Synthesis and Reactions of Isoquinoline Derivatives II.[1] Synthesis of 3-Chloroisoquinoline-4-aldehydes

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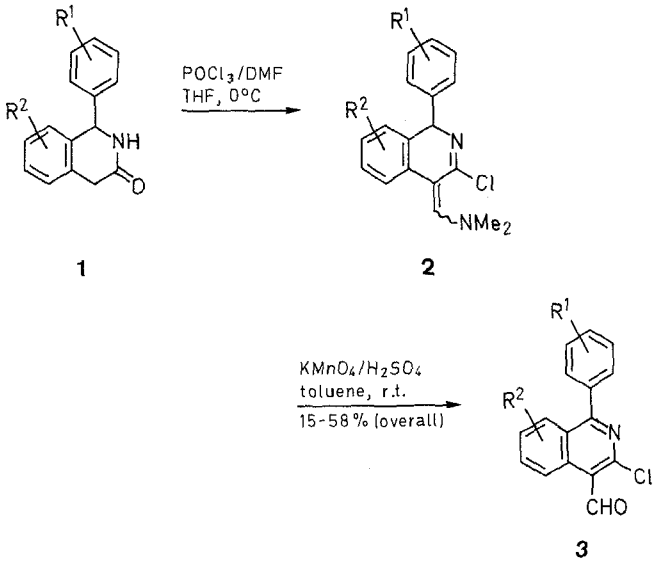
Dedicated to Prof. Rolf Huisgen on the occasion of his 68th birthday.

1-Aryl-substituted 1,4-dihydro-3(2*H*)isoquinolinones **1** are easily converted to 1-aryl-3-chloroisoquinoline-4-aldehydes **3** by a two-step procedure involving a Vilsmeier–Haack reaction followed by subsequent oxidation with potassium permanganate under acidic conditions.

Isoquinoline derivatives are of great interest to synthetic as well as pharmaceutical organic chemists.[2,3] However, isoquinolines carrying substituents in position 3 and 4 are often difficult to prepare by the classical cyclization reactions.[4–13] Since it is not easy to functionalize the preformed isoquinoline backbone in these positions,[14–23] we wish to describe a newly developed and versatile synthetic route to this class of compounds.[24]

Our approach is based on the Vilsmeier–Haack acylation reaction[25] which converts α-methyleneketones into β-chlorovinylaldehydes. This reaction is accomplished in two steps (Scheme **A**).



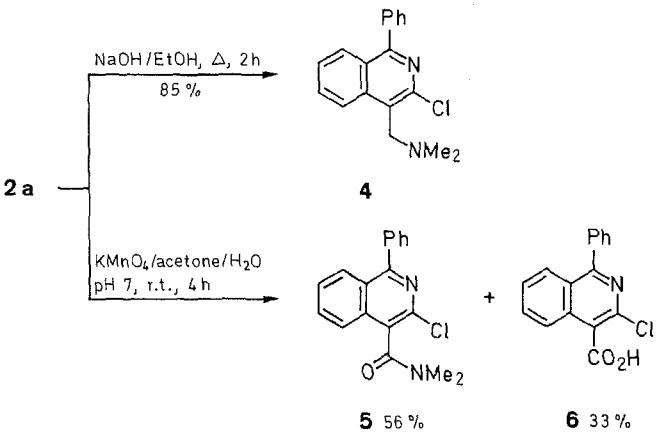
1–3	R^1	R^2	1–3	R^1	R^2
a	H	H	**g**	H	6-Cl
b	2-CH_3	H	**h**	H	6,7-$(CH_3O)_2$
c	2-F	H	**i**	4-Cl	6,7-$(CH_3O)_2$
d	2,4-Cl_2	H	**j**	2-CH_3	6-Cl
e	H	5-CH_3	**k**	H	6,7-$(CH_2)_3$
f	H	6-CH_3	**l**	2-F	6-F

Scheme **A**

1-Aryl-substituted 1,4-dihydro-3(2*H*)isoquinolinones **1**, easily obtained by condensation of the corresponding benzaldehydes with phenylacetonitril,[26] are first treated with an excess of the dimethylformamide-phosphorus oxychloride complex in tetrahydrofuran at 0 °C, and the resulting 1-aryl-3-chloro-4-dimethylaminomethylene-1,4-dihydroisoquinolines **2** oxidized with potassium permanganate in acidic solution to yield 1-aryl-3-chloroisoquinoline-4-aldehydes **3**.

This reaction sequence needs the following comments. The intermediates **2** are yellow or orange-red compounds which are stable only in the crystalline state. Under basic conditions they isomerize to their aromatic counterparts; e. g. **2a** yields 3-chloro-4-dimethylaminomethylene-1-phenylisoquinoline (**4**)[12] (Scheme **B**). In the presence of amines, e. g. *N*-methylpiperazine, isomerization to **4** is also more rapid than the nucleophilic substitution. In principle, crude **2** can be purified by recrystallization from toluene/petroleum ether, but due to low yields it is preferable not to isolate them.

The oxidation by potassium permanganate has to take place in an acidic environment with immediate removal of the product. Under neutral conditions in acetone solution **2a** is oxidized to a mixture of the amide **5** and the acid **6** (Scheme **B**).



Scheme **B**

Due to these restrictions the Vilsmeier–Haack reaction mixture is preferably hydrolyzed by a two-phase toluene/sodium hydroxide mixture, thereby extracting **2** into the organic layer immediately after its formation. The organic phase is first treated with diluted sulfuric acid and then with potassium permanganate so that the product **3** can easily be isolated from the organic solution. The compounds listed in Table 1 are synthesized according to this method and are stable crystalline compounds.

Alternatively, isolated **2** may be dissolved in diluted sulfuric acid and treated with powdered potassium permanganate without use of an organic co-solvent. In this case, very pure crystalline aldehydes **3** precipitate directly out of the solution.

The reaction sequence, Vilsmeier–Haack reaction, and oxidation in acidic medium can also be successfully applied to other isoquinolinone derivatives. This is exemplified by the transformation of **7**[27] and **9**[28] into the corresponding aldehydes **8** and **10** (Scheme **C**).

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Table 1. 3-Chloro-1-phenylisoquinoline-4-aldehydes **3** Prepared

Product	Yield[a] (%)	mp[b] (°C)	Molecular Formula[c]	IR (KBr)[d] $\nu_{C=O}$ (cm^{-1})	MS (70 eV)[e] *m/z* (M^+, %)	^{1}H-NMR ($CDCl_3$/TMS)[f] δ, *J* (Hz)
3a	54	170–172	$C_{16}H_{10}ClNO$ (267.7)	1683	267 (100)	7.4–8.4 (m, 8 H_{arom}); 9.33 (dd, 1H, $J = \sim 9.4$, ~ 1.0, H-5); 10.93 (s, 1H, CHO)
3b	37	140–142	$C_{17}H_{12}ClNO$ (281.7)	1681	281 (70)	2.13 (s, 3H, CH_3); 7.2–8.05 (m, 7 H_{arom}); 9.25 (dd, 1H, $J = \sim 8.4$, 1.0, H-5); 10.91 (s, 1H, CHO)
3c	58	187–189	$C_{16}H_9ClFNO$ (285.7)	1689	285 (100)	7.0–8.1 (m, 7 H_{arom}); 9.22 (dd, 1H, $J = \sim 9.2$, < 1.0, H-5); 10.89 (s, 1H, CHO)
3d	32	192–193	$C_{16}H_8Cl_3NO$ (336.6)	1685	335 (100) 336 (60)	7.2–8.1 (m, 6 H_{arom}); 9.2 (dd, 1H, $J = \sim 8.2$, < 1.0, H-5); 10.84 (s, 1H, CHO)
3e	36	134–136	$C_{17}H_{12}ClNO$ (281.8)	1706, 1688	281 (100)	2.51 (s, 3H, CH_3); 7.3–7.85 (m, 7 H_{arom}); 8.0 (dd, $J = \sim 8.0$, ~ 2.0, H-8); 10.93 (s, 1H, CHO)
3f	37	149–153	$C_{17}H_{12}ClNO$ (281.8)	1684	281 (100)	2.62 (s, 3H, CH_3); 7.2–7.8 (m, 6 H_{arom}); 8.0 (d, 1H, $J = \sim 8.0$, H-8); 9.07 (s, 1H, H-5); 10.9 (s, 1H, CHO)
3g	48	166–171	$C_{16}H_9Cl_2NO$ (302.1)	1685	301 (100) 302 (70)	7.4–7.8 (m, 6 H_{arom}); 8.1 (d, 1H, $J = \sim 8.8$, H-8); 9.23 (d, 1H, $J = \sim 2$, H-5); 10.73 (s, 1H, CHO)
3h	33	208–210	$C_{18}H_{14}ClNO_3$ (327.8)	1674	327 (70)	3.84 (s, 3H, OCH_3); 4.1 (s, 3H, OCH_3); 7.2–7.85 (m, 6 H_{arom}); 8.78 (s, 1H, H-5); 10.84 (s, 1H, CHO)
3i	27	263–265	$C_{18}H_{13}Cl_2NO_3$ (362.2)	1681	361 (100)	3.87 (s, 3H, OCH_3); 4.1 (s, 3H, OCH_3); 7.3 (s, 1H, H-8); 7.4–7.8 (m, 4 H_{arom}); 8.8 (s, 1H, H-5); 10.86 (s, 1H, CHO)
3j	32	155–158	$C_{17}H_{11}Cl_2NO$ (316.2)	1686	314 (M–H, 100)	2.1 (s, 3H, CH_3); 7.0–7.8 (m, 6 H_{arom}); 9.32 (d, 1H, $J = \sim 1.5$, H-5); 10.86 (s, 1H, CHO)
3k	15	145–148	$C_{19}H_{14}ClNO$ (307.8)	1682	307 (100)	1.9–2.5 (m, 2H, CH_2); 2.6–3.4 (m, 4H, CH_2CH_2); 7.0–8.0 (m, 5 H_{arom}); 7.9 (s, 1H, H-8); 9.07 (s, 1H, H-5); 10.83 (s, 1H, CHO)
3l	30	175–176	$C_{16}H_8ClF_2NO$ (303.7)	1690	303 (100)	7.0–8.1 (m, 6 H_{arom}); 8.96 (dd, 1H, $J = \sim 11.6$, ~ 2.2, H-5); 10.87 (s, 1H, CHO)

[a] Yield of crude product **3** based on **1**, not optimized.
[b] Uncorrected, measured on a Büchi melting point apparatus (Dr. Tottoli).
[c] Satisfactory microanalyses obtained: C ±0.40, H ±0.30, N ±0.20, Cl ±0.30, F ±0.30.
[d] Recorded on a Perkin-Elmer 683 Infrared Spectrophotometer.
[e] Recorded on a Kratos MS 30 or Kratos 902 S Spectrometer.
[f] Obtained on a Varian T 60 or Bruker WP 60 Spectrometer at 60 MHz.

Table 2. Physical Data of New Compounds Prepared

Product	Yield (%)	mp[b] (°C)	Molecular Formula[c]	IR (KBr)[d] ν (cm^{-1})	MS (70 eV)[e] *m/z* (M^+, %)	^{1}H-NMR ($CDCl_3$/TMS)[f] δ, *J* (Hz)
2a	70	128–132	$C_{18}H_{17}ClN_2$ (296.9)	1580 (C=N)	296 (37)	3.02 (s, 6H, NMe_2); 5.7 (s, 1H, H-1); 6.8–7.4 (m, 8 H_{arom}); 7.35 (s, 1H, H-5)
4	86	75–77	$C_{18}H_{17}ClN_2$ (296.9)	–	296 (50)	2.42 (s, 6H, NMe_2); 4.03 (s, 2H, CH_2); 7.1–8.45 (m, 9 H_{arom})
5	56	109–111	$C_{18}H_{15}ClN_2O$ (310.8)	1630 (C=O)	310 (55)	2.95 (s, 3H, CH_3); 3.31 (s, 3H, CH_3); 7.4–7.9 (m, 8 H_{arom}); 8.15 (dd, 1H, $J = \sim 8.2$, < 1.0, H-5)
6	33	214–216	$C_{16}H_{10}ClNO_2$ (283.7)	1715 (C=O)	283 (100)	7.2–8.3 (m, 9 H_{arom})
8	72	120–126[g]	$C_{10}H_6ClNO$ (191.6)	1683 (C=O)	191 (100)	7.8–8.2 (m, 3 H_{arom}); 9.13 (dd, 1H, $J = \sim 8.4$, < 1.0, H-5); 9.2 (s, 1H, H-1); 10.86 (s, 1H, CHO)
10	80	oil	$C_{16}H_{14}ClNO$ (271.7)	–	271 (17)	1.4–2.05 (m, 4H, CH_2CH_2); 2.5–2.85 (m, 2H, CH_2Ar); 3.0–3.4 (m, 2H, CH_2Ar); 7.30 (s, 5 H_{arom}); 10.28 (s, 1H, CHO)
12	25	143–144[h]	$C_{17}H_{14}ClNO$ (283.8)	–		3.37 (s, 3H, CH_3); 5.6 (s, 1H, H-1); 6.9–7.5 (m, 8 H_{arom}); 8.73 (dd, 1H, $J = \sim 7.4$, ~ 2.0, H-5); 10.13 (s, 1H, CHO)
14	94	201–203[h]	$C_{25}H_{30}ClN_3O_2$ (440.0)	1621, 1604 (C=N)	439 (100)	1.5–3.1 (m, 8H, ring CH_2); 2.96 (s, 6H, NMe_2); 3.67 (s, 2H, $PhCH_2$); 3.87 (s, 6H, 2 × OCH_3); 6.59 (s, 1H, =CH); 6.8 (s, 1 H_{arom}); 6.95–7.5 (m, 6 H_{arom})
15	92	215–217	$C_{22}H_{23}ClN_2O_3$ (398.9)	1668 (C=O)	398 (30)	1.3–3.0 (m, 8H, ring CH_2); 3.7 (s, 2H, $PhCH_2$); 3.95 (s, 3H, OCH_3); 4.02 (s, 3H, OCH_3); 6.95 (s, 1H, H-8); 7.1–7.6 (m, 5 H_{arom}); 7.54 (s, 1H, H-5)

[a,b,d–f] Refers to a, b, d–f in Table 1.
[c] Satisfactory microanalyses obtained: C ±0.40, H ±0.30, N ±0.20, Cl ±0.30.
[g] Recrystallized from acetone.
[h] Recrystallized from EtOAc.

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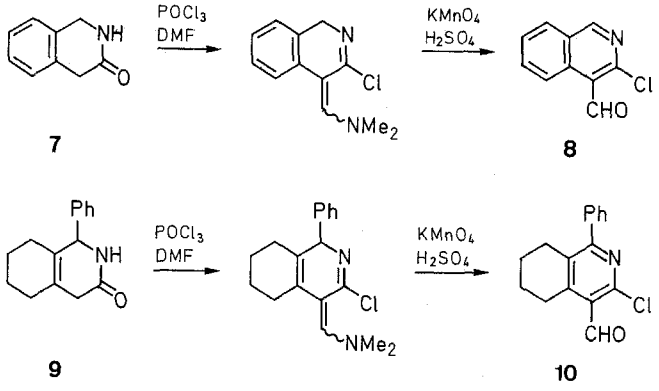
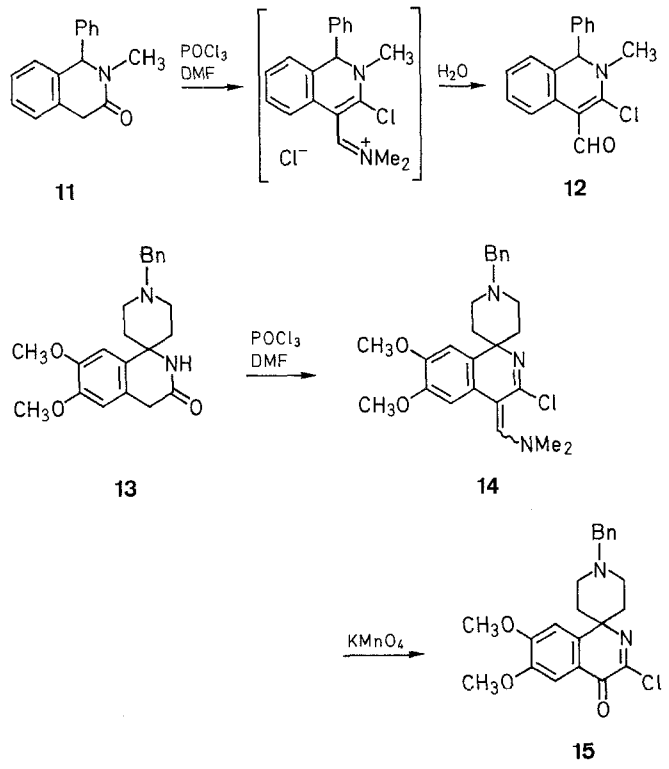


Scheme C

In contrast, blocking the nitrogen atom as e.g. in **11**[29] directly leads to the 1,2-dihydroisoquinoline-4-aldehyde (**12**), which is not very stable and decomposes slowly in solution even at room temperature (Scheme **D**).

If position 1 of the isoquinoline is blocked by disubstitution as e.g. in **13**,[30] the Vilsmeier–Haack reaction produces the dimethylaminomethylene compound **14**. Oxidation by potassium permanganate in neutral solution yields **15**, probably by attack at the exocyclic double bond[31,32] followed by elimination of dimethylformamide (Scheme **D**).



Scheme D

The 3-chloroisoquinoline-4-aldehydes **3** described in this paper open the field for various synthetic manipulations, which will be the subject of forthcoming papers.[33]

1-Aryl-3-chloroisoquinoline-4-aldehydes 3,8 and 10; General Procedure:
To a mixture of $POCl_3$ (118 mL, 1.27 mol) and DMF (97.3 g, 1.3 mol) in THF (300 mL), the appropriate **1**, **7** or **9** (0.33 mol) is added at 0 °C in portions during 40 min. The mixture is stirred at 0 °C for 1 h and then poured into 2N NaOH (2 L), ice (5 kg) and toluene (1 L). The organic phase is separated, the aqueous phase extracted once more with toluene, the combined organic phase is washed with water, evaporated to a volume of about 1 L at low temperature *in vacuo*, mixed with 2N H_2SO_4 (1.4 L) under vigorous stirring, and then finely ground $KMnO_4$ (34 g, 0.215 mol) is added in portions at room temperature. The mixture is stirred for another 6 h, the organic phase is separated, dried ($MgSO_4$), and evaporated. The residue is crystallized from EtOAc (Tables 1 and 2). Further quantities of the product can be isolated from the mother liquor.

1-Aryl-3-chloro-4-dimethylaminomethylene-1,4-dihydroisoquinolines 2 and 14, and the Aldehyde 12; General Procedure:
The Vilsmeier reagent composed of DMF (73 g, 1 mol) and $POCl_3$ (146 g, 0.95 mol) in THF (400 mL) is treated with appropriate **1**, **11** or **13** (0.25 mol) at 0 °C during 30 min. The mixture is stirred 15 h at room temperature and then hydrolyzed by pouring it into 2N NaOH (1 L), ice (3.5 kg) and toluene (1 L). After 2 h at 0 °C the toluene phase is separated, washed with water, dried ($MgSO_4$) and evaporated *in vacuo* at temperatures below 30 °C. The residue crystallizes on treatment with ether (Table 2).

3-Chloro-1-phenylisoquinoline-4-aldehyde (3a):
To a solution of **2a** (14.8 g, 55 mmol) dissolved in 2N H_2SO_4 (200 mL), $KMnO_4$ (4.75 g, 30 mmol) is added in portions. After two hours at room temperature the precipitate is collected by filtration, washed with water and recrystallized from EtOAc. Yield: 9.4 g (70%); mp 170–172 °C.

3-Chloro-4-dimethylaminomethyl-1-phenylisoquinoline (4):
To a solution of **2a** (1.75 g, 6.4 mmol) in EtOH (40 mL) 1N NaOH (6 mL) is added dropwise and the mixture refluxed for 2 h. The EtOH is evaporated *in vacuo*, the residue is partitioned between toluene and water, the organic phase is separated, dried ($MgSO_4$) and evaporated. The residue is crystallized from petroleum ether; yield: 1.5 g (85%); mp 75–77 °C; Hydrochloride: mp 244–246 °C.

***N,N*-Dimethyl-3-chloro-1-phenylisoquinoline-4-carboxamide (5) and 3-Chloro-1-phenylisoquinoline-4-carboxylic acid (6):**
To a suspension of **2a** (30 g, 0.11 mol) in acetone (700 mL) in the presence of a phosphate buffer (210 mL, pH 7), finely ground $KMnO_4$ (20 g, 0.127 mol) is added in portions. After 4 h $NaHSO_3$ (10 g) is added, the mixture stirred for 10 min and the inorganic precipitate removed by filtration. The filtrate is extracted with ether, the organic phase dried (Na_2SO_4) and evaporated. The residue is identified as the amide **5**; yield: 18.3 g (56%); mp 109–111 °C.

The aqueous phase is acidified to pH 2 by conc. HCl and extracted with ether, the organic phase dried and evaporated to give the acid **6**; yield: 9.5 g (33%); mp 205–207 °C.

Spiro-1′-benzyl-3-chloro-6,7-dimethoxy-1,4-dihydroisoquinolin-4-one-(1,4′)-piperidine (15):
To a suspension of **14** (11 g, 0.025 mol) in acetone (500 mL) and phosphate buffer (150 mL, pH 7) is added $KMnO_4$ (9.5 g, 0.057 mol) and the mixture stirred vigorously for 3 h. The solution is then filtered, the acetone evaporated and the residue extracted with $CHCl_3$. The organic phase is dried ($MgSO_4$), evaporated and the crude product crystallized from EtOAc; yield: 9.2 g (92%); mp 215–217 °C.

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