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Synthesis of 2,4-dihydroxyquinazolines using carbon dioxide in the presence of DBU under mild conditions

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Abstract

Chemical fixation of carbon dioxide was performed under mild conditions. Carbon dioxide (1 atm) easily reacted with 2-aminobenzonitriles at 20°C, assisted by DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) to give 2,4-dihydroxyquinazolines in excellent yields.

Keywords: carbonylation; cyclisation; quinazolines; quinazolinones.

Substituted 2,4-dihydroxyquinazolines **1** have been interesting for their biological activities. For example, 7-chloro-1-carboxymethyl-3-(4′-bromo-2′-fluorophenylmethyl)-2,4(1*H*,3*H*)quinazolinone (FK 366, Zenarestat®) was developed as an aldol reductase inhibitor for a remedy of complications of diabetes mellitus.[1] Generally, synthesis of **1** is carried out by anthranilic acid with urea,[2] anthranilamide with phosgene[3] or carbon monoxide with sulfur,[4] and anthranilic acid with potassium cyanate (Scheme 1).[5] However, these methods are considerably limited because of high toxicity of reagents or use of drastic conditions. We herein wish to report a new and convenient synthesis of 2,4-dihydroxyquinazolines **1** from 2-aminobenzonitriles **2** and carbon dioxide under mild conditions (1 atm, 20°C) in the presence of DBU.

The typical procedure is as follows: The DMF solution (20 mL) containing 2-aminobenzonitrile **2a** (1.18 g, 10 mmol) and DBU (4.49 mL, 30 mmol) was vigorously stirred under carbon dioxide (1 atm) at 20°C for 24 h. The reaction mixture was then poured into 1N HCl (200 mL) and deposited solid was washed with toluene (100 mL) and diethyl ether (100 mL). 2,4-Dihydroxyquinazoline **1a** (1.57 g, 97%) was afforded as a pure form. Shorter reaction time (6 h) lowered the yield of **1a** (57%).

A variety of base was examined for this carbonylation of **2a** using carbon dioxide under similar reaction conditions for 24 h. DBU and DBN (1,5-diazabicyclo[4.3.0]non-5-ene) brought about the good results of synthesis of **1a** (97%, 94%, respectively). However, other bases (Dabco™ (1,4-diazabicyclo[2.2.2]-octane), triethylamine, pyridine, K_2CO_3, $NaHCO_3$, NaOH, and none) did not give product **1a** at all.[6]

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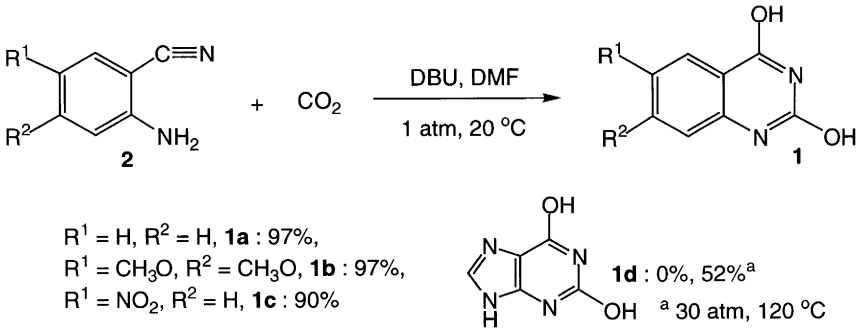
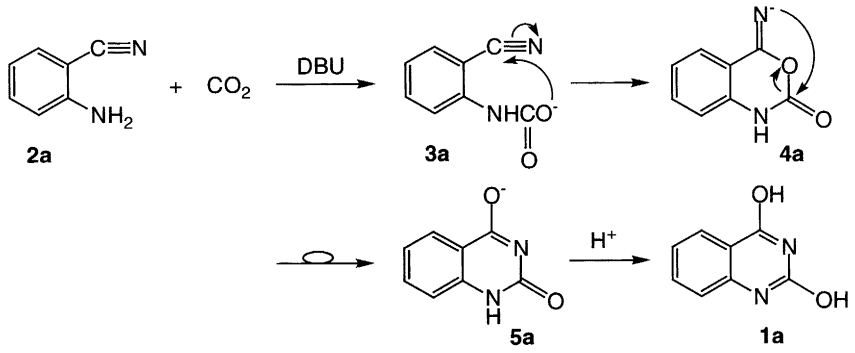


Scheme 1.

Several 2,4-dihydroxyquinazolines **1a**–**c** were synthesized similarly from corresponding 2-aminobenzonitriles **2a**–**c** with carbon dioxide in the presence of DBU in excellent yields. Xanthine **1d** from 5-amino-4-cyanoimidazole **2d** was also afforded in 52% under severer reaction conditions (30 atm, 120°C, 4 h).

Scheme 2 shows a plausible pathway for the formation of **1a** from **2a** with carbon dioxide by DBU. The carbonylation of **2a** with carbon dioxide generates carbamate salt **3a** in the presence of DBU. Then nucleophilic cyclisation of **3a** into **4a** followed by rearrangement of **4a** gives **5a**. Then, hydrolysis of **5a** affords final product **1a**.[8]



Scheme 2.

From a viewpoint of simple operation, mild conditions, good yields and high purities of products, safety of reagents, and utilization of carbon dioxide, the present reaction may provide a useful method for the synthesis of 2,4-dihydroxyquinazolines **1**.

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