A PRACTICAL ONE POT SYNTHESIS OF 4-ALKOXY-3-FORMYLINDOLES[1]

Masanori Somei,* Fumio Yamada, Masako Kunimoto, and
Chikara Kaneko
Faculty of Pharmaceutical Sciences, Kanazawa University,
13-1 Takara-machi, Kanazawa 920, Japan

Abstract ——— A simple and regioselective one pot synthetic method of 4-methoxy-, 4-benzyloxy-, and 4-ethoxy-3-formylindoles from 3-formylindole is described.

In our continuing work on regioselective synthesis of 4-substituted indoles,[2] we have developed a practical one pot synthetic method from 3-formylindole (1) for 4-alkoxy-3-formylindoles (2a-c), which are useful building blocks for the alkaloids of Mitragyna species[3] and psilocin analogues.[4]

The one pot synthetic method consists of the following sequential three operations : 1) thallation of 1 to form (3-formylindol-4-yl)thallium (III) bis-trifluoroacetate (3),[5] 2) conversion of 3 into 3-formyl-4-iodoindole (4),[5] 3) alkoxylation of 4. In the examination of each operations, the following new results were disclosed. Thus, in the first operation, we found that the thallation of 1 was attained completely within 2 h at 25-30°C when 1.5 mol eq of thallium (III) trifluoroacetate (TTFA) in trifluoroacetic acid (TFA)[6] was used and without isolation of 3 the residue obtained after evaporation of the solvent was sufficient to use for the next step. The direct treatment of 3 with sodium alkoxide did not afford the desired products. In the second operation, we have newly found that the combination of molecular iodine and cuprous iodide (CuI) is a reagent of choice for effective conversion of 3 into 4 in N,N-dimethylformamide (DMF) at room temperature. Treatment of 3 either with molecular iodine[7] or CuI gave poor yield of 4 and the results are summarized in Table I. In the third operation, it should be noted that without rearrangement of the substituent at the 3-position[8] the compound (4) was successfully converted to 2a in 83.2% yield by the treatment with CuI (2 mol eq) and sodium methoxide (16 mol eq) in DMF at 100-120°C.

When the above three operations were carried out successively without isolation of the products formed in each operation, a one pot synthesis of 4-alkoxy-3-formylindoles (2a-c) was attained. In the one pot procedure, the relative amount of molecular iodine, CuI, and sodium alkoxide to the starting material (1) was found to be a decisive factor in varying the yield of 2a-c. The best overall yield was achieved by using three mol eq of molecular iodine, four mol eq of CuI, and thirty eight mol eq of sodium alkoxide.

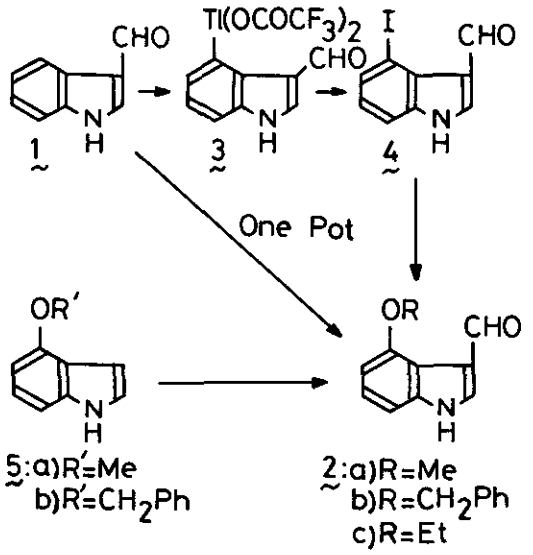
The structures of 2a and 2b were established unequivocally by the alternative synthesis. Thus, the compounds (2a) and (2b) were prepared in 71.3% and 55.7% yields, respectively, by Vilsmeier-Haack reaction of authentic 4-methoxy- (5a)[9] and 4-benzyloxyindole (5b).[10]

Now, 4-alkoxy-3-formylindoles are readily accessible, since the one pot synthetic reaction could be carried out in a multi-gram scale. We are further investigating the direct introduction of alkylthio and alkylamino groups into the 4-position of indole ring. Further investigation for applying the method to benzene derivatives is in progress.

Table. I. Preparation of 3-Formyl-4-iodoindole (4) from (3-Formylindole-4-yl)-thallium(III) Bis-trifluoroacetate (3)

Iodinating Reagent (mol eq to 3)	Solvent	Yield (%) of 4
CuI (2)	DMF	31.8
I_2 (3)	DMF	31.5
CuI (2) and I_2 (3)	DMF	94.0
KI* (5.5)	H_2O	70.7

All experiments were carried out for 1 h at 25°C.
* See also the data obtained by R.A. Hollins et al.: reference 5.



EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a Shimadzu IR-420 spectrophotometer, and NMR spectra with a JEOL JNM-C-60H spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Hitachi M-80 spectrometer. Preparative thin-layer chromatography (p-TLC) was performed on Merck Kieselgel GF_{254} (Type 60, SiO_2). Column chromatography was performed on silica gel (SiO_2, 100-200 mesh), purchased from Kanto Chemical Co., Inc.

3-Formyl-4-iodoindole (4) ——— i) from (3-formylindol-4-yl)thallium (III) bistrifluoroacetate (3): A solution of 3 (572.7 mg), I_2 (787.8 mg, 3.1 mol eq), and CuI (380.6 mg, 2 mol eq) in DMF (6 ml) was stirred for 1 h at 18°C. After addition of 5% MeOH in CH_2Cl_2 (100 ml) to the reaction mixture, the precipitates were removed by filtration through celite. The filtrate was washed with 10% aq. sodium thiosulfate, brine, and dried over Na_2SO_4. The solvent was evaporated off under a reduced pressure to leave a crystalline solid, which was subjected to p-TLC on SiO_2 with 1% MeOH in CH_2Cl_2-Et_2O (5:1, v/v) as a developing solvent to afford 4 (254.1 mg, 94.1%). 4: mp 184-186°C (colorless prisms from MeOH-H_2O, lit.[5] mp 182-183°C). IR (KBr) cm^{-1}: 3165, 1628. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 6.83 (1H, t, J=8.0 Hz), 7.37 (1H, d, J=8.0 Hz), 7.62 (1H, d, J=8.0 Hz), 7.96 (1H, s), 10.88 (1H, s). MS m/e: 271 (M^+).

ii) from 4-iodoindole ——— A solution of 4-iodoindole[5] (63.0 mg) in abs. DMF (1.0 ml) was added to a mixture of $POCl_3$ (130 mg) and abs. DMF (0.5 ml) and stirring was continued for 9 h at 25°C. After addition of ice and H_2O, the whole was extracted with 5% MeOH in CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated to leave a crystalline solid, which was purified by column chromatography on SiO_2 with 5% MeOH in CH_2Cl_2 as an eluent to afford 4 (70.0 mg, 99.6%). Melting point and all spectral data were identical with those of the sample obtained by the above procedure (i).

3-Formyl-4-methoxyindole (2a) ——— i) from 3-formyl-4-iodoindole (4): A solution of 4 (61.0 mg) and CuI (86.7 mg, 2 mol eq) in DMF (3 ml) was added to a solution of sodium (81.8 mg, 15.8 mol eq) in abs. MeOH (1 ml) and the whole was heated for 0.5 h at 110-120°C. After removal of the solvent under a reduced pressure, H_2O and 5% MeOH in CH_2Cl_2 were added to the residue. The whole was filtered through celite and the organic layer was separated. The water layer was further extracted with 5% MeOH in CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated to leave a crystalline solid, which was subjected to p-TLC on SiO_2 with 3% MeOH in CH_2Cl_2-Et_2O (2:1, v/v) as a developing solvent to afford 2a (32.8 mg, 83.2%). 2a: mp 162-163°C (colorless prisms from MeOH). IR (KBr) cm^{-1}: 3220, 1635. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 3.90 (3H, s), 6.56 (1H, dd, J=6.0 and 2.2 Hz), 6.70-7.23 (2H, m), 7.77 (1H, br s), 10.17 (1H, s). High resolution MS m/e: Calcd for $C_{10}H_9NO_2$: 175.0632. Found: 175.0635.

ii) from 4-methoxyindole (5a) ——— A solution of 4-methoxyindole[9] (5a, 92.5 mg) in abs. DMF (2 ml) was added to a mixture of $POCl_3$ (0.1 ml) and abs. DMF (0.4 ml). After stirring for 0.5 h at 21°C, the whole was made alkaline by adding 10% aq. NaOH and extracted with 5% MeOH in CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated under a reduced pressure to leave a crystalline solid, which was subjected to p-TLC on SiO_2 with 3% MeOH in CH_2Cl_2-Et_2O (5:1, v/v) as a developing solvent to afford 2a (78.5 mg, 71.3%). Melting point and all spectral data were identical with those of the sample obtained by the above procedure (i).

4-Benzyloxy-3-formylindole (2b) from 4-benzyloxyindole (5b) ——— A solution of 4-benzyloxyindole[10] (5b, 530.5 mg) in abs. DMF (4 ml) was added to a mixture of $POCl_3$ (1 ml) and abs. DMF (4 ml). After stirring for 2 h at 31°C, the whole was made alkaline by adding 40% aq. NaOH and extracted with 5% MeOH in CH_2Cl_2. The

extract was washed with brine, dried over Na_2SO_4, and evaporated to leave an oil, which was subjected to column chromatography on SiO_2 with 1% MeOH in CH_2Cl_2 as an eluent to give 2b (332.3 mg, 55.7%). 2b: mp 164-169°C (colorless prisms from MeOH). IR (KBr) cm^{-1}: 3080, 1608. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 5.16 (2H, s), 6.66 (1H, dd, J=5.5 and 2.8 Hz), 6.79-7.58 (7H, m), 7.81 (1H, br s), 10.26 (1H, s). High resolution MS m/e: Calcd for $C_{16}H_{13}NO_2$: 251.0944. Found: 251.0944.

A One Pot Synthetic Procedure of 4-Alkoxy-3-formylindoles ——— General Procedure: A 0.88 mol solution of TTFA in TFA[6] (1.5 mol eq) was added to 3-formylindole (1, 0.7 mmol) and the mixture was stirred for 2 h at 30°C. After evaporation of the solvent under a reduced pressure, I_2 (3 mol eq), CuI (4 mol eq), and DMF (5 ml) were added to the residue. Stirring was continued for 1 h at 25°C and freshly prepared sodium alkoxide (38 mol eq) was added. The whole was heated at 100-110°C for 1 h. The reaction mixture was cooled and 5% MeOH in CH_2Cl_2 (50 ml) was added. The precipitates were removed by filtration through celite and the filtrate was washed with brine, dried over Na_2SO_4, and evaporated to dryness in vacuo. The crude product was purified by p-TLC on SiO_2 with 1% MeOH in CH_2Cl_2 as a developing solvent to afford 4-alkoxy-3-formylindoles.

i) 3-Formyl-4-methoxyindole (2a) ——— In the general procedure, 104.1 mg of 1 and sodium methoxide were used. After work-up and subsequent p-TLC, as described above, 2a (108.2 mg, 86.1%) was obtained. Melting point and all spectral data were identical with those of the sample obtained from 4-methoxyindole (5a).

ii) 4-Benzyloxy-3-formylindole (2b) ——— In the general procedure, 99.4 mg of 1 and sodium benzyl oxide were used. After work-up and subsequent p-TLC, as described above, 2b (100.0 mg, 58.1%) was obtained. Melting point and all spectral data were identical with those of the sample obtained from 4-benzyloxyindole (5b).

iii) 4-Ethoxy-3-formylindole (2c) ——— In the general procedure, 104.2 mg of 1 and sodium ethoxide were used. After work-up and subsequent p-TLC, as described above, 2c (67.3 mg, 49.6%) was obtained. 2c: mp 124-126°C (colorless prisms from MeOH). IR (KBr) cm^{-1}: 3160, 1640. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 1.49 (3H, t, J=7.0 Hz), 4.17 (2H, q, J=7.0 Hz), 6.56 (1H, dd, J=6.0 and 2.5 Hz), 6.79-7.26 (2H, m), 7.80 (1H, s), 10.30 (1H, s). High resolution MS m/e: Calcd for $C_{11}H_{11}NO_2$: 189.0788. Found: 189.0783

REFERENCES AND NOTES

1. This report is part XXII of a series entitled "The Chemistry of Indoles". Part XXI: see reference 2.
2. M. Somei, T. Hasegawa, and C. Kaneko, Heterocycles, 20, 1983 (1983).
3. J.E. Saxton, "The Alkaloids", Vol. 8, ed. by R.H.F. Manske, Academic Press, New York, 1965, Chapter 5.
4. a) A. Hoffman, A, Frey, H. Ott, Th. Petzilka, and F. Troxler, Experientia, 14, 397 (1958). b) D.B. Repke and W.J. Ferguson, J. Heterocyclic Chem., 19, 845 (1982) and references cited therein.
5. Although Hollins et al. succeeded in the preparation of 4 from 3 by the reaction with aqueous potassium iodide in 60% yield, the structure was deduced only by the spectral analysis: R.A. Hollins, L.A. Colnago, V.M. Salim, and M.C. Seidl, J. Heterocyclic Chem., 16, 993 (1979). We have now confirmed their result

unequivocally by the alternative synthesis, as described in the experimental section, from 4-iodoindole which was synthesized by our reliable synthetic method for 4-substituted indoles: M. Somei and M. Tsuchiya, Chem. Pharm. Bull., 29, 3145 (1981).

6. A. McKillop, J.D. Hunt, M.J. Zelesko, J.S. Fowler, E.C. Taylor, G. McGillivray, and F. Kienzle, J. Am. Chem. Soc., 93, 4841 (1971).
7. Although Ishikawa et al. reported that molecular iodine in DMF did not react with organothallium compounds, we believe that thallation could not be realized in their procedure: N. Ishikawa and A. Sekiya, Bull. Chem. Soc. Japan, 47, 1680 (1974).
8. By the similar treatment of 5-bromo-1,2,3,4-tetrahydrocarbazole, Kikugawa et al. obtained skeletal rearranged product in poor yield. In the case of N-substituted 1,2,3,4-tetrahydrocarbazoles, the rearranged products were not formed: Y. Kikugawa, Y. Miyake, and M. Kawase, Chem. Pharm. Bull., 29, 1231 (1981). Methoxylation of 5- and 6-bromoindoles: K. Saito and Y. Kikugawa, J. Heterocyclic Chem., 16, 1325 (1979); Y. Miyake and Y. Kikugawa, ibid., 20, 349 (1983).
9. The compound (5a) was prepared in 52.8% overall yield from 2-methoxy-6-nitrotoluene by the improved Leimgruber-Batcho method using $TiCl_3$ and NH_4OAc. 5a: mp 68-69°C (lit.[4b] mp 67°C). IR (KBr) cm^{-1}: 3350, 1614, 1585. ^{1}H-NMR (CCl_4) δ: 3.80 (3H, s), 6.23 (1H, dd, J=7.0 and 1.5 Hz), 6.37 (1H, ddd, J=3.0, 2.2, and 0.8 Hz), 6.51-7.00 (3H, m), 7.60 (1H, br s). MS m/e: 147 (M^+).
10. M. Somei, S. Inoue, S. Tokutake, F. Yamada, and C. Kaneko, Chem. Pharm. Bull., 29, 726 (1981).

Received, 9th December, 1983