Organic Chemistry
Current Research
ISSN: 2161-0401

Ghoneim and El-Farargy, Organic Chem Curr Res 2016, 5:1
DOI: 10.4172/2161-0401.1000159

Research Article Open Access

Synthesis of Some Novel Fused Heterocyclic Compounds Derivatives from Bis-chalcones

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Abstract

A chalcone was prepared by the reaction of 1,4-diacetylbenzene with benzaldehyde. Reaction of this chalcone with cynanothioacetamide/guanidine hydrochloride and malnonitrile in presence of piperdene afforded the corresponding pyridine, pyrimidine, and pyrans derivatives in good yields respectively. Further, bis-chalcone 1 was cyclized to pyrazole analogs by using thiosemicarbazide, semicarbazide and tertiarybutylcarbazate. The newly heterocyclic compounds have been characterized by IR, 1H-NMR and elemental analyses.

Keywords: 1,4-Diacetylbenzene; Tertiarybutylcarbazate; Cynano-thioacetamide

Introduction

α,β-Unsaturated are an important aromatic compound ketone which consider forms the central core for a variety of important biological compounds, which are known collectively as flavonoids or chalcones. Chalcones and their derivatives display a wide range of biological activities such as, anti-neoplastic, anti-hypertensive, anti-retroviral, anti-inflammatory [1], anti-histaminic, anti-malarial, anti-oxidant, anti-fungal, anti-obesity, anti-platelet, anti-tubercular, immunosuppressant, anti-arrhythmic, hypnotic, anti-gout, anxiolytic, anti-spasmodic, anti-nociceptive, anti-diabetic, hypolipidemic, anti-filarial, anti-angiogenic [2], anti-protozoal, anti-bacterial, anti-steroidal [3]. Newly, the bis a heterocyclic compound of different ring with different heteroatoms has accepted a great deal of observation because of have compounds for main chain polymers and have many biologically active natural and industrial chemical products had molecular similarity [4-11].

Experimental

Melting points are uncorrected and were recorded on Buchi 510 apparatus. IR spectra were recorded as KBr disks on a perkin-Elmer 383 spectrometer and FTIR-spectrometer Nicolet, impact 400. ^{1}H -NMR spectra was recorded on a Varian Mercury Plus-400 or Bruer-300 in DMSO-d_6 with TMS as an internal standard. The types of signals are indicated by the following letters: s=singlet, d=doublet, t=triplet, q=quartet. Elemental analysis was carried out LECO Analyser CHNS-932. Micro analytical were carried out at micro analytical center and Cairo University, Egypt.

1,4-Diacetylbenzene chalcone (1)

A mixture of 1,4-diacetylbenzene (0.01 mol) and benzaldehyde (0.02 mol) and added (40%, 15 mL) of Alcoholic KOH was stirring at room temperature for 8 hr. Then it was poured onto crushed ice, and acidified with dil. Hydrochloric acid. The precipitated solid was filtered and recrystallized from ethanol.

1, 4-Bis (1,2,3,4-tetrahydro-4,6-diphenyl-2-thioxopyridine-3-carbonitrile) benzene (2)

A mixture of bis-chalcone **1** (4.1 gm, 10 mmol) in 30 ml ethanol, and cynanothioacetamide (20 mmol) was heated under reflux in presence of drops of piperidine for 4 hr. After cooling the precipitated solid was filtered and crystallized from ethanol to give compound **2.** Yield: 74%; m.p. 223°C; IR (KBr) *v* max cm^{-1}: 3225 (NH), 2924 (C-H), 2215 (CN), 1361 (C=S); ^{1}HNMR (DMSO-*d*6, δ, ppm): 10.08 (s, 2H, NH), 7.26-7.13 (m, 14H, Ar-H), 6.24 (d, 2H, pyridin-H), 2.45 (s, 2H, C-H), 2.17 (s, 2H, C-H). Anal. calc. for $C_{30}H_{22}N_4S_2$ (502.65): C, 71.68; H, 4.41; N, 11.15; S, 12.76. Found: C, 71.65; H, 4.29; N, 11.19; S, 12.74.

1,4-Bis (4,6-diphenylpyrimidin-2-amine)benzene (3)

A mixture of bis-chalcone **1** (0.1 mol), Guanidine hydrochloride (0.2 mol) and sodium ethoxide (0.4 mol) in absolute ethanol (50 mL) was heated under reflux on a water bath for 12 hr. The reaction mixture was poured into ice water and the solid precipitated was formed. Then filtrated off and recrystallized from ethanol. Yield: 69%; m.p. 223°C; IR (KBr) *v* max cm^{-1}: 3325 (NH_2), 2924 (C-H), 1564 (C=N); ^{1}HNMR (DMSO-*d*6, δ, ppm): 8.23 (s, 4H, NH_2), 7.26 (s, 4H, Ar-H), 7.13 (s, 2H, Ar-Pym),7.04 (s, 2H, thiophene-H), 2.45 (s, CH3), 2.17 (s, CH3). Anal. calc. for $C_{26}H_{20}N_6$ (416.48): C, 74.98; H, 4.84; N, 20.18. Found: C, 74.95; H, 4.80; N, 20.21.

1,4 -Bis (2-amino-4,6-diphenyl-4H-pyran-3-carbonitrile) benzene (4)

A mixture of bis-chalcone **1** (1 mmol) and malononitrile (0.14 gm, 2 mmol) with drops of piperidine in 50 ml absolute ethanol. The reaction mixture was refluxed for 6 hrs. After cooling the precipitated was formed and collected by filtration, and recrystallized from ethanol to yield compound **4.** IR (KBr) *v* max cm^{-1}: 3225 (NH), 2924 (C-H), 2215 (CN), 1361 (C=S); ^{1}HNMR (DMSO-*d*6, δ, ppm): 10.08 (s, 2H, NH), 7.26-7.13 (m, 14H, Ar-H), 6.24 (d, 2H, pyridin-H), 2.45 (s, 2H, C-H), 2.17 (s, 2H, C-H). Anal. calc. for $C_{30}H_{22}N_4O_2$ (470.52): C, 76.58; H, 4.71; N, 11.91. Found: C, 76.54; H, 4.69; N, 11.88.

Bisphenyl (4,5-dihydro-3,5-diphenylpyrazole-1-carbothio-amide)

A mixture of bis-chalcone **1** (0.004 mol), thiosemicarbazide (0.009 mol) and sodium hydroxide (0.002 mol) in dry ethanol (30 mL) was

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Received: September 09, 2015; **Accepted:** January 19, 2016; **Published:** January 26, 2016

Citation: Ghoneim AA, El-Farargy AF (2016) Synthesis of Some Novel Fused Heterocyclic Compounds Derivatives from Bis-chalcones. Organic Chem Curr Res 5: 159. doi:10.4172/2161-0401.1000159

heated under reflux at 80 °C for 12 h. The progress of reaction was monitored by TLC. After the completion of reaction, the reaction mixture was poured into acidic ice water adjusted by HCl. The solid was filtered off and the solid was recrystallized from ethanol. Yield 72.6%; m.p. IR (KBr) *v* max cm^{-1}: 3253, (arom), 1365 (CS); ^{1}HNMR (DMSO-*d*6, δ, ppm): 7.34-7.79 (m, 14H, Ar-H), 4.53 (t, 2H, 2CH-pyrazole), 2.89 (d, 4H, $2CH_2$), 4.32 (s, 4H, NH_2). Anal. calc. $C_{26}H_{24}N_6S_2$ (484.64): C, 64.44; H, 4.99; N, 17.34; S, 13.23. Found: C, 64.48; H, 4.96; N, 17.39; S, 13.12.

3-(4-(1-carbamoyl-4,5-dihydro-5-phenyl-1H-pyrazol-3-yl) phenyl)-4,5-dihydro-5-phenylpyrazole-1-carboxamide(6)

A mixture of bis-chalcone **1** (0.004 mol), semicarbazide (0.009 mol) and sodium hydroxide (0.002 mol) in dry ethanol (30 mL) was heated under reflux at 80 °C for 12 h. The progress of reaction was monitored by TLC. After the completion of reaction, the reaction mixture was poured into acidic ice water adjusted by HCl. The solid was filtered off and the solid was recrystallized from ethanol. Yield 68%; m.p. IR (KBr) *v* max cm^{-1}: 3253, (arom), 1678 (CO); ^{1}HNMR (DMSO-*d*6, δ, ppm): 7.34-7.79 (m, 14H, Ar-H), 4.32 (t, 2H, 2CH-pyrazole), 3.56 (d, 4H, $2CH_2$), 5.32 (s, 4H, NH_2). Anal. calc. $C_{26}H_{24}N_6O_2$ (452.51): C, 69.01; H, 5.35; N, 18.57. Found: C, 69.04; H, 5.39; N, 18.54.

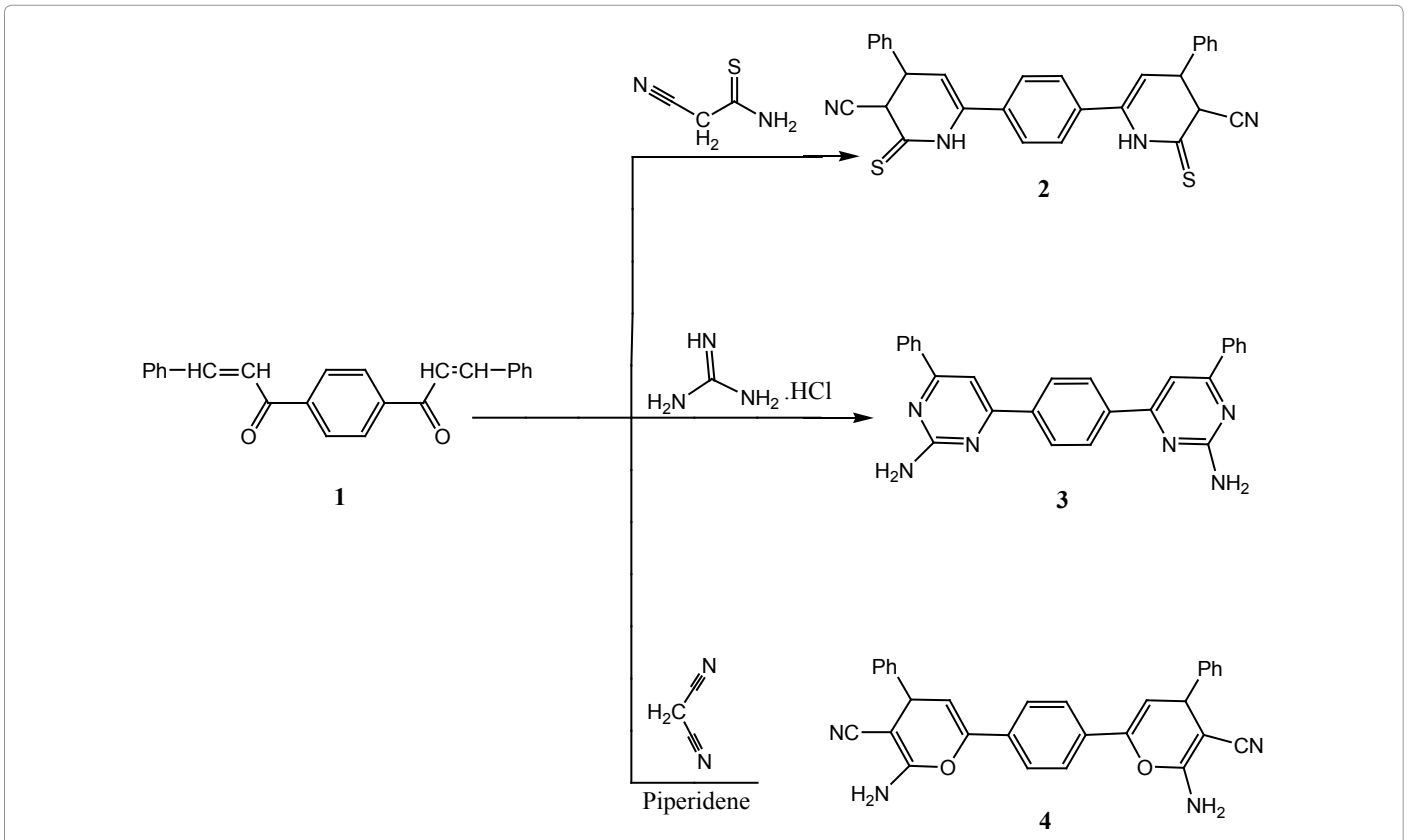
Bis phenyl (tert-butyl 4,5-dihydro-3,5-diphenylpyrazole-1-carboxylate(7)

Bis-chalcone **1** (0.02 mol) and tertiary butyl carbazate (0.04 mol) were dissolved in ethanolic sodium hydroxide (10 ml) and refluxed for 6 h. Then the mixture poured into ice cold water for an hour and then kept in refrigerator for 12 hours. The solid obtained was filtered and recrystallized from absolute ethanol. IR (KBr) *v* max cm^{-1}: 3345, (arom), 1715 (CO); ^{1}HNMR (DMSO-*d*6, δ, ppm): 7.21-7.89 (m, 14H, Ar-H), 5.61(m, 2H, 2CH-pyrazole), 3.42 (d, 4H, $2CH_2$), 1.41 (s, 18H, $9(CH_3)$). Anal. calc. $C_{34}H_{38}N_4O_4$) 566.69: C, 72.06; H, 6.76; N, 9.89. Found: C, 72.17; H, 6.74; N, 9.85.

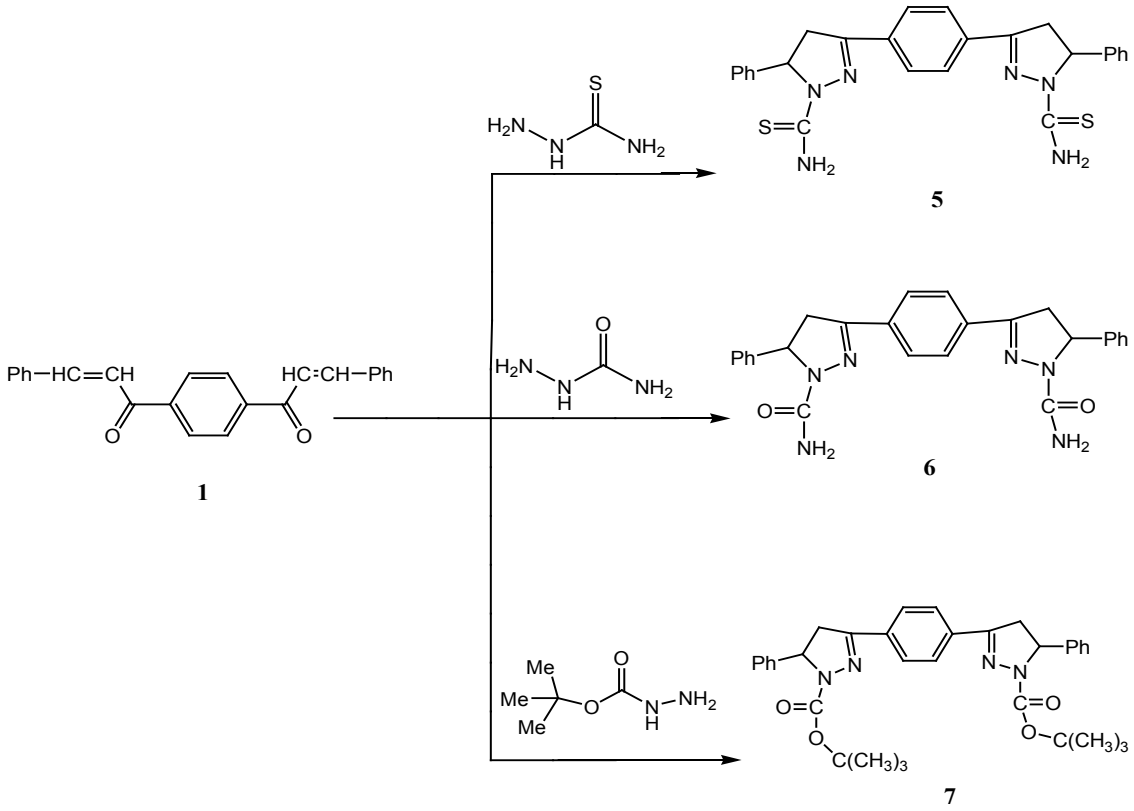
Results and Discussion

The condensation of 1, 4-diacetylbenzene with benzaldehyde in the presence of 15% KOH through Claisen Schmidt yielded the intermediate α, β-unsaturated ketones **1**. When compound **1** was allowed to react with cynanothioacetamide in the presence of piperidine it yielded compound **2.** The ^{1}HNMR spectrum of compound **2** exhibited singlet proton at δ 10.08 ppm corresponding to NH. The IR spectra of **2** showed absorption bands at 2215 cm^{-1} for the CN group. The reaction of bis-Chalcone **1** with guanidine hydrochloride to give the cyclization compound bis-pyrimidine derivatives **3.** Compound **1** was allowed to react with malononitrile by cyclo condensation in the presence of dimethyl formamide and piperidene to give bis-pyrans derivative **4.** The ^{1}HNMR spectrum of compound **4** showed a singlet peak at 6.11 for NH_2 group and a doublet peak at 6.34 for 1H proton of pyran ring the aromatic protons appeared at 7.36-8.20 (Scheme 1). Condensation of bis-chalcone **1** with thiosemicabazide in sodium hydroxide gave a colorless crystalline solid that was the expected pyrazoline derivative **5.** Similarly, addition semicarbazide and tertiary butyl carbazate to compound **1** afforded the cyclization compound pyrazoline derivatives **6** and **7** respectively. The structures of these pyrazoline derivative **5**, **6** were established by ^{1}HNMR spectroscopy, mass spectrometry and IR spectrum (Scheme 2).

In summary, pyridine derivatives, pyrimidine derivatives and pyrans derivatives were prepared from cyanothioacetamide, guanidine hydrochloride and malononitrile with bis-chalcone. The synthesis of



Scheme 1: Synthesis of pyridines, pyrimidines and pyrans derivatives.



Scheme 2: Synthesis of pyrazine derivatives.

pyrazoles derivatives were achieved by the reaction of tertiary butyl carbazate, thiosemicarbazide and semicarbazide with bis-chalcone.

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