Synthesis of Some New Heterocyclic Compounds from 3-Chloro-4(indol-3-yl)pyridazine

G. H. SAYED*, M. S. ABDEL HALIM, A. RADWAN AND M. KHALIL
Chemistry Department, Faculties of Science and Engineering, Ain Shams University and Al-Azhar University for Girls, Cairo, Egypt

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Summary: The title compound was allowed to react with *p*-aminoacetophenone followed by condensation with benzaldehyde to give chalcone which is used in the preparation of new compounds containing the pyrazoline, isoxozoline, pyrimidone and pyrimidine thione moiety through its reaction with hydrazines, hydroxylamine hydrochloride, urea and thiourea. The product of *p*-aminoacetophenone when treated with bromine - acetic acid mixture gave the dibromo derivative which on reaction with thiourea gave the 2-aminothiazole derivative. The reaction of the title compound with sulfanilamide is also described.

Introduction

Chalcones are used as key intermediates in several cyclization reactions to produce heterocyclic compounds containing the pyrazoline [1], isoxazoline [2], pyrimidone and pyrimidinethione rings [3]. These rings play a vital role in many biological processes as well as medicinal and agriculture applications. This prompted us to synthesize new chalcone through the reaction of 3-chloro-4-(indol-3-yl)-6-(3,4-dimethylphenyl) pyridazine (**1**) with *p*-aminoacetophenone to give 3-(*p*-acetyl-anilino)-4-(indol-3-yl)-6-(3,4-dimethylphenyl) pyridazine (**2**) which was then allowed to undergo Claisen - Schmidt condensation with aromatic aldehyde namely, benzaldehyde in presence of 10% sodium.hydroxide to give the corresponding chalcone 3-(*p*-cinnamoylanilino)-4-(indol-3-yl)-6-(3,4-dimethylphenyl) pyridazine (**3**).

Results and Discussion

The structure of (**2**) was derived from its IR* spectrum showing νC=O at 1665, νC=N at 1590 and νNH at 3460 and its ^{1}H-NMR (DMSO-d_6) spectrum which showed signals at 8.2-7.2 (13H, m, ArH, CHNH + H-pyridazine) and at 2.5 (9H, s, $2CH_3$ + $COCH_3$).

The IR spectrum of (**3**) showed νC=O at 1675, νC=N at 1610 and νNH at 3200.

Pyrazolines have been tested for their insecticidal activities [4] fungicidal activities [5] and also have considerable pharmacological potentials [6-8].

Condensation of (**3**) with hydrazine hydrate or phenylhydrazine in ethanol afforded 3-[*p*-(5-phenyl-2-pyrazolin-3-yl)-anilino]-4-(indol-3-yl)-6-(3,4-dimethylphenyl)-pyridazine (**4a**) and 3-[*p*-(1,5-diphenyl-2-pyrazolin-3-yl)anilino]-4-(indol-3-yl)-6-(3,4-dime-thylphenyl) pyridazine (**4b**).

The IR spectra of (**4a**) and (**4b**) showed νC=N at 1610 - 1600 and νNH at 3200 - 3100. The ^{1}H-NMR (DMSO-d_6) spectrum of (**4a**) showed signals at 7.8-6.8 (18H, m, ArH + CHNH + H - pyridazine), at 4.78-3.24 (3H, m, CH_2-CH (pyrazoline ring)] and at 2.3 (6H, s, $2CH_3$).

Reaction of (**3**) with hydroxylamine hydrochloride in boiling ethanol gave the corresponding 3-[*p*-(5-phenyl-2-isoxazolin-3-yl)-anilino]-4-(indol-3-yl)-6-(3,4-dimethylphenyl) pyridazine (**5**). Its IR spectrum showed νC=N at 1610 and νNH at 3200.

The interesting pharmacological properties of pyrimidine derivative as anticancer [9] led us to synthesis pyrimidine derivatives (**6a**) and (**6b**) *via* the reaction of the chalcone **3** with each of urea and thiourea to give 3-[*p*-1,2,5,6-tetrahydro-2-oxo-6-phenyl-4-pyrimidinyl)anilino]-4-(indol-3-yl)-6-(3,4-dimethylphenyl) pyridazine (**6a**) and the pyrimidine-2-thione derivative (**6b**), respectively. The IR spectrum of (**6a**) showed νC=O at 1660, νC=N at 1610 and νNH at 3240 whereas the IR spectrum of (**6b**) showed νC=N at 1605, νC=S at 1175 and νNH at 3250.

*To whom all correspondance should be addressed.

*IR ν_{max} here and elsewhere in the paper in cm^{-1}.

A large number of thiazole derivatives have been found to exhibit pharmacological activity, anti-inflammatory properties and used as an anthelmintic and fungicide [10].

This prompted us to synthesise 2-aminothiazole derivative through the reaction of (2) with bromine in acetic acid to give 3-[*p*-bromoacetyl)-anilino]-4-(indol-3-yl)-5-bromo-6-(3,4-dimethylphenyl) pyridazine (7) followed by the reaction of (7) with thiourea in the presence of sodium hydroxide to give the 2-aminothiazole derivative (8).

The introduction of bromine in position 5 in compound (7) can be mechanistically explained on the basis that the first step is addition of bromine on the double bond (position 4-5) followed by elimination of hydrogen bromide. This is in accordance with a previous result [11].

The IR spectrum of (7) showed νC=O at 1725 [12], νC=N at 1580 and νNH at 3360. While the IR spectrum of (8) showed νC=N at 1620 and νNH at 3240.

Interestingly, reaction of (1) with sulfanilamide in presence of hydrochloric acid gave the 3-(*p*-sulfamoylanilino)-4-(indol-3-yl)-6-(3,4-dimethylphenyl) pyridazine (9). Its IR spectrum showed νC=N at 1620, νSO_2 at 1150, νSO_2 at 1150 and νNH at 3270. The ^{1}H-NMR (DMSO-d_6) spectrum of (9) showed signals at 8.1-7.2 (13H, m, Ar-H, CHNH + H - pyridazine) and at 2.3 (6H, s, $2CH_3$).

Experimental

Melting points are uncorrected. IR spectra in KBr were recorded on a Unicam SP 1200 spectrophotometer, PMR spectra on a Varian VN 1009 (S-60 T) instrument using TMS as internal standard and mass spectra on an AET-MS 902 mass spectrometer at 70eV electron energy, 6KV accelerating voltage at 130° ion source temperature using a direct insertion probe.

Preparation of compounds (2) *and* (9)

A mixture of (1) (0.01 mol) and *p*-aminoacetophenone or sulfanilamide (0.01 mol) in absolute ethanol (50 ml) in presence of few drops of HCl was refluxed for 3 h. The solid obtained after concentration and cooling was crystallized from toluene (2) or benzene (9).

(2): m.p. 215 °C, yield 65% (Found C, 77.93; H, 5.4; N, 13.2 % $C_{28}H_{24}N_4O$ Requires: C, 77.75; H, 5.59; N, 12.95%); MS m/z 316 (M^+-indol-3-yl).

(9): m.p. 206 °C, yield 55% (Found C, 66.3; H, 5.2; N, 14.6% $C_{26}H_{23}N_5O_2S$ requires: C, 66.50; H, 4.93; N, 14.91%) MS m/z 469 (M^+).

Reaction of (2) *with benzaldehyde: Formation of* (3)

A warm solution of (2) (0.01 mol) and benzaldehyde (0.01 mol) in 20 ml (10%) ethanolic sodium hydroxide solution was refluxed for 2 h, cooled and poured onto cold dilute HCl. The solid obtained was crystallised from toluene to give (3), m.p. 140° decomp., yield 46% (Found: C, 80.4; H, 5.5; N, 10.9%. $C_{35}H_{28}N_4O$ requires: C, 80.74; H, 5.42; N, 10.76%). MS m/z 520 (M^+).

Reaction of (3) *with hydrazines and hydroxylamine hydrochloride: Formation of* (4a), (4b) *and* (5).

To a solution of (3) (0.01 mol) in ethanol (20 ml), hydrazine hydrate, phenylhydrazine or hydroxylamine hydrochloride (0.01 mol) was added and the reaction mixture refluxed for 10 h. The solid that separated on cooling was crystallized from petroleum ether 60-80 °C (4a) (5) and toluene (4b).

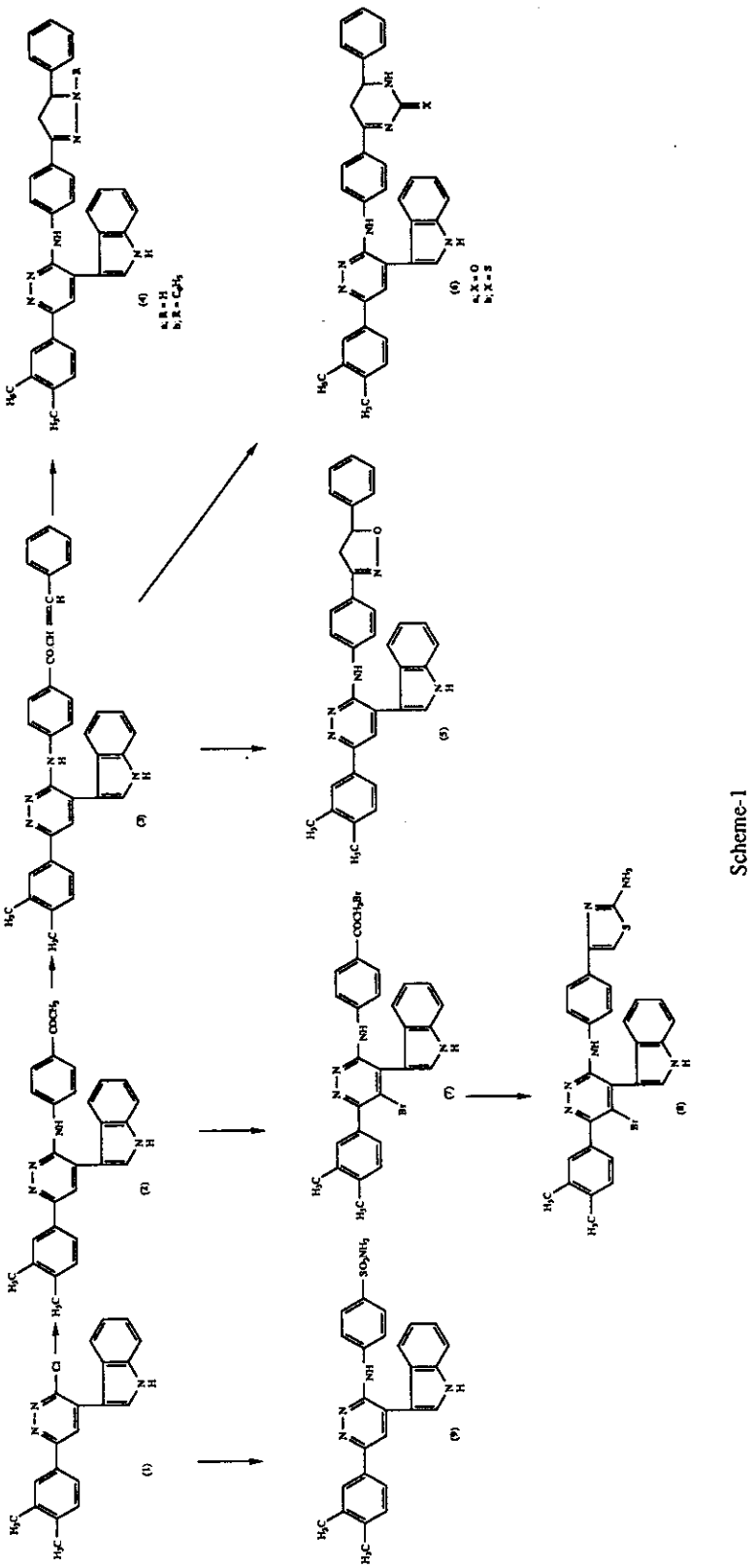
(4a): m.p. 100 °C, yield 72% (Found: C, 78.9; H, 5.6; N, 15.8%. $C_{35}H_{30}N_6$ Requires: C, 78.62; H, 5.65; N, 15.72%) MS m/z 534 (M^+)

(4b): m.p. 210 °C, yield 64% (Found: C, 80.7; H, 5.8; N, 13.5%. $C_{41}H_{34}N_6$ Requires: C, 80.62; H, 5.61; N, 13.76%). MS m/z 610 (M^+).

(5): m.p. 110°C, yield 52% (Found: C, 78.7; H, 5.6; N, 12.8% $C_{35}H_{29}N_5O$ Requires: C, 78.47; H, 5.45; N, 13.07 %) MS m/z 535 (M^+) .

Reaction of (3) *with urea: Formation of* (6a)

A mixture of (3) (0.01 mol) and urea (0.01 mol) in ethanol (50 ml) in presence of conc. HCl (5 ml) was refluxed for 5 h. The solid obtained after con-



Scheme-1

centration and cooling was crystallized from benzene to give (**6a**), m.p. 245°C, yield 45% (Found: C, 76.9; H, 5.5; N, 15.2 $C_{36}H_{30}N_6O$ Requires: C, 76.84; H, 5.37; N, 14.93%). MS m/z 562 (M^+).

Reaction of (**3**) *and* (**7**) *with thiourea: Formation of* (**6b**) *and* (**8**)

A mixture of (**3**) or (**7**) (0.01 mol) and thiourea (0.01 mol) in ethanol (50 ml) in presence of sodium hydroxide (0.1 g) was refluxed for 3 h. The solid obtained after concentration and cooling was crystallized from petroleum ether 60 - 80°C (**6b**) and benzene (**8**).

(**6b**): m.p. 180 °C, yield 60% (Found: C, 75.0; H, 5.4; N, 14.6 $C_{36}H_{30}N_6S$ Requires: C, 74.71; H, 5.22; N, 14.52%). MS m/.z 578 (M^+)

(**8**): m.p. 190 °C, yield 55% (Found: C, 61.5; H, 3.8; N, 14.9 $C_{29}H_{23}BrN_6S$ Requires: C, 61.37; H, 4.08; N, 14.81%). MS m/z 566 (M^+) ^{79}Br).

Action of bromine - acetic acid mixture of (**2**)*: Formation of* (**7**)

The solution of (**2**) (0.01 mol) in glacial acetic acid (20 ml) was stirred and treated dropwise with bromine (0.01 mol) at 60-70°. The solution was further stirred for 2 h, then cooled in ice. The precipitated product was filtered off, washed with light petroleum 40-60° C, stirred with conc. ammonium hydroxide for 15 minutes. The solid product was crystallized from ethanol to give (**7**), m.p. > 360 °C, yield 30% (Found: C, 57.1; H, 3.7; N, 9.8%) $C_{28}H_{22}Br_2N_4O$ Requires: C, 56.96; H, 3.75; N, 9.49%) MS m/z 588 (M^+) (^{79}Br).

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