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Interaction of polyfluorinated 2-chloroquinolines with ammonia

Alexandrina D. Skolyapova [a], Galina A. Selivanova [a, *], Evgeny V. Tretyakov [a], Tatjana F. Bogdanova [a], Lyudmila N. Shchegoleva [a], Irina Yu. Bagryanskaya [a, b], Larisa Yu. Gurskaya [a], Vitalij D. Shteingarts [a, 1]

[a] N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, 9 Ac. Lavrentiev Avenue, Novosibirsk, 630090, Russia
[b] Novosibirsk State University, 2 Pirogova Str., Novosibirsk, 630090, Russia

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ABSTRACT

We have studied the interaction of polyfluorinated (in the benzene moiety) 2-chloroquinolines with liquid and aqueous ammonia as an approach to the synthesis of halogen-containing aminoquinolines. 5,7-Difluoro-, 5,6,8-trifluoro-, and 5,7,8-trifluoro-2-chloroquinolines mostly form products of substitution of the Cl atom, whereas 5,7-difluoro-2,6-dichloroquinoline, 5,6,7,8-tetrafluoro-, and 6,7-difluoro-2-chloroquinolines yield products of substitution of an F atom at various positions. The replacement of liquid ammonia with aqueous causes an increase in the proportion of the products of amino-dechlorination relative to the products of aminodefluorination. For 2-chloro-6,8-difluoroquinoline this replacement leads to 2-amino-6,8-difluoroquinoline as the main product instead of the 8-amino-derivative. Activation energy values estimated by DFT calculations for the reactions in question agree with the reaction regioselectivity observed experimentally.

1. Introduction

Compounds containing the quinoline core possess a broad range of biological activities and are widely used in pharmacology.[1] Fluorinated quinolines are of special interest,[1,2] because the presence of several fluorine atoms in a quinolone – in addition to its possible specific effects on bioactivity[3] – makes functionalization of the benzene moiety considerably easier and potentially more diverse.[4] Substituted quinolines are also known to easily form chelate complexes with Zn and Al cations; these complexes show enhanced fluorescence as compared with the quinolines themselves.[5] The use of fluorinated quinolines may shed light on the fundamental relationship between the number and location of fluorine atoms in the benzene ring, and on the complexation reaction with metal ions as well as physical properties of the metal complexes.

Until recently, the polyfluorinated quinolines were a group of compounds that were difficult to obtain. Fortunately, convenient methods of selective hydrodehalogenation of perfluoroarenes (and particularly *ortho*-hydrodefluorination of readily available *N*-acetylpolyfluoroarylamines using zinc in aqueous ammonia) were developed recently.[6] The same method was also applied to selective hydrodechlorination of polyfluorochloroarylamines without their prior transformation into *N*-acetyl derivatives.[7] This approach provided a relatively simple route for the synthesis of a broad family of 2-chloroquinolines polyfluorinated on the benzene moiety.[8]

The amino group is one of the functional groups that is promising in terms of the development of methods for more profound functionalization of polyfluorinated quinolines. This can explain the emergence of relatively novel studies devoted to the development of methods for introduction of an amino group into polyfluoroquinolines. In particular, the interaction of polyfluorinated quinolines with uncharged nitrogen-centered nucleophiles was shown to lead to substitution of a fluorine atom in the benzene ring,[9] whereas charged nitrogen-centered nucleophiles are added to the pyridine moiety.[10] The reaction of the perfluorinated quinoline with benzylamine was found to yield substitution products of the fluorine atom at position 2 or 4.[11] Regarding previous research on fluorinated quinolines containing a Cl atom at position 2, in the reactions with nitrogen-centered nucleophiles (ethylamine, acetamide, and piperazine) only monofluoroderivatives were studied. They undergo aminodechlorination exclusively, forming the corresponding 2-aminoquinolines.[12] With 2-chloroquinolines

* Corresponding author.
E-mail address: galseliv@nioch.nsc.ru (G.A. Selivanova).
[1] Deceased 12.02.2015.

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containing two or more fluorine atoms in the benzene ring, the ratio of the rates of substitution of fluorine and chlorine atoms may start favoring the process of aminodefluorination, which can lead to useful (in terms of synthesis) functionalization of the benzene moiety. Here we studied the interaction of 5,6,7,8-tetrafluoro- (**1a**), 5,6,7-trifluoro- (**1b**), 5,7,8-trifluoro- (**1c**), 5,7-difluoro- (**1d**), 6,7-difluoro- (**1e**), and 6,8-difluoro- (**1f**) 2-chloroquinolines and 2,6-dichloro-5,7-difluoroquinoline (**1g**) with aqueous or liquid ammonia in order to determine the dependence of the orientation of aminodehalogenation on reaction conditions and on the number and positions of fluorine atoms in the substrate. Starting materials **1a-1g** were synthesized by literature methods,[8] from polyfluoroanilines obtained as described in supporting information. The new 3,4-difluoroanilide of cinnamic acid (**1ea**), 6,7-difluoroquinolin-2-one (**1eb**), 4-chloro-3,5-difluoroanilide of cinnamic acid (**1ga**), 6-chloro-5,7-difluoroquinolin-2-one (**1gb**), 6,8-difluoroquinolin-2-one (**1fb**), and the known 2,4-difluoroanilide of cinnamic acid (**1fa**) described in the experimental section were obtained as reaction intermediates in the synthesis of **1e-1g**.

2. Result and discussion

2.1. Reactions with liquid ammonia

The reaction of quinoline **1a** with liquid ammonia at 70 °C in a steel autoclave leads to a substitution of both the chlorine atom and fluorine atom resulting in formation of 2-amino-5,6,7,8-tetrafluoroquinoline (**2**), 6-amino-2-chloro-5,7,8-trifluoro- (**3**), and 7-amino-2-chloro-5,6,8-trifluoroquinoline (**4**) in the ratio 1:1:12, respectively (Table 1, entry 1).

Aminoquinolines **3** (5%) and **4** (65%) are new compounds. Quinoline **2** (5%) was obtained earlier via the interaction of 5,6,7,8-tetrafluoroquinoline with potassium amide (11%).[10]

The predominance of aminodefluorination over aminodechlorination, characterized by $\Omega \approx 0.1$, where Ω is a molar ratio of aminodechlorination product to aminodefluorination products, points to a stronger activating effect of the four fluorine atoms relative to the nitrogen of the heterocycle. Aminodefluorination of **1a** is realized at position 7 (6-NH_2/7-NH_2 ≈ 1:11) and is consistent with orientation of the substitution of a fluorine atom in 5,6,7,8-tetrafluoroquinoline under the influence of either liquid or aqueous ammonia (6-NH_2/7-NH_2 = 1:5 and 1:4 respectively).[9] The observed regioselectivity is the result, on the one hand, of the influence of atoms F(5) and F(8), which deactivate each other but at the same time activate atoms F(6) and F(7), and on the other hand, of the −M-effect of the N atom of the heterocycle.

Assuming that the presence of *para*-arranged fluorine atoms may determine the direction of aminodehalogenation, we introduced into the reaction compounds **1b** and **1c** lacking a fluorine atom either at position 6 or 7. In both cases, products of aminodechlorination [2-amino-5,6,8-trifluoroquinoline (**5**) and 2-amino-5,7,8-trifluoroquinoline (**7**), respectively] turn out to be the main products, whereas the products of aminodefluorination [6-amino-2-chloro-5,8-difluoroquinoline (**6**) and 7-amino-2-chloro-5,8-difluoroquinoline (**8**)] are formed in small amounts: for **1b** Ω ≈ 49.0, for **1c** Ω ≈ 11.2 (Table 1, entries 2 and 3). It should be noted that orientation of aminodefluorination **1b** and **1c** is in agreement with the results of ammonolysis of 5,6,8-trifluoro- and 5,7,8-trifluoroquinolines by aqueous ammonia.[9]

Only quinoline **7** (55%) was previously known and obtained with the yield of 12% by the interaction of 5,7,8-trifluoroquinoline with potassium amide.[10] The other aminoquinolines, **5** (70%), and **8** (11%), were obtained for the first time. Ammonolysis of trifluoroquinolines **1b** and **1c** by liquid ammonia is somewhat more difficult than that of tetrafluoroquinoline **1a** but markedly easier than ammonolysis of difluoroquinoline **1e**, where aminodefluorination again starts to dominate (Table 1, compare entries 1–3 with 4). Nonetheless, the interaction of **1e** with liquid ammonia produced 2-amino-6,7-difluoroquinoline (**9**), 6-amino-2-chloro-7-fluoroquinoline (**10**), and 7-amino-2-chloro-6-fluoroquinoline (**11**) in the ratio 4:1:15 (Ω = 0.2) with yields 14%, 4%, and 65%, respectively (Table 1, entry 4).

That is, two *ortho*-arranged fluorine atoms at positions 6 and 7 turned out to be sufficient for predominance of aminodefluorination, and the presence of *para*-arranged fluorine atoms was not crucial for the direction of the reaction.

The reaction of difluoroquinoline **1d** with liquid ammonia yields 2-amino-5,7-difluoroquinoline (**12**) mostly, and two isomeric products of aminodefluorination: 5-amino-2-chloro-7-fluoroquinoline (**13**) and 7-amino-2-chloro-5-fluoroquinoline (**14**) in the ratio 15:4:1, Ω = 2.9 (Table 1, entry 5). Therefore, in the case of **1d**, the aminodechlorination is preferred due to the inductive effect of the nitrogen atom of the heterocycle. The formation of quinoline **12** (as well as isomeric 4-amino-5,7-difluoroquinoline) was observed previously in a reaction of 5,7-difluoroquinoline with potassium amide, but compound **12** was not isolated.[10] Quinolines **12**–**14** were obtained with yields of 49%, 11%, and 3%, respectively. Regioselectivity of aminodefluorination of **1d** at position 5 corresponded closely to that for the interaction of 5,7-difluoroquinoline with aqueous ammonia.[9]

Ammonolysis of **1g** by liquid ammonia also leads to three products: 2-amino-6-chloro-5,7-difluoroquinoline (**15**), isomeric 5-amino-2,6-dichloro-7-fluoroquinoline (**16**), and 7-amino-2,6-dichloro-5-fluoroquinoline (**17**) in the ratio 1:7:1, Ω = 0.1 (Table 1, entry 6). Novel aminoquinolines **15**–**17** were obtained with yields 7%, 53%, and 11%, respectively. Therefore, introduction of a chlorine atom at position 6 leads to noticeable activation of the benzene cycle in the reaction with ammonia in comparison with its structural analog **1d** and allows for introduction of an amino group mostly at position 5.

Like quinoline **1d**, difluoroquinoline **1f** contains *meta*-arranged to each other fluorine atoms, but its ammonolysis by liquid ammonia at 90 °C leads to 2-amino-6,8-difluoroquinoline (**18**) and 8-amino-2-chloro-6-fluoroquinoline (**19**), with predominance of the product of aminodefluorination, Ω = 0.3 (Table 1, entry 7). Quinolines **18** and **19** are isolated with the yield 20% and 59%, respectively. Orientation of aminodefluorination of **1f** is consistent with the orientation of methoxydefluorination of 6,8-difluoroquinoline by means of sodium methylate, where only the substitution of the fluorine atom at position 8 was observed.[13] In both compounds, position 8 is activated by both the -I effect of the nitrogen atom of the heterocycle and the *meta*-atom of fluorine.

Ammonolysis of **1f** at 150 °C, i.e., at the temperature above critical for ammonia (T_{crit} ≈ 132 °C),[14] leads to formation of compound **19**, also as the main product (Table 1, entry 8), albeit at a greater value of Ω = 0.5. ^{19}F NMR spectroscopy and gas chromatography with mass spectrometry (GC-MS) detected trace amounts of 2,8-diamino-6-fluoroquinoline (**20**) in the reaction mixture. Thus, elevation of the temperature of the reaction above critical does not change the direction of ammonolysis but noticeably affects the ratio of products.

2.2. Reactions with aqueous ammonia

In aqueous ammonia, ammonolysis requires somewhat more rigid reaction conditions than in liquid ammonia (a dipolar aprotic solvent) because the molecules of ammonia in an aqueous solution are solvated and are also partially in the state of the conjugated acid NH_4^+, and their nucleophilicity is lower. For example, to achieve high conversion, we had to keep **1a** at 85 °C for 24 h. Meanwhile,