

SYNTHESIS AND CHARACTERIZATION OF HETEROCYCLIC CHALCONES CONTAINING HALOGENATED THIOPHENES

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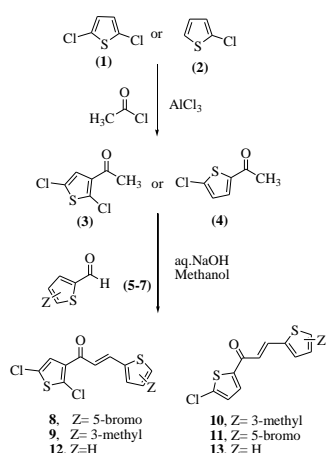
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Graphical abstract



Abstract

Heterocyclic chalcones containing halogenated thiophenes were synthesized. The first step was to synthesize 3-acetyl-2,5-dichlorothiophene and 2-acetyl-5-chlorothiophene as heterocyclic ketones by using Friedel-Crafts acylation. The ketones were then used to synthesize thiophene chalcones through Claisen-Schmidt reaction with the respective heterocyclic aldehydes such as 5-bromothiophene-2-carboxaldehyde, 3-methyl-2-thiophene carboxaldehyde and 2-thiophene carboxaldehyde with 3-acetyl-2,5-dichlorothiophene or 2-acetyl-5-chlorothiophene in presence of basic medium, sodium hydroxide to form the corresponding chalcones. Structures of the synthetic compounds were confirmed by IR, MS, ¹H and ¹³C NMR spectral data.

Keywords: Heterocyclic Chalcone, Claisen-Schmidt condensation, Halogenated thiophene

Abstrak

Kalkon heterosiklik mengandungi tiofena terhalogen telah disintesis. Langkah pertama adalah untuk mensintesis 3-asetil-2,5-diklorotiofena dan 2-asetil-5-klorotiofena sebagai keton heterosiklik dengan menggunakan pengasilan Friedel-Crafts. Keton tersebut digunakan untuk mensintesis kalkon tiofena melalui tindakbalas Claisen-Schmidt dengan aldehyd heterosiklik seperti 5-bromotiofena-2-karbaldehid, 3-metil-2-tiofena karboksaldehid dan 2-tiofena karboksaldehid dengan 3-asetil-2,5-diklorotiofena atau 2-asetil-5-klorotiofena menggunakan medium bes, natrium hidroksida bagi menghasilkan kalkon. Struktur sebatian sintesis telah disahkan menggunakan data spektrum IR, MS, ¹H dan ¹³C NMR.

Kata kunci: kalkonheterosiklik, KondensasiClaisen-Schmidt, Tiofeneterhalogen

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1.0 INTRODUCTION

Chalcones consist of two phenyl rings A and B connected by three carbon α , β -unsaturated carbonyl system. The A-ring at the left side carries the prime number which is bonded to the carbonyl group of α , β -unsaturated carbonyl while the ring B is at the right side [1]. In other word chalcones are open chain flavonoid [2] as shown in Figure 1.

Chalcones and heterocyclic chalcone derivatives play important roles against diverse human diseases such as anti-inflammatory [3, 4], anti-leishmanial [5-7], anti-malarial [8, 9], anti-fungal [10], anti-oxidant [11, 12], anti-cancer [13, 14], anti-AIDS [15, 16] and anti-bacterial agents [17, 18].

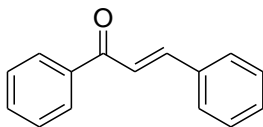


Figure 1 Chemical structure of a chalcone

Several methods and reactions for the syntheses of chalcones based on the formation of carbon-carbon bond have been reported. Claisen-Schmidt condensation is the main method for synthesis of chalcone in the presence of aqueous alkaline base [19].

Other methods include Friedel-Crafts acylation [20], Suzuki coupling reaction [21,22], microwave irradiation [23], ultrasound irradiation [24], grinding technique [25] and boron trifluoride etherate reaction [26].

Chalcones have been synthesized by condensation between aldehydes and ketones. Chalcone is one of important intermediate in the synthesis of five and six membered ring [27]. In addition, chalcones can be used as an intermediate in the biosynthesis of flavonoids [28].

Many studies have synthesized chalcones and their anti-bacterial and anti-breast cancer activities, but not using thiophene chalcone containing two thiophene rings. So, the present study deals with the synthesis of thiophene chalcones containing two thiophene rings and their bioactivities towards antimicrobe and anti-cancer.

2.0 EXPERIMENTAL

2.1 Materials

All the chemicals (reagent and solvent) were purchased from (Qrec, Acros organics, Sigma-Aldrich, Scharlau, M Tedia, Lancaster, Tci and HmbG Chemicals Malaysia). The purity of these chemicals was 90-99% and used without further purification and distillation.

2.2 General Experimental Procedures

Melting points (uncorrected) were measured on a Leica Gallen III Kofler micro melting points apparatus. ^1H and ^{13}C NMR spectra (400 MHz and 100 MHz respectively) were recorded on Bruker Avance II spectrometer using deuterated chloroform (CDCl_3) as solvent. Infrared (IR) spectra were recorded on Perkin Elmer FT-IR spectrometer. Mass spectra were obtained from NUS Mass Spectrometry Service, Singapore. Thin layer chromatography (TLC) alumina sheets precoated with silica gel 60 F254 (0.2 mm thickness) was used to monitor and detect compounds, and the spots were visualized under UV lamp at 254 nm.

2.2.1 General Procedure for the Synthesis of 3-Acetyl-2,5-dichlorothiophene (3) and 2-Acetyl-5-chlorothiophene (4)

3-Acetyl-2,5-dichlorothiophene (3) and 2-acetyl-5-chlorothiophene (4) were synthesized according to literature procedure [29] by using solution of 2,5-dichlorothiophene (1) (100 mmol) or 2-chlorothiophene (2) (100 mmol), acetyl chloride (10 mL) and carbon disulfide (10 mL). The anhydrous aluminum chloride was added slowly to the mixture over fifteen minutes. The reaction mixture was stirred at room temperature overnight. The reaction mixture was cooled and poured into ice water. The carbon disulfide layer was separated and washed three times with water and solvent was evaporated to give solid product:

(3) (14.96 g, 76.69%); IR ν_{max} cm^{-1} : 3102 (C-H sp^2), 3003 (C-H sp^3), 1659 (C=O); ^1H NMR (DMSO): δ 2.50 (3H, s) and δ 7.53 (1H, s).

(4) (14.96 g, 76.69%); ^1H NMR (CDCl_3): δ 2.54 (3H, s), δ 7.00 (1H, d, $J = 2.4$) and δ 7.52 (1H, d, $J = 2.4$).

2.2.2 General Procedure for the Synthesis of Thiophene chalcones

A mixture of 3-acetyl-2,5-dichlorothiophene (3) or 2-acetyl-5-chlorothiophene (4) (0.03 mol) with different heterocyclic aldehydes (5-7) (0.03 mmol) was dissolved in methanol (25 mL). Aqueous sodium hydroxide (15 mL) was added dropwise and the resulting mixture was stirred overnight at room temperature. The precipitate was collected, dried and purified by recrystallization from ethanol to give thiophene chalcones (8-13).

(E)-3-(5-Bromothiophen-2-yl)-1-(2,5-dichlorothiophen-3-yl)-2-propen-1-one (8)

Yellow needle crystal, yield: 83.59%; m.p.: 100-102°C; IR ν_{max} cm^{-1} : 3078 (Ar-H), 1644 (C=O), 1579, 1512 (Ar-C=C), C-Cl (1020); ^1H NMR (CDCl_3): δ 7.07 (1H, d, $J = 4$ Hz, H-5), δ 7.08 (1H, d, $J = 15.2$ Hz, H-2), δ 7.12 (1H, d, $J = 4$ Hz, H-6), δ 7.19 (1H, s, H-11), δ 7.76 (1H, d, $J = 15.2$ Hz, H-3); ^{13}C NMR (CDCl_3): δ 117.2 (C-7), δ 122.6 (C-5), δ 127.1 (C-11), δ 127.1 (C-8), δ 131.3 (C-9), δ 131.5 (C-2), δ 132.9 (C-6), δ 136.6 (C-3), δ 137.6 (C-10), δ 141.6 (C-4), δ 182.8 (C-1); Found (HRS-ESI): 388.8247 $[\text{M}+\text{Na}]^+$ and 389.8280 $[\text{M}+\text{H}+\text{Na}]^+$, ($\text{C}_{11}\text{H}_5\text{BrCl}_2\text{OS}_2$ requires, 388.8240 and 389.8318).

(E)-1-(2,5-Dichlorothiophen-3-yl)-3-(3-methylthiophen-2-yl)-2-propen-1-one (9)

Yellow powder, yield: 21.57%; m.p.: 62-64°C; IR ν_{max} cm^{-1} : 3102 (Ar-H), 1640 (C=O), 1524, 1562 (Ar-C=C); ^1H NMR (CDCl_3): δ 2.39 (3H, s, H-6), δ 6.92 (1H, d, $J = 4.8$ Hz, H-7), δ 7.12 (1H, d, $J = 15.4$ Hz, H-2), δ 7.2 (1H, s, H-12), δ 7.35 (1H, d, $J = 4.8$ Hz, H-8), δ 7.9 (1H, d, $J = 15.4$ Hz, H-3); ^{13}C NMR (CDCl_3): δ 14.3 (C-6), δ 121.4 (C-2), δ 126.9 (C-9), δ 127.1 (C-12), δ 128.2 (C-8), δ 131.0 (C-7), δ 131.6 (C-5), δ 134.3 (C-10), δ 136.2 (C-3), δ 137.9 (C-

11), δ 143.5 (C-4), δ 183.0 (C-1); Found (HRS-ESI): 302.9468 [M+H]⁺, (C₁₂H₈Cl₂OS₂ requires, 302.9472).

(E)-1-(5-Chlorothiophen-2-yl)-3-(3-methylthiophen-2-yl)-2-propen-1-one (**10**)

Orange solid, yield: 85.30%; m.p: 102-104°C; IR ν_{\max} cm⁻¹: 3079 (Ar-H), 1634 (C=O), 1572, 1523 (Ar-C=C), 1013(C-Cl); ¹H NMR (CDCl₃): δ 2.42 (3 H, s, H-6), δ 6.94 (1H, d, *J* = 4.8 Hz, H-11), δ 7.02 (1H, d, *J* = 4.0 Hz, H-8), δ 7.07 (1H, d, *J* = 15.2 Hz, H-2), δ 7.35 (1H, d, *J* = 5.2 Hz, H-7), δ 7.64 (1H, d, *J* = 4.0 Hz, H-10), δ 8.06 (1H, d, *J* = 15.2 Hz, H-3); ¹³C NMR (CDCl₃): δ 14.3 (C-6), δ 118.2 (C-2), δ 127.6 (C-7, C-8), δ 130.8 (C-10), δ 131.5 (C-11), δ 134.2 (C-3), δ 135.3 (C-5), δ 139.4 (C-12), δ 143.3 (C-4), δ 144.4 (C-9), δ 180.7 (C-1); Found (HRS-ESI): 290.9688 [M+Na]⁺, (C₁₂H₉ClOS₂ requires, 290.9681).

(E)-3-(5-Bromothiophene-2-yl)-1-(5-chlorothiophen-2-yl)-2-propen-1-one (**11**) [30]

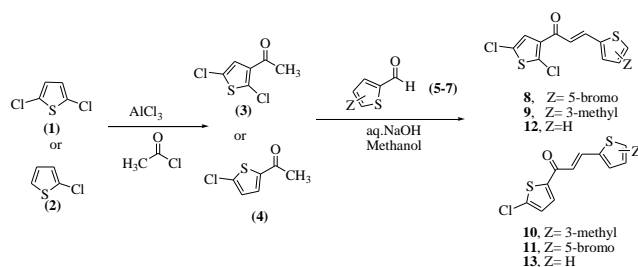
Yellow powder, yield: 90.84%; m.p: 139-141°C; IR ν_{\max} cm⁻¹: 3083 (Ar-H), 1645 (C=O), 1585, 1528 (Ar-C=C), 1014 (C-Cl). ¹H NMR (CDCl₃): δ 7.12 (1H, dd, *J* = 4.8 Hz, H-6), δ 7.19 (1H, d, *J* = 15.2 Hz, H-2), δ 7.21 (1H, s, H-11), δ 7.39 (1H, d, *J* = 3.6 Hz, H-5), δ 7.47 (1H, d, *J* = 5.2 Hz, H-7), δ 7.90 (1H, d, *J* = 15.2 Hz, H-3).

(E)-1-(2,5-Dichlorothiophen-3-yl)-3-(thiophen-2-yl)-2-propen-1-one (**12**) [31]

Yellow solid, yield: 32.00%; m.p: 64-66°C; IR ν_{\max} cm⁻¹: 3091 (Ar-H), 1643 (C=O), 1567, 1525 (Ar-C=C), 1018 (C-Cl). ¹H NMR (CDCl₃): δ 7.12 (1H, d, *J* = 5.0 Hz, H-6), δ 7.19 (1H, d, *J* = 15.2 Hz, H-2), δ 7.21 (1H, s, H-11), δ 7.39 (1H, d, *J* = 3.6 Hz, H-5), δ 7.47 (1H, d, *J* = 5.0 Hz, H-7), δ 7.90 (1H, d, *J* = 15.2 Hz, H-3).

(E)-1-(5-Chlorothiophen-2-yl)-3-(thiophen-2-yl)-2-propen-1-one (**13**) [32]

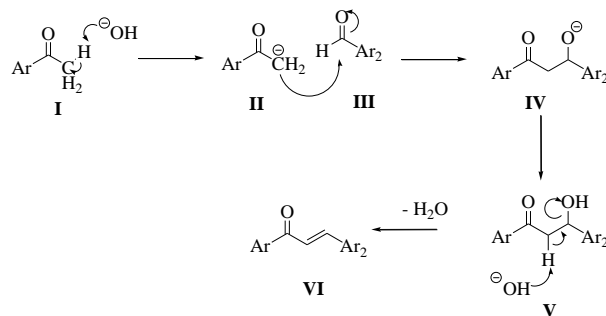
Orange needle crystal, yield: 35.49%; m.p: 84-66°C; IR ν_{\max} cm⁻¹: 3080 (Ar-H), 1637 (C=O), 1574, 1528 (Ar-C=C), 1014 (C-Cl). ¹H NMR (CDCl₃): δ 7.03 (1H, d, *J* = 4 Hz, H-5), δ 7.13 (1H, t, *J* = Hz, H-6), δ 7.134 (1H, d, *J* = 15.2 Hz, H-2), δ 7.40 (1H, d, *J* = 3.6 Hz, H-10), δ 7.47 (1H, d, *J* = 4.8 Hz, H-7), δ 7.65 (1H, d, *J* = 4.0 Hz, H-9), δ 7.98 (1H, d, *J* = 15.2 Hz, H-3).



Scheme 1 Synthesis of heterocyclic chalcones containing halogenated thiophenes

3.0 RESULTS AND DISCUSSION

In this study, six thiophene chalcones (**8-13**) have been successfully synthesized under Claisen-Schmidt condensation by reaction between heterocyclic aldehydes (**5-7**) namely, 5-bromothiophene-2-carbaldehyde, 3-methyl-2-thiophenecarboxaldehyde and 2-thiophenecarboxaldehyde with heterocyclic ketones such as 3-acetyl-2,5-dichlorothiophene (**3**) or 2-acetyl-5-chlorothiophene (**4**) using sodium hydroxide as a base (Scheme 1). The mechanism of reaction involves the production of enolate (**II**) where sodium hydroxide removes the α -proton from 3-acetyl-2,5-dichlorothiophene or from 2-acetyl-5-chlorothiophene in the first step. Nucleophilic attack at the carbonyl carbon of the aldehyde (**III**) by the enolate ion followed by the addition of a proton from a water molecule gave a β -hydroxyketone (**V**). Dehydration to eliminate a water molecule produced the desired heterocyclic chalcone (**VI**) (Scheme 2).



Scheme 2 Reaction mechanism for the synthesis of heterocyclic chalcones

These compounds were characterized by IR, ¹H NMR, ¹³C NMR, 2D NMR and MS. The IR spectrum of chalcone (**9**) showed the carbonyl peak (C=O) at 1640 cm⁻¹. Chalcone (**9**) showed absorption bands corresponding to C-H sp² at 3102 cm⁻¹.

The ¹H NMR spectrum exhibited six signals integrating for eight protons (3 for the thiophene rings, 2 for α,β -unsaturated double bond and 3 for methyl protons). The vinylic proton, H-3 at δ 7.98 (1H, d, *J* = 15.4 Hz) was coupled with H-2 at δ 7.12 (1H, d, *J* = 15.4 Hz) suggested that they are in *trans*-orientation.

The ¹³C NMR and DEPT NMR spectra of chalcone (**9**) (Figure 2) showed the presence of twelve carbons, consisted of five quaternary (C-4, C-5, C-9, C-10, C-11) and deshielded carbon signal at δ 183.0 ppm was assigned to carbonyl group (C=O) at (C-1). The olefinic carbon C-2 and C-3 were observed at 121.4 and 136.2 ppm, respectively. The HMQC spectrum of this compound showed correlation between signal of protons at (H-2, H-3, H-7, H-8, H-12) with signals of carbons at (C-2, C-3, C-7, C-8, C-12), respectively. High resolution mass spectrometry found (HRS-ESI): 302.9468 [M+H]⁺ which matched with the molecular formula, C₁₂H₈Cl₂OS₂ requires, 302.9472

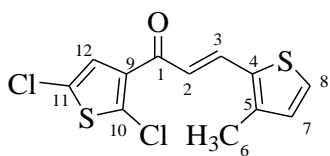


Figure 2 (E)-1-(2,5-Dichlorothiophen-3-yl)-3-(3-methylthiophen-2-yl)-2-propen-1-one (**9**)

4.0 CONCLUSION

The synthesis of 3-acetyl-2,5-dichlorothiophene (**3**) and 2-acetyl-5-chlorothiophene (**4**) were carried out by Friedel-Crafts acylation. The reaction was accomplished by treatment of 2,5-dichlorothiophene (**1**) or 2-chlorothiophene (**2**) with acetyl chloride in the presence of aluminium chloride as a catalyst. Compound (**3**) or (**4**) was used as the starting material and reacted with different heterocyclic aldehydes to form chalcones.

Six chalcones (**8-13**) have been successively synthesized by Claisen-Schmidt condensation reaction in the presence of base, sodium hydroxide as catalyst in low to moderate yield. The structures of synthesized chalcones (**8-13**), 3-acetyl-2,5-dichlorothiophene (**3**) and 2-acetyl-2-chlorothiophene (**4**) have been established using MS, IR, ¹H NMR and ¹³C NMR spectral data.

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