SYNTHESIS OF SOME NEW SPIROPYRIMIDOQUINAZOLINE DERIVATIVES

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Abstract

2-Methyl-3,4-dihydroquinazolin-4-ones **1a,b** reacted with cyclic ketones **2a-d** in the presence of fused sodium acetate to yield 2-methinylcycloalkylidene-3H-quinazolin-4-one derivatives **3a-h**. Quinazoline derivatives **3a-h** reacted with hydrobromic acid in glacial acetic acid to give the bromo derivatives **4a-h**. Compounds **4a-h** reacted with ammonium carbonate and/or hexamethyl-enetetramine to afford 2-methylenylaminocycloalkane quinazoline derivatives **5a-h** in good yields. Cyclization of **5a-h** with acetic anhydride and acetic acid yielded the spiropyrimidoquinazoline derivatives **6a-h** in excellent yields. All the synthesized quinazoline derivatives were identified by conventional methods (IR, ^{1}H NMR) and elemental analyses.

Introduction

Several authors reported the synthesis and the applications of spiroheterocyclic derivatives(1-10). From this point of view and in continuation of our previous work(11-16), we report herein the synthesis of some new spiropyrimido-quinazoline derivatives.

Experimental

The time required for completion of the reaction was monitored by thin layer chromatography (TLC). Melting points were determined in open glass capillaries and are uncorrected. IR spectra were recorded on a Pye-Unicam SP 200 G spectrophotometer. ^{1}H NMR spectra were measured on an EM-360 90 MHz NMR spectrophotometer. Microanalyses were determined on a Perkin-Elmer 240 C microanalyser, EI Mass spectra were recorded on a Varian MAT 311A spectrometer.

Synthesis of 2-methinylcycloalkylidene-3H-quinazolin-4-one derivatives 3a-h:

General Procedure:

2-Methyl-3,4-dihydroquinazolin-4-ones **1a,b** (0.01 mole) was fused with each cyclic ketones **2a-d** (0.01 mole) in the presence of anhydrous sodium acetate

1a,b
a; X = H
b; X = Br
2a-d
a; n = O, R1 = R2 = H
b; n = 1, R1 = R2 = H
c; n = O, R1, R2 =
d; n = 1, R1, R2 =
CH3COONa
Fusion
3a-h
HBr
CH3COOH
4a-h
(NH4)2CO3
or (CH2)6N4
5a-h
Ac2O
CH3COOH
6a-h
In compounds 3-6
a: X = H, n = 0, R1 = R2 = H
b: X = Br, n = 0, R1 = R2 = H
c: X = H, n = 1, R1 = R2 = H
d; X = Br, n = 1, R1 = R2 = H
e X = H, n = 0, R1, R2 =
f X = Br, n = 0, R1, R2 =
g X = H, n = 1, R1, R2 =
h; X = Br, n = 1, R1, R2 =

Scheme 1

(0.01 mole) for ½ hr. The reaction mixture was cooled to room temperature, poured into cold water whereby the target compounds 3a-h were precipitated, filtered off, dried and recrystallized from ethanol (Table I).

Synthesis of 2-methylenyl-1`-bromocycloalkylquinazoline derivatives 4a-h:

General Procedure:

Each compound **3a-h** (0.01 mole) was dissolved in 25 ml of glacial acetic acid, then hydrobromic acid (0.01 mole) was added to the reaction mixture. The reaction mixture was refluxed for 2 hr, cooled to room temperature whereby the target products **4a-b** were precipitated, filtered off, dried and recrystallized from acetic acid (Table II).

Synthesis of 2-methylenylaminocycloalkylquinazoline derivatives 5a-h:

Each compound **4a-h** (0.01 mole) was fused with ammonium carbonate (0.01 mole) for ½ hr. The reaction mixture was cooled to room temperature, poured into cold water (50 ml) whereby the desired products **5a-h** were precipitated, filtered off, dried and recrystallized from ethanol (Table III).

Synthesis of spiropyrimidoquinazoline derivatives, 6a-h:

General Procedure:

Each compound **5a-h** (0.01 mole) was dissolved in a mixture of acetic anhydride and acetic acid (25 ml, 1:1) then the reaction mixture was refluxed for 6 hrs. The solvents were removed by distillation and the residue was poured into 25 ml of ether whereby compounds 6a-h were precipitated, filtered off, dried and recrystallized from ethanol (Table IV).

Results and Discussions:

2-Methyl-3H-quinazolin-4-ones **1a,b** reacted with the cyclic ketones **2a-d** in the presence of fused sodium acetate to yield 2-methinylcycloalkylidene-3H-quinazolin-4-derivatives **3a-h** (Scheme 1). The structures of compounds **3a-h** were established from their elemental analysis and spectroscopic data (Table I). Quinazoline derivatives **3a-h** reacted with hydrobromic acid in glacial acetic acid to give the bromo derivatives **4a-h** (Scheme 1). The structures of compounds **4a-h** were confirmed on the basis of their elemental analysis and spectroscopic data (Table II). For the synthesis of the target spiropyrimido-quinazoline derivatives **6a-h**, the bromoquinazoline derivatives **4a-h** were allowed to react with ammonium carbonate and/or hexamethylenetetramine to give 2-methyleneaminocycloalkanequinazoline derivatives **5a-h** in good yields (Scheme 1). Cyclizations of **5a-h** with acetic anhydride and acetic acid yielded the target compounds **6a-h**. The structures of the aminoquinazoline derivatives

Table (I) Physical Data of 2-methinylcycloalkylidene-3H-quinazolin-4-one Derivatives **3a-h**.

Compound No.	Yield (%)	MP (°C)	Molecular formula (Solvent of Crystallization)	IR (Kbr), cm^{-1}	^{1}H-NMR (Solvent), δ (TMS)
3a	82	205-207	$C_{18}H_{14}N_2O$ (ethanol)	3185 (NH), 3050 (CH arom), 2930 (CH aliph), 1680 (C=O), 1630 (C=N)	(DMSO-d_6) 2.40 (2H, t, CH_2), 2.60 (2H, t, CH_2), 4.10 (1H, s, CH), 5.20 (1H, s, NH), 7.40-8.20 (8H, m, aromatic protons).
3b	85	270-272	$C_{18}H_{13}N_2OBr$ (ethanol)	3200 (NH), 3040 (CH arom), 2929 (CH aliph), 1685 (C=O), 1630 (C=N)	(DMSO-d_6) 2.40 (2H, t, CH_2), 2.60 (2H, t, CH_2), 4.10 (1H, s, CH), 5.20 (1H, s, NH), 7.40-8.20 (8H, m, aromatic protons).
3c	80	100-102	$C_{19}H_{16}N_2O$ (ethanol)	3180 (NH), 3040 (CH arom), 2940 (CH aliph), 1680 (C=O), 1630 (C=N)	(DMSO-d_6) 2.30 (2H, t, CH_2), 2.40 (2H, t, CH_2) 2.60 (2H, s, CH_2), 4.10 (1H, s, CH), 5.20 (1H, s, NH), 7.30-8.10 (8H, m, aromatic protons).
3d	81	120-122	$C_{19}H_{15}N_2OBr$ (ethanol)	3200 (NH), 3040 (CH arom), 2940 (CH aliph), 1680 (C=O), 1630 (C=N)	(DMSO-d_6) 2.30 (2H, t, CH_2), 2.40 (2H, t, CH_2), 2.60 (2H, s, CH_2), 4.10 (1H, s, CH), 5.20 (1H, s, NH), 7.30-8.10 (7H, m, aromatic protons).
3e	75	75-67	$C_{22}H_{14}N_2O$ (ethanol)	3200 (NH), 3040 (CH arom), 2940 (CH aliph), 1685 (C=O), 1630 (C=N)	(DMSO-d_6) 4.10 (1H, t, CH_2), 5.20 (1H, s, NH), 7.50-8.20 (12H, m, aromatic protons).
3f	73	70-72	$C_{22}H_{13}N_2OBr$ (ethanol)	3200 (NH), 3040 (CH arom), 2940 (CH aliph), 1685 (C=O), 1630 (C=N).	(DMSO-d_6) 4.10 (1H, t, CH_2), 5.20 (1H, s, NH), 7.50-8.10 (11H, m, aromatic protons).
3g	82	110-112	$C_{23}H_{16}N_2O$ (ethanol)	3185 (NH), 3050 (CH arom), 2940 (CH aliph), 1680 (C=O), 1630 (C=N)	(DMSO-d_6) 2.85 (2H, t, CH_2), 2.10 (1H, t, CH_2), 5.10 (1H, s, NH), 7.40-8.10 (12H, m, aromatic protons).
3h	80	250-252	$C_{23}H_{15}N_2OBr$ (ethanol)	3180 (NH), 3040 (CH arom), 2940 (CH aliph), 1680 (C=O), 1620 (C=N)	(DMSO-d_6) 2.80 (2H, t, CH_2), 4.10 (1H, s, CH), 5 10 (1h, s, NH), 7.30-8.10 (11H, m, aromatic protons).

Table (II) Physical Data of 2-methylenyl-1'-bromocycloalkylquinazoline Derivatives **4a-h**.

Compound No.	Yield (%)	MP (°C)	Molecular formula (Solvent of Crystallization)	IR (Kbr), cm^{-1}	^{1}H-NMR (Solvent), δ (TMS)
4a	90	152-154	$C_{18}H_{12}N_2OBr$ (acetic acid)	3175 (NH), 3040 (CH arom), 2940 (CH aliph), 1680 (C=O), 1630 (C=N)	(DMSO-d_6) 2.40 (2H, t, CH_2), 2.60 (2H, t, CH_2), 2.80 (2H, s, CH_2) 5.20 (1H, s, NH), 7.40-8.10 (8H, m, aromatic protons).
4b	85	270-272	$C_{18}H_{14}N_2OBr_2$ (acetic acid)	3180 (NH), 3050 (CH arom), 2940 (CH aliph), 1680 (C=O), 1620 (C=N)	(DMSO-d_6) 2.40 (2H, t, CH_2), 2.60 (2H, t, CH_2), 2.80 (2H, s, CH_2), 5.20 (1H, s, NH), 7.30-8.10 (7H, m, aromatic protons).
4c	82	110-112	$C_{19}H_{17}N_2OBr$ (acetic acid)	3200 (NH), 3040 (CH arom), 2930 (CH aliph), 1685 (C=O), 1620 (C=N)	(DMSO-d_6) 2.35 (2H, t, CH_2), 2.40 (2H, t, CH_2), 2.60 (2H s, CH_2), 2.80 (2H, s, CH_2). 5.10 (1H, s, NH), 7.30-8.10(8H, m, aromatic protons).
4d	80	120-122	$C_{19}H_{16}N_2OBr_2$ (acetic acid)	3180 (NH), 3050 (CH arom), 2940 (CH aliph), 1680 (C=O), 1630 (C=N)	(DMSO-d_6) 2.30 (2H, t, CH_2), 2.40 (2H, t, CH_2), 2.40 (2H, s, CH_2), 2.80 (2H, s, CH_2). 5.10 (1H, s, NH), 7.30-8.10(7H, m, aromatic protons).
4e	75	115-117	$C_{21}H_{17}N_2OBr$ (acetic acid)	3280 (NH), 3050 (CH arom), 2917 (CH aliph), 1680 (C=O), 1620 (C=N)	(DMSO-d_6) 2.80 (2H, t CH_2), 5.10 (1H, s, NH), 7.40-8.10 (12H, m, aromatic protons).
4f	77	110-112	$C_{22}H_{14}N_2OBr_2$ (acetic acid)	3200 (NH), 3040 (CH arom), 2920 (CH aliph), 1680 (C=O), 1630 (C=N).	(DMSO-d_6) 2.80 (2H, t, CH_2), 5.10 (1H, s, NH), 7.40-8.20 (11H, m, aromatic protons).
4g	75	210-212	$C_{23}H_{16}N_2OBr_2$ (acetic acid)	3175 (NH), 3040 (CH aromatic), 2920 (CH aliph), 1680 (C=O), 1630 (C=N)	(DMSO-d_6) 2.80 (2H, t, CH_2), 2.90 (2H, s, CH_2), 5.10 (1H, s, NH), 7.40-8.20 (12H, m, aromatic protons).
4h	73	142-144	$C_{23}H_{14}N_2OBr$ (ethanol)	3180 (NH), 3050 (CH arom), 2917 (CH aliph), 1685 (C=O), 1620 (C=N)	(DMSO-d_6) 2.80 (2H, t, CH_2), 2.90 (2H, s, CH_2), 7.40-8.20 (11H, m aromatic protons).

Table (III) Physical Data of 2-methylenylaminocycloalkylquinazoline Derivatives **5a-h**.

Compound No.	Yield (%)	MP (°C)	Molecular formula (Solvent of Crystalllization)	IR (Kbr), cm^{-1}	^{1}H-NMR (Solvent), δ (TMS)
5a	72	170-172	$C_{18}H_{17}N_3O$ (ethanol)	3318, 3250 (NH_2), 3209 (NH), 3060 (CH arom), 2940 (CH aliph), 1670 (C=O), 1632 (C=N)	(DMSO-d_6) 2.40 (2H, t, CH_2), 2.60 (2H, t, CH_2), 2.80 (2H, s, CH_2), 5.20 (2H, s, NH), 7.40-8.10 (8H, m, aromatic protons), 8.30 (2H, s, NH_2).
5b	75	240-242	$C_{18}H_{16}N_3OBr$ (ethanol)	3318 3250 (NH_2), 3210 (NH), 3060 (CH arom), 2940 (CH aliph), 1670 (C=O), 1632 (C=N)	(DMSO-d_6) 2.40 (2H, t, CH_2), 2.60 (2H, t, CH_2), 2.80 (2H, s, CH_2), 5.20 (2H, s, NH), 7.40-8.10 (7H, m, aromatic protons), 8.30 (2H, s, NH_2).
5c	76	130-132	$C_{19}H_{19}N_3O$ (ethanol)	3320, 3250 (NH_2), 3200 (NH), 3060 (CH arom), 2940 (CH aliph), 1680 (C=O), 1630 (C=N)	(DMSO-d_6) 2.35 (2H, m, CH_2), 2.40 (2H, s, CH_2), 2.60 (2H, t, CH_2), 2.80 (2H, s, CH_2), 5.10 (1H, s, NH), 7.30-8.10 (8H, m, aromatic protons), 8.30 (2H, s, NH_2).
5d	73	290-292	$C_{19}H_{18}N_3OBr$ (ethanol)	3325, 3250 (NH_2), 3200 (NH), 3050 (CH arom), 2917 (CH aliph), 1680 (C=O), 1620 (C=N)	(DMSO-d_6) 2.35 (2H, m, CH_2), 2.40 (2H, t, CH_2), 2.40 (2H, t, CH_2), 2.60 (2H, t, CH_2), 2.80 (2H, s, NH_2), 5.10 (1H, s, NH), 7.20-8.15 (7H, m, aromatic protons), 8.30 (2H, s, NH_2).
5e	70	150-152	$C_{22}H_{17}N_3O$ (ethanol)	3325, 3250 (NH_2), 3180 (NH), 3050 (CH arom), 2918 (CH aliph), 1680 (C=O), 1630 (C=N)	(DMSO-d_6) 2.80 (2H, s, CH_2), 5.10 (1H, s, NH), 7.40-8.20 (12H, m, aromatic protons), 8.40 (2H, s, NH_2).
5f	71	175-177	$C_{22}H_{16}N_3OBr$ (ethanol)	3320,3250(NH_2),3175 (NH), 3050 (CH arom), 2920 (CH aliph),1677(C=O),1620(C=N	(DMSO-d_6) 2.80 (2H s, CH_2), 5.10 (1H, s, NH), 7.40-8.20 (11H, m, aromatic protons), 8.40 (2H, s, NH_2).
5g	67	195-197	$C_{23}H_{19}N_3O$ (ethanol)	3310, 3260 (NH_2), 3175 (NH), 3060 (CH arom), 2920 (CH aliph), 1680 (C=O), 1620 (C=N)	(DMSO-d_6) 2.80 (2H, s, CH_2), 2.90 (2H, s, CH_2), 2.90 (2H s, CH_2), 5 10 (1H, s, NH), 7.20-8.10 (12H, m, aromatic protons), 8.30 (2H, s, NH_2).
5h	66	170-172	$C_{23}H_{18}N_3OBr$ (ethanol)	3320, 3250 (NH_2), 3175 (NH), 3060 (CH arom), 2917 (CH aliph), 1680 (C=O), 1630 (C=N)	(DMSO-d_6) 2.80 (2H, t, CH_2), 2.90 (2H, s, CH_2), 5 10 (1H, s, NH), 7.20-8.10 (11H, m, aromatic protons), 8.30 (2H, s, NH_2).

Table (IV) Physical Data of Spiropyrimidoquinazoline Derivatives **4a-h**.

Compound No.	Yield (%)	MP (°C)	Molecular formula (Solvent of Crystallization)	IR (Kbr), cm^{-1}	^{1}H-NMR (Solvent), δ (TMS)
6a	65	210-212	$C_{20}H_{17}N_3O$ (ethanol)	3060 (CH arom), 2920 (CH aliph), 1680 (C=O), 1630 (C=N)	(DMSO-d_6) 2.40 (2H, t, CH_2), 2.60 (2H, t, CH_2), 2.80 (2H, s, CH_2), 2.20 (3H, s, CH_3), 7.20-8.10 (8H, m, aromatic protons).
6b	63	270-272	$C_{21}H_{16}N_3OBr$ (ethanol)	3050 (CH arom), 2917 (CH aliph), 1680 (C=O), 1630 (C=N)	(DMSO-d_6) 2.40 (2H, t, CH_2), 2.60 (2H, t, CH_2), 2.80 (2H, s, CH_2), 2.20 (3H, s, CH_3), 7.40-8.10 (7H, m, aromatic protons).
6c	62	280-282	$C_{21}H_{19}N_3O$ (ethanol)	3060 (CH arom), 2920 (CH aliph), 1680 (C=O), 1620 (C=N)	(DMSO-d_6) 2.30 (2H, m, CH_2), 2.40 (2H, m, CH_2), 2.40 (2H, t, CH_2), 2.60 (2H, t, CH_2), 2.80(2H, s, CH_2), 2.25 (3H, s, CH_3), 7.20-8.10 (8H, m, aromatic protons).
6d	60	270-272	$C_{21}H_{18}N_3OBr$ (ethanol)	3050 (CH arom), 2917 (CH aliph), 1675 (C=O), 1630 (C=N)	(DMSO-d_6) 2.30 (2H, m, CH_2), 2.40 (2H, t, CH_2), 2.40(2H, t,CH_2),2.60(2H, t, CH_2), 2.80 (2H, s, CH_2), 2.25 (3H, s, CH_3), 7.20-8.10 (7H, m, aromatic protons).
6e	58	200-202	$C_{21}H_{17}N_3O$ (ethanol)	3040 (CH arom), 2920 (CH aliph), 1680 (C=O), 1630 (C=N)	(DMSO-d_6) 2.80 (2H, s, CH_2), 2.20 (3H, s, CH_3), 7.40-8.10 (12H, m, aromatic protons).
6f	57	160-162	$C_{24}H_{16}N_3OBr$ (ethanol)	3050 (CH arom), 2917 (CH aliph), 1677 (C=O), 1630 (C=N)	(DMSO-d_6) 2.80 (2H, s, CH_2), 2.20 (3H, s, CH_3), 7.40-8.10 (11H, m, aromatic protons).
6g	55	170-172	$C_{24}H_{19}N_3O$ (ethanol)	3060 (CH arom), 2960 (CH aliph), 1680 (C=O), 1630 (C=N)	(DMSO-d_6) 2.80 (2H, s, CH_2), 2.90 (3H, s, CH_2), 2.20 (3H, s, CH_3), 7.20-8.10 (12H, m, aromatic protons).
6h	53	160-162	$C_{21}H_{18}N_3OBr$ (ethanol)	3050 (CH arom), 2917 (CH aliph), 1677 (C=O), 1620 (C=N)	(DMSO-d_5) 2.80 (2H, s, CH_2), 2.90 (2H, s, CH_2), 2.20 (3H, s. CH_3), 7.10-8.00 (11H, m, aromatic protons).

5a-h were established from their elemental analysis and spectroscopic data (Table III).

The structures of the new synthesized spiroheterocyclic derivatives **6a-h** were confirmed on the basis of their elemental analysis and their spectral data (Table IV).

Conclusions

This work reports a facile method for the synthesis of spiropyrimido-quinazoline derivatives.

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Received on Februarv 2, 2002