Solvent-Free Reaction between Anthranilic Acids and Isocyanides: A Novel Approach for the Synthesis of 2-Unsubstituted 4(3*H*)-Quinazolinones

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Abstract: A novel synthesis of 2-unsubstituted 4(3*H*)-quinazolinones is described. Heating a mixture of an anthranilic acid and an isocyanide under solvent-free conditions afforded the title compounds in good to excellent yields.

Key words: anthranilic acids, isocyanides, 2-unsubstituted 4(3*H*)-quinazolinones, solvent-free synthesis, cyclizations, heterocycles

4(3*H*)-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] anti-inflammatory,[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 importance of 2-unsubstituted 4-(arylamino)quinazolines as tyrosine kinase inhibitors[11] has meant that many different syntheses of the 2-unsubstituted 4(3*H*)-quinazolinone precursors have been performed during the recent decade. The original Niementowski route to 2-unsubstituted 4(3*H*)-quinazolinones involved heating anthranilic acids with formamide.[12] This procedure was then improved by use of formamidine acetate under thermal conditions[13] and microwave irradiation.[14] Other synthetic approaches to the 2-unsubstituted 4(3*H*)-quinazolinones involve dimerization of anthranilic acids under Vilsmeier conditions,[15] reductive cyclization of 2-azido/2-nitrobenzoic acids by Zn–HCO_2NH_4 under microwave irradiation,[16] reaction of anthranilic acid, trialkyl orthoformate, and amines in the presence of $La(NO_3)_3{\cdot}6H_2O$,[17] *p*-toluenesulfonic acid,[17] $Bi(TFA)_3$ immobilized on [nbp]$FeCl_4$[18] or silica gel/$FeCl_3$.[19] However, most of these multistep procedures have significant drawbacks such as long reaction times, low yields of the products, harsh reaction conditions, difficult workup, and 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(3*H*)-quinazolinones are therefore desirable.

There are several reports in literature concerning the reaction between carboxylic acids and isocyanides in different conditions leading to various amide types,[20] amidine carbocations,[21] imidic structures,[22] *N*-thioacetal amides,[22] 3-aryl-2-acyloxyacrylamides,[23] and formimidate carboxylate mixed anhydride intermediates.[24]

There is only one report in the literature concerning synthesis of quinazolinones from isocyanides. Descotes et al. reported the $HgCl_2$-catalyzed reaction of a glycosyl isocyanide with methyl anthranilate leading to the corresponding glycosyl quinazolinone.[25]

Knowing the chemical and pharmacological importance of the 4(3*H*)-quinazolinones and as part of our continuing efforts on the development of new routes for the preparation of biologically active heterocyclic compounds,[26] very recently we have reported a solvent- and catalyst-free reaction between the in situ generated amidoximes and anthranilic acids, which resulted in 2-aryl/alkyl-4(3*H*)-quinazolinones.[27] Herein we report a novel synthesis of 2-unsubstituted 4(3*H*)-quinazolinones. Thus, a mixture of an anthranilic acid (**1**) and an isocyanide **2** was heated at 150 °C under solvent-free conditions to produce the corresponding 4(3*H*)-quinazolinones **3a–l** in 76–92% yields (Table 1). All the reactions went to completion within two hours. ^{1}H NMR analysis of the reaction mixtures clearly indicated formation of the corresponding 4(3*H*)-quinazolinones in excellent yields.[28]

The isolated products **3** were characterized on the basis of mass spectrometry, elemental analysis, IR, ^{1}H NMR, and ^{13}C NMR spectroscopy,. The IR spectrum of **3l** showed an absorption at 1662 cm^{-1} indicative of an amide functionality. The mass spectrum of **3l** displayed the molecular ion [M$^+$] peaks at *m/z* = 294 and 292, which are 18 mass units (H_2O) lower than that of the 1:1 adduct of 2-amino-5-chlorobenzoic acid and 1,1,3,3-tetramethylbutyl isocyanide. The ^{1}H NMR spectrum of **3l** exhibited three sharp singlets arising from the CMe_3 (δ = 0.81 ppm), CMe_2 (δ = 1.75 ppm), methylene (δ = 2.22 ppm) groups and the C2H of the quinazolinone ring (δ = 8.26 ppm) along with characteristic signals with appropriate chemical shifts and coupling constants for the other three aromatic H atoms. The ^{1}H-decoupled ^{13}C NMR spectrum of **3l** showed characteristic signals for the tetramethylbutyl {δ = 30.00 [C(CH_3)$_2$], 31.24 [C(CH_3)$_3$], 31.93 [C(CH_3)$_3$], 48.88

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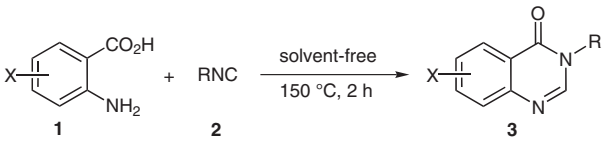
(CH_2), 64.76 [$C(CH_3)_2$] ppm} substituent. Four signals were observed for the three CH of the phenylene moiety and the C2H of the quinazolinone ring. The carbonyl group resonated at δ = 161.41 ppm and the other three quaternary carbon atoms of the quinazolinone ring were observed at appropriate chemical shifts.[28]

Table 1 Synthesis of 4(3*H*)-Quinazolinones **3a–l**

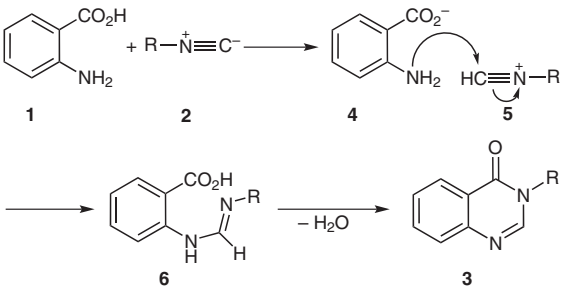


1 2 3

Compd **3**[a]	R	X	Yield (%)[b]
3a	cyclohexyl	H	90
3b	*t*-Bu	H	91
3c	1,1,3,3-tetramethylbutyl	H	92
3d	cyclohexyl	4-Me	87
3e	*t*-Bu	4-Me	90
3f	1,1,3,3-tetramethylbutyl	4-Me	86
3g	cyclohexyl	5-Me	90
3h	*t*-Bu	5-Me	92
3i	1,1,3,3-tetramethylbutyl	5-Me	87
3j	cyclohexyl	5-Cl	82
3k	*t*-Bu	5-Cl	85
3l	1,1,3,3-tetramethylbutyl	5-Cl	76

[a] Compounds **3a–i** were purified by precipitation in acetone from the reaction mixture and then recrystallization from *n*-hexane–EtOAc; and compounds **3j–l** were purified by column chromatography using *n*-hexane–EtOAc (3:1) as eluent.[28,]
[b] Isolated yield.

A mechanistic rationalization for this reaction is provided in Scheme 1. On the basis of the well-established chemistry of isocyanides,[29] it is reasonable to assume that the 4(3*H*)-quinazolinones **3** result from initial protonation of the isocyanide **2** by the anthranilic acid **1**. Subsequent nucleophilic attack of the conjugate base of the acid **4** from amino group of the anthranilate to the isonitrilium cation **5** may form the iminomethyl anthranilic acid intermediate **6**, which may be cyclized under the reaction conditions to produce the isolated 4(3*H*)-quinazolinones **3**.



1 2 4 5 6 3

Scheme 1

In conclusion, we have developed a novel reaction between anthranilic acids and isocyanides for the preparation of 4(3*H*)-quinazolinones, which are of potential synthetic and pharmacological interest. Simple and readily available starting materials, good to excellent yields of the products, fairly fast reaction times, neutral reaction conditions, and solvent- and catalyst-free conditions are the main advantages of this reaction. We believe this experimentally simple approach could be a useful addition to the quinazolinones syntheses so far reported.

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(28) **General Procedure for the Preparation of Compounds 3a–l**
A mixture of the appropriate anthranilic acid (2 mmol) and isocyanide (2.2 mmol) was stirred at 150 °C for 2 h. Progress of the reaction was indicated by TLC monitoring. Next, the reaction mixture was cooled to r.t. and acetone (2 mL) was added, and stirring was continued for 10 min at ambient temperature. The precipitate was filtered and washed with cold acetone (2 mL), and the product was recrystallized from *n*-hexane–EtOAc (1:1). Compounds **3a–i** were purified by this procedure, and compounds **3j–l** were purified by column chromatography using *n*-hexane–EtOAc (3:1) as eluent.
3-Cyclohexyl-4(3*H*)-quinazolinone (3a)
Yield 0.41g (90%); colorless crystals; mp 126–127 °C. IR (KBr): 1659 (C=O), 1596, 1564, 1468, 1399, 1334, 1240, 1172, 1132, 1024, 956, 894, 805, 766, 695 cm^{-1}. ^1H NMR (300.1 MHz, $CDCl_3$): δ = 1.20–2.04 [m, 10 H, CH(CH_2)$_5$], 4.77–4.86 [m, 1 H, C*H*(CH_2)$_5$], 7.49 (dd, *J* = 7.2, 7.4 Hz, 1 H, CH), 7.68 (d, *J* = 7.6 Hz, 1 H, CH), 7.74 (dd, *J* = 7.0, 7.9 Hz, 1 H, CH), 8.12 (s, 1 H, CH), 8.31 (d, *J* = 8.0 Hz, 1 H, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 25.27, 25.89 and 32.60 (3 × CH_2), 53.54 (NCH), 121.93 (C), 126.95, 127.10, 127.24, 134.10 and 143.91 (5 × CH), 147.50 (C), 160.70 (C=O). MS (EI): *m/z* (%) = 228 (24) [M^+], 192 (7), 181 (5), 171 (4), 160 (7), 147 (100), 129 (8), 118 (10), 102 (5), 90 (7), 77 (9), 67 (14), 55 (16), 41 (22). Anal. Calcd for $C_{14}H_{16}N_2O$ (228.29): C, 73.66; H, 7.06; N, 12.27. Found: C, 73.6; H, 7.2; N, 12.1.
6-Chloro-3-cyclohexyl-4(3*H*)-quinazolinone (3j)
Yield 0.43 g (82%); colorless crystals; mp 137–138 °C. IR (KBr): 1668 (C=O), 1597, 1552, 1465, 1388, 1358, 1320, 1240, 1137, 1072, 1022, 947, 895, 822, 775 cm^{-1}. ^1H NMR (300.1 MHz, $CDCl_3$): δ = 1.25–1.97 [m, 10 H, CH(CH_2)$_5$], 4.76–4.84 [m, 1 H, C*H*(CH_2)$_5$], 7.60 (d, *J* = 8.8 Hz, 1 H, CH), 7.63 (dd, *J* = 2.1, 8.8 Hz, 1 H, CH), 8.11 (d, *J* = 2.1 Hz, 1 H, CH), 8.26 (s, 1 H, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 25.22, 25.28, and 32.56 (3 × CH_2), 53.59 (NCH), 122.97 (C), 126.30 and 128.95 (2 × CH), 132.88 (C), 134.52 and 144.08 (2 × CH), 146.02 (C), 159.68 (C=O). MS (EI): *m/z* (%) = 264 (8) [M^+ ^{37}Cl], 262 (22) [M^+ ^{35}Cl], 228 (5), 205 (3), 181 (100), 163 (4), 147 (18), 136 (7), 124 (5), 110 (5), 97 (4), 82 (9), 67 (20), 55 (18), 41 (23). Anal. Calcd for $C_{14}H_{15}ClN_2O$ (262.74): C, 64.00; H, 5.75; N, 10.66. Found: C, 63.9; H, 5.7; N, 10.6.
6-Chloro-3-(1,1,3,3-tetramethylbutyl)-4(3*H*)-quinazolinone (3l)
Yield 0.44 g (76%); colorless crystals; mp 118–119 °C. IR (KBr): 1662 (C=O), 1592, 1560, 1467, 1362, 1324, 1285, 1219, 1128, 1075, 918, 835, 805, 754, 712 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 0.81 [s, 9 H, C(CH_3)$_3$], 1.75 [s, 6 H, C(CH_3)$_2$], 2.22 (s, 2 H, CH_2), 7.56 (d, *J* = 8.9 Hz, 1 H, CH), 7.60 (dd, *J* = 2.2, 8.9 Hz, 1 H, CH), 8.20 (d, *J* = 2.2 Hz, 1 H, CH), 8.26 (s, 1 H, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 30.00 [C(*C*H_3)$_2$], 31.24 [C(*C*H_3)$_3$], 31.93 [*C*(CH_3)$_3$], 48.88 (CH_2), 64.76 [*C*(CH_3)$_2$], 124.13 (C), 126.23 and 128.55 (2 × CH), 132.66 (C), 134.34 and 144.84 (2 × CH), 145.85 (C), 161.41 (C=O). MS (EI): *m/z* (%) = 294 (1) [M^+ ^{37}Cl], 292 (3) [M^+ ^{35}Cl], 235 (8), 180 (100), 163 (9), 153 (8), 138 (7), 124 (6), 112 (26), 97 (68), 69 (10), 57 (54), 41 (31). Anal. Calcd for $C_{16}H_{21}ClN_2O$ (292.81): C, 65.63; H, 7.23; N, 9.57. Found: C, 65.7; H, 7.4; N, 9.4.
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