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Microwave-assisted one-pot synthesis of 2,3-disubstituted 3*H*-quinazolin-4-ones

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Abstract—A practical synthesis of 2,3-disubstituted 3*H*-quinazolin-4-ones **1** with broad chemistry scope is described. The key step is the microwave promoted one-pot, two-step reaction sequence combining anthranilic acids, carboxylic acids, and amines providing efficient access to this important class of heterocycles.

2,3-Disubstituted 3*H*-quinazolin-4-ones **1** are a privileged structure present in many biologically active compounds such as sedative-hypnotic **2** (methaqualone),[1] antitussive **3** (chloroqualone),[2] and anticonvulsant **4** (piriqualone)[3] (Fig. 1). Although there are many reports describing the synthesis of this class of compounds, most of these approaches are limited in that only phenyl groups at R^2 are tolerated.[4] There are only a few specific reports on the preparation of the simple aliphatic, Bn, and other heterocyclic functional group substituted 2,3-disubstituted *3H*-quinazolin-4-ones.[5] A general method for the synthesis of the 2,3-disubstituted 3*H*-quinazolin-4-ones would be required in order to more comprehensively explore this chemical space through the variation of the R^2 substituent to include a diverse sampling of aliphatic, benzylic, aromatic, and heteroaromatic groups.

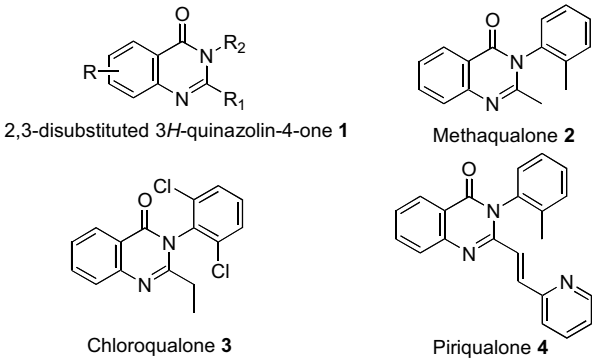

Figure 1. Biologically relevant 2,3-disubstituted 3*H*-quinazolin-4-one analogs.

In an effort to develop a more widely applicable methodology, we chose to evaluate one of the more commonly employed synthetic strategies via benzoxazinone **9** as an intermediate.[4a–c] This synthesis begins with the condensation of an anthranilic acid **5**, with either an acylchloride **6** or a carboxylic acid **7** followed by dehydration to form the intermediate benzoxazinones **9**. Subsequent addition of an aniline **10** (R^2 = Ar) initially provides the transient amidine salt species **11**,[4b] which rapidly cyclizes to yield the desired 2,3-disubstituted 3*H*-quinazolin-4-ones **1** (R^2 = Ar) (Scheme 1). In addition, Sillion demonstrated that diamide **12** (R^2 = Ar) could not cyclize under the conventional heating conditions to give the 2,3-disubstituted 3*H*-quinazolin-4-ones **1** (R^2 = Ar), which indicated that diamide **12** (R^2 = Ar) was not the precursor of **1** (R^2 = Ar).[4c] However, while adapting this method to the parallel synthesis of a diverse set of analogs, we found that when aliphatic and benzylic amines were used under the standard conventional heating conditions, instead of forming the intermediate **11**, the reaction surprisingly generated diamides **12** (Scheme 2). Consequently, we examined the possibility that microwave irradiation could facilitate this cyclization step

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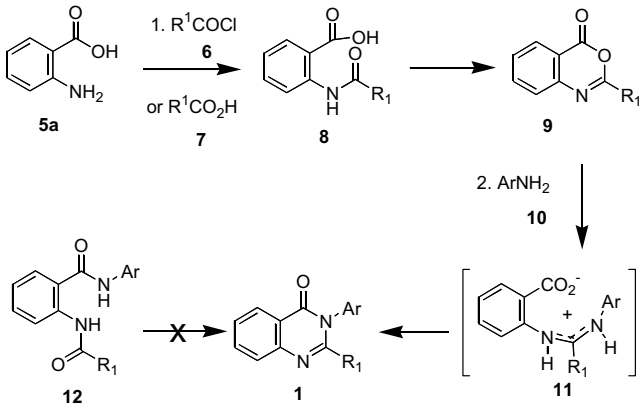
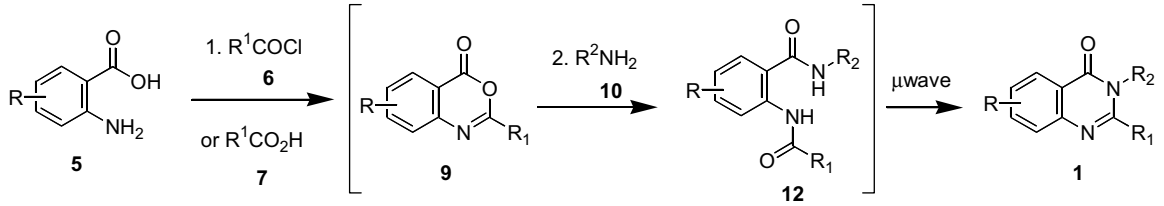


Scheme 1. Synthesis of 2,3-disubstituted 3*H*-quinazolin-4-ones **1** by reaction of benzoxazinones **9** with anilines **10**.[4a–c]

from the diamides **12** to form the desired products. The details of this effort, including an optimized one-pot, two-step microwave-assisted synthesis providing an efficient route to 2,3-disubstituted 3*H*-quinazolin-4-ones **1**, are described.

Experimentation on a simple model system was initiated to understand the impact of microwave irradiation on this known procedure (Scheme 2).[4a–c] A reaction mixture consisting of anthranilic acid (1.0 equiv), benzoyl chloride (1.0 equiv) in pyridine was prepared and then stirred at room temperature according to the literature method, which afforded benzoxazinone **9**. Cyclohexylamine (1.0 equiv) and $P(PhO)_3$ (1.2 equiv) were then added and the mixture was heated at 120 °C under conventional heating conditions providing <50% conversion of cyclized product **1b**,[7] along with the diamide **12**[6] and multiple side products. However, when microwave irradiation was applied at >200 °C to the same reaction mixture, the desired product **1b** was formed as the major component along with diamide **12** as a minor by-product. Further optimization of amounts of reagents used, the reaction time, solvent, and temperature resulted in **1b** in 90% conversion with 60% isolated yield (entry 2, Table 1).[8] This initial result clearly indicated that microwave irradiation played a critical role in driving this reaction to completion and providing access to a uniquely substituted heterocyclic scaffold not available from conventional heating. Subsequently, it was also discovered that microwave conditions promoted the initial condensation of the anthranilic acid with a carboxylic acid, further expanding the scope of this chemistry.

With these exciting results in hand, we applied our optimized microwave reaction conditions to a variety of anthranilic acids and both acyl chlorides (R^1COCl) and carboxylic acids (R^1CO_2H)[9] in the presence of the coupling reagent ($P(PhO)_3$) to generate the intermediate benzoxazinones **9**, followed by the addition of amines to yield the 2,3-disubstituted 3*H*-quinazolin-4-ones **1** (Table 1). The results confirmed that aromatic acyl



Scheme 2. Optimized one-pot microwave promoted synthesis of 2,3-disubstituted 3*H*-quinazolin-4-ones **1**. Optimized conditions: (1) For R^1COCl (1.5 equiv), $P(PhO)_3$ (1.2 equiv), pyridine (2.0 mL), 25 °C, 60 min; or for R^1CO_2H (1.0 equiv), $P(PhO)_3$ (1.2 equiv), pyridine (1.0 mL), μwave, 150 °C, 10 min; (2) R^2NH_2 (1.5 equiv) when R^1COCl used, R^2NH_2 (1.0 equiv) when R^1CO_2H used, μwave, 250 °C, 3–10 min.

Table 1. Chemistry scope of the microwave promoted synthesis of 2,3-disubstituted 3*H*-quinazolin-4-ones **1**

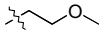
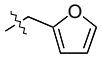
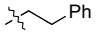
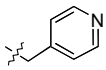
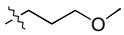
Entry	R	R^1	R^2	Reaction time (min)	Yield[a] of **1**[b] (%)	
1	H	Ph[c]	Ph	3	100 (88)	(**1a**)
2	H	Ph[c]		6	90 (60)	(**1b**)
3	H	Ph[c]	Bn	3	95 (80)	(**1c**)
4	H	Ph[c]		3	100 (85)	(**1d**)
5	H	Ph[c]		5	95 (66)	(**1e**)
6	H	Bn[d]		3	100 (62)	(**1f**)
7	H			6	94 (46)	(**1g**)
8	H			6	100 (53)	(**1h**)

Table 1 (*continued*)

Entry	R	R^1	R^2	Reaction time (min)	Yield[a] of **1**[b] (%)	
9	H			6	95 (50)	(**1i**)
10	H	Et[d]	Bn	3	100 (64)	(**1j**)
11	5-Me	Me[d]		6	100 (59)	(**1k**)
12	4-Cl		Bn	6	100 (66)	(**1l**)
13	4,5-$(OMe)_2$	4-OMe–Bn[d]		6	100 (64)	(**1m**)
14	Note[e]	Ph[c]	Bn	6	95 (68)	(**1n**)
15	H	Me[d]		3	95 (65)	(**1o**)

[a] The yields are determined by HPLC (ELSD) from LC–MS results of the reaction mixture. In parentheses, isolated yields by preparative TLC or flash column chromatography.
[b] Characterized by ^{1}H NMR, ^{13}C NMR, and HRMS.
[c] R^1COCl used: 25 °C/60 min.
[d] R^1CO_2H used: μwave/150 °C/10 min.
[e] 2-Aminonicotinic acid used.

chlorides (entries 1–5, 8, and 14), and aliphatic carboxylic acids (entries 6, 7, and 9–13) all worked smoothly providing overall yields ranging from 46% to 88% with all conversion >90%. Aliphatic amines (entries 2–14) performed as well as aromatic amines (entry 1), expanding the scope of this chemistry from that previously reported.[4] The reaction was also extended to include anthranilic acids containing both electron-donating (entries 11 and 13), and electron-withdrawing (entry 12) substituents, as well as aza-anthranilic acids (entry 14). Moreover, sulfonyl hydrazide (entry 15) also worked as good as amines and reported methods.[10] In addition to the broad range of tolerated reagents, all of the reactions were conducted in a one-pot, two-step fashion without the need for intermediate work-ups, which provided an efficient and convenient solution-phase parallel synthesis protocol.

In summary, we have developed an efficient microwave-assisted, one-pot, two-step synthesis of 2,3-disubstituted 3*H*-quinazolin-4-ones from anthranilic acids, carboxylic acids or acyl chlorides, and amines. These results demonstrate the value of microwave-assisted chemistry not only to provide increased yields and shortened reaction times, but also to expand the accessible chemical space by generating otherwise unavailable reaction products. This method has now been adapted to the synthesis of diverse screening libraries of related quinazolin-4-ones and also to the total synthesis of a number of natural products that contain this heterocyclic scaffold, which will be published in due course.

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Supplementary data

The supplementary data is available online with the paper in ScienceDirect. ^{1}HNMR, ^{13}CNMR, and HRMS for compounds **1a**–**o** are available as supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.01.008.

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7. Errede and others reported that conversion of **12a** ($R^1 = R^2 = Ph$, R = H) to **1a** requied fusion temperature of about 250 °C, although yield was not given. Errede, L. A.; Oien, H. T.; Yarian, D. R. *J. Org. Chem.* **1977**, *42*, 12–18, and related references therein.
8. General reaction procedure to synthesis 2,3-disubstituted *3H*-quinazolin-4-ones **1** from acyl chlorides in Table 1: In a conical-bottomed Smith Process vial, anthranilic acid **5a** (200 μmol), benzoyl chloride (300 μmol), and triphenyl phosphite (63 μL, 220 μmol) in 2 mL of anhydrous pyridine were charged. The resulting mixture was stirred at room temperature for 1 h. Upon consumption of anthranilic acid, an amine (300 μmol) was added and the vial was irradiated under microwave conditions in the sealed reaction vessel for 3–6 min at 250 °C. After cooling, the reaction mixture was concentrated in vacuo and the residue was purified by preparative TLC (ethyl acetate/hexanes) to give the desired product. **1d**: 3-(2-Methoxy-ethyl)-2-phenyl-*3H*-quinazolin-4-one; 47.5 mg (85%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.16 (s, 3H), 3.60 (t, J = 5.1 Hz, 2H), 4.28 (t, J = 5.1 Hz, 2H), 7.53–7.60 (m, 6H), 8.35 (br d, J = 8.10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 46.04, 58.97, 69.10, 120.35, 125.35, 127.34, 128.19, 128.75, 128.98, 131.06, 132.68, 135.54, 144.25, 158.42, 161.47; HRMS calcd for ($C_{17}H_{16}N_2O_2 + Na^+$) 303.1111, found 303.1097.
9. General reaction procedure to 2,3-disubstituted *3H*-quinazolin-4-ones **1** from carboxylic acids in Table 1: In a conical-bottomed Smith Process vial, anthranilic acid **5a** (200 μmol), phenylacetic acid (200 μmol), and triphenyl phosphite (63 μL, 220 μmol) in 1 mL of anhydrous pyridine were charged. The vial was irradiated under microwave conditions in the sealed reaction vessel at 150 °C for 10 min. Upon consumption of anthranilic acid, an amine (200 μmol) was added and the resulting mixture was heated in microwave at 250 °C for 3–6 min. The reaction mixture was concentrated in vacuo, and the residue was purified by silica gel flash chromatography (ethyl acetate/hexanes) to give the desired product. **1j**: 3-Benzyl-2-ethyl-*3H*-quinazolin-4-one; 34 mg (64%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32 (t, J = 7.2 Hz, 3H), 2.77 (q, J = 7.2 Hz, 2H), 5.42 (s, 2H), 7.17 (dd, J = 8.1, 1.5 Hz, 2H), 7.25–7.35 (m, 3H), 7.43–7.49 (m, 1H), 7.66–7.77 (m, 2H), 8.31 (dd, J = 7.8, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.51, 28.57, 46.47, 120.61, 126.60, 126.68, 127.29, 127.31, 127.82, 129.15, 134.53, 136.42, 147.66, 158.18, 162.82; HRMS calcd for ($C_{17}H_{16}N_2O$ + H) 265.1335, found 265.1350.
10. When this manuscript was in preparation, a method of synthesis of 3-sulfonamide-substituted quinazolinones was reported Zhou, Y.; Murphy, D. E.; Sun, Z.; Gregor, V. E. *Tetrahedron Lett.* **2004**, *45*, 8049–8051, in which neat benzoxazinones and sulfonyl hydrazides reacted under melting temperature (130 °C) generated target products. However, when we applied reported method to aliphatic amines (Table 1, entry 3 combination), we only obtained <10% cyclized prodcut **1c** along with >85% diamide **12**. In contrast, sulfonyl hydrazides worked very well under our reaction conditions.