Microwave-Assisted Synthesis of Novel 5-Substituted-2,3-dihydroimidazo[1,2-c]thieno[3,2-e]pyrimidines

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Abstract: A novel, facile microwave-assisted route for the synthesis of imidazo[1,2-c]thieno[3,2-e]pyrimidines 4 in quantitative yields is reported. The intermediates 4-chlorothieno[2,3-d]pyrimidines 3 were synthesized under one-pot reaction conditions.

Key words: imidazo[1,2-c]thieno[3,2-e]pyrimidines, microwave irradiation, one-pot synthesis, 2-substituted-4-chlorothienopyrimidines

Bronchial asthma is a chronic debilitating disease, which in its severe forms can even threaten life. It is, in general, characterized by both broncho-constriction and airway inflammation which leads to bronchial hyper-responsiveness. 1 Although different classes of drugs have been employed, methylxanthines continue to enjoy significant status as drugs of choice in asthma therapy, despite a narrow therapeutic index.

Currently, new tricyclic heterocyclic compounds designed on the basis of the xanthine skeleton are being investigated as possible bronchodilators with a wider margin of safety. While reviewing the recent perspectives in the design of antiasthmatic agents,2 we observed that different angularly fused heterocyclic ring systems like imidazoquinolines,3 imidazolothienodihydropyrimidines,4 benzimidazolquinazolines,5,6 imidazoquinazolines,5 and benzimidazolopyridopyrimidines8 have been identified as potentially useful compounds. The encouraging bronchodilatory activity of these compounds led us to attempt the isosteric replacement of benzene by thiophene.9

The source of regulation of energy has not normally received proper recognition in synthetic organic chemistry. Microwaves have the capacity to alter that, because of the fact that the energy is directly transferred and concentrated in the reaction mixture and also because of the convenience in performing organic transformation with microwave apparatus.10 In recent years, reagents impregnated on mineral solid support and assisted by microwaves has gained popularity in the synthesis of various heterocyclic compounds like quinoxalinones,11 triazoles,12 quinolines,13,14 benzofurans,15 quinazolines,16 etc. This is probably due to the enhanced selectivity, improved reaction rates, associated ease of manipulation, and above all, the eco-friendliness of this method. Although the synthesis of a few imidazothienopyrimidines and their pharmacological activity is described in literature,17,18 we wish to report here a simple and novel synthetic route involving a microwave-assisted cyclization using silica gel as solid support for 5-substituted-2,3-dihydroimidazo[1,2-c]8,9-dimethyl/tetrahydrobenzol[6]thieno[3,2-e]pyrimidines 4. The two-step synthesis of 2-substituted-4-chlorothieno[2,3-d]pyrimidines 2a–j has been reported in the literature.19 However, we have prepared them in a single pot reaction from 2-amino-3-carbethoxy-4,5-disubstituted/tetrasubstituted thiophenes 1 using nitriles to give the intermediates 2-substituted-4-hydroxythieno[2,3-d]pyrimidines; subsequent heating under reflux in phosphorous oxychloride gave compounds 2a–j in 40%–60% yields (Scheme).

Equimolar mixtures of 2-substituted-4-chlorothieno[2,3-d]pyrimidines 2a–j, aminoethanol and triethylamine in dioxygen were heated for eight hours to give 2-substituted-4-hydroxythieno[2,3-d]pyrimidines 3a–j in high yields (80–90%). The IR spectrum of compounds 3a–j showed a broad peak at 3400–3500 cm⁻¹ for hydroxy group, and a peak at 3200–3400 cm⁻¹ for secondary amino group, which indicated formation of the expected products. In the NMR spectrum, an exchangeable (D₂O) amino signal at δ = 6.0 ppm, and two triplets for the methylene protons of aminoethanol in the range of δ = 3.5–4.5 ppm confirmed the product formation. Further, the mass spectrum exhibited a prominent molecular ion peak (48–100%) and the absence of isotopic peak (M+2) confirming the loss of chloride in all the derivatives.

Compounds 3a–j underwent cyclization under microwave irradiation to result in the target compounds 4a–j in quantitative yields (81–88%). The disappearance of peaks corresponding to amino and hydroxyl groups in the IR spectra, and signals at δ = 6.0 ppm and 4.8 ppm corresponding to NH and OH, respectively, in their NMR spectra inferred product formation. The four dihydroimidazolyl methane protons of the corresponding 5-aryl/heteroaryl derivatives 4f, 4g, and 4j appeared as two triplets at δ = 4.0–4.5 ppm (Scheme). Interestingly, the same protons of the corresponding 5-alkyl/aryalkyl derivatives 4a–e, 4h, and 4i exhibited an upfield shift (δ = 3.5–4.0 ppm). The mass spectrum of 4a–j revealed the...
molecular ion (M⁺) appearing as base peak (100%). Based on the spectral data, the compounds, 4a–j were characterized as 5-substituted-2,3-dihydropyrimidazolo[1,2-c]8,9-dimethyl/tetrahydrobenzol[f]thieno[3,2-e]pyrimidines.

Thus, the present microwave-assisted route, besides being advantageous in simple reaction conditions and easy work-up procedures, has resulted in improved yields over the conventional methods. 17

Mps (uncorrected) were determined in open capillaries on a Thermonik melting point apparatus, Mumbai, India. IR spectra (KBr) were recorded on a Perkin Elmer spectrophotometer (577 model). 1H NMR spectra were recorded on a Bruker WM-400 spectrometer (Bruker, Flawil, Switzerland); chemical shifts are given in ppm relative to TMS as internal standard. Mass spectra (EI-MS) were recorded on a Jeol D-300 spectrometer at 70 eV. Elemental analyses were performed on Carlo-Erba 1108 elemental analyser (Heraeus, Hanau, Germany). Microwave heating was carried out using a domestic oven, 600 Watt, BPL 7070M (Mumbai, India).

2-Substituted-4-chlorothieno[2,3-d]pyrimidines (2); One-Pot General Procedure
A stream of dry HCl was passed through a mixture of 2-amino-3-ethoxycarbonyl-4,5-dimethyl/tetramethylene thiophene 1 (100 mmol) and alkyl/aryl nitriles (100 mmol) in dioxane (20 mL) for 3 h. The reaction mixture was flushed with N₂ and excess nitrile was distilled off under vacuum. Phosphorous oxychloride (15.3 g, 100 mmol) was added to the residue, and the mixture was heated under reflux for 3 h. After cooling, excess phosphorous oxychloride was distilled off under vacuum. Phosphorous oxychloride (15.3 g, 100 mmol) was added to the residue, and the mixture was heated under reflux for 3 h. After cooling, excess phosphorous oxychloride was distilled off under vacuum. Phosphorous oxychloride (15.3 g, 100 mmol) was added to the residue, and the mixture was heated under reflux for 3 h. After cooling, excess phosphorous oxychloride was distilled off under vacuum.

2-Substituted-4-[(2-hydroxy)ethyl]aminothieno[2,3-d]pyrimidines (3); General Procedure
A mixture of 2-substituted-4-chlorothieno[2,3-d]pyrimidines (10 mmol), aminoethanol (0.61 g, 10 mmol) and Et₃N (11 mmol) was refluxed in dioxane (20 mL) for 8 h. The reaction mixture was poured onto crushed ice and neutralized with 5% NaHCO₃. The separated solid was filtered, and dried to give compounds 2a–j, which were used directly for next step without further purification.

2-Methyl-4-[(2-hydroxy)ethyl]amino-5,6,7,8-tetrahydrobenzo(b)thieno[2,3-d]pyrimidine (3a)
Yield: 2.13 g (90%).

Scheme a) R₁ = R₂ = R₃ = CH₃; b) R₁ = R₂ = -(CH₂)₄-, R₃ = CH₃; c) R₁ = R₂ = -(CH₂)₄-, R₃ = C₆H₅; d) R₁ = R₂ = -(CH₂)₄-, R₃ = n-C₆H₄; e) R₁ = R₂ = CH₃, R₃ = -(CH₂)₄-; f) R₁ = R₂ = CH₃, R₃ = n-C₆H₄; g) R₁ = R₂ = -(CH₂)₄-, R₃ = C₆H₅; h) R₁ = R₂ = CH₃, R₃ = -(CH₂)₄-; i) R₁ = R₂ = -(CH₂)₄-, R₃ = CH₃.
2-Propyl-4-[(2-hydroxy)ethyl]amino-5,6-dimethylthieno[2,3-d]pyrimidine (3f)
Yield: 2.30 g (87%).

H NMR (CDCl₃): δ = 1.06–1.18 (t, 3 H, CH₃-), 1.71–1.88 (sextet, 2 H, CH₂CH₂CH₂-), 2.51 (s, 6 H, CH₃-), 2.98–3.11 (t, 2 H, J = 7.0, CH₂CH₂CH₂-), 3.83–3.91 (t, 2 H, J = 11.2, -CH₂OH), 4.13–4.22 (t, 2 H, J = 10.5, -NHCH₂-), 4.46–4.81 (br s, 1 H, OH, D₂O exchangeable), 5.65–7.82 (br s, 1 H, NH, D₂O exchangeable).

MS: m/z (%): 265 (100) [M⁺].

Anal. Calcd for C₁₇H₁₉N₃OS: C, 58.84; H, 7.22; N, 15.83. Found: C, 60.08; H, 7.25; N, 16.10.

2-Phenyl-4-[(2-hydroxy)ethyl]amino-5,6-dimethylthieno[2,3-d]pyrimidine (3g)
Yield: 2.51 g (84%).

H NMR (CDCl₃): δ = 1.23–1.35 (t, 3 H, CH₃), 2.42 (s, 3 H, CH₃-5), 2.67 (s, 3 H, CH₃-6), 3.56–3.81 (m, 4 H, CH₂-2, -3). 3.83–3.93 (t, 2 H, J = 9.5, -NHCH₂-3), 4.58–5.00 (br s, 1 H, OH, D₂O exchangeable), 5.67–6.13 (br s, 1 H, NH, D₂O exchangeable), 7.22–7.45 (m, 5 H, C₆H₅).

MS: m/z (%): 339 (68) [M⁺].


2-Pyrindyl-4-[(2-hydroxy)ethyl]amino-5,6,7,8-tetrahydrobenzo-[d]thieno[2,3-d]pyrimidine (3j)
Yield: 2.60 g (80%).

H NMR (CDCl₃): δ = 1.68–1.89 (m, 4 H, CH₂-6, -7), 2.67–2.98 (m, 4 H, CH₂-5, -8), 3.80–3.91 (t, 2 H, J = 10.0, -CH₂OH), 3.96–4.11 (t, 2 H, J = 9.4, -CH₂NH₃), 4.56–4.97 (br s, 1 H, OH, D₂O exchangeable), 5.59–5.67 (br s, 1 H, NH, D₂O exchangeable), 8.21–9.10 (m, 4 H, C₆H₄N).

MS: m/z (%): 326 (58) [M⁺].


5-Substituted-2,3-dihydroimidazo[1,2-c][8,9-dimethyltetra]thieno[3,2-e]pyrimidines (4); General Procedure
5-Substituted-4-[(2-hydroxy)ethyl]amino thieno[2,3-d]pyrimidines 3a-j (10 mmol) and phosphorous oxychloride (0.153 g, 10 mmol) were adsorbed onto silica gel, placed in a tube, and subjected to microwave heating for 1 min in a domestic oven (600 Watt, BPL 700T); then allowed to reach r.t. The solid was extracted with CHCl₃ (10 mL) and the organic layer was washed successively with H₂SO₄ (5%), NaHCO₃, and distilled water. The dried solution was concentrated to dryness and the crude products were purified by column chromatography on silica gel (CHCl₃, CH₃OH, methanol, ethyl acetate, etc.) to give final compounds 4a-j in 80–90% yields.

5-Methyl-2,3-dihydroimidazo[1,2-c][8,9-dimethylthieno[3,2-e]pyrimidine (4a)
Yield: 1.92 g (88%).

H NMR (CDCl₃): δ = 1.81–1.94 (m, 4 H, CH₂-6, -7), 2.69–2.85 (t, 2 H, J = 7.2, CH₂-8), 3.65–3.80 (m, 4 H, -CH₂-2, -3).

MS: m/z (%): 219 (100) [M⁺].

Anal. Calcd for C₁₉H₂₁N₃OS: C, 60.24; H, 5.97; N, 19.16. Found: C, 60.54; H, 6.20; N, 19.35.

5-Methyl-2,3-dihydroimidazo[1,2-c][8,9,10,11-tetrathieno[3,2-e]pyrimidine (4b)
Yield: 2.13 g (87%).

H NMR (CDCl₃): δ = 1.81–1.94 (m, 4 H, CH₂-6, -7), 2.35 (s, 3 H, CH₃), 2.69–2.85 (t, 2 H, J = 7.2, CH₂-8), 3.65–3.80 (m, 4 H, -CH₂-2, -3).

MS: m/z (%): 245 (100) [M⁺].

Anal. Calcd for C₁₉H₂₁N₃OS: C, 63.64; H, 6.16; N, 17.13. Found: C, 63.75; H, 6.25; N, 17.35.

5-Ethyl-2,3-dihydroimidazo[1,2-c][8,9,10,11-tetrahydrobenzo-[β]thieno[3,2-e]pyrimidine (4c)
Yield: 2.25 g (87%).

H NMR (CDCl₃): δ = 1.23–1.35 (t, 3 H, J = 7.4, CH₂CH₂-), 1.73–2.01 (m, 4 H, CH₂-6, -7), 2.58–3.93 (m, 6 H, CH₂CH₂-, CH₂-8, -11), 3.90–4.21 (m, 4 H, CH₂-2, -3).

MS: m/z (%): 259 (100) [M⁺].

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5-Propyl-2,3-dihydroimidazo[1,2-c]8,9,10,11-tetrahydrobenzo-1,3-thieno[3,2-e]pyrimidine (4d)

Yield: 2.56 g (85%).

Mp 142–144 °C.

Yield: 2.32 g (85%).

Mp 150–153 °C.

Yield: 2.64 g (86%).

Mp 150–153 °C.

Yield: 2.56 g (87%).

Mp 122–124 °C.

Yield: 2.27 g (85%) (Lit. yield: 77%).

Mp 72–74 °C (Lit. mp 78–79 °C).

1H NMR (CDCl₃): δ = 1.75–2.03 (m, 2 H, C₆H₅-CH₂), 2.45–2.67 (m, 4 H, CH₂-9, -10), 2.70–2.96 (m, 4 H, CH₂-8, -11), 3.62–3.71 (t, 2 H, J = 10.4, CH₂-2), 3.85–3.96 (t, 2 H, J = 10.4, CH₂-3), 7.12–7.34 (m, 5 H, C₆H₅).

MS: m/z (%) = 321 (100) [M⁺].


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