



A novel, one-pot, solvent-, and catalyst-free synthesis of 2-aryl/alkyl-4(3H)-quinazolinones

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ABSTRACT

A novel and one-pot synthesis of 2-aryl/alkyl-4(3H)-quinazolinones is described. The in situ prepared amidoximes from the reaction between nitriles and hydroxylamine are condensed with anthranilic acids under solvent- and catalyst-free conditions to produce the title compounds in excellent yields.

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4(3H)-Quinazolinones, an important class of fused heterocyclic compounds,^{1,2} have attracted much synthetic attention because of their wide range of pharmacological and therapeutic activities such as anticancer,³ antiinflammatory,⁴ anticonvulsant,⁵ antiulcer,⁶ and hypolipidemic.⁷ Some quinazolinones have been reported as potent chemotherapeutic agents in the treatment of tuberculosis.⁸ The bioactive natural products, febrifugine and isofebrifugine, contain a quinazolinone moiety and possess antimalarial activity.^{9,10}

The most common approach for the preparation of 2-aryl/alkyl-4(3H)-quinazolinones involves amidation of anthranilonitrile, anthranilic acid, or anthranilamide followed by cyclization of the resulting intermediate.^{11–13} Other methods involve condensation of imidates with anthranilic acid,^{14,15} hetero-Diels–Alder reaction of 1-aryl-4-dimethylamino-2-phenyl-1,3-diaza-1,3-butadienes and phenyl isocyanate,¹⁶ reaction of nitriles with lithiated anthranilamides,¹⁷ thermolysis of 3-arylideneamino-1,2,3-benzotriazin-4-ones,¹⁸ and direct condensation of aldehydes and anthranilamide or its derivatives in the presence of CuCl₂.¹⁹ However, most of these multi-step procedures have significant drawbacks such as long reaction times, low yields of the products, harsh reaction conditions, difficult work-up, and the use of expensive and environmentally toxic catalysts, reagents, or media. Furthermore, some of the starting materials have to be synthesized and purified first, hence these methods are time-consuming. The development

of simple and efficient methods for the synthesis of 4(3H)-quinazolinones is therefore desirable.

Taking into account the pharmacological importance of 4(3H)-quinazolinones, and as part of our continuing efforts on the development of new routes for the preparation of biologically active heterocyclic compounds,²⁰ we have recently focused on improving the synthesis of this nucleus.

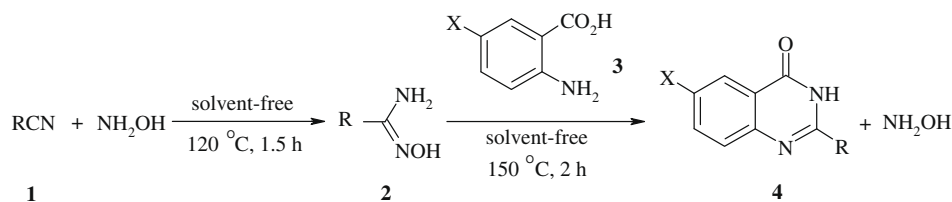
Herein we report a novel synthesis of 4(3H)-quinazolinones via a one-pot reaction. Thus, a mixture of a nitrile **1** and hydroxylamine was converted in situ into amidoxime **2**. Next, the amidoxime was condensed with anthranilic acids **3** under solvent- and catalyst-free conditions to produce 2-aryl/alkyl-4(3H)-quinazolinones **4a–s** in 85–93% yields (Scheme 1).

The reactions were carried out by first heating the mixture of the nitrile and hydroxylamine under solvent-free conditions. After nearly complete conversion into an intermediate presumed to be amidoxime **2** (as indicated by TLC), the anthranilic acid **3** was added to the reaction mixture which was heated for a further 2 h at 150 °C. ¹H NMR analysis of the reaction mixtures clearly indicated formation of 4(3H)-quinazolinones **4** in excellent yields.²¹

When the reaction was performed by heating a mixture of a nitrile, hydroxylamine, and an anthranilic acid via a one-step procedure, the corresponding 4(3H)-quinazolinone was obtained in much lower yields on the basis of NMR analysis of the reaction mixture. On the other hand, when hydroxylamine was omitted from the reaction mixture, the corresponding 4(3H)-quinazolinone was formed in much lower yields under the same conditions.

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4	R	X	% Yield ^a
a	C ₆ H ₅	H	90
b	4-H ₃ CC ₆ H ₄	H	91
c	4-FC ₆ H ₄	H	92
d	3-ClC ₆ H ₄	H	87
e	4-ClC ₆ H ₄	H	91
f	4-BrC ₆ H ₄	H	85
g	4-CH ₃ OC ₆ H ₄	H	89
h	4-O ₂ NC ₆ H ₄	H	90
i	C ₆ H ₅	Cl	88
j	4-H ₃ CC ₆ H ₄	Cl	90
k	4-FC ₆ H ₄	Cl	92
l	3-ClC ₆ H ₄	Cl	86
m	4-ClC ₆ H ₄	Cl	90
n	4-CH ₃ OC ₆ H ₄	Cl	88
o	CH ₂ C ₆ H ₅	H	93
p	CH ₂ C ₆ H ₅	Cl	90
q	CH ₂ CH ₂ C ₆ H ₅	H	92
r	CH ₂ CH ₂ C ₆ H ₅	Cl	88
s	CH ₂ CH ₂ CH ₃	H	89

^a Isolated yield

Scheme 1.

When the reactions were carried out using an amine such as aniline or benzylamine, instead of hydroxylamine, a complex mixture was obtained and most of the anthranilic acid, the nitrile, and the amine were recovered unchanged. The nucleophilicity of these amines is less than that of hydroxylamine and amidoxime formation is not possible as a result.

The structures of the isolated products were confirmed by elemental analyses and from spectral data (mass, ¹H, and ¹³C NMR spectra) and by comparison of their mp values with those of authentic samples.²¹

In conclusion, we have developed a novel and one-pot reaction of nitriles, hydroxylamine, and anthranilic acids for the preparation of 4(3H)-quinazolinones of potential synthetic and pharmacological interest. The simplicity of the starting materials, excellent yields of the products, fairly fast reaction time, neutral reaction conditions as well as solvent- and catalyst-free conditions are the advantages of this method. Furthermore, product isolation does not require purification by column chromatography. We believe that this experimentally simple approach could be a useful addition to reported methods.^{11–19,22}

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21. The procedure for the preparation of 2-(4-methylphenyl)-4(3H)-quinazolinone **4b** is described as an example: A mixture of 4-methylbenzotrile (0.23 g, 2 mmol) and hydroxylamine (50%, 0.20 g, 3 mmol) was stirred at 120 °C for 1.5 h. After nearly complete conversion into an intermediate presumed to be the corresponding amidoxime (as indicated by TLC), anthranilic acid (0.27 g, 2 mmol) was added to the reaction mixture, which was stirred at 150 °C for a further 2 h. Next, the reaction mixture was cooled to room temperature and the product was purified by crystallization from ethanol as colorless crystals, mp 242 °C (lit 240–242 °C),²³ yield: 0.43 g, 91%. EI-MS, *m/z* (%): 236 (*M*⁺, 97), 219 (6), 192 (8), 165 (6), 119 (9), 103 (6), 91 (24), 76 (6), 65 (12). Anal. Calcd for C₁₅H₁₂N₂O (236.27): C, 76.25; H, 5.12; N, 11.86. Found: C, 76.1; H, 5.3; N, 11.7. ¹H NMR (500.1 MHz, CDCl₃): δ 2.47 (3H, s, CH₃), 7.38 (2H, d, *J* = 8.2 Hz, 2CH), 7.50 (1H, dt, *J* = 1.5, 8.1 Hz, CH), 7.80 (1H, dt, *J* = 1.5, 8.1 Hz, CH), 7.83 (1H, d, *J* = 6.9 Hz, CH), 8.15 (2H, d, *J* = 8.2 Hz, 2CH), 8.34 (1H, d, *J* = 7.8 Hz, CH), 11.51 (1H, s, NH). ¹³C NMR (125.8 MHz, CDCl₃): δ 21.51 (CH₃), 120.83 (C), 126.38, 126.56, 127.25, 127.93, and 129.77 (7CH), 130.00 (C), 134.81 (CH), 142.20, 149.65, and 151.70 (3C), 163.73 (C=O). 2-Benzyl-4(3H)-quinazolinone (**4o**): colorless crystals, mp 247–249 °C, yield: 0.44 g, 93%. Anal. Calcd for C₁₅H₁₂N₂O (236.27): C, 76.25; H, 5.12; N, 11.86. Found: C, 76.2; H, 5.2; N, 11.7. ¹H NMR (500.1 MHz, CDCl₃): δ 3.94 (2H, s, CH₂), 7.22 (1H, t, *J* = 7.2 Hz, CH), 7.30 (2H, t, *J* = 7.4 Hz, 2CH), 7.38 (2H, d, *J* = 7.5 Hz, 2CH), 7.44 (1H, t, *J* = 7.5 Hz, CH), 7.59 (1H, d, *J* = 8.1 Hz, CH), 7.74 (1H, t, *J* = 7.5 Hz, CH), 8.07 (1H, d, *J* = 7.8 Hz, CH), 12.39 (1H, br s, NH). ¹³C NMR (125.8 MHz, CDCl₃): δ 40.73 (CH₂), 120.71 (C), 125.63, 126.08, 126.70, 126.86, 128.40, 128.80, and 134.26 (9CH), 136.50, 148.87, and 155.88 (3C), 161.80 (C=O). 2-Phenethyl-4(3H)-quinazolinone (**4q**) colorless crystals, mp 208 °C, yield: 0.46 g, 92%. Anal. Calcd for C₁₆H₁₄N₂O (250.30): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.6; H, 5.8; N, 11.0. ¹H NMR (500.1 MHz, CDCl₃): δ 2.89 (2H, t, *J* = 7.5 Hz, CH₂), 3.04 (2H, t, *J* = 7.5 Hz, CH₂), 7.16–7.20 (1H, m, CH), 7.25–7.29 (4H, m, 4CH), 7.45 (1H, t, *J* = 7.8 Hz, CH), 7.61 (1H, d, *J* = 8.1 Hz, CH), 7.77 (1H, dt, *J* = 1.5, 8.1 Hz, CH), 8.07 (1H, d, *J* = 7.9 Hz, CH), 12.23 (1H, br s, NH). ¹³C NMR (125.8 MHz, CDCl₃): δ 32.39 and 36.23 (2CH₂), 120.79 (C), 125.63, 125.93, 126.00, 126.75, 128.26, 128.28, and 134.21 (9CH), 140.69, 148.83, and 156.53 (3C), 161.72 (C=O).
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