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A NEW SYNTHESIS OF 2-ARYL-2H-PYRAZINO[2,1-b]QUINAZOLIN-3,6(1H,4H)-DIONES

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ABSTRACT: A new synthesis of 2-aryl-2H-pyrazino[2,1-b]quinazolin-3,6(1H,4H)-diones starting from 2-chloromethylquinazolin-4(3H)-one is described.

Pyrazino [2,1-b] quinazolin-6-ones are known to exhibit sedative, hypnotic and tranquilizing activity[1]. They were synthesised earlier by reacting anthranilic acid with piperazine derivatives[1-3], or through anthranilic acid peptide intermediates[4]. We report here a simple and efficient synthesis of the title compounds starting from 2-chloromethylquinazolin-4(3H)-one **(3)**, **3** is prepared by us in 58% yield by a new procedure involving dehydrative cyclisation of 2-ω-chloroacetylaminobenzamide **(2)** in PPE. 2-Chloromethylquinazolin-4(3H)-one **(3)** reacts with aniline, 4-methyl-, 4-ethyl-, 4-methoxy-, 4-ethoxy-, and 4-chloroanilines in ethanol to yield the corresponding 2-arylaminomethylquinazolin-4(3H)-ones **(4)** in 40-52%. The structures

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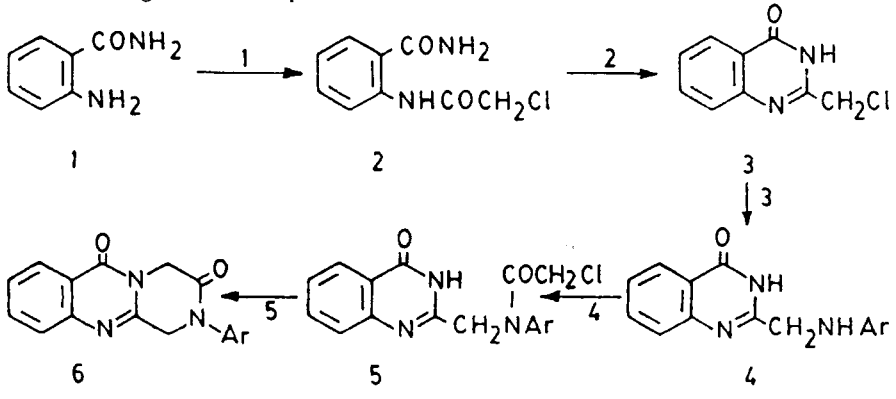
were confirmed by IR (ν NH 3400, ν CONH 3150 and ν CO 1670-1680 cm^{-1}), ^{1}H-NMR (δ NH 5.1 - 5.8, δ CH_2 4.0 - 4.3) and mass spectral data. Reaction of **4** with chloroacetic anhydride or chloroacetyl chloride resulted in regeospecific acylation of aniline NH to yield 2-N-chloroacetylarylaminomethylquinazolin-4(3H)-ones **(5)**. The methylene protons appeared as a singlet in the ^{1}H-NMR spectrum due to the absence of vicinal NH. When stirred in dioxane-triethyl amine mixture, **5** underwent dehydrochlorinative cyclisation to yield 2-aryl-2H-pyrazino [2,1-b] quinazolin-3,6(1H,4H)-diones **(6)**. In the 90 MHz ^{1}H-NMR spectra of **6**, an interesting feature is that the two methylene group protons have the same chemical shift value. But, the decoupled ^{13}C-NMR spectrum of **6d** showed two separate signals for the two methylene carbons (δ 53.76 and 55.51). Earlier Rajappa and Advani[3] also reported similar pattern for 2-methyl-2H-pyrazino [2,1-b] quinazolin-3,6(1H,4H)-dione. The mass spectra of **6** showed loss of CO, ArNCO & $ArN(CH_2)_2CO$ from $M^{+\cdot}$ as the characteristic fragmentation pattern.



1. $ClCOCH_2Cl$, 2. PPE, 3. $ArNH_2$, 4. $(ClCH_2CO)_2O$ or $ClCOCH_2Cl$, . Et_3N

4/5/6	a	b	c	d	e	f
Ar	C_6H_5	4-$H_3CC_6H_4$	4-$H_5C_2C_6H_4$	4-$H_3COC_6H_4$	4-$H_5C_2OC_6H_4$	4-ClC_6H_4

EXPERIMENTAL

2-ω-Chloroacetylaminobenzamide (2)

Chloroacetyl chloride (5 ml, b.p. 105-106 °C, Fluka) in benzene (50 ml) was added dropwise to a mixture of 2-aminobenzamide (**1**, 5g, Fluka), pyridine (10 ml, b.p. 115°C, Merck) and benzene (50 ml) and stirred for 1 h. 2-ω-Chloroacetyl aminobenzamide **(2)** separated out from the reaction mixture. It was filtered, washed with water (250 ml), dried and recrystallised from benzene-methanol (1:1) solvent mixture, yield 71%, m.p. 170-171°C (lit. m.p. 171°C)[5].

2-Chloromethylquinazolin-4(3H)-one (3)

2-ω-Chloroacetylaminobenzamide (**2**, 2.1 g, 1 mmol) was dissolved in polyphosphateethyl ester (20 ml) by warming on a steam bath and heated further for 8 h, cooled and poured in cold water (100 ml). 2-Chloromethylquinazolin-4(3H)-one **(3)** that separated out from the aqueous solution was filtered, dried and recrystallised from acetic acid, yield 82%, m.p. 247-248°C (lit. m.p. 247-248°C)[6].

2-Arylaminomethylquinazolin-4(3H)-one (4): General procedure

A mixture of 2-chloromethylquinazolin-4(3H)-one (**3**, 2.0 g, 10 mmol) and the appropriate aniline (20 mmol) was refluxed in ethanol (60 ml). The refluxing time varied with the nature of the substituent in aniline. 2-Arylaminomethylquinazolin-4(3H)-one **(4)** separated out from the cooled reaction mixture, filtered, dried and recrystallised from ethanol.

4a: 6 h, 52%, 222-224°C (lit. m.p. 222-224)[6], M^+ at m/z 251; λmax 315 (log ε 3.90), 302 (log ε 4.02), 264 (log ε 4.27) and 231 nm (log ε 4.76); νArNH 3400, νCONH 3150 and νCO 1670 cm^{-1}.

4b: 1 h, 49%, 201-203°C, M^+ at m/z 265; λmax 314 (log ε 3.70), 303 (log ε 3.86), 263 (log ε 4.08) and 227 nm (log ε 4.56); νArNH 3400, νCONH 3150 and νCO 1675 cm^{-1} ; ^{1}H-NMR (DMSO-d_6) : δ 2.08 (s, 3H, CH_3), 4.02 (d, 2H, CH_2), 5.42 (t, 1H, NH), 6.55 (ABq, 4H, ArH) and 7.18 - 7.98 (m, 4-ArH, 1NH).

4c: 2 h, 47%, 188-189°C, M^+ at m/z 279; λmax 314 (log ε 3.84), 303 (log ε 3.87), 262 (log ε 4.14) and 227 nm (log ε 4.58); νArNH 3400, νCONH 3150 and νCO 1675 cm^{-1}.

4d: 1 h, 42%, 186-188°C; M^+ at m/z 281; λmax 315 (log ε 3.75), 303 (log ε 3.91), 261 (log ε 4.10) and 227 nm (log ε 4.58); νArNH 3400,

ν CONH 3150 and ν CO 1675 cm^{-1} ; ^{1}H-NMR (DMSO-d_6): δ 4.0 (s, 3H, OCH_3), 4.3 (d, 2H, CH_2), 5.8 (t, 1H, NH), 6.62 (ABq, 4H, ArH) and 7.5 - 8.1 (m, 4ArNH, 1NH).

4e: 1 h, 40%, 184-185^{o}C; $M^{+\cdot}$ at m/z 295; λ max 315 (log ε 3.78), 303 (log ε 3.85), 262 (log ε 4.04) and 228 nm (log ε 4.52); ν ArNH 3410, ν CONH 3160 and ν CO 1680 cm^{-1} ; ^{1}H-NMR (DMSO-d_6) : δ 1.25 (t, 3H, CH_3), 3.75 (q, 2H, OCH_2), 3.95 (s, 2H, CH_2), 5.1 (t, 1H, NH), 6.66 (ABq, 4H, ArH) and 7.52 - 8.2 (m, 4ArH, 1NH).

4f: 7 h, 41%, 213-215^{o}C; $M^{+\cdot}$ at m/z 285; λ max 315 (log ε 3.89), 303 (log ε 3.96), 248 (log ε 4.46) and 226 nm (log ε 4.60); ν ArNH 3400, ν CONH 3160 and ν CO 1670 cm^{-1}.

2-N-Chloroacetylarylaminomethylquinazolin-4(3H)-ones (5): General procedure

Method i : A mixture of 2-arylaminomethylquinazolin-4(3H)-one (**4**, 1g) and chloroacetic anhydride (1 g, m.p. 56-59^{o}C, Aldrich) in methylene chloride (40 ml) was stirred at room temperature. The reaction time varied with the substituent in aniline moiety. After the completion of the reaction (vide tlc) the solvent was removed and the residue was treated with water (2 x 10 ml). 2-N-Chloroacetylarylaminomethylquinazolin-4(3H)-ones **(5),** thus obtained was filtered and recrystallised from benzene.

Method ii: To a mixture of 2-arylaminomethylquinazolin-4(3H)-one (**4**, 1g) and potassium carbonate (2 g, Merck) in acetone (80 ml), chloroacetyl chloride (1 ml, b.p. 105-106°C, Fluka) was added and the reaction mixture was refluxed for 6 h. The solution was filtered, and the solid portion was washed with water (100 ml) dried and recrystallised from benzene.

5a: 5 h, 77% (72%), 161-163°C; M^+ at m/z 327; λ max 315 (log ε 4.03), 304 (log ε 4.12), 265 (log ε 4.35) and 225 nm (log ε 4.95); ν CONH 3160 and ν CO 1685 & 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 3.91 (s, 2H, CH_2), 4.87 (s, 2H, CH_2), 7.13 - 7.83 (m, 8ArH, 1NH) and 8.3 (d, 1H, ArH).

5b: 1 h, 78% (70%), 173-174°C; M^+ at m/z 341; λ max 315 (log ε 3.83), 304 (log ε 3.91), 263 (log ε 4.12) and 224 nm (log ε 4.72); ν CONH 3150 and ν CO 1690 & 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.35 (s, 3H, CH_3), 3.92 (s, 2H, CH_2), 4.88 (s, 2H, CH_2), 6.96 - 7.74 (m, 7ArH, 1NH) and 8.32 (d, 1H, ArH).

5c: 1 h, 79% (71%), 189-190°C; M^+ at m/z 355; λ max 319 (log ε 3.93), 304 (log ε 3.99), 265 (log ε 4.24) and 224 nm (log ε 4.86); ν CONH 3150 and ν CO 1695 & 1655 cm^{-1}.

5d: 1 h, 84% (74%), 183-185°C; M^+ at m/z 357; λ max 317 (log ε 3.93), 303 (log ε 4.06), 266 (log ε 4.26), and 225 nm (log ε 4.86); ν CONH 3150 and ν CO 1690 & 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.8 (s, 3H, OCH_3), 4.0 (s, 2H, CH_2), 4.8 (s, 2H, CH_2), 6.6 - 7.6 (m, 7ArH, 1NH) and 8.0 (d, 1H, ArH).

5e: 1 h, 60% (62%), 174-175°C; M^+ at m/z 371; λmax 315 (log ε 3.96), 303 (log ε 4.01), 265 (log ε 4.30) and 230 nm (log ε 4.88); νCONH 3175 and νCO 1685 & 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.48 (t, 3H, CH_3), 4.01 (q, 4H, OCH_2, CH_2), 4.86 (s, 2H, CH_2), 6.69 - 7.74 (m, 7ArH, 1NH) and 8.17 (d, 1H, ArH).

5f: 6 h, 82% (79%), 131-132°C; M^+ at m/z 361; λmax 314 (log ε 3.94), 304 (log ε 4.02), 265 (log ε 4.59) and 225 nm (log ε 4.86); νCONH 3175 and νCO 1675 & 1650 cm^{-1}.

2-Aryl-2H-pyrazino [2,1-b] quinazolin-3,6(1H,4H)-diones (6): General procedure

To a solution of 2-N-chloroacetylarylaminomethylquinazolin-4(3H)-one (**5**, 0.6 g) in hot dioxane (15 ml, b.p. 100-102°C, Merck) triethylamine (1 ml, b.p. 89°C, Merck) was added. The reaction mixture was stirred for 24 h at room temperature and poured in water (120 ml). 2-Aryl-2H-pyrazino [2,1-b] quinazolin-3,6(1H,4H)-diones **(6)** that separated out from the aqueous solution was filtered, dried and recrystallised from benzene.

6a: 93%, 195-196°C, M^+ at m/z 291; λmax 317 (log ε 3.84), 304 (log ε 3.92), 268 (log ε 4.27) and 225 nm (log ε 4.79); νCO 1685 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.9 (s, 2H, CH_2), 5.1 (s, 2H, CH_2), 7.22 - 7.92 (m, 8H, ArH) and 8.43 (d, 1H, ArH).

6b: 93%, 199-201°C; M^+ at m/z 305; λmax 316 (log ε 3.65), 304 (log ε 3.72), 267 (log ε 4.06) and 225 nm (log ε 4.59); νCO 1685 & 1675 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.37 (s, 3H, CH_3), 4.93 (s, 4H, 2 x CH_2), 7.23 - 7.72 (m, 7H, ArH) and 8.42 (d, 1H, ArH).

6c: 92%, 212-213°C; M^+ at m/z 319; λmax 316 (log ε 3.82), 304 (log ε 3.89), 267 (log ε 4.26) and 225 nm (log ε 4.77); νCO 1685 & 1675 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.21 (t, 3H, CH_3), 2.58 (q, 2H, CH_2), 4.89 (s, 4H, 2 x CH_2), 7.18 - 7.75 (m, 7H, ArH) and 8.28 (d, 1H, ArH).

6d: 83%, 206-208°C; M^+ at m/z 321; λmax 316 (log ε 3.68), 304 (log ε 3.72), 268 (log ε 4.11) and 225 nm (log ε 4.59); νCO 1675 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 3.82 (s, 3H, OCH_3), 4.91 (s, 4H, 2 x CH_2), 6.89 - 7.81 (m, 7H, ArH) and 8.38 (d, 1H, ArH); ^{13}C-NMR ($CDCl_3$) δ 45.537 (OCH_3), 53.763(1), 55.510(4), 114.650(2'), 120.280(6a), 126.333(10), 126.956(8), 127.113(7), 127.460(3'), 132.414(1'), 134.867(9), 147.163(10a), 148.368(4'), 158.646(11a), 160.100(6) and 164.209(3).

6e: 92%, 233-234°C; M^+ at m/z 335; λmax 316 (log ε 3.92), 304 (log ε 4.02), 268 (log ε 4.45) and 225 nm (log ε 4.91); νCO 1690 & 1665 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.51 (t, 3H, CH_3), 4.04 (q, 2H, CH_2), 5.06 (s, 4H, 2 x CH_2), 6.98 - 7.79 (m, 7H, ArH) and 8.26 (d, 1H, ArH).

6f: 83%, 244-245°C; M^+ at m/z 325; λmax 315 (log ε 3.99), 304 (log ε 4.07) and 266 nm (log ε 4.48); νCO 1690 & 1675 cm^{-1}.

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