Synthesis of 2-(3-chloro-4-nitro-1-benzothien-2-yl)-1,3,4-oxadiazole-1,3,4-thiadiazole and 5-(3-chloro-4-nitro-1-benzothien-2-yl)-4H-1,2,4-triazole-3-thiol

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الخلاصة

تـم فـي هـذا البحـث تحـضير عـدد مـن معوضـات 1،3،4-اوكـسادايازول و1،3،4-ثايادايازول و 1،2،4-ترايازول. حضر 3-كلورو-4-نيترو-2-كلورو كربونيـل بنزو [b] ثايوفين (1) من تفاعل حامض 2-نيتروسينماميك مع كلوريد الثايونيل ثنـائي مثيـل فورماميد في البيريدين. تم تحويل كلوريد الحامض (1) الى هيدرازيد الحامض (2) من خلال تفاعله مع الهيدرازين المائي في الكلوروفورم. أعطت مفاعلة هيدرازيد الحامض مع حـامض الفورميك، 3-كلورو-4-نيترو-2-[N-فورميل هيدرازين الحامض] بنزو [b] ثايوفين (3). والذي تم تحويله إلى معوضات 3،1،4-اوكسادايازول و 1،3،4-ثايادايازول (4،5) من خلال تفاعله مع خماسي اوكسيد الفسفور وخماسي كبريتيد الفسفور على التوالي.

أعطت مفاعلة هيدرازيد الحامض (2) مع ايسوثايوسيانات الفنيـل ثايوسـيمكاربازيد معوض (6) والذي تم تحويله إلى 1،2،4-ترايازول معوض (7) باستخدام محلول هيدروكسيد الصوديوم. أعطت مفاعلة المركب (1) مع الهيدرازيد في البنزين الجـاف ثايوسـيمكاربازيد معوض (8) والذي تم تحولقه باستخدام محلول هيدروكسيد الـصوديوم إلـى 5-معـوض - 1،2،4-ترايازول -3-ثايول (9). الكلة 1،2،4-ترايازول المعوض من خلال تفاعلـه مـع كلوريد البروبيل/البيوتيل في الايثانول 5-(3-كلورو-4-نيترو-1-بنزوثايين-2-يـل)-H4-1،2،4-ترايازول-3-بروبيل/بيوتيل ثايول (10،11) على التـوالي. شخـصت المركبـات المحضرة بالطرائق الطيفية والفيزياوية.

ABSTRACT

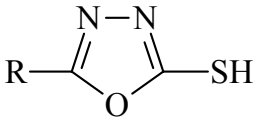
In this paper the synthesis of some substituted 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole is reported. 3-chloro-4-nitro-2-chloro

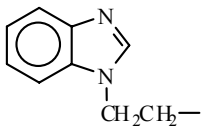
carbonyl benzo [b] thiophene(1) was synthesized from 2-nitrocinnamic acid by its reaction with thionyl chloride/dimethyl formamide in pyridine. Acid chloride(1) was converted to acid hydrazide(2) by its reaction with hydrazine hydrate in chloroform. The hydrazide (2) was treated with formic acid to give 3-chloro-4-nitro-2-[N-formyl acid hydrazide] benzo [b] thiophene (3), which was converted to substituted 1,3,4-oxadiazole and 1,3,4-thiadiazole (4,5) by its reaction with phosphorus pentoxide and phosphorus pentasulfide respectively. Treatment of acid hydrazide (2) with phenyl isothiocyanate gave substituted thiosemicabazide (6), which cyclized with sodium hydroxide solution to substituted 1,2,4-triazole (7). Compound (1) was treated with thiosemicarbzide in dry benzene to give substituted thiosemicarbazide (8), the substituted thiosemicarbazide (8) was cyclized with sodium hydroxide solution to give 5-substituted 1,2,4-triazole 3-thiol (9), alkylation of 1,2,4- triazole (9) with propyl / butyl chloride in ethanol gave 5-(3-chloro-4-nitro-1-benzothien-2-yl)-4H-1,2,4-triazole-3-propyl/butyl thiol (10,11) respectively. The structures of the synthesized compounds were confirmed by spectral and physical methods.

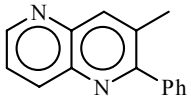
INTRODUCTION

Derivatives of 1,3,4-oxadiazole and 1,3,4-thiadiazole have been found to possess a wide spectrum of pharmacological, medical and biological activities[1,2]. Moreover derivatives of 1,2,4-triazole are known to exhibit anti inflammatory[3,4], antiviral[5], analgesics[6] antimicrobial[7] anticonvulsant[8] and antidepressant activities[9].

Substituted 1,3,4-oxadiazoles were synthesized using various methods, acid hydrazides were treated with carbon disulfide in aqueous potassium hydroxide to gave substituted 1,3,4-oxadiazole as compounds (I,II)[10,11].



(I) R= 

(II) R= 

Thiosemicarbazides were converted to substituted 1,3,4-oxadiazole by their reaction with mercuric oxide[12] in methanol or from the reaction of hydrazide and carboxylic acids in presence of phosphorus oxychloride whereas 1,3,4-thiadiazole derivatives were synthesized from the reaction of carboxylic acids with thiosemicarbazide in acidic condition[14] or from substituted thiosemicarbazide by its reaction with phosphoric acid[15].

The synthesis of 1,2,4-triazoles were achieved by the reaction of substituted thiosemicarbazide with ethanolic sodium hydroxide[16]. In this

paper the synthesis of some substituted 1,3,4-oxadiazoles, 1,3,4-thiadiazole and 1,2,4-triazoles is reported.

EXPERIMENTAL

The melting points were measured on an Electrothermal melting point apparatus (uncorrected). IR spectra were recorded on Infrared Spectrophotometer Model Tensor 27, Bruker Co., Germany, using KBr discs. UV spectra were recorded on Shimadzu Double-Beam Spectrophotometer UV-210 A using ethanol as a solvent.

3-chloro-4-nitro-2-chlorocarbonyl benzo [b] thiophene (1)[17]

To a mixture of 2-nitrocinnamic acid (4.4g, 0.023 mole), pyridine (0.5 ml) with dimethyl formamide (1 ml), thionyl chloride (6 ml) was added drop wise. After stirring for 30 minutes at 140 °C. The reaction mixture taken up in (100 ml) of dry hexane heated and decant from the gummy resdiue the yellow decanted solution was solidified to give compound (1).

m.p = 58-60 °C; yield 61%. Pale yellow crystals, IR (υ cm^{-1}), 1772 (C=O), 1604 (C=C), 1523, 1325 (NO_2, Asym, Sym), 3102 ($C\text{-}H_{aromatic}$), 1109, (C=C-Cl) and 682 (C-S-C); UV (λ_{max}) 292 nm.

3-chloro-4-nirobenzo [b] thiophene-2-carboxylic acid hydrazide (2)

A mixture of acid chloride (1) (0.275 g, 0.001 mole) in chloroform (5 ml) and hydrazine hydrate (0.0018 mole) was refluxed for one houre. The solvent then evaporated to give the hydrazide (2), which was recrystallized from ethanol.

m.p. 113-116 °C; yield 55%, orange powder; IR, (υ cm^{-1}), 3193 (N-H), 3031 (C-H), 1644 (C=O), 1606 (C=C), 1077(C=C-Cl), 691 (C-S-C) and 1531, 1320 (NO_2, Asym, Sym); UV (λ_{max}) 299 nm.

3-chloro-4-nitro-2-(N-Formyl acid hydrazide) benzo [b] thiophene (3)

Hydrazide (2) (2.70 g, 0.01 mole) was dissolved in formic acid (20 ml), the mixture was refluxed for (30 min.), excess formic acid was evaporated under reduced pressure, the solid product was recrystallized from methanol.

m.p.>300 °C; yield 67%, brown powder; IR (υ cm^{-1}), 3192 (N-H), 1645, 1710 (C=O), 3031 ($C\text{-}H_{aromatic}$), 1607 (C=C) and 1531, 1311 (NO_2 Asym, Sym); UV (λ_{max}) 313 nm.

2-(3-chloro-4-nitro-1-benzothien-2-yl)1,3,4-oxadiazole (4)

A mixture of compound (3) (2.98 g, 0.01 mole) and (1.4 g, 0.01 mol) and phosphorus pentoxide; in xylene (50 ml) was refluxed for one hour, after cooling water (10 ml) was added, the product was extracted with chloroform the solvent was evaporated and the residue was recrystallized from benzene to give compound (4).

m.p.=154 dec.°C; yield 51%, brown powder; IR (υ cm^{-1}), 1640 (C=N), 1607 (C=C), 1530, 1312 (NO_2 Asym, Sym), 1245, 1017 (C-O-C) and 3030 (C-H); UV (λ_{max}) 272 nm.

2-(3-chloro-4-nitro-1-benzothien-2-yl)-1,3,4-thiadiazole (5)

A mixture of substituted hydrazide (3) (2.90 g, 0.01 mole), phosphorous pentasulfide (2.2 g, 0.01 mole) in xylene (50 ml) was refluxed for one hour, the solvent was evaporated and water (10 ml) then added to the residue, extraction with chloroform the solvent was dried and evaporated to give compound (5).

m.p.=191 dec.°C; yield 63%, pale brown powder; IR (υ cm^{-1}), 1644 (C=N), 1606 (C=C), 3031 (C-H) and 688 (C-S-C); UV (λ_{max}) 320 nm.

1-(3-chloro-4-nitrobenzo [b] thiophene-2-yl)carbonyl-4-phenyl-thiosemicarbazide (6)

Hydrazide (2) (2.5 g, 0.01 mole) and phenylisothiocyanate (1.35 g, 0.01 mole) in dry hexane was refluxed for 6 hours, the mixture then cooled to room temperature, the solid was filtered, dried and recrystallized from ethanol.

m.p.=127-128 °C.; yield 74%, brown powder; IR (υ cm^{-1}), 1650 (C=O), 1240 (C=S), 1458, 1308 (NO_2 Asym, Sym); UV (λ_{max}) 314 nm.

5-(3-chloro-4-nitro-1-benzothien-2-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol (7)

A mixture of substituted thiosemicarbazide (6) (4.06 g, 0.01 mole) and 4% sodium hydroxide solution (10 ml) was refluxed for four hours. The mixture left to cool then acidified with dilute hydrochloric acid, the precipitate was formed, filtered dried and recrystallized from ethyl acetate.

m.p.=118-120 °C; yield 70%, pale brown powder; IR (υ cm^{-1}), 3448 (N-H), 1638 (C=N), 1559 (C=C), 1314 (C=S); UV (λ_{max}) 310 nm.

(3-chloro-4-nitrobenzo [b] thiophene-2-carbonylic thiosemicarbazide (8)

Compound (1) (1.93 g, 0.01 mole) was dissolved in dry benzene thiosemicarbazide (0.81 g, 0.01 mole) was added. The mixture was refluxed for two hours, cool and filtered, the product recrystallized from ethanol water.

m.p.=180-181°C; yield 60%, yellow powder; IR (υ cm^{-1}), 3263 (N-H), 1645 (C=O), 1532 (C=C) and 1163 (C=S); UV (λ_{max}) 282 nm.

5-(3-chloro-4-nitro-1-benzothien-2-yl)-4H-1,2,4-triazole-3-thiol (9)

Substituted thiosemicarbazide (8) (3.3 g, 0.01 mole) was dissolved in 4% sodium hydroxide (10 ml), the reactants were refluxed for three hours, cool acidified with dilute hydrochloric acid. The precipitate was filtered , dried and recrystallized from ethanol.

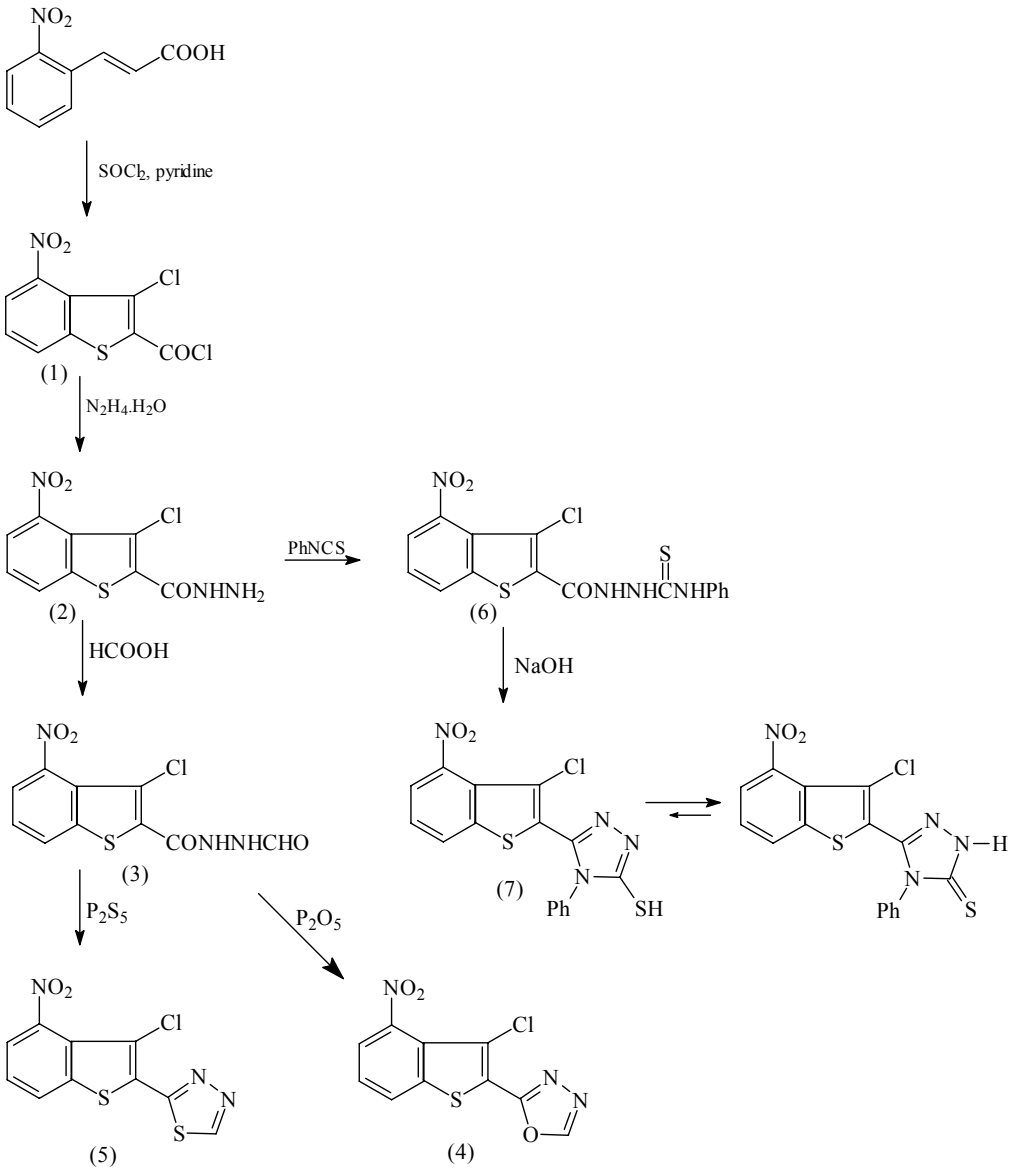
m.p.=300 d.; yield 53%, white powder; IR (υ cm^{-1}), 3424 (N-H), 3050 (C-H), 1572 (C=C), 1523, 1315 (NO_2 Asym, Sym), 1202 (C=S), 2650 (SH) and 1631 (C=N); UV (λ_{max}) 292 nm.

5-(3-chloro-4-nitro-1-benzothien-2-yl)-4H-1,2,4-triazole-3-propyl/butyl thiol (10,11)

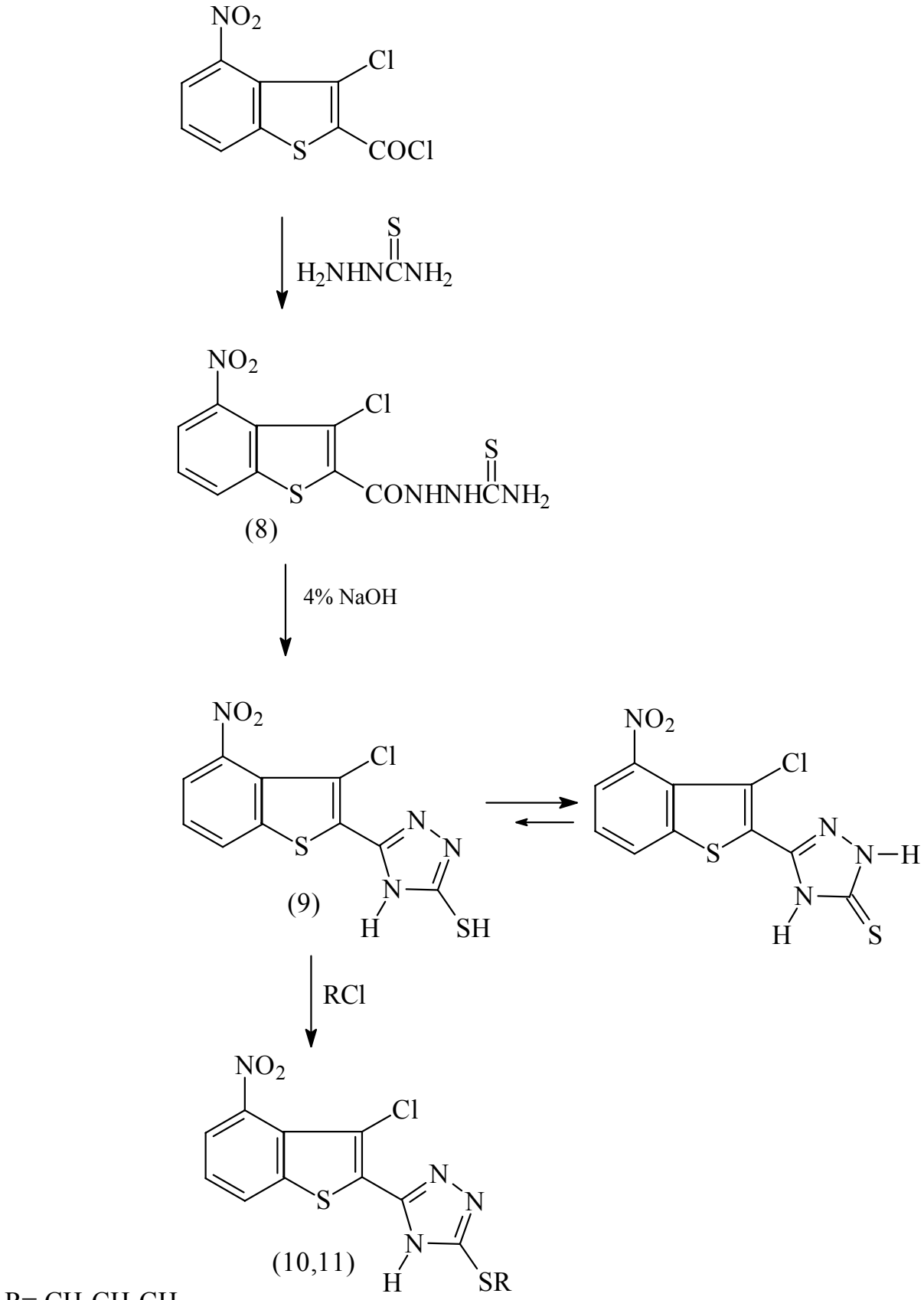
Substituted 1,2,4-triazole (9) (0.311 g, 0.001 mole) was refluxed with sodium acetate (0.194, 0.0024 mole), alkyl halide (0.001 mole) in ethanol (20 ml) for three hours. The mixture was poured on to crushed ice (30 g), the product filtered , dried and recrystallized from acetone.

(10) m.p.=74-76 °C; yield 75%, white powder; IR (υ cm^{-1}), 3452 (N-H), 1637 (C=N), 2930 (C-H), 1457(S-C) and 1508, 1320 (NO_2 Asym, Sym), 668 (C-S); UV (λ_{max}) 246 nm.

(11) yield 66%, pale brown oil; IR (υ cm^{-1}), 3447 (N-H), 2922 (C-H), 1637 (C=N), 1560 (C=C), 1508, 1384, (NO_2 Asym, Sym) and 874 (C-S, 1458 (C-R); UV (λ_{max}) 278 nm.



Scheme (1)



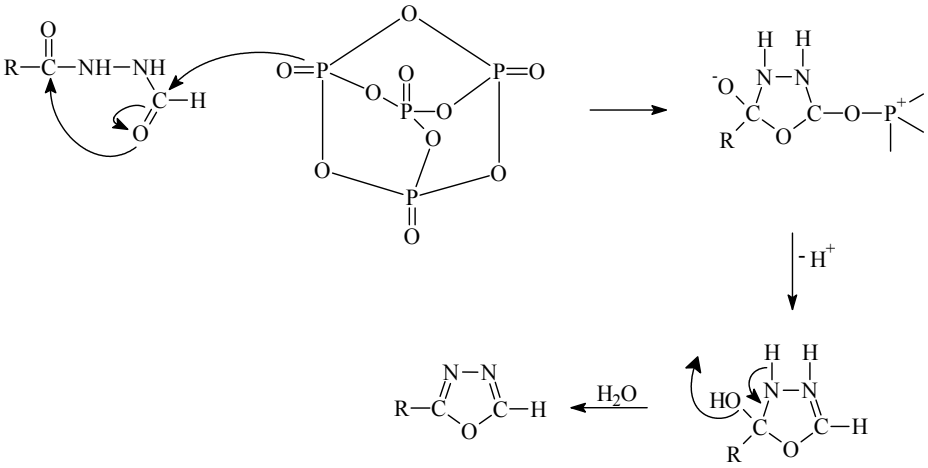
R= $CH_2CH_2CH_3$

R= $CH_2CH_2CH_2CH_3$

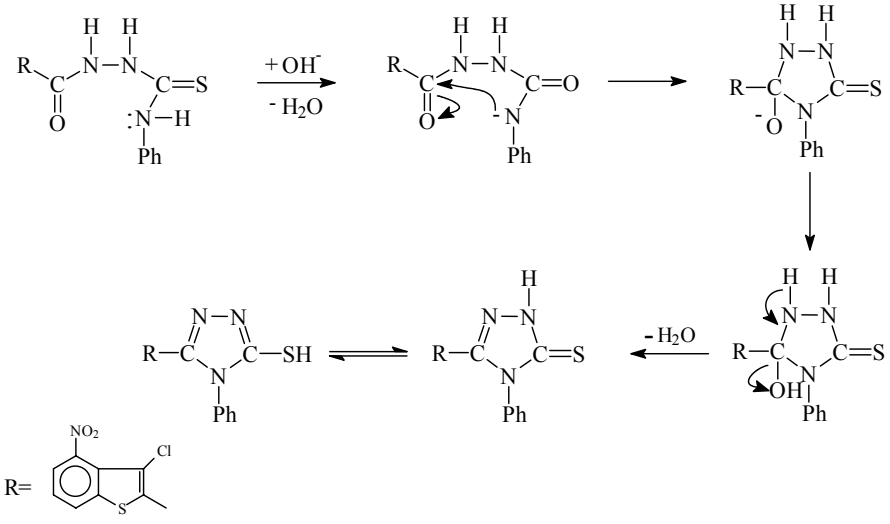
Scheme (2)

RESULTS AND DISCUSSION

In this work 3-chloro-4-nitro-2-chlorocarbonyl benzo [b] thiophene (1) was prepared from 2-nitrocinnamic acid and thionyl chloride, IR (υ cm^{-1}): 3102 (C-H aromatic), 1772 (C=O), 1604 (C=C), 1523, 1325 (NO_2 Asym, Sym) 1104 (=C-C-Cl and 682 (C-S-C); UV (λ_{max}) 292 nm. The acid chloride (1) was then converted into the acid hydrazide (2) by its reaction with hydrazine hydrate in ethanol, IR (υ cm^{-1}): 3193 (N-H), 1644 (C=O), 1606 (C=C); UV (λ_{max}) 299 nm. Reaction of acid hydrazide (1) with formic acid gave formyl acid hydrazide (3), IR (υ cm^{-1}): 1645, 1710 (C=O), 1607 (C=C) and 1531, 1311 (NO_2 Asym, Sym); UV (λ_{max}) 313 nm. Compound (3) was treated with phosphorus pentaoxide and with phosphorus pentasulfide to give substituted 1,3,4-oxadiazole (4) and 1,3,4-thiadiazole (5) respectively. Compound (4) shows IR υ cm^{-1}): 1640 (C=N), 1607 (C=C) and 1530, 1312 (NO_2 Asym, Sym); UV (λ_{max}) 272 nm the mechanism of cyclization is as followa[18]:



While compound (5) shows IR (υ cm^{-1}): 1644 (C=N), 1606 (C=C), 688 (C-S-C); UV (λ_{max}) 320 nm. Acid hydrazide (2) was treated with phenyl isothiocyanate to give substituted thiosemicarbazide (6) IR (υ cm^{-1}): 1650 (C=C), 1240 (C=S); UV (λ_{max}) 314 nm. This was cyclized to substituted 1,2,4-triazole (7) IR (υ cm^{-1}): 1638 (C=N), 1314 (C=S); UV (λ_{max}) 310 nm. (Scheme 1). The mechanism of cyclization as follows [19].



The acid chloride (1) was treated with thiosemicarbazide to give substituted thiosemicarbazide (8), IR (υ cm^{-1}): 1645 (C=O) and 1163 (C=S), UV (λ_{max}) 282 nm. Substituted thiosemicarbazide (8) was converted into substituted 1,2,4-triazole (9), IR (υ cm^{-1}): 1572 (C=C), 1523, 1315 (NO_2 Asym, Sym) 1202 (C=S) and 1631 (C=N); UV (λ_{max}) 292 nm. Alkylation of 1,2,4-triazole-3-thiol (9) gave propyl/butyl thiol (10,11), IR for compound (10) shows 1637 (C=N) 1457 (S-R), 1508, 1320 (NO_2 Asym, Sym) and for compound (11) 1637 (C=N), 1560 (C=C), 1508, 1384 (NO_2 Asym, Sym), UV (λ_{max}) 278 nm. (scheme 2).

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