Studies with polyfunctionally substituted heteroaromatics: synthesis of new heterocyclic aromatic amines as potential intermediates for preparation of dyes for thermal diffusion printing

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Abstract: Several new dibenzopyrans as well as novel thiadiazaacenaphthenes are obtained via 4 + 2 addition of the thienocoumarins (1) and thienopyridazines (2) to electron-poor olefins.

Key words : pyridazines, thienopyridazines, phthalazines, coumarines, thiadiazaacenaphthenes.

Résumé : L'addition 4 + 2 de thiénocoumarines (1) et de thiénopyridazines (2) sur des oléfines pauvres en électron permet d'obtenir plusieurs dibenzopyranes et thiadiazaacénaphtènes nouveaux.

Mots clés : pyridazines, thiénopyridazines, phtalazines, coumarines, thiadiazaacénaphtènes.

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Introduction

Heterocyclic aromatic amines are interesting compounds because of considerable utility as intermediates in both the pharmaceutical and dye industries (1–6). In the last years we were involved in a program to develop new polyfunctional substituted heterocyclic amines for use as agrochemicals and as intermediates in the dye industry (7–9). During this phase of our research we have developed a synthesis of benzo-fused azines via addition of electron-poor olefins and acetylenes to aminothienoazines. It is well documented that thiophene and its derivatives are reluctant partners in [4+2] cycloadditions with dienophiles containing a double bond in general and with dimethyl fumarate in particular. For instance, Gaertner and Tonkyn (10) failed to add maleic anhydride to tetramethylthiophene even when the reaction was carried out in boiling nitrobenzene (bp 211°C). A similar failure was also reported by Clapp (11), who attempted to induce tetraphenylthiophene to react with maleic anhydride. Similarly, thiophene fails to undergo [4+2] cycloaddition with dienophiles (12) such as dimethyl maleate, dimethyl fumarate, methyl acrylate, acrylonitrile, or acrylaldehyde, even under high pressure. A Diels–Alder adduct was obtained, however, with maleic anhydride (100°C, 15 kbar, 3 h) (1 bar = 100 kPa) (12). However, it should be noted that at atmospheric pressure diene reactivity towards compounds containing a double bond has been observed with 2,5-dimethoxythiophene (13), 2,4-bis-(*N*-isopropyl-*N*-phenylamino)thiophene (14), and 2,3,4,5-di(naphthalene-1,8-diyl)thiophene (15). However, aminothienopyridazines, being both electron-rich and strained molecules, add readily to electron-poor olefins to yield aminophthalazines via [4+2] cycloaddition reaction followed by ring opening and aromatization through loss of hydrogen sulfide or elimination of hydrogen depending on the nature of the reagent and applied reaction condition (15, 16). To our knowledge this was the first reported addition of an electron-rich strained thiophene to an electron-poor olefin. Recently Dopp and coworkers (17) have reported the addition of dimethyl fumarate and dimethyl acetylenedicarboxylate to 3-amino-4-imino-4H-thieno[3,4-*c*]-benzopyran. Although the reaction of dimethyl fumarate afforded dibenzopyran via a reaction sequence similar to that observed earlier by us (15), the cycloadduct from reaction with dimethyl acetylene dicarboxylate underwent a novel type of rearrangement that afforded benzopyrano-thiepine (17). In conjunction of this work we reported here synthesis of 3-aminothieno[3,4-*c*]coumarin (1) and thieno[3,4-*d*]pyridazin-1-carboxylates (2) and their reactivity toward electron-poor olefins.

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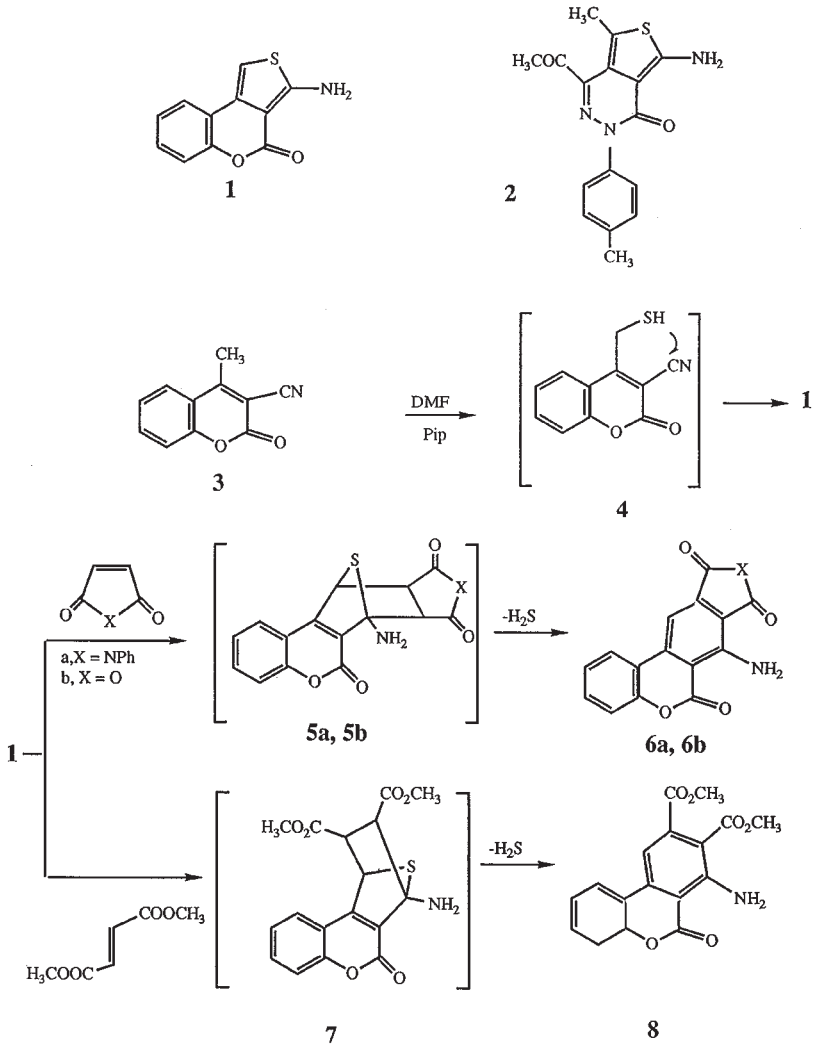
Results and discussion

Thus, we have found that 4-methylcoumarin-3-carbonitrile (3) reacts readily with sulfur in refluxing dimethylformamide in the presence of ethanolic piperidine to yield the thienobenzopyran derivative **1** via the intermediate **4**. This compound readily added *N*-phenylmaleimide and



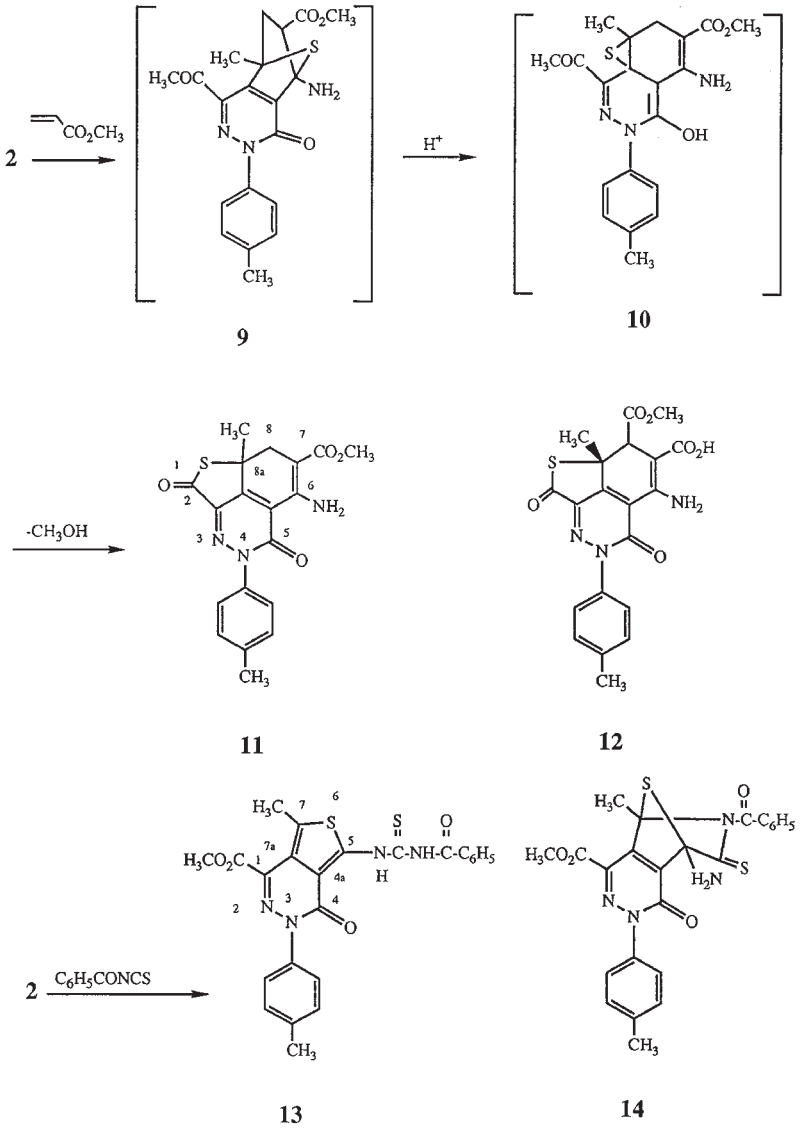
maleic anhydride to yield the condensed dibenzopyran **6a**,**b**. Formation of **6** is assumed to proceed via initial [4+2] cycloaddition of the olefinic double bond to diene system of **1**, yielding intermediate cycloadducts **5a** and **5b** that then loses hydrogen sulfide to yield the final isolable product. This is similar to the recently reported (17) behaviour of 3-amino-4-imino-4H-thieno[3,4-*c*][1]benzopyran toward dimethyl fumarate. Similar to this, it has also found that **1** reacts with dimethyl fumarate to yield the dibenzopyrane derivative **8,** most likely via the intermediate of the cycloadduct **7**.

Compound **2** reacted with methyl acrylate when refluxed in dioxane containing few drops of acetic acid to yield products of addition and methanol elimination. These are assigned structure **11** and are assumed to be formed via rearrangement of the initially formed cycloadduct **9** to **10** in presence of acid medium. The latter cyclized via loss of methanol to give **11**. If **10** would lose hydrogen sulphide to yield a phthalazine, the methyl and ester function in this product would experience large steric interactions. The structure proposed for compound **11** was established with ^{13}C NMR. Furthermore ^{1}H NMR showed an AB multiplet near δ 3.00 ppm for CH_2 protons at position C-8. Similarly, the reaction of maleic anhydride with **2** afforded **12**. It is believed that the methanol eliminated during formation of **12** effects ring opening of the anhydride ring.

Compound **2** reacted with benzoyl isothiocyanate to yield a 1:1 adduct. The ^{1}H NMR of this adduct revealed the presence of two lower field D_2O exchangeable hydrogen atoms at δ 12.10 and 15.20 ppm. The absence of any amino hydrogens excludes the possibility that the cycloadduct **14** was formed. It is most likely that this product is the benzoyl thiourea derivative **13**. This assumption is further supported by ^{13}C NMR data, which did not show any signals for sp^3 hybridized besides carbons those of the methyl and methoxy group (further detail cf. experimentat section).

Experimental

All melting points are uncorrected, IR spectra were obtained on a Pye Unicam SP 1000 spectrophotometer using KBr discs. The ^{1}H NMR were recorded on a varian EM 390-90 MHz, and Bruker WM 300 MHz using TMS as internal reference. The chemical shifts were expressed as a δ ppm GCMS-QP 1000-EX Shimadzu, Japan. Analytical data were obtained from the microanalytical data unit at Cairo University.



3-Aminothieno[3,4-*c*]coumarin (1)

To a solution of **3** (1.8 g, 0.01 mol) in DMF (15 mL) containing few drops of piperidine was added elemental sulfur (0.32 g, 0.01 mol). The reaction mixture was heated under reflux for 5 h, then left to cool. The resulting solution was poured on ice water and acidified with few drops of hydrochloric acid. The resulting precipitate was collected by filtration and crystallized from ethanol to give yellow plates (1.9 g, 87%), mp 195°C. IR, ν (KBr): 3400–3300 (NH_2) and 1680 cm^{-1} (C=O). ^1H NMR (DMSO), δ: 3.45 (br, 2H, NH_2), 6.9–8.15 ppm (M, 5H, Ar-H, and thiophene H). Anal. calcd. for $C_{11}H_7NO_2S$ (217): C 60.8, H 3.2, N 6.4, S 14.7; found: C 60.7, H 3.1, N 6.2, S 14.5.

4-Methylcoumarin-3-carbonitrile (3)

In a flask fitted with a Dean–Stark trap, a solution of *o*-hydroxy-acetophenone (1.36 g, 0.01 mol) in a mixture of acetic acid (10 mL) and toluene (10 mL), ammonium acetate (2 g), and malononitrile (0.66 g, 0.01 mol) was refluxed for 6 h. The solvents were evaporated in vacuo, and the remaining solid was collected and crystallized from acetic acid to give yellow needles, mp 184°C.

9-(*N*-Phenyl)-8,10-dioxoisoindolo[5,6-*c*]coumarin-7-amine (6a)

A solution of **1** (2.17 g, 0.01 mol) in a mixture of acetic acid (10 mL) and dioxane (10 mL) was treated with *N*-phenylmaleimide (1.7 g, 0.01 mol) and refluxed for 8 h. After evaporation of the solvents the solid product was collected by filtration and crystallized from dioxane to give yellow needles (3.3 g, 94%), mp > 300°C. IR, ν (KBr): 3440–3322 (NH_2), 3043 (CH aromatic), 1760–1709 (3 C=O), and 1630 cm^{-1} (C=C). ^1H NMR (DMSO), δ: 7.74–7.39 (m, 9H, Ar-H), 8.06 (s, 1H, H-11), and 8.60 ppm (br, 2H, NH_2). Anal. calcd. for $C_{21}H_{12}N_2O_4$ (356): C 70.7, H 3.3, N 7.8; found: C 70.7, H 3.2, N 7.5. Mass, *m*/*z*: 356 (M^+).

8,10-Dioxoisobenzofuro[5,6-*c*]coumarin-7-amine (6b)

A solution of **1** (2.17 g, 0.01 mol) in a mixture of acetic acid (10 mL) was treated with maleic anhydride (0.98 g, 0.01 mol) and refluxed for 3 h. The solvents were evaporated, and the solid product was washed with ethanol, collected by filtration, and crystallized from ethanol to give yellow needles (2.2 g, 78%), mp 194°C. IR, ν (KBr): 3433–3340 (NH_2), 3084 (CH aromatic), 1835–1763(3 C=O), and

1630 cm^{-1} (C=C). ^1H NMR (DMSO), δ: 7.20–7.82 (m, 4H, Ar-H), 8.00 (s, 1H, H-11), and 8.50 ppm (br, 2H, NH_2). Anal. calcd. for $C_{15}H_7NO_5$ (281): C 64.0, H 2.4, N 4.9; found: C 63.9, H 2.3, N 4.7. Mass, *m*/*z*: 281 (M^+).

Dimethyl 4-aminobenzo[c]coumarin-2,3-dicarboxylate (8)

A mixture of **1** (2.17 g, 0.01 mol) and dimethyl fumarate (1.44 g, 0.01 mol) was heated in an oil bath at 170°C for 4 h. The reaction mixture was cooled, then triturated with ethanol. The solid product, so formed, was collected by filtration and crystallized from dioxane as brown needles, (2.5 g, 76%), mp > 300°C. IR, ν (KBr): 3464–3351 (NH_2), 3095 (CH aromatic), and 1721–1608 cm^{-1} (3 C=O). ^1H NMR (300 MHz, $CDCl_3$), δ: 3.68 (3 H, s, CO_2Me), 3.74 (3H, s, CO_2Me), 6.69–7.06 (1H, dd, *J* = 8.19 and 1.15, 7-H), 7.02 (1H, s, 1-H), 7.05–7.15 (1H, ddd, *J* = 7.91, 7.69, and 1.18, 9-H), 7.27–7.36 (1H, ddd, *J* = 8.16, 7.75, and 1.47, 8-H), 7.74–7.78 (1H, dd, *J* = 8.11 and 1.41, 10-H), 9.05 (2H, br s, NH_2). Anal. calcd. for $C_{17}H_{13}NO_6$ (327): C 62.3, H 3.9, N 4.2; found: C 62.2, H 3.8, N 4.1. Mass, *m*/*z*: 327 (M^+).

Methyl 6-amino-8,8a-dihydro-2,5-dioxo-8a-methyl-4-(*p*-tolyl)-1,3,4-thiadiazaacenaphthene-7-carboxylate (11)

A solution of **2** (3.2 g, 0.01 mol) in dioxane (20 mL) and few drops of acetic acid was treated with methyl acrylate (0.86 g, 0.01 mol). The reaction mixture was refluxed for 10 h, then evaporated in vacuo. The remaining product was triturated with water, and the resulting solid product was collected by filtration and crystallized from dioxane as red needles (3 g, 79%), mp 201°C. IR, ν (KBr): 3402–3292 (NH_2), 2987 (CH_3), 1711 (C=O), 1676 (ring CO), 1675 (CO), and 1620 cm^{-1} (C=C). ^1H NMR (300 MHz, DMSO), δ: 1.82 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.95 and 3.16 (AB system, 2H, CH_2, JAB = 15.7 Hz), 3.70 (s, 3H, OCH_3), 7.31–7.68 (m, 4H, aromatic protons), and 8.10 ppm (br, 2H, NH_2); ^{13}C NMR, δ: 194.20 (C-2), 171.35 (C=O ester), 163.29 (C-5), 153.07 (C-2a), 146.01 (C-6), 144.22, 133.11, 131.20, 129.42 (aromatic ring), 124.35 (C-5a), 104.0 (C-7), 80.56 (C-8a), 50.91 (C-8), 54.82 (CH_3), 15.48 (CH_3). Anal. calcd. for $C_{19}H_{17}N_3O_4S$ (383): C 59.5, H 4.4, N 10.9, S 8.3; found: C 59.3, H 4.2, N 10.8, S 8.2. Mass, *m*/*z*: 383 (M^+).

Methyl 6-amino-8,8a-dihydro-2,5-dioxo-8a-methyl-4-(*p*-tolyl)-1,3,4-thiadiazaacenaphthene-7-carboxy-8-carboxylate (12)

A solution of **2** (3.2 g, 0.01 mol) in a mixture of acetic acid (10 mL) and dioxane (10 mL) was treated with maleic anhydride (0.98 g, 0.01 mol). The reaction mixture was refluxed for 10 h. The reaction mixture was evaporated, then washed with ethanol. The solid product, so formed, was collected by filtration and crystallized from ethanol–dioxane as orange needles (3 g, 71%), mp 280°C. IR, ν (KBr): 3446–3251 (NH_2), 3035 (CH aromatic), 2953 (CH_3), 1830–1731–1673 (4 C=O), and 1637 cm^{-1} (C=C). ^1H NMR (DMSO), δ: 2.40 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 3.40 (s, 3H, OCH_3), 3.98 (s, 1H, C-8), 7.3–7.7 (m, 4H, Ar-H), 8.88 (br, protons of NH_2), and 11.70 ppm (s, 1H, COOH) (the downfield shift of the amino group due to the effect of the amino acid moiety). Anal. calcd. for $C_{20}H_{17}N_3O_6S$ (427): C 56.2, H 3.9, N 9.8, S 7.4; found: C 56.0, H 3.6, N 9.5, S 7.1. Mass, *m*/*z*: 427 (M^+).

1-Benzyl-5-[7-methyl-3,4-dihydro-7-methyl-3-(*p*-tolyl)-4-oxo-thieno[3,4-*d*]pyridazin-1-carboxylate]-3-ylthiourea (13)

To a suspension of ammonium thiocyanate (0.76 g, 0.01 mol) in dry acetone (20 mL), benzoyl chloride (1.4 g, 0.01 mol) was added. The reaction mixture was refluxed for 5 min then treated with **2** (3.2 g, 0.01 mol). The reaction mixture was refluxed for 3 h, then left to cool. The resulting solution was poured onto ice water. The solid product, so formed, was collected by filtration and crystallized from dioxane as yellow needles (4.8 g, 97%), mp 270°C. IR, ν (KBr): 3350–3220 (2 NH), 2948 (CH_3), 1732 (ester CO), 1675 (2 C=O), and 1641 cm^{-1} (C=C). ^1H NMR (DMSO), δ: 2.40 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3), 7.3–7.7 (m, 9H, Ar-H), 12.10 (br, 1H, NH), and 15.20 ppm (br, 1H, NH). ^{13}C NMR, δ: 177.08 (C=O), 174.32 (C=O), 169.26 (C=S), 165.71 (ring C=O), 159.12 (C-1), 147.95 (C-5), 139.31–125.65 (phenyl ring), 121.96 (C-7), 117.38 (C-7a), 106.42 (C-4a), 54.65 (CH_3), 22.26 (CH_3), 14.92 (CH_3). Anal. calcd. for $C_{24}H_{20}N_4S_2O_4$(492): C 58.5, H 4.0, N 11.3, S 13.0; found: C 58.2, H 3.9, N 11.1, S 12.6. Mass, *m*/*z*: 492(M^+).

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