A New Synthesis of Aryl Substituted Quinazolin-4(1*H*)-ones

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Treatment of a variety of substituted 2-aminobenzonitriles with formic acid under strong acid catalysis provides the corresponding quinazolin-4(1*H*)-ones in good yield. A potential reaction pathway is described.

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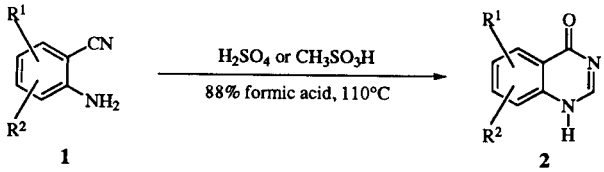
Substituted quinazolin-4(1*H*)-ones (4-hydroxyquinazolines) are key intermediates in the syntheses of a variety of biologically active derivatives [1]. Historically, quinzolin-4(1*H*)-ones have been prepared by the Neimentowski reaction of anthranilic acids [2]. Other literature methods [3] include cyclization of orthoesters [4], Gold's reagent [5] and ethoxymethylenemalononitrile [6] with o-aminobenzamides. The aminolysis of benzoxazinones has also been utilized [7]. A recent report describes the synthesis of quinazoline derivatives *via* a palladium catalyzed reductive cyclization method [8].

We would like to describe a new cyclization reaction of aryl substituted 2-aminobenzonitriles (**1**) which affords good yields of quinazolin-4(1*H*)-ones (**2**). Substituted 2-aminobenzonitriles are often more readily accessible synthetic targets than the corresponding anthranilic acids [9]. This new cyclization is operationally simple and delivers the desired products in good purity following dilution of the reaction mixture with water [10]. The preparative value of the reaction is evident from the entries in Tables I, II and III.

From a mechanistic view point, the current reaction is also of considerable interest. Quantitative monitoring of the reaction by an internal standard gas chromatography method reveals rapid disappearance of 2-aminobenzonitrile **1d** (Scheme I) with complete conversion to quinazolin-4(1*H*)-one **2d** within twenty minutes. One can envision several reasonable reaction pathways all leading the observed product. For example, rapid nitrile hydrolysis, *N*-formylation with formic acid followed by cyclization/-dehydration. However, exposure of 2-amino-3-fluorobenzamide (**3**) to the reaction conditions does provide **2d** but at a reduced rate compared with that of the cyclization reaction (Scheme I). Thus, we conclude that this is not the primary

Table I
Cyclization of Substituted 2-Aminobenzonitriles



1 **2**

Entry	R^1	R^2	Product (% yield[a])
1a	H	3-CH_3	**2a** (86%)
1b	H	5-NO_2	**2b** (90%)
1c	H	5-OCH_3	**2c** (61%)
1d	H	3-F	**2d** (88%)
1e	H	3-Cl	**2e** (68%)
1f	H	5-Cl	**2f** (84%)
1g	H	6-Cl	**2g** (94%)
1h	3-F	5-Cl	**2h** (63%)

[a] isolated, unoptimized yields

Table III
Analytical Data for Quinozolin-4(1*H*)-ones **2a-h**

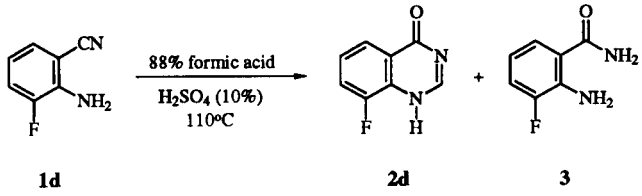
Entry	MP°C	Formula	Analysis Found C	Found H	Found N	Calcd. C	Calcd. H	Calcd. N
2a	253-254	$C_9H_8N_2O$	67.8	5.0	17.2	67.48	5.03	17.49
2b	282-284	$C_8H_5N_3O_3$	50.3	2.4	21.6	50.27	2.64	21.98
2c	245-246	$C_9H_8N_2O_2$	61.4	4.5	15.7	61.36	4.58	15.90
2d	272-273	$C_8H_5FN_2O$	58.5	2.6	16.8	58.54	3.07	17.07
2e	>300	$C_8H_5ClN_2O$	53.4	2.5	15.3	53.21	2.79	15.51
2f	268	$C_8H_5ClN_2O$	53.4	2.5	15.3	53.21	2.79	15.51
2g	279	$C_8H_5ClN_2O$	53.1	2.6	15.4	53.21	2.79	15.51
2h	>300	$C_8H_4ClFN_2O$	48.4	1.8	13.8	48.39	2.03	14.11

Table II
Spectral Properties of Quinazolin-4(1*H*)-ones **2a-h**

Entry	Mp °C	Proton NMR (delta in ppm, J in Hz)	Formula	HRMS (70 eV, *m/e*) calcd.	HRMS (70 eV, *m/e*) found
2a	252-53	2.53 (s, 3H), 7.40 (apparent t, J = 7, 1H), 7.68 (d, J = 7, 1H), 7.96 (d, J = 8, 1H), 8.12 (s, 1H)	$C_9H_8N_2O$	160.0637	160.0636
2b	decomp.	7.86 (d, J = 9, 1H), 8.31 (s, 1H), 8.55 (dd, J = 9, 3, 1H), 8.80 (d, J = 3, 1H)	$C_8H_5N_3O_3$	191.0331	191.0320
2c	244-45	3.86 (s, 3H), 7.40 (dd, J = 9, 2, 1H), 7.50 (d, J = 2, 1H), 7.61 (d, J = 9, 1H), 8.00 (s, 1H)	$C_9H_8N_2O_2$	176.0586	176.0589
2d	272-273	7.50 (m, 1H), 7.67 (apparent t, J = 4, 1H), 7.92 (d, J = 8, 1H), 8.14 (s, 1H)	$C_8H_5FN_2O$	164.0385	164.0387
2e	296-99	7.50 (t, J = 8, 1H), 7.97 (dd, J = 7, 1, 1H), 8.08 (dd, J = 8, 1, 1H), 8.22 (s, 1H)	$C_8H_5ClN_2O$	180.0090	180.0089
2f	235-45 (d)	7.69 (d, J = 8, 1H), 7.85 (dd, J = 8, 2, 1H), 8.06 (d, J = 2, 1H), 8.15 (s, 1H)	$C_8H_5ClN_2O$	180.0090	180.0087
2g	279	7.64 (d, J = 8, 1H), 7.67 (d, J = 8, 1H), 7.83 (t, J = 8, 1H), 8.70 (s, 1H)	$C_8H_5ClN_2O$	180.0090	180.0085
2h	> 300	7.45 (m, 1H), 7.65 (d, J = 2, 1H), 8.18 (s, 1H)	$C_8H_4ClFN_2O$	197.9994	197.9990

reaction pathway. Replacing formic acid with the much less nucleophilic trifluoroacetic acid affects hydrolysis to **3** at a diminished rate compared to the cyclization reaction. Although this data is not conclusive, we propose a potential reaction pathway (Scheme II) which involves initial acid catalyzed addition of formic acid to the nitrile carbon followed by rapid inter or intramolecular acyl transfer. Cyclization/dehydration then affords **2d**. The initial formic acid addition product also hydrolyses to **3** which then more slowly cyclizes to quinazolin-4(1*H*)-one **2d**.

Scheme I
Rate of formation of **2d** from **1d**

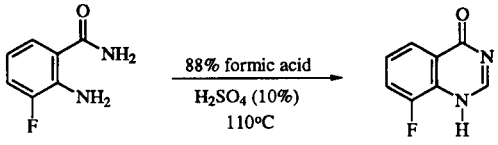


1d **2d** **3**

Percent

Time (min)	1d	2d	3
5	0	91	91
18	0	99	99

Rate of Formation of **2d** From **3**

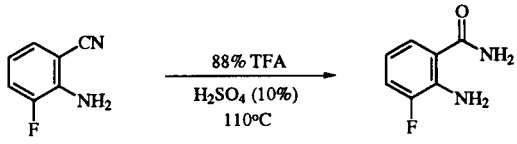


3 **2d**

Percent

Time (min)	3	2d
5	43	57
18	7	93

Rate of Formation of **3** from **1d**



1d **3**

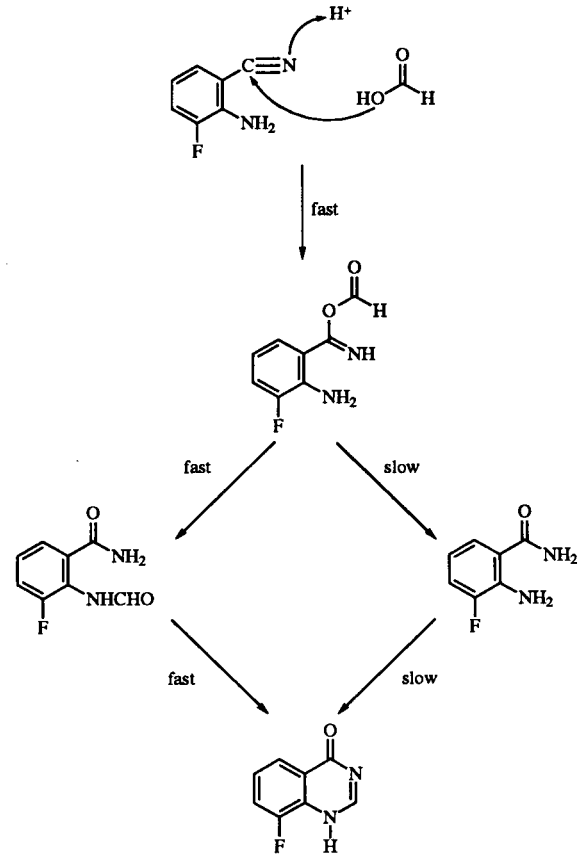
Percent

Time (min)	1d	3
5	95	5
18	76	24
140	20	80

EXPERIMENTAL

Melting points were determined using a Thomas Hoover capillary melting point apparatus and are uncorrected. Proton nmr spectra were obtained using a Bruker AC-300 instrument in DMSO-d_6 with tetramethylsilane (TMS) as the internal standard. High resolution mass spectrometry (hrms) measurements were made using a VG/Fisons autospec instrument with direct exposure probe sample introduction. Reaction rate measurements were made *via* gas chromatography on a Hewlett Packard 5890 instrument equipped with a flame ionization detector. Analyses were conducted on a Restek Rtx-1701 column (15 m x 0.32 mm id, 0.25 micron film) under the following conditions: temperature 1 = 80°C, time 1 = 1 minute, rate = 15°C/minute, temperature 2 = 250°C. Reverse phase hplc analyses were conducted on a Keystone Scientific Phenyl Hypersil-1 column (250 x 4.6 mm, 5 micron) using 50/50 acetonitrile/water (0.05% orthophosphoric acid) as the eluent. The flow rate was 1.0 ml/min and detection was accomplished at 230 nm.

Scheme II
A Possible Reaction Pathway



General Procedure for Cyclization.

The general procedure is exemplified by description of the cyclization of 2-amino-3-fluorobenzonitrile (**1d**) to provide 8-fluoroquinoazolin-4(1*H*)-one (**2d**). The 2-aminobenzonitrile (**1d**, 3.0 g, 22 mmoles) was added in portions [11] over 1 hour to a mildly refluxing (oil bath temperature of 105-115°C) mixture of 88% formic acid (30 ml) and sulfuric acid (1.0 g). After an additional 15 minutes, the mixture was allowed to cool to *ca.* 60°C, poured into ice water (100 ml) and allowed to stand cold for 15 minutes. The resulting precipitate was collected and washed

well with water. Drying to a constant weight provided **2d** as an off white solid (3.17 g, 88%).

General Procedure for Rate Measurements.

To a refluxing mixture of 88 wt % carboxylic acid (8.7 g) and sulfuric (1.0 g) was added **2d** (300 mg, 1.71 mmoles) in one portion. Weighed aliquots of the reaction mixture were taken at the specified time (Scheme I) and added to *N,N*-dimethylformamide containing a known amount of fluoranthene as the internal standard. A 0.5 micro liter sample was then analyzed by gc.

Acknowledgements.

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REFERENCES AND NOTES

[1] For selected examples of the uses of quinazolin-4(1*H*)-ones as pharmaceutical and Agro chemical intermediates see: N. Singhal, I. S. Gupta and P. C. Bansal, *J. Indian Chem. Soc.*, **61**, 690 (1984). R. A. LeMahieu, M. Carson, W. C. Nason, D. R. Parrish, A. F. Wleton, H. W. Baruth and B. Yaremko, *J. Med. Chem.*, **26**, 420 (1983). J. J. Tai, J. W. Ringer, K. L. Krumel and R. C. Krauss, US Patent 5,214,144 (1993).

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[9] Most of the 2-aminobenzonitriles utilized in this study were prepared either by the Rosenmund-von Braun cyanation of 2-haloanilines or the aminolysis of 2-fluorobenzonitriles.

[10] Quinazolin-4(1*H*)-ones **2a-h** were obtained at 96+ area percent purity by reverse phase hplc analysis. Yields presented in Table I are unoptimized and based on dried materials isolated directly from the reaction mixture. Recrystallization from ethanol/water or *N,N*-dimethylformamide/water can provide analytically pure materials listed in Table III.

[11] For convenience, the 2-aminobenzonitrile may be dissolved in 88% formic acid and added to the reaction *via* a dropping funnel.