Synthesis and Nucleophilic Reactions of Cyano Substituted *N*-Methoxyisoquinolinium Salts

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Starting from isoquinoline, the cyano substituted *N*-methoxyisoquinolinium salts **1.1** and **1.4** are prepared. Their behaviour in the presence of O-, C- and N-nucleophiles in different aprotic solvents is examined: from the 1-cyano substituted isoquinolinium derivative **1.1**, 1- and 3-aminals or 1-iminium salts are obtained depending on the amine used, and *N*-methoxyisocarbostyril **4.1.1** in H_2O and OH^-. The reaction of the 4-cyano-*N*-methoxyisoquinolinium salt **1.4** with amines yields 1-aminals and with OH^- the corresponding hemiaminal. Conversion with CN^- results in dinitrile derivatives and *N*-oxides.

Synthese und nucleophile Substitutionsreaktionen cyansubstituierter *N*-Methoxyisochinoliniumsalze

Ausgehend von Isochinolin werden die cyansubstituierten *N*-Methoxyisochinoliniumsalze **1.1** und **1.4** dargestellt. Ihr Reaktionsverhalten in Gegenwart von O-, C- und N-Nucleophilen in verschiedenen Lösungsmitteln wird untersucht: aus dem 1-cyansubstituierten Isochinolinium-Derivat **1.1** werden 1- und 3-Aminale oder 1-Iminiumsalze in Abhängigkeit vom verwendeten Amin erhalten sowie *N*-Methoxyisocarbostyril **4.1.1** in H_2O und OH^-. Die Reaktion des 4-Cyan-N-methoxyisochinoliniumsalzes **1.4** mit Aminen ergibt 1-Aminale und mit OH^- die entspr. Hemiaminale. Umsetzung mit CN^- führt zu Dinitril-Derivaten und N-Oxiden.

During the investigations on degradation reactions of *N*-methoxypyridinium-2- and 4-aldoximes, which are attracting interest as potential acetylcholine esterase reactivators, *Schnekenburger*[2] showed that, depending on the solvent and the substituents in various positions of the heteroaromatic ring system, different but no ring-opened products were achieved. Introduction of electron-withdrawing groups such as CN, $CONH_2$, etc. into the pyridine ring initiated extensive studies of their nucleophilic substitution reactions[3,5-8]. Attack of the reagent at the sterically less hindered C-N-bond resulted in a ring-opened product whose all-*trans*-configuration of the conjugated double bonds was deduced from NMR spectra[3]. Rearrangement in aqueous solution in the presence of alkali or ammonia following a typical ANRORC-mechanism[4] yielded derivatives of 2-pyridone and 2-pyrrolidone[5], whereas 2- and 4-chloro substituted *N*-methoxypyridinium salts reacted with nucleophiles by substitution of the halogen atom[6]. An additional introduction of a nitro group enhanced the electrophilicity of these latter compounds: their reactions were often characterized by attack on position 6 of the pyridine and subsequent ring cleavage[7]. Cyano substituted *N*-methoxyquinolinium salts[8] did not show these types of reaction. Cyanide ions, O-, N-, and C-nucleophiles attacked C-2 yielding 2-substituted 1,2-dihydroquinoline derivatives followed by elimination of methanol and HCN, respectively, depending on the reaction conditions and steric hindrance.

Whereas the reaction of *N*-methoxyisoquinolinium perchlorate (**1**) with piperidine showed degradation to the N-oxide **2** and isoquinoline (**3**)[9], reaction with the nucleophilic cyanide ions yielded the 1-cyano substituted isoquinoline[10]. Hydroxylamine-methylether used as nucleophilic agent in HMPT led to the degradation products **2** and **3** and additionally to the isomeric mixture of the ring opened 2-(2-methoxyaminoethyl)-benzaldehyde-*O*-methyloxime[11]. The reaction of *N*-methyl-5-bromo-8-nitroisoquinolinium salt with alkali resulted in the corresponding *N*-methyl-1-isoquinolone and *N*-methyl-1,2-dihydroisoquinoline by disproportionation of *N*-methyl-5-bromo-1-hydroxy-8-nitro-1,2-dihydroisoquinoline (so called pseudobase)[11].

In this paper we present results concerning nucleophilic substitution reactions with cyano substituted *N*-methoxyisoquinolinium salts **1.1** and **1.4**. As shown by means of ^{13}C-NMR studies[12], the C-1 has the lowest electron density in the 4-cyano-N-methoxyisoquinolinium ion **1.4** and C-3 is the one with lowest electron density in the 1-cyano substituted *N*-methoxyisoquinolinium salt **1.1**.

Synthesis of 1- and 4-cyano-N-methoxyisoquinolinium salts **1.1** *and* **1.4**

Starting from *N*-methoxyisoquinolinium perchlorate, 1-cyanoisoquinoline is obtained by nucleophilic substitution reaction with cyanide and simultaneous elimination of methanol[10]. Subsequent oxidation with hydrogen peroxide in glacial acetic acid (analogous to *Ochiai*[13]) yields the corresponding *N*-oxide. Because of the C-1-substituent, alkylation with H_3CI or dimethylsulphate does not succeed. The reaction of the *N*-oxide with methyl trifluoromethanesulphonate, which is one of the strongest available alkylating agents, leads to the 1-cyano-*N*-methoxyisoquinolinium trifluoromethanesulphonate **1.1**. The 4-cyano-*N*-methoxyisoquinolinium salt **1.4** is obtained starting from 4-bromoisoquinoline[14] by conversion to the 4-cyanoisoquinoline with Cu(I)CN[15] followed by the above procedure.

Nucleophilic substitution reactions

1. *Reaction with solvents*

Before studying the reactivity of the cyano-*N*-methoxyisoquinolinium salts against nucleophilic agents the stability of **1.1** and **1.4** is screened in the appropriate solvents by ^1H-NMR- and UV-spectroscopic methods.

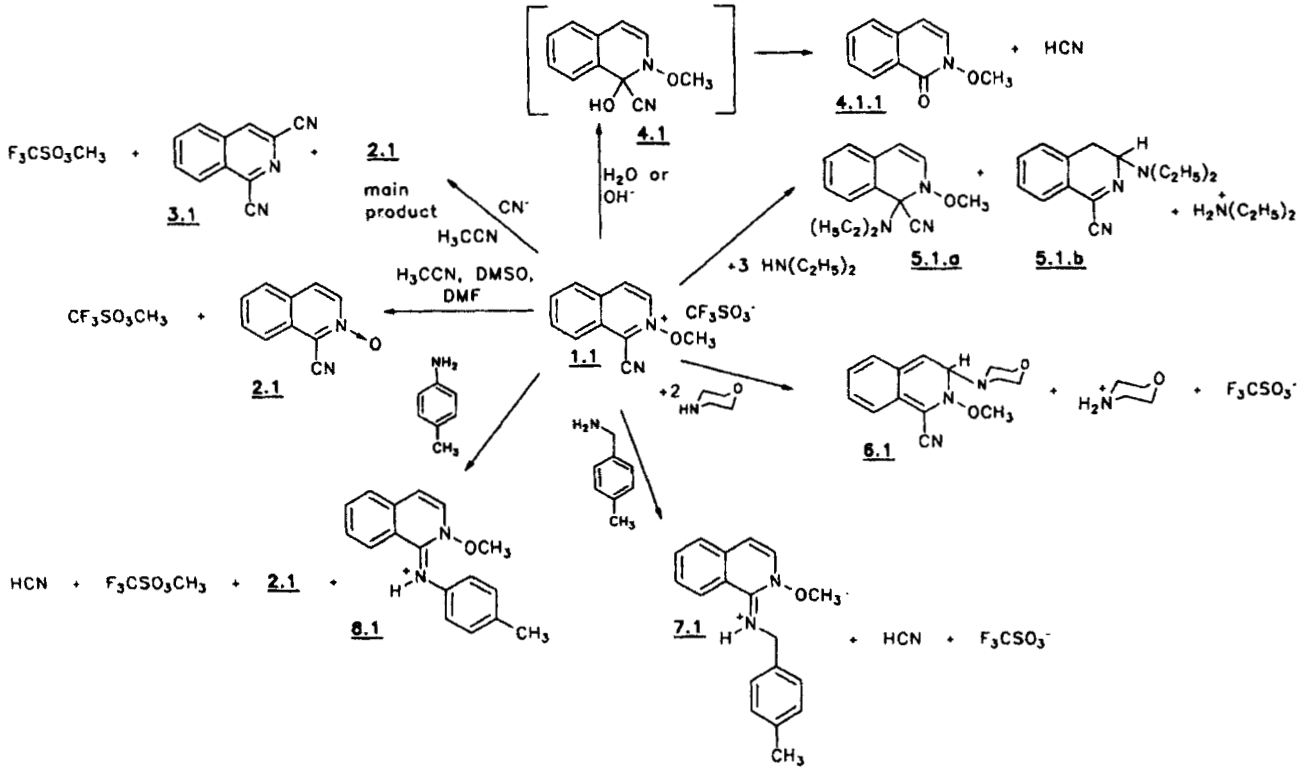
The 4-cyano substituted isoquinolinium salt **1.4** does not show any decomposition in the dipolar aprotic solvents DMF, DMSO, or CH_3CN. In contrast, the 1-cyanoisoquinolinium salt **1.1** decomposes in CH_3CN to the corresponding *N*-oxide. This degradation observed by ^{1}H-NMR spectroscopy is accompanied by the reaction of the trifluoromethanesulphonate anion, a hard base, with the positively charged carbon atom of the methoxy group forming methyl trifluoromethanesulphonate (Scheme 1). This ester is characterized by a singlet at δ = 4.0 ppm in its ^{1}H-NMR spectrum. The spectrum of the mixture obtained by the reaction of **1.1** in [D_7]DMF is more complicated because the methyl trifluoromethanesulphonate formed seems to be hydrolyzed by the residual water, and methanol is obtained. Further singlets appear at δ = 4.5 and 3.7 ppm indicating the methylation of the solvent [D_7]DMF by the alkylating agent. The latter reaction is observed also in a mixture of [D_7]DMF and methyl trifluoromethanesulphonate in a NMR tube.

The 4-cyano isoquinolinium salt **1.4** reacts very slowly with water. After 6 days about 6% of 4-cyanoisoquinoline **2.4** are formed (Scheme 2). As a hard base, water attacks a hydrogen atom of the methoxy group of **1.4**, and it is likely that H_3O^+ and HCHO are formed.

In contrast to the 4-cyanoisoquinolinium salt **1.4**, the 1-cyano substituted salt **1.1** reacts more quickly with the nucleophilic water forming first 1-cyano-1,2-dihydro-1-hydroxy-*N*-methoxyisoquinoline **4.1** and second *N*-methoxyisoquinolone **4.1.1** (often called isocarbostyril, Scheme 1) by subsequent elimination of HCN. The nucleophilic attack at C-1 is surprising because it is known from ^{13}C-NMR spectra[12], that the electron density at C-3 is lower than that at C-1. The reason for the attack of water at C-1 could be the stabilization of the hemiaminal **4.1** by elimination of the good leaving group CN^-. The alternative hemiaminal formed at C-3 could only be stabilized by elimination of H^- or cleavage, which is quite unusual.

2. *Reaction with cyanide ions*

As deduced from the chemical shifts of the C-atoms, position 1 in the 4-cyano-*N*-methoxyisoquinolinium salt **1.4** is the most electrophilic one. Therefore, in presence of CN^- **1.4** forms 1,4-dicyanoisoquinoline **3.4** by nucleophilic attack at C-1 and elimination of methanol. This result is comparable with the reaction of the unsubstituted *N*-methoxyisoquinolinium salt **1** with CN^- mentioned above and the observations of *Schnekenburger et al.* concerning 2- and 4-cyano substituted *N*-methoxyquinolinium salts[8]. Accordingly, the 1,3-dicyanoisoquinoline **3.1** is expected to be formed from the reaction of **1.1** with CN^- in absol. CH_3CN. This is a by-product in comparison with the large amount of 1-cyanoisoquinoline-*N*-oxide **2.1** formed as described above.



Scheme 1: Reactions of the 1-cyano-*N*-methoxyisoquinolinium salt **1.1** (the first number marks the starting product **1** and the subsequent reactions **2** to **8**, the second number characterizes the position of the cyano group in the isoquinolinium skeleton, here **1**).

3. *Reaction with hydroxide ions and amines*

Attempts to isolate products from the reactions of **1.1** or **1.4** with OH^- or amines failed. Therefore, the reactions were carried out in a NMR tube and ^{1}H-NMR spectra were taken at several time intervals.

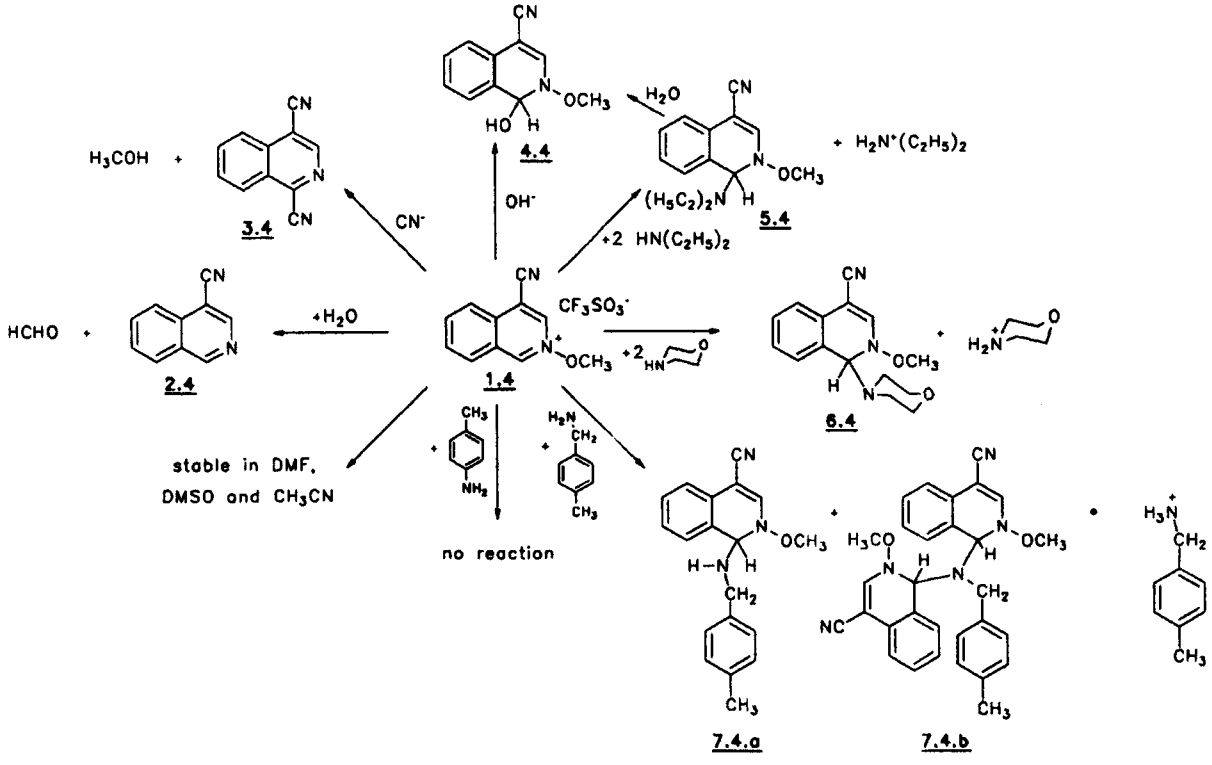
3a. *Reaction with NaOD*

In CD_3CN and a twofold excess of NaOD, 4-cyano-*N*-methoxyisoquinolinium salt **1.4** shows a spectrum with one set of signals characterized by a singlet at $\delta = 3.82$ ppm and a doublet at $\delta = 6.18$ ppm ($J = 1.3$ Hz). This is consistent with the structure of the hemiaminal **4.4** (Scheme 2) resulting from an attack of OD^- on the most electrophilic position C-1. Despite numerous experiments, isolation of this hemiaminal **4.4** did not succeed because of the instability of these compounds. Reaction of equimolar amounts of **1.4** and OH^- in a NMR tube results in a mixture of **1.4** and **4.4** in a ratio of 1:1. HPLC of this NMR batch reveals the reformation of the isoquinolinium salt **1.4**; only traces of **4.4** are observable.

Being a 1-cyano-*N*-methoxyisoquinolinium salt, **1.1** reacts with water to give the isoquinolone **4.1.1**, the same product is expected from the reaction with OH^-. Therefore, it is remarkable that the ^{1}H-NMR spectrum, measured immediately after mixing **1.1** and NaOD in CH_3CN, shows, beside the signals the **1.1** and **4.1.1**, a third set of signals which decreases at the same time as the signals for the isoquinolone increase. Comparison of these signals with those of **4.4** shows that the hemiaminal **4.1** is formed as an intermediate. The question then raised is why this intermediate was not seen in the reaction of **1.1** with water. The reason could be the instability of the hemiaminals or pseudobases[16-18] in acidic media. During the reaction of **1.1** with water, trifluoromethanesulphonic acid is formed and causes lower pH values. The pseudobase **4.1** reacts immediately to give the lactam **4.1.1**. In the reaction of **1.1** with OD^-, the resulting acid is neutralized at once and, therefore, the hemiaminal is observable.

3b. *Reaction with secondary aliphatic amines*

Analogous to the reaction of **1.4** with the hard base OH^-, this salt reacts with a twofold excess of diethylamine yielding the aminal **5.4** (Scheme 2). Additionally, the signals of the protonated diethylamine are observed in the ^{1}H-NMR spectrum. The reaction kinetics, measured by means of UV-spectroscopy, show that the amine ($t_{1/2} = 15$ s) reacts more quickly than does OH^- ($t_{1/2} = 30$ min) although OH^- is the stronger base and the stronger nucleophile. Addition of D_2O to the reaction mixture of **1.4** and diethylamine causes partial conversion of **5.4** to the hemiaminal **4.4** which can be explained by an electrophilic substitution of the amino group (cf.[8]). The final ^{1}H-NMR spectrum of the reaction of **1.1** with diethylamine is much more complicated. Beside the signals belonging to the aminals **5.1.a** and **5.1.b** (Scheme 1) and to the protonated amine, a fourth set of signals appears whose origin could not be elucidated.



Scheme 2: Reactions of the 4-cyano-*N*-methoxyisoquinolinium salt **1.4**

Morpholine as a nucleophile reacts with **1.4** in the same manner as diethylamine does yielding the aminal **6.4** (Scheme 2) as deterimined by ^{1}H-NMR spectroscopy. The reaction of **1.1** with morpholine results in the C-3 aminal **6.1** only (Scheme 1). This selectivity of the attack by morpholine at C-3 might be explained by the weak nucleophilicity of this amine (pK_a 8.33) in comparison with diethylamine (pK_a 10.71; see below).

3c. *Reaction with a primary aliphatic amine*

The basicity of the primary araliphatic amine 4-methylbenzylamine (4-MBA) lies between those of morpholine and diethylamine with a pK_a-value of about 9.4. By analogy to previous results, formation of aminals should be expected.

In the case of the 4-cyano substituted N-methoxyisoquinolinium salt **1.4** two aminals are obtained, a mono- and a diisoquinoline product, **7.4.a** and **7.4.b**, created by an attack at C-1 (Scheme 2). The ^{1}H-NMR spectra of both derivatives are similar as expected for the 4-MBA portion of the molecule and the hydrogen atoms at C-5 to C-8 of the isoquinoline skeleton. The spectrum of the mono product **7.4.a** is characterized by the chemical shift of 1-H and 3-H at δ = 6.36 and 7.99 ppm, respectively, whereas the chemical shifts are more widely separated in the bisproduct **7.4.b**: 6.03 and 8.02 ppm. The upfield shift of 1-H in **7.4.b** in comparison with that of **7.4.a** is caused by the additional isoquinoline substitution attached to the aminal -N (cf.[17]). Although two centres of chirality are formed in this reaction, no mixture of diastereomers is observed.

1-Cyano-N-methoxyisoquinolinium salt **1.1** reacts with equimolar 4-MBA yielding only one product which is characterized by an amidinium moiety (Scheme 1). Formation of a hemiaminal comparable with the reactions of the other amines and observed in the ^{1}H-NMR spectrum at the beginning of the reaction (3-H and 4-H show typical chemical shifts at δ = 6.97 and 6.22 ppm), HCN elimination and N-protonation may be the intermediate steps of this reaction which lasts about 5 d (compare with[8]). The ^{1}H-NMR spectrum of the derivative **7.1** exhibits a downfield shift of almost all H-atoms of the skeleton, especially of 3-H and 4-H resonating at δ = 8.32 and 7.52 ppm, respectively.

3d. *Reaction with a primary aromatic amine*

4-Methylaniline is a very weak base which does not react with **1.4**. Equimolar addition of *p*-toluidine to the isoquinolinium salt **1.1** in CH_3CN yields the ^{1}H-NMR spectra of **1.1** and of the corresponding *N*-oxide **2.1** in a ratio of 1:1.3. Addition of a twofold excess of *p*-toluidine to **1.1** in CD_3CN leads, after 5 days, to an amidinium salt **8.1** besides the *N*-oxide **2.1**. When carrying out the experiment in [D_6]DMSO, the ^{1}H-NMR spectrum shows immediately the signals of **8.1**. In CD_3CN the competitive reaction of the trifluoromethanesulphonate anion with the methoxy group leads to the N-oxide. In DMSO the nucleophilicity of the amine is high enough to react as fast as necessary with **1.1** to suppress the slower reaction of the trifluoromethanesulphonate anion.

Results of semiempirical calculations and conclusions

As outlined in Table 2, the chemical shifts of the C-atoms of **1** and **1.4** correspond to the charges of C-1, C-3, and C-4, approximately calculated by the AM1 method (MOPAC No. 581, Bloomington, USA). From both methods it can be deduced that C-1 is the most electrophilic one. This is in good accordance with the experiments yielding products only which derive from an attack at this C-atom. In the case of the 1-CN-substituted derivative **1.1** the results of the ^{13}C-NMR spectrum and the semiempirical calculation seem to be different: whereas the NMR spectrum assigns the most electrophilic position to C-3, the theoretical calculations attribute it to C-1, which is occupied by the cyano group changing the conditions in comparison with **1.4**. The latter result is confirmed in the experiments: The nucleophilic reagents have attacked C-1 with only one exception, morpholine. In summary, it can be stated for all derivatives discussed here that C-1 of the *N*-methoxyisoquinolinium salts is the most reactive one with regard to the attack of nucleophilic agents.

This paper is dedicated to the memory of Professor Dr. *J. Schnekenburger* who died on July 1988 and who initiated the research on this class of compounds and their reactions with nucleophilic agents.

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Experimental Part

Melting points: melting point microscope Fa. Reichert; not corrected.- NMR spectra: Bruker AM 400 (400.134 MHz for ^{1}H-NMR spectra, 100.614 MHz for ^{13}C-NMR spectra; TMS as internal reference for CD_3CN, TPS Na salt as internal reference for [D_6]DMSO, [D_7]DMF and D_2O).- Mass spectrum: Finnigan MAT 8230, 70 eV.- IR spectra: Beckman Acculab 10 (KBr discs).- Elemental analysis: Mikroanalytisches Labor Ilse Beetz, Kronach.- Column chromatography: silica gel 60, 70-230 mesh, Merck Nr. 7734.

*4-Cyanoisoquinoline (**2.4**) (modified synthesis according to Tyson[15])*

A mixture of 4-bromoisoquinoline (4.16 g, 0.02 mmol) and CuCN (2.68 g, 0.03 mmol) is melted in a round-bottom flask. As soon as fusion is observed (after 10 to 15 min), the product **2.4** is distilled in high vacuum. Yield 1.45 g (47%).- M.p. 104°C (CH_3OH).- IR: 3080 (C-H); 2240 (C≡N); 1630 cm^{-1} (C=N).- ^{1}H-NMR (CD_3CN): δ (ppm) = 9.48 (s; 1H, 1-H), 8.92 (s; 1H, 3-H), 8.22 (d; J = 8.2 Hz, 1H, 5-H), 8.15 (d; J = 8.4 Hz, 1H, 8-H), 8.00 (t; J = 8.4 Hz, 1H, 7-H), 7.85 (t; J = 8.2 Hz, 1H, 6-H).

1-Cyanoisoquinoline (modified synthesis according to Okamoto and Tani[10])

To a solution of *N*-methoxyisoquinolinium perchlorate (1.3 g, 5 mmol) in 25 ml dioxane/water (7/3 v/v) KCN (0.65 g, 0.01 mol) in dioxane (70%)

is added slowly at ambient temp. After 2 h water (100 ml) is added, and the mixture is extracted three times with CH_2Cl_2 (30 ml). After removal of the org. solvent 1-cyanoisoquinoline is obtained. Yield 0.6 g (79%).- M.p. 91°C (cyclohexane).- IR: 3058 (C-H); 2220 (C≡N); 1620 cm^{-1} (C=N).- ^{1}H-NMR (CD_3CN): δ (ppm) = 8.64 (d; J = 5.6 Hz, 1H, 3-H), 8.29 (d; J = 7.3 Hz, 1H, 8-H), 8.07 (d; J = 8.0 Hz, 1H, 5-H), 8.07 (d; J = 5.6 Hz, 1H, 4-H), 7.87 (m; 2H, 6-H, 7-H).

1,4-Dicyanoisoquinoline (**3.4**)

A solution of **1.4** (5.0 g, 0.015 mol) is converted with KCN (1.95 g, 0.03 mol) as described for 1-cyanoisoquinoline. The resulting mixture of products is purified by column chromatography (eluent: toluene/ethylacetate 1/3). Yield 1.1 g (42%).- M.p. 183°C (ref.[20]: 178.5°C).- IR: 3090, 3060 (C-H); 2230 (C≡N); 1610 cm^{-1} (C=N).- ^{1}H-NMR (DMSO-d_6): δ (ppm) = 9.31 (s; 1H, 3-H), 8.46 (d; J = 8.4 Hz, 1H, 8-H), 8.31 (d; J = 8.3 Hz, 1H, 5-H), 8.26 (t; J = 7.5 Hz, 1H, 6-H or 7-H), 8.15 (t; J = 7.6 Hz, 1H, 7-H or 6-H).

1,3-Dicyanoisoquinoline (**3.1**)

NaCN (0.15 g, 3 mmol), suspended in CD_3CN (25 ml), is added to a solution of **1.1** (0.5 g, 1.5 mmol) in CH_3CN (10 ml). After 48 h at ambient temp. the solvent is removed i.vac., the residue is dissolved in water, and 0.22 g of a mixture of **3.1** and **2.1** is extracted with CH_2Cl_2. **3.1** is separated by column chromatography (eluent ethylacetate). Yield 0.015 g (5.6%).- M.p. 212°C (lit.[21]: 215-216°C).- IR: 3080 (C-H); 2230 (C≡N); 1620 cm^{-1} (C=N).- ^{1}H-NMR (DMSO-d_6): δ (ppm) = 9.08 (s; 1H, 4-H), 8.41 (m; 1H, 5-H or 8-H), 8.35 (m; 1H, 8-H or 5-H), 8.18 (m; 2H, 6-H, 7-H).

4-Cyanoisoquinoline-N-oxide (synthesis as described for N-oxides in general by Ochiai[13])

From **2.4** (1.25 g, 8 mmol). Yield 0.52 g (38%).- M.p. (2-propanol): 213°C (lit.[22]: 220-221°C).- IR: 3100, 3050 (C-H); 2240 (C≡N); 1620 cm^{-1} (C=N).- ^{1}H-NMR (CD_3CN): δ (ppm) = 8.92 (s; 1H, 1-H), 8.55 (d; J = 1.7 Hz, 1H, 3-H), 8.08 (m; 1H, 5-H), 7.91 (m; 1H, 8-H), 7.80 (m; 2H, 6-H, 7-H).

1-Cyanoisoquinoline-N-oxide (**2.1**)

From 1-cyanoisoquinoline (1.0 g, 6.5 mmol) as described for the 4-isomer. Yield 0.83 g (75%). M.p. 213°C (2-propanol 95%, ref.[22]: 206-207°C).- IR: 3105, 3060 (C-H); 2220 (C≡N); 1610 cm^{-1} (C=N).- ^{1}H-NMR (CD_3CN): δ (ppm) = 8.13 (d; J = 7.2 Hz, 1H, 3-H), 7.99 (d; J = 7.2 Hz, 1H, 4-H), 7.96 (d; J = 8.3 Hz, 1H, 5-H), 7.92 (dd; J = 8.3 Hz, 0.9 Hz, 1H, 8-H), 7.83 (td; J = 8.3 Hz, 1.2 Hz, 1H, 7-H), 7.70 (td; J = 8.3 Hz, 1.1 Hz, 1H, 6-H).

4-Cyano-N-methoxyisoquinolinium trifluoromethanesulphonate **1.4**

A solution of 4-cyanoisoquinoline-*N*-oxide (0.2 g, 1.2 mmol) and methyl trifluoromethanesulphonate (0.3 g, 1.8 mmol) in absol. CH_2Cl_2 is refluxed for 2 h. The precipitated product is filtered, washed with diethylether and dried. Yield 0.3 g (76%).- M.p. 180°C.- $C_{12}H_9F_3N_2O_4S$ (334.3) Calcd. 43.1 H 2.71 N 8.4 Found C 43.2 H 2.68 N 8.4.- IR: 3100, 3070, 3000 (C-H); 2240 (C≡N); 1620, 1605 cm^{-1} (C=N).- ^{1}H-NMR (CD_3CN): δ (ppm) = 10.14 (d; J = 1.9 Hz, 1H, 1-H), 9.28 (d; J = 1.9 Hz, 1H, 3-H), 8.63 (dt; J = 8.4 Hz, 1.0 Hz, 1H, 5-H), 8.49 (m; 2H, 7-H, 8-H), 8.26 (m; 1H, 6-H), 4.53 (s; 3H, OCH_3).

Table 1: ^{1}H-NMR data of the products of the reactions with nucleophiles (see text) (δ (ppm))

No.	H-1	H-3	H-4	H-5	H-6	H-7	H-8	OCH_3	others	solvent
4.1	--	6.67	6.07	7.30	*	7.42	*	3.90		CD_3CN
4.4	6.18	7.61	--	7.22 - 7.45				3.82		CD_3CN
4.1.1	--	7.47	6.56	7.64	7.70	7.52	8.32	4.02		CD_3CN
5.1.a	--	7.10	6.07	7.22 - 8.40				*	1.12; 2.79	CD_3CN
5.1.b	--	5.63	6.67	7.22 - 8.40				*	1.12; 2.79	CD_3CN
5.4	5.98	7.66	--	7.20 - 7.40				3.75	0.96; 2.59	CD_3CN
6.1	--	5.59	6.66	7.14	7.36	7.28	7.72	3.79	2.8-3.0, 3.6-3.65	CD_3CN
6.4	5.97	8.17	--	7.41	7.28	7.40	7.19	3.80	2.4-2.7; 3.4-3.5	CD_3CN
7.1	--	8.31	7.52	8.02 - 8.13		7.87	8.65	4.17	2.38, 5.10, 7.27, 7.43	DMSO-d_6
7.4a	6.36	7.98	--	7.20 - 7.50				3.93	2.28, 7.08, 7.16	DMF-d_7
7.4b	6.03	8.03	--	7.20 - 7.50				3.93	2.28, 7.08, 7.16	DMF-d_7
8.1	--	8.10	7.60	8.03	7.99	7.67	8.40	4.08	2.45, 7.37, 7.42	DMSO-d_6

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1-Cyano-N-methoxyisoquinolinium trifluoromethanesulphonate (**1.1**)

A solution of **2.1** (1 g, 0.059 mmol) and methyl trifluoromethanesulphonate (1.56 g, 0.095 mmol) in absol. CH_2Cl_2 (45 ml) is refluxed for 12 h. The product is obtained as described for **1.4**. Yield 1.6 g (81%).- M.p. 154°C.- $C_{12}H_9F_3N_2O_4S$ (334.3) Calcd. C 43.1 H 2.71 N 8.4 Found C 43.3 H 2.96 N 8.4.- IR: 3120, 3100 (C-H); 1645, 1620 cm^{-1} (C=N).- ^{1}H-NMR (CD_3CN): δ (ppm) = 9.13 (d; J = 7.1 Hz, 1H, 3-H), 8.91 (d; J = 7.1 Hz, 1H, 4-H), 8.58 (d; J = 8.5 Hz, 1H, 8-H), 8.49 (d; J = 8.4 Hz, 1H, 5-H), 8.38 (t; J = 7.7 Hz, 1H, 6-H), 8.30 (t; J = 7.8 Hz, 1H, 7-H), 4.66 (s; 3H, OCH_3).

N-Methoxy-1-isoquinolone (**4.1.1**)

A solution of **1.1** (1 g, 3 mmol) is stirred for 48 h in aqueous dioxane (20 ml, 7/3 v/v) at ambient temp. The solvent is removed i.vac., and the oil obtained is purified by sc (eluent: ethylacetate). Yield 0.35 g (67%).- $C_{10}H_9NO_2$ (175.2).- IR: 3090, 3020, 2940, 1660 (C=O); 1600, 1550 cm^{-1}.- UV (CH_3CN): λ max = 219; 223; 282; 287; 320 nm.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.46 (dd; J = 6.0 Hz, 0.5 Hz, 1H, 8-H); 7.65 (td; J = 7.2 Hz, 1.3 Hz, 1H, 6-H); 7.54 (d; J = 7.9 Hz, 1H, 5-H), 7.50 (dd; J = 7.1 Hz, 1.3 Hz, 1H, 7-H), 7.34 (d; J = 7.7 Hz, 1H, 3-H), 6.48 (d; J = 7.7 Hz, 1H, 4-H), 4.11 (s; 3H, OCH_3).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 157.5 (t; 4.1, C-1), 135.6 (m; C-4a), 131.7 (dd; 161.9, 8.4, C-6), 129.0 (dd; 184.3, 4.3, C-3), 126.9 (dd; 164.2, 7.5, C-8), 126.8 (dd; 163.6, 7.9, C-7), 126.2 (hidden), 125.7 (ddd; 167.0, 7.2, C-5), 105.8 (d; 169.4, C-4), 63.8 (q; 146.2, OCH_3).

Reactions in the NMR tube: general procedure

40 mg (0.12 mmol) of the derivatives **1.1** and **1.4** are dissolved in 0.55 ml of CD_3CN, [D_7]DMF, or [D_6]DMSO, resp. (0.22 mol/l), the solution was poured into the tube and the nucleophilic agent was added by a micropipette. a) Diethylamine 12.5 µl (0.12 mmol) or 25 µl (0.24 mmol); b) 4-methylaniline (in 20 µl of solvent): 12.9 mg (0.12 mmol) or 25.6 mg (0.24 mmol); c) 4-benzylmethylamine 15.2 µl (0.12 mmol) or 30.4 µl (0.24 mmol); d) morpholine 10.4 µl (0.12 mmol) or 20.8 µl (0.24 mmol); e) NaOD (10% in D_2O) 29.3 µl (0.12 mmol) or 58.5 µl (0.24 mmol). The tube was shaken and measured at once, after 10 min, 6 h, 24 h, and 120 h. NMR data are summarized in Table 1.

Table 2: ^{13}C-NMR chemical shifts (δ ppm)[12] and net atomic charges of **1**, **1.1** and **1.4**

No.	atom	^{13}C NMR	charges
1	C-1	144.84	0.076
	C-3	131.49	-0.062
	C-4	127.31	-0.088
1.1	C-1	128.83	0.218
	C-3	133.42	-0.049
	C-4	127.26	-0.083
1.4	C-1	149.80	0.088
	C-3	138.40	-0.032
	C-4	110.33	0.055

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