Synthesis of a Novel Heterocyclic System - Pyrimido[5′,4′:5,6]thiopyrano [2,3-*b*]indole

Jurgis Sudzius and Sigitas Tumkevicius*

Vilnius University, Department of Organic Chemistry, Naugarduko 24, LT-03225 Vilnius, Lithuania

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Abstract: An efficient protocol for the synthesis of pyrimido[5′,4′:5,6]thiopyrano[2,3-*b*]indoles by the cyclocondensation of 1,3-dihydro-2*H*-indole-2-thione with 6-chloropyrimidine-5-carbaldehydes has been developed. 4-Chloro-2-methylthiopyrimido[5′,4′:5,6]thiopyrano[2,3-*b*]indole was found to undergo smooth nucleophilic substitution with various nucleophiles to give 4-substituted pyrimido[5′,4′:5,6]thiopyrano[2,3-*b*]indoles.

Keywords: indoline-2-thione, pyrimidine-5-carbaldehydes, cyclocondensation, nucleophilic substitution, pyrimido[5′,4′:5,6] thiopyrano[2,3-*b*]indoles.

INTRODUCTION

The indole nucleus is a prominent structural motif found in numerous natural products and synthetic compounds with important biological activities [1] and thus considerable attention has been directed towards general, flexible and simple methods for the synthesis of highly functionalized indole derivatives and heterocycles containing indole moiety [2]. Several natural products having specific biological activity contain the indole-2-thiol fragment. For example, phytoalexins, such as brassilexin, sinalexin, and cyclo-brassinin occurring in plants, have a broad antimicrobial activity, playing crucial roles in their resistance to pathogen invasion [3]. 3-Arylidene-1,3-dihydroindole-2-thiones as well as their oxidation products - 2,2′-dithiobisindoles have been demonstrated as useful tyrosine kinase inhibitors [4]. 3,3-Disubstituted indole-2-thiones were found to be progesterone receptor antagonists [5].

1,3-Dihydroindole-2-thiones have been used as diverse initial materials for the synthesis of fused indole heterocycles including some natural products and their analogues. For example, the Vilsmeier formylation of 1,3-dihydroindole-2-thione and following work up of the obtained intermediates with ammonia or carbon disulphide led to the efficient synthesis of natural phytoalexins - brassilexin, sinalexin and thiopyrano[2,3-*b*:6,5-*b*′]diindole [3a,b]. Condensation of indoline-2-thiones with cyclohexyl isocyanide furnished useful intermediates for the synthesis of thieno[2,3-*b*]indoles [6]. Reaction of 1,3-dihydroindole-2-thiones with aromatic aldehydes yielded the corresponding 3-arylideneindole-2-thiones [4c, 7], some of which as diene components easily reacted in the hetero-Diels-Alder reaction to give thiopyrano[2,3-*b*]indole derivatives [7]. Nevertheless, reactions of 1,3-dihydroindole-2-thiones with heteroaromatic aldehydes bearing other reactive functional groups are studied insufficiently. In this context and in the course of our studies on the synthesis of fused pyrimidine heterocycles with anticipated biological activity [8] we report herein on a simple and efficient synthesis of a novel heterocyclic system - pyrimido[5′,4′:5,6]thiopyrano[2,3-*b*]indole.

*Address correspondence to this author at the Vilnius University, Department of Organic Chemistry, Naugarduko 24, LT-03225 Vilnius, Lithuania; E-mail: sigitas.tumkevicius@chf.vu.lt

RESULTS AND DISCUSSION

We have found that performing condensation reaction of 1,3-dihydroindole-2-thione (**1**) with pyrimidine-5-carbalde-hydes **2a** [9] or **b** in benzene at room temperature in the presence of anhydrous potassium carbonate under argon atmosphere led to formation of tetracyclic heterocycle derivatives - pyrimido[5′,4′:5,6]thiopyrano[2,3-*b*]indoles **3a,b** (Scheme **1**) [10]. The structure of **3a,b** was assigned on the basis of their spectral and elemental analysis data. In their IR spectra there is no absorption of the C=O and NH groups. In the ^{1}H NMR spectra along with signals of aromatic protons in a region 7.4-8.0 ppm and methylthio group at 2.72 ppm and 2.67 ppm, respectively, a singlet at 8.62 ppm and 8.55 ppm appeared due to C(5)-H resonance of compounds **3a,b**. ^{13}C NMR spectra of compounds **3a,b** as well as elemental analysis data are consistent with the proposed structures. In order to isolate possible reaction intermediates – corresponding S-alkylated indole or 3-(5-pyrimidinyl-methylidene)indole derivatives we performed several experiments under different conditions. However they were not successful. For example, performing the reaction of **1** with carbaldehydes **2a,b** in 2-propanol or ethanol in the presence of triethylamine or piperidine, i.e. under conditions usually leading to the corresponding 3-arylideneindole-2-thiones [4c, 7], resulted in a formation of inseparable multicomponent mixture of products.

Chloro group in **3a** appeared to be rather reactive towards various nucleophiles. Compound **3a** reacted with selected *N*-, *O*- and *S*-nucleophiles to give the corresponding 4-substituted 2-methylthiopyrimido[5′,4′:5,6]-thiopyrano[2,3-*b*]indoles (**3b-h**) (Scheme **2**) [11]. For example, displacement of chloro group in compound **3a** with methanol or ethanol to give compounds **3b,c** occured at room temperature in the presence of potassium carbonate. Treatment of **3a** with equivalent amount of aniline,

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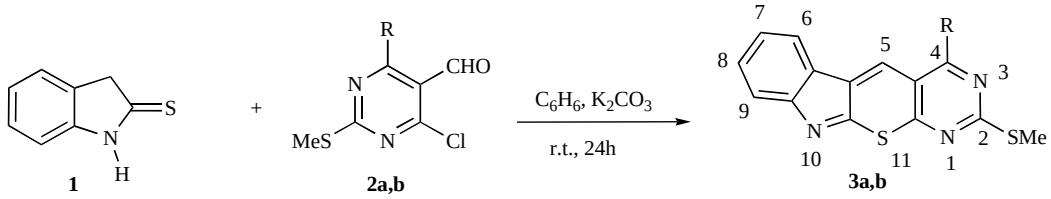
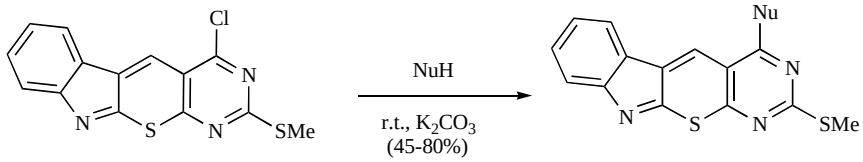


1 **2a,b** **3a,b**

R = Cl (**a**); OMe (**b**)

Scheme 1.



3a **3b-h**

Nu = OMe (**b**), OEt (**c**), NH_2 (**d**), NHPh (**e**), $N(CH_2)_4O$ (**f**), $NHCH_2CO_2Me$ (**g**), SCH_2CO_2Et (**h**)

Scheme 2.

morpholine, methyl aminoacetate or ethyl mercaptoacetate in tetrahydrofuran in the presence of potassium carbonate furnished the corresponding 4-substituted 2-methylthiopyrimido[5′,4′:5,6]thiopyrano[2,3-*b*]indoles (**3d-h**) in 45-80% yields.

In summary, we have developed a simple and efficient synthesis of a novel tetracyclic heterocyclic system - pyrimido[5′,4′:5,6]thiopyrano[2,3-*b*]indoles, containing structural units of indole, thiopyrane and pyrimidine, that makes these compounds readily available for further chemical and biological study.

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[10] Synthetic procedure for 4-chloro-2-methylthiopyrimido[5′,4′:5,6]thiopyrano[2,3-*b*]indole (**3a**). A solution of 0.15 g (1 mmol) 1,3-dihydro-indole-2-thione in 10 ml of dry benzene was flushed with argon. Then 0.22 g (1 mmol) 4,6-dichloro-2-methylthiopyrimidine-5-carbaldehyde [9] and 0.15 g (1.1 mmol) of potassium carbonate was added. The reaction mixture was stirred at room temperature for 24 h and filtered. Filtrate was concentrated under reduced pressure to dryness and the resulting solid was recrystallized to give 0.21 g (66%) of compound **3a** as orange red needle crystals, m.p. 183 ºC (dec.) (from chloroform). ^{1}H-NMR (300 MHz, $CDCl_3$) δ, ppm: 2.72 (s, 3H, SCH_3), 7.43 (td, 1H, *J* = 7.3 Hz, *J* = 1.0 Hz, C7-H), 7.63 (td, 1H, *J* = 8.0 Hz, *J* = 1.0 Hz, C8-H), 7.79 (d, 1H, *J* = 8.0 Hz, C9-H), 8.09 (d, 1H, *J* = 7.1 Hz, C6-H) 8.62 (s, 1H, C5-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ, ppm: 14.7, 115.3, 119.2, 121.6, 123.9, 124.1, 125.5, 130.6, 132.2, 154.9, 160.4, 160.7, 165.0, 171.9. Anal. Calcd. for $C_{15}H_8N_3S_2Cl$: C, 52.91; H, 2.54; N, 13,22. Found: C, 53.29; H, 2.49; N, 13.04.

[11] Spectral and physical data of compounds **3b-h**. Compound **3b**: Yield 63%, m.p. 220-222 ºC (form ethyl acetate). IR, cm^{-1}: 1549, 1502, 1427. ^{1}H-NMR (300 MHz, $CDCl_3$) δ, ppm.: 2.67 (s, 3H, SCH_3), 4.23 (s, 3H, OCH_3) 7.36 (td, 1H, *J* = 7.5 Hz, *J* = 0.9 Hz, C7-H), 7.56 (td, 1H, *J* = 7.7 Hz, *J* = 1.0 Hz, C8-H), 7.76 (d, 1H, *J* = 7.8 Hz, C9-H), 8.01 (d, 1H, *J* = 7.5 Hz, C6-H) 8.55 (s, 1H, C5-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ, ppm: 14.7, 55.4, 106.4, 119.1, 121.0, 123.4, 123.5, 125.9, 129.8, 130.0, 154.9, 161.1, 164.0, 165.7, 172.3. Compound **3c**: Yield 73%, m.p. 226.5-227 ºC (from ethyl acetate): ^{1}H-NMR (300 MHz, $CDCl_3$) δ, ppm: 1.60 (t, 3H, *J* = 7.1 Hz, CH_3), 2.68 (s, 3H, SCH_3), 4.71 (q, 2H, *J* = 7.1 Hz, OCH_2) 7.38 (t, 1H, *J* = 7.5 Hz, C7-H), 7.59 (t, 1H, *J* = 7.9 Hz, C8-H), 7.79 (d, 1H, *J* = 7.9 Hz, C9-H), 8.08 (d, 1H, *J* = 7.5 Hz, C6-H), 8.61 (s, 1H, C5-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ, ppm: 14.6, 14.7, 64.6, 106.4, 119.3, 121.4, 123.3, 123.5, 126.4, 129.7, 130.3, 155.3, 161.6, 164.4, 165.5, 172.2. Compound **3d**: Yield 80%, m.p. 320 ºC (dec.): IR, cm^{-1}: 3322, 3160 (NH). ^{1}H-NMR (300 MHz, DMSO-d_6) δ, ppm: 2.54 (s, 3H, SCH_3), 7.36 (t, 1H, *J* = 7.5 Hz, C7-H), 7.51 (t, 1H, *J* = 7.8 Hz, C8-H), 7.66 (d, 1H, *J* = 7.8 Hz, C9-H), 8.01 (d, 1H, *J* = 7.5 Hz, C6-H), 8.01 (s, 2H, NH_2), 9.09 (s, 1H, C5-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ, ppm: 14.3, 103.3, 119.0, 121.2, 123.4, 126.8, 126.9, 127.8, 129.2, 154.6, 160.1, 161.7, 163.6, 171.8. Compound **3e**: Yield 64%, m.p. 141-142 ºC (from chloroform): IR, cm^{-1}: 3436 (NH). ^{1}H-NMR (300 MHz, DMSO-d_6) δ, ppm: 2.50 (s, 3H, SCH_3), 7.25 (t, 1H, *J* = 7.4 Hz, C4′-H), 7.43 (t, 1H, *J* = 7.4 Hz,

C7-H), 7.48 (t, 2H, *J* = 7.5 Hz, C3′,5′-H), 7.57 (t, 1H, *J* = 7.4 Hz, C8-H), 7.70(d, 1H, *J* = 7.4 Hz, C9-H), 7.73 (d, 2H, *J* = 7.5 Hz, C2′,4′-H), 8.14 (d, 1H, *J* = 7.4 Hz, C6-H), 9.48 (s, 1H, C5-H), 10.33 (s, 1H, NH). Compound **3f**: Yield 45%, m.p. 184.5-185 °C (from acetone): ^{1}H-NMR (300 MHz, $CDCl_3$) δ, ppm: 2.65 (s, 3H, SCH_3), 3.80 – 3.96 [m, 8H, $N(CH_2)_4O$], 7.36 (t, 1H, *J* = 7.5 Hz, C7-H), 7.57 (t, 1H, *J* = 7.5 Hz, C8-H), 7.78(d, 1H, *J* = 7.5 Hz, C9-H), 7.99 (d, 1H, *J* = 7.5 Hz, C6-H), 8.24 (s, 1H, C5-H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ, ppm: 14.7, 50.95, 66.9, 94.9, 119.4, 120.5, 123.2, 124.9, 126.2, 126.5, 129.7, 154.7, 162.5, 163.3, 165.8, 172.1. Compound **3g**: Yield 55%, m.p. 201-202 °C (from benzene): IR (Nujol), cm^{-1}: 3520 (NH), 1746 (CO). ^{1}H-NMR (300 MHz, $CDCl_3$) δ, ppm: 2.48 (s, 3H, SCH_3), 3.71 (s, 3H, OCH_3), 4.31 (d, 2H, *J* = 5.5 Hz, NCH_2), 7.38 (t, 1H, *J* = 7.7 Hz, C7-H), 7.52 (t, 1H, *J* = 7.4 Hz, C8-H), 7.66 (d, 1H, *J* = 7.9 Hz, C9-H), 8.01 (d, 1H, *J* = 7.2 Hz, C6-H), 9.08 (s, 1H, C5-H), 9.22 (t, 1H, *J* = 5.4 Hz, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 14.2, 43.5, 52.7, 103.7, 119.2, 121.2, 123.5, 125.4, 126.8, 128.3, 129.4, 155.0, 159.3, 160.0, 163.1, 170.8, 171.4. Compound **3h**: Yield 60%, m.p. 193-194 °C (from ethyl acetate). IR (KBr), cm^{-1}: 1732 (CO). ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 1.36 (t, 3H, *J* = 7.1 Hz, CH_3), 2.63 (s, 3H, SCH_3), 4.13 (s, 2H, SCH_2), 4.29 (q, 2H, *J* = 7.0 Hz, OCH_2), 7.35 (t, 1H, *J* = 7.2 Hz, C7-H), 7.55 (t, 1H, *J* = 7.4 Hz, C8-H), 7.72 (d, 1H, *J* = 7.9 Hz, C9-H), 7.99 (d, 1H, *J* = 7.5 Hz, C6-H), 8.33 (s, 1H, C5-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 14.5, 14.7, 32.9, 62.5, 114.5, 119.4, 121.4, 122.8, 123.6, 125.8, 130.3, 130.9, 155,4, 161.0, 162.8, 168.4, 170.7.