Research Article

Ramadan Ahmed Mekheimer, Alaa M. Hayallah, Moustafa Sherief Moustafa, Saleh Mohammed Al-Mousawi*, Mohamed Abd-Elmonem, Sara M. Mostafa, Fatma A. Abo Elsoud, and Kamal Usef Sadek*

Microwave-assisted reactions: Efficient and versatile one-step synthesis of 8-substituted xanthines and substituted pyrimidopteridine-2,4,6,8-tetraones under controlled microwave heating

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Abstract: We report herein a simple and efficient one-step synthesis of 8-substituted xanthines and substituted pyrimidopteridine-2,4,6,8-tetraones via reaction of 1,3-dimethyl-5,6-diaminouracil **1** with activated double bond systems **2** assisted by controlled microwave irradiation. The obtained heterocycles are privileged biologically relevant scaffolds.

Keywords: 8-substituted xanthines, pyrimidopetridines, 5,6-diaminouracil, green synthesis

1 Introduction

Uracil derivatives are interesting heterocycles which possess a wide spectrum of biological and pharmaceutical importance [1–6]. Among uracil derivatives, xanthines, pteridines, and pyrimidopteridines have attracted great attention for their unique promising biological activities. Polyfunctionally substituted xanthines are privileged heterocycles acting as adenosine receptor antagonists via four different specific G protein-coupled receptors (A_1, A_{2A}, A_{2B}, A_3) [7,8]. Activity of such receptors proceeds via inhibition or stimulation of adenylate cyclase [9–12]. Although nature offers the necessary needs for human being, naturally occurring xanthines (e.g. caffeine, theophylline) (Figure 1) are weak non-selective alpha 2D-adrenoceptors antagonists [13,14]. It is well documented that replacing the hydrogen atom at C-8 in xanthine with a large substituent and a suitable *N*-substitution resulted in increasing both affinity and selectivity toward ARs as antagonists [15]. Xanthines have shown a wide range of bioactivities that include treatment of bronchial asthma [16], cardiovascular problems [17], anticancer and anticancer adjuvants [18,19], kidney protectives, antifibrotic, antiglaucoma, and neuroprotective agents [20,21], as well as various biological activities [22].

Naturally occurring or synthesized pteridine derivatives have structural affinity to coenzymes and ability of chemical transformations [23]. They have been reported to possess a wide range of biological activities such as anti-fungal [24], anti-microbial [25], anti-allergic [26], immune-suppressive [27], anti-inflammatory [28], antitumor [29], antiproliferative [30], and anti-bacterial [31]. Moreover, several naturally occurring pteridines act as pigments, vitamins, and alkaloids [24,32]. Examples of biologically active xanthines and pteridines are illustrated in Figure 2.

Despite wide pharmaceutical applications and belongingness to purine family, xanthine-based research has not taken up full pace resulting in very few synthesized xanthine-based molecules. The most prominent reason for this is unfavorable synthesis methodologies such as ring closure synthetic mechanism and classical condensation route for the generation of new derivatives [12,33–36].

* **Corresponding author: Saleh Mohammed Al-Mousawi,** Department of Chemistry, Faculty of Science, Kuwait University, P. O. Box 12613, Safat 13060, Kuwait, e-mail: saleh.almousawi@yahoo.com
* **Corresponding author: Kamal Usef Sadek,** Chemistry Department, Faculty of Science, Minia University, Minia 61519, Egypt, e-mail: kusadek@yahoo.com
Ramadan Ahmed Mekheimer, Mohamed Abd-Elmonem, Sara M. Mostafa: Chemistry Department, Faculty of Science, Minia University, Minia 61519, Egypt
Alaa M. Hayallah: Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Deraya University, Minia, Egypt; Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt
Moustafa Sherief Moustafa: Department of Chemistry, Faculty of Science, Kuwait University, P. O. Box 12613, Safat 13060, Kuwait
Fatma A. Abo Elsoud: Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Deraya University, Minia, Egypt

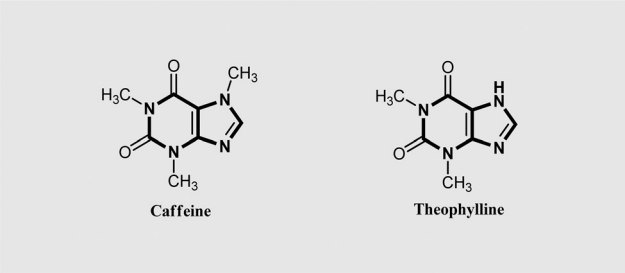


Figure 1: Caffeine and theophylline as xanthine derivatives.

A number of synthetic routes for the synthesis of 8-substituted xanthines have focused on a two-step protocol through the reaction of *N*-mono or dialkylated 5,6-diaminouracil with aldehydes in EtOH/AcOH under reflux for several hours and subsequent oxidative cyclization of the formed imines[5-(arylidene or alkylideneamino)-6-aminouracil] precursors utilizing a variety of catalysts such as $SOCl_2$ or $FeCl_3$ under refluxing conditions from 12 h to 2 days, *meta*-chloroperoxybenzoic acid in MeOH or (bromodimethyl)sulfonium bromide (BDMS) [9,37–39].

An alternative route for the synthesis of 8-substituted xanthines has been developed that relied on the coupling of diaminouracil derivative with acids utilizing several reagents such as 3-(3-dimethylaminopropyl)-carbodiimide hydrochloride [37], (1-[1-(cyano-2-ethoxy-2-oxoethylideneaminooxyl)-dimethylamino-morpholino]-methylene) methanaminium hexafluorophosphate [15], and subsequent cyclization of the formed 6-amino-5-carboxamidouracil. Several reagents for cyclization step were used such as sodium hydroxide [37] and hexamethyldisilazane in the presence of ammonium sulfate and heating under reflux [38]. Another route involving the activation of the carboxylic acid by conversion to acid chloride was alternatively used, but it possesses several drawbacks such as long reaction times for amide formation, moderate yields, less stability of acid chlorides, and an additional step for conversion of acids to acid chlorides utilizing non-environmentally hazardous chlorinating agents [40].

A one-step synthesis of 8-substituted xanthines has been developed via stoichiometric coupling of aldehydes with 1,3-diaminouracil in acetonitrile catalyzed by 10 mol% of BDMS and heating under reflux for 5 h [39].

A less extensively studied synthesis of 8-substituted xanthine scaffolds involves the reaction of 8-bromoxanthine derivatives with various nucleophiles [41–44]. Palladium-catalyzed direct alkenylation of 8-unsubstituted xanthine has been recently investigated by Liang et al. [45] utilizing bulky (2-bromoethene-1,1,2-triaryl)tribenzene and as a result of low efficiency of reaction it proceeds only in high boiling point solvent as DMF or diethylene glycol dimethyl ester (diglyme) at 150°C with moderate yields.

To the best of our knowledge, a carful inspection of literature reports has revealed a very few reports for the synthesis of 1,3-dialkyl substituted pteridine derivatives. In 1954, Blicke and Godt [46] have developed the synthesis of 1,3-dimethyllumazine derivatives via the reaction of 1,3-dimethyl-5,6-diaminouracil with glyoxal, oxalic

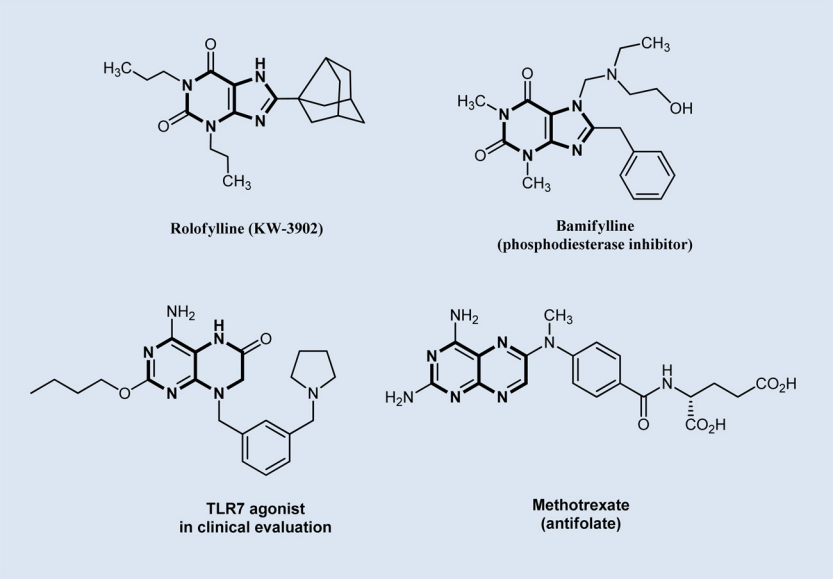


Figure 2: Biologically active xanthines and pteridines.

acid, diacetal, and benzil in 30%, 58%, 64%, and 80% yields. Moreover, the corresponding 1,3-dimethyl-7-aminolumazine could be synthesized through reaction of diaminouracil derivatives with formaldehyde and hydrocyanic acid followed by treatment of the produced 5-cyanomethylamino derivative with KOH/MeOH and H_2O_2. Not very recently, El-Sabbagh et al. [47] have reported a chemoselective reaction of 6-amino-1,3-dimethyl-5-(substituted methylidene)aminouracils with ortho esters. With triethyl orthoformate, the corresponding 6-substituted pteridines were the only isolable products, however, with triethyl orthoacetate or triethyl orthobenzoate, the corresponding xanthines were obtained.

Disadvantage aspects of such protocols are the use of external oxidants, hazardous solvents, expensive catalysts, high temperature, long reaction times, by-product formation, and low yields.

Recently, a convenient one-step synthesis of 8-substituted xanthines has been developed by Kaushik et al. [12] that relied on the reaction of 1,3-dimethyl-5,6-diaminouracil with aryl/cycloaryl/heteroaryl aldehydes in CH_3CN/H_2O (9:1) promoted with *N*-bromosuccinimide utilizing catalytic amount of 2,2′-azoisobutyronitrile at ambient temperature.

Taking into consideration such disadvantages and in continuation to our efforts to perform green and efficient one-pot synthesis of biologically relevant heterocycles assisted by controlled microwave heating [48–52], we have developed a one-pot synthesis of 8-substituted xanthines and substituted pyrimidopteridines via reaction of 1,3-dimethyl-5,6-diaminouracil with a variety of electrophilic reagents in pyridine under controlled microwave heating. It has been reported that factors modulating synthetic selectivity are temperature, solvent, catalyst, and type of reaction control [53–57].

2 Materials and methods

All chemicals were purchased from Merck or Aldrich Companies. The ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) were run in a Bruker DPX instrument (δ ppm). Mass spectra were measured by using VG Autospec Q MS 30 and MS 9 (AEI) spectrometer, with EI (70 eV) mode. Melting points were recorded in a Gallenkamp melting point apparatus and are uncorrected. All reactions were monitored by thin layer chromatography (TLC) with 1:1 ethyl acetate/petroleum ether as an eluent and were carried out until starting materials were completely consumed.

2.1 General procedure for the reaction of 1,3-dimethyl-5,6-diaminouracil 1 with arylidene malononitriles and β-nitrostyrenes 2a–e

Equimolar amounts of **1** (1 mmol) and **2** (1 mmol) in pyridine (10 mL) were heated under reflux in a Milestone Microwave Labstation at 120°C for 20 min. The solvent was removed under reduced pressure, and the solid product was isolated by filtration and recrystallized from ethanol to afford analytically pure samples.

2.2 General procedure for the reaction of 1,3-dimethyl-5,6-diaminouracil 1 with phenyl isothiocyanate 6

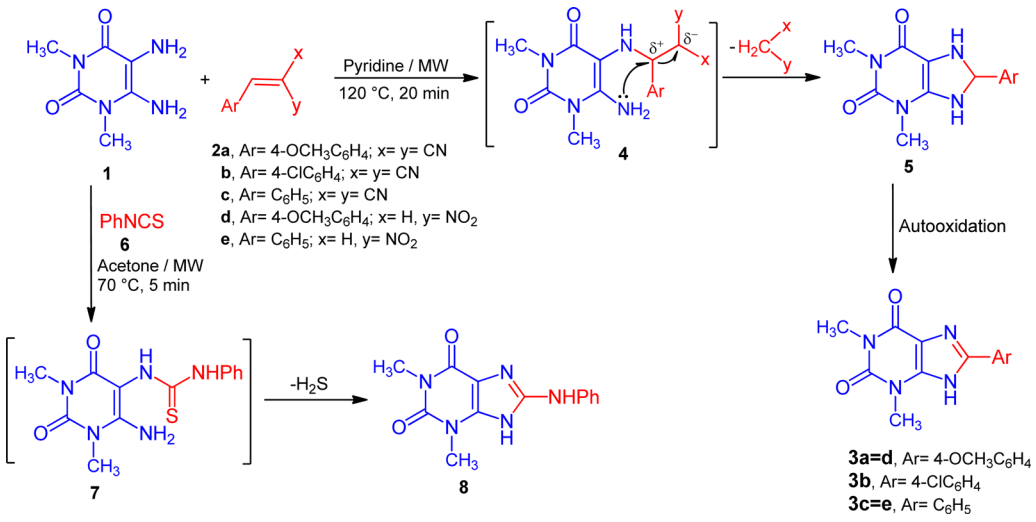
Equimolar amounts of **1** (1 mmol) and **6** (1 mmol) in acetone (10 mL) were heated under reflux at 70°C under microwave heating for 5 min. The reaction product isolated upon cooling to room temperature was collected by filtration and recrystallized from ethanol.

2.3 General procedure for the reaction of 1,3-dimethyl-5,6-diaminouracil 1 with enaminones 9a–c

Equimolar amounts of **1** (1 mmol) and **9** (1 mmol) in pyridine (10 mL) were heated under reflux in a Milestone Microwave Labstation at 120°C for 20 min. The solvent was removed under reduced pressure, and the solid product was isolated by filtration and recrystallized from ethanol to afford **11** and the rest quantity from DMF to afford **12**.

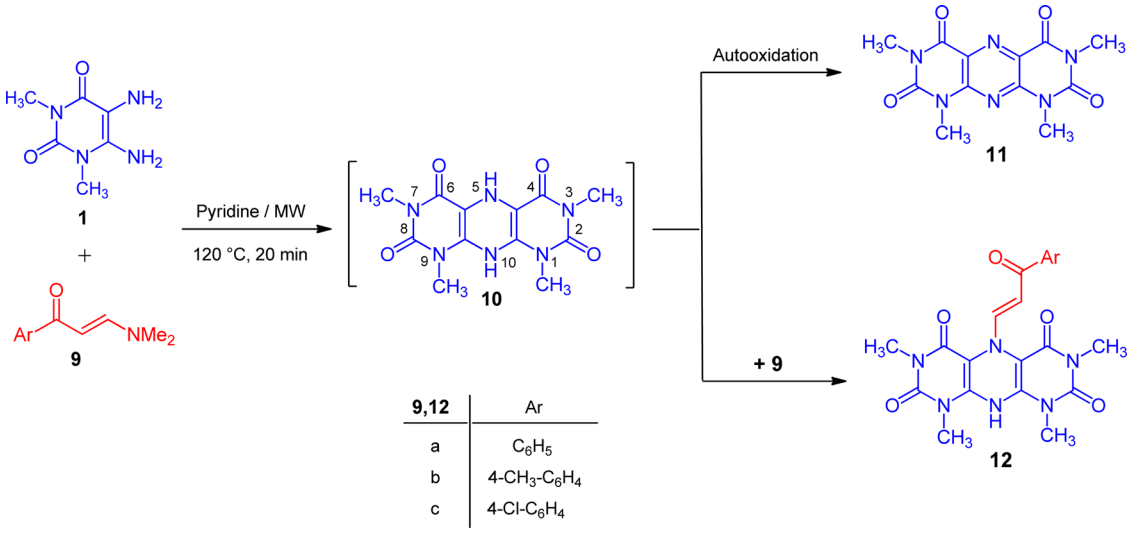
3 Results and discussion

With the initial aim of optimizing the reaction conditions, we began our study by treating 1,3-dimethyl-5,6-diaminouracil **1** with 2-(4-methoxybenzylidene)malononitrile **2a**. Under catalyst-free conditions, the reaction did not ensue when water, ethanol, acetonitrile, and dioxane were used as solvents even under reflux for prolonged heating, indicating the crucial role of the catalyst in this reaction. Pyridine was found to be the best reaction



Scheme 1: Synthesis of 8-substituted xanthines.

medium for this reaction as it has dual role as a solvent and a basic catalyst, which reduces the number of synthetic steps. Thus, heating under reflux the aforementioned mixture in pyridine for 3 h led to the formation of product **3a** in 60% yield. In order to increase energy efficiency, the reaction was promoted by microwave irradiation at 120°C for 20 min. We are delighted to obtain **3a** in 92% yield (Scheme 1). The structure of **3a** could be established based on analytical and spectral data. Mass spectrum of **3a** showed [M^+] peak at 286.01 (100%). The IR spectrum revealed the absence of NH_2 and CN functions. ^{1}H NMR showed a broad singlet at δ = 13.56 ppm due to purine NH proton and two doublets at δ = 8.08 and 7.06 ppm, which were assigned to four aromatic protons, in addition to three singlet signals at δ = 3.32, 3.48, and 3.82 ppm for two *N*-methyl groups and one methoxy group, respectively. ^{13}C NMR spectrum was compatible with the structure of the reaction product **3a**. With this promising result in hand, we investigated the influence of the aryl substrate in arylidene malononitrile **2** on the nature of the reaction product and its rate of formation. Thus, the reaction of **1** with **2b–c** under the same experimental reaction conditions afforded the corresponding 8-substituted xanthines **3b–c**, in high yields, irrespective of the aryl substrate. Although it has been previously reported [58] that the reaction of **1** with arylidene malononitriles afforded the corresponding pyrimidodiazepines, this is not favored in our case.



Scheme 2: Synthesis of substituted pyrimidopteridine-2,4,6,8-tetraones.

Table 1: Comparison of ecoscale of literature reported synthesis of xanthines

Procedure	Reaction time	Yield (%)	Ecoscale
Traver et al. [41] KO^tBu/THF/90°C/flow	20 min	21	54
Nagavelli et al. [42] CuI/THF	6–8 h	77	72.5
Bashirova et al. [44] KOH/H_2O/EtOH	90 min	91	86.5
Liang et al. [43] Pd2/dbal3 (5 mol%) Nixantphos (10 mol) t-BuONa (3 eq.)	24 h	77	88.5
Our protocol			
Pyridine/MW (**3a**)	20 min	92	92
Pyridine/MW (**3b**)	20 min	90	90
Pyridine/MW (**3c**)	20 min	88	88
Acetone/MW (**8**)	5 min	88	88

In order to explore the generality of such a protocol, the reaction of **1** with diversity activated double bond systems was examined. Thus, reaction of **1** with β-nitrostyrene **2d** and **2e**, under the same experimental conditions, yielded solid products which confirmed to be **3a** and **3c**, respectively, based on analytical and spectral data.

The reaction was proposed to proceed via Michael addition of electron-rich (C5-NH_2) in **1** to the activated double bond in **2a–e** producing Michael adduct **4** followed by cyclization through nucleophilic attack of (C6-NH_2) lone pair to the positively charged (C1) carbon and malononitrile or nitric acid elimination – as cyclization by elimination is more thermodynamically feasible – and subsequent aromatization (Scheme 1). In support of such mechanism, we performed the reaction of **1** with benzaldehyde under the same experimental reaction conditions, and the corresponding Schiff base was the only isolable product.

We extended the scope of our study to the reaction of **1** with phenyl isothiocyanate **6** and the reaction was promoted by microwave heating in acetone at 70°C for 5 min. A product of molecular formula $C_{13}H_{13}N_5O_2$ was obtained and confirmed to be the corresponding xanthine derivative **8**. The structure proposed for **8** was established based on analytical and spectral data and detection of H_2S liberation (Scheme 1).

On the other hand, the reaction of **1** with enaminones **9** proceeded via unexpected route. Thus, as example, the reaction of **1** with **9a** in pyridine promoted by microwave irradiation afforded two reaction products **11** and **12a** in 1:4 molar ratios. Compound **11** showed [M^+] peak at 303.99 (100%). ^{1}H NMR revealed two singlet signals at δ = 3.59 and 3.32 ppm integrated for four *N*-methyl functions. ^{13}C NMR revealed four carbonyl functions and four *N*-methyl groups. Based on these data, the corresponding 1,3,7,9-tetramethylpyrimido[4,5-*g*]pteridine-2,4,6,8-(1*H*,3*H*,7*H*,9*H*)-tetraone was established for the product. Compound **11** was suggested to be formed through dimerization of **1** to **10** via elimination of ammonia followed by auto-oxidation, under these reaction conditions. However, the second isolated product **12a** resulted from nucleophilic attack of the more reactive NH (no. **5**) in **10** to the more electrophilic center in enaminone **9** with elimination of dimethylamine. It is worth mentioning that the formation of dimer **11** was hypothetically proposed previously by Teimouri et al. [59] upon refluxing **1** in EtOH/*p*-TSA (10 mol%). To the best of our knowledge, this is the first reported isolation of such compound **12** (Scheme 2).

To evaluate the greenness of the reaction, we estimated the EcoScale [60] for our protocol concerning the one-step synthesis of 8-substituted xanthines and compared with other recently reported synthetic methods (Table 1).

4 Conclusion

In summary, the methods described above represent an efficient, simple, and convenient protocols for microwave assisted reaction for the synthesis of various 8-substituted xanthines and substituted pyrimidopteridine-2,4,6,8-tetraones. In some cases, the isolation of the reaction intermediate shed further light as the mechanism of its formation.

Supplementary information: The supplementary information file contains characterization data for compounds **3a**, **3b**, **3c**, **8**, **11**, **12a**, **12b**, and **12c**.

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Author contributions: Ramadan A. Mekheimer: visualization and methodology; Alaa M. Hayallah: methodology and resources; Moustafa M. Moustafa: formal analysis and data curation; Saleh M. Al-Mousawi: funding acquisition and resources; Mohamed Abd-Elmonem: writing – review and editing; Sara M. Mostafa: writing – review and editing; Fatma A. Abo-Elsoud: software and investigation; and Kamal U. Sadek: supervision and writing – original draft.

Conflict of interest: The authors state no conflict of interest.

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