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ONE-POT SYNTHESIS OF 3-(2-CYANOPHENYL)-QUINAZOLIN-4(3H)-ONE

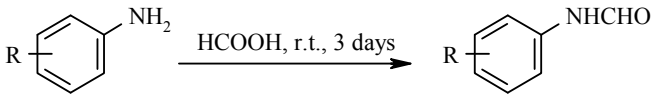
Anthranilonitrile reacting with formic acid at room temperature for three days gave 64 % of 3-(2-cyanophenyl)quinazolin-4(3H)-one. Under similar conditions anthranilic acid, 4-nitroaniline and 2,5-dichloroaniline were N-formylated in good yields.

Keywords: anthranilonitrile, 3-(2-cyanophenyl)quinazolin-4(3H)-one, N-formylation.

The title quinazolinone has been obtained for the first time quite recently [1] by a two-step reaction involving heating of anthranilonitrile (**1**) with an excess of formic acid in boiling toluene (N-formylation) followed by a treatment of the crude product with thionyl chloride and additional amount of **1**. The yield of 3-(2-cyanophenyl)quinazolin-4(3H)-one (**2**) was very low (9 %).

Recently we have found out that, in contrast to rather drastic conditions commonly used for N-formylation of anilines [2–4], anthranilic acid, 4-nitroaniline and 2,5-dichloroaniline react with formic acid at room temperature. The appropriate N-formyl derivatives precipitate from the solutions in good yields as crystalline solids (Scheme 1). This result is rather unexpected considering low pK_a values of the anilines.

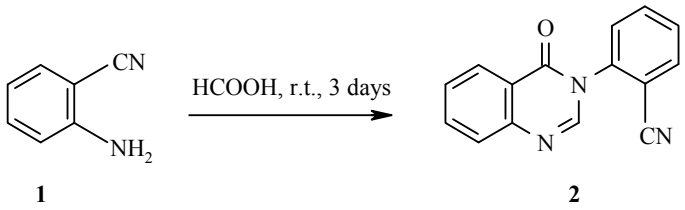
Scheme 1



R = 2-COOH, 4-NO_2, 2,5-di-Cl

Analyzing the surprisingly low yield of quinazolinone **2** reported [1], we repeated the first stage of the procedure [1] and found out that crude N-formylanthranilonitrile (**3** – postulated in [1] as an intermediate) under the Babayev's conditions is obtained in moderate yield (40 %), Moreover, it is contaminated by several impurities. Thus, we assumed that an improvement in N-formylation of **1,** using our conditions for formylation of anilines, would lead to a substantial increase in the total yield of **2**. Unexpectedly, **1** dissolved in an excess of anhydrous formic acid and left for three days at 20–22 °C afforded the title quinazolinone **2** in the yield of 64 % (Scheme 2).

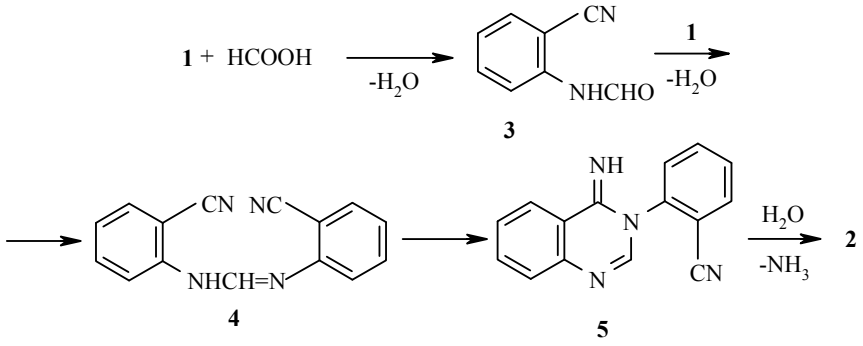
Scheme 2



1 **2**

We assume the formation of **2** from **1** and formic acid occurs according to the Scheme 3. Partial N-formylation of **1** leading to **3** is followed by the condensation of unconverted **1** with **3** to give the amidine **4** that undergoes intramolecular cyclization to 4-iminoquinazolinone (**5**). The compound **5** is hydrolyzed to quinazolinone **2** by water formed in the condensations or present in formic acid.

Scheme 3



An alternative route of **2** formation from **1** and formic acid, *via* 2-amino-N-(2-cyanophenyl)benzamidine and its cyclization followed by hydrolysis, can be ruled out considering our recent report [5] on the easy and efficient conversion of 2-amino-N-arylbenzamidines into respective 4-arylaminoquinazolines in formic acid solution.

Attempts to shorten the reaction time of our **2** synthesis (no toluene added) by the temperature increase were unsuccessful; yields of **2** dropped below 40 % though the post-reaction mixtures contained neither unconverted **1** nor **3**. Comparison of our latter results with those of the first stage of Babaev's method (no formation of **2**) clearly points out to the toluene presence in the reaction medium as an important factor affecting the product structures. The mixture of anthranilonitrile, formic acid and toluene used in [1] is not homogeneous hindering contacts between **1** and **3**, necessary for the formation of **2**.

EXPERIMENTAL

Reaction of anilines with formic acid (general procedure). A solution of aniline derivative (0.01 mole) in 98–100 % formic acid (5 ml) was left for three days at room temperature (ca. 20 °C). Solids forming from anthranilic acid, 4-nitroaniline and 2,5-dichloroaniline were collected, washed with a little volume of formic acid, air dried and recrystallized then from a suitable solvent.

N-Formylanthranilic acid, 67.5 %, white crystals (ethyl acetate), m.p. 166–167 °C (167 °C [2]).

N-Formyl-*p*-nitroaniline, 79.5 %, yellow crystals (water), m.p. 194–196 °C (194–196 °C [3]).

N-Formyl-2,5-dichloroaniline, 67 %, white crystals (methanol), m.p. 144–146 °C (148 °C [4]).

Reaction of anthranilonitrile with formic acid produced after three days a clear solution. It was poured into water (60 ml), stirred for 10 min. The formed precipitate was collected, air dried and recrystallized from ethanol to give 3-(2-cyanophenyl)quinazolin-4(3H)-one, 64 %, white crystals, m.p. 196–197 °C (191–192 °C [1]).

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