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A PRACTICAL AND SHORT ACCESS TO 4-HYDROXY-3-INDOLECARBALDEHYDE AND ITS APPLICATION FOR THE SYNTHESIS OF PINDOLOL ANALOG[1]

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Abstract ——— 4-Hydroxy-3-indolecarbaldehyde (1) is produced simply by heating (3-formylindol-4-yl)thallium bis-trifluoroacetate with copper sulfate in N,N-dimethylformamide and water. Alkylation of 1 afforded predominantly 1-alkyl derivatives. Utilizing these results pindolol analog, 1-allyl-4-(3-t-butylamino-2-hydroxypropoxy)-3-indolecarbaldehyde was synthesized.

With an aim to synthesize pindolol analogs, psilocybin, and mitomycin derivatives, we have settled 4-hydroxy-3-indolecarbaldehyde (1) as a common synthetic building block, which has so far been obtained in laborious long steps.[2] In this paper, we report a practical and short synthetic method for 1 and its application for the synthesis of pindolol analog, 1-allyl-4-(3-t-butylamino-2-hydroxypropoxy)-3-indolecarbaldehyde (16).

In the previous paper,[3] we have reported the synthesis of (3-formylindol-4-yl)thallium bis-trifluoroacetate (3) in 77% yield from 3-indolecarbaldehyde (2). In our continuing efforts to develop an effective synthetic method for 1, we have found that the desired compound (1, mp 198.0-200.0°C) can be produced simply by heating 3 at reflux in N,N-dimethylformamide (DMF) and water in the presence of copper salt. The reaction of 3 with various copper salts was examined and the representative results are summarized in Table I. Under reaction conditions described in entry 4, 1 was obtained in 73% yield.

In contrast, the reaction of 4-iodo-3-indolecarbaldehyde[4] (4) with copper salts under similar reaction conditions described above, afforded less successful results and they are shown in Table II.

Although arylthallium compounds were reported to be converted to the corresponding

Table I. Preparation of 4-Hydroxy-3-indolecarbaldehyde (1) from (3-Formylindole-4-yl)thallium Bis-trifluoroacetate (3)

Entry	Copper Salt (3 mol eq.)	Reaction Conditions Additive	Reaction Time (h)	Yield (%) of 1
1	CuF_2	-	1	20.6
2	CuF_2	Bipyridine*	1	0
3	$Cu(OAc)_2 \cdot H_2O$	-	12	18.7
4	$CuSO_4 \cdot 5H_2O$	-	12	72.8

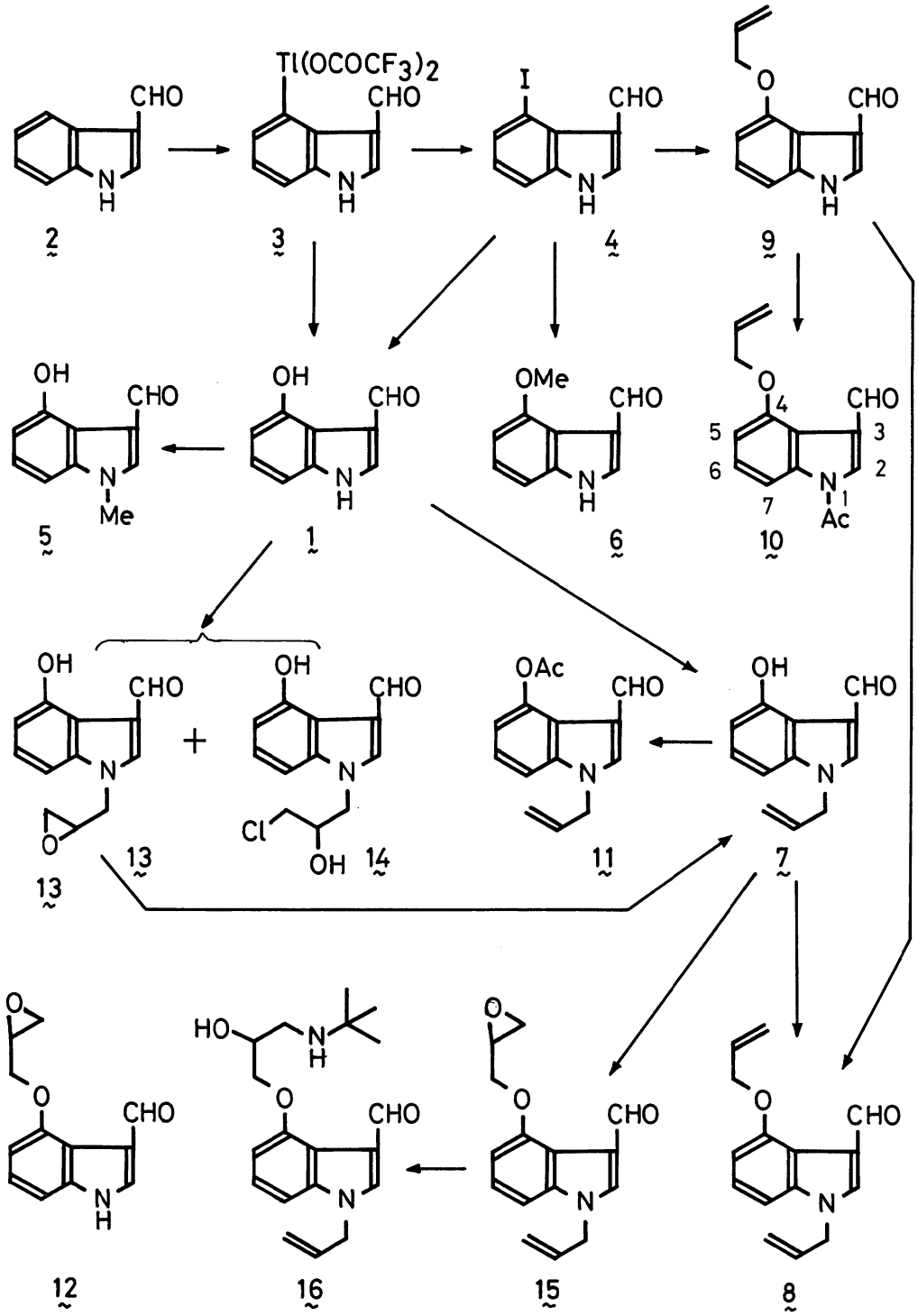
All reactions were carried out at 125-130°C in DMF-H_2O (1:1, v/v) with stirring. *6 mol eq. was used.

Table II. Preparation of 4-Hydroxy-3-indolecarbaldehyde (1) from 4-Iodo-3-indolecarbaldehyde (4)

Entry	Copper Salt (2 mol eq.)	Reaction Conditions Additive	Reaction Time (h)	Yield (%) of 1	4
1	CuI	20% NaOH*	6	1.7	5.8
2	CuF_2	-	12.5	10.0	55.4
3	$Cu(OAc)_2 \cdot H_2O$	-	6	27.3	8.9
4	$CuSO_4 \cdot 5H_2O$	28% NH_4OH (excess)	6	0	0
5	$CuSO_4 \cdot 5H_2O$	-	12	21.8	13.9
6	$CuSO_4 \cdot 5H_2O$	-	24	39.5	9.0

All reactions were carried out at 125-130°C in DMF-H_2O (1:1, v/v) with stirring. *In this case, DMF-20% NaOH (1:1, v/v) were used as a solvent.

phenols, moisture sensitive reaction such as boration[5] and oxidation[6] with lead tetraacetate used as an essential step limited their versatility. Our new reaction proceeds in the presence of water and no special precautions are needed. We are now extending this simple reaction as a general method for preparing phenol derivatives. With 4-hydroxy-3-indolecarbaldehyde (1) in hand, we next examined alkylation reaction in alkaline conditions and found that alkyl group is predominantly introduced into the nitrogen at the 1-position instead of the oxygen at the 4-position. Thus, methylation of 1 with methyl iodide in the presence of potassium carbonate (K_2CO_3) afforded 94% yield of 4-hydroxy-1-methyl-3-indolecarbaldehyde (5, mp 128.0-129.0°C). Its structure was unequivocally proved by the direct comparison with the authentic


CHO
N
H
2
Tl(OCOCF3)2
3
I
4
O
9
OH
5
Me
1
OMe
6
4
5
3
6
2
7
1
Ac
10
OAc
11
7
13
Cl
OH
14
HO
12
16
15
8

4-methoxy-3-indolecarbaldehyde (6, mp 162.0-163.0°C), prepared from 4 according to our reported procedure.[4]

Allylation of 1 with allyl bromide in the presence of K_2CO_3 produced 1-allyl-4-hydroxy-3-indolecarbaldehyde (7, mp 78.0-79.0°C) in 74% yield. Under similar reaction conditions, further allylation of 7 took place to give 1-allyl-4-allyloxy-3-indolecarbaldehyde (8, mp 67.5-68.5°C) in 60% yield. On the other hand, 4-allyloxy-3-indolecarbaldehyde (9, mp 138.0-139.0°C) was prepared in 34% yield by the reaction of 4 with sodium allyl oxide in the presence of copper iodide.[4] Further allylation of 9 gave the diallyl compound (8), which was identical with the compound prepared from 7. Structural confirmation of 9 was further attempted by leading it to 1-acetyl-4-allyloxy-3-indolecarbaldehyde[7a] (10) in 84% yield by treating with acetic anhydride. Its proton nuclear magnetic resonance (^{1}H-NMR) spectrum revealed the C_7-proton signal at the lower magnetic field by ca. 1 ppm compared with that of 9[7b] by the anisotropy effect of 1-acetyl group. This fact clearly proved that the acetyl group of 10 was bound to the 1-position. In accord with this result, acetyl group of 4-acetoxy-1-allyl-3-indolecarbaldehyde (11),[8] prepared from 7 in 95% yield by the treatment with acetic anhydride, showed no anisotropic effect on the aromatic protons in its ^{1}H-NMR spectrum.

Helmut and co-workers reported in their patent[2] that the reaction of 1 with epichlorohydrin in ethanol in the presence of sodium ethoxide gave 4-(2,3-epoxypropoxy-3-indolecarbaldehyde (12, mp[2] 108-110°C) in 50% yield. Very strong tendency for 1-alkylation of 1 suggests that their results are doubtful. We therefore followed up their reported procedure and found that 1-(2,3-epoxyprop-1-yl)-4-hydroxy-3-indolecarbaldehyde (13, mp 111.0-112.0°C) and 1-[(3-chloro-2-hydroxy)prop-1-yl]-4-hydroxy-3-indolecarbaldehyde (14, mp 131.0-133.0°C) were actually produced in 44% and 42% yields, respectively. Comparison of their mp and yields clearly showed that 13 should be the product that Helmut and co-workers claimed to be 12. Structure of the product (13) was unequivocally established by converting it to the authentic 1-allyl-4-hydroxy-3-indolecarbaldehyde (7) in 31% yield by the reaction with triphenylphosphine in refluxing DMF.

Treatment of 7 with epichlorohydrin in the presence of K_2CO_3 afforded 1-allyl-4-(2,3-epoxypropoxy)-3-indolecarbaldehyde (15, mp 101.0-102.0°C) in 84% yield. Subsequent reaction of 15 with t-butylamine in isopropanol produced the desired pindolol analog, 1-allyl-4-(3-t-butylamino-2-hydroxypropoxy)-3-indolecarbaldehyde (16, caramel) in 85% yield.

Attempts to prepare various pindolol analogs, psilocybin, and mitomycin derivatives are in progress. Biological evaluation of the products in this paper is also in progress.

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7. a) mp 143.0-144.0°C. ^{1}H-NMR ($CDCl_3$) δ: 2.65 (3H, s), 4.67 (2H, d, J=5 Hz), 4.94-5.61 (2H, m), 5.76-6.42 (1H, m), 6.72 (1H, d, J=8 Hz), 7.21 (1H, t, J=8 Hz), 7.94 (1H, s), 7.96 (1H, d, J=8 Hz, C_7-H), 10.44 (1H, s).
   b) ^{1}H-NMR ($CDCl_3$) δ: 4.66 (2H, dt, J=5 and 1.2 Hz), 5.10-5.60 (2H, m), 5.76-6.42 (1H, m), 6.59 (1H, dd, J=6.4 and 3 Hz), 6.87-7.26 (2H, m), 7.80 (1H, d, J=3.2 Hz), 9.71 (1H, br s, NH), 10.40 (1H, s).
8. mp 80.0-81.0°C. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 4.61 (2H, dt, J=5.2 and 1.4 Hz), 4.90-5.40 (2H, m), 5.56-6.23 (1H, m), 6.86 (1H, dd, J=5.6 and 2.4 Hz), 7.00-7.27 (2H, m), 7.57 (1H, s), 9.67 (1H, s).

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