Pak. j. sci. ind. res., vol. 35, no. 6, June 1992

USE OF N-PHENYL-2-AMINO-4H-3, 1-BENZOXAZIN-4-ONE IN THE SYNTHESIS OF HETROCYCLES AND THEIR DERIVATIVES

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(Received February 3, 1992)

5-(N-phenyl-2-aminoquinazoline-4-yloxomethyl)-1,2,4- triazole-3-thiol (4) was prepared via alkylation of N-phenyl-2- amino-4(3H)-quinazolone (2) with ethylchloro acetate yielding 4- carbethoxymethoxy-N-phenyl-2-aminoquinazolone (3), followed by condensation of 3 with thiosemicarbazide. Compound 4 reacts as a thiol with nitrogen nucleophiles, alkylation and activated olefinic compounds to yield the 5-substituted -1,2,4-triazole-3N- substituted-amino derivative (5a,b), the 5-substituted 1,2,4- triazole-3-ylthioalkyl (8a,b) and the Mickael a ducts (11, 12). Treatment of 4 and 5 a,b with aromatic aldehydes yielded α- arylidene-5-substituted-1,2,4-triazole-3-thiol (9a,b), 5- substituted -1H-3-arylidenehydrazino-1,2,4-triazole (6 a,b) and N- (β-cyano-3-nitrocinnamoyl)-N`-(5-substituted-1,2,4-triazole-3- .yl)-hydrazine (7).

Key words. Synthesis, Reactions, Triazole thiol.

Introduction

Diverse pharmacological properties have been found to be associated with triazole derivatives [1-8]. These include anti-inflammatory, anticholinergic, antidepressant, analgesic, sedative, antihypertensive, antiasthmatic and tranquilizing properties.

Similar to what has been reported earlier [9] in the present study anthranilic acid reacted with phenylisocyanate in the presence of acetone to give N-phenyl-2-amino-4H-3, 1-benzoxazin-4- one (1) as a key starting material for the preparation of heterocyclic compounds containing triazole thiol and quinazoline moieties. Such compounds are expected to show pharmacological activity.

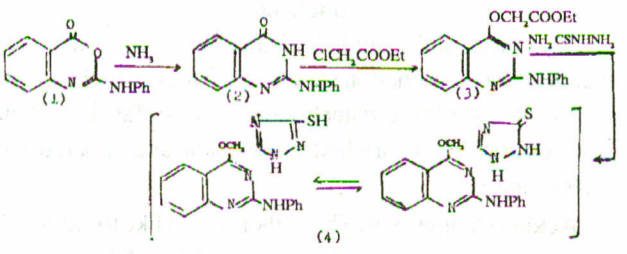
Results and Discussion

Aminolysis of N-phenyl-2-amino-4H-3, 1 benzoxazin-4-one (1) with ammonia from ammonium acetate or formamide by fusion at 150°, gave the corresponding N-phenyl-2-amino-4(3H)-quinazolone (2, Scheme 1). Their IR spectra showed stretching frequencies at 3440, 3290 and 1680 cm^{-1} for OH, NH and CO functions, respectively. These IR data infer that quinazolone 2 exists in a lactam $\rightleftharpoons$ lactim tautomeric equilibrium.

5-(N-phenyl-2-amino quinozoline-4-yloxomethyl)-1,2, 4-triazole-3-thiol (4) was prepared by a route shown in Scheme 1. It involved alkylation of N-phenyl-2-amino-4 (3H)-quinazolone (2) with ethylchloroacetate yielding 4-carbethoxymethoxy-2N- phenylamino-quinazoline (3), followed by condensation of 3 with thiosemicarbazide. The structures of 3 and 4 were supported by their spectral data. The IR spectrum of 3 showed bands due to estre CO (1745), ether linkage (1220 and 1210) and NH (3270 cm^{-1}), while that of 4 exhibited bands due to C=N (1630), C=C (1610), 1250 (C=S), SH (2650) and 3200 – 3280 cm^{-1} (NH). This indicates that compound 4 exists in thiol $\rightleftharpoons$ thione equilibrium. This dynamic equilibrium was more elucidated by the PMR spectrum showing signals at δ 4.3 (s, 2H, -O-CH_2-), 6.8-8.1 (m, 10H, Ar-H and NH), 9.9 (br's, ~0.6 H of -NH-C=S), 4.6 (br,s, ~0.4 H of SH) and 10.4 (s, 1H, NH).

This tautomeric equilibrium in 4 was further established by chemical reaction. Thus, compound 4 reacted as a thiol with nitrogen nucleophiles [10] such as hydrazine hydrate and cyanoacetylhydrazine to give the corresponding 5-(N-phenyl-2- amino-quinazoline-4-yloxomethyl)-3-hydrazino derivatives-1,2,4- triazole (5 a,b; Scheme 2). Their IR spectra showed bands attributable to CO, C≡N, C=N, C=C and NH functions at 1680, 2240, 1630, 1610 and 3280,-3210 cm^{-1} respectively. The PMR spectrum of 5b in (CF_3 COOD) showed signals at δ 2.4 (s, 2H,-CH_2CN), 4.2 (s, 2H,-O-CH_2), 6.6-8.1 (m, 11 H, Ar-H, NH) and 10.2-10.4 (br s, 2H, NH).

Condensation of this hydrazine 5a with aromatic aldehydes, namely 4-hydroxybenzaldehyde or 3-nitrobenzaldehyde resulted in the formation 5-(N-phenyl-2-aminoquinazoline-4-yloxamethyl)-3- arylidene hydrazino-1,2,4-triazole (6 a, b; Scheme 2). The IR spectrum of 6 showed bands at 1630 (C=N), 1610 (C=C), 3280 (NH) and 3605 cm^{-1} (OH). The



Scheme 1.

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PMR (CF_3 COOD) spectrum of 6b showed signals at δ 4.2 (s, 2H,-O-CH_2-), 6.6-8.3 (m, 15 H, Ar - H and NH) and 10.3 (s, 1H, NH).

The ethanolic solution of 5b with 3-nitrobenzaldehyde in the presence of drops piperidine afforded the corresponding N- (β- cyano-3-nitrocinnamoyl) -N` [5-(N-phenyl -2-aminoquinazoline-4-yloxomethyl)-1,2,4-triazole-3-yl]-hydrazine (7, Scheme 2). The IR spectrum of 7 showed bands at 1680 (CO), 1630 (C=N), 1605 (C=C), 2235 (C=N) and 3282-3200 cm^{-1} (NH).

Alkylation of 4 with alkyl halides, namely methyliodide or ethyliodide in the presence of sodium ethoxide solution afforded the corresponding 5-(N-phenyl-2-aminoquinazoline -4-yloxomethyl)- 1,2,4-triazole-3-ylthioalkyl (8 a,b, scheme2). The IR spectrum of 8 showed characteristic absorption bands due to C=N, C=C and NH functions at 1630, 1605 and 3280 - 3240 cm^{-1} respectively. The PMR (CF_3 COOD) spectrum of 8a showed signals at δ2.1 (s, 3H,- SCH_3), 4.2 (s, 2H,-OCH_2), 6.7-8.1 (m, 10 H, Ar-H and NH) and 10.2 (S, 1H, NH).

Compound 4 reacted with aromatic aldehydes [11] such as 4-N, N-dimethylaminobenzaldehyde and 4-hydroxybenzaldehyde in the presence of piperidine under fusion (150°) yielded α-arylidene- 5-(N-phenyl -2-amino-quinazoline-4-yloxomethyl)-1,2,4-triazole-3- thiol (9a,b; Scheme 2). The IR spectrum of 9 showed strong absorption bands at 1630 (C=N), C=C (1610), 1255 (C=S), 2555 (SH) and 3550-3200 cm^{-1} (NH and OH). The PMR spectrum of 9a in ($CDCl_3$) showed signals at δ2.8-3.0 (br s, 6H, 2x CH_3-N) 6.6. - 8.1 (m. 11H, Ar- H, olefinic proton and NH), 9.8 (br,s,~0.6H of NH-C=S), 4.6 (br,s, 0.4 H of SH) and 10.3 (s, 1H, NH).

The ethanolic solution of 9b with hydrazine hydrate afforded the corresponding α-4-hydroxybenzylidene-5-(N-phenyl -2- aminoquinozaline-4-yloxomethyl)-1,2,4-triazole-3-hydrazine (10, Scheme 2). The IR spectra of 10 showed strong absorption bands at 1630 (C=N), 1605 (C=C) and 3390-3240 (NH and NH_2).

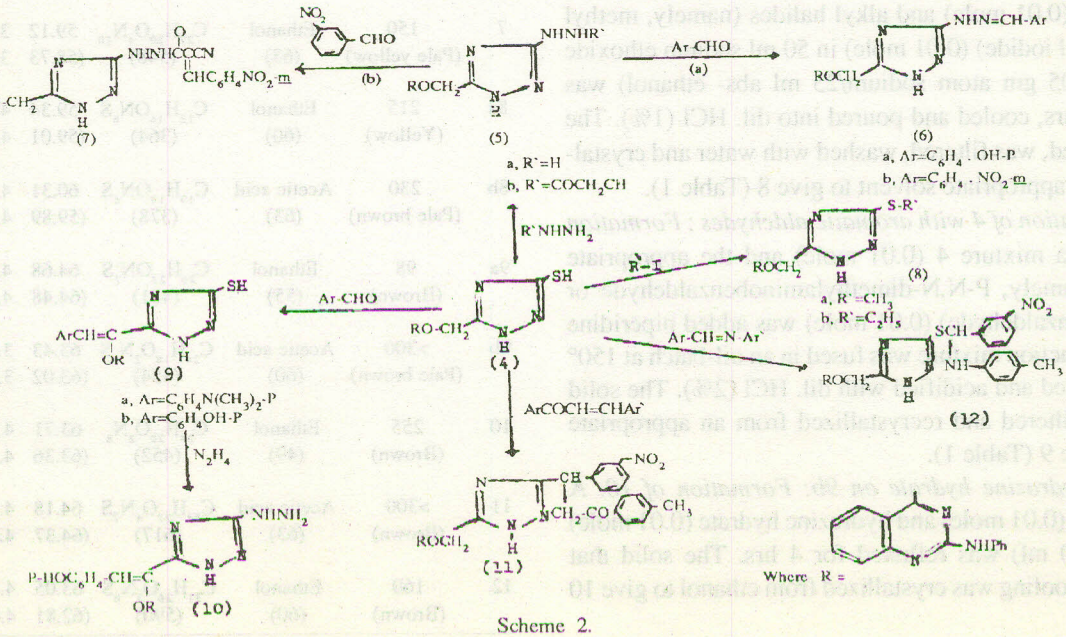
However, the reaction of 4 with activated olefinic compounds [12] such as β-(4-methyl benzoyl)-3-nitrostyrene and 3- nitrobenzylidine-4-methylaniline under Michael reaction conditions in the presence of sodium ethoxide afforded the corresponding Mickael aducts (11, 12; Scheme 2). The IR spectrum of 11 and 12; showed absorptions characteristic of ketonic CO, C=N, C=C, NH and NO_2 functions at 1695, 1630, 1610, 3290-3220 and 1560 11350 cm^{-1}, respectively. The PMR spectrum of 11 in (CF_3 COOD)showed signals at δ 2.1 (S, 3H,-CH_3), 2.4 (d, 2H,-CH_2CO-), 3.4 (t, 1H, S-CH-), 4.3(s, 2H,-OCH_2-), 6.6-3.2 (m, 18H, Ar-H and NH) and 10.3 (s,1H, NH).

Experimental

IR spectra were recorded in KBr on a Unicam SP 1200 spectrometer and PMR spectra on a Varian EM-360-60 MHz NMR spectrometer. All m.p. reported are uncorrected.

N-phenyl 2-amino-4H-3, 1-benzoxazin-4-one (1). A mixture of anthranilic acid (0.01 mole) and phenyl isocyanate (0.01 mole) in acetone (70 ml) was refluxed for 4 hrs. The reaction mixture was cooled, the solid obtained, was filtered, washed with water, air dried and crystallized from a proper solvent to give 1 (Table 1).

Aminolysis of 1: Formation of 2. A mixture of 1 (0.01 mole) and formamide or ammonium acetate (0.03 mole) was fused in an oilbath at 150° for 3 hrs, and poured into water. The solid obtained was crystallized from an appropriate solvent to give 2 (Table 1).



Scheme 2.

Alkylation of 2 with ethyl chloroacetate.:Formation of 3. A mixture of 2 (23.7gm; 0.01 mole), ethyl chloro acetate (11.4 ml, 0.01 mole) and anhydrous potassium carbonate (15gm) in dry acetone (200 ml) was refluxed on a water-bath for 24 hrs. The reaction mixture was cooled and poured into water. The resultant solid was filtered and crystallized from appropriate solvent to give 3 (Table 1).

Condensation of 3 with thiosemicarbazide: Formation of 4. A mixture of 3 (0.01 mole) and thiosemicarbazide (0.01 mole) in 50 ml sodium ethoxide solution (0.005gm atom sodium/25 ml abs. ethanol) was heated for 6 hrs cooled and poured into dil. HCl (1%). The solid, thus separated, was filtered, washed with water and crystallized from a proper solvent to give 4 (Table 1).

Action of hydrazines on 4: Formation of 5 a,b. A solution of 4 (0.01 mole and the hydrazine derivative (namely, hydrazine hydrate or cyanoacetyl hydrazide) (0.01 mole) in ethanol (70 ml) was refluxed for 6 hrs. The solid that separated on cooling was crystallized from an appropriate solvent to give 5 (Table 1).

Condensation of 5a with aromatic aldehydes: Formation of 6 a,b. A solution of 5 a (0.01 mole) with aromatic aldehydes (namely, hydroxy benzaldehyde or m-nitro benzaldehyde) (0.01 mole) in acetic acid (50 ml) was refluxed for 4 hrs. The solid that separated on cooling was crystallized from an appropriate solvent to give 6 (Table 1).

Reaction of 5 b with 3-nitrobenzaldehyde :Formation of 7. A mixture of 5 b (0.01 mole), 3. nitrobenzaldehyde (0.01 mole) and piperidine (1 ml) was refluxed for 6 hrs, cooled and acidified with dil. HCl (2%). The solid formed was filtered and recrystallized from a proper solvent to give 7 (Table 1).

Alkylation of 4 with alkyl halides : Formation of 8 a,b. A mixture of 4 (0.01 mole) and alkyl halides (namely, methyl iodide or ethyl iodide) (0.01 mole) in 50 ml sodium ethoxide solution (0.005 gm atom sodium/25 ml abs- ethanol) was heated for 4 hrs, cooled and poured into dil. HCl (1%). The solid, separated, was filtered, washed with water and crystallized from an appropriate solvent to give 8 (Table 1).

Condensation of 4 with aromatic aldehydes : Formation of 9 a,b. To a mixture 4 (0.01 mole) and the appropriate aldehydes (namely, P-N,N-dimethylaminobenzaldehyde or P-hydroxy benzaldehyde) (0.01 mole) was added piperidine (1 ml). The reaction mixture was fused in an oil-batch at 150° for 6 hrs, cooled and acidified with dil. HCl (2%). The solid formed was filtered and recrystallized from an appropriate solvent to give 9 (Table 1).

Action hydrazine hydrate on 9b: Formation of 10. A solution of 9b (0.01 mole) and hydrazine hydrate (0.01 mole) in ethanol (50 ml) was refluxed for 4 hrs. The solid that separated on cooling was crystallized from ethanol to give 10 (Table 1),

Reaction of 4 with active olefinic compounds: Formation of 11 and 12. A mixture of 4 (0.01 mole) and the active olefinic compound, namely β-(4-methylbenzoyl)-3-nitrostyrene or 3-nitrobenzylidene-4-methylcaniline (0.01 mole) in 50 ml sodium ethoxide (0.005 gm atom sodium/25ml ethanol) was refluxed for 6 hrs, cooled and poured into dil. HCl (1%). The solid, thus separated was filtered, washed with water and crystallized from a proper solvent to give 11 sand 12 (Table 1).

Table 1. Characterisation Data of the Compounds 1-12.

Compd	M.P. °C (colour)	Crystallized from (yield %)	Mol. formula	Microanalyses % Calcd / (Found) C	H	N	S
1	185 (Colourless)	Acetone (85)	$C_{14}H_{10}O_2N_2$ (238)	70.58 (70.21	4.2 4.0	11.76 11.41	- -)
2	260 (Pale yellow)	Ethanol (50)	$C_{14}H_{11}ON_3$ (237)	70.88 (70.50	4.64 4.31	17.72 17.41	- -)
3	147 (Colourless)	Acetone (63)	$C_{18}H_{17}O_3N_3$ (323)	66.87 (66.42	5.26 4.98	13.00 12.81	- -)
4	188 (Yellow)	Acetic acid (60)	$C_{17}H_{14}ON_6S$ (350)	58.28 (58.01	4.0 3.76	24.00 23.70	9.14 9.00
5a	204 (Colourless)	Acetic acid (65)	$C_{17}H_{16}ON_8$ (348)	58.62 (58.20	4.59 4.31	32.18 31.92	- -)
5b	207 (Brown)	Ethanol (63)	$C_{20}H_{17}O_2N_9$ (415)	57.83 (57.42	3.85 3.51	30.36 29.96	- -)
6a	260 (Yellow)	Acetic acid (65)	$C_{24}H_{20}O_2N_8$ (452)	63.71 (63.33	4.42 4.21	24.77 24.46	-) -)
6b	180 (Pale yellow)	Ethanol (55)	$C_{24}H_{19}O_3N_9$ (481)	59.87 (59.47	3.95 3.56	26.19 25.88	-) -)
7	150 (Pale yellow)	Ethanol (63)	$C_{27}H_{20}O_4N_{10}$ (548)	59.12 (58.73	3.64 3.36	25.54 25.21	-) -)
8a	215 (Yellow)	Ethanol (60)	$C_{18}H_{16}ON_6S$ (364)	59.34 (59.01	4.39 4.03	23.07 22.79	8.79) 8.51)
8b	230 (Pale brown)	Acetic acid (63)	$C_{19}H_{18}ON_6S$ (378)	60.31 (59.89	4.76 4.41	22.22 22.00	8.46 8.07)
9a	98 (Brown)	Ethanol (55)	$C_{26}H_{23}ON_7S$ (481)	64.68 (64.48	4.78 4.51	20.37 19.88	6.65 6.30)
9b	>300 (Pale brown)	Acetic acid (60)	$C_{24}H_{18}O_2N_6S$ (454)	63.43 (63.02	3.96 3.53	18.50 18.20	7.04 6.83)
10	255 (Brown)	Ethanol (49)	$C_{24}H_{20}O_2N_8$ (452)	63.71 (63.36	4.42 4.08	24.77 24.50	- -)
11	>300 (Brown)	Acetic acid (63)	$C_{33}H_{27}O_4N_7S$ (617)	64.18 (64.37	4.37 4.01	15.88 15.49	5.18 5.00)
12	160 (Brown)	Ethanol (60)	$C_{31}H_{26}O_3N_8S$ (590)	63.05 (62.81	4.40 4.03	18.89 18.57	5.42 5.01)

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