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2-FORMYLATION OF 3-ARYLINDOLES

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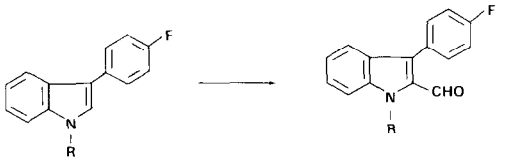
Abstract: The preparation of N-substituted-3-(4-fluorophenyl)indoles (R = H, CH_3, i-Pr) and their direct formylation at the 2-position by Vilsmeier-Haack or Friedel-Crafts methodologies is described.

In connection with on-going research programs in our laboratory, a simple, direct method for the preparation of 3-arylindole-2-carboxaldehydes was required. Since previously reported syntheses of these compounds, which involved either the transformation of an incorporated moiety (usually an ester function)[1] or the reaction of the 2-lithiated indole with N-methylformanilide[2] did not appear attractive,[3,4] an alternate methodology was sought.

Encouraged by a report that the reaction of skatole, under Vilsmeier-Haack formylation conditions ($POCl_3$/DMF), gave 3-methylindole-2-carboxaldehyde as a minor product,[5] we decided to examine the utility of this pathway for the preparation of our desired 2-formyl-indole systems. We now wish to report the results of this preliminary study which show that indoles 1 can be formylated under these reaction conditions to yield indole-2-carboxaldehydes 2.

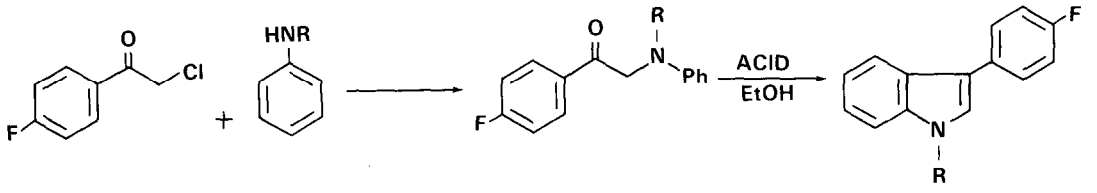


1 2

(R = H, CH_3, i-Pr)

Starting indoles 1 a-c were prepared according to the general method of Brown and Mann[6] using an acid catalyzed cyclization of the corresponding phenacylarylamines 3 derived from α-chloro-p-fluoroacetophenone[7] (Scheme I, Table I).

Scheme I

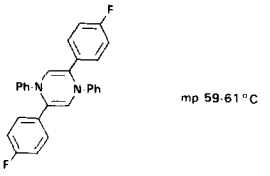


3 1

Table I. Preparation of Substituted Phenacylarylamines and Indoles

	R	Yield, %	mp, °C	Comments
3a,	H[8]	44	109-111	a,b
3b,	CH_3	82	107-108	b
3c,	i-Pr	80.2	78-81	b,c
1a,	H	41	186.5-187	d
1b,	CH_3	75	72-73.5	e
1c,	i-Pr	81	94.5-95.5	e

a) Reaction performed in presence of NaOAc to inhibit autocatalytic cyclization mediated by $PhNH_2Cl^-$.
b) Thermally labile intermediate.
c) Conditions: 1 eq. α-chloro-p-fluoroacetophenone/2 eq. N-isopropylaniline/DMF/100°C (10 hrs)/recryst. EtOH.
d) Yield from α-chloro-p-fluoroacetophenone (2-steps). Cyclization catalyzed by $PhNH_2Cl^-$ formed in situ. The use of $ZnCl_2$ promotes the formation of a dimeric condensation product identified as:



mp 59-61°C

e) Conditions: 1 mol phenacylarylamine 3/7 mol $ZnCl_2$/EtOH/100-105°C (3-5 hrs)/recryst. EtOH.

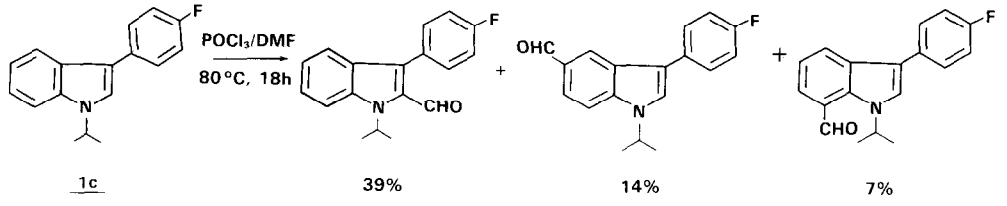
These indoles were then subjected to Vilsmeier-Haack conditions. While the reaction of 1a and 1b yielded the 2-formylated indoles 2a and 2b as sole products, compound 1c gave small amounts of 5- and 7-formylated isomers (Scheme II) in addition to the desired 2c, presumably due to the increased steric requirements of the N-isopropyl moiety (Table II).

Table II. Preparation of 2-Formyl Indoles by Vilsmeier-Haack Method [a]

	R	Rxn. Time	Solvent	Yield, %	mp, °C
2a,	H	1 hr	DMF	38[b]	282-283[c]
2b,	CH_3	3 hrs	DMF	86.2	80.5-81.5[d]
2c,	i-Pr	5 hrs (100°C)	DMF	50.4	90-91[e]
		16 hrs	$ClCH_2CH_2Cl$	56	90-91[e]

a) Standard Conditions: 1.1-1.4 moles $POCl_3$: 1 mole indole, excess DMF as solvent, 80°C. Hydrolyze cooled mixture cautiously with 50% aq. NaOH, extract, recrystallize.
b) No attempt made to optimize reaction conditions.
c) Chromatographic isolation (silica gel/CH_3OH-CH_2Cl_2).
d) Recrystallized from EtOH.
e) Recrystallized from isopropyl alcohol.

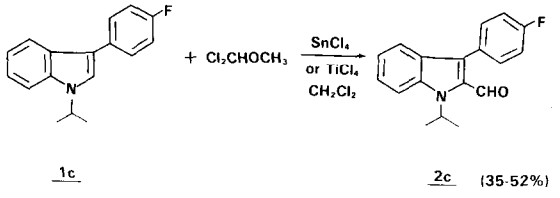
Scheme II [a]



a) Initial experiment; mass balance accounted for by unreacted 1c.

Indole 1c was also found to react with 1,1-dichloromethyl-methyl ether, in the presence of a slight molar excess of either $TiCl_4$ or $SnCl_4$ (refluxing CH_2Cl_2; 5.5 and 4.5 hrs, respectively), to yield the 2-formylated product (35% and 52% yield, respectively after chromatography; Scheme III).

Scheme III



These methods present a direct, efficient synthesis of 2-formylindoles from 3-arylindoles.[9]

Acknowledgement: The authors thank Dr. M. Shapiro, Mr. M. Kolpak, Mr. L. Janaskie, and Dr. E. Fu for providing spectroscopic measurements and analyses.

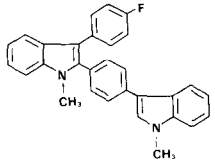
References and Notes

1. Remers, W.A. in "The Chemistry of Heterocyclic Compounds", Weissberger, A. and Taylor, E.C., Eds.; Volume 25 (Indoles-Part Three; Houlihan, W.J., Ed.), John Wiley and Sons, New York, N.Y., 1979, pp. 357-369 and references therein.

2. Hoffmann, K., Rossi, A., Keberle, J., Ger. Patent 1,093,365 (November 4, 1958).

3. The preparation of the N-unsubstituted indole-2-carboxylate by the Fisher indole synthesis, followed by N-alkylation is not an attractive alternative when the N-alkyl substituent to be introduced = i-Pr or larger (cf: Sukata, K., Bull. Chem. Soc. Jap. **1983**, 56, 280).

4. The major product obtained from the reaction of n-butyllithium with 1-methyl-3-(4-fluorophenyl)-1H-indole has been tentatively identified as:



on the basis of ^{1}H NMR data and CI-MS (isobutane, M^+=430). This product presumably arises via an SET process.

5. Chatterjee, A., Biswas, K.M., J. Org. Chem. **1973**, 38, 4002; The major product (71% yield) from this reaction was N-formyl-3-methylindole as expected.

6. a) Brown, F., Mann, F.G., J. Chem. Soc. **1948**, 847; b) Ibid, p. 858.

7. Hann, R.M., Wetherill, J.P., J. Wash. Acad. Sci. **1934**, 24, 526.

8. Abdulla, R.F., Lahiri, S.K., Crabb, T.A., Cahill, R., Z. Naturforsch. B, **1971**, 26(2), 95.

9. Spectroscopic and analytical data for new compounds reported in this communication are as follows:

   a) **Compound 1a:** ^{1}H NMR (90 MHz, DMSO-d_6): δ 6.59-6.71 (m, 1H), 6.82-7.20 (m, 4H), 7.23-7.81 (m, 4H), 11.16 (s, broad, 1H).
   Analysis calc'd: C (79.6%), H (4.77%), N (6.63%)
   found: C (79.5%), H (4.8%), N (6.5%)

   b) **Compound 1b:** ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.79 (s, 3H), 6.96-7.40 (m, 6H), 7.45-7.67 (m, 2H), 7.76-7.94 (m, 1H).

   c) **Compound 1c:** ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48 (d, J=7.5, 6H), 4.60 (hept., J=7.5, 1H), 7.00-7.39 (m, 6H), 7.49-7.61 (m, 2H), 7.80-7.89 (m, 1H); Mass Spectrum (CI-isobutane): MH^+=254; EI-MS (35eV): M^+=253.

   d) **Compound 2a:** ^{1}H NMR (90 MHz, acetone-d_6): δ 2.65 (s, broad, 1H), 7.18-7.58 (m, 5H), 7.70-7.96 (m, 2H), 8.23-8.40 (m, 1H), 10.07 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 184.90, 168.32, 157.27, 147.38, 135.68, 131.91, 131.52, 126.25, 126.12, 125.66, 123.32, 122.02, 120.72, 116.04, 115.06, 113.57, 111.62
   Analysis calc'd: C (75.3%), H (4.2%), N (5.8%)
   found: C (74.6%), H (4.3%), N (5.7%)

   e) **Compound 2b:** ^{1}H NMR (90 MHz, $CDCl_3$): δ 4.12 (s, 3H), 6.99-7.73 (m, 8H), 9.83 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 183.34, 164.83, 159.90, 139.25, 132.27, 132.13, 130.76, 129.97, 127.89, 127.84, 127.22, 125.50, 121.59, 121.06, 115.66, 115.22, 110.17, 31.51.

   f) **Compound 2c:** ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.68 (d, J=6.8, 6H), 5.90 (hept., J=6.8, 1H), 6.96-7.69 (m, 8H), 9.80 (s, 1H); ^{13}C NMR ($CDCl_3$): δ183.32, 168.04, 157.05, 137.80, 132.73, 132.34, 131.82, 130.58, 128.18, 128.05, 126.88, 122.06, 120.76, 115.92, 114.98, 113.09, 47.93, 21.27; Mass Spectrum (EI-35eV): M^+=281.

   g) **Compound 3b:** ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.10 (s, 3H), 4.73 (s, 2H), 6.57-6.85 (m, 3H), 7.03-7.36 (m, 4H), 7.90-8.13 (m, 2H).

   h) **Compound 3c:** ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.19 (d, J=6.8, 6H), 4.20 (hept., J=6.8, 1H), 4.57 (s, 2H), 6.48-6.79 (m, 3H), 6.94-7.29 (m, 4H), 7.85-8.13 (m, 2H).

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