John B. Hynes, Johnny P. Campbell and John D. Hynes

Department of Pharmaceutical Sciences, Medical University of South Carolina,
Charleston, South Carolina 29425

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The reactions of ten *ortho*-fluoroketones with guanidine carbonate in *N,N*-dimethylacetamide were investigated as a new synthetic approach to 2-amino-4-alkyl- and 2-amino-4-arylquinazolines. The yields obtained ranged from low to moderate and were highly dependent upon the nature of the substituents on the reactant. Eight new quinazolines were elaborated in this study.

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The quinazoline ring system provides the backbone for compounds having widely diverse pharmacologic activities such as sedative, analgesic, diuretic, antihypertensive, antimicrobial and antineoplastic [1]. Noteworthy compounds containing the quinazoline nucleus in current medical use are the diuretic quinethazone, the antihypertensive agent prazosin and the dihydrofolate reductase inhibitor trimetrexate. The last of these not only displays significant antitumor effects, but is also being employed in clinical trials for the treatment of opportunistic microbial infections in AIDS patients [2].

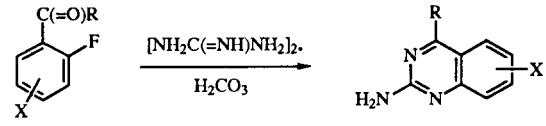
Earlier synthetic efforts from this laboratory have demonstrated that a variety of *ortho*-fluorobenzonitriles, when heated with guanidine carbonate in *N,N*-dimethylacetamide yield 2,4-diaminoquinazolines in good to excellent yields [3]. Even 2,3,6- 2,4,5- and 2,3,4-trifluorobenzonitriles gave the three isomeric difluorinated 2,4-diaminoquinazolines demonstrating the regiospecificity of this reaction [4]. The substitution of formamidine acetate or acetamidine acetate for guanidine carbonate in the aforementioned reaction gave several of the corresponding 4-amino- and 4-amino-2-methylquinazolines, respectively [5].

In the current study we have extended this synthetic approach to the reaction of *ortho*-fluoroketones with guanidine carbonate as a potential direct route to a variety of novel 2-amino-4-alkyl- and 2-amino-4-arylquinazolines. The results obtained together with the physical properties of newly synthesized compounds are presented in Table 1.

In general, the optimal reaction conditions appear to be heating the reaction mixture in *N,N*-dimethylacetamide at

Table 1

Physical and Analytical Data for 2-Aminoquinazolines Prepared from *ortho*-Fluoroketones



Compound No.	R	X	Reaction Time, Hours	Molar Ratio Ketone/Guanidine Carbonate	Yield %	MS m/e	Emperical Formula	Analyses % Calcd./Found C	H	N
1	CH_3	—	9	1:2	31	159	$C_9H_9N_3$			
2	CH_3	5-F	9	1:1.5	50	177	$C_9H_8FN_3$	61.01	4.55	23.72
								60.94	4.43	23.38
3	CH_3	6-F	5	1:1.5	50	177	$C_9H_8FN_3$	61.01	4.55	23.72
								61.22	4.46	23.45
4	CH_3	7-F	6	1:1.5	30	177	$C_9H_8FN_3$	61.01	4.55	23.72
								60.82	4.46	23.76
5	CH_3	7-OCH_3	6	1:1.5	65	189	$C_{10}H_{11}N_3O$	63.48	5.86	22.21
								63.56	5.86	22.29
6	CH_3	6-F,7-Cl	5	1:1.5	33	211,213	$C_9H_7ClFN_3$	51.08	3.33	19.86
								51.02	3.37	19.76
7	C_2H_5	—	3	1:1.5	7	173	$C_{10}H_{11}N_3$	69.34	6.40	24.26
								69.28	6.33	24.33
8	C_2H_5	5-F	3.5	1:1.5	53	191	$C_{10}H_{10}FN_3$	62.82	5.27	21.98
								62.81	4.99	21.94
9	C_6H_5	—	5	1:2	28	221	$C_{14}H_{11}N_3$			
10	C_6H_5	5-F	5.5	1:1.5	33	239	$C_{14}H_{10}FN_3$	70.28	4.21	17.56
								70.00	3.92	17.55

ca. 140° for 3.5 to 9 hours using a molar ration of guanidine carbonate to ketone of 1.5:1 or 2:1. In many instances the reactions failed to proceed to completion as adjudged by tlc and longer reaction times only led to an increase in the amount and number of side reaction products. In the case of *ortho*-fluoroacetophenone, the reaction ratios were varied stepwise from 1.5:1 to 2.5:1 with little change in the resulting yield. The presence of an additional fluorine atom *ortho* to the carbonyl group had a beneficial effect upon yield as compared to that obtained with the correspondence unsubstituted *ortho*-fluoroketone. However, in the case of 2,4,5-trifluoroacetophenone, the reaction was unsuccessful and the major product appeared to result from the nucleophilic displacement of either the 4- or 5-fluorine of the reactant by guanidine as indicated by nmr and mass spectral analysis (experimental results not presented).

It may be concluded that the reaction of *ortho*-fluoroketones with guanidine carbonate is of value for the preparation of certain otherwise difficult to access quinazolines. However, the reactions are not nearly as clean as in the case of *ortho*-fluorobenzonitriles [1].

EXPERIMENTAL

Melting points were determined on a Mel-temp apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. after vacuum drying at 100°. Each reaction was conducted at 135° or 140° in *N,N*-dimethylacetamide using the molar ratios and reaction times shown in Table 1. Final compounds were free of significant impurities by tlc using silica gel media (Kodak-13181 with fluorescent indicator). The ^{1}H nmr spectra were obtained in DMSO-d_6 using 300 MHz (Varian Gemini 300) or 400 MHz (Varian VXR-400) instruments. The ^{1}H chemical shifts are presented in parts per million downfield from tetramethylsilane as the internal standard and the relative peak areas are given to the nearest whole number. The electron impact mass spectra were obtained using a Finnigan 4521 GC/MS spectrometer.

General Methods for Preparing Compounds **1-10**.

2-Amino-4-methylquinazoline (**1**).

A mixture of 3.45 g (0.025 mole) of *ortho*-fluoroacetophenone, 9.0 g (0.05 mole) of guanidine carbonate in 250 ml of *N,N*-dimethylacetamide was heated at 135° under a nitrogen purge for nine hours. The solvent was removed under vacuum. To the resulting paste was added 500 ml of cold water and after stirring the resulting solid was separated by filtration and washed with water. The solid was recrystallized from water separated by filtration and dried over phosphorus pentoxide under vacuum to yield 1.24 g (31%) of cream colored solid, tlc (tetrahydrofuran:*n*-heptane-1:1), mp 156-158° (lit [6] mp 155°).

2-Amino-5-fluoro-4-methylquinazoline (**2**).

The crude solid was obtained from 2,6-difluoroacetophenone, 1.95 g (0.013 mole), in an analogous fashion as described above. It was recrystallized from ethyl alcohol, separated by filtration and dried over phosphorus pentoxide to yield 1.1 g (50%) of off white crystalline solid tlc (ethyl acetate), mp 186-188°, ^{1}H nmr: 400 MHz δ 2.77 (d, 3H, CH_3, J = 6.1 Hz), 6.85 (br s, 2H, NH_2), 6.92 (dd, 1-H, 6-H, J = 11.9 Hz, J = 7.9 Hz), 7.23 (d, 1H, 8-H, J = 8 Hz), 7.60 (m, 1-H, H-7).

2-Amino-6-fluoro-4-methylquinazoline (**3**).

The brown oily solid obtained from the reaction of 2,5-difluoroacetophenone, (2.85 g, 0.018 mole) was stirred in water and the resulting solid separated by filtration, washed successively with water and diethyl ether and air dried. It was crystallized from ethyl acetate-*n*-hexane to yield 1.60 g (50%) of a beige crystalline solid, tlc (ethyl acetate), mp 215-216.5°; ^{1}H nmr: 300 MHz δ 2.69 (s, 3H, CH_3), 6.71 (br s, 2H, NH_2), 7.45 (m, 1H), 7.56 (m, 1H), 7.71 (m, 1H).

2-Amino-7-fluoro-4-methylquinazoline (**4**).

The residue obtained from the reaction of 2,4-difluoroacetophenone (1.95 g, 0.0125 mole) was suspended in water and the solid separated by filtration and washed with water. Recrystallization from water and drying over phosphorus pentoxide gave 0.66 g (30%) of white crystals, tlc (ethyl acetate), mp 189-190°; ^{1}H nmr: 400 MHz δ 2.69 (s, 3H, CH_3), 6.86 (br s, 2H, NH_2), 7.06 (m, 2H, 6-H + 8-H), 8.02 (dd, 1H, 5-H, J = 7.6, J = 6.6).

2-Amino-7-methoxy-4-methylquinazoline (**5**).

The residue obtained from the reaction of 2-fluoro-4-methoxyacetophenone (1.68 g, 0.01 mole) was stirred in water and the resulting solid separated by filtration and dried. This material was recrystallized from a 1:1 mixture of ethyl acetate and toluene by the addition of *n*-heptane at the boiling point produced 1.23 g (65%) of white crystals, tlc (ethyl acetate), mp 173.5-175°; ^{1}H nmr: 300 MHz δ 2.64 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 6.68 (br s, 2H, NH_2), 6.80-6.82 (m, 2H, 6-H + 8-H), 7.82 (d, 1H, 5-H, J = 9.6 Hz).

2-Amino-7-chloro-6-fluoro-4-methylquinazoline (**6**).

After removal of the solvent at reduced pressure from the reaction of 4-chloro-2,5-difluoroacetophenone, 3.81 g (0.02 mole), water was added and resulting solid was separated by filtration, washed with water and *n*-hexane. It was recrystallized from ethyl acetate-*n*-hexane (charcoal) separated by filtration and washed with *n*-hexane. A second recrystallization from ethyl acetate gave 1.38 g (33%) of yellow crystals, tlc (ethyl acetate:toluene, 4:1), mp 208-210°; ^{1}H nmr: 300 MHz δ 2.69 (s, 3H, CH_3), 6.92 (br s, 2H, NH_2), 7.57 (d, 1H, 8-H, J = 6.9 Hz), 7.97 (d, 1H, 5-H, J = 9.9 Hz).

2-Amino-4-ethylquinazoline (**7**).

Water was added to the residue obtained from the reaction of 3.04 g (0.02 mole) of 2-fluoropropiophenone with guanidine carbonate to produce a cream colored solid which was separated by filtration, washed with water and air dried. Recrystallization from benzene-*n*-heptane (charcoal) gave after drying over phosphorus pentoxide 0.25 g (7%) of yellow solid, tlc (toluene-ethyl acetate, 1:3) mp 103-104.5°, ^{1}H nmr: 300 MHz δ 1.30 (t, 3H, CH_3, J = 7.4 Hz), 3.08 (q, 2H, CH_2, J = 7.4 Hz), 6.72 (s, 2H, NH_2), 7.19 (app. t, 1H, 6-H or 7-H), 7.43 (d, 1H, 8-H, J = 8.49 Hz), 7.64 (app. t, 1H, 6-H or 7-H), 7.85 (d, 1H, 5-H, J = 7.95 Hz).

2-Amino-5-fluoro-4-ethylquinazoline (**8**).

The residue obtained from 3.4 g (0.02 mole) of 2,6-difluoropropiophenone obtained by removal of the solvent at reduced pressure was stirred in water and the solid isolated by filtration. This material was recrystallized from ethanol-water (charcoal) to produce cream colored crystalline solid, tlc (toluene:ethyl acetate, 10:1), which after vacuum drying over phosphorus pentoxide melted at 142.5-144°, 2.02 g (53%); ^{1}H nmr: 300 MHz δ 1.26 (t, 3H, CH_3), 3.09 (m, 2H, CH_2), 6.89 (dd, 1H, 6-H or 7-H, J = 10.2 Hz, J = 8.3 Hz), 6.96 (s, 2H, NH_2), 7.25 (d, 1H, 8-H, J = 8.5 Hz), 7.57 (dd, 1H, 6-H or 7-H, J = 10.8 Hz, J = 7.5 Hz).

2-Amino-4-phenylquinazoline (**9**).

A mixture of 2.0 g (0.01 mole) of *ortho*-fluorobenzophenone, 3.6 g (0.02 mole) of guanidine carbonate in 60 ml of *N,N*-dimethylacetamide was heated at 140° for 5 hours with magnetic stirring. The addition of water to the cold mixture produced a yellow oily solid, which was isolated by decantation and dried. Recrystallization from benzene-*n*-pentane gave 0.63 g (28%) of a light yellow crystalline solid, tlc (tetrahydrofuran:toluene, 1:2), which after vacuum drying at 100° melted at 165-166.5° (lit [7] mp 169-170°). A substantial amount of unreacted ketone was detected during the workup procedure.

2-Amino-5-fluoro-4-phenylquinazoline (**10**).

The residue obtained from 2.18 g (0.01 mole) of 2,6-difluorobenzophenone was dissolved in boiling acetone. After filtration to remove insoluble material, the solution was reheated and made just cloudy by the addition of water. The resulting white solid was separated by filtration and washed with toluene-*n*-hexane (3:1) and dried over phosphorus pentoxide to yield 0.8 g (33%) of off white crystals, tlc (toluene:*n*-hexane, 2:1), mp 138-139°. The analytical sample was recrystallized from carbon tetrachloride-*n*-heptane, mp 142-143°; ^{1}H nmr: 300 MHz δ 6.89 (dd, 1H, J = 9.8 Hz, J = 8.0 Hz), 7.08 (br s, 1H, NH_2), 7.34 (d, 1H, 8-H, J = 8.25), 7.47-7.55 (m, 6H), 7.67 (m, 1H).

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