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A Facile Synthesis of 3-Substituted-2-styryl-4-quinazolones

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2-Methyl-3,1-benzoxazine-4-one (**3**), generated by cyclizing of N-acetyl-anthranilic acid with ethyl chloroformate in benzene containing triethyl-amine, reacts with primary amine and subsequently aromatic aldehyde when heated under reflux in glacial acetic acid to give 3-substituted 2-styryl-3,4-dihydro-4-quinazolones (**7**).

Key Words: Synthesis, 3-Substituted-2-styryl quinazolones.

INTRODUCTION

Condensation of anils with nitrogen heteroaromatics bearing methyl group is known in literature[1,2]. However, simultaneous introduction of arylidene and amino moieties in suitable heterocycles is not yet explored. The present investigation has been undertaken with a view to studying the possibility of using an amino compound with an aromatic aldehyde, in one pot conversion of suitable O-C=N- heterocycles bearing a methyl group at the imino carbon atom, into N-C=N heterocycles having a styryl moiety in places of methyl group. For this purpose 3-substituted 2-styryl-3,4-dihydro-4-quinazolones (**7**) were synthesized from N-acetylanthranilic acid (**1**) (**Scheme-I**).

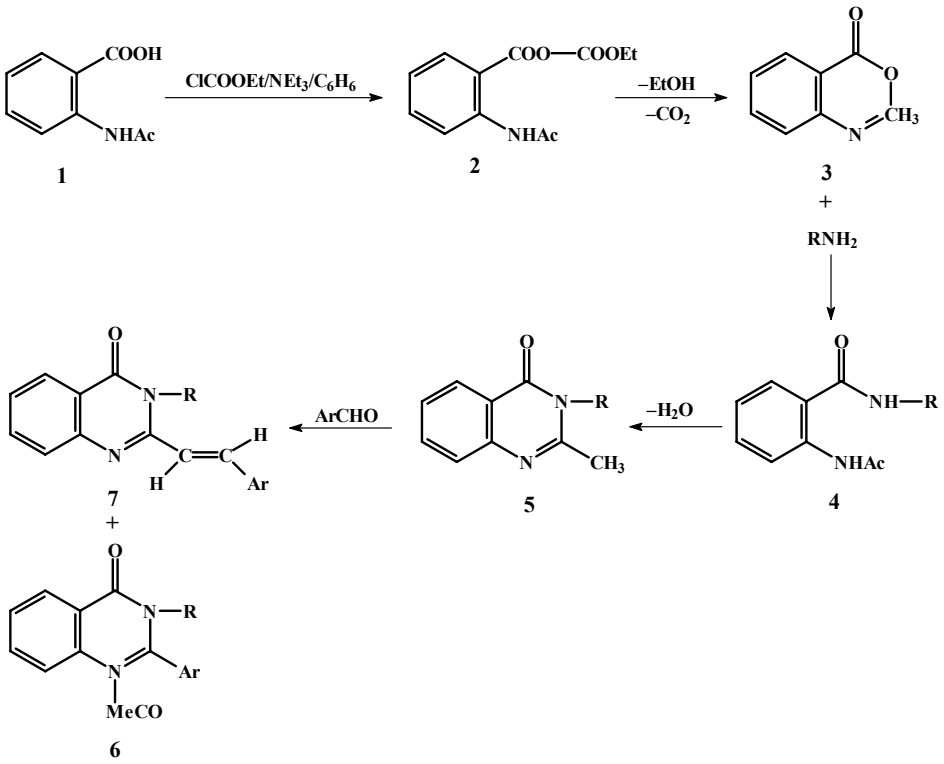
Quinazolin-4-ones are an important class of compounds and their chemistry continues to be of considerable interest[3-5]. 2-Styryl quinazolones having similar structure as stilbenzenes, are thought of having biological activity. As this class of compounds are quinazolone derivatives, they are of immense importance. They are reported as antibacterial and antifungicidal[6]. They also have antiinflammatory[7] activity along with antimicrobial[8] properties.

EXPERIMENTAL

All the chemicals used were of LR grade and the melting points reported were determined in open capillary tube and are uncorrected. IR spectra were recorded in Nujol and the ^{1}H NMR spectra was also recorded.

General procedure:

3-Substituted-2-styrylquinazolin-4-ones: To a suspension of N-acetyl anthranilic acid (1.0 mol) in dry benzene (25 mL/g of N-acetyl anthranilic acid) containing triethylamine (2.2 mol), ethyl chloroformate (1.01 mol) was added and the mixture



Scheme-I

salts separated out which were filtered off and washed with dry benzene. The filtrate and the washings were combined and concentrated to dryness under reduced pressure. To the residue primary amine (1.1 mol) and glacial acetic acid (10 mL/g of N-acetyl anthranilic acid) were added and the mixture heated under reflux for 10 min. Subsequently an aromatic aldehyde (1.1 mol) was added and heating was continued for 2.5 h, using freshly fused sodium acetate as a catalyst. The solution was concentrated to dryness over a steam bath, triturated with ethyl alcohol, filtered and the crude product was recrystallized from ethyl alcohol. The relevant data are given in the Table-1.

Reaction of 2-phenyl-3,1-benzoxazine-4-one (9) with aniline and benzaldehyde as above procedure: Formation of 2-benzamidobenzanilide (**11**) and benzaldehyde-N-benzoylanthranilic acid was converted to (**9**) and allowed to react with aniline and benzaldehyde as above procedure. On work-up and treatment with aq. ethanol (**11**) was obtained which was recrystallized from glacial acetic acid, yield 44 %, m.p 278-279 ºC.

Benzaldehyde obtained from ethanolic solution was isolated and identified as its phenylhydrazone derivative.

TABLE-1
PREPARATION OF 3-SUBSTITUTED-2-STYRYL QUINAZOLIN-4-ONES

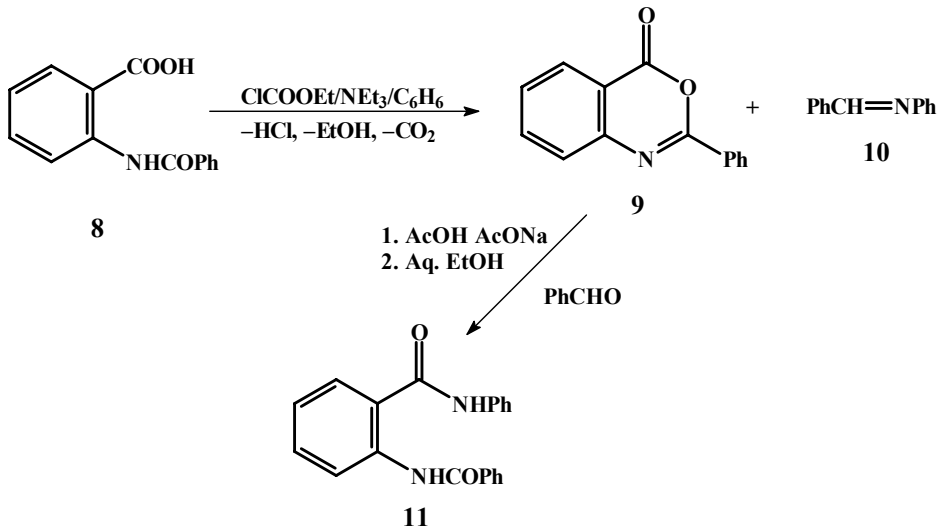
Sr. No.	Ar	R	Yield (%)	m.p. (°C)	IR (Nujol) (cm^{-1})	PMR ($CDCl_3$/TMS), δ ppm
1	C_6H_5	C_6H_5	24.79	201	1683, 1632	6.46 (d, IH, *J* = 16 Hz, PhCH=CH), 7.3-8.2 (m, 14H, Ar-H), 8.5 (d, IH, *J* = 16Hz, PhCH=CH).
2	C_6H_5	4-Cl-C_6H_4	23.61	> 280	1680, 1640	6.46 (d, IH, *J* = 16 Hz, PhCH=CH), 7.2-7.5 (m, 13H, Ar-H, 7.7, d, IH, *J* = 16 Hz, PhCH=CH)
3	C_6H_5	4-HOOC-C_6H_4	20.72	284	3430, 1685, 1607, 1465	-
4	C_6H_5	N-CH_3, -C_6H_5	44.56	> 280	3201, 1685, 1607, 1580	-
5	2-HO-C_6H_4	4-Cl-C_6H_4	48.22	102	3430, 1681, 1586	-
6	2-HO-C_6H_4	4-HOOC-C_6H_4	54.12	258	3413, 1682, 1602	-
7	2-HO-C_6H_4	N-CH_3, -C_6H_5	60.73	268	3201, 1685, 1607, 1586	-
8	4-HO, 3-OCH_3, -C_6H_3	4-Cl-C_6H_4	58.44	182	3403, 1655, 1685, 1582	-
9	4-HO, 3-OCH_3, -C_6H_3	4-HOOC-C_6H_4	43.67	266	3201, 1685, 1586, 1506	-
10	4-HO, 3-OCH_3, -C_6H_3	N-CH_3, -C_6H_5	31.32	264	3205, 1607, 1586	-
11	C_6H_5	4-OCH_3, - C_6H_4	77.73	204	3435, 1636, 1608, 1553	-
12	2-HO-C_6H_4	4-OCH_3, - C_6H_4	32.50	264	3354, 1607, 1685, 1550	-
13	4-HO, 3-OCH_3, -C_6H_3	4-OCH_3, - C_6H_4	36.96	186	1681, 1608, 1584	
14	4-OCH_3, - C_6H_4	C_6H_5	40.10	178	1713, 3369	-
15	4-OCH_3, - C_6H_4	4-Cl- C_6H_4	52.06	203	1685, 3789, 1463	-
16	3-NO_2-C_6H_4	C_6H_5	24.24	198	3062, 1680, 1531	-
17	3-NO_2-C_6H_4	4-HOOC-C_6H_4	19.28	> 280	3244, 1684	-

RESULTS AND DISCUSSION

In connection with our studies in heterocycles carrying an activated methyl group, the title reaction was investigated. The synthesis of (**7**) is usually carried out in a step-wise fashion[1], but in the present method, all the steps were carried out in the same flask. For this purpose, N-acetylanthranilic acid (**1**) was cyclized with ethyl chloroformate in the presence of triethylamine in dry benzene. 2-Methyl-3,1-benzoxazin-4-ones (**3**) thus generated was treated under reflux with different amines and aromatic aldehydes in glacial acetic acid containing a catalytic amount of fused sodium acetate, when the expected 3-substituted-2-styryl-3,4-dihydro-4-quniazolones (**7**) were obtained in moderate to good yields. It should be mentioned that benzene was found unsuitable as a solvent in this reaction.

The lactone bond of (**3**) is quite vulnerable, as is evidenced by its facile hydrolysis on treatment with cold water or by prolonged exposure to moisture. It is therefore likely that the formation of 2-styryl-4-quinazolones (**7**) by the present procedure is initiated by cleavage of the benzoxazinone ring by attack of an amine generating 2-methyl-4-quinazolone (**5**) and it condenses with aldehyde which ultimately affords the expected 2-styryl-4-quinazolone (**7**). After the products were characterized by spectral data, the alternate structure (**6**) was ruled out.

With a view to ascertaining such a formulation, 2-phenyl benoxazinone (**9**), which does not have a reactive methyl group and rules out a Michael type addition, was allowed to react with aniline and subsequently their benzaldehyde in glacial acetic acid. On work-up and treatment with aq. ethanol, N-benzoylanthranilide (**11**) was obtained (**Scheme-II**).



Scheme-II

This can only be explained by the attack of aniline on the carbonyl group leading to the formation of an unstable adduct which gets hydrolyzed during work up to give (**11**) which shows that it has not reacted with benzaldehyde. It should be emphasized that the present procedure involving several steps can be carried out in one flask and in view of the easy availability of reactants, greater speed, mild reaction conditions and better overall yield, the reaction is potentially important. All the 4-quinazolone derivatives were crystallized from alcohol to get crystalline solids. Most of the compounds prepared showed a stable yellow colour. Yields and relevant physical data are given in the Table-1.

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