

A new facile route to synthesize thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine derivatives

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Abstract

A new facile route for synthesis of 3-(aryl)-8,9-di(alkyl)thieno[3,2-*e*][1,2,4]triazolo pyrimidines derivative from the same starting material, 2-amino-4,5-di(alkyl)thiophene-3-carboxamide, has been developed through heterocyclization of the corresponding aryldiene-hydrazino-5,6-di(alkyl)thieno[2,3-*d*]pyrimidine under refluxing condition with acetic anhydride followed by air oxidation. The 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 can be extended to the preparation of a wide variety of isomeric triazoles using 2-aminothiophene-3-carboxamide bifunctional derivatives.

Keywords: Thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines, heterocyclization, acetic anhydride, air oxidation.

Introduction

Fused pyrimidines are found in a variety of natural products (e.g., purines, pyrrolopyrimidines, pyridopyrimidines, pteridines), agrochemicals and veterinary products [1–3]. Pyrimidine derivatives and heterocyclic annelated pyrimidines continue to attract great interest due to the wide

variety of interesting biological activities observed for these compounds, such as anticancer [4], antiviral [5], antitumor [6], anti-inflammatory [7], antimicrobial [8], antifungal [9], antihistaminic [10] and analgesic [11] activities.

Further, when a fused pyrimidine such as thieno[2,3-*d*]pyrimidine links the pyrimidine

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ring to triazol ring, it plays significant roles such as antimicrobial, antitumor [12] and adenosine receptor [13]. 2-Aminothiophene-3-carboxamide derivatives are useful substrates for the preparation of various condensed pyrimidine heterocyclic systems [14].

As indicated by its organic chemistry, acetic anhydride is a versatile reagent for acetylations, the introduction of acetyl groups to organic substrates. In these conversions, acetic anhydride is viewed as a source of CH_3CO^+ [15]. Acetic anhydride is mainly used for acetylations, leading to commercially significant materials. Its largest application is for the conversion of cellulose to cellulose acetate, which is a component of photographic film and other coated materials. Similarly, it is used in the production of aspirin, which is prepared by the acetylation of salicylic acid [16].

To the best of our knowledge, heterocyclization of arylidene-hydrazino-5,6-di(alkyl)thieno[2,3-*d*]pyrimidine derivatives with acetic anhydride followed by air oxidation and isolation of the variety of thienotriazolopyrimidines has not been reported in the literature. Due to our interest in the synthesis of new heterocyclic compounds with potential biological activities [17], the synthesis of novel

arylidene-hydrazino-5,6-di(alkyl)thieno[2,3-*d*]pyrimidine derivatives was carried out.

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 GF₂₅₄ 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}). ^1H 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.

General procedure for the synthesis of arylidene-hydrazino-5,6-di(alkyl)thieno[2,3-*d*]pyrimidine (6a-6d)

Compounds (4a-4d) were prepared according to the literature [20]. To synthesize (6a-6d), a mixture of hydrazino compound (2b) (2 mmol) and aromatic aldehydes (3a-3e) (3

mmol) in ethanol (10 cm³) were refluxed at 80 °C for 3 hours with continuous stirring. The progress of the reaction was monitored by TLC (ethyl acetate: *n*-hexane, 1:1, *v/v*) and showed complete conversion of the reactant to the product. The reaction mixture was then left to cool overnight to room temperature for complete precipitation. The solid was filtered off, dried and recrystallized from ethanol to give arylidene-hydrazino-5,6-di(alkyl)thieno[2,3-*d*]pyrimidines (**6a-6d**) in good yield.

4-(4-Methylbenzylidenehydrazino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (6a)

Brown crystals, Yield: 86 %, (0.55 g), mp: 219-220 °C. IR (ν , cm⁻¹): 3255 (NH), 3055 (CH-aromatic), 2924 (CH-aliphatic), 1620 (C=N) cm⁻¹. ¹H NMR (CDCl₃); δ (ppm): 1.80-1.92 (*m*, 4H, 2CH₂), 2.40 (*s*, 3H, CH₃), 2.75-2.84 (*m*, 2H, CH₂), 2.84-2.93 (*m*, 2H, CH₂), 7.20-7.69 (*dd*, 4H-aromatic ring), 8.00 (*br s*, 1H, NH), 8.46 (*s*, 1H, N=CH), 8.63 (*s*, 1H, CH-pyrimidine). ¹³C NMR (CDCl₃); δ (ppm): 21.56, 22.24, 23.04, 25.59, 119.26, 127.03, 128.16, 131.31, 132.42, 139.76, 144.40, 148.64, 153.48, 157.12. Anal. calcd. for C₁₈H₁₈N₄S (322.43): C (67.05), H (5.63), N (17.38), S (9.94). Found: C (66.95), H (5.72), N (17.25), S (10.08) (%).

4-(4-Nitrobenzylidenehydrazino)-5,6,7,8-

tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (6b)

Red crystals, Yield: 90 %, (0.63 g), mp: 270-271 °C. IR (ν , cm⁻¹): 3325 (NH), 3055 (CH-aromatic), 2931 (CH-aliphatic), 1620 (C=N) cm⁻¹. ¹H NMR (DMSO-*d*₆); (δ ppm): 1.70-2.00 (*m*, 4H, 2CH₂), 2.70-2.80 (*m*, 2H, CH₂), 2.95-3.05 (*m*, 2H, CH₂), 7.88 (*s*, 1H, N=CH), 8.16-8.31 (*dd*, 4H-aromatic ring), 8.49 (*s*, 1H, CH-pyrimidine), 12.12 (*br s*, 1H, NH). ¹³C NMR (DMSO-*d*₆); (δ ppm): 22.47, 22.88, 25.11, 27.07, 119.32, 123.07, 126.69, 127.02, 132.42, 141.03, 144.41, 148.66, 149.46, 153.42, 157.18. Anal. calcd. for C₁₇H₁₅N₅O₂S (353.40): C (57.78), H (4.28), N (19.82), S (9.07). Found: C (57.49), H (4.43), N (19.65), S (8.92) (%).

4-(4-Chlorobenzylidenehydrazino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (6c)

Brown crystals, Yield: 89 %, (0.61 g), mp: 192-193 °C. IR (ν , cm⁻¹): 3309 (NH), 3063 (CH-aromatic), 2932 (CH-aliphatic), 1620 (C=N) cm⁻¹. ¹H NMR (CDCl₃); (δ ppm): 1.80-1.93 (*m*, 4H, 2CH₂), 2.75-2.84 (*m*, 2H, CH₂), 2.84-2.92 (*m*, 2H, CH₂), 7.34-7.77 (*dd*, 4H-aromatic ring), 7.99 (*br s*, 1H, NH), 8.44 (*s*, 1H, N=CH), 8.64 (*s*, 1H, CH-pyrimidine). ¹³C NMR (CDCl₃); (δ ppm): 18.46, 22.52, 25.36, 26.78, 119.37, 128.65, 128.95, 131.31, 132.43, 133.20, 135.61, 144.42, 148.67,

153.43, 157.19. Anal. calcd. for C₁₇H₁₅CIN₄S (342.84): C (59.56), H (4.41), N (16.34), S (9.35). Found: C (59.43), H (4.55), N (16.20), S (9.51) (%).

4-(4-Hydroxybenzylidenehydrazino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidine (6d)

Bright brown crystals, Yield: 92 %, (0.59 g), mp: 265-266 °C. IR (ν, cm⁻¹): 3740-2100 (OH), 3340 (NH), 3030 (CH-aromatic), 2932 (CH-aliphatic), 1581 (C=N) cm⁻¹. ¹H NMR (DMSO-d₆); (δ ppm): 1.67-1.88 (*m*, 4H, 2CH₂), 2.65-2.80 (*m*, 2H, CH₂), 2.90-3.05 (*m*, 2H, CH₂), 6.77-7.82 (*dd*, 4H-aromatic ring), 7.73 (*br s*, 1H, OH), 8.28 (*s*, 1H, N=CH), 9.86 (*s*, 1H, CH-pyrimidine), 11.69 (*br s*, 1H, NH). ¹³C NMR (DMSO-d₆); (δ ppm): 22.48, 22.87, 25.11, 27.01, 115.87, 119.36, 127.02, 129.96, 131.30, 132.42, 144.41, 148.66, 153.42, 157.18, 159.64. Anal. calcd. for C₁₇H₁₆N₄OS (324.40): C (62.94), H (4.97), N (17.27), S (9.88). Found: C (63.22), H (4.84), N (17.39), S (9.95) (%).

General procedure for the synthesis of 3-(aryl)-8,9-di(alkyl)thieno[3,2-e][1,2,4]triazolo pyrimidines [(5a-5d) & (7a-7d)]

A mixture of arylidene-hydrazino-5,6-di(alkyl)thieno[2,3-d]pyrimidines [(4a-4d) & (6a-6d)] (2 mmol) and acetic anhydride (20 cm³) was refluxed for 15 hours. The progress

of the reaction was monitored by TLC (ethyl acetate: *n*-hexane, 1:1, v/v). After completion of the reaction, the excess amount of acetic anhydride was removed by distillation under reduced pressure then methanol (10-20 cm³) was added and the mixture was boiled for a few minutes and left to cool at 0 °C overnight. A solid was formed that was collected by filtration, dried and recrystallized from MeOH to achieve [(5a-5d) & (7a-7d)] good yield.

3-(4-Methylphenyl)-8,9-dimethylthieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (5a)

Bright brown crystals, Yield: 87 %, (0.51 g), mp: 196-197 °C. IR (ν, cm⁻¹): 3050 (CH-aromatic), 2916 (CH-aliphatic), 1605 (C=N) cm⁻¹. ¹H NMR (CDCl₃); (δ ppm): 2.50 (*s*, 3H, CH₃), 2.58 (*s*, 3H, CH₃), 2.80 (*s*, 3H, CH₃), 7.41-7.83 (*dd*, 4H-aromatic ring), 8.90 (*s*, 1H, CH-pyrimidine). ¹³C NMR (CDCl₃); (δ ppm): 13.29, 13.67, 21.58, 118.96, 123.46, 128.08, 129.04, 130.22, 131.27, 139.86, 141.17, 146.01, 146.69, 149.90. Anal. calcd. for C₁₆H₁₄N₄S (294.37): C (65.28), H (4.79), N (19.03), S (10.89). Found: C (65.41), H (4.65), N (19.15), S (10.79) (%).

3-(4-Nitrophenyl)-8,9-dimethylthieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (5b)

Brown crystals, Yield: 91 %, (0.59 g), mp: 286-287 °C. IR (ν, cm⁻¹): 3078 (CH-

aromatic), 2924 (CH-aliphatic), 1605 (C=N) cm^{-1} . ^1H NMR (CDCl_3); (δ ppm): 2.61 (*s*, 3H, CH_3), 2.81 (*s*, 3H, CH_3), 8.11-8.55 (*dd*, 4H-aromatic ring), 8.97 (*s*, 1H, *CH*-pyrimidine). ^{13}C NMR (CDCl_3); (δ ppm): 13.38, 13.81, 119.02, 124.06, 128.17, 129.12, 130.41, 132.28, 140.06, 141.10, 146.27, 147.02, 150.20. Anal. calcd. for $\text{C}_{15}\text{H}_{11}\text{N}_5\text{O}_2\text{S}$ (325.35): C (55.38), H (3.41), N (21.53), S (9.86). Found: C (55.22), H (3.49), N (21.41), S (9.72) (%).

3-(4-Chlorophenyl)-8,9-dimethylthieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (5c)

Bright brown crystals, Yield: 88 %, (0.55 g), mp: 251-252 °C. IR (ν , cm^{-1}): 3070 (CH-aromatic), 2920 (CH-aliphatic), 1605 (C=N) cm^{-1} . ^1H NMR (CDCl_3); (δ ppm): 2.55 (*s*, 3H, CH_3), 2.74 (*s*, 3H, CH_3), 7.40-8.30 (*dd*, 4H-aromatic ring), 8.85 (*s*, 1H, *CH*-pyrimidine). ^{13}C NMR (CDCl_3); (δ ppm): 13.36, 13.74, 120.17, 124.39, 128.22, 129.78, 129.87, 131.33, 136.70, 137.04, 145.00, 147.35, 148.75. Anal. calcd. for $\text{C}_{15}\text{H}_{11}\text{ClN}_4\text{S}$ (314.79): C (57.23), H (3.52), N (17.80), S (10.19). Found: C (57.11), H (3.65), N (17.88), S (10.11) (%).

3-(4-Acetoxyphenyl)-8,9-dimethylthieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (5d)

Bright brown crystals, Yield: 90 %, (0.61 g),

mp: 245-246 °C. IR (ν , cm^{-1}): 3078 (CH-aromatic), 2924 (CH-aliphatic), 1759 (C=O), 1605 (C=N) cm^{-1} . ^1H NMR (CDCl_3); (δ ppm): 2.34 (*s*, 3H, CH_3), 2.51 (*s*, 3H, CH_3), 2.69 (*s*, 3H, CH_3), 7.20-8.10 (*dd*, 4H-aromatic ring), 8.84 (*s*, 1H, *CH*-pyrimidine). ^{13}C NMR (CDCl_3); (δ ppm): 13.31, 13.69, 21.18, 120.05, 122.89, 123.51, 128.13, 129.84, 131.57, 136.46, 145.22, 147.18, 148.64, 152.40, 169.07. Anal. calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}_2\text{S}$ (338.38): C (60.34), H (4.17), N (16.56), S (9.48). Found: C (60.47), H (4.00), N (16.67), S (9.60) (%).

3-(4-Methylphenyl)-7,8,9,10-tetrahydro[1]benzothieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (7a)

Bright brown crystals, Yield: 88 %, (0.56 g), mp: 216-217 °C. IR (ν , cm^{-1}): 3032 (CH-aromatic), 2939 (CH-aliphatic), 1605 (C=N) cm^{-1} . ^1H NMR (CDCl_3); (δ ppm): 1.95-2.20 (*m*, 4H, 2CH_2), 2.49 (*s*, 3H, CH_3), 2.92-3.15 (*m*, 2H, CH_2), 3.25-3.45 (*m*, 2H, CH_2), 7.41-7.98 (*dd*, 4H-aromatic ring), 8.91 (*s*, 1H, *CH*-pyrimidine). ^{13}C NMR (CDCl_3); (δ ppm): 21.55, 22.23, 23.03, 25.58, 118.92, 123.06, 128.48, 129.02, 130.24, 131.87, 139.26, 141.11, 146.07, 146.99, 149.60. Anal. calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_4\text{S}$ (320.41): C (67.47), H (5.03), N (17.49), S (10.01). Found: C (67.59), H (4.95), N (17.63), S (9.92) (%).

3-(4-Nitrophenyl)-7,8,9,10-tetrahydro[1]benzothieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (7b)

Brown crystals, Yield: 92 %, (0.64 g), mp: 305-306 °C. IR (v, cm⁻¹): 3078 (CH-aromatic), 2932 (CH-aliphatic), 1605 (C=N) cm⁻¹. ¹H NMR (CDCl₃); (δ ppm): 1.95-2.12 (m, 4H, 2CH₂), 2.92-3.06 (m, 2H, CH₂), 3.24-3.45 (m, 2H, CH₂), 8.10-8.55 (dd, 4H-aromatic ring), 8.98 (s, 1H, CH-pyrimidine). ¹³C NMR (CDCl₃); (δ ppm): 22.20, 23.00, 25.57, 25.59, 119.12, 124.16, 128.27, 129.32, 130.14, 132.38, 140.16, 141.20, 146.17, 147.12, 150.30. Anal. calcd. for C₁₇H₁₃N₅O₂S (351.38): C (58.11), H (3.73), N (19.93), S (9.13). Found: C (58.24), H (3.60), N (20.05), S (9.25) (%).

3-(4-Chlorophenyl)-7,8,9,10-tetrahydro[1]benzothieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (7c)

Bright brown crystals, Yield: 87 %, (0.59 g), mp: 271-272 °C. IR (v, cm⁻¹): 3070 (CH-aromatic), 2932 (CH-aliphatic), 1605 (C=N) cm⁻¹. ¹H NMR (CDCl₃); (δ ppm): 1.92-2.10 (m, 4H, 2CH₂), 2.91-3.05 (m, 2H, CH₂), 3.23-3.40 (m, 2H, CH₂), 7.57-7.88 (dd, 4H-aromatic ring), 8.89 (s, 1H, CH-pyrimidine). ¹³C NMR (CDCl₃); (δ ppm): 22.20, 23.00, 25.57, 25.59, 118.91, 124.47, 129.80, 129.89, 130.25, 131.33, 137.07, 139.73, 144.97, 147.24, 149.77. Anal. calcd. for C₁₇H₁₃ClN₄S

(340.83): C (59.91), H (3.84), N (16.44), S (9.41). Found: C (60.05), H (3.95), N (16.34), S (9.54) (%).

3-(4-Acetoxyphenyl)-7,8,9,10-tetrahydro[1]benzothieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (7d)

Bright brown crystals, Yield: 91 %, (0.66 g), mp: 263-264 °C. IR (v, cm⁻¹): 3078 (CH-aromatic), 2924 (CH-aliphatic), 1759 (C=O), 1605 (C=N) cm⁻¹. ¹H NMR (CDCl₃); (δ ppm): 1.95-2.08 (m, 4H, 2CH₂), 2.38 (s, 3H, CH₃), 2.92-3.03 (m, 2H, CH₂), 3.25-3.37 (m, 2H, CH₂), 7.35-7.95 (dd, 4H-aromatic ring), 8.92 (s, 1H, CH-pyrimidine). ¹³C NMR (CDCl₃); (δ ppm): 21.18, 22.22, 23.02, 25.58, 118.92, 122.94, 123.60, 129.85, 130.25, 131.53, 139.59, 145.21, 147.18, 149.76, 152.48, 169.08. Anal. calcd. for C₁₉H₁₆N₄O₂S (364.42): C (62.62), H (4.43), N (15.37), S (8.80). Found: C (62.51), H (4.50), N (15.25), S (8.93) (%).

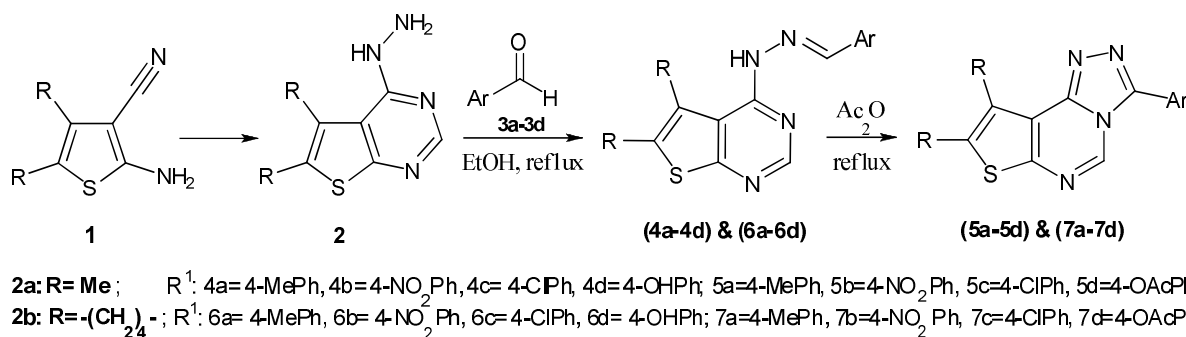
Results and discussion

The synthesis of compound **4** was begun according to the literature [18-22]. Treatment of hydrazine derivatives of **2a-2b** with aromatic aldehydes **3a-3d** in ethanol under refluxing condition resulted in the corresponding arylidene-hydrazino-5,6-di(alkyl)thieno[2,3-*d*]pyrimidines **4a-4d** and **6a-6d**, from which **6a-6d** were novel compounds (Scheme 1). The structures of **6a-**

6d were established from their spectral and microanalytical data, and in the case of **4a-4d**, the spectral data were correlated to those reported in the literature [20]. The IR spectrum of compound **6a** was devoid of the NH₂ absorption, but a new single absorption at 1620 cm⁻¹ (C=N) and absorption at 3255 cm⁻¹(NH) were seen. The ¹H NMR spectrum showed a singlet at 2.40 ppm for the methyl protons, two doublets for four aromatic protons at δ = 7.20-7.69 ppm, and finally a sharp signal at δ = 8.46 ppm for the proton on the imine. The ¹³C-NMR spectrum showed distinct resonances in agreement with the proposed structure. Similar spectral patterns were observed for the other derivatives of **6**.

The novel heterocyclic compounds **5a-5d** and **7a-7d** were readily prepared from the reaction of **4a-4d** and **6a-6d** with acetic

anhydride (Scheme 1). It is noteworthy to mention that in the case of **7d** and **9d**, the hydroxyl group was also acetylated due to the presence of an excessive amount of acetic anhydride in the reaction mixture. The structure of new compounds, **5a-5d** and **7a-7d**, was confirmed by spectral and microanalytical data. For example, the IR spectrum of compound **7d** displayed stretching absorptions at 3078 and 2924 cm⁻¹ for C-H stretching of aromatic and aliphatic, respectively. Also, the absorption bands at δ = 1759 (C=O) and 1605 cm⁻¹ (C=N) were observed. The ¹H NMR spectrum of **7d** in CDCl₃ showed a distinguished singlet at δ = 2.38 ppm for the methyl protons and two doublets for four aromatic protons at δ = 7.35-7.95 ppm. The ¹³C-NMR spectrum showed recognizable resonances in agreement with the proposed structure.



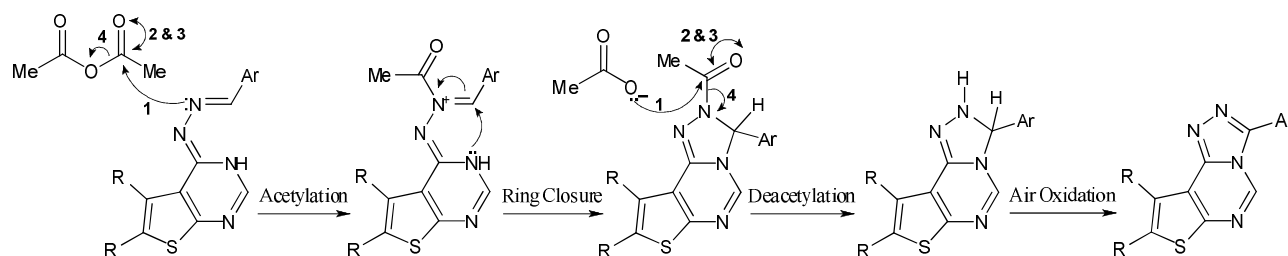
Scheme 1. Synthesis of 3-(aryl)-8,9-di(alkyl)thieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidines

The formation of the products **5a-5d** and **7a-7d** was assumed to proceed *via* the air

oxidation, because when the final reaction mixture [4a-4d and 6a-6d] was refluxed

under a nitrogen atmosphere, the reaction did not proceed to form these products. It is important to note that if the acetic anhydride is replaced with another solvent system, such as acetic acid, similar results are obtained, but the reaction yield is very low. Therefore, according to the proposed mechanism (Scheme 2), the major role of acetic anhydride in this reaction is that of a reagent that can facilitate the ring closure through the

acetylation of the Schiff base nitrogen in the first step. Presumably, ring closure occurs through the formation of an aminoral (a functional group or type of chemical compound that has two amine groups attached to the same carbon atom) that is then deacetylated to dihydro triazole by acetate anion and is finally oxidized to the triazole ring by atmospheric oxygen.



Scheme 2. The proposed mechanism for the synthesis of products

Conclusion

A practical synthetic approach for derivatives of thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine is described in high yields. The products were purified without using chromatographic methods. Further investigation is necessary to identify the medical property of the synthesized compounds. This general synthetic route can be used for the preparation of a wide range of isomeric triazoles using 2-aminothiophene-3-carboxamide bifunctional derivatives.

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