Regioselective heteroannelation in quinazolin-4-one derivatives. Synthesis of 2,5-dioxo-1,2,4,5-tetrahydropyrrolo[1,2-*a*]quinazoline-3-carbonitriles

Yulian M. Volovenko and Elizaveta V. Resnyanskaya*

Department of Chemistry, T. G. Shevchenko Kiev National University, 01033 Kiev, Ukraine. E-mail: atver@mail.univ.kiev.ua

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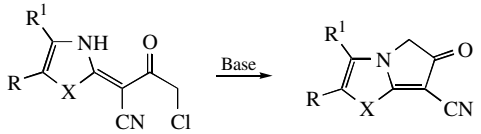
The regioselective heteroannelation in 2-(4-oxo-3,4-dihydro-2-quinazolinyl)acetonitriles to form 2,5-dioxo-1,2,4,5-tetrahydropyrrolo-[1,2-*a*]quinazoline-3-carbonitriles is reported.

Previously,[1–3] it was found that the intramolecular alkylation of the nitrogen atom in 4-chloro-2-hetaryl-3-oxobutanenitriles **1** leads to pyrrolo annelated heterocycles **2** (Scheme 1). However, in all cases, there was no alternative direction for alkylation in **1** because the X atom could not be alkylated in principle or because the heterocyclic moiety was symmetrical like that in benzimidazole (X = NH, RR^1 = benzo).

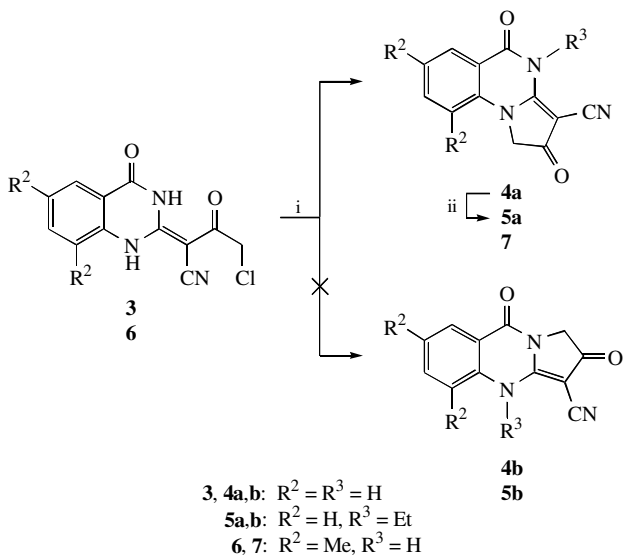


1 **2**

Scheme 1

4-Chloro-3-oxo-2-(4-oxo-1,2,4,5-tetrahydro-2-quinazolinylidene)-butanenitrile **3** was prepared in our laboratory by the acylation of 2-(4-oxo-3,4-dihydro-2-quinazolinyl)acetonitrile with chloroacetyl chloride.[4] On the contrary to butanenitriles **1**, the intramolecular alkylation of **3** can occur in two ways (Scheme 2): with the participation of either N1 of the quinazoline moiety, yielding 2,5-dioxo-1,2,4,5-tetrahydropyrrolo[1,2-*a*]quinazoline-3-carbonitrile **4a**, or N3, leading to isomeric 2,5-dioxo-2,3,5,10-tetrahydropyrrolo[2,1-*b*]quinazoline-1-carbonitrile **4b**. The alkylation of a quinazolin-4-one moiety is known to lead in most cases to the products of N3 alkylation.[5–8] However, sometimes N1 alkylation was observed[9–11] or even the mixtures of N1 and N3 alkylated compounds were obtained.[12–14] Thus, the reaction pathway in this case cannot be predicted based on published data.

The treatment of compound **3** with Et_3N in dioxane† resulted in the formation of a compound containing no chlorine, to which the structure of **4a** or **4b** might be assigned. Its ^{1}H NMR spectrum shows a two-proton singlet of a methylene group at



3, **4a**,**b**: $R^2 = R^3 = H$
5a,**b**: $R^2 = H$, $R^3 = Et$
6, **7**: $R^2 = Me$, $R^3 = H$

Scheme 2 *Reagents and conditions*: i, Et_3N, dioxane; ii, EtI, K_2CO_3, DMSO.

δ 4.49 ppm and four one-proton signals of aromatic protons. Therefore, the choice between the structures of **4a** and **4b** cannot be made based only on these data.

To elucidate the structure of the compound obtained, a NOESY experiment should be carried out. However, to make the choice more clear, we would like to have a compound, giving alternative NOEs for each structure. For this purpose, compound **4** was alkylated with EtI under standard conditions‡ (K_2CO_3, DMSO) to yield an N-ethyl derivative,§ to which the structure of **5a** or **5b** could be assigned.

The NOESY experiment performed with the ethyl derivative revealed positive NOE between the protons of the methylene group in the pyrroline ring at δ 4.59 ppm and the aromatic proton at δ 7.37 ppm, whereas the methylene of ethyl group showed no correlation, except with methyl itself. These data confirm undoubtedly the structure of **5a** for the ethylated compound and exclude the structure of **5b**. Hence, the structure of compound **4** should be assigned as **4a**. Therefore, intramolecular alkylation in butanenitrile **3** regioselectively occurs at N1 of the quinazoline moiety.

To change the site of intramolecular alkylation, it seemed reasonable to create steric hindrances near N1. This was achieved by preparation of 4-chloro-3-oxo-2-(6,8-dimethyl-4-oxo-1,2,4,5-tetrahydro-2-quinazolinylidene)butanenitrile **6**¶ from 2-(6,8-dimethyl-4-oxo-3,4-dihydro-2-quinazolinyl)acetonitrile.[15] Nevertheless, the heating of butanenitrile **6** in dioxane in the presence of Et_3N yielded only one product, 7,9-dimethyl-2,5-dioxo-1,2,4,5-tetrahydropyrrolo[1,2-*a*]quinazoline-3-carbonitrile **7**.†† In the ^{1}H NMR spectrum of compound **7**, a two-proton singlet of the

† *2,5-Dioxo-1,2,4,5-tetrahydropyrrolo[1,2-*a*]quinazoline-3-carbonitrile* **4a**. To a hot suspension of 0.78 g (0.003 mol) of 4-chloro-3-oxo-2-(4-oxo-1,2,4,5-tetrahydro-2-quinazolinylidene)butanenitrile[4] **3** in 5 ml of absolute dioxane 0.5 ml (0.0036 mol) of Et_3N was added. The resulted solution was refluxed for 1 h. After cooling the formed precipitate was filtered off and washed with water and MeOH to yield 0.54 g (81%) of **4a**; mp > 300 °C (dioxane). ^{1}H NMR (300 MHz, [$^2H_6$]DMSO) δ: 4.49 (s, 2H, 1-H), 7.37 (d, 1H, 9-H, *J* 8.0 Hz), 7.45 (t, 1H, 7-H, *J* 8.0 Hz), 7.83 (t, 1H, 8-H, *J* 8.0 Hz), 8.02 (d, 1H, 6-H, *J* 8.0 Hz), 13.3 (br. s, 1H, NH). ^{13}C NMR (100 MHz) δ: 53.58 (1-C), 71.25 (3-C), 113.13 (CN), 114.99 (9-C), 115.81 (5a-C), 124.24 (7-C), 127.58 (6-C), 135.94 (8-C), 138.26 (9a-C), 159.19 (3a-C), 160.97 (5-C), 188.47 (2-C). IR (KBr, ν/cm^{-1}): 3100 (NH), 2203 (CN), 1660 (CO). Found (%): C, 64.15; H, 3.01; N, 18.88. Calc. for $C_{12}H_7N_3O_2$ (%): C, 64.00; H, 3.13; N, 18.66.

‡ *4-Ethyl-2,5-dioxo-1,2,4,5-tetrahydropyrrolo[1,2-*a*]quinazoline-3-carbonitrile* **5a**. Ethyl iodide (0.5 ml, 0.6 mol) was added to a mixture of 0.67 g (0.003 mol) of compound **4a** and 0.7 g (0.005 mol) of K_2CO_3 in 6 ml of DMSO. The resulted mixture was allowed to stand at 50–60 °C for 12 h and then poured into water. The precipitate formed was filtered off to give 0.45 g (62%) of **5a**, mp 257 °C (dioxane). ^{1}H NMR (300 MHz, [$^2H_6$]DMSO) δ: 1.32 (t, 3H, *Me*CH_2, *J* 7.0 Hz), 4.26 (q, 2H, MeCH_2, *J* 7.0 Hz), 4.59 (s, 2H, 1-H), 7.37 (dd, 1H, 9-H, J_1 8.5 Hz, J_2 2.0 Hz), 7.45 (td, 1H, 7-H, J_1 8.5 Hz, J_2 2.0 Hz), 7.87 (td, 1H, 8-H, J_1 8.5 Hz, J_2 2.0 Hz), 8.11 (dd, 1H, 6-H, J_1 8.5 Hz, J_2 2.0 Hz). ^{13}C NMR (100 MHz) δ: 13.88 (Me), 39.79 (CH_2Me), 53.95 (1-C), 72.65 (3-C), 114.13 (CN), 114.75 (5a-C), 115.48 (9-C), 124.89 (7-C), 128.34 (6-C), 136.57 (8-C), 137.81 (9a-C), 158.28 (3a-C), 160.48 (5-C), 189.21 (2-C). IR (KBr, ν/cm^{-1}): 2986 (CH), 2216 (CN), 1709 (CO). Found (%): C, 66.52; H, 4.21; N, 16.76. Calc. for $C_{14}H_{11}N_3O_2$ (%): C, 66.40; H, 4.38; N, 16.59.

§ N- rather than O-alkylation was confirmed by a comparison of the ^{13}C NMR spectra of compounds **4a** and **5a**, which revealed the presence of two carbonyl groups in both cases.

methylene group at 4.92 ppm and two three-proton singlets of methyl groups at 2.32 and 2.63 ppm were observed. The site of intramolecular alkylation in **6** was confirmed by the NOESY experiment. It indicated positive NOE between the protons of methylene and methyl groups at 4.92 and 2.63 ppm, respectively, thus proving the structure of **7** for the compound. Hence, steric hindrances around the N1 atom of a quinazoline moiety does not crucially influence the reaction pathway.

To summarise, regioselective intramolecular alkylation in quinazoline-4-one at N1 atom has been reported. The influence of the steric arrangement of N1 on the reaction pathway has been examined. Moreover, the reaction can serve as a convenient method for the synthesis of 2,5-dioxo-1,2,4,5-tetrahydropyrrolo[1,2-*a*]quinazoline-3-carbonitriles. Note that this is a rare example among all known methods for the synthesis of a pyrrolo[1,2-*a*]quinazoline ring system,[16–22] when the last step is the formation of the C(1)–N(10) bond.

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¶ *4-Chloro-3-oxo-2-(6,8-dimethyl-4-oxo-1,2,4,5-tetrahydro-2-quinazolinylidene)butanenitrile* **6**. Chloroacetyl chloride (0.8 ml, 0.01 mol) was added with caution to a solution of 2-(6,8-dimethyl-4-oxo-3,4-dihydro-2-quinazolinyl)acetonitrile[15] (2 g, 0.01 mol) and pyridine (0.9 ml, 0.012 mol) in 10 ml of dioxane. The mixture was heated on a water bath for 3 h. After cooling, the precipitate was filtered off and washed with water to yield 2.2 g of **6** (78%), mp 292 °C (dioxane). ^{1}H NMR (300 MHz, [$^2H_6$]DMSO): 2.38 (s, 3H, Me), 2.41 (s, 3H, Me), 4.56 (s, 2H, CH_2), 7.57 (s, 1H, 7′-H), 7.68 (s, 1H, 5′-H), 12.5 (br. s, 2H, NH). IR (KBr, ν/cm^{-1}): 3150 (NH), 2189 (CN), 1709 (CO). Found (%): C, 58.16; H, 4.23; N, 14.76; Cl, 12.11. Calc. for $C_{14}H_{12}ClN_3O_2$ (%): C, 58.04; H, 4.17; N, 14.50; Cl, 12.24.

†† *7,9-Dimethyl-2,5-dioxo-1,2,4,5-tetrahydropyrrolo[1,2-*a*]quinazoline-3-carbonitrile* **7** was obtained starting from butanenitrile **6** according to the procedure described for compound **4a**. Yield 75%, mp > 300 °C (dioxane). ^{1}H NMR (300 MHz, [$^2H_6$]DMSO) δ: 2.32 (s, 3H, Me), 2.63 (s, 3H, Me), 4.92 (s, 2H, 1-H), 7.45 (s, 1H, 8-H), 7.74 (s, 1H, 6-H), 13.3 (br. s, 1H, NH). ^{13}C NMR (100 MHz) δ: 19.83 (Me), 20.92 (Me), 58.33 (1-C), 70.63 (3-C), 113.02 (CN), 117.09 (5a-C), 125.24 (9-C), 125.66 (6-C), 133.86 (7-C), 135.58 (9a-C), 140.56 (8-C), 159.02 (3a-C), 161.16 (5-C), 188.44 (2-C). IR (KBr, ν/cm^{-1}): 3170 (NH), 2203 (CN), 1680 (CO). Found (%): C, 66.62; H, 4.21; N, 16.81. Calc. for $C_{14}H_{11}N_3O_2$ (%): C, 66.40; H, 4.38; N, 16.59.

References

1 F. S. Babichev and Yu. M. Volovenko, *Khim. Geterotsikl. Soedin*., 1976, 1147 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1976, **12**, 949].
2 Yu. M. Volovenko, T. V. Shokol, A. S. Merkulov and F. S. Babichev, *Ukr. Khim. Zh. (Russ. Ed.)*, 1993, **59**, 55.
3 Yu. M. Volovenko, T. A. Volovnenko and A. V. Tverdokhlebov, *Khim. Geterotsikl. Soedin*., 2001, 1101 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 2001, **37**, 1011].
4 Yu. M. Volovenko, G. G. Dubinina, T. V. Shokol and F. S. Babichev, *Dopov. Akad. Nauk Ukr. RSR, Ser. B*, 1994, **10**, 126.
5 B. Baker, M. Querry, A. Kadish and J. Williams, *J. Org. Chem.*, 1952, **17**, 35.
6 F. Georgescu, E. I. Georgescu, M. T. Caproiu and C. Draghici, *Rev. Roum. Chim*., 1999, **44**, 341.
7 S. Enomoto, K. Sato and M. Sugihara, *Jpn. Pat.*, 7533076, 1975 (*Chem. Abstr*., 1976, **85**, 46733z).
8 C. O. Usifoh and G. Scriba, *Arch. Pharm*., 2000, **333** (8), 261.
9 P. Wippich, M. Gutschow and S. Leistner, *Synthesis*, 2000, **5**, 714.
10 K. K. Jain, S. P. Rout and H. K. Pujari, *Indian J. Chem*., 1990, **29**, 379.
11 H. K. Gakhar, S. Kiran and S. Gupta, *J. Indian Chem. Soc*., 1982, **59**, 666.
12 J. Reisch, M. Iding and C. O. Usifoh, *J. Heterocycl. Chem*., 1993, **30**, 1117.
13 M. A. Ashirmatov, B. A. Urakov and Kh. M. Shakhidoyatov, *Khim. Geterotsikl. Soedin*., 1996, **6**, 821 (in Russian).
14 G. Fantin, M. Fogagnolo, A. Medici and P. Pedrini, *J. Org. Chem*., 1993, **58**, 741.
15 Yu. M. Volovenko, O. V. Khilya, T. A. Volovnenko and T. V. Shokol, *Khim. Geterotsikl. Soedin*., 2002, 350 (in Russian).
16 T. Kurihara and T. Tani, *J. Heterocycl. Chem*., 1980, **17**, 945.
17 K. Osaki, Y. Yamada and T. Oine, *Chem. Pharm. Bull*., 1983, **31**, 2234.
18 H. G. Hehning and H. Haber, *Monatsch. Chem*., 1988, **119**, 1405.
19 M. Suesse, *Ger. (East) Pat.*, 142333, C07D, 1980 (*Chem. Abstr*., 1981, **94**, 175162x).
20 F. S. Babichev and Yu. M. Volovenko, *Ukr. Khim. Zh. (Russ. Ed.)*, 1977, **43**, 711.
21 E. V. Resnyanskaya, T. V. Shokol, Yu. M. Volovenko and A. V. Tverdokhlebov, *Khim. Geterotsikl. Soedin*., 1999, 1412 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1999, **35**, 1230].
22 Yu. M. Volovenko, E. V. Resnyanskaya and A. V. Tverdokhlebov, *Khim. Geterotsikl. Soedin*., 2002, 360 (in Russian).

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