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Synthesis and characterization of derived imines from 4-imino-5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidin-3(4H)-amine

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Abstract

The synthesis and characterization of derived imines from 4-imino-5,6,7,8-tetrahydro-1-benzo thieno[2,3-d]pyrimidin-3(4H)-amine **3** have been developed in three steps through the reaction of heteroaromatic *o*-aminonitrile **1** with triethyl orthoformate. The process afforded the corresponding of imido ester **2** and was followed by cyclization with hydrazine hydrate to furnish iminothienopyrimidineamine **3** and, finally, the imination of **3** with aromatic aldehydes generated the corresponding imines (**5a-5h**). It is worth mentioning that the process was done at room temperature. The new products were obtained in high yield with an easy work-up in simple reaction along with the purification of products by non-chromatographic method. This general synthetic procedure which can be extended to the preparation of wide variety of imines using *o*-aminonitrile bifunctional derivatives can also be synthesized by Gewald reaction.

Keywords: Thieno[2,3-d]pyrimidines, *o*-aminonitrile, imination, Gewald reaction

Introduction

Thieno[2,3-d]pyrimidines are a large group of heterocycles with diverse and interesting biological activities. These compounds are reported to possess significant analgesic [1,5,10], antifungal [2], anti-bacterial [2,3], antimicrobial [4,9], anti-inflammatory [1,5,10], antiatherosclerotic [6], antihistaminic [7], antitumor [8], CNS depressant [9] and ulcerogenic index [10] activities. Various methods have already been proposed for the synthesis of these compounds. One of the most general ones

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involves cyclocondensation of suitably functionalizedthiophenes with different electrophiles such as chloroformamidine [11], α-substituted acetonitriles [12], formic acid [13], phosgene [14], ethyl chlorofor- mate [14] and guanidine [15]. It is worth mentioning that the synthesis of derived imines from 4-imino-5,6,7,8-tetrahydro-1-benzothieno [2,3-d] pyrimidin-3(4H)-amine 3 has not been reported in the literature.

Prompted by these findings, and due to our interest in the synthesis of new heterocyclic compounds with potential biological activities [16], as well as in continuation of our works on the synthesis of thieno [2,3-d]pyrimidine derivatives [16], we report, herein, the synthesis of *N*-(arylmethylene)-4-imino-5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidin-3(4H)-amines (**5a–5h**) in 3 steps through the imina- tion of 3 at room temperature with aromatic aldehydes.

Experimental

General

Melting points were recorded with Electrothermal 9100 apparatus. Evaporation of solvents was performed under reduced pressure on a Buchi rotary evaporator. Thin layer chromatography was performed on Kieselgel GF_{254} and visualization was accomplished by iodine Flask or UV Lamp. The IR spectra were recorded on a Shimadzu 8400 instrument (the samples as KBr disks for the range 400-4000 cm^{-1}).^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ and DMSO-d_6 as solvents) with a BRUKER DRX-400 AVANCE spectrometer. Chemical shifts were reported in δ unit (ppm) with reference to TMS as an internal standard. Elemental analysis was performed on a Thermo Finnigan (San Jose, CA, USA) Flash EA microanalyzer, and the results were found to match satisfactorily with the calculated and observed values.

Procedure for the synthesis of 2- (ethoxymethylideneamino)-4,5,6,7-tetrahydrobenzo-1-thiophene-3-carbonitrile (2)

A mixture of compound **1** (10 mmol) and triethyl orthoformate (20 mmol) in ethanol (10-15 mL) was refluxed for 9 h with continuous stirring. The progress of the reaction was monitored by TLC (ethyl acetate: *n*-hexane, 1:1, v/v) on silica gel and showed complete conversion of the reactant to the product. After completing the reaction, the excess triethyl orthoformate and ethanol was removed by distillation under reduced pressure, and then Petroleum ether (10-20 mL) was added and boiled for a short period of time and, then,

left to cool at 0 °C overnight. The generated solid was collected by filtration, dried and crystallized from Petroleum ether in order to afford **2** in good yield.

Orange crystals, Yield: 74 %, (1.73 g), mp 51-52 °C. IR (υ, cm^{-1}): 2931 (CH-aliphatic), 2214 (CN), 1620 (C=N), 1257, 1211 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 1.39 (t, 3H, CH_3), 1.77-1.92 (m, 4H, $2CH_2$), 2.55-2.72 (m, 4H, $2CH_2$), 4.40 (q, 2H, CH_2), 7.94 (s, 1H, N=CH). ^{13}C NMR ($CDCl_3$) δ ppm: 14.01, 21.55, 22.23, 23.03, 25, 58, 64.10, 101.66, 114.79, 128.50, 134.11, 157.31, 157.40. Anal. calcd. for $C_{12}H_{14}N_2OS$ (234.32): C (61.51), H (6.02), N (11.96), O (6.83), S (13.68). Found: C (61.44), H (6.10), N (11.87), O (6.75), S (13.61) (%).

Procedure for the synthesis of 4-imino-5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidin-3(4H)-amine (3)

A mixture of compound **2** (10 mmol) and hydrazine hydrate (20 mmol) in dioxane (10-15 mL) was refluxed for 12 h with continuous stirring. After completing the reaction (monitored by TLC, chloroform: methanol, 9:1, v/v), and cooling at 0 °C, the separated solid was collected by filtration, dried and crystallized from dioxane to afford compound **3** in good yield.

Milky crystals, Yield: 79 %, (1.74 g), mp 183-184 °C. IR (υ, cm^{-1}): 3100-3400 (NH, NH2), 2939 (CH- aliphatic), 1630 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 1.84-1.98 (m, 4H, $2CH_2$), 2.77-2.85 (m, 2H, CH_2), 2.85-2.94 (m, 2H, CH_2), 4.16 (br s, 2H, NH_2), 6.53 (br s, 1H, NH), 8.45 (s, 1H, CH-pyrimidine). ^{13}C NMR ($CDCl_3$) δ ppm: 22.44, 22.49, 25.41, 26.25, 115.45, 125.34, 134.06, 152.62, 158.93, 165.10. Anal. calcd. for $C_{10}H_{12}N_4S$ (220.29): C (54.52), H (5.49), N (25.43), S (14.56). Found: C (54.45), H (5.60), N (25.36), O (25.31), S (14.49) (%).

General procedure for the synthesis of *N*-(Arylmethylene)-4-imino-5,6,7,8–tetrahydro-1- benzothieno[2,3-d]pyrimidin-3(4H)-amine (5a-5h)

A mixture of compound **3** (2 mmol) and aromatic aldehydes **4a-4h** (3 mmol) in ethanol (15 mL) was mixed at room temperature for 24 h with continuous stirring. The progress of the reaction was monitored by TLC (chloroform: methanol, 9:1, v/v) on silica gel and showed complete conversion of the reactant to the product. The precipitated solid was, then, filtered off, dried and recrystallized from ethanol to give derivatives (**5a-5h**) in good yield.

***N*-(4-toluenemethylene)-4-imino-5,6,7,8-tetra hydro-1-benzothieno[2,3-d] pyrimidin-3(4H)- amine (5a)**

Bright yellow crystals, Yield: 86 %, (0.55 g), mp 223-224 °C. IR (υ, cm^{-1}): 3255 (NH), 3055 (CH-aromatic), 2924 (CH-aliphatic), 1620 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 1.80-1.93 (m, 4H, $2CH_2$), 2.40 (s, 3H, CH_3), 2.75-2.84 (m, 2H, CH_2), 2.84-2.93 (m, 2H, CH_2), 7.21-7.72 (dd, 4H-aromatic ring H), 7.99 (br s, 1H, NH), 8.46 (s, 1H, CH- pyrimidine), 8.63 (s, 1H, N=CH).^{13}C NMR ($CDCl_3$) δ ppm: 21.54, 22.44, 22.49, 25.41, 26.25, 119.26, 127.12, 128.13, 129.66, 131.22, 132.31, 139.63, 144.33, 148.55, 153.34, 157.09. Anal. calcd. for $C_{18}H_{18}N_4S$ (322.43): C (67.05), H (5.63), N (17.38), S (9.94). Found: C (66.92), H (5.70), N (17.29), S (9.88) (%).

_N_-(4-nitrophenylmethylene)-4-imino-5,6,7,8tetrahydro-1-benzothieno[2,3-d]pyrimidin-3(4H)-amine (5b)

Red crystals, Yield: 90 %, (0.63 g), mp 272-273 °C. IR (υ, cm-1): 3325 (NH), 3055 (CH-aromatic), 2931 (CH-aliphatic), 1620 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6) δ ppm: 1.70-1.90 (m, 4H, $2CH_2$), 2.70-2.80 (m, 2H, CH_2), 2.95-3.05 (m, 2H, CH_2), 8.16-8.30 (dd, 4H-aromatic ring H), 7.89 (s, 1H, CH-pyrimidine), 8.50 (s, 1H, N=CH), 12.13 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 22.48, 22.89, 25.02, 27.12, 119.16, 123.13, 124.03, 129.76, 132.31, 138.83, 144.23, 148.45, 149.25, 153.33, 157.29. Anal. calcd. for $C_{17}H_{15}N_5O_2S$ (353.40): C (57.78), H (4.28), N (19.82), O (9.05), S (9.07). Found: C (57.43), H (4.45), N (19.67), O (9.15), S (8.96) (%).

_N_-(phenylmethylene)-4-imino-5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidin-3(4H)- amine (5c)

Bright yellow crystals, Yield: 87 %, (0.53 g), mp 160-161 °C. IR (υ, cm): 3317 (NH), 3063 (CH- aromatic), 2924 (CH-aliphatic), 1620 (C=N) cm. ^1H NMR ($CDCl_3$) δ ppm: 1.80-1.93 (m, 4H, $2CH_2$), 2.75-2.83 (m, 2H, CH_2), 2.83-2.91 (m, 2H, CH_2), 7.35-7.83 (dd, 4H-aromatic ring H), 8.02 (br s, 1H, NH), 8.49 (s, 1H, CH-pyrimidine), 8.64 (s, 1H, N=CH). ^{13}C NMR ($CDCl_3$) δ ppm: 22.55, 25.37, 26.77, 119.35, 128.03, 128.93, 129.95, 131.21, 132.45, 133.81, 144.32, 148.54, 153.53, 157.28. Anal. calcd. for $C_{17}H_{16}N_4S$ (308.40): C (66.21), H (5.23), N (18.17), S (10.40). Found: C (66.09), H (5.36), N (18.02), S (10.52) (%).

_N_-(4-chlorophenylmethylene)-4-imino-5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidin-3(4H)-amine (5d)

Bright yellow crystals, Yield: 89 %, (0.61 g), mp 193-194 °C. IR (υ, cm): 3309 (NH),

3063 (CH- aromatic), 2924 (CH-aliphatic), 1628 (C=N) cm. ^{1}H NMR ($CDCl_3$) δ ppm: 1.80-1.93 (m, 4H, 2CH2), 2.77-2.85 (m, 2H, CH2), 2.85-2.92 (m, 2H, CH2), 7.46-7.73 (dd, 4H-aromatic ring H), 8.00 (br s, 1H, NH), 8.44 (s, 1H, CH-pyrimidine), 8.64 (s, 1H, N=CH). ^{13}C NMR ($CDCl_3$) δ ppm: 22.53, 22.88, 25.37, 26.73, 118.45, 127.92, 128.85, 129.65, 130.86, 131.30, 135.65, 143.51, 147.53, 152.54, 156.29. Anal. calcd. for $C_{17}H_{15}C_lN_4S$ (342.84): C (59.56), H (4.41), N (16.34), S (9.35). Found: C (59.49), H (4.53), N (16.17), S (9.46) (%).

_N_-(4-bromophenylmethylene)-4-imino-5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidin-3(4H)-amine (5e)

Yellow crystals, Yield: 87 %, (0.67 g), mp 196-197 °C. IR (υ, cm^{-1}): 3294 (NH), 3063 (CH-aromatic), 2932 (CH-aliphatic), 1620 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ ppm: 1.80-1.93 (m, 4H, $2CH_2$), 2.77-2.84 (m, 2H, CH_2), 2.84-2.92 (m, 2H, CH_2),7.51-7.67 (dd, 4H-aromatic ring H), 7.97 (br s, 1H, NH), 8.42 (s, 1H, CH-pyrimidine), 8.64 (s, 1H, N=CH). ^{13}C NMR ($CDCl_3$) δ ppm: 22.52, 22.88, 25.36, 26.72, 118.35, 124.45, 127.52, 128.95, 130.76, 131.40, 132.05, 143.41, 147.63, 152.43, 156.15. Anal. calcd. for $C_{17}H_{15}BrN_4S$ (387.29): C (52.72), H (3.90), N (14.47), S (8.28). Found: C (52.55), H (4.09), N (14.39), S (8.40) (%).

_N_-(4-hydroxyphenylmethylene)-4-imino-5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidin-3 (4H)-amine (5f)

Bright pink crystals, Yield: 92 %, (0.59 g), mp 264-265 °C. IR (υ, cm^{-1}): 3750-2000 (OH), 3348 (NH), 3009 (CH-aromatic), 2932 (CH-aliphatic), 1574 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ ppm: 1.65-1.95 (m, 4H, $2CH_2$), 2.65-2.80 (m, 2H, CH_2), 2.90-3.05 (m, 2H, CH_2), 6.76-7.90 (dd, 4H-aromatic ring H), 7.73 (br s, 1H, OH), 8.27 (s, 1H, CH-pyrimidine), 9.84 (s, ^{1}H, N=CH), 11.69 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 22.49, 22.88, 25.12, 27.02, 115.86, 119.36, 127.02, 129.96, 131.32, 132.41, 144.43, 148.65, 153.44, 157.19, 159.65. Anal. calcd. for $C_{17}H_{16}N_4OS$ (324.40): C (62.94), H (4.97), N (17.27), O (4.93), S (9.88). Found: C (63.03), H (4.91), N (17.32), O (4.86), S (9.92) (%).

_N_-(4-methoxyphenylmethylene)-4-imino-5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidin-3 (4H)-amine (5g)

Bright yellow crystals, Yield: 90 %, (0.61 g), mp 198-199 °C. IR (υ, cm^{-1}): 3225 (NH), 3055 (CH-aromatic), 2939 (CH-

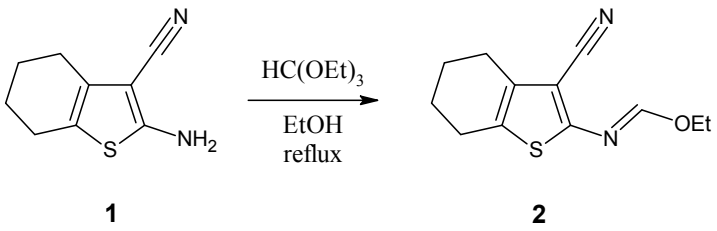
aliphatic), 1620 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 1.81-1.93 (m, 4H, $2CH_2$), 2.75-2.83 (m, 2H, CH_2), 2.83-2.93 (m, 2H, CH_2), 3.86 (s, 3H, CH_3), 6.91-7.80 (dd, 4H-aromatic ring H), 7.97 (br s, 1H, NH), 8.44 (s, 1H, CH- pyrimidine), 8.62 (s, 1H, N=CH). ^{13}C NMR ($CDCl_3$) δ ppm: 22.56, 22.91, 25.34, 26.74, 55.37, 114.15, 119.33, 125.73, 129.16, 129.99, 132.43, 144.42, 148.64, 153.46, 157.27, 162.68. Anal. calcd. for $C_{18}H_{18}N_4OS$ (338.43): C (63.88), H (5.36), N (16.56), O (4.73), S (9.47). Found: C (63.70), H (5.53), N (16.49), O (4.80), S (9.56) (%).

_N_-(4-dimethylaminophenylmethylene)-4-imino-5,6,7,8-tetrahydro-1-benzothieno[2,3-d] pyrimidin-3(4H)-amine (5h)

Yellow crystals, Yield: 88 %, (0.62 g), mp 265-266 °C. IR (υ, cm^{-1}): 3255 (NH), 3093 (CH-aromatic), 2916 (CH-aliphatic), 1605 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 1.80-1.92 (m, 4H, $2CH_2$), 2.76-2.82 (m, 2H, CH_2), 2.82-2.90 (m, 2H, CH_2), 3.04 (s, 6H, $2CH_3$), 6.68-7.67 (dd, 4H-aromatic ring H), 7.92 (br s, 1H, NH), 8.40 (s, 1H, CH-pyrimidine), 8.61 (s, 1H, N=CH). ^{13}C NMR ($CDCl_3$) δ ppm: 21.54, 22.44, 25.41, 26.25, 40.21, 113.95, 119.37, 125.25, 130.06, 131.31, 132.45, 144.42, 148.64, 153.43, 155.40, 157.18. Anal. calcd. for $C_{19}H_{21}N_5S$ (351.47): C (64.93), H (6.02), N (19.93), S (9.12). Found: C (64.85), H (6.18), N (19.82), S (9.01) (%).

Results and discussion

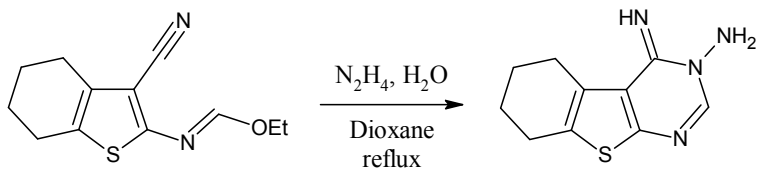
During the first step of our investigation, we began the synthesis of *o*-aminonitrile **1** according to the Gewald reaction [17]. Treatment of compound **1** with triethyl orthoformate in ethanol under reflux afforded 2-(ethoxymethylideneamino)-4,5,6,7-tetrahydrobenzo-1 thiophene-3-carbonitrile **2** (Scheme 1). The structure of the new product **2** was established from its spectral and microanalytical data. The IR spectrum of compound **2** was devoid of the NH_2 absorption, but instead showed new single absorption at 1620 cm^{-1} for imine and 2214 cm^{-1} for nitrile group. The ^1H NMR spectrum in $CDCl_3$ showed a triplet at δ 1.39 ppm for the methyl protons and a quartet at δ 4.40 ppm for the methylene protons, two multiplet at δ 1.77-1.92 ppm and 2.55-2.72 for four methylene groups and finally a sharp singlet at δ 7.94 ppm for imine proton. ^{13}C-NMR spectrum showed distinct resonances of 14.01, 64.10 and 157.40 ppm for ethyl and imine carbons, respectively, in agreement with the proposed structure.



1 **2**

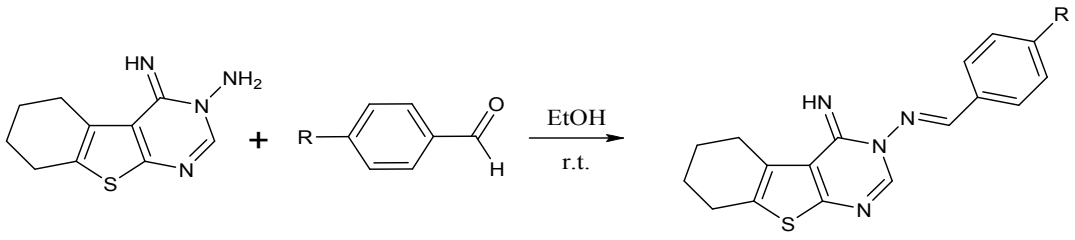
Scheme 1. Synthesis of 2-(ethoxymethylideneamino)-4,5,6,7-tetrahydrobenzo-1-thiophene-3-carbonitrile

In the next step, the reaction **2** with hydrazine hydrate in dioxane under reflux was carried out and 4-imino-5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidin-3(4H)-amine **3** was produced (Scheme 2). The IR spectrum was devoid of nitrile group but instead showed new absorptions at 3100-3400 cm^{-1} (NH, NH_2) and 1630 cm^{-1} (C=N). The ^1H NMR spectrum in $CDCl_3$ showed broad singlets at δ 4.16, 6.53 ppm for NH_2 and NH protons, respectively which disappeared in D_2O. The ^{13}C-NMR spectrum **3** was devoid of ethyl and nitril groups but instead showed distinct resonances in agreement with the formed pyrimidine ring and it also matched with the microanalytical data. Moreover, in the next step, the derived imines from **3** which can be called (**5a-5h**) were readily synthesized from the reaction **3** with aromatic aldehydes (**4a-4h**) at room temperature (Scheme 3). The structure of new derivatives (**5a-5h**), was confirmed by spectral and microanalytical data. For example, the absence of NH_2 absorption in the IR spectrum **5a** was observed. The ^1H NMR spectrum **5a** showed a singlet at δ 2.40 ppm for the methyl protons, two doublets for four aromatic protons at δ 7.21-7.72 ppm, and finally a sharp signal at δ 8.63 ppm for the proton on the imine. The ^{13}C-NMR spectrum **5a** showed distinct resonances in agreement with the proposed structure.



2 **3**

Scheme 2. Synthesis of 4-imino-5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidin-3(4H)-amine



3 **4a-4h** **5a-5h**

R: a = Me, b = NO_2 , c = H, d = Cl, e = Br, f = OH, g = OMe, h = NMe_2

Scheme 3. Synthesis of N-(Arylmethylene)-4-imino-5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidin-3(4H)-amines

Conclusions

We have described the synthesis and characterization of derived imines from 4-imino-5,6,7,8-tetrahydro-1-benzothieno[2,3-d]pyrimidin-3(4H) amine in 3 steps. More investigations are necessary to identify the medical property of the synthesized compounds.

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