New Synthesis of Substituted Quinoline *N*-Oxides via Cyclization of Alkylidene *o*-Nitroarylacetonitriles

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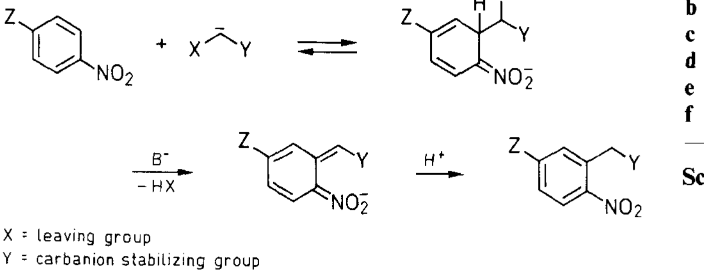
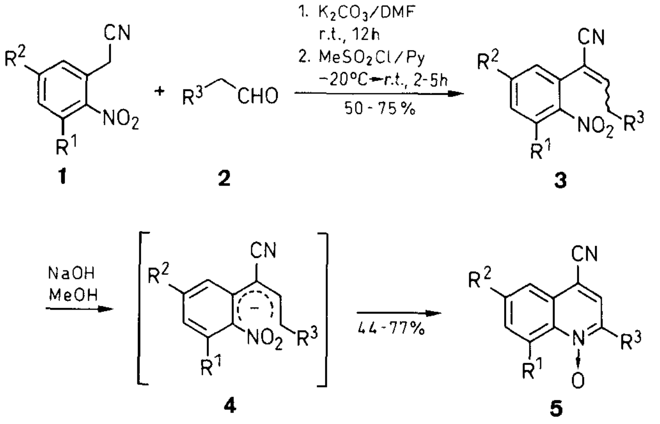
Substituted quinoline *N*-oxides are prepared via base induced cyclization of alkylidene derivatives of *o*-nitroarylacetonitriles which are readily available via the vicarious nucleophilic substitution cyanomethylation of nitroarenes followed by the Knoevenagel condensation.

Intramolecular cyclization of the systems containing aromatic nitro group and a carbanionic center positioned at the proper distance from it in the ortho side chain are well known in the synthesis of many nitrogen containing 5- and 6-membered heterocycles.[1] Since one of the most facile way of introducing the functionalized substituents in the ortho position of nitroarenes is the vicarious nucleophilic substitution (VNS) reaction (Scheme 1),[2] there is a reasonable expectation that the VNS products should be versatile starting materials for the synthesis of the cyclizable systems.



Scheme 1

One example of such an approach for the synthesis of heterocyclic compounds has already been presented. It consists in the treatment of *o*-nitroarylmethyl phenyl sulfones with diethyl maleate or fumarate in the presence of potassium carbonate as a base which resulted in direct formation of diethyl quinoline-2,3-dicarboxylate *N*-oxide derivatives in good yields.[3] Based on this work, we presumed that compounds of the general structure **3**, easily available from the VNS products via the Knoevenagel condensation with aldehydes should be able to react in a similar way. In such compounds there is an electron-withdrawing substituent in the position conjugated with the reaction centre, hence they should form carbanions of the similar nucleophilicity and ability to enter the cyclization (Scheme 2).



1-5	R^1	R^2	R^3
a	H	Cl	H
b	H	Cl	Me
c	H	Cl	Et
d	Cl	Cl	H
e	H	Cl	i-C_3H_7
f	H	Br	H

Scheme 2

Indeed, a solution of 2-(5-chloro-2-nitrophenyl)-2-hexenenitrile (**3c**), (obtained from 4-chloronitrobenzene and chloroacetonitrile via the VNS reaction[4] followed by the Knoevenagel condensation with butyraldehyde[5]) in methanol, upon addition of methanolic sodium hydroxide turned blue, probably due to the formation of conjugated anion **4**. After a while this colour disappeared and 6-chloro-4-cyano-2-ethylquinoline *N*-oxide (**5c**) precipitated as a brown solid. The reaction was over within approximately 5 min. Other compounds **3** reacted in a similar way (Table).

Since the described procedure for the Knoevenagel condensation of **1** and low-boiling aldehydes to form **3**[5] had been found to give erratic results, another approach was developed. (5-Chloro-2-nitrophenyl)acetonitrile (**1a**) was treated with an excess of an aldehyde **2** in dimethylformamide in the presence of a catalytic amount of potassium carbonate to give an aldol type product which in the crude state was subsequently dehydrated using methanesulfonyl chloride/pyridine system.

The cyclization reaction has not been optimized. The scope and limitations are under investigation. Taking into account the facile synthesis of *o*-nitroarylacetonitriles via the VNS reaction[4,6,7] and simple further processes leading to the quinoline derivatives shown in Scheme 2, the method reported here can be of substantial value in the synthesis of substituted quinoline derivatives.

2-(5-Choro-2-nitrophenyl)-2-butenenitrile (3a); General Procedure: To a stirred solution of (5-chloro-2-nitrophenyl)acetonitrile (**1a**; 393 mg, 2 mmol) and freshly distilled acetaldehyde (**2a**; 2.3 mL, 40 mmol) in DMF (5 mL) was added K_2CO_3 (30 mg). The reaction vessel was sealed with Parafilm and the mixture stirred at r.t. for 12 h. The mixture was poured into sat. NH_4Cl solution (100 mL) and extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine and dried ($MgSO_4$). The solvent was evaporated,

Table. Compounds 3 and 5 Prepared

Product	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[b]	IR (KBr) (cm^{-1}) $\nu_{C\equiv N}$	ν_{NO_2}	$\nu_{N\rightarrow O}$	^{1}H NMR (CDCl$_3$/TMS)[c] δ, J (Hz)
3a[d]	50	63–78 (EtOH/hexane)	$C_{10}H_7ClN_2O_2$ (222.6)	2230	1540, 1340	–	*Z*: 2.25 (d, J = 7.0, 3H), 6.61 (q, J = 7.0, 1H), 7.41 (d, J = 2.3, 1H), 7.55 (dd, J = 8.8, 2.3, 1H), 8.06 (d, J = 8.7, 1H) *E*: 1.75 (d, J = 7.3, 3H), 6.86 (q, J = 7.3, 1H), 7.38 (d, J = 2.29, 1H), 7.59 (q, J = 8.8, 2.29, 1H), 8.16 (d, J = 8.8, 1H)
3b	58	79–81 (EtOH/hexane)	$C_{11}H_9ClN_2O_2$ (236.7)	2230	1545, 1345	–	1.22 (t, J = 7.6, 3H), 2.62 (m, 2H), 6.53 (t, J = 7.5, 1H), 7.41 (d, J = 2.3, 1H), 7.55 (dd, J = 8.8, 2.3, 1H), 8.06 (d, J = 8.8, 1H)
3d[d]	75	53–56 (MeOH/H_2O)	$C_{10}H_6Cl_2N_2O_2$ (257.1)	2235	1525, 1335	–	*Z*: 2.21 (d, J = 7.1, 3H), 6.72 (q, J = 7.1, 1H), 7.40 (d, J = 2.1, 1H), 7.56 (d, J = 2.1, 1H) *E*: 1.79 (d, J = 7.2, 3H), 6.94 (q, J = 7.2, 1H), 7.29 (d, J = 2.1, 1H), 7.63 (d, J = 2.1, 1H)
3e	70	oil	$C_{13}H_{13}ClN_2O_2$ (229.3)	2225[e]	1525, 1335[e]	–	1.05 (d, J = 6.7, 6H), 1.92 (m, 1H), 2.50 (dd, J = 7.9, 6.7, 2H), 6.55 (t, J = 7.9, 1H), 7.40 (d, J = 2.41, 1H), 7.54 (dd, J = 8.8, 2.41, 1H), 8.05 (d, J = 8.8, 1H)
3f	63	68–78 (EtOH/hexane)	$C_{10}H_7BrN_2O_2$ (267.2)	2230	1510, 1335	–	2.25 (d, J = 7.0, 3H), 6.63 (q, J = 7.0, 1H), 7.57 (d, J = 2.1, 1H), 7.71 (dd, J = 8.7, 2.1, 1H), 7.97 (d, J = 8.7, 1H)
5a	77	207–208 (EtOH)	$C_{10}H_5ClN_2O$ (204.6)	2230	–	1305	7.71 (d, J = 6.43, 1H), 7.80 (dd, J = 9.34, 2.1, 1H), 8.20 (d, J = 2.1, 1H), 8.47 (d, J = 6.4, 1H), 6.87 (d, J = 9.3, 1H)
5b	44	201–203 (EtOH/hexane)	$C_{11}H_7ClN_2O$ (218.7)	2225	–	1315	2.61 (s, 3H), 7.92 (dd, J = 9.2, 2.1, 1H), 8.11 (d, J = 2.1, 1H), 8.19 (s, 1H), 8.67 (d, J = 9.2, 1H)
5c	71	182–185 (EtOH)	$C_{12}H_9ClN_2O$ (232.7)	2240	–	1305	1.40 (t, J = 7.5, 3H), 3.09 (q, J = 7.5, 2H), 7.72 (s, 1H), 7.77 (dd, J = 9.3, 2.1, 1H), 8.15 (d, J = 2.1, 1H), 8.69 (d, J = 9.3, 1H)
5d	63	200–202 (EtOH)	$C_{10}H_4Cl_2N_2O$ (239.1)	2245	–	1295	7.93 (d, J = 2.2, 1H), 8.06 (d, J = 6.6, 1H), 8.09 (d, J = 2.2, 1H), 8.55 (d, J = 6.6, 1H)
5e	51	133–136 (cyclohexane)	$C_{13}H_{11}ClN_2O$ (246.7)	2225	–	1285	1.40 (d, J = 6.9, 6H), 3.83 (m, 1H), 7.92 (dd, J = 9.3, 2.1, 1H), 8.09 (dd, J = 2.1, 0.5, 1H), 8.14 (s, 1H), 8.67 (dd, J = 9.3, 0.5, 1H)
5f	61	227–229 (EtOH)	$C_{10}H_5BrN_2O$ (249.2)	2245	–	1305	8.05–8.11 (m, 2H), 8.32 (d, J = 1.9, 1H), 8.56 (d, J = 9.1, 1H), 8.65 (d, J = 6.6, 1H)

[a] Yield of isolated product.

[b] Satisfactory HRMS values obtained: ± 0.00219 amu.

[c] ^{1}H NMR of compounds **5b, d–f** were recorded in acetone-d_6.

[d] Mixture of diastereoisomers, $Z/E = 5:1$.

[e] Recorded as thin film.

the residue dissolved in CH_2Cl_2 (2 mL) and cooled to −20 °C. Pyridine (20 mL) and then $MeSO_2Cl$ (1 mL) were added. The resulting mixture was allowed to warm to r.t., then stirred without cooling until the reaction was complete (2–5 h, TLC control) and poured into cold 10% HCl (150 mL). The mixture was extracted with Et_2O (3 × 30 mL), the combined extracts were dried, the solvent evaporated and the residue purified by column chromatography on silica gel using EtOAc/hexane (1 : 8) as eluent, yield: 214 mg (50%) (Table).

6-Chloro-4-cyanochinoline *N*-Oxide (5a); General Procedure:

To a solution of **3a** (160 mg, 0.75 mmol) in MeOH (3 mL) was added a 1 M solution of NaOH in MeOH (0.75 mL, 0.75 mmol) in one portion and the mixture was stirred at r.t. Initial blue colour turned to light brown within 2 min and a solid precipitated. The mixture was poured into ice-cold 10% HCl (50 mL), extracted with EtOAc (5 × 20 mL), the combined extracts were dried ($MgSO_4$) and the solvent evaporated. The residue was recrystallized from EtOH/hexane to afford pure **5a**; yield: 118 mg (77%) (Table).

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