Chem. Pharm. Bull.
31(8)2892—2894(1983)

Formylation of Indoles with Formic Acid

MASATO KASHIMURA and YASUO KIKUGAWA*

Faculty of Pharmaceutical Sciences, Josai University,
1-1 Keyakidai, Sakado-shi, Saitama 350-02, Japan

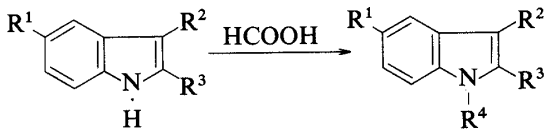
(Received January 20, 1983)

Formylation of indoles was carried out in formic acid. 3-Unsubstituted indoles were formylated preferentially at C-3 and 3-substituted indoles were formylated at N-1; C-2 was not formylated in either case.

Keywords——formylation; indole; formic acid; formylindole; tryptophan

Although acylation of indoles and metalloindoles is well documented,[1] formylation of indoles has not been investigated so far except for the preparation of 3-formylindole by means of the Vilsmeier–Haack reaction. Indoles which are substituted at C-3 are also formylated at N-1 by the same method,[1] but 3-methylindole was formylated to give a mixture of 1-formyl-3-methylindole and 2-formyl-3-methylindole.[2] Few other examples of formylation of other indoles have been reported, and generally the yields of formylated indoles are not satisfactory except in the case of 3-formylindole. Tryptophan and tryptophan-containing peptides react in formic acid–hydrochloric acid solutions, giving the corresponding 1-formyltryptophan derivatives, and the reaction has been proposed for the chemical modification of tryptophan

TABLE I. Formylation of Indoles



1

2: R^4=CHO
3: R^3=CHO, R^4=H
4: R^2=CHO, R^4=H

1	R^1	R^2	R^3	Reaction time (h)	Product	Yield (%)	Literature method[a]	
							Product	Yield (%)
a	H	CH_3	H	1.5	**2a**	87.6	**2a**	71.0[b]
							3a	22.5
b	H	CH_3	CH_3	10	**2b**	89.9	**2b**	52.1[b]
c	H	CH_2CO_2H	H	9	**2c**	62.0	—	—
d	CH_3O	$CH_2CO_2C_2H_5$	CH_3	15	**2d**	79.6	—	—
e	H	$CH_2CHCO_2C_2H_5$ NHCOCH$_3$	H	9	**2e**	85.8	—	—
f	H	$-(CH_2)_4-$		8.5[c]	**2f**	81.8	**2f**	65.0[d]
g	H	$-(CH=CH)_2-$		20	**2g**	74.3	—	—
h	H	H	CH_3	0.25	**4h**	56.0	—	—
i	H	H	H	—	—	—	**4i**	95.5[e]

a) Vilsmeier–Haack formylation. *b*) Ref. 2. *c*) Reaction temperature: 85 °C. *d*) Ref. 10. *e*) Ref. 11.

residues in proteins.[3] This method is only applicable to acid-stable indoles, because 3-methylindole (**1a**) was subjected to the same reaction to give a mixture of 1-formyl-3-methylindole (**2a**) (23% yield) and diskatole (**5**) (60% yield), which was obtained by the acid-catalyzed dimerization of 3-methylindole (**1a**).[4]

In the course of studies on the catalytic transfer hydrogenation of indoles with palladium on carbon in formic acid,[5] we have found that the indole nucleus is formylated in boiling formic acid. We wish to report here a general method for the formylation of indoles with

Table II. Physical Data for Formylindoles and Diskatole

Product No.	mp (°C) (Recrystn. solvent)	bp (°C) (mmHg)	Formula	Analysis (%) Calcd (Found) C	H	N	Others
2a	—	121 (4)[a]					
2b	87—87.5[b] (Cyclohexane)	—					
2c	128—131 (Benzene–hexane)		$C_{11}H_9NO_3$	65.02 (65.09	4.46 4.68	6.89 6.72)	MS *m/e*: 203 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). NMR (DMSO-d_6) δ: 3.76 (2H, s, CH_2), 7.12—7.82 (4H, m, Ar-H), 8.15 (1H, br s, C_7-H), 9.41 (1H, br s, CHO).
2d	116—118 (Ethanol)	—	$C_{15}H_{17}NO_4$	65.44 (65.64	6.22 6.19	5.09 5.13)	MS *m/e*: 275 (M^+). IR ν_{max}^{Nujol} 1710 (C=O). NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.53 (3H, s, CH_3), 3.60 (2H, s, CH_2), 3.85 (3H, s, OCH_3), 4.15 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 6.23—7.08 (2H, m, Ar-H), 8.20 (1H, br d, J=9 Hz, C_7-H), 9.21 (1H, s, CHO).
2e	106—107 (Benzene–hexane)	—	$C_{16}H_{18}N_2O_4$	63.56 (63.70	6.00 6.18	9.27 9.27)	MS *m/e*: 302 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1660—1730 (C=O). NMR ($CDCl_3$) δ: 1.21 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.98 (3H, s, $COCH_3$), 3.23 (2H, d, J=6 Hz, CH_2), 4.12 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.71—5.19 (1H, m, α-H), 6.10—6.61 (1H, br d, J=7 Hz, NHCO), 6.95—8.67 (5H, m, Ar-H), 9.18 (1H, br s, CHO).
2f	—	170 (6)[c]					
2g	98—98.5 (Benzene–hexane)	—	$C_{13}H_9NO$	79.98 (79.85	4.65 4.93	7.17 7.25)	MS *m/e*: 195 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1725—1750 (C=O). NMR ($CDCl_3$) δ: 7.05—8.76 (8H, m, Ar-H), 9.57 (1H, s, CHO).
4h	201.5—203[d] (Ethanol)	—					
5	127—128[e] (Ligroin)	—					

a) Lit.[2] 98—100 °C (0.03 mmHg). *b*) Lit.[2] 87—88 °C. *c*) Lit.[10] 175—185 °C (4 mmHg).
d) Lit.[12] 197—199 °C. *e*) Lit.[4] 125—127 °C.

formic acid. Formic acid acts as both the formylating agent and the reaction solvent. As is described in "Experimental," the procedure is very simple, that is, indoles are mixed with formic acid and the mixture is boiled for several hours. The order of susceptibility to the electrophile for positions 1—3 of the indole nucleus was reported[6] to be C-3 > N-1 > C-2. In our case the same order (C-3 > N-1) was observed; the tendency to substitution at N-1 rather than C-2 of 3-substituted indoles is striking in contrast with C-2 substitution in the Vilsmeier–Haack formylation of 3-methylindole (**1a**).[2] In the case of formylation of indole (**1i**), thin layer chromatography of the reaction mixture on silica gel showed several spots, probably due to the instability of indole in formic acid.

Experimental

All melting points are uncorrected. The following instruments were used to obtain physical data: infrared (IR) spectra, Shimadzu IR-400; nuclear magnetic resonance (NMR) spectra (tetramethylsilane as an internal standard), JNM-C-60HL spectrometer; mass spectra (MS), Shimadzu LKB-9000 machine.

Materials——Formic acid (99% Wako Pure Chem. Ind. Ltd.), compound **1b** (Aldrich Chem. Company, Inc.), and compounds **1a**, **c**, **g**—**i** (Tokyo Kasei Kogyo Co.) were obtained commercially and used without purification. Compound **1e**, mp 107—108 °C (lit.[7] mp 109—109.5 °C) and compound **1f**, mp 116—118 °C (lit.[8] mp 115—116 °C) were prepared by the reported methods. Compound **1d** was prepared by a modification of the reported method.[9] Physical data for new compounds are listed in Table II.

1-Formyl-3-methylindole (2a)——A mixture of 99% formic acid (5 ml) and **1a** (201.3 mg, 1.54 mmol) was refluxed for 1.5 h. The solution was concentrated *in vacuo*, 10% $NaHCO_3$ (30 ml) was added to the residue, and the aqueous layer was extracted with AcOEt (30 × 2 ml). The combined extract was washed with sat. NaCl and dried over anhyd. Na_2SO_4. After removal of the solvent by evaporation, the residue was purified by silica gel column chromatography [benzene–hexane (1 : 1) for elution] to give **2a** (214.1 mg, yield 87.6%).

Diskatole (5) and 1-Formyl-3-methylindole (2a)——A solution of **1a** (202.0 mg, 1.54 mmol) in 99% formic acid (5 ml) saturated with gaseous HCl was stirred at room temperature for 1 h. After removal of the solvent, the residue was taken up in 10% $NaHCO_3$ and the solution was extracted with CH_2Cl_2 (30 × 2 ml). The combined extract was washed with sat. NaCl and dried over anhyd. Na_2SO_4. After removal of the solvent, the residue was purified by silica gel column chromatography [benzene–hexane (1 : 1) for elution] to give **5** (121.4 mg, yield 60.1%) and **2a** (57.3 mg, yield 23.4%).

Acknowledgement We thank Prof. Shun-ichi Yamada, of this university, for his encouragement during this work.

References and Notes

1) *a*) R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, N.Y., 1970, pp. 33—39, 412—417; *b*) W. A. Remers and R. K. Brown, "The Chemistry of Heterocyclic Compounds," Vol. 25, Part 1, ed. by W. J. Houlihan, Wiley-Interscience, New York, N.Y., 1972, pp. 116—120, 133—134.
2) A. Chatterjee and K. M. Biswas, *J. Org. Chem.*, **38**, 4002 (1973).
3) A. Previero, M. A. Coletti-Previero, and J.-C. Cavadere, *Biochim. Biophys. Acta*, **147**, 453 (1967).
4) R. L. Hinman and E. R. Shull, *J. Org Chem.*, **26**, 2339 (1961).
5) Y. Kikugawa and M. Kashimura, *Synthesis*, **1982**, 785.
6) A. Cipiciani, S. Clementi, P. Linda, G. Marino, and G. Savalli, *J. Chem. Soc., Perkin Trans. 2*, **1977**, 1284.
7) J. R. Spies, *J. Am. Chem. Soc.*, **70**, 3717 (1948).
8) C. V. Rogers and R. B. Corson, "Organic Syntheses," Coll. Vol. 4, ed. by N. Rabjohn, John Wiley & Sons Inc., New York, 1963, P. 884.
9) H. Yamamoto, M. Nakao, and A. Kobayashi, *Chem. Pharm. Bull.*, **16**, 647 (1968).
10) N. F. Kucherova, V. P. Evdakov, and N. K. Kochetkov, *Zhur. Obshch. Khim.*, **27**, 1049 (1957) [*Chem. Abstr.*, **52**, 3763 (1958)].
11) G. M. Smith, *J. Chem. Soc.*, **1954**, 3842.
12) A. R. Snyder, S. Swaminathan, and H. J. Sims, *J. Am. Chem. Soc.*, **74**, 5110 (1952).