Polycyclic *N*-heterocyclic compounds. Part 52.[1] One-step syntheses of imidazo[1,5-*a*]pyridines, imidazo[1,5-*a*]quinolines and imidazo[5,1-*a*]isoquinolines by Vilsmeier reactions of pyridine-2-carbonitriles, quinoline-2-carbonitriles and isoquinoline-1-carbonitriles

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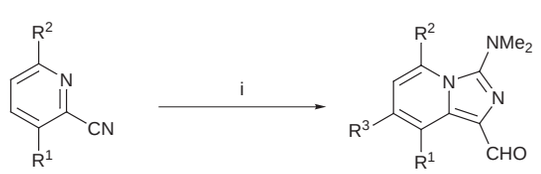
The versatile, one-step synthesis of imidazo[1,5-*a*]pyridines by the reaction of pyridine-2-carbonitriles with DMF under Vilsmeier conditions is described. This reaction was applied to the syntheses of imidazo[1,5-*a*]quinolines from quinoline-2-carbonitriles, and of imidazo[5,1-*a*]isoquinolines from isoquinoline-1-carbonitriles.

The Vilsmeier reaction is a moderate method for formylation of aromatic and active aliphatic compounds. Sometimes unexpected cyclizations under Vilsmeier conditions were observed, and have been reviewed.[2] Previously we have also reported some novel syntheses of heterocyclic systems.[3–7] In these reactions, the methylene moiety preferentially reacted with the Vilsmeier reagent which behaves as a source of a one carbon unit. Therefore, we were interested in an attempt to use a similar reaction for pyridine-2-carbonitrile which has no active methylene moiety. If the Vilsmeier reagent can work as in the previous reaction,[3–7] it was expected that the imidazo-[1,5-*a*]pyridine ring system would be obtained in one step. Syntheses of the imidazo[1,5-*a*]pyridine ring are well established in the literature;[8–10] however, all of them need several steps from the starting material (pyridine-2-carbonitrile or pyridine-2-carbaldehyde) for preparing that ring system.

In this paper we describe the versatile one-step synthesis of the imidazo[1,5-*a*]pyridine ring system from pyridine-2-carbonitrile derivatives. The extension of the same reaction to quinoline-2-carbonitriles and isoquinoline-1-carbonitriles to afford imidazo[1,5-*a*]quinolines and imidazo[5,1-*a*]isoquinolines, respectively, is also described.

Results and discussion

As shown in Scheme 1, the Vilsmeier reaction of pyridine-2-carbonitrile **1a** with the Vilsmeier reagent prepared from DMF and $POCl_3$ gave two products (**2a** and **3a**). Both products



1a $R^1 = R^2 = H$
1b R^1 = Me, $R^2 = H$
1c $R^1 = H$, R^2 = Me

2a $R^1 = R^2 = R^3 = H$
2b R^1 = Me, $R^2 = R^3 = H$
2c $R^1 = R^3 = H$, R^2 = Me
3a $R^1 = R^2$= H, R^3 = Cl
3b R^1 = Me, R^2 = H, R^3 = Cl
3c $R^1 = H$, R^2 = Me, R^3 = Cl

Scheme 1 *Reagents and conditions*: i, DMF, $POCl_3$, 80 °C, 1–12 h.

2a and **3a** had a strong absorption for the carbonyl group at ~1660 cm^{-1} in their IR spectra. In the ^1H NMR spectrum of **2a** (Table 1), one can observe four protons of the pyridine ring, and *N*,*N*-dimethylamino and formyl protons as well. Taking these results into consideration with mass spectral and elemental analysis, compound **2a** could be assigned as an imidazo[1,5-*a*]pyridine having dimethylamino and formyl groups as substituents. It is easy to restrict the positions of these substituents to C-3 and C-1, because of the absence of imidazole ring protons (1-H and 3-H) in its ^1H NMR spectrum. It was reported that 5-H was observed at δ 9.46 in the ^1H NMR spectrum of 3-formylimidazo[1,5-*a*]pyridine; on the other hand, the corresponding proton of 1-formylimidazo[1,5-*a*]-pyridine was found at δ 8.26.[11] That is, 5-H should undergo a low-field shift of 1.2 ppm by the anisotropic effect of the formyl group at C-3 in such a ring system. The lower-field signals, except for the formyl group, were observed at δ 8.25 (br t, *J* 9 Hz) and δ 7.95 (br t, *J* 7 Hz) in the case of compound **2a**. Paudler *et al.*,[10] Fuentes and Paudler,[11] and Ford *et al.*[12] have reported that both $J_{5,6}$ and $J_{6,7}$ are ~7 Hz and $J_{7,8}$ is ~9 Hz in the ^1H NMR spectrum of imidazo[1,5-*a*]pyridines. From their reports it is clear that the above two protons at δ 8.25 and δ 7.95 could be assigned as 8-H and 5-H, respectively. If compound **2a** has a formyl group at C-3, the chemical shift of 5-H at δ 8.25 is deemed to be too high even if the additional factor of the dimethylamino group at C-1 is taken into account. Therefore it is clear that 5-H of compound **2a** receives no anisotropic effect from the formyl group, and the sites of the formyl and dimethylamino groups of compound **2a** were determined as C-1 and C-3, respectively.

On the other hand, in the ^1H NMR spectrum of compound **3a** (Table 1), one can observe aromatic protons with an AB quartet pattern centred at δ 6.80 and 7.85, and a broad singlet for one proton at δ 8.29. These observations are consistent with a 2,4-disubstituted pyridine moiety. This spectrum also exhibited the presence of formyl and dimethylamino groups. The mass spectrum of compound **3a** showed the presence of a chloro group. Taking these results into consideration with the elemental analysis, the structure of compound **3a** seemed to be a chloro derivative of compound **2a**, and the site of the chloro group was able to be restricted to C-6 or C-7 at this stage. From the resonating ^1H NMR pattern, the protons of the AB quartet should be (5-H and 6-H) or (7-H and 8-H). In the case of compound **3a**, the coupling constant of the AB pattern is

Table 1 ^{1}H NMR spectral data of imidazo[1,5-*a*]pyridines **2**, **3**

	Chemical shifts (δ) and coupling pattern							Coupling constants (Hz)		
Compd.	5-H	6-H	7-H	8-H	CHO	NMe_2	Me	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$
2a	7.95, br d	6.85–7.30, m	6.85–7.30, m	8.25, br d	10.04, s	2.96, s		7	[a]	9
3a	7.85, br d	6.80, dd		8.29, br s	9.98, s	2.93, s		6.8		
2b	6.66–7.89, m	6.66–7.89, m	6.66–7.89, m		9.82, s	2.87, s	2.87, s	[a]	[a]	
3b	7.66, d	6.72, d			9.87, s	2.87, s	2.87, s	7		
2c		6.55, br d	7.02, dd	8.13, br d	10.02, s	2.85, s	2.91, s		6.5	8
3c		6.52, br s		8.15, br s	9.97, s	2.84, s	2.88, s			

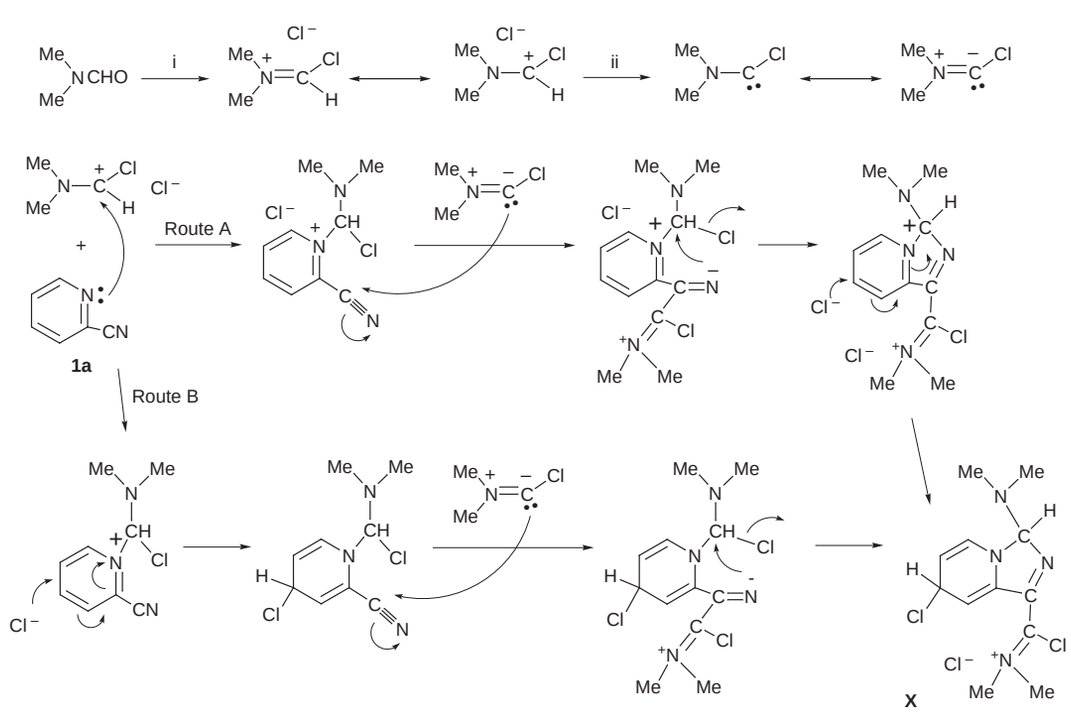
[a] Observed as multiplet.

6.8 Hz. Thus, these protons could be assigned as 5-H (δ 7.85) and 6-H (δ 6.80). The remaining proton, resonating at δ 8.29, could be assigned as 8-H. From the report of Fuentes and Paudler[11] in which 8-H of 1-formylimidazo[1,5-*a*]pyridine was observed at δ 8.08, the chemical shift of 8-H of compound **3a** seems to be reasonable. Compared with the chemical shift of 5-H of 1-formylimidazo[1,5-*a*]pyridine, which was observed at δ 8.26,[11] that of 5-H (δ 7.85) of compound **3a** is shifted upfield. We think this phenomenon was caused by the effect of the dimethylamino group.

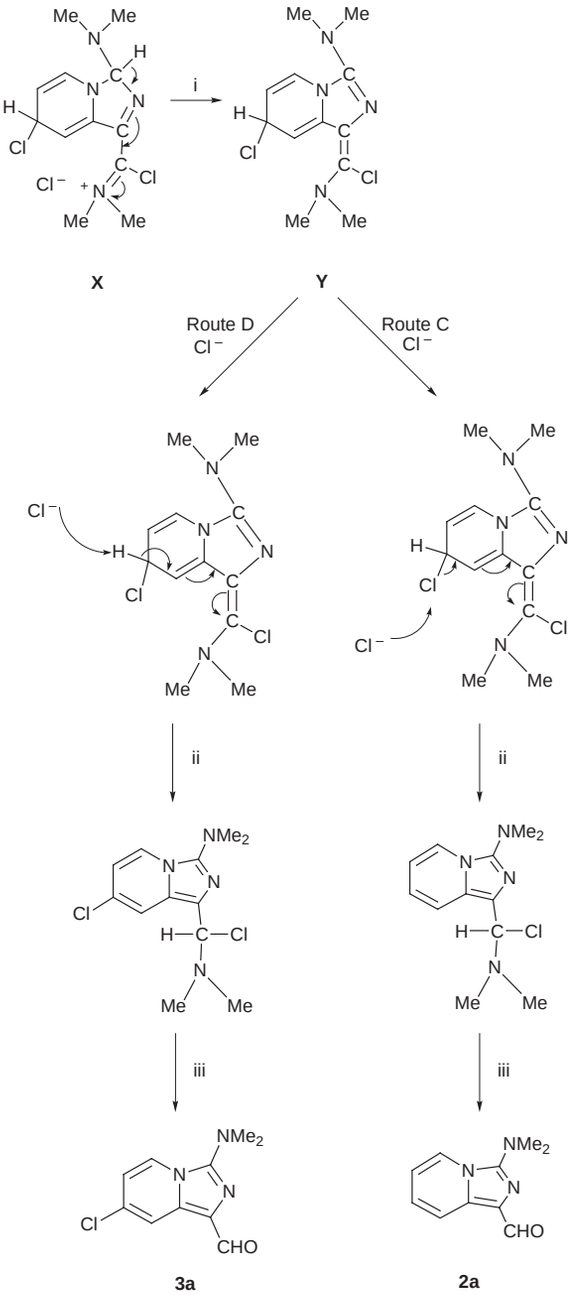
Several reactions were performed to optimize reaction conditions. As a result, the reaction of three equivalents of DMF and six equivalents of $POCl_3$ with one equivalent of **1a** gave the best results, and this synthetic approach seemed to provide a new, general route to 1,3-difunctionalized imidazo[1,5-*a*]-pyridine derivatives.

Recently, Meth-Cohn and co-workers[13] have reported the ready deprotonation of Vilsmeier reagents using *N*-methylformamide under mild conditions (at 80 °C under nitrogen) with a nitrogen-containing base (pyridine or *N*-methylmorpholine) in $POCl_3$ solution, giving non-isolated aminochlorocarbenes from which a variety of products are derived. In their case, 0.5 mol of *N*-methylformamide, 0.1 mol of $POCl_3$ and 0.05 mol of base were employed. Therefore, the formation of a similar aminochlorocarbene can also be expected in our case. Although any intermediate could not be isolated in our reaction, and it is not clear when chlorination of the pyridine ring occurred, considering the presence of this carbene, we want to postulate two possible routes for the formation of the key intermediate **X** as shown in Scheme 2. One is Route A in which the chlorination occurs after formation of the imidazole ring and the other is Route B in which the chlorination occurs before the cyclization to give species **X**. As shown in Scheme 3, we think that an elimination of a chlorine molecule from intermediate **Y**, which was formed from salt **X** (Route C), affords product **2a** and that elimination of hydrogen chloride likewise from intermediate **Y** (Route D) gave chloro product **3a**, respectively. The similar reaction of compound **1a** with $POCl_3$ and *N*,*N*-dimethylbenzamide, which has no removable (aldehyde) proton, gave a cyclized product of different type[14] and this result seemed to be able to explain the participation of an aminochlorocarbene in the formation of products **2a** and **3a**, indirectly.

For an application of this one-step synthesis of imidazo-[1,5-*a*]pyridines, the Vilsmeier reactions of 3-methylpyridine-2-carbonitrile **1b** and 6-methylpyridine-2-carbonitrile **1c** were performed. As expected, reaction of compound **1b** gave 7-chloro-3-dimethylamino-1-formyl-8-methylimidazo[1,5-*a*]-pyridine **3b** in 51% yield and 3-dimethylamino-1-formyl-8-methylimidazo[1,5-*a*]pyridine **2b** in 25% yield, and the reaction of nitrile **1c** afforded 7-chloro-3-dimethylamino-1-formyl-5-methylimidazo[1,5-*a*]pyridine **3c** in 28% yield and 3-dimethylamino-1-formyl-5-methylimidazo[1,5-*a*]pyridine **2c** in 10% yield, respectively. The ^{1}H NMR data of these products are listed in Table 1 and those data of analogues **2c** and **3c** gave an additional certification of the assignments of 5-H and 8-H of product **3a** as follows; compounds **2b** and **3b**, both of which



Scheme 2 Possible reaction mechanism for intermediate **X**. *Reagents*: i, $POCl_3$; ii, base.

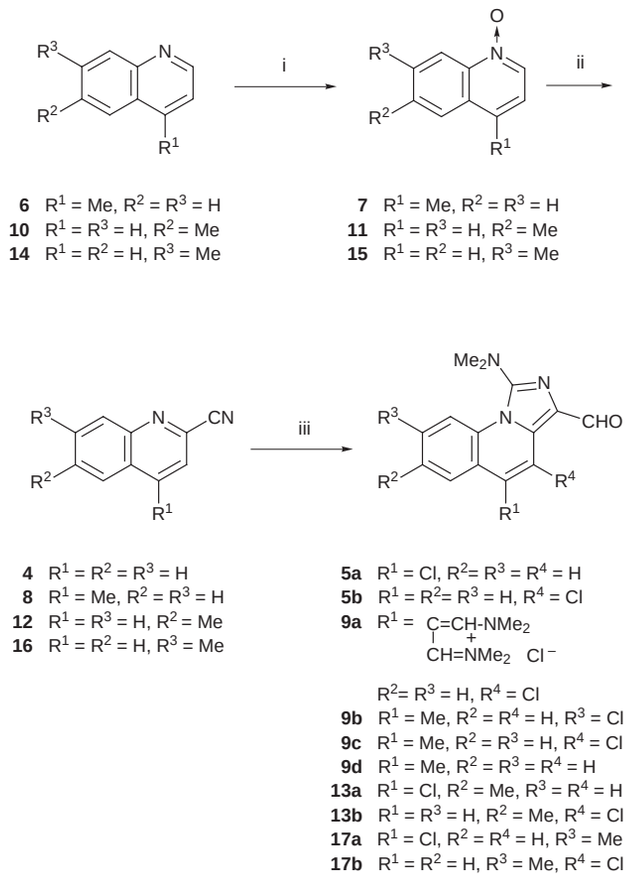


Scheme 3 Possible reaction mechanism for imidazopyridines **2a** and **3a**. *Reagents and conditions*: i, − HCl; ii, H^+; iii, work-up.

lack an 8-H atom, showed no signal to lower field than δ 7.9 except for the formyl proton. This means the chemical shift of 5-H is upfield of δ 7.9. Therefore, it is reasonable that the chemical shift of 5-H of compound **3a** is δ 7.85. Furthermore, compounds **2c** and **3c**, both of which lack a proton at C-5, showed 8-H at δ 8.13 and δ 8.15, respectively. This result is not in conflict with the observation of 8-H at δ 8.29 in the case of compound **3a** which has no electron-releasing group in the pyridine moiety.

Compared with nitrile **1a**, the much shorter reaction time of compound **1c** seemed to be caused by the increase in the electronegativity of the pyridine nitrogen atom induced by the 6-methyl group.

Next, we applied this reaction to quinoline-2-carbonitriles to provide a general route to 1,3-difunctionalized imidazo-[1,5-*a*]quinolines. The chemistry of imidazo[1,5-*a*]quinolines is not extensively documented.[15] This fact also prompted us to prepare this ring system. In these reactions, the same reaction conditions as described above were employed. As shown in Scheme 4, when quinoline-2-carbonitrile **4** was used as a



6 R^1 = Me, R^2 = R^3 = H
10 R^1 = R^3 = H, R^2 = Me
14 R^1 = R^2 = H, R^3 = Me

7 R^1 = Me, R^2 = R^3 = H
11 R^1 = R^3 = H, R^2 = Me
15 R^1 = R^2 = H, R^3 = Me

4 R^1 = R^2 = R^3 = H
8 R^1 = Me, R^2 = R^3 = H
12 R^1 = R^3 = H, R^2 = Me
16 R^1 = R^2 = H, R^3 = Me

5a R^1 = Cl, R^2= R^3 = R^4 = H
5b R^1 = R^2= R^3 = H, R^4 = Cl
9a R^1 = C=CH-NMe$_2$ / CH=NMe$_2$ Cl⁻, R^2= R^3 = H, R^4 = Cl
9b R^1 = Me, R^2 = R^4 = H, R^3 = Cl
9c R^1 = Me, R^2 = R^3 = H, R^4 = Cl
9d R^1 = Me, R^2 = R^3 = R^4 = H
13a R^1 = Cl, R^2 = Me, R^3 = R^4 = H
13b R^1 = R^3 = H, R^2 = Me, R^4 = Cl
17a R^1 = Cl, R^2 = R^4 = H, R^3 = Me
17b R^1 = R^2 = H, R^3 = Me, R^4 = Cl

Scheme 4 *Reagents and conditions*: i, 30% H_2O_2, AcOH, 70 °C, 8–20 h; ii, TMSCN, Et_3N, MeCN, reflux, 19 h–4 days; iii, DMF, $POCl_3$, 80 °C, 0.5–1.5 h (in the case of substrate **8**, reflux for 30 min in $CHCl_3$).

starting material, two kinds of product, **5a** and **5b**, were obtained. From their instrumental and elemental analyses it was found that both of them had a parent structure based on imidazo[1,5-*a*]quinoline and were isomeric, having one dimethylamino (at C-1), one formyl (at C-3), and one chloro (at different sites) group as a substituent. In their ^{1}H NMR data (Table 2), the presence of four protons of the benzene moiety of the quinoline ring indicated that the site of the chloro group was C-4 or C-5 in both products **5a** and **5b**. It is clear that a singlet resonating at δ 8.22 (**5a**) or at δ 7.46 (**5b**) is attributable to 4-H or 5-H. If the site of the chloro group is C-5, 4-H should resonate at δ ~8.3, which is the corresponding position to that of 8-H of compound **3a**. Therefore, the site of the chloro group of **5a**, which showed a singlet at δ 8.22, was identified as C-5, and that of the chloro group of isomer **5b**, in which a similar signal was found at δ 7.46, was identified as C-4. The proton at the 5-position of the quinoline (corresponding to 6-H of compound **5a**) is usually observed at δ 7.68,[16] so that the low-field shift (from δ 7.68 to δ 8.17) for 6-H of compound **5a** is thought to be caused by the chloro group at the *peri*-position, and this shift also showed the site of the chloro group as being C-4.

Subsequently, the application to other methylquinoline-2-carbonitriles **8**, **12** and **16** as starting materials for this Vilsmeier reaction was tried, however, these compounds were not commercially available. In particular, compound **16** was unknown in the literature as far as we knew. Compounds **8** and **12** have been already prepared from the corresponding methylquinoline in a few steps.[17,18] However, in this paper we chose a more simplified method for preparing them as follows. Namely, as shown in Scheme 4, the requisite methylquinoline-2-carbonitriles were prepared from corresponding methylquinolines **6**, **10** and **14** *via* their *N*-oxides **7**, **11** and **15**, followed by treatment

Table 2 ^{1}H NMR spectral data of imidazo[1,5-*a*]quinolines **5**, **9**, **13**, **17**

	Chemical shifts (δ) and coupling pattern										Coupling constants (Hz)		
Compd.	4-H	5-H	6-H	7-H	8-H	9-H	CHO	NMe_2	Me	Others	$J_{6,7}$	$J_{7,8}$	$J_{8,9}$
5a	8.22, s		8.17, br d	7.58, br t	7.72, bt t	9.03, br d	10.06, s	2.94, s			8	8	8
5b		7.46, s	7.52, br d	7.62–7.70, m	7.62–7.70, m	8.99, br d	10.74, s	2.97, s			7	[a]	9
9a			7.61–7.75, m	7.61–7.75, m	7.61–7.75, m	9.05, s	10.73, s	2.97, s		[b]	[a]	[a]	8.3
9b	8.17, s		8.05, d	7.41, dd		8.83, br s	10.05, s	2.95, s	2.61, s		8.3		
9c			7.88, dd	7.54, m	7.66, td	9.07, br d	10.77, s	2.95, s	2.69, s		8	8	8
9d	7.96, s		7.87, dd	7.54, m	7.67, td	9.06, dd	10.07, s	2.95, s	2.59, s		8	8	8
13a	8.21, s		7.95, br s		7.52, dd	8.90, d	10.05, s	2.93, s	2.55, s				8.8
13b		7.38, s	7.43, br s		7.45, br d	8.83, d	10.71, s	2.94, s	2.49, s				9
17a	8.14, s		8.03, d	7.39, br d		8.81, br s	10.04, s	2.94, s	2.60, s		8		
17b		7.34, s	7.55, d	7.33, br d		8.78, br s	10.73, s	2.97, s	2.58, s		8		

[a] Observed as multiplet. [b] Six protons (δ 2.56, s), 6 protons (δ 3.47, s) and 2 protons (δ 9.48, br s) were observed as the vinylogous amidinium salt protons.

Table 3 ^{1}H NMR spectral data of imidazo[5,1-*a*]isoquinolines **19**, **23**

	Chemical shifts (δ) and coupling pattern									Coupling constants (Hz)			
Compd.	5-H	6-H	7-H	8-H	9-H	10-H	CHO	NMe_2	Me	$J_{5,6}$	$J_{7,8}$	$J_{8,9}$	$J_{9,10}$
19	7.77, d	7.09, br d	7.66–7.72, m	7.66–7.72, m	7.66–7.72, m	9.71, m	10.24, s	3.02, s		7	[a]	[a]	[a]
23		6.77, br s	7.55–7.61, m	7.55–7.61, m	7.55–7.61, m	9.72, m	10.18, s	2.87, s	2.90, s		[a]	[a]	[a]

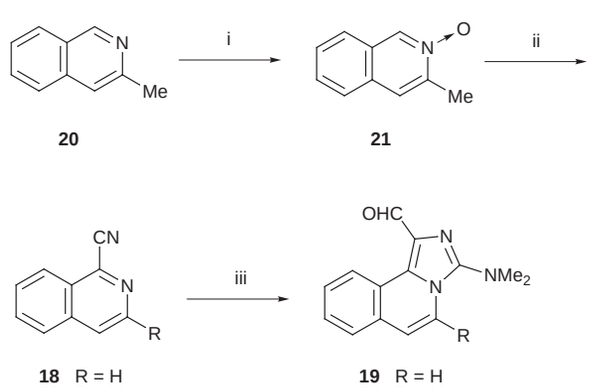
[a] Observed as multiplet.

with trimethylsilyl cyanide (TMSCN) by the method of Sakamoto *et al.*[19] Instrumental analyses of these materials (**8**, **12** and **16**) confirmed their structures.

The Vilsmeier reaction of thus obtained nitrile **8** under conditions similar to those described above gave four kinds of product, **9a**–**d**. In the ^{1}H NMR spectrum of compound **9a**, the methyl signal (δ 2.75) of substrate **8** disappeared and protons of three dimethyl groups were observed at δ 2.56, 2.97 and 3.47, each as six-proton singlets. Ciernik reported the diformylation of the methyl group of 4-methylquinoline by the Vilsmeier reaction.[20] Therefore, compound **9a** seems to be formed *via* a similar diformylation of substrate **8**. Furthermore, the mass spectrum of product **9a** showed the presence of one chloro group, whose site was identified as C-4 because of the lack of a signal for 4-H in its ^{1}H NMR spectrum. The structures (especially the site of the chloro group) of analogous products **9b**–**d** were mainly identified by the resonating-signal pattern of their ^{1}H NMR spectra in a similar way.

The Vilsmeier reactions of 6-methyl- and 7-methylquinoline-2-carbonitrile **12** and **16**, in which an electron-releasing group (methyl group) is attached to the benzene moiety of the quinoline ring, gave 5-chloro-1-dimethylamino-3-formyl-7-methylimidazo[1,5-*a*]quinoline **13a** in 40% yield, its 4-chloro isomer **13b** in 4% yield, 5-chloro-1-dimethylamino-3-formyl-8-methylimidazo[1,5-*a*]quinoline **17a** in 37% yield, and its 4-chloro isomer **17b** in 15% yield, respectively. The structures of products **13** and **17** were consistent with their instrumental and elemental analyses. In both cases (**13** and **17**) the yield of the 5-chloro isomer was higher than that of the 4-chloro isomer, and the introduction of the chloro group into the benzene moiety of the product (as in compound **9b**) could not be found. Compound **12** had the same reaction time as that of its isomer **16** and these were shorter (by one-third) than that of parent nitrile **4** but longer than that of their other isomer **8**. It is reasonable to think that these phenomena arise from the differences in reactivity of the starting materials caused by the respective methyl group. In the case of compound **8**, this methyl group seemed to play a role not only as an electron-releasing group but also as an active methylene to give diformylation product **9a**.

Finally, we investigated the Vilsmeier reaction of isoquinoline-1-carbonitriles **18** and **22**. Compound **22** was a literature-known material but not commercially available. It has been prepared from 3-methylisoquinoline **20** in a few steps.[21] However, in this paper, compound **22** was prepared from substrate **20** by Sakamoto's method[19] similar to the reaction of isomer **6** because of its simplicity. As shown in Scheme 5, the Vilsmeier reaction of nitrile **18** under the



Scheme 5 *Reagents and conditions*: i, 30% H_2O_2, AcOH, 70 °C, 3 days; ii, TMSCN, Et_3N, MeCN, reflux, 6 days; iii, DMF, $POCl_3$, 80 °C, 13–24 h.

same reaction conditions as described in the synthesis of compound **5** afforded the expected product, 3-dimethylamino-1-formylimidazo[5,1-*a*]isoquinoline **19** in 38% yield. The same reaction of analogous nitrile **22** afforded only 3-dimethylamino-1-formyl-5-methylimidazo[5,1-*a*]isoquinoline **23**, in 42% yield. Reimlinger *et al.*[22] have already reported the synthesis of imidazo[5,1-*a*]isoquinoline derivatives, but their method needs five steps from nitrile **18** to final imidazo[5,1-*a*]isoquinoline derivatives. The structure of products **19** and **23** was consistent with their instrumental (Table 3) and elemental analyses. In the reaction of both substrates **18** and **22**, no chloro derivative could be found.

Experimental

All mps were determined on a Yanagimoto micro-melting point apparatus, and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-5 CHN Corder elemental analyser. The EI-mass and FAB-mass spectra were measured on a VG 70 mass spectrometer. In the case of FAB-mass, glycerol or *m*-nitrobenzyl alcohol was used as matrix agent. The IR spectra were recorded on a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer and frequencies are expressed in cm^{-1}. ^1H NMR spectra were recorded on a Varian VXR-200 instrument working at 200 MHz, using the solvent indicated with tetramethylsilane as the internal standard. Chemical shifts are given in ppm (δ) and *J*-values in Hz.

Vilsmeier reaction of pyridine-2-carbonitriles, quinoline-2-carbonitriles or isoquinoline-1-carbonitriles with DMF. General procedure

A mixture of dry DMF (30 mmol) and $POCl_3$ (60 mmol) was stirred under ice-cooling for 30 min. After addition of a carbonitrile (10 mmol) to the mixture, the resulting mixture was further stirred at 80 °C for 0.5–24 h. After evaporation off of $POCl_3$, water (50 cm^3) was poured onto the residue. The mixture was basified with Na_2CO_3 and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was chromatographed over a silica gel column, using hexane–ethyl acetate as eluent.

Reaction of pyridine-2-carbonitrile 1a. Stirred at 80 °C for 4 h. Column chromatography [hexane–ethyl acetate (1 : 1 v/v)] gave two compounds: the less polar **3a** (39%), and more polar **2a** (10%). Both were isolated as *crystalline products*, mp 128–129 °C (**3a**, yellow needles from hexane–cyclohexane) and mp 67–70 °C (**2a**, yellow needles from cyclohexane–benzene), respectively.

3a (Found: C, 53.6; H, 4.8; N, 18.7. $C_{10}H_{10}ClN_3O$ requires C, 53.70; H, 4.51; N, 18.79%); ν_{max}(KBr)/cm^{-1} 1660 (CHO); *m*/*z* (EI) 223 (M^+).

2a (Found: C, 63.7; H, 5.7; N, 22.4. $C_{10}H_{11}N_3O$ requires C, 63.48; H, 5.86; N, 22.21%); ν_{max}(KBr)/cm^{-1} 1650 (CHO); *m*/*z* (EI) 189 (M^+).

Reaction of 3-methylpyridine-2-carbonitrile 1b. Stirred at 80 °C for 12 h. Column chromatography [hexane–ethyl acetate (1 : 1 v/v)] afforded less polar product **3b** (51%) and more polar **2b** (25%). Both were isolated as *crystalline products*, mp 94–96 °C (**3b**, yellow needles from hexane) and mp 119–121 °C (**2b**, yellow needles from cyclohexane), respectively.

3b (Found: C, 55.3; H, 5.2; N, 17.7. $C_{11}H_{12}ClN_3O$ requires C, 55.59; H, 5.09; N, 17.68%); ν_{max}(KBr)/cm^{-1} 1660 (CHO); *m*/*z* (EI) 237 (M^+).

2b (Found: C, 64.8; H, 6.5; N, 20.6. $C_{11}H_{13}N_3O$ requires C, 65.01; H, 6.45; N, 20.68%); ν_{max}(KBr)/cm^{-1} 1670 (CHO); *m*/*z* (FAB) 204 (MH^+).

Reaction of 6-methylpyridine-2-carbonitrile 1c. Stirred at 80 °C for 1 h. Column chromatography [hexane–ethyl acetate (1 : 1 v/v)] afforded less polar compound **3c** (28%) and more polar **2c** (10%). Both were isolated as *crystalline products*, mp 112–115 °C (**3c**, yellow plates from hexane) and mp 81–83 °C (**2c**, yellow needles from hexane), respectively.

3c (Found: C, 55.5; H, 5.2; N, 17.8%); ν_{max}(KBr)/cm^{-1} 1660 (CHO); *m*/*z* (FAB) 238 (MH^+).

2c (Found: C, 64.9; H, 6.3; N, 20.55%); ν_{max}(KBr)/cm^{-1} 1640 (CHO); *m*/*z* (FAB) 204 (MH^+).

Reaction of quinoline-2-carbonitrile 4. Stirred at 80 °C for 1.5 h. Column chromatography [hexane–ethyl acetate (3 : 1 v/v)] afforded less polar compound **5a** (64%) and more polar **5b** (7%). Both were isolated as *crystalline products*, mp 150–153 °C (**5a**, yellow needles from hexane) and mp 206–207 °C (**5b**, yellow needles from cyclohexane), respectively.

5a (Found: C, 61.7; H, 4.7; N, 15.3. $C_{14}H_{12}ClN_3O$ requires C, 61.43; H, 4.42; N, 15.35%); ν_{max}(KBr)/cm^{-1} 1660 (CHO); *m*/*z* (EI) 273 (M^+).

5b (Found: C, 61.4; H, 4.6; N, 15.2%); ν_{max}(KBr)/cm^{-1} 1660 (CHO); *m*/*z* (EI) 273 (M^+).

Preparation of methylquinoline *N*-oxides or 3-methylisoquinoline *N*-oxide. General procedure

To a solution of methylquinoline or methylisoquinoline (100 mmol) in acetic acid (30 cm^3) was added 30% aq. hydrogen peroxide (9.0 cm^3) and the mixture was stirred at 70 °C for 8 h–3 days. After evaporation of the mixture, the residue was basified with aq. sodium carbonate. The resulting mixture was extracted with chloroform. The organic layer was treated in the usual manner, the resulting residue was triturated with diethyl ether, and the insoluble fraction was recrystallized.

Preparation of 4-methylquinoline *N*-oxide 7. Stirred for 8 h. Recrystallized from cyclohexane–benzene to give **7** (78%) as needles, mp 113–116 °C (lit.,[23] 120–121 °C; lit.,[24] 113–115 °C); $\delta_H(CDCl_3)$ 2.67 (3 H, s, Me), 7.12 (1 H, br d, *J* 6, 3-H), 7.62–8.08 (3 H, m, 5-, 6-, 7-H), 8.44 (1 H, d, *J* 6, 2-H) and 8.75–8.92 (1 H, m, 8-H); *m*/*z* (FAB) 160 (MH^+).

Preparation of methylquinoline-2-carbonitriles or methylisoquinoline-1-carbonitrile. General procedure

A mixture of *N*-oxide (20 mmol), trimethylsilyl cyanide (TMSCN) (8.0 cm^3, 60 mmol) and triethylamine (5.6 cm^3, 40 mmol) in acetonitrile (20 cm^3) was refluxed for 19 h–6 days. After evaporation of the mixture, the residue was basified with aq. sodium carbonate and the resulting mixture was extracted with dichloromethane. The organic layer was treated in the usual manner. Column chromatography of the residue on silica gel was with benzene as eluent and the resulting eluate was worked up and the product was recrystallized. At this stage the resulting methylquinoline-2-carbonitriles and methylisoquinoline-1-carbonitrile, respectively, behaved as a single spot on TLC, so that these compounds were used in the next step without further purification.

Preparation of 4-methylquinoline-2-carbonitrile 8. Refluxed for 22 h. Recrystallization from hexane gave compound **8** (79%) as needles, mp 99–101 °C (lit.,[17] 96–98 °C); ν_{max}(KBr)/cm^{-1} 2230 (CN); $\delta_H(CDCl_3)$ 2.75 (3 H, s, Me), 7.51 (1 H, br s, 3-H) and 7.65–8.24 (4 H, m, 5-, 6-, 7-, 8-H); *m*/*z* (EI) 168 (M^+).

*Reaction of compound **8** with DMF.* A mixture of compound **8** (1.68 g, 10 mmol), Vilsmeier reagent prepared from dry DMF (5.4 cm^3, 70 mmol) and $POCl_3$ (6.5 cm^3, 70 mmol), and dry $CHCl_3$ (6 cm^3) was refluxed for 30 min. After evaporation of the mixture, water (50 cm^3) was added to the residue. The mixture was neutralized with sodium carbonate, and extracted with chloroform. The organic layer was washed with water and the resulting washings were evaporated to dryness. The residue was recrystallized from ethyl acetate–acetonitrile to give iminium salt **9a** (3.24 g, 72%) as yellow needles, mp 276–278 °C. On the other hand, the chloroform layer, after washing, was worked up in the usual manner and column chromatography [hexane–ethyl acetate (3 : 1 v/v)] gave two isomers and one more compound: the less polar compound **9b** (0.06 g, 2%), more polar compound **9c** (0.20 g, 7%), and dechlorinated product **9d** (0.22 g, 9%). All were isolated as *crystalline products*, mp 180–182 °C (**9b**, yellow needles from hexane–cyclohexane), mp 202–204 °C (**9c**, yellow needles from cyclohexane–benzene), and mp 147–148 °C (**9d**, yellow needles from cyclohexane), respectively.

9a (Found: C, 56.0; H, 5.95; N, 15.4. $C_{21}H_{25}Cl_2N_5O{\cdot}H_2O$ requires C, 55.76; H, 6.02; N, 15.48%); ν_{max}(KBr)/cm^{-1} 1660 (CHO); *m*/*z* (FAB) 398 ($MH^+ - HCl$).

9b (Found: C, 62.7; H, 5.1; N, 14.4. $C_{15}H_{14}ClN_3O$ requires C, 62.61; H, 4.90; N, 14.60%); ν_{max}(KBr)/cm^{-1} 1670 (CHO); *m*/*z* (EI) 287 (M^+).

9c (Found: C, 62.8; H, 5.0; N, 14.6%); ν_{max}(KBr)/cm^{-1} 1660 (CHO); *m*/*z* (EI) 287 (M^+).

9d (Found: C, 71.15; H, 5.95; N, 16.7. $C_{15}H_{15}N_3O$ requires C, 71.13; H, 5.97; N, 16.59%); ν_{max}(KBr)/cm^{-1} 1660 (CHO); *m*/*z* (EI) 253 (M^+).

Preparation of 6-methylquinoline *N*-oxide 11. Stirred for 12 h. Recrystallized from cyclohexane–benzene to afford compound **11** (64%) as needles, mp 76–78 °C (lit.,[23] 80–82 °C; lit.,[25] 75 °C); δ_H($CDCl_3$) 2.54 (3 H, s, Me), 7.11–7.73 (4 H, m, 3-, 4-, 5-, 7-H) and 8.42–8.73 (2 H, m, 2-, 8-H); *m*/*z* (FAB) 160 (MH^+).

Preparation of 6-methylquinoline-2-carbonitrile 12. Refluxed for 4 days. Recrystallization from hexane gave compound **12** (47%) as needles, mp 125–127 °C (lit.,[18] 130–131 °C); ν_{max}(KBr)/cm^{-1} 2240 (CN); δ_H($CDCl_3$) 2.56 (3 H, s, Me), 7.58–7.72 (3 H, m, 3-, 4-, 5-H) and 7.99–8.28 (2 H, m, 7-, 8-H); *m*/*z* (EI) 168 (M^+).

*Reaction of compound **12** with DMF.* Stirred at 80 °C for 0.5 h. Column chromatography [hexane–ethyl acetate (3 : 1 v/v)] afforded less polar compound **13a** (40%) and more polar **13b** (4%). Both were isolated as *crystalline products*, mp 175–177 °C (**13a**, yellow needles from hexane–cyclohexane) and mp 181–184 °C (**13b**, yellow needles from cyclohexane), respectively.

13a (Found: C, 62.8; H, 5.0; N, 14.6. $C_{15}H_{14}ClN_3O$ requires C, 62.61; H, 4.90; N, 14.60%); ν_{max}(KBr)/cm^{-1} 1660 (CHO); *m*/*z* (EI) 287 (M^+).

13b (Found: C, 62.5; H, 5.0; N, 14.4%); ν_{max}(KBr)/cm^{-1} 1650 (CHO); *m*/*z* (EI) 287 (M^+).

Preparation of 7-methylquinoline *N*-oxide 15. Stirred for 20 h. Recrystallization from cyclohexane–benzene gave oxide **15** (52%) as needles, mp 76–80 °C (lit.,[23] 81–84 °C); δ_H($CDCl_3$) 2.60 (3 H, s, Me), 7.12 (1 H, br d, *J* 6, 6-H), 7.62–8.08 (3 H, m, 3-, 4-, 5-H), 8.44 (1 H, d, *J* 6, 2-H) and 8.75–8.92 (1 H, m, 8-H); *m*/*z* (FAB) 160 (MH^+).

Preparation of 7-methylquinoline-2-carbonitrile 16. Refluxed for 19 h. Recrystallization from hexane gave compound **16** (58%) as needles, mp 101–103 °C (Found: C, 78.4; H, 4.9; N, 16.5. $C_{11}H_8N_2$ requires C, 78.55; H, 4.79; N, 16.66%); ν_{max}(KBr)/cm^{-1} 2240 (CN); δ_H($CDCl_3$) 2.60 (3 H, s, Me), 7.45–7.93 (4 H, m, 3-, 4-, 5-, 6-H) and 8.17 (1 H, s, 8-H); *m*/*z* (EI) 168 (M^+).

*Reaction of compound **16** with DMF.* Stirred at 80 °C for 0.5 h. Column chromatography [hexane–ethyl acetate (1 : 1 v/v)] afforded less polar compound **17a** (37%) and more polar **17b** (15%). Both were isolated as *crystalline products*, mp 180–181 °C (**17a**, yellow needles from hexane) and mp 173–176 °C (**17b**, yellow granules from cyclohexane), respectively.

17a (Found: C, 62.8; H, 5.1; N, 14.7. $C_{15}H_{14}ClN_3O$ requires C, 62.61; H, 4.90; N, 14.60%); ν_{max}(KBr)/cm^{-1} 1660 (CHO); *m*/*z* (EI) 287 (M^+).

17b (Found: C, 62.6; H, 5.0; N, 14.65%); ν_{max}(KBr)/cm^{-1} 1660 (CHO); *m*/*z* (EI) 287 (M^+).

*Reaction of isoquinoline-1-carbonitrile **18** with DMF.* Stirred at 80 °C for 24 h. Column chromatography [benzene–ethyl acetate (9 : 1, v/v)] gave *tricycle* **19** (38%) as yellow needles, mp 111–113 °C (from cyclohexane) (Found: C, 70.0; H, 5.3; N, 17.3. $C_{14}H_{13}N_3O$ requires C, 70.28; H, 5.48; N, 17.56%); ν_{max}(KBr)/cm^{-1} 1660 (CHO); *m*/*z* (FAB) 240 (MH^+).

Preparation of 3-methylisoquinoline *N*-oxide 21. Stirred for 3 days. Recrystallization from cyclohexane–benzene afforded oxide **21** (82%) as needles, mp 137–139 °C (lit.,[26] 136–138 °C); δ_H($CDCl_3$) 2.66 (3 H, s, Me), 7.38–7.73 (5 H, m, 4-, 5-, 6-, 7-, 8-H) and 8.86 (1 H, s, 1-H); *m*/*z* (FAB) 160 (MH^+).

Preparation of 3-methylisoquinoline-1-carbonitrile 22. Refluxed for 6 days. Recrystallization from hexane gave compound **22** (78%) as needles, mp 105–106 °C (lit.,[21]105–106 °C); ν_{max}(KBr)/cm^{-1} 2220 (CN); δ_H($CDCl_3$) 2.75 (3 H, s, Me), 7.69–7.85 (4 H, m, 4-, 5-, 6-, 7-H) and 8.34 (1 H, br d, *J* 5.9, 8-H); *m*/*z* (EI) 168 (M^+).

*Reaction of compound **22** with DMF.* Stirred at 80 °C for 13 h. Column chromatography [benzene–ethyl acetate (3 : 1, v/v)] afforded *tricycle* **23** (42%) as pale yellow needles, mp 117–119 °C (from hexane–cyclohexane) (Found: C, 71.2; H, 6.1; N, 16.5. $C_{15}H_{15}N_3O$ requires C, 71.13; H, 5.97; N, 16.59%); ν_{max}(KBr)/cm^{-1} 1670 (CHO); *m*/*z* (FAB) 254 (MH^+).

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