The first total synthesis of bufobutanoic acid by two routes based on nucleophilic substitution reaction on indole nucleus

THE FIRST TOTAL SYNTHESIS OF BUFOBUTANOIC ACID BY TWO ROUTES BASED ON NUCLEOPHILIC SUBSTITUTION REACTION ON INDOLE NUCLEUS[1]

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Abstract — Regioselective nucleophilic substitution reaction of 1-hydroxytryptamines led to establish two novel routes for the first synthesis of bufobutanoic acid. An effective synthesis of 5-benzyloxytryptamine from tryptamine is also reported.

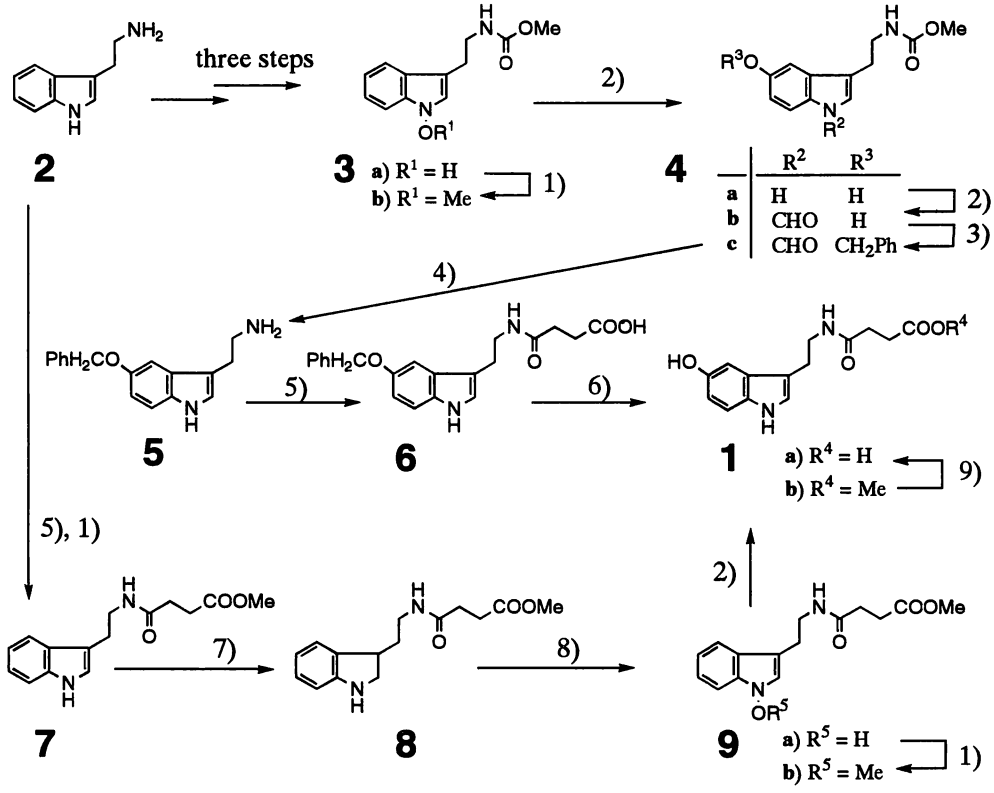
In 1999, Kamano and co-workers[2] isolated bufobutanoic acid (**1a**, Scheme 1) as a cytotoxic substance against murine P388 lymphocytic leukemia cells from Ch'an Su and determined its structure. From our ongoing project for developing biologically active novel compounds,[3] we have much interested in **1a** and intended to establish a methodology applicable for producing its various congeners. To meet our end, we initially needed simple synthesis of **1a**. Now, we have succeeded in developing two routes based on 1-hydroxyindole chemistry.[4]

The first route is the one utilizing 1-hydroxy-*Nb*-methoxycarbonyltryptamine (**3a**) as an intermediate, a potent inhibitor of platelet aggregation.[5] Thus, **3a**, obtained in three steps from tryptamine (**2**) in 62% overall yield as described before,[6] was converted to **4b** in 48% yield by the regioselective hydroxylation at the 5-position upon the reaction with 85% HCOOH at room temperature for 24 h. Interestingly, the corresponding 1-methoxy-*Nb*-methoxycarbonyltryptamine[6] (**3b**) provided **4a** selectively in 69% yield by the similar treatment with 85% HCOOH at 80°C for 20 min. Subsequent reaction of **4a** with 85% HCOOH at room temperature for 2 days provided **4b** in 70% yield together with 10% yield of starting material.

The reaction of **4b** with benzyl bromide in the presence of K_2CO_3 in DMF afforded **4c** in 94% yield. Alkaline hydrolysis of **4c** with 10% NaOH in refluxing MeOH provided 96% yield of 5-benzyloxytryptamine (**5**).[7] With an useful building block for preparing various serotonin derivatives in hand, it was converted to **6** in 96% yield by the reaction with succinic anhydride in THF. Catalytic hydrogenation of **6** over 10% Pd/C at room temperature produced **1a** in 99% yield. The spectra of **1a** are identical with those reported in the literature.[2] Thus, the first synthesis of **1a** was achieved in eight steps from **2** in 25% overall yield with 33% originality rate.[8]

As the second one, six-steps synthesis of **1a** in 13% overall yield with 43% originality rate was developed. Tryptamine (**2**) was initially reacted with succinic anhydride in THF at room temperature, followed by methylation with CH_2N_2 in one pot procedure to give *Nb*-methoxysuccinyltryptamine (**7**) in 89% yield. Subsequent reduction of **7** with Et_3SiH in CF_3COOH[9] at 60 °C provided the corresponding 2,3-dihydroindole (**8**) in 99% yield. Our 1-hydroxyindole synthetic method using $Na_2WO_4 \cdot 2H_2O$[4] and

Scheme 1



1) CH_2N_2; 2) 85% HCOOH; 3) $PhCH_2Br$, K_2CO_3, DMF; 4) 10% NaOH, MeOH; 5) succinic anhydride, THF; 6) 10% Pd/C, H_2; 7) Et_3SiH, CF_3COOH; 8) $Na_2WO_4 \cdot 2H_2O$, 30% H_2O_2; 9)1_M K_2CO_3, MeOH.

30% H_2O_2 at room temperature was successfully applied to **8** giving the desired 1-hydroxytryptamine (**9a**) in 56% yield. Structure of **9a** was confirmed by converting it to 1-methoxytryptamine (**9b**) in 86% yield by the reaction with CH_2N_2. Then, **9a** was treated with 85% HCOOH at 50°C for *50 min to* give serotonin derivative (**1b**) in 38% yield. Finally, ester part of **1b** was hydrolyzed with 1_M K_2CO_3 in MeOH at 50°C to provide **1a** in 70% yield.

In conclusion, we have disclosed that nucleophilic substitution reaction[10] of 1-hydroxytryptamines[11] is a suitable methodology for the preparations of serotonin congeners.

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gave satisfactory spectral and elemental analysis or high-resolution MS data for crystals or gums, respectively. **1b**, gum; **4a**, gum; **4b**, gum; **4c**, gum; **5**, mp 97.5—99.5℃; **6**, mp 145—147°C; **7**, mp 118—120°C; **8**, mp 74—75°C; **9a**, mp 151.5—153.5°C.

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