The Use of Thiochroman-4-one In The Synthesis of Some Benzothiopyranopyrimidines and Bis-thiochrom-2-ene-4-one of Pharmaceutical Interest

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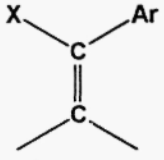
Abstract The reaction of the title compound with anisaldehyde, 5-aminotetrazole monohydrate (and/or urea) in presence of HCl gas in n-butanol afforded the bnezothiopyranopyrimidines (4,8). The reaction with anisaldehyde in presence of HCl gas in n-butanol resulted in the formation of the bis-thiochrom-2-ene-4-one (9).

Introduction:

It has been reported that the central carbon atom of molecules containing a subunit such as 1 would be expected to undergo electrophilic addition[1,2,3] by nucleophiles such as sulphhydryl (as in cysteine) and hydroxyl (as in serine) and, as result, interfer with the normal enzymatic reactions these amino acids (e.g. serine proteases).



1, X = N, S.

Our interest in 1 was gained from the biological activities reported for their derivatives containing an SP^2 carbon atom bonded to one heteroatom.[3,4,5]

Thiochroman-4-ones possess significant biological properties[6]. Derivatives of pyrimidines form an integral part of a large number of therapeutically important compounds. Only a few examples are known in the literature for the synthesis of

polycyclic systems from thiochroman-4-ones. This might be due to unsuccessful attempts in the preparation of derivatives of thiochroman-4-ones (by convenient methods) having suitable functional groups adjacent to the carbonyl function necessary for ring closure reactions.

Results and Discussion:

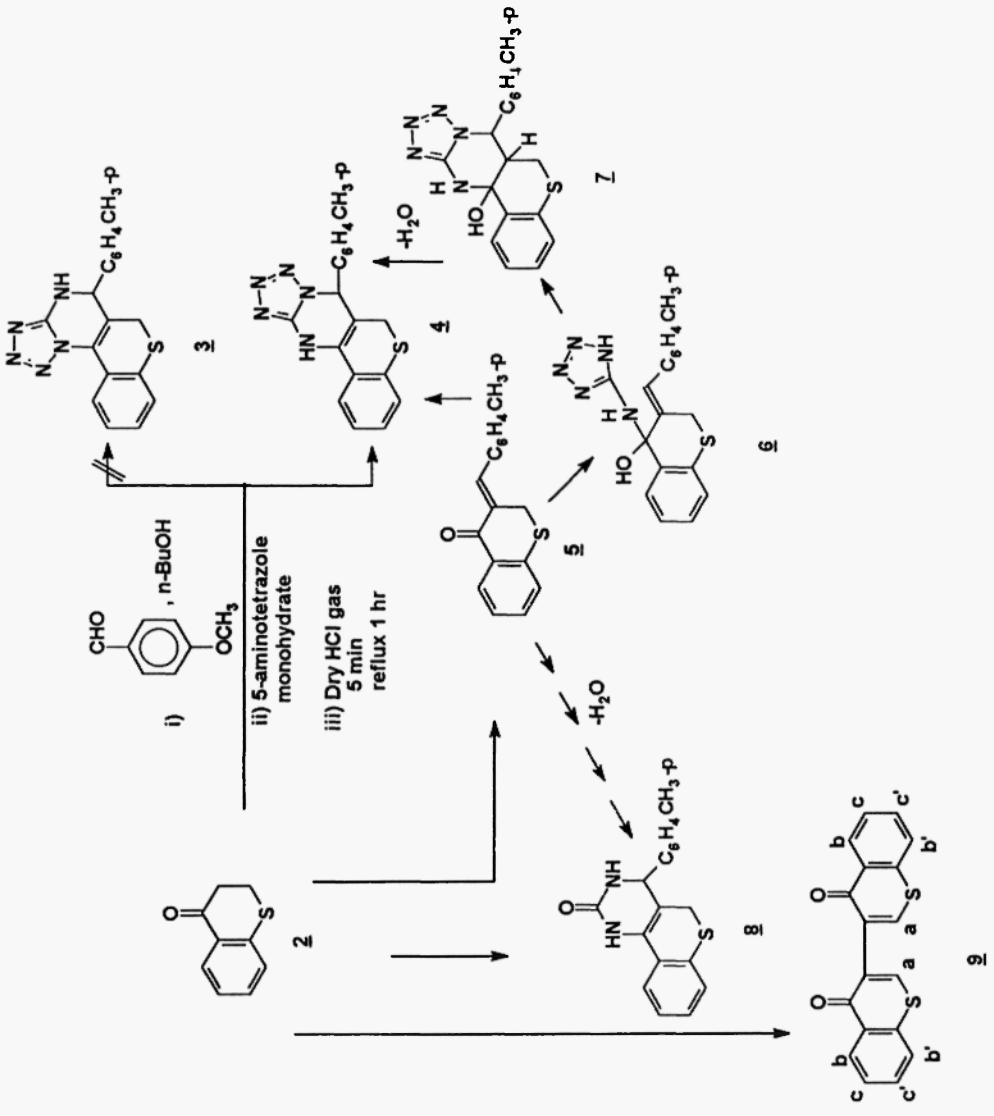
In continuation of our previous work[1], this paper describes in situ functionalization of C_3 with reagents such as anisaldehyde to afford one-pot synthesis of polycyclic systems from thiochroman-4-one 2. The condensation of 2 with amisaldehyde, 5-aminotetrazole in presence of HCl gas in n-butanol can conceivably afford the pyrimidine derivative 3 or 4. However, our previous studies[1,7-10], IR and ^{1}H-NMR spectrum favour the linear condensation product 4 rather than the angular product 3. Thus, 3-anisylidine thiochroman-4-one (5) appears to be the most probable intermediate in this reaction which reacts with 5-aminotetrazole to form the aminol derivative intermediate (6 and 7). Cyclodehydration of the performed aminol derivatives was continued in refluxing n-butanol/HCl gas, to give the final product 4. The IR spectrum showed absorption band at 3225 cm^{-1} (NH). The ^{1}H-NMR spectrum displayed signals characteristic for OMe, SCH_2, and NH (see Experimental).

Under analogous reaction conditions, the condensation of thiochroman-4-one, anisaldehyde, urea in presence of HCl gas in n-butanol via anisylidine derivative 5 and addition cyclization gave the only possible product, pyrimidine derivative 8. The ^{1}H-NMR and IR spectra (see Experimental), the above findings and our previous work[1,7-10] supported the condensation product 8.

An attempts to obtain the anisylidine derivative 5 upon treatment 2 with anisaldehyde in n-butanol were failed and instead, the bis-thiochrom-2-ene-4-one (9) was the only the product obtained. The ^{1}H-NMR spectrum (400 MHz) displayed signals at δ 6.55 (s, 2H, 2 olefinic protons), 7.55 (d, 1H, Ha), 7.65 (d, 1H, Hb′), 7.40 (dd, 1H, Hc) and 7.45 (dd, 1H, HC′).

Experimental

All melting points are uncorrected. Elemental analysis was performed in the Microanalytical Unit, Mansoura University. IR spectra (in cm^{-1}) were recorded by


i) , n-BuOH
ii) 5-aminotetrazole monohydrate
iii) Dry HCl gas 5 min reflux 1 hr
-H2O
-H2O

means of KBr on a Perkin-Elmer 883 Infrared Spectrophotometer. ^{1}H-NMR spectra were recorded on a Brucker 400 MHz apparatus in $CDCl_3$.

Condensation of 2 with anisaldehyde and 5-aminotetrazole: Formation of 4:

To a mixture of 2 (0.004 mole) anisaldehyde (0.004 mole) and 5-aminotetrazole monohydrate (0.004 mole) in n-butanol (5 ml) was passed dry HCl gas for 5 minutes. The reaction mixture was refluxed for one hour, left to stand at room temperature. The solid product that obtained was filtered off, dried and recrystallized from benzene to give compound 4 as colourless crystals, m.p. 277°C, in 71% yield.

Analysis $C_{18}H_{15}N_5SO$ (349)

Calcd	C 61.89	H 4.29	N 20.05	S 9.16
Found	C 62.11	H 4.35	N 20.15	S 9.25

^{1}H-NMR ($CDCl_3$), δ (ppm): 3.06 (d, 3.17(d), 3.4(s), 3.76(s), 6.8(d), 7.25(m), 7.33(m), 7.36(d), 7.61 (br.d).

4-Anisyl-5H-(1-benzthiopyrano)-(4,3-d)-1,2,3,4-tetrahydropyrimidine-2-one (8):

Following the above procedure, compound (8) was crystallized from pet. ether as colourless crystals, m.p. > 300°C in 61% yield.

Analysis $C_{18}H_{16}N_2SO_2$ (324)

Calcd	C 66.66	H 4.9	N 8.64	S 9.87
Found	C 66.79	H 4.81	N 8.75	S 9.95

IR(KBr) γ = 1650, 1695, 3260, 3300 cm^{-1}.
^{1}H-NMR ($CDCl_3$), δ (ppm): 2.96(d, 3/14(d), 3.8(s), 5.09(s), 6.88(d), 7.2(m), 7.32(m), 8.1(d), 8.12(d).

Bis-(thiothrom-2-ene-4-one) 9:

To a mixture of 2 (0.005 mole), and anisaldehyde (0.005 mole) in n-butanol (10 ml) was passed dry HCl gas for 5 minutes. The reaction mixture was refluxed for one hour, left to stand at room temperature. The solid product that obtained was filtered off, dried and recrystallized from benzene to give compound 9 as colourless crystals, m.p. 204°C, in yield 75%.

Analysis $C_{18}H_{10}S_2O_2$ (322)
Calcd C 67.0H 3.1 S 19.87
Found C 67.3H 3 3 S 19.69

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