Journal of Chemistry and Technologies, 2021, *29*(4), 504-511

Journal of Chemistry and Technologies

pISSN 2663-2934 (Print), ISSN 2663-2942 (Online).

journal homepage: http://chemistry.dnu.dp.ua

UDC 678.686

SILICA SULFURIC ACID CATALYZED SYNTHESIS OF PYRIMIDINES AND NEW FUSED PYRIMIDO-PURINES *via* BIGINELLI REACTION

Ichrak Bouguessa[1], Mohamed Dehamchia[2*], Samir Bayou[1], Abdelkrim Gouasmia[3] and Zine Régaïnia[4,5].

[1] El Oued University, PO Box 789, 39000, Algeria.
[2]El Oued University, PO Box 789, 39000, Algeria
[3] Laarbi Tebessi University, Constantine Road, Tebessa, 12000, Algeria
[4]Mohamed Cherif Messadia University, Souk Ahras 41000, Algeria
[5] Badji Mokhtar University PO Box 12 Annaba-Algeria.

Received 5 October 2021; accepted 15 November 2021; available online 21 January 2022

Abstract

Studies on strategies for the synthesis of pyrimidine derivatives have generated great interest in the chemistry of heterocyclic compounds due to the pharmacological properties of pyrimidines. The most common method for pyrimidine skeleton synthesis is the traditional synthetic approach using the multicomponent Biginelli reaction. A convenient and efficient one-pot three-component synthesis of a new class of pyrimido[1,2-g]purine-7,8-dicarboxylate, pyrimido[2,1-e]purine-8,9-dicarboxylate, and pyrimido[1,6-a]pyrimidine-3,4-dicarboxylate under Biginelli reaction conditions has been described. These compounds were prepared by condensation of sodium diethyl oxalacetate, substituted aromatic aldehyde, and nucleobase (adenine, guanine, or cytosine) using hydrochloric acid, mild heterogeneous solid silica sulfuric acid (SSA), or p-toluenesulfonic acid (TsOH) as a catalyst. The chemical structures of the synthesized compounds were confirmed using infrared spectroscopy (IR), proton (1H) nuclear magnetic resonance (NMR), and mass spectrometric analysis.

Keywords: Dihydropyrimidine-2-one; purines; multicomponent reaction; Biginelli reaction; silica sulfuric acid; nucleobases

КАТАЛІТИЧНИЙ СИНТЕЗ ПІРИМІДИНІВ І НОВИХ СКЛАДНИХ ПІРИМІДО-ПУРИНІВ ШЛЯХОМ РЕАКЦІЇ БІГІНЕЛЛІ

Ірак Бугесса[1], Мохамед Дехамчія[2*], Самір Байю[1], Абделькрім Гуасмія,[3] Зіне Регаінія[4, 5]

[1] Університет Ель-Уед, поштова скринька 789, 39000, Алжир.
[2] Університет Ель-Уед, поштова скринька 789, 39000, Алжир.
[3] Університет Лаарбі Тебессі, Костянтинівська дорога, Тебесса, 12000, Алжир
[4] Університет Мохаммеда Шерифа Мессадія, Сук Ахрас 41000, Алжир
[5] Університет Баджи Мохтар, поштова скринька 12 Аннаба-Алжир.

Стратегії синтезу піримідинових похідних викликають великий інтерес у дослідників в області хімії гетероциклічних сполук. Найбільш поширеним методом синтезу піримідинового скелета є традиційний підхід з використанням багатокомпонентної реакції Біджінеллі. У даній роботі описано зручний та ефективний однореакторний трикомпонентний синтез нового класу піримідо[1,2-g]пурин-7,8-дикарбоксилату, піримідо[2,1-e]пурин-8,9-дикарбоксилату та піримідо[1,6-a]піримідин-3,4-дикарбоксилату в умовах реакції Бігінеллі. Ці сполуки були отримані шляхом конденсації діетилоксалацетату натрію, заміщеного ароматичного альдегіду і азотистої основи (аденіну, гуаніну або цитозину) з використанням хлоридної кислоти, м'якого гетерогенного твердого кремнезему сірчаної кислоти (SSA) або п-толуолсульфонової кислоти (TsOH) в якості каталізатора. Хімічні структури синтезованих сполук були підтверджені за допомогою інфрачервоної спектроскопії(ІК), протонного (1H) ядерного магнітного резонансу (ЯМР) і мас-спектрометричного аналізу.

Ключові слова: Дигідропіримідин-2-он; пурини; багатокомпонентна реакція; реакція Бігінеллі; сірчанокислий кремній; азотисті основи.

**Corresponding author: e-mail: mohchar5@yahoo.fr*

doi: 10.15421/jchemtech.v29i4.241661

Journal of Chemistry and Technologies, 2021, *29*(4), 504-511

КАТАЛИТИЧЕСКИЙ СИНТЕЗ ПИРИМИДИНОВ И НОВЫХ СЛОЖНЫХ ПИРИМИДО-ПУРИНОВ ПУТЕМ РЕАКЦИИ БИГИНЕЛЛИ

Ичрак Бугесса[1], Мохамед Дехамчия[2*], Самир Байю[1], Абделькрим Гуасмия[3] и Зине Регаиния[4,5].

[1] Лаборатория VTRS, Химический факультет, Университет Эль-Уэд, почтовый ящик 789, 39000, Алжир.

[2] Лаборатория биоразнообразия и применения биотехнологий в сельскохозяйственной среде, Биологический факультет, Университет Эль-Уэд, почтовый ящик 789, 39000, Алжир.

[3] Лаборатория органических материалов и гетерохимии, Химический факультет, Университет Лаарби Тебесси, Константиновская дорога, Тебесса, 12000, Алжир

[4] Университет Мохамеда Шерифа Мессадия, Факультет наук и технологий Сук Ахрас 41000, Алжир

[5] Лаборатория прикладной органической химии (LCOA), группа гетероциклической химии, Факультет наук, кафедра химии, Университет Баджи Мохтар, почтовый ящик 12, Аннаба-Алжир.

Аннотация

Стратегии синтеза пиримидиновых производных вызывают большой интерес у иследователей в области химии гетероциклических соединений. Наиболее распространенным методом синтеза пиримидинового скелета является традиционный подход с использованием многокомпонентной реакции Биджинелли. В данной работе описан удобный и эффективный однореакторный трехкомпонентный синтез нового класса пиримидо[1,2-g]пурин-7,8-дикарбоксилата, пиримидо[2,1-e]пурин-8,9-дикарбоксилата и пиримидо[1,6-a]пиримидин-3,4-дикарбоксилата в условиях реакции Бигинелли. Эти соединения были получены путем конденсации диэтилоксалацетата натрия, замещенного ароматического альдегида и азотистого основания (аденина, гуанина или цитозина) с использованием хлоридной кислоты, мягкого гетерогенного твердого кремнезема серной кислоты (SSA) или п-толуолсульфоновой кислоты (TsOH) в качестве катализатора. Химические структуры синтезированных соединений были подтверждены с помощью инфракрасной спектроскопии (ИК), протонного (1H) ядерного магнитного резонанса (ЯМР) и масс-спектрометрического анализа.

Ключевые слова: Дигидропиримидин-2-он; пурины; многокомпонентная реакция; реакция Бигинелли; сернокислый кремний; азотистые основания.

Introduction

The pyrimidine skeleton (1,3-diazine) exists in many natural products including DNA, RNA, thiamine (Vitamin B1), and alloxan [1-2] (Figure 1). It is also present in many useful synthetic therapeutic agents such as the human immunodeficiency virus (HIV) drug zidovudine (AZT) [3] and barbiturates [4] (Figure 1). Moreover, pyrimidines contain heterocycles, and their fused analogues have been reported to possess a wide variety of biological activities [5] that include anticancer [6], antifungal [7-8], antileishmanial [9], antimicrobial [10-11], anticonvulsant [12], antiviral [13], antioxidant [14], anti-inflammatory [15], and antidiabetic activities [16].

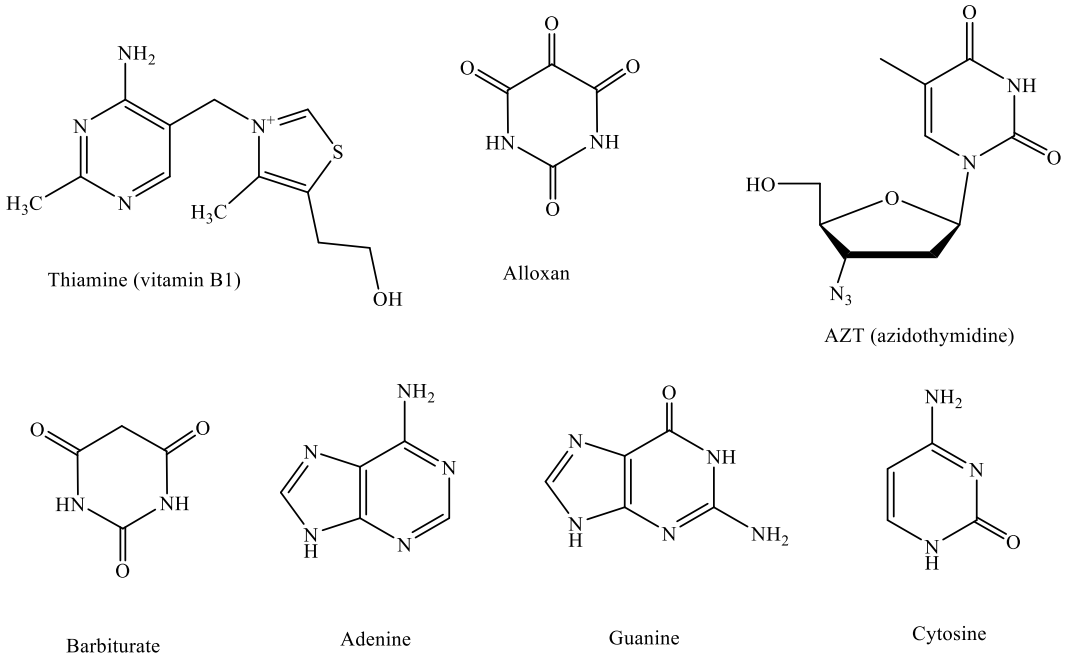

Fig. 1. General structures of natural and synthetic pyrimidines derivatives.

Therefore, studies on strategies for the synthesis of pyrimidine derivatives have received great interest in heterocyclic chemistry. In this case, several traditional and non-conventional strategies have been developed for the synthesis of dihydropyrimidin-2-ones derivatives [17–24]. The most common method for the synthesis of pyrimidine skeleton is the typical, traditional and

useful synthetic approach via the Biginelli multicomponent reaction [25]. This reaction provides a ready access to a broad range of pyrimidinones derivatives with various biological activities [6–16].

Within the last two decades, the Biginelli pyrimidines synthesis has attracted considerable attention, and many developments and modifications have been reported. In this regard, various homogeneous and heterogeneous catalysts have been utilized, including H_2SO_4 based on silica gel or alumina [26], silica sulfuric acid (SSA) [27], polymer Zeolite (TS-1) [28], and HZSM-5 [29].

To continue our interest in the synthesis of biologically fused heterocyclic compounds [30-31], we report herein an efficient one-pot multicomponent reaction for the synthesis of novel fused pyrimido-purines by cyclocondensation of nucleobases (adenine, guanine, and cytosine) (Fig. 1), diethyloxalacetate, and substituted aromatic aldehydes in the presence of silica sulfuric acid (SSA) as a heterogeneous acidic catalyst under Biginelli reaction conditions [32-34].

Experimental

Instrumental techniques

^{1}H NMR spectra were recorded on a Bruker Avance 400 spectrometer at ambient temperature. The chemical shifts (δ) are reported in ppm and were measured in dimethylsulfoxide (DMSO-d_6) relative to tetramethylsilane (TMS, δ= 0.0 ppm), which was used as the internal standard. ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer (101 MHz) with complete proton decoupling. Infrared spectra were recorded on an Agilent Cary 630 FTIR spectrometer. ESI-MS spectra were obtained on Mariner (ESI TOF) and API 365 (ESI 3Q) mass spectrometers using methanol as a spray solvent. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60Å F254 precoated plates. Melting points (Mp) were determined using a Reichert Thermovar or an Electrothermal 9200 apparatus and were not corrected. All solvents and reagents were commercially available and were used without further purification.

Chemical synthesis. Synthesis of silica sulfuric acid

The silica sulfuric acid was prepared in accordance with a reported procedure [35-37]. Briefly, 60.0 g of silica gel were charged into a 500 mL suction flask that was equipped with a constant pressure dropping funnel containing chlorosulfonic acid (23.3 g, 0.2 mol) and a gas inlet tube for conducting HCl gas over an adsorbing solution (*i.e*. H_2O). The chlorosulfonic acid was slowly added for 30 min at room temperature. After the addition was complete, the reaction was allowed to proceed for 30 min. SSA was obtained as a white solid.

General procedure for the synthesis of pyrimidine-4,5-dicarboxylates derivatives 1a-c using SSA as a catalyst. A mixture of equimolar amounts of sodium diethyl oxalacetate, 1,3-diamines (urea, sulfamide or thiourea), aromatic aldehyde, and 10 mol % of SSA in ethanol was stirred and heated at 90°C for 3 h. After the reaction was completed (followed by TLC), the mixture was cooled to room temperature with ice water. The precipitate was filtered off, washed with two portions of water and several times with hexane and petroleum ether to remove traces of aldehyde. The SSA catalyst was separated from the product after dilution of the reaction mixture with CH_2Cl_2. Recrystallization from ethanol/water (50:50) at a low temperature or chromatography on silica gel (CH_2Cl_2, MeOH 95:5) provided the pure expected product in 54%-58% yields.

Diethyl 6-phenyl-2-oxo-1,2,3,6-tetrahydro-pyrimidine-4,5-dicarboxylate **(1a)** [32]. This compound was obtained as a pale-yellow solid in 55% yield. Mp 172-174 °C (reported 173-175°C, ref [21]). IR (KBr, ν cm^{-1}): 1660 (C=C), 1714 (C=O), 1747 (C=O), 2985 (CH), 3263 (NH). ^{1}HNMR (400 MHz, DMSO-d_6, ppm): 1.05 (t, J = 7.0 Hz, 3H, CH_3); 1.25 (t, J = 7.0, 3H, CH_3); 3.97 (q, J = 7.0 Hz, 2H, CH_2); 4.20 (q, J = 7.0 Hz, 2H, CH_2); 5.15 (d, J = 3.0 Hz, 1H, 6-CH); 7.23-7.42 (m, 5H, H*arm*); 7.91 (d*(br)*, J = 3.01 Hz, 1H, NH); 9.89 (s (*br*), 1H, NH). HRMS ESI$^+$ (*m/z*): 319.1281 (MH$^+$ $C_{16}H_{19}N_2O_5$ requires 319. 1293), 341 [MNa$^+$].

Diethyl 6-(4-bromophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(1b)** [32]**.** This compound was obtained as colorless oil in 58% yield. IR (KBr, ν cm^{-1}): 1658 (C=C), 1699 (C=O), 1745 (C=O), 2926 (CH), 3245 (NH). ^{1}HNMR (400 MHz, DMSO-d_6, ppm): 1.06 (t, J = 7.0, 3H, CH_3); 1.25 (t, J = 7.0, 3H, CH_3); 3.97 (q, J = 7.0, 2H, CH_2); 4.20 (q, J = 7.0, 2H, CH_2); 5.14 (d, J = 3.0, 1H, CH); 7.19 (d, J = 8.4, 2H, H Ar); 7.57 (d, J = 8.4, 2H, H *arom*); 7.93 (s(*br*), 1H, NH); 9.94 (s(*br*), 1H, NH). HRMS-ESI$^+$ (*m/z*): 397.0383 (MH$^+$ $C_{16}H_{18}BrN_2O_5$ requires 397.0399), 420 (55%, MNa$^+$).

Diethyl 3-phenyl-1,1-dioxo-2,3,6-trihydro-1,2,6-thiadiazine-4,5-dicarboxylate **(1c).** This compound was obtained as colorless oil in yield= 48% using conc. HCl and 54% using SSA. IR (KBr,

ν cm^{-1}): 1165 (SO_2), 1312 (SO_2), 1585 (C-N), 1695 (C=O), 1721 (C=O), 3063 (NH). ^{1}HNMR (400 MHz, DMSO-d_6, ppm): 1.17 (t, *J*= 7.0 Hz, 3H, CH_3), 1.22 (t, *J*= 7.0 Hz, 3H, CH_3), 4.09 (q, *J*= 7.0 Hz, 2H, CH_2), 4.26 (q, *J*= 7.0 Hz, 2H, CH_2), 4.89 (s, 1H, CH-Ph), 7.22– 8.11 (m, 5H, H*arom*), 10.03 (s, 1H, NH), 12.85 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm): 167.7, 167.6, 133.2, 133.1, 131.2, 129.9, 129.7, 129.6, 128.9, 128.9, 61.7, 61.7, 40.1, 14.3; HRMS-ESI$^+$ (*m/z*): 356.0951 (MH^+, $C_{15}H_{20}N_2O_6S$ requires: 355.0963), 378 $[MNa]^+$.

General procedure for the synthesis of fused pyrimidines derivatives **(2a-b), (3a-b)** *and* **(4a-b)** *using conc. HCl as a catalyst.* A mixture of sodium diethyl oxalacetate (one equivalent), nucleobase (adenine, guanine or cytosine) (one equivalent), aromatic aldehyde (one equivalents), and 10 mol % of a catalyst (TsOH) or 2 drops of *conc*. HCl in ethanol was stirred at reflux for 3 hours. After the reaction was completed (as indicated by TLC), the mixture was poured into cool water and acidified using H_2SO_4 or H_3PO_4. The precipitate was filtered, washed with water, and several times with hexane or petroleum ether. The separated solid was recrystallized in ethanol/water (50:50) at a low temperature or using flash chromatography on silica gel (eluent: CH_2Cl_2, MeOH 95:5) to supply the pure fused pyrimidines in 33% -59% yields.

General procedure for the synthesis of fused pyrimidines derivatives **(2a-b), (3a-b)** *and* **(4a-b)** *using SSA as catalyst***.** A mixture of equimolar amounts of sodium diethyl oxalacetate, nucleobase (adenine, guanine, or cytosine), aromatic aldehyde, and 10 mol % of SSA in ethanol was stirred and heated at 90°C for 5 h. After the reaction was complete (followed by TLC), the mixture was cooled to room temperature using ice water. The solid that was obtained was filtered and washed with two portions of water and several times with hexane and petroleum ether to remove traces of aldehyde. The SSA catalyst was separated from the product after dilution of the reaction mixture with CH_2Cl_2. Recrystallization from ethanol/water (50:50) at a low temperature or chromatography on silica gel (CH_2Cl_2, MeOH 95:5) provided the pure expected substance in yields ranging from 41%–62%.

Diethyl 2-phenyl- 6-oxo-6,7-di(H)pyrimido[1,6-a]pyrimidine-3,4-dicarboxylate **(2a)**. This compound was prepared according to the general procedure using sodium diethyl oxalacetate (1.05g, 5 mmol), cytosine (0.56g, 5 mmol) and benzaldehyde (0.53g, 5 mmol). Compound (**2a**) was obtained as a white solid in yield= 48% using conc. HCl and 53% using SSA; Mp 135–137◦C. IR (KBr, ῡ cm^{-1}): 1742 (C=O), 1710 (C=O), 1671 (C=N), 3253 (NH); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.02 (t, *J*= 7.1 Hz, 3H, CH_3), 1.06 (t, *J*= 7.1 Hz, 3H, CH_3), 4.03 (q, *J*= 6.9 Hz, 2H, CH_2), 4.08 (q, *J*= 6.9 Hz, 2H, CH_2), 6.14 (s, 1H, CH-Ph), 7.31-7.41 (m, 7H, H-Ar), 12.2 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO-d_6): 14.3, 60.6, 79.7, 117.6, 127.9, 129.0, 129.6, 129.6, 136.2, 148.3, 161.6, 168.5. HRMS-ESI$^+$ (*m/z*): 370.1397 (MH^+, $C_{19}H_{20}N_3O_5$ requires: 370.1403), 392 $[MNa]^+$.

Diethyl 2-(4-hydroxy-3-methoxyphenyl)- 6-oxo-6,7-di(H)pyrimido[1,6-a]pyrimidine-3,4-dicarboxylate **(2b)**. This compound was prepared according to the general procedure using sodium diethyl oxalacetate (1.05g, 5 mmol), cytosine (0.56g, 5 mmol) and vanilin (0.76g, 5 mmol). Compound (**2b**) was obtained as a white solid in yield= 48% using conc. HCl and 52% using SSA. Mp 160 ◦C. IR (KBr, ῡ cm^{-1}): 1660 (C=O), 1740 (C=O), 3163 (NH), 3023 (CH *arom*), 1583 (Arom). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.10 (t, *J*= 7.1 Hz, 3H, CH_3), 1.15 (t, *J*= 7.1 Hz, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4.03 (q, *J*= 6.9 Hz, 2H, CH_2), 4.05 (q, *J*= 3.8 Hz, 2H, CH_2), 5.87 (s, 1H, CH), 6.59 (d, *J*= 8.2 Hz, 1H, CH*ethyl*), 6.63 (s, 1H, CH), 6.92 (d, *J*=1.9 Hz, 1H, H*ethyl*), 7.20 (d, *J*= 7.0 Hz, 1H, H*arom*), 7.81 (s, 1H, H *arom*), 8.92 (s, 1H, NH), 11.48 (s, 1H, OH). ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm): 166.4, 162.3, 160.2, 155.7, 153.5, 148.6, 147.60, 147.2, 146.5, 128.1, 119.8, 115.5, 113.7, 95.4, 60.3, 59.1, 56.0, 14.4. HRMS-ESI$^+$ (*m/z*): 416.1458 (MH^+, $C_{20}H_{22}N_3O_7$ requires: 416.1458), 438 $[MNa]^+$.

Diethyl 9-phenyl-3,9- di(H)pyrimido[1,2-g]purine-7,8-dicarboxylate **(3a)**. This compound was prepared according to the general procedure, using sodium diethyl oxalacetate (1.05g, 5 mmol), adenine (0.675g, 5 mmol) and benzaldehyde (0.53g, 5 mmol). Compound (**3a**) was obtained as a white solid in yield = 51% using conc. HCl and 54% using SSA; R_f = 0.30 [SiO_2, CH_2Cl_2-MeOH (9:1)]; Mp 105–107◦C. IR (KBr, ῡ cm^{-1}): 1742 (C=O), 1710 (C=O), 1668 (C=N), 3208 (NH). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.16 (t, *J*=7.1, 3H, CH_3), 1.24 (t, *J*=7.1, 3H, CH_3), 4.08 (q, *J*=7.1 Hz, 2H, CH_2), 4.16 (q, *J*= 7.1 Hz, 2H, CH_2), 6.14 (s, 1H, CH-Ph), 7.30-7.44 (m, 5H, H*arom*), 7.65 (s, 1H, CH), 8.12 (s, 1H, CH), 12.19 (s, 1H, NH). HRMS-ESI$^+$ (*m/z*) : 394.1503 (MH^+, $C_{20}H_{20}N_5O_4$ requires : 394.1515), 416 $[MNa]^+$.

Diethyl 9-(4-hydroxy-3-methoxyphenyl)-3,9-di(H)pyrimido[1,2-g]purine-7,8-dicarboxylate **(3b)**. This compound was prepared according to the general procedure, using sodium diethyl

oxalacetate (1.05g, 5 mmol), adenine (0.675g, 5 mmol) and vanilin (0.76g, 5 mmol). Compound (**3b**) was obtained as a white solid in yield = 43% using conc. HCl and 57% using SSA. Mp 78–80◦C. IR (KBr, ῡ cm^{-1}): 1704 (C=O), 1691(C=O), 1664 (C=N), 1589 (Arom), 3070 (CH *arom*), 3163 (NH), 3471 (OH). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.22 (t, *J*= 7.1 Hz, 3H, CH_3), 1.23 (t, *J*= 7.1 Hz, 3H, CH_3), 3.84 (s, 3H, CH_3), 3.86 (s, 1H, CH-Ph), 4.08 (q, *J*=7.1 Hz, 2H, O-CH_2), 4.20 (q, *J*=7.1 Hz, 2H, O-CH_2), 6.81 (s, 1H, CH-Ph), 6.98-7.44 (m, 5H, Ar), 7.63 (s, 1H, CH), 8.12 (s, 1H, CH), 9.78 (s, 1H, OH), 10.23 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm): 14.3, 60.6, 79.8, 117.6, (127, 128, 129), 136.2, 148.3, 161.6, 168.5. HRMS-ESI$^+$ (*m/z*): 440.1566 (MH^+, $C_{21}H_{22}N_5O_6$ requires: 440.1570), 462 $[MNa]^+$

Diethyl 6-phenyl-10-oxo-3,5,6,10-tetrahydro-pyrimido[1,2-f]purine-7,8-dicarboxylate **(4a).** This compound was prepared according to the general procedure using sodium diethyl oxalacetate (1.05g, 5 mmol), guanine (0.75g, 5 mmol) and benzaldehyde (0.53g, 5 mmol). Compound (**4a**) was obtained as a white solid in yield= 33% using conc. HCl and 41% using SSA; Mp 384˚C. IR (KBr, ῡ cm^{-1}): 1693 (C=O), 1660 (C=N), 1575 (Ar), 3093 (NH), .^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 0.22 – 0.57 (m, 6H, 2CH_3), 2.73 (dd, *J*= 4.9, 2.1 Hz, 1H, CH), 3.31 (m, 2H, CH_2), 3.48 (m, 2H, CH_2), 6.47 – 6.32 (m, 2H, H*arom*), 6.52 – 6.49 (m, 1H, H-Ar), 6.60 – 6.54 (m, 2H, H*arom*), 6.62 (s, 1H, CH), 10.10 (s, 1H, NH), 11.58 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm): 164.6, 143.9, 129.0, 128.9, 128.6, 128.1, 127.6, 127.3, 126.9, 60.5, 60.3, 58.9, 14.4. HRMS-ESI$^+$ (*m/z*): 410.1452 (MH^+, $C_{20}H_{20}N_5O_5$ requires: 410, 1464), 432 $[MNa]^+$.

Diethyl 6-(2-hydroxylphenyl)-10-oxo-3,5,6,10-tetra(H)pyrimido[1,2-f]purine-7,8-dicarboxylate **(4b)**. This compound was prepared according to the general procedure using sodium diethyl oxalacetate (1.05g, 5 mmol), guanine (0.75g, 5 mmol) and salicylaldehyde (0.76g, 5 mmol). Compound (**4b**) was obtained as a white solid in yield= 39% using conc. HCl and 45% using SSA; Mp 346◦C. IR (KBr, ῡ cm^{-1}): 1692 (C=O), 1663 (C=N), 2900 (NH), 3314 (OH). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 0.99-1.39 (m, 6H, 2CH_3), 4.02 (q, 2H, CH_2), 4.20 (q, 2H, CH_2), 4.39 (m, 1H, CH), 7.09–7.76 (m, 4H, H*arom*), 8.76 (s, 1H, CH), 9.60 (s, 1H, OH), 10.53 (s, 1H, NH), 11.38 (s, 1H, NH); HRMS-ESI$^+$ (*m/z*): 426.1402 (MH^+, $C_{20}H_{20}N_5O_6$ requires: 426,1413).

Results and Discussions

According to the literature [2**5**], diethyl 2-oxo-pyrimidine-4,5-dicarboxylate derivatives **1a-c** (Scheme 1) were prepared with a one-pot three-component cyclo-condensation of aromatic aldehydes, diethyl oxalacetic ester and urea using hydrochloric acid (HCl) as a catalyst in ethanol (EtOH).

To explore the effect of different catalysts, these reactions were performed using silica sulfuric acid (SSA) as a reusable solid acid catalyst under the same conditions (EtOH/reflux). Products **1a–c** were also obtained in moderate yields and the results are summarized in Table 1. Compared with other reported catalysts (*e.g.*, conc. HCl) [2**5**], SSA is beneficial to reaction yields under the same conditions.

To develop and study the Biginelli reaction [18], the substitution of urea by nucleobases, characterized by a single amino group (NH_2) as nitrogen donors (1,3-diamines), was investigated (Figure 1), in this case and three types of acid catalysts (conc. HCl, SSA, and p-toluenesulfonic acid [TsOH]) under the same conditions (EtOH/reflux) [2**8**-**30**]. A new series of fused pyrimido[1,6-a]pyrimidine-3,4-dicarboxylate **2a-b**, pyrimido[1,2-g]purine-7,8-dicarboxylate **3a-b**, and pyrimido[2,1-e]purine-8,9-dicarboxylate **4a-b** were synthesized using one-pot three-component cyclo-condensation of sodium diethyloxalacete, aromatic aldehydes, and nucleobase (adenine, guanine, or cytosine) (Scheme 1).

The mixture was stirred at 90 °C for an appropriate time until the condensation was complete (Table 1). The progress of the reaction was monitored using thin-layer chromatography (TLC). In this method, we used a catalytic amount (10 mol %) of catalyst (SSA or TsOH) or two drops of conc. HCl. The results in Table 1 show that all fused pyrimido-purines derivatives **2a-b**, **3a-b**, and **4a-b** were obtained in moderate yields within 3-5 hours.

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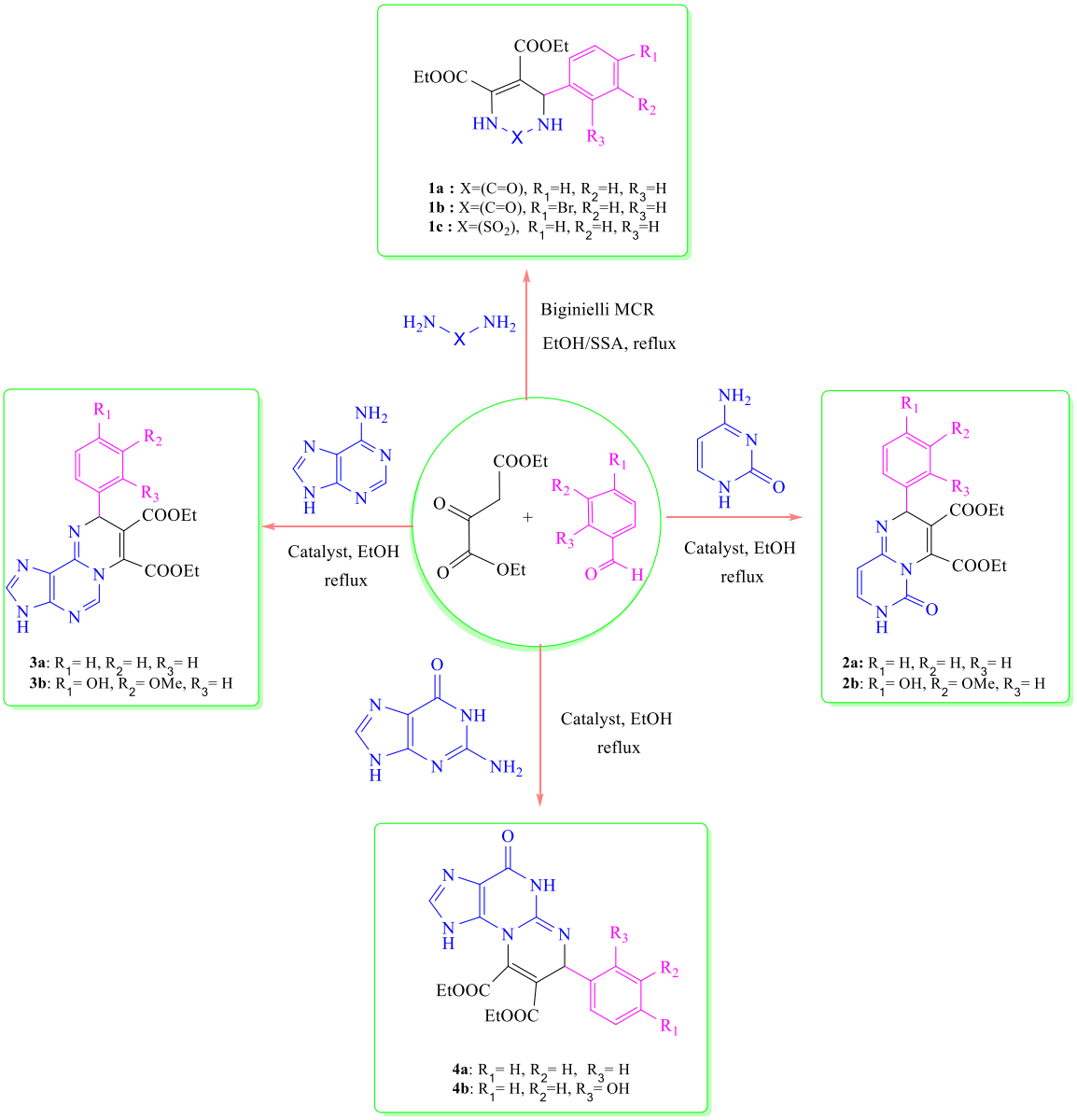

Scheme 1. **Multicomponent synthesis of fused pyrimido-purines derivatives using nucleobases.**

The reaction yield with adenine derivatives (pyrimido[1,2-g]purine-7,8-dicarboxylates) was higher than that with cytosine and guanine derivatives. This may be due to the absence of the carbonyl group in the adenine structure. The results of the condensation reaction under various conditions are presented in Table.

Table

Catalyst, time and isolated yields of pyrimidines and fused pyrimidines derivatives in EtOH as solvent.

Comp	1,3-diamine	Aldehyde	Catalyst	Time (h)	Yield (%)
1a [21]	Urea	*Benzaldehyde*	*conc.* HCl	3	27 ref. [25]
			SSA	3	55
1b [21]	Urea	*4-bromobenzaldehyde*	*conc.* HCl	8	56 ref. [25]
			SSA	3	58
1c	Sulfamide	*Benzaldehyde*	*conc.* HCl	3.5	48
			SSA	3.5	54
2a	Cytosine	*Benzaldehyde*	*conc.* HCl	3	48
			SSA	3	53
2b		*Vanilin*	TsOH	3	48
			SSA	3	52
3a	Adenine	*Benzaldehyde*	conc. HCl	3	51

			SSA	3	54
3b		*Vanilin*	conc. HCl	3	43
			SSA	3	57
4a	Guanine	*Benzaldehyde*	TsOH	5	33
			SSA	5	41
4b		*Salicylaldehyde*	conc. HCl	5	39
			SSA	5	45

All the synthesized compounds were characterized using proton (^{1}H) nuclear magnetic resonance (NMR), carbon-13 (^{13}C) NMR, infrared (IR) spectroscopy, and mass spectrometric analysis (MS). The Fourier transform (FT)-IR spectra confirmed that the desired Biginelli products were obtained by the appearance of a strong absorption bands at $\bar{\upsilon}$ = 1700 cm^{-1}, which corresponds to C=O groups. In addition, all IR spectra showed a characteristic band over 1600 cm^{-1}, which corresponds to aromatic ring stretch for all pyrimidines derivatives. The ^{1}H NMR spectra of synthetized compounds revealed signals at 7.00 parts per million (ppm) that were assigned to aromatic ring protons. In addition, the ^{1}H NMR spectra of fused products revealed the presence of amine protons (NH). Furthermore, the electrospray ionization (ESI) mass spectra of all products showed peaks at *m/z*=[M+1] and *m/z*=[M+23], which correspond to the molecular mass of ions $[M+H]^+$ and $[M+Na]^+$, respectively.

Conclusion

In summary, we demonstrated the synthesis of dihydropyrimidin-2(*H*)-one-4,5-dicarboxylate derivatives using SSA as mild heterogeneous solid acid catalyst *via* one-pot three-component condensation under Biginelli reaction conditions. We demonstrated the extension of this procedure in the synthesis of three series of fused pyrimidines (pyrimido[1,2-g]purine-7,8-dicarboxylate, pyrimido[1,2-f]purine-7,8-dicarboxylate, and pyrimido[1,6-a]pyrimidine-3,4-dicarboxylate) using nucleobases as 1,3-diamine reagents under the same conditions. These novel fused pyrimidines are currently undergoing biological studies.

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Funding

This research received no external funding

Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

Acknowledgements

The authors are thankful to Technical Center on Physico-Chemical Analysis (CRAPC) for providing all the necessary of spectral analysis.

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