A Novel Transformation of 3-Alkoxyisoquinolines to 3-Chloroisoquinolines and an Unusual Decyanation of 1,3-Dialkoxy-4-cyano-5,6,7,8-tetrahydroisoquinolines Under Vilsmeier-Haack Conditions

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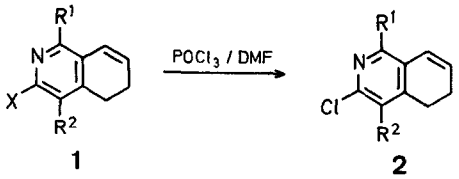
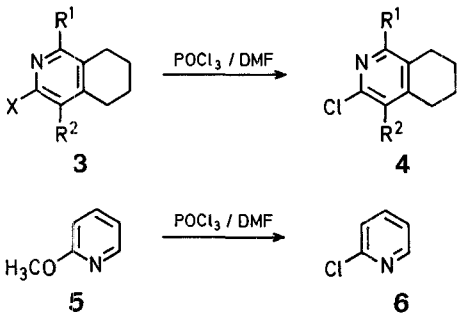
We report here a one step transformation of 3-alkoxy-5,6-dihydroisoquinolines **1** and 3-alkoxy-5,6,7,8-tetrahydroisoquinolines **3**[1] to the corresponding 3-chloro compounds **2** and **4** under Vilsmeier-Haack conditions[2]. Phosphoryl chloride (2 equiv.) was added slowly to an ice-cooled solution of compound **1** or **3** (1 equiv.) in anhydrous dimethylformamide and then heated at 80 °C for 1 h, when the corresponding chloro compounds **2** or **4** (Table 1) were obtained in 20–70% yield.

We have generalized the above reaction by applying it to simple 2-alkoxypyridines. Thus, the reaction of 2-methoxypyridine (**5**)[3] under Vilsmeier-Haack conditions gave 2-chloropyridine (**6**) in about 40% yield. The conversion of 2-alkoxy-pyridines and 3-alkoxy isoquinolines by phosphoryl chloride in dimethylformamide to the corresponding chloro derivatives has hitherto not been reported in the literature.



1 **2**

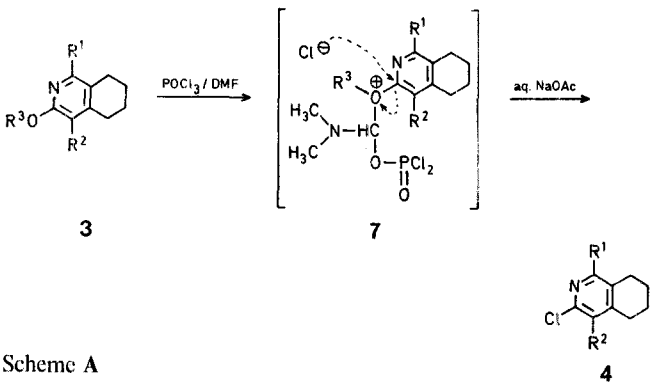


3 **4**

5 **6**

The mechanism of formation of **2** or **4** might involve the initial attack of the Vilsmeier-Haack complex on the oxygen of the alkoxy group, followed by the attack of chloride ion at C-3 and cleavage of the ether (Scheme **A**). Evidence supporting the intermediacy of **7** in the conversion of **3** to **4** is offered by the isolation of:

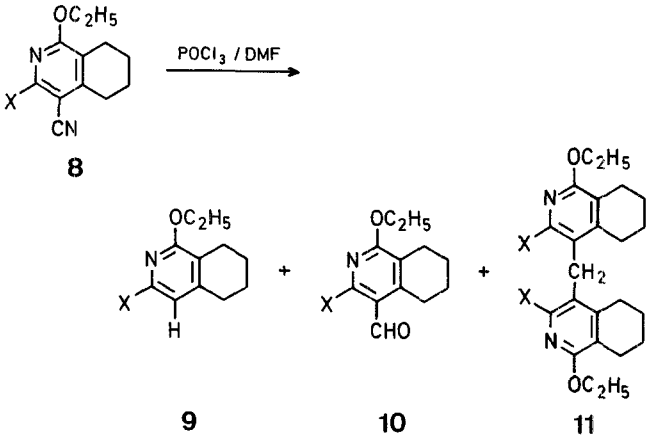
- benzyl acetate when the reaction was carried out with **3f**,
- only the starting material when compound **1a** was refluxed for 72 h with phosphoryl chloride alone,
- 4-cyano-1-methyl-5,6-dihydro-3(2*H*)-isoquinolone in quantitative yield when hydrogen chloride gas was bubbled through an ice-cooled solution of **1a** in dry dimethylformamide.



3 **7** **4**

Scheme **A**

An electron donating group at C-1, changes the course of the reaction entirely. For example, the usual Vilsmeier-Haack reaction on the 1,3-dialkoxy-4-cyano-isoquinoline derivative **8** yielded three products **9**, **10** and **11** (Tables 2 and 3; Scheme **B**). When the above reaction mixture was quenched with dry methanol or deuterated water, the methyl ester **13** or deuterated compound **14** was obtained respectively. This indicates the attack of Vilsmeier-Haack complex on the cyano group giving a ketenimine type intermediate **12** which upon hydrolysis and decarboxylation gives **9a** (Scheme **C**).



8

9 **10** **11**

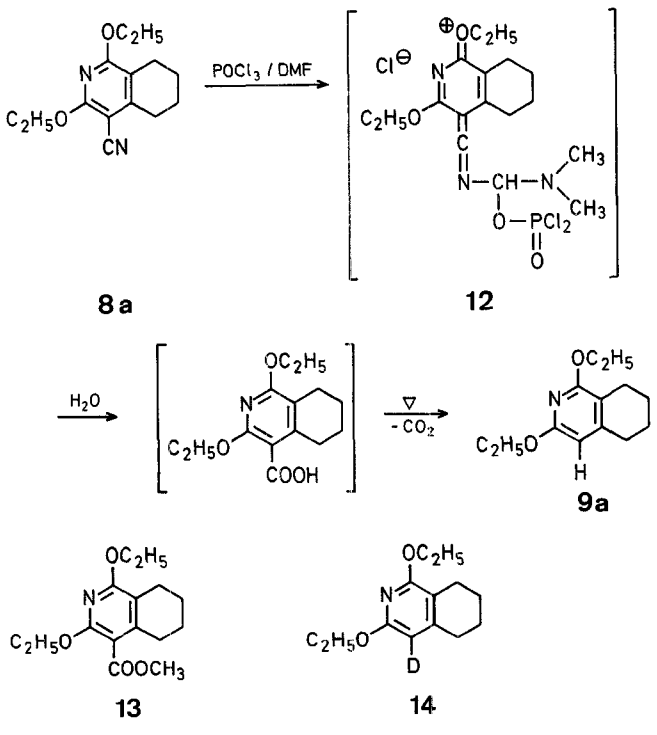
8-11	a	b
X	OC_2H_5	OCH_3

Scheme **B**

Table 1. Substituted 3-Chloroisoquinolines **2a–c** and **4a–d** prepared

Substrate No.	R^1	R^2	X	Product	Reaction conditions Temp. [°C]/ Time [h]	Yield [%]	m.p.[a] [°C]	Molecular formula[b]	I.R. (Nujol)[c] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[d] δ [ppm]
1a	CH_3	CN	OCH_3	**2a**	80°/1	69	110°	$C_{11}H_9ClN_2$[e] (204.7)	2230, 1575, 1565	2.2–3.15 (m, 4H); 2.5 (s, 3H); 6.05–6.64 (m, 2H)
1b	C_6H_5—CH_2	CN	OCH_3	**2b**	80°/1	40	72°	$C_{17}H_{13}ClN_2$ (280.7)	2250, 1590, 1580	2.07–3.1 (m, 4H); 4.1 (s, 2H); 5.6–6.6 (m, 2H); 7.24 (s, 5H)
1c	CH_3	H	OCH_3	**2c**	120°/5	65	78–79°	$C_{10}H_{10}ClN$ (179.6)	1625, 1600, 1580, 1560	2.2–2.9 (m, 4H); 2.45 (s, 3H); 6.0–6.25 (m, 1H); 6.38–6.67 (br. d, 1H); 6.84 (s, 1H)
3a	CH_3	CN	OCH_3	**4a**	80°/1	70	105°	$C_{11}H_{11}ClN_2$[e] (206.7)	2220, 1570, 1540	1.7–2.07 (m, 4H); 2.47 (s, 3H); 2.34–3.07 (m, 4H)
3b	C_6H_5—CH_2	CN	OCH_3	**4b**	80°/1	52	68°	$C_{17}H_{15}ClN_2$ (282.8)	2250, 1570, 1540	1.6–1.9 (m, 4H); 2.6–3.0 (m, 4H); 4.1 (s, 2H); 7.2 (s, 5H)
3c	CH_3	H	OCH_3	**4c**	120°/5	56	57°	$C_{10}H_{12}ClN$ (181.7)	1580, 1560	1.5–1.9 (m, 4H); 2.3 (s, 3H); 2.34–2.7 (m, 4H); 6.67 (s, 1H)[f]
3d	H	CN	OCH_3	**4d**	80°/1	20	85–86°	$C_{10}H_9ClN_2$ (192.6)	2230, 1590, 1580	1.62–1.9 (m, 4H); 2.48–3.0 (m, 4H); 6.9 (s, 1H)
3e	CH_3	CN	OH	**4a**	80°/5	38		see above		
3f	CH_3	CN	C_6H_5—CH_2—O	**4a**	80°/1	70		see above		

[a] Melting points (hot stage) are uncorrected.
[b] Satisfactory microanalyses obtained: C ± 0.29, H ± 0.38, N ± 0.28. Exceptions: **2b**, N + 0.49; **4a**, N + 0.52.
[c] I.R. spectra were recorded on a Perkin Elmer 397 or 700 spectrophotometer.
[d] ^{1}H-N.M.R. spectra were recorded on a Varian T60, Varian HA 100 spectrometer.
[e] Satisfactory mass spectra were also obtained.
[f] Measured in carbon tetrachloride.



Scheme C

Table 2. Decyanation of 4-Cyano-1,3-dialkoxy-5,6,7,8-tetrahydroisoquinolines **8**

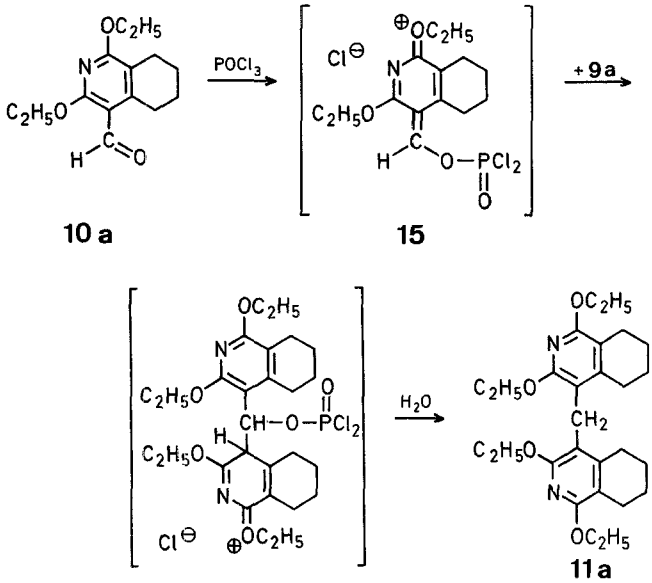
Amount of Phosphoryl Chloride (equiv.)	Amount of DMF to 1 g of substrate (ml)	Reaction conditions Temp. [°C]/ Time [h]	Yield of products [%] 9	10	11
3	8	80°/3	80	5	–
4.5	16	80°/5	3	82	5
6	8	80°/6	–	5	86

The expected aldehyde **10a** was formed in good yield (96%) when 1,3-diethoxy-5,6,7,8-tetrahydroisoquinoline **(9a)** was treated with Vilsmeier-Haack reagent. Structure of bis[1,3-diethoxy-5,6,7,8-tetrahydro-4-isoquinolyl]methane **(11a)** was confirmed by spectral data and also by direct synthesis by two different methods. Addition of compound **9a** to a mixture of phosphoryl chloride and the aldehyde **10a** in dry dichloromethane which perhaps forms the Vilsmeier-type complex **15**, followed by the reflux of the mixture gave **11a** (Scheme **D**). Compound **11a** was also prepared by a procedure similar to the one reported[7] for bis[2-hydroxy-1-naphthyl]methane.

Table 3. Physical Data of 1-Ethoxy-substituted Isoquinolines

Product No.	m.p.[a] [°C]	Molecular formula[b,c]	I.R. (Nujol)[d] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[e] δ [ppm]
9a	38°	$C_{13}H_{19}NO_2$ (221.3)	1610, 1580	1.28 (t, J = 7 Hz, 3H); 1.32 (t, J = 7 Hz, 3H); 1.76–1.9 (m, 4H); 2.35–2.7 (m, 4H); 4.22 (q, J = 7 Hz, 2H); 4.3 (q, J = 7 Hz, 2H); 5.89 (s, 1H)
9b	51°	$C_{12}H_{17}NO_2$ (207.3)	1605, 1570	1.34 (t, J = 7 Hz, 3H); 1.5–1.87 (m, 4H); 2.3–2.74 (m, 4H); 3.75 (s, 3H); 4.34 (q, J = 7 Hz, 2H); 5.94 (s, 1H)
10a	58°	$C_{14}H_{19}NO_3$ (249.30)	1710, 1580	1.38 (t, J = 7 Hz, 3H); 1.41 (t, J = 7 Hz, 3H); 1.6–1.8 (m, 4H); 2.3–2.64 (br.m, 2H); 2.8–3.14 (br.m, 2H); 4.34 (q, J = 7 Hz, 2H); 4.47 (q, J = 7 Hz, 2H), 10.5 (s, 1H)
10b	44°	$C_{13}H_{17}NO_3$ (235.3)	1700, 1580	1.38 (t, J = 7 Hz, 3H); 1.54–1.8 (m, 4H); 2.27–2.6 (br.m, 2H); 2.84–3.17 (br.m, 2H); 3.9 (s, 3H); 4.4 (q, J = 7 Hz, 2H); 10.3 (s, 1H)
11a	145–146°	$C_{27}H_{38}N_2O_4$ (454.6)	1600, 1590	1.22 (t, J = 7 Hz, 6H); 1.32 (t, J = 7 Hz, 6H); 1.5–1.9 (m, 8H); 2.3–2.7 (m, 8H); 3.75 (s, 2H); 4.22 (q, J = 7 Hz, 4H); 4.30 (q, J = 7 Hz, 4H)
11b	134–135°	$C_{25}H_{34}N_2O_4$ (426.5)	1600, 1575	1.3 (t, J = 6 Hz, 3H); 1.5–1.77 (m, 8H); 2.3–2.64 (m, 8H); 3.7 (s, 2H); 3.77 (s, 6H); 4.27 (q, J = 6 Hz, 4H)
13	39–40°	$C_{15}H_{21}NO_4$ (279.3)	1720, 1620, 1580	1.33 (t, J = 7 Hz, 3H); 1.36 (t, J = 7 Hz, 3H); 1.6–1.86 (m, 4H); 2.36–2.8 (m, 4H); 3.76 (s, 3H); 4.3 (q, J = 7 Hz, 2H); 4.34 (q, J = 7 Hz, 2H)
14	37–38°	$C_{13}H_{18}DNO_2$[f] (222.3)	1605, 1590	1.3 (t, J = 7 Hz, 3H); 1.33 (t, J = 7 Hz, 3H); 1.54–1.84 (m, 4H) 2.3–2.7 (m, 4H); 4.17 (q, J = 7 Hz, 2H); 4.25 (q, J = 7 Hz, 2H)

[a] Melting points (hot stage) are uncorrected.
[b] Satisfactory microanalyses obtained: C ±0.44, H ±0.34, N ±0.41.
[c] Satisfactory mass spectra were also obtained.
[d] I.R. spectra were recorded on a Perkin Elmer 397 or 700 spectrophotometer.
[e] ^{1}H-N.M.R. spectra were obtained on Varian T60 or Varian HA100 spectrometers.
[f] Mass spectra of **9a** and **14** are compared. **9a** (**14**); M.S.: m/e = 221 (222), 206 (207), 192 (193), 178 (179), 164 (165), 150 (151), 137 (138), 121 (122), 109 (110), 91 (92), 77 (78), 65 (66), 53 (53).



Scheme **D**

The 3-alkoxyisoquinolines required were synthesized by reported procedure[1].

3-Chloro-4-cyano-1-methyl-5,6-dihydroisoquinoline (2a); Typical Procedure:

To a stirred solution of 4-cyano-3-methoxy-1-methyl-5,6-dihydroisoquinoline (*1a*; 2 g, 0.01 mol) in dry dimethylformamide (16 ml) at 0 °C, phosphoryl chloride (1.9 ml, 0.02 mol) is added dropwise. The stirring is continued for 1 h more and the mixture is heated at 80 °C for 1 h. It is cooled to 0 °C, quenched by adding saturated sodium acetate solution and warmed on water bath for 30 min. After cooling, the mixture is extracted with ether (4 × 75 ml). The ether extract is thoroughly washed with water (6 × 50 ml) and dried over anhydrous sodium sulphate. The crude product obtained after removal of the solvent is chromatographed over neutral alumina. Elution with benzene gives product **2a**, which is further purified by crystallisation; yield 1.4 g (69%); m.p. 110 °C (benzene).

Decyanation of 1,3-Dialkoxy-4-cyano-isoquinolines **8** *to Isoquinolines* **9–14**: This is carried out analogous to the typical procedure described for the preparation of **2a**. The products are separated by chromatography on alumina eluting with benzene. For obtaining the methyl ester **13** and the deuteroproduct **14**, the reaction mixture is quenched with dry methanol or deuterated water, respectively (Tables 2 and 3).

2-Chloropyridine (6):

This is prepared similarly by dropwise addition of phosphoryl chloride (3 g, 19.6 mmol) to a solution of 2-methoxypyridine (1 g, 9.2 mmol) in dimethylformamide (8 ml) with stirring at 0 °C followed by heating at 80 °C (2 h) and working up as given above; 2-chloropyridine; yield 0.4 g (39%); b.p. 173–175/760 torr; (Lit.[6], b.p. 166 °C/714 torr).

Bis-[1,3-diethoxy-5,6,7,8-tetrahydro-4-isoquinolyl]methane (11a):

Procedure A: To a well stirred solution of **10a** (250 mg, 0.001 mol) in dry dichloromethane (10 ml) at 0 °C, phosphoryl chloride (0.2 ml, 0.002 mol) in dry dichloromethane (5 ml) is added dropwise, followed by the addition of compound **9a** (220 mg, 0.001 mol). It is then refluxed for 2 h, cooled to 0 °C, quenched by the addition of saturated sodium acetate solution (25 ml), extracted with dichloromethane (3 × 20 ml), washed with water (5 × 20 ml) and dried over anhydrous sodium sulphate. The crude product, obtained after removal of the solvent is chromatographed over neutral alumina. Elution with benzene gives product **11a** which is further purified by crystallisation (ether methanol); yield 350 mg (77%), m.p. 145–146 °C.

Procedure B[7]: Formaldehyde (40% solution, 95 mg) is added to a solution of sodium sulphite (315 mg) in water (1.3 ml) containing **9a** (280 mg) in suspension. This is heated to 100 °C for 15 min, cooled and extracted with ether (3 × 50 ml). Solvent is removed and the residue is crystallised (ether/methanol) to give pure **11a**; yield 200 mg (70%); m.p. 145–146 °C.

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