A Short Preparation of Pyrroloquinoxalinones via a Cascade Reaction of *N*-Aryl-5-alkylamino-2-nitrosoanilines with Methyl 2-Cyanoalkanoates: Unexpected Direction of Nucleophilic Substitution of Hydrogen

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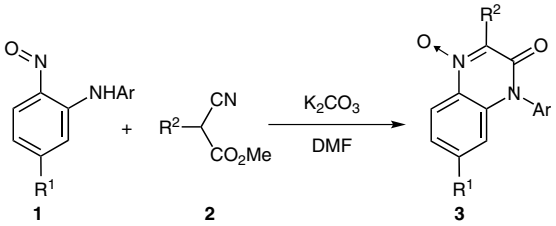
Received: 18.01.2013; Accepted after revision: 17.03.2013

Abstract: *N*-Aryl-2-nitrosoanilines possessing 5-alkylamino groups undergo a bisheteroannulation reaction with anions of 2-cyanoalkanecarboxylates resulting in pyrroloquinoxalinone derivatives. The cascade reaction involves condensation of the cyanoester anions with the nitroso group, unusual nucleophilic substitution of hydrogen in the nitrosoaniline-derived intermediate with the second carbanion molecule, and double intramolecular acylation of the amino functions.

Key words: carbanions, condensation, heterocycles, annulation, nucleophilic aromatic substitution

Cascade reactions have been the subject of intense research during recent years since they make possible the creation of complex molecules from simple and easily available substrates in one-pot processes.[1] Here we report a multistep, three-component cascade reaction leading to bisannulation of *N*-aryl-2-nitrosoanilines, providing a new method for the synthesis of substituted fused oxindole derivatives.

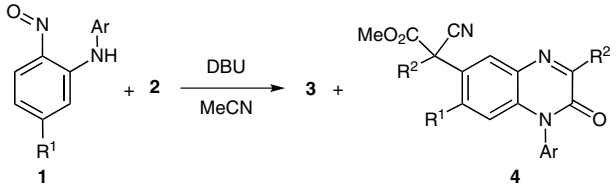
In 2007 we described a simple method for the preparation of *N*-aryl-2-nitrosoanilines via nucleophilic substitution of hydrogen in nitroarenes with anilines in the presence of potassium *tert*-butoxide.[2] Like prevailing S_NHAr reactions described earlier,[3] this reaction proceeds faster than conventional nucleophilic substitution of halogens. We have also demonstrated that *N*-aryl-2-nitrosoanilines are versatile educts in the synthesis of a variety of nitrogen heterocyclic compounds such as phenazines,[2a,4] benzimidazoles,[5] and quinoxalin-2(*H*)-ones.[6] Recently, we found that in the reaction of *N*-aryl-2-nitroso-5-alkylanilines and alkylated cyanoacetic esters **2** a number of quinoxalin-2(*H*)-one *N*-oxides **3** can be obtained (Scheme 1).[7]



Scheme 1

For R = F, Cl, Ph, OMe, and numerous aryl substituents the reaction, carried out in DBU/MeCN or K_2CO_3/DMF systems, proceeded smoothly and effectively and resulted in the formation of the corresponding quinoxalinone oxides **3** in moderate to excellent yields. However, when 5-methoxy-2-nitroso-*N*-(4-methylphenyl)aniline (**1**: R^1 = OMe; Ar = 4-MeC_6H_4) was reacted with two equivalents of methyl 2-cyanobutanoate **2** (R^2 = Et) in DBU/MeCN system, two products in ca. 2:3 ratio were formed (Table 1, entry 1). The more polar product was the expected quinoxalin-2(*H*)-one *N*-oxide **3a** whereas the less polar, according to ^{1}H NMR and MS analyses, was a result of a reaction of one molecule of **1** with two molecules of the cyanoacetic ester. The first one formed a heterocyclic ring, whereas the second was attached to the carbocyclic ring.

Table 1 The Reactions of *N*-Aryl-2-nitrosoanilines with Methyl 2-Cyanobutanoates[8]



Ar = 2,6-$Me_2C_6H_3$

Entry	R^1	R^2	Time (h)	Yield of **3** (%)[a,b]	Yield of **4** (%)[a,b]
1	OMe	Et	5	**3a** 29 (65)	**4a** 45 (0)
2	OMe	*n*-Bu	2	**3b** 33	**4b** 37
3	OMe	*i*-Pr	2.5	**3c** 22 (45)	**4c** 52 (0)
4	OBn	Et	2.5	**3d** 33	**4d** 49

[a] Isolated yield.
[b] The yields reported earlier[7] for the reaction carried out in K_2CO_3/DMF are given in parentheses.

Initially, the assumed structure of this product was **5** (Figure 1), and the way of its formation seemed to be the oxidative nucleophilic substitution of hydrogen (ONSH) in **3a** with an anion of another molecule of cyanoacetic ester

SYNLETT 2013, 24, 0973–0976
Advanced online publication: 10.04.2013
DOI: 10.1055/s-0032-1316903; Art ID: ST-2013-D0062-L

at the expense of the oxygen of the nitrone function. Similar intramolecular oxidative substitution reactions are well known for quinoline *N*-oxide systems, although they are limited to the substitution of hydrogen *ortho* to the *N*-oxide function in the heterocyclic ring.[9]

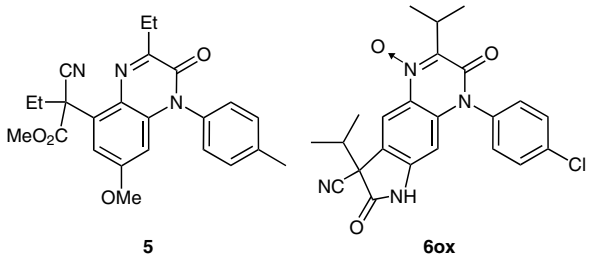


Figure 1

In a separate experiment, however, it was found that **3a** did not react with **2** (R^2 = Et) under the reaction conditions thus, this possibility was unequivocally ruled out. Moreover, ^{1}H NMR, ^{13}C NMR, and ^{15}N NMR spectra revealed that the new product contained the cyanoacetic ester moiety attached *meta* to the formerly present nitroso group (Scheme 2).

A structure of product of type **4** was confirmed by some important NMR observations. A decrease in the ^{15}N NMR shielding of ca. 30 ppm regarding **3** confirms lack in the oxygen atom at the sp^2-hybridized nitrogen atom.[10] Further proof of the structure of **4** is the absence of the $J_{H–H}$ coupling typical for aromatic systems. In case of **3** a $^4J_{H–H}$ coupling is about 2.6 Hz, whereas in case of **4** $J_{H–H}$ is not observed. It means that both aromatic protons (δ = 7.92 and 6.12 ppm) have to be in a *para* arrangement, where $^5J_{H–H}$ is usually less than 1 Hz. Additionally, using results of NOESY 1D measurements both alkyl groups show NOE with ring protons, and only one NOE is observed after irradiation of the methyl protons of the methoxy group (Figure 2). If the substitution occurs *ortho* to the *N*-oxide function irradiation of the protons corresponding to the methyl of the methoxy group should lead to NOE enhancement at both aromatic protons. In this particular case only one effect is observed and that is why the structure **5** with the cyanoacetate substituent in *ortho* position can be excluded.

The unexpected formation of **4** was observed only for 5-alkoxy-substituted 2-nitrosoanilines **1**, while 5-halogen and 5-aryl derivatives reacted with **2** leading exclusively to the quinoxalinones **3**.

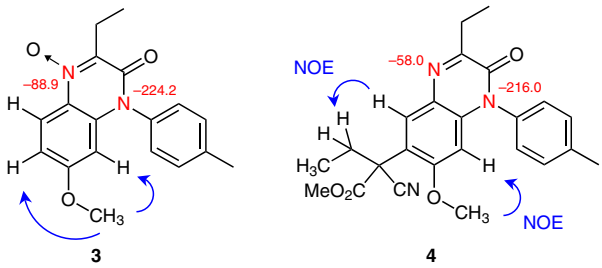


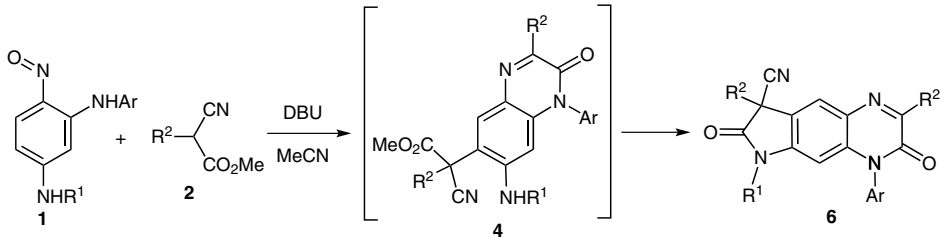
Figure 2

The influence of the alkoxy group seems to be a result of the conjugative electron-donating effect of this substituent.

A similar, and even more pronounced effect could be expected for nitrogen-based substituents such as alkylamino groups, in addition capable of a subsequent in situ cyclization with the adjacent ester function.[11] This expectation was fully confirmed by the reaction of 5-*n*-propylamino-2-nitroso-*N*-(4-methylphenyl)aniline with two equivalents of methyl 2-cyanobutanoate in the presence of an excess of DBU in acetonitrile which delivered pyrroloquinoxalinone **6a** in 67% yield (Scheme 2). The exclusive formation of **6** definitely confirmed that the addition of the second molecule of the nucleophile took place at the *meta* position to the position formerly occupied by the nitroso group.

This multistep, one-pot cascade reaction provides a new method for the synthesis of substituted fused oxindole derivatives. Some further examples of the reaction collected in Table 2 show the scope of the reaction that proceeded with 2-nitrosoanilines possessing variously substituted primary alkylamino group at C-5.[12] The last step of the reaction sequence seems to be sterically tolerant as besides primary alkyl groups, also secondary and even tertiary substituents can be attached to the nitrogen atom without negative influence on the product yield. On the other hand, for at the moment unknown reasons, an unsubstituted amino group gave worse results (Table 2, entry 7) and the desired product **6g** (20%) was accompanied by its 4-*N*-oxide **6ox** (19%).

Also the lower yields of product and more complicated reaction course observed in some other cases (Table 2, entries 6, 8, and 9) could not be rationalized. The reactions



Scheme 2

of **2** with 5-amino-substituted *N*-aryl-2-nitrosoanilines are much slower than with any other 5-substituted substrates, including 5-alkoxy-2-nitrosoanilines.[7] In some cases it took several days to complete the reaction but, nevertheless, the whole cascade was selective and efficient. The most obvious reason is the deactivating effect of the lone pair of the amino group conjugated with the *para*-located nitroso function. The same phenomenon, however, is apparently responsible for subsequent addition of the cyanoacetate anion as well as for the bisannulation.

Table 2 The Cascade Synthesis of Pyrroloquinoxalinones **6**[8,12]

Entry	R^1	Ar	R^2	Time (d)	Yield of **6** (%)[a]
1	*n*-Pr	4-MeC_6H_4	Et	10	**6a** 67
2	*t*-Bu	4-ClC_6H_4	Et	1	**6b** 72
3	*t*-Bu	4-ClC_6H_4	*i*-Pr	14	**6c** 73
4	*n*-Bu	4-ClC_6H_4	Et	5	**6d** 71
5	*n*-Bu	4-$EtOC_6H_4$	Et	5	**6e** 63
6	*n*-Bu	2,6-$Me_2C_6H_3$	Et	8	**6f** 28
7	H	4-ClC_6H_4	*i*-Pr	7	**6g** 20 (19)[b]
8	*t*-Bu	4-ClC_6H_4	Me	1	**6h** 52 (24)[c]
9	Me	4-ClC_6H_4	Me	6	**6i** 32
10	*i*-Pr	4-FC_6H_4	*n*-Bu	3	**6j** 68

[a] Isolated yield.
[b] The yield of **6ox** is given in parentheses
[c] The yield of **3e** (R^1 = N*t*-Bu; R^2 = Me; Ar = 4-ClC_6H_4) is given in parentheses.

On the basis of the tentative mechanism of the reaction of alkylated cyanoacetates, proposed in our previous work,[7] the following pathway for the formation of **4** can be cautiously formulated (Scheme 3). Addition of the carbanion to the nitroso group of **1** leads to intermediate **7**, which eliminates cyanide anion to form nitrone **8**.[13] Mesomeric structures of **8** show possible conjugation of both the arylamino group and the substituent Y, provided the latter is a +M substituent such as OR or NHR. This effect should strongly favor the quinoid structures with partial negative charge on the peripheral carbon atom, promoting a proton transfer from the adjacent nitrogen atom. This process creates the quinoid structure **9**,[14] a crucial intermediate making the 4-position of the initial nitrosoaniline susceptible to the nucleophilic attack. If the conjugation of the nitrone with Y does not exist simple intramolecular cyclization of **8** produces **3**.[15] Multiple intermolecular and/or intramolecular proton transfer leads to the elimination of water from intermediate σ^H-adduct **10** providing **11** which in turn undergoes intramolecular cyclization to **4** then, if Y is an alkylamine group, to **6**.[15]

In conclusion, a new multistep reaction involving intermediate-activated addition of a carbanion *meta* to the position occupied formerly by the activating nitroso group is presented. It provides a simple method for the synthesis of some pyrroloquinoxaline systems from simple starting materials. The scope and limitations as well as a mechanism of the reaction are now under investigation.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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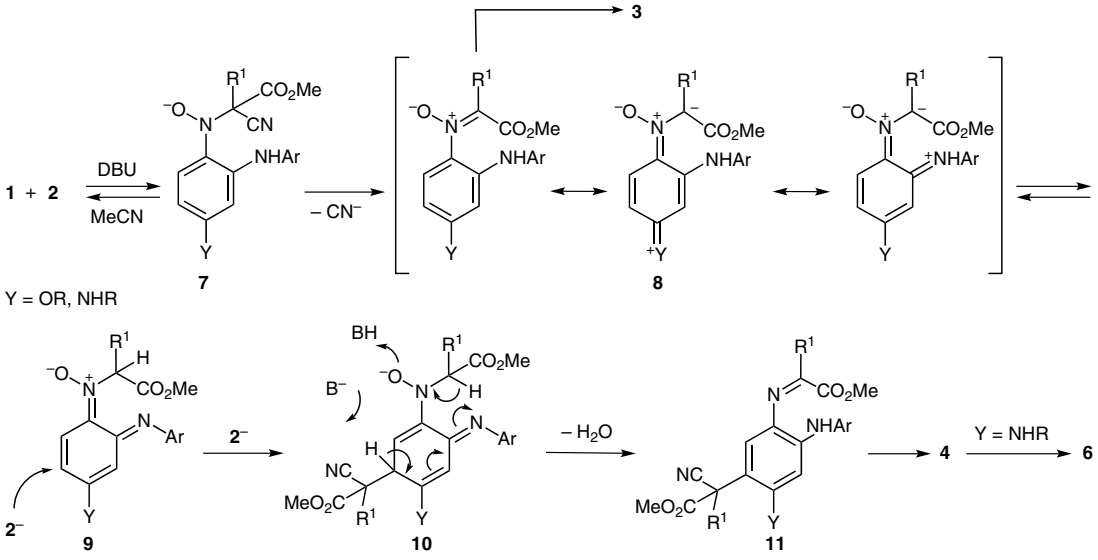

Scheme 3 Proposed mechanism for the bisheteroannulation of *N*-aryl-2-nitrosoanilines with 2-cyanoalkanoates

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(8) **Analytical Data for Representative New Products**
Compound **3e**: yellow crystals; mp 246 °C (dec.; hexane–EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (s, 9 H), 2.54 (s, 3 H), 4.15 (s, 1 H), 5.77 (d, *J* = 2.1 Hz, 1 H), 6.59 (dd, *J* = 9.2, 2.1 Hz, 1 H), 7.26-7.29 (m, 2 H), 7.58–7.61 (m, 2 H), 8.17 (d, *J* = 9.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7, 29.4, 51.4, 97.7, 112.3, 121.5, 122.6, 130.1, 130.5, 134.6, 134.8, 135.4, 135.9, 149.5, 157.2. ESI-MS: *m/z* = 380 $[M + Na]^+$, 358 $[M + H]^+$. ESI-HRMS: *m/z* calcd for $C_{19}H_{21}N_3O_2{}^{35}Cl$ $[M + H]^+$: 358.1322; found: 358.1234.
Compound **4a**: white crystals; mp 179–180 °C (hexane–EtOAc). IR (KBr): 2236 (CN), 1755, 1672, 1621 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.4 Hz, 3 H), 1.35 (t, *J* = 7.4 Hz, 3 H), 2.38–2.45 (m, 2 H), 2.46 (s, 3 H), 2.96 (q, *J* = 7.4 Hz, 2 H), 3.64 (s, 3 H), 3.78 (s, 3 H), 6.11 (s, 1 H), 7.14–7.18 (m, 1 H), 7.38–7.43 (m, 1 H), 7.92 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.7, 10.8, 21.3, 27.1, 28.5, 50.0, 54.5, 56.0, 97.7, 118.1, 120.6, 126.9, 127.7, 127.8, 128.6, 130.9, 131.0, 132.9, 135.8, 139.7, 154.8, 156.9, 160.4, 168.7. MS (EI): *m/z* 420 (16), 419 (57), 390 (10), 361 (27), 360 (100), 333 (12). HRMS (EI): *m/z* calcd for $C_{24}H_{25}N_3O_4$: 419.1845; found: 419.1841.
Compound **6b**: yellow crystals; mp 148–151 °C (hexane–EtOAc). IR (KBr): 2241 (CN), 1731, 1670, 1627 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.4 Hz, 3 H), 1.36 (t, *J* = 7.4 Hz, 3 H), 1.51 (s, 9 H), 2.18–2.30 (m, 2 H), 2.93–3.02 (m, 2 H), 6.51 (s, 1 H), 7.25–7.29 (m, 2 H), 7.61–7.65 (m, 2 H), 7.85 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.0, 10.5, 27.0, 28.7, 31.6, 47.2, 59.3, 99.9, 117.0, 121.6, 124.9, 128.3, 129.5, 129.6, 130.6, 130.7, 134.2, 135.0, 135.8, 144.1, 154.4, 160.9, 170.9. MS (EI): *m/z* (%) = 450 (16), 449 (17), 448 (34), 395 (15), 394 (47), 393 (40), 392 (100), 365 (17), 364 (19), 363 (27), 337 (21), 336 (20), 335 (43). HRMS (EI): *m/z* calcd for $C_{25}H_{25}N_4O_2Cl$: 448.1666; found: 448.1687.
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(12) **General Procedure for the Synthesis of Pyrroloquinoxalinones 6a–j**
5-Amino-*N*-aryl-2-nitrosoaniline (0.5 mmol) and methyl 2-cyanoalkanoate (1.1 mmol) were dissolved in dry MeCN (5 mL). DBU (0.4 mL, 2.68 mmol) was added in one portion, and the mixture was stirred at r.t. for the time specified in Table 2. The mixture was poured into sat. NH_4Cl (10 mL) and H_2O (10 mL), extracted with EtOAc (3 × 20 mL), dried with Na_2SO_4, and the crude product was chromatographed.
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