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Transformations of *o*-Nitroarylallyl Carbanions. Synthesis of Quinoline N-Oxides and N-Hydroxyindoles.[1]

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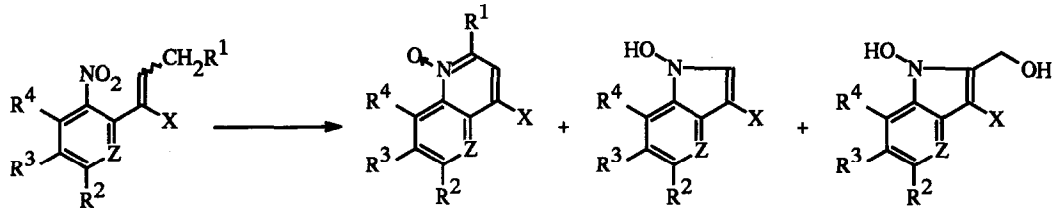
Abstract: Nitriles and esters of 2-(*o*-nitroaryl)crotonic acids are converted under basic conditions into substituted quinoline N-oxides, N-hydroxyindoles and N-hydroxy-2-hydroxymethyl indoles. Factors governing the reaction course and mechanistic pathways are discussed.

Many nitrogen heterocycles can be efficiently synthesized from nitroarenes containing a functionalized carbon substituent in the *ortho* position. These processes, which involve neighboring groups interactions are described in numerous papers and reviews.[2] Wide practical application of such reactions is somewhat limited since synthesis of starting *o*-substituted nitroarenes is not always an easy task. One of solutions of this problem is offered by vicarious nucleophilic substitution of hydrogen (VNS), a reaction between nitroarenes and carbanions containing a leaving group at the carbanion center.[3] In this process functionalized alkyl substituents can be readily introduced into positions *ortho*- and *para*- to the nitro group. An important feature of this reaction is the possibility to control the orientation[4] and usually strong preference for the VNS of hydrogen as compared with conventional S_NAr of halogen *o*- or *p*- to the nitro group.[5] We have already described use of the VNS products in synthesis of such heterocyclic compounds as indoles[6] and quinolines.[7] Particularly interesting is possibility of substituted quinoline N-oxide synthesis via reactions of allylic carbanions with the *ortho* located nitro group.[8]

In our preceding paper we have reported that some unsaturated nitriles **1** upon treatment with sodium hydroxide in methanol undergo smooth cyclization to substituted quinoline N-oxides.[8] However in our attempts to extend this process onto other nitriles **1** we have observed not only formation of expected substituted quinoline N-oxides **2** but also two other products: N-hydroxyindoles **3** and N-hydroxy-2-hydroxymethylindoles **4** (Scheme 1). Unusual formation of 5-membered heterocyclic rings in the reaction of terminally activated three carbon atoms side chain with the *o*-nitro group, accompanied with lost of one carbon unit promped us to investigate this problem in detail.

RESULTS AND DISCUSSION

The precursors of the *o*-nitroarylallyl carbanions, 1-(*o*-nitroaryl)-1-cyanoalkenes **1**, were obtained in a Knoevenagel type condensation of *o*-nitroarylacetonitriles with aliphatic aldehydes, most frequently acetaldehyde. Unsaturated nitriles **1** are relatively strong CH acids because upon deprotonation they form allylic carbanions stabilized by the nitroaryl moiety and the cyano group. In order to study effects of substituents on the reaction course a number of nitriles and esters **1a-j** were prepared. Results of the cyclization of compounds **1a-j** under standard conditions in which **1a-c** gave the quinoline N-oxides **2** as the only products, are shown in Table 1. For example treatment of **1d** with methanolic NaOH gave a mixture of three products differing in polarity. They were separated by column chromatography ($CHCl_3$ - i-PrOH 100:1 as eluent). The least polar product was the expected quinoline N-oxide **2d**, a more polar product showed molecular peak 12 units lower than **2d** (lost of H_2O and C in relation to **1d**) and one exchangeable proton, the third, most polar product showed molecular peak of the same mass as **1d** and two exchangeable protons. On the basis of ^1H NMR and ^{13}C NMR, including the DEPT 135° technique, as well as other analytical and spectral data, these products were identified as correspondingly: N-hydroxy-3-cyano-5-fluoroindole **3d** and N-hydroxy-2-hydroxy methyl-3-cyano-5-fluoroindole **4d** respectively.



1 **2** **3** **4**

	X	R^1	Z	R^2	R^3	R^4		X	R^1	Z	R^2	R^3	R^4
1a	CN	H	CH	Cl	H	Cl	**1k**	CN	H	CH	SPh	H	H
1b	CN	H	CH	Cl	H	H	**1l**	CN	i-Pr	N	OMe	H	H
1c	CN	H	CH	Br	H	H	**1m**	CN	Me	CH	SO_2Ph	H	H
1d	CN	H	CH	F	H	H	**1n**	CN	Me	CH	OMe	H	H
1e	CN	H	CH	OBn	H	H	**1o**	CO_2Et	H	N	OMe	H	H
1f	CN	H	CH	OMe	H	H	**1p**	CN	H	CN	Ph	H	H
1g	CN	H	CH	SMe	H	H	**1r**	CN	H	N	OMe	H	H
1h	CO_2Bu-t	H	CH	Cl	H	H	**1s**	CN	Me	[a]	-	-	-
1i	CO_2Bu-t	H	CH	OMe	$(CH=CH)_2$								
1j	CN	H	CH	SO_2Ph	H	H							

a) Ar= 2-nitrothienyl-3

Scheme 1

Table 1. Conversion of **1a-j** in Methanolic NaOH Solution.

Entry	Substrate	Products, yield (%)		
		2	**3**	**4**
1	**1a**	63[a)]	-	-
2	**1b**	77[a)]	-	-
3	**1c**	61[a)]	-	-
4	**1d**	60	26	5
5	**1e**	10	48	19
6	**1f**[b)]	13	65	-
7	**1g**	-	52	-
8	**1h**[b)]	-	53	9
9	**1i**[b)]	-	36	-
10	**1j**	80	-	-

a) lit.[7], b) entries 6,8,9 no reaction in MeOH; MeOH:DMSO in ratio 15:1, 3:1 and 2:3 correspondingly was used.

Products of the transformation of other nitriles **1** presented in Table 1 were identified in a similar way. These results indicate that the outcome of the reaction of nitriles **1** in methanolic NaOH solution are strongly affected by their acidity which is governed by the kind of substituents in the aromatic ring. Electron-withdrawing substituents such as Cl, Br or SO_2Ph favour the 6-membered ring formation (entries 1,2,3,10) whereas substituents decreasing acidity of nitriles **1**, such as OMe, SMe etc. shift the reaction towards formation of the hydroxy indole derivatives (**3** and **4**). When CH acidity of the nitriles is substantially diminished by the ring substituents the cyclization reactions were not observed under standard conditions (NaOH, MeOH). In order to induce the reaction it was necessary to increase activity of OH^- anions by addition of some amounts of DMSO to the methanolic NaOH. For example a solution of **1f** (1 mmole) in MeOH (3 ml) containing NaOH (1 mmole) is colourless and **1f** is not consumed. Upon addition of DMSO (0.2 ml) the mixture turned pale green and the reaction was completed within 1hour. Similar type of the cyclization was observed when esters of *o*-nitroarylacetic acids were treated with methanolic NaOH. In these reactions it was also necessary to enhance the basicity of the system by addition of DMSO.

Because of the apparently high sensitivity of the reaction course to basicity of the systems this problem was studied using **1d** as the model compound. Results of the transformation of **1d** under various basic conditions are shown in Table 2. They indicate that strongly basic conditions (1M or 5M solution of NaOH in MeOH used in an excess) favour formation of quinoline N-oxide **2d** (entries 1,2), while in weakly basic systems (K_2CO_3, MeOH) hydroxyindole **4d** was the major product (entry 6), whereas in systems of intermediate basicity (0.1 M NaOH) (entry 5) substantial amounts of **3d** were also formed. Thus via manipulation of the conditions it is possible to convert **1d** into **2d** or **4d** with good yields and selectivities. All these results were obtained in highly protic media, just by changing the basicity of the system. Selective conversion **1d** → **2d** could be also done using the completely different system triethylamine - trimethylchlorosilane in DMF. Under these conditions the conversion **1d** → **2d** was the most selective and gave the highest yield so they could be recommended for preparative purpose (Table 3).

Table 2. Transformations of **1d** under Various Conditions.

Entry	Conditions	yield (%)[a]		
		2d	**3d**	**4d**
1.	1M[b] NaOH(1eq.)/MeOH/rt/20min	60[c]	26[c,d]	5[c]
2.	5M[b](5eq.)/MeOH/rt/15min	60	tr.	tr.
3.	PTC[e]/rt/3h	45	tr.	tr.
4.	1M[b]NaOH(1eq.)[f]/MeOH/rt/6h	20	30	34
5.	0.1M[b]NaOH(1eq.)[f]/MeOH/rt/2h	tr.	44	48.5
6.	0.05M[b]K_2CO_3(1eq.)[f]/MeOH/rt/3days	tr.	5	74
7.	Et_3N(5eq.)/DMF/rt/1h	tr.	tr.	tr.
8.	Et_3N(5eq.)-Me_3SiCl(5eq.)/DMF/rt/1h	89	-	-

a) isolated yields, b) in MeOH, c) average from 3 experiments, d) CH_2O was trapped, e) excess of 50% aq. NaOH/CH_2Cl_2/n-$Bu_4N^+Br^-$ (5% mol.), f) solution of the base added slowly to a solution of the substrate

Table 3. Conversion of **1** → **2** in Et_3N, Me_3SiCl System at Room Temperature.

Entry	Substr.	time (h)	yield (%)[a]	Entry	Substr.	time (h)	yield (%)[a]
1	**1b**	1	84.5	8	**1k**	1	93.5
2	**1c**	1	88	9	**1l**	6	48
3	**1d**	1	89	10	**1m**	1.5	78
4	**1e**	6	85	11	**1n**	26	90
5	**1f**	3	74	12	**1o**	1	85[b]
6	**1h**	5	28[b]	13	**1p**	1.5	87
7	**1j**	0.5	99	14	**1s**	0.3	90

a) isolated yields, b) DBU was used instead of Et_3N

It should be stressed that this synthesis of substituted quinoline N-oxides is not limited to the reaction of *o*-nitroarylderivatives of unsaturated nitriles with triethyl amine - trimethylchlorosilane system. A similar transformation takes place with corresponding unsaturated esters **1** as well as with unsaturated esters and nitriles containing *o*-nitroheteroaromatic rings. In the latter cases derivatives of naphthyridines and thienopyridines are formed. These transformations are also sensitive to the acidity of **1**, so that when the starting compounds are less acidic as are **1h, 1o,** the reaction did not proceed in the presence of triethylamine. Application of a stronger base such as DBU assure the desired conversion. The conversion of **1** → **4** which is limited to relatively acidic **1** needs also some comments. For this process to occur selectively it is necessary

to use really a weak base in low concentration namely via slow addition of K_2CO_3 to a solution of substrate in methanol otherwise, as well as the desired **4**, substantial amounts of **3** are formed (Table 4).

Table 4. Conversion of **1** → **4** in K_2CO_3, MeOH system.

Entry	Substrate	Addition time (h)	yield (%)[a)]
1	**1b**	33	67[b)]
2	**1c**	72	74
3	**1d**	72	74[c)]
4	**1k**	12	45[d)]
5	**1p**	96	70
6	**1e**[e)]	72	53

a). isolated yields, b) traces of **3b** also isolated, c) see Table 2 entry 7; 55% of **3d** also isolated, d) **3d**, 31% also isolated, e) 2-cyanomethyl-5-methoxy-3-nitropyridine (1eq.) and CH_3CHO(5eq.) were used instead of **1r**, only 0.25 eq. of K_2CO_3 was necessary to complete the reaction **2r**, 6% also isolated

These results demonstrate that one can convert selectively unsaturated nitriles **1** into quinoline N-oxides **2** or N-hydroxy-2-hydroxymethylindoles **4** in good yields as shown in Tables 3 and 4.

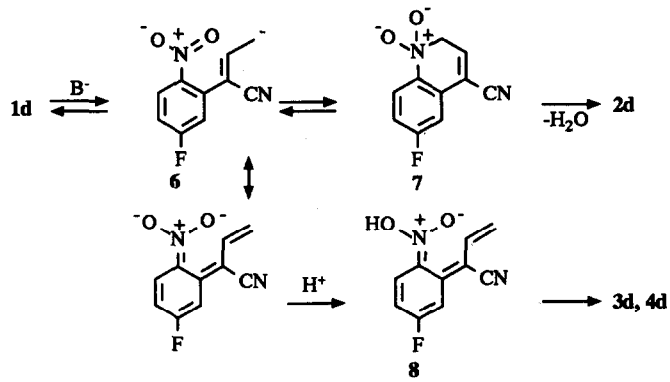
Mechanistic rationalization of these results is not a simple task. First of all in separate experiments it was shown that under conditions in which these transformations are carried out there is no interconversion between products **2d**, **3d** and **4d**.

Then there is a question in which form the one carbon unit is lost in order to form **3d**. From stoichiometry of the reaction it should be formaldehyde. Indeed formaldehyde was trapped in form of its dimedone derivative[9] when in a separate experiment analogous to entry 1 in Table 2, nitrogen was bubbled through the reaction mixture and then passed into alkaline methanolic solution of dimedone.

A speculative mechanistic picture of these reactions (Scheme 2) should address differentiation between the closure of six- and five-membered rings and take into account that the final reaction outcome: transformation of **1** into **2**, **3** and **4** is governed by basicity of the reaction medium. Since the formation of the quinoline-N-oxides takes place under the most basic conditions or in the presence of triethylamine-trimethylchlorosilane (TEA/TMCS) system one could suppose that the carbanion **6** formed upon deprotonation of **1d** adds irreversibly to the nitro group with the formation of adduct **7**.

Subsequent elimination of OH^- anion leading to **2d** is a relatively slow process, so under less basic conditions, because of reversibility of the formation of **7**, reprotonation of carbanion **6** to nitronic acid **8** opens an avenue to the indole derivatives. Although TEA/TMCS is of moderate basicity the intermediate adduct **7** is apparently silylated so the elimination of trimethyl silanol to **2d** become the dominating process. Formation of the indole derivatives seems to proceed *via* **8** which could enter cycloaddition processes similar to those known for nitrones[10] and nitronic acid esters.[11] For the related transformations also [2+2] cycloadditions were proposed as the crucial steps.[12] In general, however, mechanistic pathways of the formation of **3** and **4** are not clear.

The transformations of *o*-nitroarylallylic carbanions can provide a variety of valuable heterocyclic systems



Scheme 2

difficult to prepare in other ways. The course of these reactions can be efficiently controlled by the conditions.

EXPERIMENTAL

Melting points are uncorrected. The infrared spectra were measured on Acculab 1 (Beckman). The ^1H and ^{13}C-NMR spectra were measured on Varian Gemini (200 MHz). Chemical shifts were expressed in ppm using TMS as an internal standard. The mass spectra were obtained on AMD-604 (AMD Interctra GmbH Germany), Silica gel (70-230 mesh, Merck) was used for column chromatography. (5-Chloro-2-nitrophenyl)acetonitrile,[15] (5-fluoro-2-nitrophenyl)acetonitrile,[15] (5-benzyloxy-2-nitrophenyl)acetonitrile,[16] (5-methoxy-2-nitrophenyl)acetonitrile,[15] (5-methylthio-2-nitrophenyl)acetonitrile,[15] t-butyl(5-chloro-2-nitrophenyl)acetate,[15] t-butyl(4-methoxy-1-nitro-2-naphthyl)acetate,[17] (5-phenylthio-2-nitrophenyl)acetonitrile,[15] 2-cyanomethyl-6-methoxy-3-nitropyridine,[16] (2-nitro-5-phenylphenyl)acetonitrile,[15] (1-nitro-2-napthyl)acetonitrile,[15] (2-nitro-3-thienyl)acetonitrile[18] were prepared via the VNS of hydrogen in nitroarenes according to the reported procedures. (5-Bromo-2-nitrophenyl)acetonitrile and 2-ethoxycarbonylmethyl-6-methoxy-3-nitropyridine were prepared analogously to lit.[16]

(5-Bromo-2-nitrophenyl)acetonitrile: yield 80%; mp 108-110°C (EtOH); ^1H-NMR ($CDCl_3$): 4.22 (s, 2H), 7.72 (dd, J= 8.8, 2.1 Hz, 1H), 7.91 (d, y=2.1 Hz, 1H), 8.09 (d, J=8.8 Hz, 1H).

2-Ethoxycarbonylmethyl-6-methoxy-3-nitropyridine: yield, 65%; oil, ^1H-NMR ($CDCl_3$): 1.28 (t, J=7.1 Hz, 3H), 4.02 (s, 3H), 4.20 (q, J=7.1 Hz, 2H), 4.23 (s, 2H), 6.78 (d, J=9.1 Hz, 1H), 8.37 (d, J=9.1 Hz, 1H).

Preparation of the substrates **1**.

The synthesis of nitriles **1b** and **1c** have been already described.[7] The following nitriles and esters were prepared according to the same procedure.

1d: 72%; mp 76-79°C (EtOH), single isomer; IR (KBr): 2225 (CN), 1535, 1350 (NO_2): ^1H-NMR (acetone-d_6): 2.21 (d, J=7.0 Hz, 3H), 6.94 (q, J=7.0 Hz, 1H), 7.41-7.54 (m, 2H), 8.24 (dd, J=9.0 and 5.0 Hz, 1H); ^1H-NMR ($CDCl_3$): 2.25 (d, J=7.1 Hz, 3H), 6.60 (q, J=7.1 Hz, 1H), 7.11 (dd, J=8.3 and 2.8 Hz, 1H), 7.25 (ddd, J=9.1 and 7.1 and 2.8 Hz, 1H), 8.16 (dd, J=9.1 and 5.0 Hz, 1H); ^{13}C-NMR (acetone-d_6): 165.49 (d, J=254.7 Hz), 149.45, 144.70, 133.46 (d, J=9.8 Hz), 128.99 (d, J=10.1 Hz), 119.84 (d, J=24.9 Hz), 118.00 (d, J=23.4 Hz), 133.56, 133.37, 17.88; MS (m/e): 206, 189, 181, 173, 162, 158, 152, 137, 134, 121, 107; Anal. calcd: for $C_{10}H_7N_2O_2F$: C, 58.25; H, 3.42; N, 13.59%; found: C, 58.21; H, 3.39; N, 13.60%.

1e: 87%; mp 103-106°C (EtOH), single isomer; IR (KBr): 2220 (CN), 1515, 1345 (NO_2); ^{1}H-NMR ($CDCl_3$): 2.22 (d, J=7.1 Hz, 3H), 5.17 (s, 2H), 6.51 (q, J=7.1 Hz, 1H), 6.90 (d, J=2.7 Hz, 1H), 7.05 (dd, J=9.1 and 2.7 Hz, 1H), 7.39-7.44 (m, 5H), 8.15 (d, J=9.1 Hz, 1H); MS (m/e): 294, 262, 91, 65; Anal. calcd for $C_{17}H_{14}N_2O_3$: C, 69.37; H, 4.79; N, 9.52%; found: C, 68.99; H, 4.66; N, 9.10%.

1f: 69%; mp 98-100°C (EtOH-hexane), 2 isomers (14:1);IR (KBr): 2220 (CN), 1580, 1510, 1340 (NO_2); ^{1}H-NMR ($CDCl_3$): major isomer, 2.22 (d, J=7.0 Hz, 3H), 3.92 (s, 3H), 6.53 (q, J=7.0 Hz, 1H), 6.81 (d, J=2.8 Hz, 1H). 6.99 (dd, J=9.2 and 2.8 Hz, 1H), 8.16 (d, J=9.2 Hz, 1H); minor isomer, 1.74 (d, J=7.2 Hz), 3.9 (s), 6.78 (d), 8.24 (d, J=9.1 Hz), other signals overlapped with those of major isomer; MS (m/e): 218, 203, 175, 164, 149, 147, 131, 128, 120, 106, Anal. calcd for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84%, found: C, 60.57; H, 4.56; N, 12.76%

1g: 65%; mp 137-141°C (EtOH), 2 isomers (10:1); IR (KBr): 2220 (CN), 1505, 1335 (NO_2); ^{1}H-NMR ($CDCl_3$): major isomer, 2.23 (d, J=7.0 Hz, 3H), 2.56 (s, 3H), 6.64 (q, J=7.0 Hz, 1H), 7.10 (d, J=2.2 Hz, 1H), 7.30 (dd, J=8.7 and 2.2 Hz, 1H), 8.06 (dd, J=8.7 and 2.7 Hz, 1H); minor isomer, 1.72 (d, J=7.2 Hz), 6.82 (q, J=7.2 Hz), 7.08 (d), 8.13 (d), other signals overlapped with those of major isomer; MS (m/e): 234, 217, 202, 187, 147, 140, 114; HRMS: 34.0462 (M^+), calcd for $C_{11}H_{10}N_2O_2S$ 234.0463.

1h: 87%; mp 52°C (CCl_4-hexane), single isomer; IR (KBr): 1725 (CO), 1535, 1350 (NO_2); ^{1}H-NMR ($CDCl_3$): 1.40 (s, 9H), 1.75 (d, J=7.3 Hz, 3H), 7.15 (q, J=7.3Hz, 1H), 7.24 (d, J=2.3 Hz, 1H), 7.46 (dd, J=8.8 and 2.3 Hz, 1H), 8.09 (d, J=8.8 Hz, 1H); MS (m/e): 297, 241, 224, 195, 180, 168, 154, 126, 117; Anal. calcd for $C_{14}H_{16}NO_4Cl$: C, 56.47; H, 5.42; N, 4.71%; found: C, 56.15; H, 5.75; N, 4.91%

1i: 79.5%; mp 112-114°C (MeOH), single isomer; IR (KBr): 1705 (CO), 1515, 1350 (NO_2); ^{1}H-NMR ($CDCl_3$): 1.69 (d, J=7.2 Hz, 3H), 4.06 (s, 3H), 7.15 (q, J=7.2 Hz, 1H), 7.54-7.70 (m, 2H), 7.96 (m, 1H), 8.42 (m, 1H); MS (m/e): 343, 327, 311, 297, 270, 255, 241, 226, 211, 195, 183; HRMS: found 343.1422 (M^+), calcd for $C_{19}H_{21}NO_5$ 343.1420.

1k: 79%; mp 88-90°C (EtOH-hexane), single isomer; IR (KBr): 2220 (CN), 1505, 1330 (NO_2); ^{1}H-NMR ($CDCl_3$): 2.19 (d, J=7.0 Hz, 3H), 6.47 (q, J=7.0 Hz, 1H), 7.05 (d, J=2.1 Hz, 1H), 7.12 (dd, J=8.6 and 2.1 Hz, 1H), 7.46-7.58 (m, 5H), 7.96 (d, J=8.6 Hz, 1H); MS (m/e): 296, 264, 248, 224; Anal. calcd for $C_{16}H_{12}NO_2S$: C, 64.85; H, 4.08; N, 9.45; S, 10.82%; found: C, 64.70; H, 3.85; N, 9.35; S, 10.64

1n: 78%; mp 58-60°C (EtOH-hexane), single isomer; IR (KBr): 2215 (CN), 1510, 1335 (NO_2); ^{1}H-NMR ($CDCl_3$): 1.19 (t, J=7.5 Hz, 3H), 2.61 quint., J=7.5 Hz, 2H), 3.92 (s, 3H), 6.44 (t, J=7.5 Hz, 1H), 6.81 (d, J=2.8 Hz, 1H), 6.99 (dd, J=9.2 and 2.8 Hz, 1H), 8.15 (d, J=9.2 Hz, 1H); MS (m/e): 232, 203, 185, 175, 147, 131, 120, 102; Anal. calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.07%; found: C, 62.34; H, 4.89; 12.11%.

1o: 50%; mp 65-79°C (hexane), 2 isomers (10:1); IR ($CHCl_3$): 1725 (CO), 1590, 1510 (NO_2); ^{1}H-NMR ($CDCl_3$): major isomer, 1.21 (t, J=7.2 Hz, 3H), 1.82 (d, J=7.3 Hz, 3H), 4.01 (s, 3H)), 4.18 (q, J=7.2 Hz, 2H), 6.82 (d, J=9.0 Hz, 1H), 7.25 (q, J=7.3 Hz), 1H), 8.38 (d, J=9.0 Hz, 1H); minor isomer, 1.20 (t, J=7.2 Hz), 2.35 (d, J=7.4 Hz), 4.04 (s), 6.90 (q, J = 7.4 Hz), 8.28 (d, J=9.0 Hz), other signals overlapped with those of major isomer; MS (m/e): 266, 251, 234, 220, 206, 192, 177, 164, 151, 134, 121; HRMS: found 266.0913 (M^+), calcd for $C_{12}H_{14}N_2O_5$ 266.0903.

1p: 75%; mp 104-106°C (EtOH-hexane), single isomer; IR (KBr): 2215 (CN), 1505, 1330 (NO_2); ^{1}H-NMR ($CDCl_3$): 2.25 (d, J=7.0 Hz, 3H), 6.62 (q, J=7.0 Hz, 1H), 7.45-7.65 (m, 6H), 7.75 (dd, J=8.6 and 2.1 Hz, 1H), 8.16 (d, J+8.6 Hz, 1H); MS (m/e): 264, 247, 232, 221, 210 195, 192, 178, 166, 152, 140, 115; Anal. calcd for $C_{16}H_{12}N_2O_2$: C,54.13; H, 5.30; N, 10.52%; found: C, 54.06; H, 5.08; N, 10.54%

1s: 69%; mp 132-134°C (MeOH-H_2O), single isomer; IR (KBr): 2220 (CN), 1495, 1315 (NO_2); ^{1}H-NMR (acetone-d_6): 2.27 (d, J=7.1 Hz, 3H), 6.28 (q, J=7.1 Hz, 1H), 7.02 (d, J=5.5 Hz, 1H), 7.52 (d, J=5.5 Hz, 1H); MS (m/e): 194, 177, 163, 149, 125, 105, 95; Anal. calcd for $C_8H_6N_2O_2S$: C, 49.47; H, 3.12; N, 14.43; S, 16.51; found: C,49.45; H, 2.95; N, 14.24; S, 16.27.

Preparation of **1j**: Sulfide **1k** (1.5 mmol, 444 mg) was dissolved in methylene chloride (2 mL) and glacial

acetic acid (5 mL) and treated with 30% H_2O_2 (3.0 mmol, 309 μL), than stirred at room temperature until the substrate and very polar sulfoxide formed as an intermediate were consumed (the control, about 7 days). The mixture was poured into cold water extracted with methylene chloride (3 x 20 mL), extracts dried, the solvent evaporated and the residue recrystallized to give **1j**, 375 mg, 76%.

1j: mp 115-117°C (MeOH-H_2O), single isomer; IR (KBr): 2215 (CN), 1525, 1340 (NO_2), 1300, 1150 (SO_2); ^{1}H-NMR ($CDCl_3$): 2.27 (d, J=7.1 Hz, 3H), 6.69 (q, J=7.1 Hz, 1H), 7.54-7.72 (m, 3H), 7.97 (m, 2H), 8.11 (m, 1H); MS (m/e): 328, 311, 301, 296, 286, 274, 259, 203, 171, 140, 125; Anal. calcd $C_{16}H_{12}N_2O_4S$: C, 58.52; H, 3.69; N, 8.53%; found: C, 58.31; H, 3.31; N, 8.31%.

Preparation of **1m**. This compound was prepared via condensation of 2-cyanomethyl-4-phenylthionitrobenzene with propionaldehyde followed by oxidation of the crude reaction mixture according to the procedure described above for **1j**, yield 64%.

1m: 92-92°C (EtOH), single isomer; IR (KBr): 2225 (CN), 1545, 1335 (NO_2), 1305, 1170 (SO_2); ^{1}H-NMR (acetone-d_6): 1.19 (t, J=7.5 Hz, 2H), 2.61 (quint, J=7.5 Hz, 2H), 6.99 (t, J=7.5 Hz, 1H), 7.62-7.82 (m, 3H), 8.04-8.11 (m, 2H), 8.23-8.29 (m,2H); MS (m/e): 342, 310, 299, 295, 285, 243, 217, 185, 156, 141, 125, 115; Anal. calcd for $C_{17}H_{14}N_2O_4S$: C, 59.63; H, 4.12; N, 8.18; S, 9.37%; found: C, 59.66; H, 4.19; N, 8.24; S, 9.35%

Preparation of **1l**. This compound was obtained via condensation of 2-cyanomethyl-6-methoxy-3-nitropyridine with isobutyraldehyde similarly to the literature method[14] and isolated via column chromatography, yield 56%.

1d: oil, 2 isomers (7:1); IR (neat): 2220 (CN), 1515 (NO_2); ^{1}H-NMR ($CDCl_3$): major isomer, 1.05 (d, J=6.7 Hz, 6H), 1.96 (m, 1H), 2.55 (dd, J=8.0 and 7.8 Hz, 2H), 4.05 (s, 3H), 6.83 (d, J=8.9 Hz, 1H), 7.06 (t, J=8.0 Hz, 1H), 8.24 (d, J=8.9 Hz, 1H); minor isomer, 0.88 (d, J=6.6 Hz), 4.03 (s),8.38 (d, J=9.0 Hz), other signals overlapped with those of major isomer; MS (m/e): 261, 244, 229, 214, 202, 190, 176, 162,146, 134, 118; HRMS: found 261.1119 (M^+), calcd for $C_{13}H_{15}N_3O_3$ 261.1113.

A. Cyclization reactions in NaOH-methanol systems. General procedure.

Nitrile or ester **1** (1 mmol) was dissolved (or suspended) in methanol (3 mL) and treated with of methanolic NaOH (1 mL; in some cases DMSO was added, see Table 3). The mixture was stirred at room temperature until all the substrate was consumed (2 min to 3 h, TLC control). After acidic work-up and extraction with ethyl acetate (5 x 20 mL) the products were separated via column chromatography using chloroform - i-propanol (100:1) mixture as a solvent (Table 1, entry 4) or ethyl acetate - hexane (1:2 to 1:1) mixtures in other cases. For analytical purposes products were additionally recrystallized from the proper solvents.

B. Cyclizations to quinoline N-oxides in Et_3N - Me_3SiCl/DMF system. General procedure.

A solution of **1** (1 mmol) in dry DMF (3 mL) was treated with Me_3SiCl (5 mmol, 0.63 mL) followed by the addition of Et_3N (5 mmol, 0.70 mL) at room temperature. After stirring for the time indicated in Table 3 the reaction mixture was poured into aq. HCl (50 mL), extracted with ethyl acetate (5 x 20 mL), the extract was dried, solvent evaporated and the residue recrystallized from the proper solvent. In the case of **2h** (Table 3, entry 6) the product was isolated via column chromatography ethyl acetate - hexane (1:4) as eluent.

C. Cyclization reactions in K_2CO_3 - methanol system. General procedure.

To a solution of **1** (1 mmol) in methanol (10 ml, 20 mL in the case of 1k; Table 4, entry 4) a solution of K_2CO_3 (1 mmol, 138 mg) in 20 mL of methanol was added dropwise during the time indicated in Table 4. After the reaction was completed the mixture was worked-up and the products isolated as in procedure A.

2b: procedure B; R_f and spectral data correspond with lit.[7]

2c: procedure B; R_f and spectral data correspond with lit.[7]

2d: procedure A, B; mp 176-181°C (EtOAc); IR (KBr): 2220 (CN), 1305 (N→O) ^{1}H-NMR (C_6D_6): 6.07 (d, J=6.5 Hz, 1H), 6.61 (ddd, J=9.5 and 7.8 and 2.6 Hz, 1H), 7.31 (dd, J=8.2 and 2.6 Hz, 1H), 7.38 (d, J=6.5 Hz, 1H), 8.33 (dd, J=9.5 and 5.1 Hz, 1H); ^{13}C-NMR (acetone-d_6): 164.03 (d, J=251.7 Hz), 140.38, 135.74, 131.63 (d, J=10.7 Hz), 129.39, 124.38 (d, J=9.8 Hz), 121.83 (d, J=26.0 Hz), 116.0, 110.6 (d, J=25.0 Hz), 105.51 (d, J=5.0 Hz); DEPT 135°: 135.74, 129.43, 124.38 (d), 121.83 (d), 110.65 (d); MS (m/e): 188, 172, 160, 145, 133, 106; Anal. calcd for $C_{10}H_5N_2FO$: C, 63.83; H, 2.68; N, 14.89%; found: C, 63.69; h, 2.49; N, 14.95%.

2e: procedure A,B; mp 165-168°C (EtOH); IR (KBr): 2220 (CN), 1300 (N→O); ^{1}H-NMR (acetone-d_6): 5.42 (s), 7.38-7.66 (m, 7H), 7.94 (d, J=6.5 Hz, 1H), 8.46 (d, J=6.5 Hz, 1H), 8.56 (d, J=9.6 Hz, 1H); MS (m/e): 276, 260, 91; Anal. calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14%; found: C. 73.97; H, 4.29; N, 9.93%

2f: procedure A, B; mp 225-230°C (EtOH-hexane); IR (KBr): 2220 (CN), 1310 (N→O); ^{1}H-NMR (acetone-d_6): 4.09 (s, 3H), 7.41 (d, J=2.6 Hz, 1H), 7.55 (dd, J=9.6 and 2.6 Hz, 1H), 7.96 (d, J=6.5 Hz, 1H), 8.46 (d, J=6.5 Hz, 1H), 8.55 (d, J=9.6 Hz, 1H); MS (m/e): 200, 184, 157, 154, 141, 129, 114, 102; HRMS: found 200.0586 (M^+), calcd for $C_{11}H_8N_2O_2$: 200.0586

2h: procedure B; mp 166-167°C (EtOH-hexane); IR (KBr): 1715 (CO), 1290 (N→O); ^{1}H-NMR (acetone-d_6): 1.68 (s, 9H), 7.83 (dd, J=9.3 and 2.3 Hz, 1H), 8.12 (d, J=6.5 Hz, 1H), 8.49 (d, J=6.5 Hz, 1H), 8.66 (d, J=9.3 Hz, 1H), 9.20 (d, J=2.3 Hz, 1H), MS (m/e): 279, 263, 223, 207, 190, 178, 162, 149, 139, 123; HRMS: found 279.0663 (M^+), calcd for $C_{14}H_{14}NO_3Cl$ 279.0662;

2j: procedure A,B; mp 197-201°C (EtOAc); IR (KBr): 2215 (CN), 1295 (N→O); ^{1}H-NMR (DMSO-d_6): 7.63-7.82 (m, 3H), 8.08-8.14 (m, 2H), 8.31 (d, J=6.5 Hz, 1H), 8.33 (dd, J=9.2 and 2.0 Hz, 1H), 8.66 (d, J=2.0 Hz, 1H), 8.71 (d, J=9.2 Hz, 1H), 8.87 (d, J=6.5 Hz, 1H); MS (m/e): 310, 294, 262, 229, 217, 201, 173 153, 141, 125, 114; Anal. calcd for $C_{16}H_{10}N_2O_3S$: C, 61.98; H, 3.25; N, 9.04%; found: C, 61.57; H, 3.42; N, 9.04%

2k: procedure B; mp 196-198°C (EtOAc); IR (KBr): 2220 (CN), 1310 (N→O); ^{1}H-NMR (acetone-d_6): 7.53-7.58 (m, 3H), 7.61-7.69 (m, 3H), 7.72 (s, 1H), 7.95 (d, J=6.5 Hz, 1H), 8.49-8.56 (q overlapped with d, J=6.5 Hz, 2H); MS (m/e): 278, 262, 249, 235, 229, 222, 190, 131; Anal. calcd for $C_{16}H_{10}N_2OS$: C, 69.05; H, 3.62; N, 10.07%; found: C, 69.04; H, 3.43; N, 9.88%

2l: procedure B; mp 160-161°C (EtOAc - hexane); IR (KBr): 2220 (CN), 1295 (N→O): ^{1}H-NMR (acetone-d_6): 1.38 (d, J=7.0 Hz, 6H), 3.77 (sept., J=7.0 Hz, 1H), 4.13 (s, 1H), 7.28 (d, J=9.4 Hz, 1H), 8.11 (s, 1H), 8.76 (d, J=9.4 Hz, 1H); MS (m/e): 243, 226, 215, 212, 210, 198, 182, 170, 155; Anal. calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27; found: C, 64.27; H, 5.38; N, 17.30

2m: procedure B; mp 198-200°C (MEK); IR (KBr): 2215 (CN), 1315 (N→O) ^{1}H-NMR (acetone-d_6): 2.63 (s, 3H), 7.62-7.80 (m, 3H), 8.10-8.17 (m, 2H), 8.29 (s, 1H), 8.32 (dd, J=(9.1 and 1.9 Hz, 1H), 8.74 (d, J=1.9 Hz, 1H), 8.78 (d, J=9.1 Hz, 1H); MS (m/e): 324, 308, 215, 125; Anal. calcd for $C_{17}H_{12}N_2O_3S$: C, 62.95; H, 3.73; N, 8.64; S, 9.88%; found: C, 63.14; H, 3.69; N, 8.37; S, 9.8%

2n: procedure B; mp 201-204°C (EtOAc); IR (KBr): 2220 (CN), 1325 (N→O); ^{1}H-NMR (acetone-d_6): 2.57 (s, 3H), 4.06 (s, 3H), 7.37 (d, J=2.7 Hz, 1H), 7.52 (dd, J=9.6 and 2.7 Hz, 1H), 8.05 (s, 1H), 8.57 (d, J=9.6 Hz, 1H); MS (m/e): 214, 197, 183, 170, 155 140, 127, 115, 101; Anal. calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08%, found: C, 67.28; H, 4.87; N, 12.89%

2o: procedure B; mp 128-130°C (EtOH-hexane); IR (KBr): 1705 (CO), 1305 (N→O); ^{1}H-NMR (acetone-d_6): 1.24 (t, J=7.1 Hz, 3H); 4.10 (s, 3H), 4.45 (q, J=7.1 Hz, 2H), 7.23 (d, J=9.4 Hz, 1H), 7.88 (d, J=6.5 Hz), 1H), 8.42 (d, J=6.5 Hz, 1H), 8.79 (d, J=9.4 Hz, 1H); MS (m/e): 248, 231, 219, 203, 185, 176, 160, 147, 133; Anal. calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29%; found: C, 58.00; H, 4.81; N, 11.27%.

2p: procedure B; mp 178-181°C (EtOH); IR (KBr): 2225 (CN), 1315 (N→O); ^{1}H-NMR (acetone-d_6): 7.56-7.63 (m, 3H), 7.90 (m, 2H), 8.05 (d, J=6.4 Hz, 1H), 8.27 (dd, J=9.0 and 0.9 Hz, 1H), 8.31 (d, J=0.9 Hz, 1H), 8.63 (d, J=6.4 Hz, 1H); 8.71 (d, J=9.0 Hz, 1H); MS (m/e): 246, 230, 218, 201, 190, 175, 164, 151, 140; HRMS: found 246.0795 (M^+), calcd for $C_{16}H_{10}N_2O$ 246.0793.

2r: procedure C; mp 180-183°C (EtOAc); IR (KBr): 2225 (CN), 1295 (N→O); ^{1}H-NMR (acetone-d_6): 4.16 (s,

3H), 7.34 (d, J=9.4 Hz, 1H), 8.09 (d, J=6.6 Hz, 1H), 8.50 (d, J=6.6 Hz, 1H), 8.75 (d, J=9.4 Hz, 1H); MS (m/e): 201, 185, 171, 155, 142, 128, 116; HRMS: found 201.0536 (M^+), calcd for $C_{10}H_7N_3O_2$ 201.0538.

2s: procedure B; mp 199-200°C (AcOEt); IR (KBr) 2226 (CN), 1285 (N→O); ^{1}H-NMR (acetone-d_6): 7.63 (d, J=5.8 Hz, 1H), 7.98 (d, J=6.5 Hz, 1H), 8.18 (d, J=5.8 Hz, 1H), 8.50 (d, J=6.5 Hz, 1H), MS (m/e): 176, 160, 148, 133, 121, 116; HRMS: found 176.0034 (M^+), calcd for $C_8H_4N_2OS$ 176.0042.

3b: procedure C: mp 181-184°C (EtOAc); ^{1}H-NMR (acetone-d_6): 7.36 (dd, J=8.7 and 1.9 Hz, 1H), 7.61 (dd, J=8.7 and o.6 Hz, 1H), 7.67 (dd, J=1.9 and o.6 Hz, 1H), 8.25 (s, 1H); MS (m/e): 192, 176, 149, 141, 137, 114; HRMS: found 192.0092 (M^+), calcd for $C_9H_3N_2OCl$ 192.0090.

3d: procedure A: mp 168-170°C (EtOAc); IR (KBr): 2230 (CN): ^{1}H-NMR (acetone-d_6): 7.20 (dt, J=9.2 and 2.3 Hz, 1H), 7.40 (dd, J=9.0 and 2.3 Hz, 1H), 7.63 (dd, J=9.0 and 4.3 Hz, 1H), 8.26 (s, 1H); ^{13}C-NMR (acetone-d_6): 160.16 (d, J=236.4 Hz), 133.90, 130.81, 125.46 (d, J=25.2 Hz), 115.23, 113.45 (d, J=26.7 Hz), 112.13 (d, J=4.6 Hz), 104.87 (d, J=25.2 Hz), 61.52 (d, J=3.5 Hz); DEPT 135°: 133.96, 113.45 (d), 112.14 (d), 104.87 (d); MS (m/e): 176, 160, 149, 133, 121, 106; Anal. calcd for $C_5H_5N_2OF$: C, 61.36; H, 2.86; N, 15.91%; found: C, 61.34; H, 2.68; N, 15.97%.

3e: procedure A; mp 125-130°C (EtOH); IR (KBr): 2200 (CN); ^{1}H-NMR (acetone-d_6): 5.22 (s, 2H), 7.09 (dd, J=8.9 and 2.3 Hz, 1H), 7.24 (d, J=2.3 Hz, 1H), 7.29-7.57 (m, 6H), 8.10 (s, 1H); MS (m/e): 264, 248, 219, 170, 157, 129, 91; HRMS: found 264.0899 (M^+), calcd for $C_{16}H_{12}N_2O_2$ 264.0899.

3f: procedure A; mp 176-180°C ($PhCH_3$); IR (KBr): 2215 (CN); ^{1}H-NMR (acetone-d_6): 3.89 (s, 3H), 6.99 (dd, J=9.0 and 2.3 Hz, 1H), 7.12 (d, J=2.3 Hz, 1H), 7.48 (d, J=9.0 Hz, 1H), 8.09 (s, 1H); MS (m/e): 188, 172, 157, 142, 129, 114, 102; Anal. calcd: for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89%; found: C, 64.04; H, 4.25; N, 14.65%.

3g: procedure A; mp 166-168°C ($CHCl_3$ - CCl_4); IR (KBr): 2210 (CN); ^{1}H-NMR (acetone-d_6): 2.57 (s, 3H), 7.33 (dd, J=8.7 and 1.7 Hz, 1H), 7.54 (d, J=8.7 Hz, 1H), 7.56 (s, 1H), 8.15 (s, 1H); MS (m/e): 204, 188, 173, 155, 142, 129, 114; HRMS: found 204.0357 (M^+), calcd for $C_{10}H_8N_2OS$ 204.0357.

3h: procedure A; mp 150-154°C (CCl_4 - hexane); IR (KBr): 1700 (CO); ^{1}H-NMR (acetone-d_6): 1.60 (s, 9H), 7.27 (dd, J=8.8 and 2.0 Hz, 1H), 7.52 (dd, J=8.8 and 0.6 Hz, 1H), 8.00 (s, 1H), 8.08 (dd, J=2.0 and 0.6 Hz, 1H); ^{13}C-NMR (acetone-d_6): 163.98, 133.36, 132.05, 127.97, 124.68, 123.78, 121.27, 111.34, 104.50, 80.37, 30.95 MS (m/e): 267, 251, 210, 195, 178, 166, 150, 123, 114; Anal. calcd for $C_{13}H_{14}ClNO_3$: C, 58.32; H, 5.27; N, 5.23%; found: C, 58.04; H, 5.07; N, 5.41%.

3i: procedure A; mp 135-138°C dec. ($CHCl_3$); IR (KBr): 1665 (CO); ^{1}H-NMR (acetone-d_6): 1.64 (s, 9H), 4.06 (s, 3H), 7.45-7.65 (m, 2H), 7.68 (s, 1H), 7.86 (s, 1H), 8.32 (ddd, J=8.4 Hz, 1H), 8.86 (ddd, J=8.4 Hz, 1H); MS (m/e): 313, 297, 257, 241, 226, 198; HRMS: found 313.1319, calcd for $C_{18}H_{19}NO_4$ 313.1318; LSIMS: 336 $(M+Na)^+$, 313 (M^+), 297, 258, 240.

3k: procedure C; oil; IR ($CHCl_3$): 2210 (CN);^{1}H-NMR (acetone-d_6): 7.19-7.38 (m, 5H), 7.43 (dd, J= 8.6 and 1.6 Hz, 1H), 7.64 (dd, J=8.6 and 0.6 Hz, 1H), 7.76 (dd, J=1.6 and 0.6 Hz, 1H), 8.26 (s, 1H); MS (m/e): 226, 258, 221, 195; HRMS: found 266.0509 (M^+), calcd for $C_{15}H_{10}N_2OS$ 266.0513.

4b: procedure C; mp 169-170°C dec. (EtOAc); IR (KBr): 2220 (CN); ^{1}H-NMR (acetone-d_6): 4.93 (s, 2H), 7.35 (dd, J=8.7 and 1.9 Hz, 1H), 7.59 (dd, J=8.7 and 0.6 Hz, 1H); 7.64 (dd, J=1.9 and 0.6 Hz, 1H); MS (m/e): 222, 206, 204, 188, 176, 161, 148, 141, 126, 114; HRMS: found 222.0197 (M^+), calcd for $C_{10}H_7N_2O_2Cl$ 222.0196;

4c: procedure C; mp 186-187°C dec. (EtOAc); IR (KBr): 2220 (CN); ^{1}H-NMR (acetone-d_6): 4.93 (s, 2H), 7.48 (dd, J=8.7 and 1.7 Hz, 1H), 7.53 (dd, J=8.7 and 0.4 Hz, 1H), 7.78 (d, J=0.4 Hz, 1H); MS (m/e) 268, 266, 250, 248, 234, 232, 222, 220, 205, 192, 153, 141; 267.9670; Anal. calcd for $C_{10}H_7N_2O_2Br$: C, 44.97; H, 2.64; N, 10.49%; found: C, 45.16; H, 2.62; N, 10.38%.

4d: procedure A,C; mp 160-161°C (EtOAc); IR (KBr): 2220 (CN); ^{1}H-NMR (acetone-d_6): 4.93 (s, 2H), 7.16 (dt, J=9.2 and 2.4 Hz, 1H), 7.35 (ddd, J=9.0 and 2.4 and 0.5 Hz, 1H), 7.58 (ddd, J=9.0 and 4.4 and 0.5 Hz, 1H); ^{13}C-NMR (acetone-d_6): 160.05 (d, J=236.0 Hz), 146.61, 130.82, 124.66 (d, J=10.8 Hz), 115.29, 113.16

(d, J=26.6 Hz), 111.81 (d, J=10.0 Hz), 104.65 (d, J=25.2 Hz), 80.82 (d, J=4.5 Hz), 54.52; DEPT 135°: 113,16(d), 111.81(d), 104.65(d), 54.52 (negative); MS (m/e): 206, 188, 172, 160, 145, 133, 121, 106; Anal. calcd for $C_{10}H_7N_2O_2F$: C, 58.25; H, 3.42; N, 13.59%; found: C, 58.29; H, 3.19; N, 13.29%.

4e: procedure A; mp 186-190°C (EtOH - hexane); IR (KBr): 2220 (CN); ^{1}H-NMR (acetone-d_6): 4.89 (s, 2H), 5.22 (s, 2H), 7.07 (dd, J=8.9 and 2.2 Hz, 1H), 7.21 (d, J=2.2 Hz, 1H), 7.32-7.56 (m, 6H); MS (m/e): 294, 278, 262, 200; Anal calcd for $C_{17}H_{14}N_2O_3$: C, 69.37; H, 4.79; N, 9.52%, found: C, 68.93; H, 4.59; N, 9.57%.

4h: procedure A; mp 173-174°C (EtOH); IR (KBr): 1650 (CO); ^{1}H-NMR ($CDCl_3$): 1.62 (s, 9H), 4.94 (s, 2H), 7.15 (d, J=1.2 Hz, 2H), 7.43 (s, 1H); MS (m/e): 297, 279, 223, 206, 195, 178, 172; HRMS: found 297.0742 (M^+), calcd for $C_{14}H_{14}NO_4Cl$ 297.0746; Anal. calcd: C, 56.47; H, 5.41; N, 4.71%; found: C, 56.00; H, 5.29; N, 4.51%.

4k: procedure C; mp 173-175°C dec. (EtOAc); IR (KBr): 2220 (CN); ^{1}H-NMR (acetone-d_6): 4.95 (s, 2H), 7.22-7.37 (m, 5H), 7.42 (dd, J=8.6 and 1.6 Hz, 1H), 7.62 (dd, J=8.6 and 0.6 Hz, 1H), 7.74 (dd, J=1.6 and 0.6 Hz, 1H); MS (m/e): 296, 294, 280, 278, 262, 249, 235, 222, 190; HRMS: found: 296.0607 (M^+), calcd for $C_{16}H_{12}N_2O_2S$ 296.0620.

4p: procedure C; mp 198-201°C dec. (EtOAc); IR (KBr) 2225 (CN); ^{1}H-NMR (acetone-d_6): 4.96 (s, 2H), 7.33-7.41 (m, 1H), 7.44-7.53 (m, 2H), 7.65-7.67 (m, 2H), 7.71-7.77 (m, 2H), 7.87 (t, J=1.2 Hz, 1H); MS (m/e): 264, 246, 230, 218, 203, 190, 176, 164, HRMS: found 264.0896 (M^+), calcd for $C_{16}H_{12}N_2O_2$ 264.0899.

4r: procedure C; mp 183-185°C dec. (EtOAc); IR (KBr): 2215 (CN), ^{1}H-NMR (acetone-d_6): 3.96 (s, 3H), 4.92 (s, 2H), 6.75 (d, J=8.9 Hz, 1H), 7.85 (d, J=8.9 Hz, 1H); MS (m/e): 219, 201, 184, 172, 156, 143, 129, 116; HRMS: found 219.0645 (M^+), calcd for $C_{10}H_9N_3O_3$ 219.0644.

Reaction with trapping of formaldehyde. **1d** (1 mmol, 206 mg) was dissolved in methanol (3 mL). A stream of N_2 was bubbled through the resulted mixure and then passed by the solution containing NaOH (10 mmol, 0.4 g) and dimedone (10 mmol, 1.4 g) in MeOH (20 mL) while NaOH (1 mL of 1M methanolic solution) was added to the reaction mixture. The reaction was carried out for 1 hr, than worked up as described in procedure A. The solution containing dimedone was poured into aq. HCl, extracted with CH_2Cl_2 (5 x 10 mL), the extract was dried, evaporated and the residue chromatographed using AcOEt - hexane (1:30) mixture as eluent. A few miligrams of formaldehyde-dimedone adduct was isolated. Mp 189°C (EtOH - hexane); MS (m/e): 292, 277, 249, 233, 208, 191, 180, 165, 152, 140, 125; ^{1}H-NMR ($CDCl_3$): 1.05 (s, 12H), 2.29 (s, 8H), 3.16 (s, 2H), 11.55 (s, 2H). The product was identical with an authentic sample obtained by the literature method[9].

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