Synthesis of New Thieno[2,3-d] Pyrimidine Derivatives

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Summary: The o-aminoester(1) reacted with benzoylisothiocyanate and phenylisothiocyante to afford the urea derivative(3) and the thiourea derivative(5) respectively. Similarly the o-aminonitrile derivative(2) reacted with phenyl isothiocyanate, benzoylisothiocyanate and ethoxycarbonylisothiocyanate to afford the thiourea derivative(6) and he urea derivatives(9a) and (9b) respectively. The thiourea derivative(6) was cyclized in pyridine to the thienopyrimidine(8). Compound(2) reacted with formic acid to yield compounds(10) and (11) depending on the reaction conditions. The thienopyrimidine derivative(12) was obtained upon reaction of(2) with formamide. Compound(2) reacted with carbon disulphide to give the oxazine derivative(15) which formed(16) with ammonia.

Introduction

o-Aminoesters and o-aminonitriles are versatile compounds which can be considered as a building block for the synthesis of condensed heterocycles [1-4]. In the present paper the 2-amino-3-ethoxycarbonylthiophene derivative(1) and the 2-amino-3-cyanothiophene derivative(2) was used as starting materials for the synthesis of thieno[2,3-d] pyrimidine derivatives.

Compound (1) reacted with benzoylisothiocyanate to yield the urea derivative (3) together with the benzoyl derivative (4). Also (1) reacts with phenyl isothiocyanate to afford the thiourea derivative (5). Attempts to affect cyclization of (3) and (5) to the corresponding pyrimidine derivatives could not materialise. Compound (3) was probably formed via thiourea derivative, which converted to the urea derivatives on hydrolytic removal of sulphur under the reaction conditions.

Similarly compound (2) reacted with phenyl isothiocyanate to give the thiourea derivative (6). The compound (6) on refluxing in pyridine was cyclized to a product for which structure (8) could be assigned. The formation of (8) may be accounted through a Dimorth-type rearrangement. The rearrangement of N-substituted pyrimidines into alkylpyrimidines has already been reported previously [5].

Compound (2) reacts with benzoylisothiocyanate and ethoxycarbonylisothiocyanate to afford the urea derivatives (9a) and (9b) respectively. Trials to affect cyclization of (5a) and (5b) to the pyrimidine derivatives were unsuccessful. Compounds (9a) and (9b) were suggested to be formed via the same sequence for the formation of (3).

Both aromatic and heterocyclic o-aminonitriles react with formic acid to give o-formylamino nitriles [6]. The compound (2) also reacts with formic acid at room temperature to give the formyl- amino derivative (10). On the other hand, the thienopyrimidine derivative (11) was obtained by refluxing (2) with formic acid- acetic acid mixture. The compound (11) is probably formed via (10) which was cyclized under the reaction conditions to give the final product. It has already been reported [7] that o-acylaminonitriles can be converted by acid or base to condensed pyrimidines.

4-Aminothieno[2,3-d]pyrimidine derivative (12) was formed directly upon treatment of (2) with formamide. Compound (12) was assumed to be formed via o-cyanoformamidine intermediate which cyclizes under the reaction conditions to afford the final isolable product (12). Compound (12) is found to be identical with that obtained by Taylor and Berger [8].

Compound (2) reacts with carbon disulphide to give a product for which structure (15) was assigned on the basis of spectral data. It was suggested to be formed via formation of the dithiocarbamate derivative (13), hydrolysis of SH to OH and then cyclization to the final oxazine derivative (11). It has been reported [9] that the oxazine

derivatives are readily cleaved by ammonia or amines. The compound (15) was likewise converted into the thienopyrimidine derivative (16) upon treatment with ammonia solution.

The proposed structures of the newly synthesized compounds were inferred from their correct analytical, IR and ^{1}H-NMR spectra.

Experimental

All melting points are uncorrected. IR spectra were determined on a Pye Unicam SP 1000 instrument. ^{1}H-NMR spectra were recorded on a Varian A-60 MHz spectrometer using TMS as internal standard and chemical shifts are expressed as ppm. Analytical data were obtained from the Microanalytical Data Unit at Cairo University.

Reaction of (1) with benzoylisothiocyanate

A solution of (1) (0.01 mole) in dioxane (40 ml) was added to a solution of isothiocyanate (prepared from 0.12 mole of NH_4SCN and the appropriate quantity of benzoyl chloride as has been described [10]) and the reaction mixture was refluxed for 3 h then evaporated in vacuo. The remaining oily product was triturated with ethanol and the solid product, so formed, was filtered off. Added alcohol and boiled, filtered the soluble part; the filtrate was cooled and the compound was identified as (3). The precipitate was crystallized from the proper solvent and was identified as (4). The ^{1}H-NMR of (3) (DMSO) showed the following signals: 1.33 (t, 3H, CH_3); 1.65 and 2.5 (m,8H, cyclohexyl protons); 4.35 (q, 2H, CH_2); 7.4-7.89 (m, 5H, aromatic protons), 11.2 (s, 1H, NH) and 14.6 (s, 1H, NH).

Reaction of (1) with benzoyl chloride

A suspension of (1) (0.01 mole) in 20 ml benzoyl chloride was refluxed for 2 h, the reaction mixture was poured on water while stirring, the solid product, so formed was filtered off and crystallized from the proper solvent. The product was identified as (4) (m.p. and mixed m.p.) (cf. Table 1).

Reaction of (1) with phenyl isothiocyanate

A solution of (1) (0.01 mole) in dioxane (30 ml) was treated with phenyl isothiocyanate (0.01 mole) and the reaction mixture was refluxed for 2 h. The solvent was then removed by evaporation in vacuo. The resulting solid product was collected by filtration, crystallized from the proper solvent and identified as (5) (cf. Table 1). The ^{1}H-NMR of (5) (DMSO) showed the following signals: 1.33 (t, 3H, CH_3); 1.65 and 2.5 (m, 8H, cyclohexyl protons); 4.35 (q, 2H, CH_2); 7.3-7.7 (m, 5H, aromatic protons); 11.2 (s, 1H, NH) and 12.3 (s, 1H, NH).

Reaction of (2) with phenyl isothiocyanate

Compound (2) reacts with phenyl isothiocyanate under the same conditions described above for the synthesis of (5) and the reaction product was identified as (6) (cf. Table 1). The ^{1}H-NMR of (6) (DMSO) showed signals at 1.65 and 2.5 (m, 8H cyclohexyl protons); 7.4-7.9 (m, 5H, aromatic protons); 11.3 (s, 1H, NH) and 12.2 (s, 1H, NH).

Thienopyrimidine (8)

Compound (6) (1 g) was dissolved in pyridine (40 ml) and the solution was refluxed for 4 h. The solvent was then removed by evaporation in vacuo and the resulting solid product, so formed, was collected by filtration, crystallized from the proper solvent and identified as (8) (cf. Table 1). Compound (8) was insoluble in the common ^{1}H-NMR solvents.

Reaction of (2) with benzoylisothiocyanate

The same procedure described above for the reaction of (1) with the same reagent was followed and the product was identified as (9a) (cf. Table 1). ^{1}H-NMR of 9a (DMSO) showed the following signals: 1.65 and 2.5 (m, 8H, cyclohexyl protons), 7.5-7.99 (m, 5H, aromatic protons); 11.2 (s, 1H, NH) and 14.5 (s, 1H, NH).

Reaction of (2) with ethoxycarbonylisothiocyanate

The reagent was prepared as described previously for the preparation of benzoylisothiocyanate but ethyl chloroformate was used instead of benzoyl chloride and the same procedure was followed. The product was identified as (9b) (cf. Table 1). The ^{1}H-NMR of (9b) (DMSO) showed signals at: 1.33 (t, 3H, CH_3); 1.65 and 2.5 (m, 8H, cyclohexyl protons); 4.35 (q, 2H, CH_2); 11.2 (s, 1H, NH) and 14.5 (s, 1H, NH).

Table 1: Characterization data of the newly synthesized compounds.

Compound	M.P.°C (Solvent)	Yield %	Mol. Formula (Mol. Wt.)	Analysis (%) Calcd./(Found) C	H	S	IR (cm^{-1}) selected bands
(3)	148 (EtOH)	30	$C_{19}H_{20}N_2O_4S$ (372)	61.3 (61.3)	5.4 (5.1)	8.6 (8.5)	1650 (amide CO), 1670 (este CO), 1700 (benzoyl CO), 2900 (CH_2), 3300 (NH).
(4)	172 (Dioxane)	45	$C_{18}H_{19}NO_3S$ (329)	65.7 (65.8)	5.8 (5.9)	9.7 (9.9)	1675 (ester CO), 1700 (benzoyl CO), 2910 (CH_2), 3290 (NH).
(5)	181 (Dioxane)	65	$C_{18}H_{20}N_2O_2S_2$ (360)	60.1 (60.0)	5.5 (5.6)	18.0 (17.8)	1670 (ester CO), 2900 (CH_2), 3290 (NH)
(6)	254 (Dioxane)	65	$C_{16}H_{15}N_3S_2$ (313)	61.3 (61.4)	4.8 (4.6)	20.4 (20.3)	2220 (CN), 2980 (CH_2), 3300 (NH).
(8)	>300 (Dioxane)	65	$C_{16}H_{15}N_3S_2$ (313)	61.3 (61.5)	4.8 (4.6)	20.4 (20.1)	2940 (CH_2), 3290 (NH).
(9a)	212 (EtOH)	67	$C_{17}H_{15}N_3O_2S$ (325)	62.8 (63.0)	4.6 (4.5)	9.8 (9.9)	1640 (amide CO), 1680 (benzoyl CO), 2220 (CN), 2970 (CH_2), 3300 (NH).
(9b)	160 (EtOH)	64	$C_{13}H_{15}N_3O_3S$ (293)	53.2 (53.3)	5.1 (5.2)	10.9 (11.0)	1650 (amide CO), 1670 (ester CO), 2220 (CN), 3000 (CH_2), (3200 (NH).
(10)	260 (Dioxane)	66	$C_{10}H_{10}N_2OS$ (206)	58.3 (58.3)	4.9 (5.2)	15.5 (15.6)	1680 (CO), 2220 (CN), 2980 (CH_2), 3200 (NH).
(11)	194 (EtOH)	75	$C_{10}H_{10}N_2OS$ (206)	58.3 (58.3)	4.9 (5.0)	15.5 (15.3)	1680 (CO), 2980 (CH_2), 3200 (NH).
(12)	256 (AcOH)	73	$C_{10}H_{11}N_3S$ (205)	58.5 (58.5)	5.4 (4.8)	15.6 (15.4)	2980 (CH_2), 3400 (NH_2).
(15)	277 (Dioxane)	74	$C_{10}H_{10}N_2OS_2$ (238)	50.4 (50.1)	4.2 (4.3)	26.9 (27.0)	2980 (CH_2), 3200 (NH).
(16)*	>300 (Dioxane)	72	$C_{10}H_{12}N_4S$ (220)	54.5 (54.6)	5.5 (5.8)	14.5 (14.6)	2980 (CH_2), 3200 ~ 3400 (NH and NH_2)

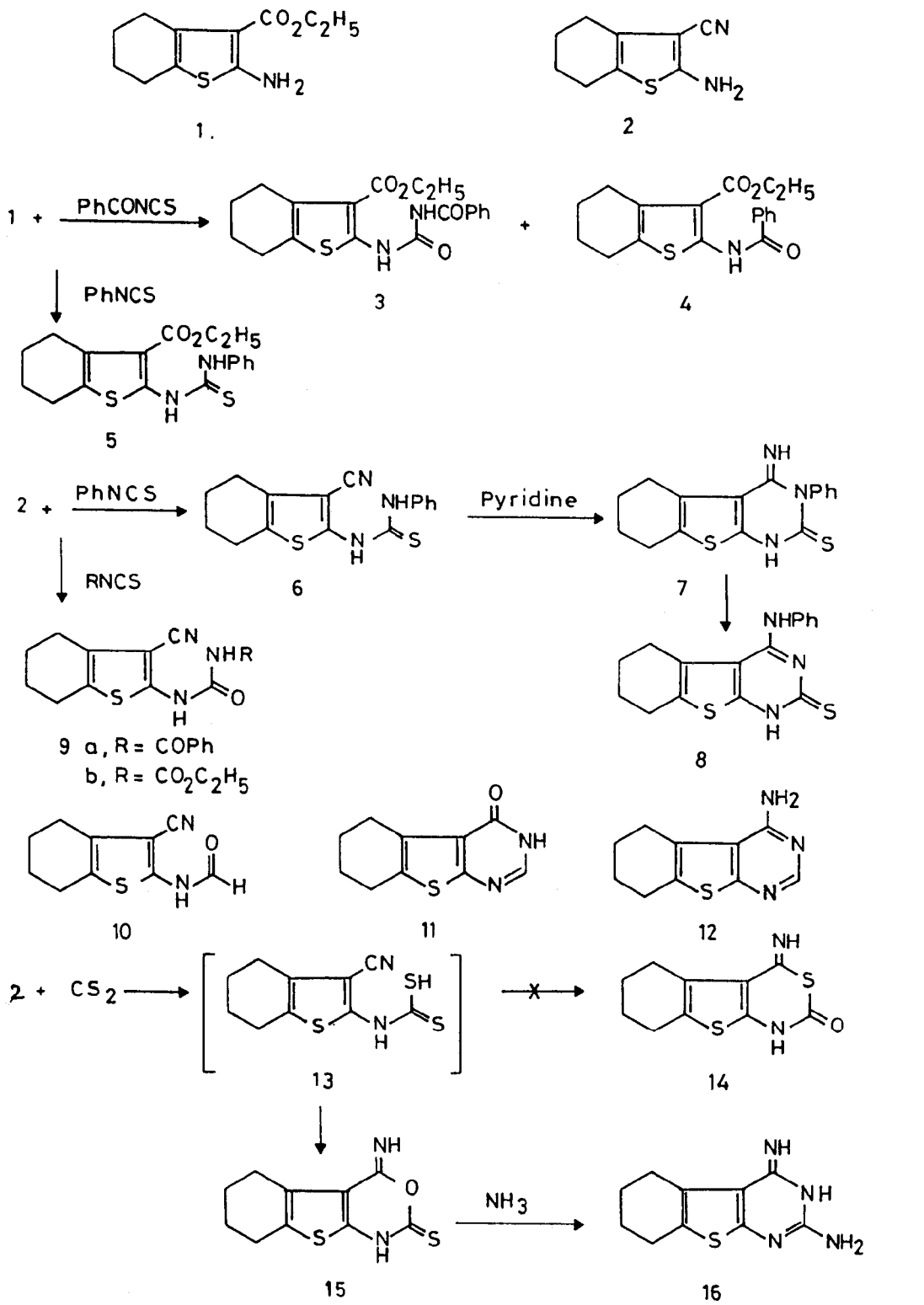
*Analysis for N, Calcd: 25.5; Found (25.3).

Reaction of (2) with formic acid on cold

To compound (2) (1 g) was added formic acid (20 ml), the reaction mixture was stirred at room temperature for 2 h and then was poured onto water. The solid product, so formed, was collected by filtration, washed with water, crystallized from the proper solvent and identified as (10) (cf. Table 1). The ^{1}H-NMR of (10) (DMSO) showed signals at: 1.65 and 2.5 (m, 8H, cyclohexyl protons), 11.2 (s, 1H, NH).

Reaction of (2) with formic acid-acetic acid mixture

To compound (2) (1 g) was added a mixture of 1:1 formic acid-acetic acid (30 ml), the reaction mixture was refluxed for 3 h and then poured onto water. The solid product formed was collected by filtration, washed with water, crystallized from the proper solvent and identified as (11) (cf. Table 1). The ^{1}H-NMR of (11) (DMSO) showed the following signals: 1.65 and 2.5 (m, 8H, cyclohexyl protons), 8.3 (s, 1H, NH).


1.
2
1 + PhCONCS
3
4
PhNCS
5
2 + PhNCS
6
Pyridine
7
8
RNCS
9 a, R= COPh
b, R= CO2C2H5
10
11
12
2 + CS2
13
14
15
16
NH3

4-Aminothieno[2,3-d]pyrimidine derivative (12).

To compound (2) (0.01 mole) was added formamide (20 ml), the reaction mixture was refluxed for 4 h at 120°C (bath temp.) and then evaporated in vacuo. The resulting solid product was filtered off, crystallized from the proper solvent and identified as (12) (cf. Table 1). Compound 12 was prepared independantly by the method described by Taylor and Berger [7] and was found to be identical (m.p. and mixed m.p.). The ^{1}H-NMR of (12) (DMSO) showed signals at: 1.65 and 2.5 (m, 8H, cyclohexyl protons) and 7.1 (s, 2H, NH_2).

Reaction of (2) with carbon disulphide

To a solution of (2) (0.01 mole) in pyridine (30 ml) was added carbon disulphide (0.01 mole) and the reaction mixture was refluxed for 3 h. The solvent was then evaporated in vacuo and the solid product formed was filtered off, crystallized from the proper solvent and identified as (15) (cf. Table 1). Compound (15) was insoluble in the commonly used ^{1}H-NMR solvents.

Reaction of (15) with ammonia solution

To a solution of (15) (0.5 g) in ethanol (20 ml) was added ammonia solution (10 ml) and the reaction mixture was refluxed for 3 h then cooled. The precipitated solid product was filtered off, crystallized from the proper solvent and identified as (16) (cf. Table 1). Compound (16) was insoluble in the common ^{1}H-NMR solvents.

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