6] (14, mp 209-209.5°C) and 6,7-dibromoindole-3-carboxaldehyde[7] (15, mp 250-251°C) to give 4,5,7-tribromoindole-3-carboxaldehyde (16, mp 295-296°C) and 4,6,7-tribromoindole-3-carboxaldehyde (17, mp >300°C) in 80% and 82% yields, respectively.

II. Preparation of Tetrahalogenoindole Derivatives

Synthesis method for 4,5,6,7-tetrahalogenated type indoles was developed as follows. Thus, thallation of 12 with TTFA (2.0 mol eq.) in TFA, followed by the treatment with $CuBr_2$ (3.6 mol eq.) in DMF, produced 4,5,6,7-tetrabromoindole-3-carboxaldehyde (18, mp >300°C) in 88% yield.

We next tried the total syntheses of 2,3,4,7-tetrahalogenated indoles which were isolated as marine alkaloids from algae, Rhodophyllis membranacea Harvey.[2f] Oxidation of 4,7-dibromoindole-3-carboxaldehyde (19d, mp 254.5-255°C), prepared according to our previous synthetic strategy,[8] with sodium chlorite in the presence of 2-methyl-2-butene in t-butanol and water cleanly produced 84% yield of 4,7-dibromoindole-3-carboxylic acid (20d, mp 222-223°C). Subsequent decarboxylation was readily carried out by refluxing a pyridine solution of 20d for 20 h resulting in the formation of 4,7-dibromoindole (21d, mp 55°C) in 75% yield. Treatment of 21d with sul-

Chart 1



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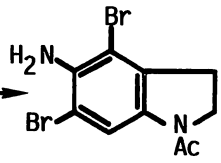

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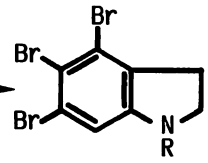
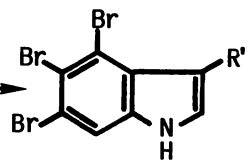
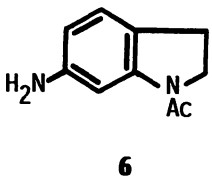


3, R = Ac
4, R = H



5, R' = H
11, R' = CHO



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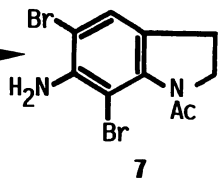

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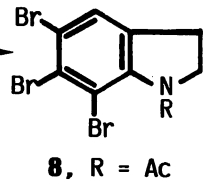
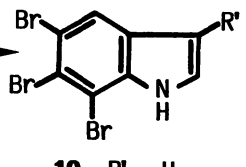
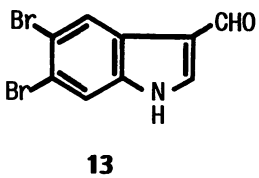


8, R = Ac
9, R = H



10, R' = H
12, R' = CHO



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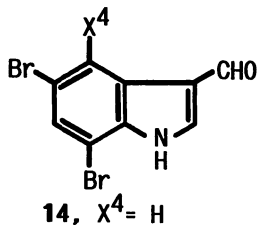
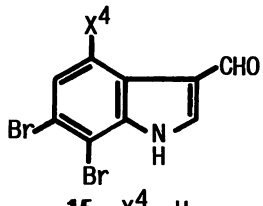
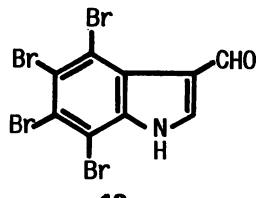


14, X^4 = H
16, X^4 = Br



15, X^4 = H
17, X^4 = Br



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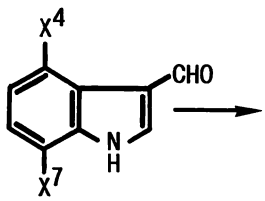
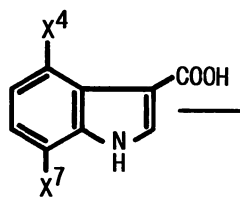


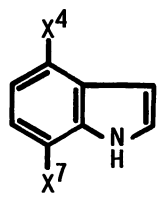
19

a; mp 237.5-238°C
b; mp 251.5-252°C
c; mp 239.5-240°C
d; mp 254.5-255°C



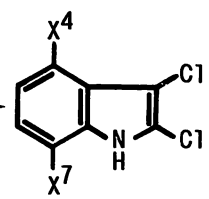
20

a; 96%, mp 232-234°C (dec)
b; 80%, mp 234-235°C (dec)
c; 83%, mp 229-230°C (dec)
d; 84%, mp 222-223°C (dec)



21

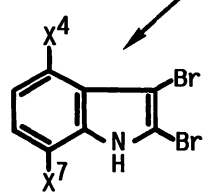
a; 87%, mp 44°C
b; 80%, mp 50°C
c; 88%, mp 48°C
d; 75%, mp 55°C



22

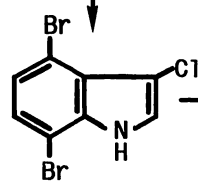
a; 59%, mp 119°C
b; 72%, mp 132-132.5°C
c; 76%, mp 128-129.5°C
d; 88%, mp 142.5-143°C

19, 20, 21, 22, 23
a; X^4 = X^7 = Cl
b; X^4 = Cl, X^7 = Br
c; X^4 = Br, X^7 = Cl
d; X^4 = X^7 = Br



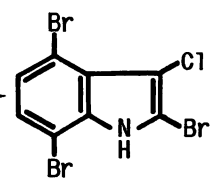
23

a; 51%, mp 128.5°C
d; 63%, mp 144-145°C



24

63%, mp 102-104°C



25

81%, mp 147.5°C

furyl chloride[9] (SO_2Cl_2, 2.2 mol eq.) in refluxing ether afforded 4,7-dibromo-2,3-dichloroindole (22d, mp 142.5-143°C) in 88% yield. On the other hand, treatment of 21d with N-bromosuccinimide (NBS, 2.1 mol eq.) in methylene chloride at room temperature furnished 2,3,4,7-tetrabromoindole (23d, mp 144-145°C) in 63% yield. Treatment of 21d with one molar equivalent of SO_2Cl_2 in ether at room temperature afforded 3-chloro-4,7-dibromoindole (24, mp 102-104°C) in 63% yield. Further treatment of 24 with NBS (1.0 mol eq.) produced 3-chloro-2,4,7-tribromoindole (25, mp 147.5°C) in 81% yield. Similarly, various tetrahalogenoindoles belonging to 2,3,4,7-tetrasubstituted compounds were prepared and their yields and melting points are summarized in Chart 1.

In conclusion, we could prepare various novel tri- and tetrahalogenoindole derivatives based on the regioselective thallation-halogenation method.[3] We have also succeeded in the first syntheses of 2,3,4,7-tetrahalogenated indoles, such as 22a-d, 23a, 23d, and 25, which are believed to be marine alkaloids.[2f]

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5. The compound (13) was obtained as follows. 1-Acetyl-6-bromo-2,3-dihydroindole[3b] was converted to 1-acetyl-5,6-dibromo-2,3-dihydroindole (mp 194.5-195°C) in 98% yield by bromination (Br_2, AcOH). Subsequent alkaline hydrolysis (NaOH, MeOH-H_2O) produced 98% yield of 5,6-dibromo-2,3-dihydroindole (mp 90.5-91°C), which was then transformed to 5,6-dibromoindole (mp 160-161°C) in 86% yield by oxidation (O_2, salcomine, MeOH). Subsequent Vilsmeier-Haack reaction ($POCl_3$, DMF) afforded 13 in 88% yield.
6. The compound (14) was obtained as follows. 1-Acetyl-7-bromo-2,3-dihydroindole[3a] was converted to 1-acetyl-5,7-dibromo-2,3-dihydroindole (mp 135.5-136°C) in 81% yield by bromination (Br_2, AcOH). Subsequent alkaline hydrolysis (NaOH, MeOH-H_2O) produced 92% yield of 5,7-dibromo-2,3-dihydroindole (colorless oil), which was then transformed to 5,7-dibromoindole (mp 69.5°C) in 96% yield by oxidation (O_2, salcomine, MeOH). Subsequent Vilsmeier-Haack reaction ($POCl_3$, DMF) afforded 14 in 89% yield.
7. The compound (15) was obtained as follows. 7-Bromoindole[3a] was converted to 7-bromoindole-3-carboxaldehyde (mp 175-176°C) in 92% yield by the Vilsmeier-Haack reaction ($POCl_3$, DMF). Subsequent oxidation (sodium chlorite, t-BuOH-H_2O), followed by methylation (CH_2N_2) produced methyl 7-bromoindole-3-carboxylate (mp 152.5-153°C) in 93% yield. The next bromination (Br_2, AcOH) furnished 84% yield of methyl 6,7-dibromoindole-3-carboxylate (mp 205-206.5°C), which was then hydrolyzed (NaOH, MeOH-H_2O) to 6,7-dibromoindole-3-carboxylic acid (mp 258-261°C (dec.)) in 98% yield. The next pyrolysis (quinoline, reflux) generated 52% yield of 6,7-dibromoindole (mp 98.5°C), which was finally transformed to 15 in 91% yield by the Vilsmeier-Haack reaction ($POCl_3$, DMF).
8. The compounds (19a-d) were obtained as follows. 7-Chloroindole[3a] was converted to 7-chloroindole-3-carboxaldehyde (mp 186-188°C) in 91% yield by the Vilsmeier-Haack reaction ($POCl_3$, DMF). Subsequent thallation (TTFA, TFA) of 7-bromo-[7] and 7-chloroindole-3-carboxaldehyde, followed by the treatment with either $CuCl_2$ or $CuBr_2$ in DMF, afforded 19a, 19b, 19c, and 19d in 88%, 86%, 82%, and 89% yields, respectively.
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