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The reaction of guanidine carbonate with various *ortho*-fluorobenzaldehydes in *N,N*-dimethylacetamide was investigated as a potential route for preparing 2-aminoquinazolines. Eleven new 2-aminoquinazolines were elaborated in this manner in low to moderate yields. In general the best results were obtained with *ortho*-fluorobenzaldehydes possessing an electron withdrawing substituent at the other *ortho* position. Complex mixtures were obtained using 2-fluorobenzaldehyde, 2,5-difluorobenzaldehyde and 2-fluoro-5-methoxybenzaldehyde which were not resolved.

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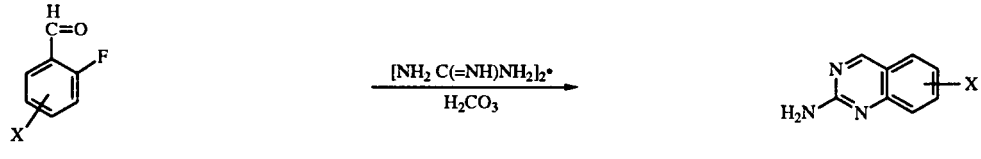
2-Aminoquinazolines possessing a hydrogen at position 4 can be prepared by the reaction of ammonia with the corresponding 2-chloroquinazoline [1,2]. Alternatively, the cyclization of *ortho*-aminobenzaldehydes with guanidine or cyanamide has been employed [3,4]. Each of these approaches has limitations due to the vigorous nature of the reaction conditions. The current study was conducted in order to evaluate the reaction of guanidine carbonate with ortho-fluorobenzaldehydes as a new method for preparing 2-aminoquinazolines. This study represents an extention of earlier research emanating from this laboratory involving the synthesis of 2,4-diaminoquinazolines from *ortho*-fluorobenzonitriles [5,6] and 2-amino-4-alkyl- or 2-amino-4-arylquinazolines from *ortho*-fluoroketones [7].

As shown in Table 1, eleven new 2-aminoquinazolines were prepared and fully characterized in the current study. It will be seen that the yields ranged from modest to low depending upon the nature of the starting aldehyde. In

Table 1

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



Compound No.	X on Quinazoline	Reaction Temperature, °C	Reaction Time, Hours	Molar Ratio Aldehyde/ Guanidine Carbonate	Yield %	MS m/z	Emperical Formula	Analyses %, Calcd./Found C	H	N
1	5-Cl	140-145	6	1:1.5	62	179, 181	$C_8H_6ClN_3$	53.50	3.37	23.40
								53.54	3.36	23.34
2	5-CF_3	115	5	1:1	63	213	$C_9H_6F_3N_3$	50.71	2.79	19.71
								50.64	2.83	19.78
3	5-F	140	2	1:1.5	41	163	$C_8H_6FN_3 \cdot 0.2H_2O$	57.62	3.87	25.20
								57.85	3.80	25.48
4	5,6-F_2	140	1	1:1.5	51	181	$C_8H_5F_2N_3$	53.04	2.78	23.20
								53.20	2.82	23.29
5	6-Br	140	6	1:1.5	39	223, 225	$C_8H_6BrN_3$	42.88	2.70	18.75
								42.95	2.71	18.84
6	6-CF_3	140	3	1:1.5	39	213	$C_9H_6F_3N_3$	50.71	2.84	19.71
								50.88	2.89	19.46
7	7-F	140	2	1:1	20	163	$C_8H_6FN_3$	58.89	3.71	25.76
								58.96	3.77	25.68
8	7-Cl	140	2	1:1.5	44	179, 181	$C_8H_6ClN_3$	53.50	3.37	23.40
								53.56	3.42	23.33
9	7-Br	140	2	1:1.5	28	223, 225	$C_8H_6BrN_3$	42.88	2.70	18.75
								43.00	2.77	18.69
10	7-CF_3	140	2.5	1:1.5	<10	213	$C_9H_6F_3N_3$	50.71	2.84	19.71
								50.87	2.92	19.79
11	8-F	140	2	1:1.5	34	163	$C_8H_6FN_3$	58.89	3.71	25.76
								58.92	3.76	25.67

general, better yields were obtained when an electron withdrawing substituent was present at position six of the reactant. This substitution pattern could assist in the stabilization of a guanidine-aldehyde adduct, which is proposed as the key intermediate, [ArCH = N-C(=NH)NH_2]. The reaction was unsuccessful with 2-fluorobenzaldehyde as well as 2-fluoro-5-methoxybenzaldehyde and 2,5-difluorobenzaldehyde (results not presented). The reaction of 2,3,6-trifluorobenzaldehyde with guanidine carbonate could produce either the 5,6-difluoro or 5,8-difluoro isomer or a mixture of the two. Only a single quinazoline was isolated, which was assigned the structure 2-amino-5,6-difluoroquinazoline, **4**, based upon the analysis of its nmr coupling constants. Similar results were reported earlier for the reaction of 2,3,6-trifluorobenzonitrile and guanidine carbonate which yielded 2,4-diamino-5,6-difluoroquinazoline, exclusively [6].

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 70°. Each reaction was conducted in anhydrous *N,N*-dimethylacetamide in a nitrogen atmosphere using the conditions indicated in Table 1. The course of each reaction was monitored by tlc. Final compounds were free of significant impurities by tlc using silica gel media (Kodak-13181 with fluorescent indicator). The ^1H nmr spectra were obtained in DMSO-d_6 using 300 MHz (Varian Gemini 300) or 400 MHz (Varian VXR-400) instruments. The ^1H 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 ^{19}F nmr chemical shifts were determined in DMSO-d_6 at 282.3 MHz and are presented in parts per million relative to fluorotrichloromethane. The electron impact mass spectra were obtained using a Finnigan 4521 GC/MS spectrometer. Compounds **2**, **3**, **4** and **5** were run by solid probe.

General Methods for Preparing Compounds **1**-**11**.

2-Amino-5-chloroquinazoline (**1**).

A mixture of 4.5 g (0.028 mole) of 2-chloro-6-fluorobenzaldehyde and 7.6 g (0.042 mole) of guanidine carbonate in 84 ml of *N,N*-dimethylacetamide was heated at 140-145° for six hours. After cooling under refrigeration the yellow precipitate was separated by filtration and washed with water and then diethyl ether. A second crop, obtained from the original filtrate by the addition of 300 ml of dichloromethane, was isolated in a similar fashion. After drying under vacuum at 70° a total of 3.15 g (62%) of yellow crystals was obtained, tlc (ethyl acetate-dichloromethane, 1:1), mp 246-251.5°, ^1H nmr: 400 MHz δ 7.14 (br s, 2H, NH_2), 7.31 (d, 1H, 6-H or 8-H, J = 7.3 Hz), 7.39 (d, 1H, 6-H or 8-H, J = 8.7 Hz), 7.64 (dd, 1H, 7-H), 9.27 (s, 1H, 4-H).

2-Amino-5-trifluoromethylquinazoline (**2**).

A mixture of 5.0 g (0.026 mole) of 2-fluoro-6-trifluoromethylbenzaldehyde and 4.71 g (0.026 mole) of guanidine carbonate in 250 ml of *N,N*-dimethylacetamide was heated under nitrogen for five hours. After cooling, the solvent was removed at reduced pressure and the resulting solid was suspended in water which was then adjusted to *p*H 8.5 with concentrated ammonium hydroxide. The solid was separated by filtration, washed with water and then dried under vacuum at 70°. This material was recrystallized from acetone to yield 3.5 g (63%) of fine light yellow crystals, tlc (ethyl acetate), mp 248-250°, ^1H nmr: 400 MHz δ 7.22 (br s, 2H, NH_2), 7.61 (d, 1H, 6-H or 8-H, J = 7.1 Hz), 7.70 (d, 1H, 6-H or 8-H, J = 8.4 Hz), 7.80 (dd, 1H, 7-H, J_1 = J_2 = 8.0 Hz), 9.20 (s, 1H, 4-H).

2-Amino-5-fluoroquinazoline (**3**) .

A mixture of 2.84 g (0.020 mole) of 2,6-difluorobenzaldehyde and 5.40 g (0.030 mole) of guanidine carbonate in 75 ml of *N,N*-dimethylacetamide was heated at 140° for 2 hours under nitrogen. A yellow solid was obtained by adding 130 ml of water to the cooled reaction mixture which was isolated by filtration. It was dissolved in 2*N* hydrochloric acid and filtered to remove insoluble materials and the filtrate was extracted two times with 25 ml portions of diethyl ether. Neutralization with 2*N* sodium hydroxide and cooling produced a solid which was isolated by filtration and air dried. The solid was recrystallized from ethyl alcohol (charcoal) to produce a cream colored crystalline solid which after drying under vacuum over phosphorus pentoxide weighed 1.34 g (41%), tlc (ethyl acetate), mp 226-229°; ^1H nmr: 300 MHz δ 6.96 (dd, 1H, 6-H or 7-H, J = 9.6 Hz, J = 8.3 Hz), 7.12 (br s, 2H, NH_2), 7.23 (d, 1H, 8-H, J = 8.49), 7.64 (dd, 1H, 6-H or 7-H, J = 14.9 Hz, J = 8.0 Hz), 9.24 (s, 1H, 4-H).

2-Amino-5,6-difluoroquinazoline (**4**).

To a solution of 2.7 g (0.017 mole) of 2,3,6-trifluorobenzaldehyde in 65 ml of *N,N*-dimethylacetamide was added 4.53 g (0.025 mole) of guanidine carbonate. After heating for one hour the solution was cooled and added to 100 ml of water and then refrigerated. The resulting solid was separated by filtration and dissolved in 40 ml of 2*N* hydrochloric acid. The solution was extracted twice with 20 ml of diethyl ether and then neutralized with 2*N* sodium hydroxide and refrigerated. The precipitate was separated by filtration and then recrystallized from ethyl alcohol-water. The precipitate was separated by filtration and dried under vacuum over phosphorus pentoxide to yield 1.56 g (51%) of light yellow powder, tlc (ethyl acetate-dichloromethane, 1:1), mp 292-294° dec; ^1H nmr: 300 MHz δ 6.92 (ddd, 1H, 8-H, J = J = 9.0 Hz, J = 3.0 Hz), 7.44 (br s, 2H, NH_2), 7.52 (ddd, 1H, 7-H, J = 10.8 Hz, J = 8.8 Hz, J = 5.0 Hz), 9.26 (d, 1H, 4-H, J = 1.4 Hz); ^{19}F nmr: 282.3 MHz δ -3.95 (ddd, 1, 6-F, J = 21.9 Hz, J = 9.6 Hz, J = 5.0 Hz), -9.95 (dd, 1, 5-F, J = 21.9 Hz, J = 11.1 Hz).

2-Amino-6-bromoquinazoline (**5**).

A mixture of 4.06 g (0.02 mole) of 5-bromo-2-fluorobenzaldehyde and 5.4 g (0.03 mole) of guanidine carbonate in 75 ml of *N,N*-dimethylacetamide was heated at 140° for six hours under nitrogen. Cooling in a freezer caused the precipitation of a solid which was separated by filtration and dried at 110° under vacuum. Recrystallization from ethyl alcohol-water gave 1.73 g (39%) of a yellow solid which had mp 270-272° after vacuum drying over phosphorus pentoxide, tlc (ethyl acetate-toluene, 1:1), ^1H nmr: 300 MHz δ 7.05 (br s, 2H, NH_2), 7.36 (d, 1H, 7-H, J = 8.7 Hz), 7.77 (d, 1H, 8-H, J = 9.0 Hz), 8.05 (s, 1H, 5-H), 9.09 (s, 1H, 4-H).

2-Amino-6-trifluoromethylquinazoline (**6**).

This compound was obtained by the reaction of 1.92 g (0.01 mole) of 2-fluoro-5-trifluoromethylbenzaldehyde and 2.70 g (0.015 mole) of guanidine carbonate in 38 ml of *N,N*-dimethylacetamide at 140° for three hours. Removal of the solvent at reduced pressure produced a brown sticky material which was triturated with boiling water. The resulting solid was separated by filtration and recrystallized from 95% ethyl alcohol (charcoal) The resulting material was separated on a funnel and dried over phosphorus pentoxide to yield 0.83 g (39%) of cream colored solid, tlc (ethyl acetate-hexane, 1:1), mp 193-195°; ^{1}H nmr: 300 MHz δ 7.29 (br s, 2H, NH_2), 7.53 (d, 1H, 7-H, J = 9.0 Hz), 7.86 (d, 1H, 8-H, J = 8.9 Hz). 8.24 (s, 1H, 5-H), 9.25 (s, 1H, 4-H).

2-Amino-7-fluoroquinazoline (**7**).

A mixture of 2.84 g (0.02 mole) of 2,4-difluorobenzaldehyde and 3.60 g (0.02 mole) of guanidine carbonate in 70 ml of *N,N*-dimethylacetamide was heated at 140° for two hours. After filtration, the solvent was removed under vacuum at 100° in the presence of 5 g of silica gel. The resulting powder was applied to a 3 x 20 cm column containing 25 g of silica gel (Silica gel 60, 35-70 μm, E. Merck) packed with ethyl acetate-dichloromethane, 1:1. The column was eluted with this solvent combination to remove front running impurities and then with ethyl acetate to elute the product. Homogeneous fractions were combined and the solvent removed at reduced pressure. The residue was recrystallized from ethyl acetate-*n*-heptane (charcoal). The resulting light yellow solid was isolated on a filter and dried under vacuum over phosphorus pentoxide to yield 0.66 g (20%), tlc (ethyl acetate), mp 248-252°; ^{1}H nmr: 300 MHz δ 7.01 (br s, 2H, NH_2), 7.06-7.12 (m, 2H), 7.87 (dd, 1H, $J_1 = J_2 = 8$ Hz), 9.08 (s, 1H, 4-H).

2-Amino-7-chloroquinazoline (**8**).

To a solution of 0.60 g (3.8 mmoles) of 4-chloro-2-fluorobenzaldehyde in 20 ml of *N,N*-dimethylacetamide was added 1.02 g (5.7 mmoles) of guanidine carbonate and the mixture was heated at 140° for two hours. Approximately 50 ml of water was added and after refrigeration, a tan solid was isolated by filtration. This was suspended in 25 ml of 2*N* hydrochloric acid and the insoluble material was removed by filtration and discarded. The acidic solution was extracted two times with 20 ml portions of diethyl ether and then neutralized to *p*H 10 with 2*N* sodium hydroxide. The resulting solid was isolated by filtration, recrystallized from ethyl alcohol and dried over phosphorus pentoxide to yield 0.30 g (44%) of a white solid, tlc (ethyl acetate), mp >276° dec; ^{1}H nmr: 300 MHz δ 7.05 (br s, 2H, NH_2), 7.22 (dd, 1H, 6-H, J = 8.5 Hz, J = 1.9 Hz), 7.42 (s, 1H, 8-H), 7.82 (d, 1H, 5-H, J = 8.5 Hz), 9.12 (s, 1H, 4-H).

2-Amino-7-bromoquinazoline (**9**).

This reaction was conducted in an analogous fashion to the procedure for **8** using 3.94 g (19.4 mmoles) of 4-bromo-2-fluorobenzaldehyde. The solid obtained by basification was separated by filtration and recrystallized from ethyl alcohol to yield 1.22 g (28%) of light orange crystals, tlc (ethyl acetate), mp >283° dec; ^{1}H nmr: 300 MHz δ 7.06 (br s, 2H, NH_2), 7.34 (d, 1H, 6-H, J = 8.1 Hz), 7.58 (s, 1H, 8-H), 7.74 (d, 1H, 5-H, J= 8.5 Hz), 9.11 (s, 1H, 4-H).

2-Amino-7-trifluoromethylquinazoline (**10**).

A mixture of 7.2 g (0.037 mole) of 2-fluoro-4-trifluoromethylbenzaldehyde and 10.1 g (0.055 mole) of guanidine carbonate in 160 ml of *N,N*-dimethylacetamide was heated at 140° for 2.5 hours. This was added to approximately 300 ml of water to cause precipitation of the product. The resulting orange solid was separated by filtration washed with water and air dried. This material was dissolved in ethyl acetate, treated with charcoal, filtered through a plug of silica gel and the solvent removed at reduced pressure. The resulting solid was stirred in *n*-heptane, separated by filtration and air dried. Finally, it was recrystallized from 95% ethyl alcohol (charcoal) to yield after drying over phosphorus pentoxide 0.53 g (7%) of off white solid, tlc (tetrahydrofuran-*n*-heptane, 1:1), mp 233-235°; ^{1}H nmr: 300 MHz δ 7.20 (br s, 2H, NH_2), 7.45 (d, 1H, 6-H, J = 8.4 Hz), 7.68 (s, 1H, 8-H), 8.02 (d, 1H, 5-H, J = 8.3 Hz), 9.26 (s, 1H, 4-H).

2-Amino-8-fluoroquinazoline (**11**).

To a solution of 1.68 g (11.8 mmoles) of 2,3-difluorobenzaldehyde in 45 ml of *N,N*-dimethylacetamide was added 3.19 g (17.7 mmoles) of guanidine carbonate and the mixture was heated at 140° for two hours. The addition of approximately 100 ml of water and refrigeration produced a tan solid which was separated by filtration and washed with water. This material was dissolved in 25 ml of 2*N* hydrochloric acid, filtered to remove insoluble materials and the filtrate was extracted two times with 20 ml portions of diethyl ether. Neutralization with 2*N* sodium hydroxide to *p*H 9 produced a solid which was separated by filtration and then recrystallized from ethyl alcohol (charcoal) to yield 0.65 g (34%) of light orange crystals, tlc (ethyl acetate), mp 263-265°; ^{1}H nmr: 300 MHz δ 7.16 (br s, 2H, NH_2), 7.16 (ddd, 1H, 6-H, J = 7.9 Hz, J = 7.7 Hz, J = 4.7 Hz), 7.50 (dd, 1H, 7-H, J = 11.5 Hz, J = 7.8 Hz), 7.62 (d, 1H, 5-H, J = 8 Hz), 9.14 (s, 1H, 4-H).

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