NEW 1,4,-BENZOXAZINE FUSED HETEROCYCLES II: SYNTHESIS OF 5-METHYL-2-PHENYL-5H-BENZO [*B*] IMIDAZO [2',1':2,3][1,3] THIAZOLO [4,5-*E*] OXAZINE.[+]

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Abstract:
Synthesis, physical and analytical properties of 5-methyl-2- phenyl-5H-benzo[b] imidazo [2',1':2,3] [1,3] thiazolo [4,5-e]oxazine **5** derivative is described. This new heterocyclic system **5** have been synthesized via the reaction of 2-(2-imino-4-methyl-2,3-dihydro-4H-benzo [b][1,3] thiazolo [4,5-e][1,4] oxazin-3-yl)-1-phenyl-1-ethen –ol **4** intermediate with phenacyl bromide, in good yield.

Introduction

In view of the general interest in the biological activity of heterocyclic systems, we are reporting here for the first time the synthesis of hitherto unreported heterocyclic system in which 1,4-benzoxazine-3-one ring is fused to a thiophene and imidazo thiazole ring. This compound has been prepared from 4-methyl-2H-1, 4-benzoxazine-3-one.

Chemistry

2H-1,4-benzoxazine–3-one derivative can be prepared in several ways reported in the literature[1-3]. Reaction of the 2-amino phenol with chloroacetic acid in methyl isobutyl ketone and $NaHCO_3$ at room temperature gave the corresponding 2H-1, 4-benzoxazine-3-one **1**, which is N-methylated with methyl iodide using potassium hydroxide as a base in methanolic solution[4] afforded N-methyl-2H-1,4-benzoxazine-3-one **2**. Previously we reported[5] that the literature survey reveals that ketones react with thiourea and halogens to give substituted phene morpholo aminoketones[6]. This (**2**) was coupled with thiourea and iodine gave 4-methyl-4H-benzo[b][1,3] thiazolo [4,5-e][1,4]oxazin-2- amine **3** as colorless needles (72%). Cyclization of (**3**) with phenacyl bromide at room temperature resulted in 2-(2-imino-4-methyl-2,3- dihydro-4H-benzo [b] [1,3] thiazolo [4,5-e] [1,4] oxazin-3-yl) –1-phenyl-1-ethen-1-ol 4(65%) as the intermediate product. Subsequently this (4) was assigned the enol form and gave 5-methyl-2-phenyl-5H-benzo [b] imidazo [2,'1':2,3] [1,3] thiazolo [4,5-e]

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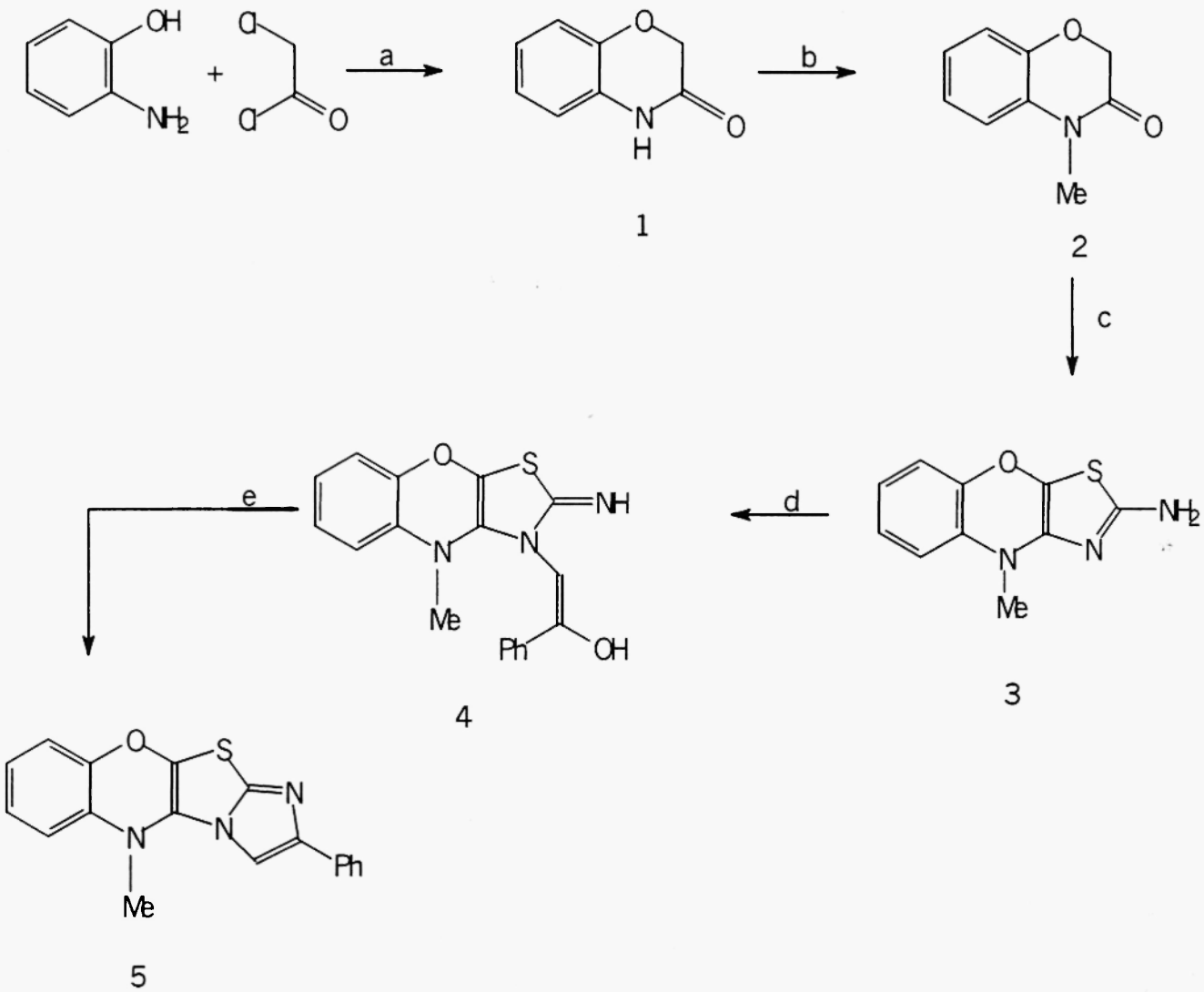
oxazine **5** (92%) by heating in ethanol (**Scheme 1**). Their structures wee established by IR, ^{1}H NMR and elemental analysis.



Reagents and Conditions:

a. $NaHCO_3$ methylisobutylketone, rt;
b. MeI, KOH
c. H_2NCSNH_2, I_2, EtOH, Reflux
d. $PhCOCH_2Br$, EtOH, RT, Overnight
e. EtOH, Reflux, 6hrs

Scheme-1

Experimental Section

Melting points were determined in open glass capillaries on a Metter FPS melting point apparatus and are uncorrected. ^{1}H NMR Spectra were recorded on a Gemini (200 MHz) spectrometers (chemical shifts in δ ppm using TMS as internal standard) and IR spectra were recorded in KBr on a perkin-Elmer bio-spectrometer. Elemental analyses were carried out with a Cario Erba Model 1106 Elemental Analyzer.

2H-1,4-benzoxazine-3-one 1.

Chloro acetyl chloride (20 mmol) was slowly added slowly over a period of 25 minutes to a pre cooled 10°C mixture of o-amino phenol (20 mmol), isobutyl ketone , and sodium bicarbonate solution while stirring. The reaction mixture was, allowed to warm to 30°C, and refluxed for 4hr. The reaction mixture was cooled to room temperature, the organic layer was separated. The resulted product was concentrated to get the corresponding **1** in 90% yield m.p. 171-172°C (lit[2].m.p.173°C). IR (KBr): ν 3130, 1695,1030 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 4.52 (2H, S, -OCH-), 10.60 (1H, S, -NH) 6.80-95(4H, m, Ar-H).

4- Methyl-2H-1,4-benzoxazin-3-one-2.

A mixture of compound **1** (5 mmol), potassium hydroxide (10 mmol) and DMSO (10 mL), methanol (12.5 mL) was stirred for 10 min before methyl iodide (10 mmol) was added. The solution was heated at 50°C under stirring for 15 hr. After cooling, the crude product precipitated when water was added. The precipitate was washed with water, dried, then recrystallized from ethanol . Yield 82%; m.p. 60°C (lit[7] m.p. 59.5°C) ; ^{1}H NMR (DMSO-d_6). δ 4.49 (H, S, -OCH2-), 3.31 (3H, S, -N-Me) and 7.25 (4H, m, Ar-H).

2-Amino-4-N-methyl thiazole [2,3,-6][1,4] benzoxazine 3.

A mixture of compound **2** (5 mmol), thiouea (1 mmol) and iodine (5 mmol) was refluxed for 36 hr in abs. ethanol (50 mL). At this point TLC showed only a slight change in the substrate. After prolonged refluxing (2,3 days until TLC showed the absence of the ketone) the resulting hydride was dissolved in hot water. The solution was filtered while hot and the clear filtrate was neutralized with a strong solution of ammonia. The resulting precipitate was washed with water and crystallized from ethanol. Yield 72%, colorless needles,m.p.242°C (dec) (lit[5] m.p 242°C), IR (KBr): ν 1670, 3388 cm-1; ^{1} H NMR (DMSO-d_6): δ 3.51(3H, S, N-Me), 7.10-7.35 (4H, m, Ar-H) and 5.86 (2H, br, S, -NH_2, D_2O exchangeable). Found : C, 54.77; H,4.13; N,19.15. Calcd for $C_{10}H_9N_3OS$: C,54.77; H,4.10; N,19.16%.

2- (2-imino-4-methyl –2,3-dihydro –4H-benzo [b] [1,3] thiazolo [4,5,-e] [1,4] oxazin-3-yl) –1- phenyl –1- ethan-1-ol 4.

A mixture of **3** (12.3 mmol) and phenacyl bromide (12.3 mmol) in ethanol (50 mL) was allowed to stand at room temperature overnight the crystals which separated was collected by filtration and washed with a small amount of ethanol to yield the corresponding intermediate 4 in 65%. Yield as colorless powder, m.p. 252°C (dec): IR (KBr): ν 3390, 3365, 2850 cm $^{-1}$; ^{1}H NMR (DMSO-d_6): δ 3,04 (3H, S , N-Me), 7.14 (1H, S, =CH), 8.76 (1H, S, -OH), 8.78 (1H , br, S, =NH) and 6.76-7.33 (9H, m, Ar-H). Found : C,64.26; H 4.20; N,12.50. Calcd for $C_{12}H_{14}N_3O_2S$: C,64.26; H, 4.19; N,12.45%.

5-Methyl – phenyl-5H benzo [b] imidazo [2',1',:2,3] [1,3] thiazolo [4,5-e] oxime 5.

A suspension of **4** (8.27 mmol) in ethanol (20 mL) was heated under reflux for 6hr . after cooling, the crystals which separated was collected by filtration to yield final product **5** in 92% as colorless powder, m.p.268°C; ^{1}H NMR (DMSO-d_6): δ 3.20 (3H, S, N-Me) 7.56 (1H, S, 3-H) and 6.58 – 7.26 (9H, m, Ar-H). Found: C,67.70; H 4.12; N,13.18. Calcd for $C_{18}H_{13}N_3OS$: C,67.69: H,4.10: N,13.15%.

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