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

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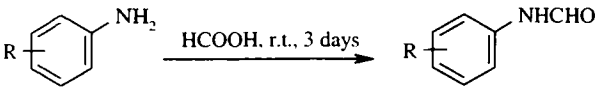
Anthranilonitrile reacting with formic acid at room temperature for three days gave 64% of 3-(2-cyanophenyl)quinazolin-4(3H)-one. Under similar conditions anthranilic acid, 4-nitroaniline, and 2,5-dichloroaniline were N-formylated in good yields.

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

The title quinazolinone was 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 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 the 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 the low pK_a values of the anilines.

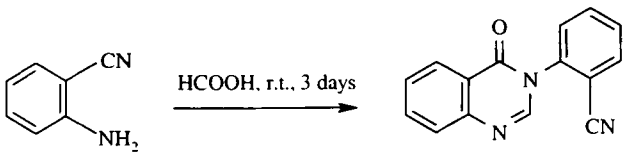
Scheme 1



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 that crude N-formylanthranilonitrile (**3** – postulated in [1] as an intermediate) under 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, when left for three days at 20-22°C, afforded the title quinazolinone **2** in 64% yield (Scheme 2).

Scheme 2



1 **2**

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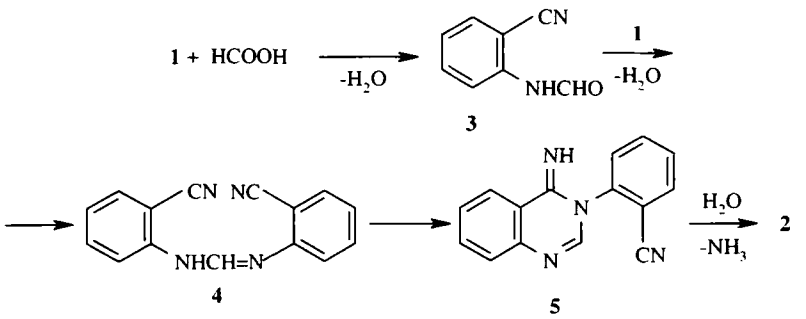
We assume the formation of **2** from **1** and formic acid occurs according to Scheme 3. Partial N-formylation of **1** leading to **3** is followed by the condensation of unconverted **1** with **3** to give the amidine **4** that undergoes intramolecular cyclization to 4-iminoquinazolinone (**5**). 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 the respective 4-arylaminoquinazolines in formic acid solution.

Attempts to shorten the reaction time of our **2** synthesis (no toluene added) by a 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 to the presence of toluene 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 mol) 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 from a suitable solvent.

N-Formylanthranilic Acid, 67.5 %, white crystals (ethyl acetate); mp 166-167°C (167°C [2]).

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

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

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

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