SYNTHESIS OF SOME NEW BENZOXAZINE DERIVATIVES OF BIOLOGICAL INTEREST

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Abstract: The synthesis of a number of biologically important imino-quinazolones has been achieved by the condensation of 3-amino-2-aryl-4-quinazolone and aromatic aldehydes.

Introduction

The progress in medicine and pharmacology is in many ways connected with the synthesis of new biologically active compounds and with the achievement of effective medical agents on that basis. The structural basis of numerous medical remedies and biologically active compounds is nitrogen, oxygen and sulphur containing heterocycles. The synthesis of benzoxazine derivatives has recently received considerable attention owing to their potential use as thermostable polymers (1-8) and also as physiologically active compounds (9-11). The benzoxazine derivatives are reported to exhibit an extremely broad spectrum of biological activities, such as anti-bacterial, anti-fungal, neuroprotective, anti-nociceptive and anti-inflammatory.(12-14) Besides their pharmacological activities, benzoxazine derivatives have no nephrotoxic effect, no reproductive toxicity, no mutagencity, no antigencity, no carcinogenesis, no ulcerogencity, no ototoxicity and no ophthalomotoxicity.(15,16) Because of their manifold reactivities, the benzoxazine derivatives are now being extensively synthesized and studied in organic chemistry and have potential physiological applications in medical sciences.(17-29) In view of the above, it was thought worthwhile to undertake the synthesis of some new benzoxazine derivatives by the condensation reaction of 3-amino-2-aryl-4-quinazolone with different aromatic aldehydes.

Experimental

Melting points were measured in open capillaries and are uncorrected. IR spectra were recorded on a JASCO FT/ IR-5300 spectrophotometer. NMR spectra were run on a JEOL FT-NMR spectrometer FX-90Q and the chemical shifts are expressed as δ/ppm, relative to TMS as internal standard. Anthranilic acid, benzoyl chloride and *p*-nitrobenzoyl chloride were commercial products (A. R. Grade) and were used after necessary purification. *p*-Anisaldehyde, vanillin, *p*-nitrobenzaldeyde, *p*-fluorobenzaldeyde, N,N-dimethylaminobenzaldehyde, 2,4-dichlorobenzaldehyde and *p*-bromobenzaldehyde were procured from Aldrich, USA and were used as received. Pyridine was purified according to Vogel's method.(30)

Preparation of 2-aryl-4H-3,1-benzoxazine-4-one: General Procedure (31)

To a stirred solution of anthranilic acid (1.37g, 0.01 mol) in pyridine (30 ml) was added dropwise benzoyl chloride/*p*-nitrobenzoyl chloride (0.02 mol) dissolved in 10 ml of pyridine. The stirring was continued for five minutes and set aside at room temperature for 25 minutes with occasional shaking. The reaction mixture was then poured into cold water (200ml) and the precipitate was filtered off, washed free of pyridine with cold water, dried at 100°C and recrystallised from ethanol.

2a: Yield (%) =89; M P=123°C

2b: Yield (%) = 90; M P=190°C

Preparation of 3-amino-2-aryl-4-quinazolone: General Procedure (32,33)

2-Aryl-4H-3,1-benzoxazine-4-one (0.028 mol) was dissolved in solvent ether (200ml) and to it was added 80% hydrazine hydrate (1.8 ml) dropwise, while stirring the mixture till complete precipitation occurred. The product was filtered, washed, dried and recrystallised from ethanol.

3a:Yield (%) = 83; M.P=187-188°C

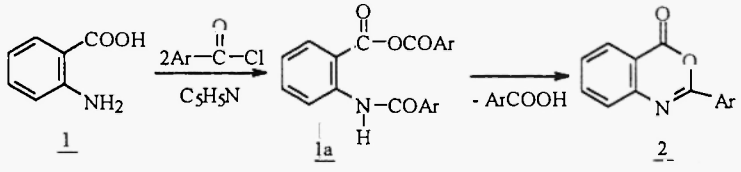
3b:Yield (%) = 85; M.P=175°C

Condensation of 3-amino-2-aryl-4-quinazolone with aromatic aldehydes: General Procedure

Equimolar quantities of 3-amino-2-aryl-4-quinazolone (0.003 mol) and aromatic aldehyde (0.003 mol) were taken in 20 ml of ethanol containing a few drop of acetic acid in a 250 ml round bottom flask. The reaction mixture was refluxed for half an hour and then worked up. The product was recrystallised from ethanol/benzene.

Result and Discussion:

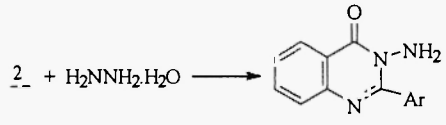
We report herein the synthesis of a variety of bioactive imino-quinazolones 5 by the condensation reaction of 3-amino-2-aryl-4-quinazolone 3 and aromatic aldehydes 4 (Scheme 1).



1 1a 2

2a: Ar = C_6H_5-

2b: Ar = p-$NO_2C_6H_4$-



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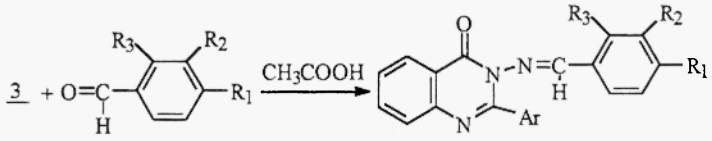

4 5

5a: Ar = C_6H_5, R_1 = OCH_3, R_2 = H, R_3 = H
5b: Ar = p-$NO_2C_6H_4$-, R_1 = OCH_3, R_2 = H, R_3 = H
5c: Ar = C_6H_5, R_1 = OH, R_2 = OCH_3, R_3 = H
5d: Ar = p-$NO_2C_6H_4$-, R_1 = OH, R_2 = OCH_3, R_3 = H
5e: Ar = C_6H_5, R_1 = NO_2, R_2 = H, R_3 = H
5f: Ar = p-$NO_2C_6H_4$-, R_1 = NO_2, R_2 = H, R_3 = H
5g: Ar = C_6H_5, R_1 = F, R_2 = H, R_3 = H
5h: Ar = p-$NO_2C_6H_4$-, R_1 = F, R_2 = H, R_3 = H
5i: Ar = C_6H_5, R_1 = -$N(CH_3)_2$, R_2 = H, R_3 = H
5j: Ar = p-$NO_2C_6H_4$-, R_1 = -$N(CH_3)_2$, R_2 = H, R_3 = H
5k: Ar = C_6H_5, R_1 = Cl, R_2 = H, R_3 = Cl
5l: Ar = p-$NO_2C_6H_4$-, R_1 = Cl, R_2 = H, R_3 = Cl
5m: Ar = C_6H_5, R_1 = Br, R_2 = H, R_3 = H
5n: Ar = p-$NO_2C_6H_4$-, R_1 = Br, R_2 = H, R_3 = H

Scheme 1

The reaction sequence involves the preparation of 2-aryl-4H-3,1-benzoxazine-4-one 2 by the acylation of anthranilic acid 1 followed by cyclization of the resulting intermediate 1a. The product 2 was subsequently treated with hydrazine hydrate (80%) in

ether to afford the 3-amino-2-aryl-4-quinazoline 3 which readily condensed with aromatic aldehydes 4a-4n to provide the final product 5. The products exhibited physico-chemical and spectral data consistent to their structures (Table 1).

Table 1: Physical and spectral data of products

Product	M.P. (°C))	Yield* (%)	Molecular formula	Molecular Weight	^{1}H-NMR (δ/ppm)
5a	194	89	$C_{22}H_{17}N_3O_2$	355.40	3.4 (s,3H,OCH_3) 6.9 (dd,4H,ArH) 7.3-7.9 (m, 9H,Ar-H) 8.4 (s,1H,CH=N)
5b	200	62	$C_{22}H_{16}N_4O_4$	400.40	3.4(s,3H,OCH_3) 6.9(dd,4H,ArH) 7.4-7.5 (m,3H,ArH) 7.9(m,3H,ArH) 8.2(d, 2H,ArH) 8.4 (s,1H,CH=N)
5c	220	59	$C_{22}H_{17}N_3O_3$	371.40	3.7(s,3H,OCH_3) 5.0 (s,1H,OH) 6.4-6.5 (m,3H,ArH) 7.3-7.9(m,9H,Ar-H) 8.4 (s,1H,CH=N)
5d	223	80	$C_{22}H_{16}N_4O_5$	416.40	3.7(s,3H,OCH_3) 5.0 (s,1H,OH) 6.4-6.5 (m,3H,ArH) 7.4-7.5(m,3H,ArH) 7.9 (m,3H,ArH) 8.2(d,2H,ArH) 8.4 (s,1H,CH=N)
5e	211	69	$C_{21}H_{14}N_4O_3$	370.37	7.3 (d,2H,ArH) 7.3-7.9(m,9H,Ar-H) 8.0 (d,2H,ArH) 8.4 (s,1H,CH=N)
5f	209	62	$C_{21}H_{13}N_5O_5$	415.37	7.3 (d,2H,ArH) 7.4-7.5(m,3H,ArH) 7.9 (m,3H,ArH) 8.0 (d,2H,ArH) 8.2(d,2H,ArH) 8.4 (s,1H,CH=N)
5g	198	66	$C_{21}H_{14}N_3OF$	343.36	6.8-7.0(dd,4H,ArH) 7.3-7.9(m,9H,Ar-H) 8.4 (s,1H,CH=N)
5h	233	94	$C_{21}H_{13}N_4O_3F$	388.36	6.8-7.0(dd,4H,ArH) 7.4-7.5(m,3H, ArH) 7.9 (m,3H,ArH) 8.2 (d,2H,ArH) 8.4(s,1H,CH=N)
5i	218	68	$C_{23}H_{20}N_4O$	368.44	2.4(s,6H,2×CH_3) 6.9(m,4H,ArH) 7.3-7.9 (m,9H,Ar-H) 8.4 (s,1H,CH=N)
5j	192	94	$C_{23}H_{19}N_5O_3$	413.43	2.4(s,6H,2×CH_3) 6.9(m,4H,ArH) 7.4-7.5 (m,3H,ArH) 7.9(m,3H,ArH) 8.2(d,2H,ArH) 8.4 (s,1H,CH=N)
5k	201	75	$C_{21}H_{13}N_3OCl_2$	394.26	6.9-7.1(m,3H,ArH) 7.3-7.9(m,9H,ArH) 8.4(s,1H,CH=N)
5l	225	86	$C_{21}H_{12}N_4O_3Cl_2$	439.21	6.9-7.1(m,3H,ArH) 7.4-7.5(m,3H,ArH), 7.9(m,3H,ArH) 8.2(d,2H,ArH) 8.4 (s,1H,CH=N)
5m	152	92	$C_{21}H_{15}N_3OBr$	404.27	6.9(d,2H,ArH) 7.3 (d,2H,ArH) 7.3-7.9 (m,9H, m, ArH) 8.4 (s,1H, CH=N)
5n	216	94	$C_{21}H_{13}N_4O_3Br$	449.27	6.9(d,2H,ArH) 7.3 (d,2H,ArH) 7.4-7.5 (m,3H,ArH) 7.9(m,3H,ArH) 8.2(d,2H,ArH) 8.4 (s,1H,CH=N)

*Isolated mass yield is based on substrate 3

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