Research article

One-pot multi-component synthesis of new bis-pyridopyrimidine and bis-pyrimidoquinolone derivatives

Milad Masoumi, Mohammad Bayat*, Fahimeh Sadat Hosseini

Department of Chemistry, Faculty of Science, Imam Khomeini International University, Qazvin, Iran

ARTICLE INFO

Keywords:
Organic chemistry
Multi-component reaction
Bis pyridopyrimidine
Pyrimidoquinolone
Aminothiouracils

ABSTRACT

A variety of bis-heterocycles such as bis(pyrimido[4,5-b]quinolone), bis(chromeno[3′,4′:5,6]pyrido[2,3-d]pyrimidine), bis(pyrido[2,3-d:6,5-d′]dipyrimidine), and bis(benzo[g]pyrimido[4,5-b]quinolone) derivatives were synthesized via one-pot, multi-component reaction of various 6-aminouracils or 6-aminothiouracils, terephthalaldehyde, and CH-acids such as 4-hydroxycoumarin, dimedone, 2-hydroxy-1,4-naphthoquinone, barbituric acid, and thiobarbituric acid in EtOH as a solvent at reflux. The mild conditions, fast rate of reaction, absence of catalyst, different functional group compatibility, simple operation and work-up involving no chromatographic process, are worth mentioning.

1. Introduction

Multi-component reactions (MCRs) have regarded as essential tools for the preparation of biologically active heterocyclic compounds because of their productivity, convergence, simple procedures, and easy execution [1]. The development of MCRs and their applications for the one-pot synthesis of various useful heterocyclic compounds are of remarkable interest in the running research articles [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13].

Heterocyclic scaffolds are widely distributed in nature and used in structure-based drug design [14]. Therefore, considerable attention has been paid to develop novel approaches to the synthesis of heterocycles [15, 16, 17, 18, 19, 20, 21, 22]. Among them pyridopyrimidine derivatives have attracted wide attention due to their broad biological activities including anticancer [23], antiviral [24], antiallergic [25], anti-HIV [26], anti-inflammatory [27], and antifolate [28] properties; and pyrimidoquinoline derivatives are of importance because of their interesting and diverse pharmacological properties; such as, antimicrobial, anti-inflammatory, anticancer [29], antiallergic [30], anti-HIV, antimalarial [31], and antibacterial [32] activities. Some biologically important pyridopyrimidines [33] and pyrimidoquinolines [34] are shown in Figure 1.

Also some bis-heterocyclic compounds exhibit a wide range of biological and pharmacological activities and have received extensive attention in recent decades [35, 36]. In 2013 Nefzi and Murru prepared a new library of oxazol-thiazole bis-heterocycles by a solution and solid-phase parallel synthesis methodology in good to excellent yields. Also in 2016 Montano et al. reported synthesis of novel unsymmetrical bis-heterocycles containing the imidazo[2,1-b]thiazole or the benzo[d]imidazo[2,1-b]thiazole frameworks bound with quinolone, chromone, or julolidine via an acid-free Groebke-Blackburn-Bienayme reaction (GBBR) under microwave-heating conditions in good to excellent yields.

As part of our continuing interest in the preparation of novel heterocyclic compounds and due to importance of pyridopyrimidine and pyrimidoquinoline derivatives as substructures in a wide range of drug-like compounds, herein we developed synthesis of new bis-pyridopyrimidines and bis-pyrimidoquinolones by one-pot, multi-component reaction of diverse 6-aminouracils, terephthalaldehyde, and CH-acids in EtOH as a solvent at reflux without a catalyst.

2. Experimental

2.1. Reagent and apparatus

The diverse 6-aminouracils, 6-aminothiouracil, terephthalaldehyde, 4-hydroxycoumarin, dimedone, 2-hydroxy-1,4-naphthoquinone, barbituric acid, thiobarbituric acid, and solvents were purchased from Sigma-Aldrich chemical company and were used as received without further purification. Melting points were measured with an electrothermo 9100 apparatus. Infrared (IR) spectra were obtained on a Bruker Tensor 27 spectrometer. Mass spectra recorded with an Agilent 5975C VL MSD with Triple-Axis Detector operating at an ionization potential of 70 eV.

* Corresponding author.
E-mail addresses: m.bayat@sci.ikiu.ac.ir, bayat_mo@yahoo.com (M. Bayat).

https://doi.org/10.1016/j.heliyon.2020.e05047
Received 1 April 2020; Received in revised form 29 May 2020; Accepted 21 September 2020
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2.2. General procedure for the synthesis of product 4a

A mixture of 6-aminothiouracil (2 mmol, 0.286 g), terephthalaldehyde (1 mmol, 0.134 g), 2-hydroxy-1,4-naphthoquinone (2 mmol, 0.348 g) and 10 mL EtOH in a 50 mL flask was stirred at reflux for 5 min. Upon completion as monitored by TLC (ethyl acetate/n-hexane, 1:1), the reaction mixture was cooled to room temperature and filtered to give the crude product. The resulting solid product was washed with EtOH to give pure product 4a in 76% yields.

2.3. Spectral data

2.3.1. 7,7′-(1,4-Phenylene)bis(10-hydroxy-9,11,12-tetrahydro-6H-chromeno[3′,4′:5,6]pyrido[2,3-d]pyrimidine-6,8(7H)-dione) (4a)

White solid: M.p.: 300–302 °C, yield: 0.510 g (76%). IR (KBr) (νmax/cm−1): 3340, 3220, 1680, 1650, 1220. MS (EI, 70 eV): m/z (%): 378 (19), 295 (24), 155 (100), 120 (39), 82 (88), 57 (38).1H NMR (300 MHz, DMSO-d6): δ 2.24 (2H, s, 2CH), 6.91 (2H, s, Ar), 7.25 (2H, s, Ar), 12.80 (2H, s, 2NH).13C NMR (62.8 MHz, DMSO-d6): 35.7 (CH), 87.5 (CC=O), 116.6 (C=O), 174.1 (C=S).

2.3.2. 7,7′-(1,4-Phenylene)bis(11,12-dihydro-6H-chromeno[3′,4′:5,6]pyrido[2,3-d]pyrimidine-6,8(7H)-dione) (4b)

White solid: M.p.: 305–307 °C, yield: 0.435 g (68%). IR (KBr) (νmax/cm−1): 3320, 3200, 1687, 1650, 1215. MS (EI, 70 eV): m/z (%): 251 (5), 162 (74), 120 (100), 92 (88), 63 (30).1H NMR (300 MHz, DMSO-d6): δ 7.81 (24H, m, Ar), 13.98 (4H, s, 4NH).13C NMR (62.8 MHz, DMSO-d6): δ 118.4, 125.0, 125.6, 127.7, 133.7, 136.7, 153.3, 155.7, 164.6, 165.9 (C=O), 166.5 (C=O), 174.1 (C=S).

2.3.3. 7,7′-(1,4-Phenylene)bis(9,11-dimethyl-11,12-dihydro-6H-chromeno[3′,4′:5,6]pyrido[2,3-d]pyrimidine-6,8,10(7H,9H)-trione) (4c)

White solid: M.p.: 331–333 °C, yield: 0.496 g (79%). IR (KBr) (νmax/cm−1): 3300, 1710, 1680, 1230. MS (EI, 70 eV): m/z (%): 378 (100), 295 (16), 266 (46), 240 (24), 143 (45), 97 (29), 83 (63), 69 (49), 57 (52).1H NMR (300 MHz, DMSO-d6): δ 0.99 (12H, s, 4CH3), 1.05 (12H, s, 4CH3), 2.24–2.39 (16H, m, 4CH3), 5.32 (4H, s, 4CH2), 6.57 (4H, s, Ar), 6.91 (4H, s, Ar), 12.01 (4H, s, 4NH).13C NMR (62.8 MHz, DMSO-d6): δ 118.4, 125.0, 125.6, 127.7, 133.7, 136.7, 153.3, 155.7, 164.6, 165.9 (C=O), 166.5 (C=O), 174.1 (C=S), 195.8 (C=O).

2.3.4. 5,5′-(1,4-Phenylene)bis(8,8-dimethyl-2-thioxo-2,3,7,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H)-trione) (4d)

Figure 1. Some biologically important pyridopyrimidines and pyrimidoquinolines.
Table 1. One-pot, multi-component synthesis of bis-heterocycles 4a-j.

| Entry | Aminouracil | CH-acid | Product | Time (min) | Yield (%) |
|-------|-------------|---------|---------|-----------|-----------|
| 1     | 6-Aminothiouracil | 2-Hydroxy-1,4-naphthoquinone | 4a | 5 | 76 |
| 2     | 6-Aminouracil | 4-Hydroxycoumarin | 4b | 5 | 68 |
| 3     | 6-Amino-1,3-dimethyluracil | 4-Hydroxycoumarin | 4c | 5 | 73 |
| 4     | 6-Aminothiouracil | Dimedone | 4d | 10 | 79 |
| 5     | 6-Amino-1,3-dimethyluracil | Dimedone | 4e | 10 | 85 |
| 6     | 6-Aminouracil | Dimedone | 4f | 30 | 65 |
| 7     | 6-Aminouracil | Thiobarbituric acid | 4g | 5 | 90 |
| 8     | 6-Aminouracil | Barbituric acid | 4h | 20 | 70 |
| 9     | 6-Amino-1,3-dimethyluracil | Barbituric acid | 4i | 20 | 72 |
| 10    | 6-Amino-1,3-dimethyluracil | 2-Hydroxy-1,4-naphthoquinone | 4j | 10 | 69 |

* Various 6-aminouracils (2 mmol), terephthalaldehyde (1 mmol), and CH-acids (2 mmol) were used in EtOH at reflux, without any catalyst.

Scheme 1. Synthetic scheme for the product 4.

Scheme 2. The two diastereoisomers of 4c.

Scheme 3. Proposed mechanism for the formation of product 4.
3. Results and discussion

In the current study, synthesis of new functionalized bis-heterocycles (such as bis(pyridyl)[4,5-b]quinolone), bis(chromeno[3′,4′;5,6]pyrido[2,3-d]pyrimidine), bis(pyrido[2,3-d;6,5-d′]pyrimidine), and bis(benzo[g]pyrimido[4,5-b]quinolone) derivatives) 4 via one-pot, multi-component reaction of various 6-aminouracils or 6-aminothiouracils, 1, terephthalaldehyde 2, and CH-acids (such as 4-hydroxycomoramin, dimedone, 2-hydroxy-1,4-naphthoquinone, barbituric acid and thio-barbituric acid) 3 in EtOH as a solvent at reflux without any catalyst is described (Scheme 1).

We tested the general scope of this reaction by varying the structure of the 6-aminouracils and CH acids 3. The reaction was completed after 5–30 min, under the same reaction conditions to give corresponding bis-heterocycles 4 in good to high yields (65–90%). The results are shown in Table 1.

The structures of products 4a-j were assigned from their IR, mass, 1H NMR, and 13C NMR spectra (see the Supporting Information). The 1H NMR spectrum of 4a exhibited a singlet at δ 5.52 ppm arising from the CH proton, multiplets for aromatic protons in the range of δ 6.74–7.79 ppm as well as three singlets for the NH protons at δ 12.13, 12.45, and 13.49 ppm. Moreover, the 13C NMR spectrum agreed with the proposed structure 4a. Resonances due to CH, CC = ONH, CC = ON, CC = O, C=O, C=O, and C=S groups appeared at δ 35.8, 92.6, 106.3, 165.9, 166.5, and 174.1 ppm, respectively. Also the mass spectrum of 4a was in agreement with the proposed structure (see the supplementary material).

Compounds 4 have two stereogenic centers, and therefore two diastereoisomers are expected. In some products, one of which is prepared in a highly stereo controlled fashion (for example 4a). Also the 1H- and 13C NMR spectra of the products 4c, 4d, 4f, 4i, 4j indicated the presence of only one diastereoisomer. Their NMR data can be extracted from the mixture of the two diastereoisomers and the 1H and 13C NMR spectra of only one diastereoisomer are given. We did not obtain the good NMR spectra of these samples because of its insolubility in any solvent. All products are very insoluble compounds. The two diastereoisomers of 4c is shown in Scheme 2.

A proposed mechanism for the synthesis of 4 is shown in Scheme 3. To form the product 4, it is possible that initially the formation of the adduct 5 occurs through Knoevenagel condensation between terephthalaldehyde 2 (1 mmol) and barbituric acid (2 mmol). Then the Knoevenagel adduct 5 undergoes Michael addition with 6-aminouracil (1 mmol) to give 6. This intermediate is converted into 7 through the imine-enamine tautomerization to prepare product 4.

4. Conclusion

The present study described a simple route for the synthesis of new bis-pyrido[4,5-b]quinoline and bis-pyrimidoquinoline derivatives by the one-pot, multi-component condensation of 6-aminouracils, terephthalaldehyde, and CH-acids in EtOH as a solvent at reflux. The notable advantages of the present work are easy accessibility of reactants, simplicity of the experimental procedures, high atom economy, absence of catalyst, short reaction time, and good product yields. In addition, various functional groups that exist in these heterocycles lead to the pharmaceutical/biological activities of them.

Declarations

Author contribution statement

Mohammad Bayat: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Fahimeh Sadat Hosseini: Analyzed and interpreted the data; Wrote the paper.
Milad Masoumi: Performed the experiments.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interest statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2020.e05047.

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