Bioorganic & Medicinal Chemistry Letters 19 (2009) 3392–3397

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis of 4-substituted pyrido[2,3-*d*]pyrimidin-4(1*H*)-one as analgesic and anti-inflammatory agents

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ARTICLE INFO

Article history:
Received 30 January 2009
Revised 23 April 2009
Accepted 12 May 2009
Available online 18 May 2009

Keywords:
Pyrido[2,3-*d*]pyrimidines
Anti-inflammatory
Analgesic activity
Ulcerogenicity

ABSTRACT

4-Substituted-pyrido[2,3-*d*]pyrimidin-4(1*H*)-ones **4a–c** were synthesized by oxidation of 4-substituted-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-ones **3a–c** which were in turn prepared from arylidenemalononitriles **1a–c** and 6-aminothiouracil **2**. The reactivity of compounds **4a–c** towards some reagents such as formamide, carbon disulfide, urea, thiourea, formic and acetic acids were studied. All the synthesized compounds were characterized by spectroscopic means and elemental analysis. Compound **4c** exhibited 64% and 72% analgesic activity. Also, compound **4b** showed 50% and 65% anti-inflammatory activity. Interestingly these compounds showed one-third of ulcer index of the reference aspirin and diclofenac.

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for the treatment of acute and chronic inflammation, pain and fever. However, long-term clinical usage of NSAIDs is associated with significant side effects such as gastrointestinal lesions, bleeding, and nephrotoxicity. Therefore, discovery of new safer anti-inflammatory drugs represents a challenging goal in a research area.[1–3] In our ongoing medicinal chemistry research program, we found that pyrimidines and condensed pyrido[2,3-*d*]pyrimidines exhibit potent central nervous system (CNS) activity, including analgesic, anti-inflammatory and anticonvulsant behavior.[4,5] Pyridopyrimidines with 7-(6-morpholin-4-ylpyridin-3-yl)-substitutions are reported to possess significant analgesic, anti-inflammatory and anticonvulsant activitiy.[6,7] We have earlier documented that some lead 2-pyrazolyl-pyridopyrimidines,[8] 2-thioxopyridipyrimidines, 2-thioxopyrimidoquinolines exhibited good analgesic and anti-inflammatory properties.[9,10]

Both pyrimidine and heterocyclic uracil structural analogues such as 2-thioxo-pyrido[2,3-*d*]pyrimidin-4-one and pyrrolo[2,3-*d*]pyrimidines have shown a wide range of biological applications. The use of Sangivamicine or Toyocamicine as antibiotics is well known, and the antiviral application of their analogues has been reported.[11] Besides, other pyrido[2,3-*d*]pyrimidine ring system is present in a number of biologically active compounds which includes antipyretic,[12] bactericides,[13] medicinal,[14] and antitumoral,[15] antihistaminic,[16] diuretic,[17,18] activities and can even be used in the treatment of neuronal diseases.[19]

In this work, we present the synthesis of several pyrido[2,3-*d*]pyrimidine derivatives from 6-aminouracil and arylidenemalononitrile derivatives. These reactions have two points of interest: first, to obtain new derivatives with potential biological applications, and second to explore into the reactivity of 6-aminouracil with electron-deficient alkenyl compounds; these reactions, as we previously reported in the case of electron-deficient α,β-unsaturated dienophiles,[20–22] could evolve through two different ways via a Michael addition at the C(5) atom of the pyrimidine ring.[23] The synthesis of pyrido[2,3-*d*]pyrimidine derivatives from 6-aminouracil and ketones, DMFDMA,[24] α,β-unsaturated ketones,[25] and via Mannich bases (arylalkanone),[26] has been reported. In our case we have used arylidenemalononitrile derivatives **1** as electron-deficient reactants with 6-aminouracil **2**.

6-Aminothiouracil **2** was reacted with an equimolar amount of arylidenemalononitrile **1a–c** according to the reported procedure.[20] We performed this reaction under dry conditions and refluxing for long time in order to prevent the formation of the 1,4-dihydropyrido[2,3-*d*]pyrimidin-4-ones **3a–c**, thus it was not necessary to purified the reaction mixture by column chromatography. The most probable mechanism to afford pyridopyrimidines **3**, which is shown in Scheme 1, involves two steps, the first a Michael addition reaction of the pyrimidine ring C-5 carbon atom to **1** to give, via zwitterionic structure **I**, the intermediate **II**, which then undergoes ring closing resulting in product **3**. The prolonged duration reaction is required to furnish the oxidized form **4a–c**.

Various 7-amino-6-cyano-5-sbstituted-2-thioxopyrido[2,3-*d*]pyrimidin-4(1*H*)-ones (**4a–c,** Scheme 2) were synthesized by condensation of arylidenemalononitriles **1a–c** and 6-aminothiouracil **2** as reported in the literature.[9] 6-Aminothiouracil on

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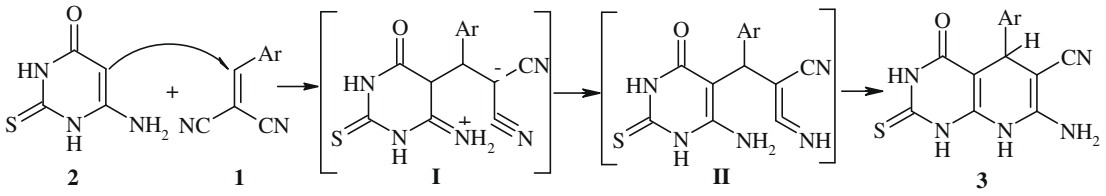
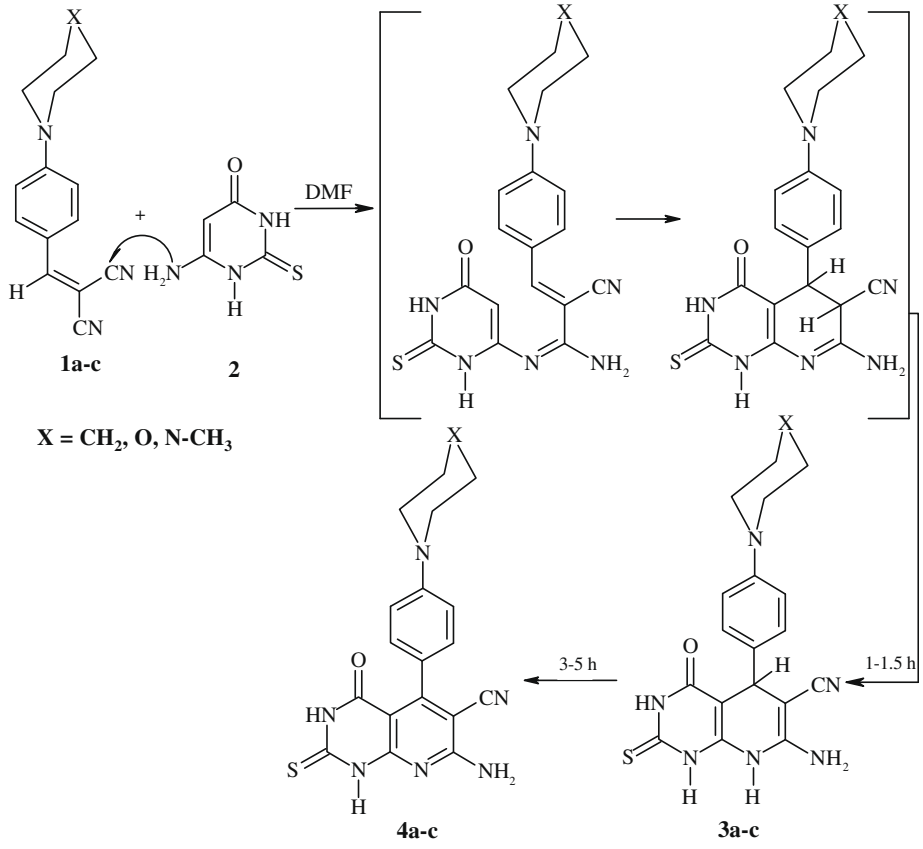
doi:10.1016/j.bmcl.2009.05.044



Scheme 1. Mechanism postulated for the reaction of 6-aminouracil and arylidenemalononitrile.



Scheme 2. Reaction of 6-aminouracil with arylidenemalononitriles **1a**–**c**.

refluxing with arylidenemalononitrile **1a** in dimethylformamide for 3–5 h gave condensed product **4a** after usual workup. Compound **4a** was purified by crystallization from dioxane to give pure 7-amino-6-cyano-5-[4-(1-piperidinyl)-phenyl]-2-thioxopyrido [2,3-*d*]pyrimidin-4(1*H*)-ones (**4a**) in 78% yield. ^{1}H NMR (500 MHz; DMSO-d_6) of **4a** showed signals at δ 1.56 (br s, 6H, piperidinyl 3 CH_2), 3.25 (br s, 4H, piperidinyl 2 NCH_2), 6.88 (AA′BB′, 2H, Ar–*H*, *J* = 8.6 Hz), 7.10 (AA′BB′, 2H, Ar–*H*, *J* = 8.6 Hz), 7.62 (br s, 2H, NH_2), 8.45 (br s, H, N*H*), 12.05 (br s, H, N*H*). Also, ^{13}C NMR (500 MHz; DMSO-d_6) of **4a** showed signals at δ 23.86, 25.09, 25.81 (3 CH_2), 48.15, 48.67 (2 NCH_2), 107.68 (CN), 113.63, 114.83, 115.64, 117.12, 120.83, 121.92, 129.18, 151.4, 153.07, 167.30, 160.98 (11 signals for 11 sp^2 carbon), 172.7 (C=O), 183.05 (C=S). IR spectra show absorption band at 3450 (NH's), 2218 (CN) and 1680 (C=O) cm^{-1}. Spectral data of **4a** fully support the structure assigned to it. Similarly the others –(4-morpholinyl) and –(4-methylpiperazinyl), that is, **4b,c** (Scheme 2) were synthesized and purified by crystallization. Spectral and analytical data of compounds **4a–c** reported in Reference and notes of this Letter fully support the structures assigned to them.

Compounds **4a–c** as a typical β-enaminonitrile derivative, reacted with formamide and aliphatic acids namely, formic and acetic acids, afforded 5-substituted-pyrido[2,3-*d*:6,5-*d*]dipyrimidine-4,6-dione derivatives (**5a–c**, **7a–f**), respectively. The IR spectra of compounds **5** displayed absorption bands around 3500 cm^{-1} (NH, NH_2) and around 1685 cm^{-1} for carbonyl group, However the IR spectra of compounds **7** displayed absorption bands around 3450 cm^{-1} (NH) and around 1670, 1685 cm^{-1} for two carbonyl groups. The ^{1}H NMR (DMSO-d_6) spectrum of **5b** showed the signals at δ 3.29 (t, 4H, morpholinyl 2 NCH_2, *J* = 5.0 Hz), 3.90 (t, 4H, morpholinyl 2 OCH_2, *J* = 5.0 Hz), 6.98 (AA′BB′, 2H, Ar–*H*, *J* = 8.7 Hz), 7.18 (AA′BB′, 2H, Ar–*H*, *J* = 8.7 Hz), 7.75 (br, s, 2H, NH_2), 8.06 (s, 1H, pyrimidine-*H*), 8.65 (br s, H, NH), 12.30 (br s, H, N*H*). Also, the ^{1}H NMR (DMSO-d_6) spectrum of compound **7b** as an example showed signals at 1.60 (br, s, 6H, piperidinyl 3 CH_2), 2.26 (s, 3H, pyrimidine-CH_3), 3.32 (br s, 4H,