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SYNTHESIS OF PYRIMIDINE ANALOGS HOMOPHTALIC ACID FROM DIMETHYL ESTER ACETONEDICARBOXYLATE BY THE BIGINELLI REACTION

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A convenient method of preparing pyrimidine analogs homophtalic acid from dimethyl ester acetondicarboxylate by the Biginelli reaction. These reactions were carried out using a cheap, non-toxic, readily soluble in water and readily available catalyst H_3PO_4. Additionally, this new reaction might be a useful tool for high-throughput organic synthesis. These compounds can serve as a basis for the synthesis of biologically active substances.
Keywords: 3,4-dihydropyrimidin-2(1H)-ones, Biginelli's reaction, homophthalic acid.

INTRODUCTION

The scaffold decoration of bioactive molecules represents one of the most vibrant research areas in organic chemistry and has a rich history within the realm of fragment-based drug design. The Biginelli 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) have been known for more than a century [1–6]. Recently, the interest in synthesis of 3,4-dihydropyrimidin-2(1H)-ones (named Biginelli compounds) and their derivatives is increasing tremendously because of their therapeutic and pharmacological properties and also because of interesting biological activities of several alkaloids which contain the dihydropyrimidine core. Dihydropyrimidinone derivatives have attracted considerable interest in recent times because of their promising activities as calcium channel blockers, α_{1a}-adrenergic receptor antagonists, mitotic kinesin inhibitors and hepatitis B virus replication inhibitors [7–14]. The DHPM core was also found in several marine derived natural products, such as Crambine, Batzelladine B (potent HIV gp-120CD4 inhibitors) and Ptilomycalin alkaloids [15–19]. Additionally, the Biginelli DHPMs are important building blocks in synthesis of multifunctionalized pyrimidines.

The most simple and straightforward procedure, reported by Biginelli in 1893, involves one-pot condensation of an aldehyde, β-ketoester and urea in the presence of an acid catalyst [1]. However, one serious drawback of Biginelli's reaction is low yields in the case of substituted aromatic and aliphatic aldehydes [20-21]. This led to the development of multi-methods which gives somewhat higher yields but it is not as easy as one-step synthesis [20–22].

In this regard, we want to get pyrimidine analogue homophthalic acid, we report herein, a simple, facile and efficient method for the preparation of some new 6-substituted DHPMs derivatives with phosphoric acid as a nontoxic, inexpensive, very soluble in water, and easily available reagent.

Homophthalic acid derivatives are important building blocks for the synthesis of alkaloids, dyes, and a variety of medicinally interesting structures [23–27]. They are also convenient precursors of *o*-quinonemethide intermediates, which readily undergo Diels–Alder cycloadditions with various reactive dienophiles (*e.g.* quinones for the synthesis of anthracyclinones) [28] or of isoquinolines through vigorous heating with zinc powder [29].

MATERIALS AND METHODS

General Procedure. Melting points were determined in the Boetius type heating appliances and are uncorrected. ^{1}H NMR spectra were recorded on a BRUKER AVANCE 400 MHz spectrometer with dimethyl-d6-sulfoxide as solvent and tetramethylsilane (TMS) as an internal standard. All reagents were obtained from commercial sources and used without further purification.

Methyl 6-methoxycarbonylmethyl-4-aryl-2-oxo(thio)-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (4a-g). A mixture of the appropriate aldehyde (0.03 mol), dimethyl-3-oxoglutarate (0.041 mol), urea (0.03 mol), and H_3PO_4 (0.03 mol) in methanol was refluxed for the time period as indicated in Table 1. After standing, the precipitate was filtered and crystallized in ethanol. All products were characterized by ^{1}H, ^{13}C NMR.

Methyl 6-methoxycarbonylmethyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a). White powder, yield 90%, mp 169-171 °C.^{1}H NMR (DMSO d_6) δ_H: 3.52 (s, 3H, CH_3), 3.69 (s, 3H, CH_3), 3.66 (d, 1H, *J*=16.8 Hz, CH_2), 3.81 (d, 1H, *J*=16.8 Hz, CH_2), 5.21 (s, 1H, CH), 7.22-7.37 (m, 5H, arom), 7.71 (s, 1H, NH), 9.26 (s, 1H, NH). ^{13}C NMR (DMSO d_6) δ_C: 36.34 (CH_2), 50.37 (CH_3), 51.29 (CH_3), 53.76 (CH), 95.31, 100.29, 126.03, 126.32, 126.82, 127.89, 144.06, 144.72, 151.64, 164.89, 168.62.

Methyl 6-methoxycarbonylmethyl-4-phenyl-2-thio-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate (4b). White powder, yield 87%, mp 167-170 °C.^{1}H NMR (DMSO d_6) δ_H: 3.50 (s, 3H, CH_3), 3.65 (s, 3H, CH_3), 3.75 (d, 1H, *J*=16.8 Hz, CH_2), 3.91 (d, 1H, *J*=16.8 Hz, CH_2), 5.21 (s, 1H, CH), 7.26-7.38 (m, 5H, arom), 9.74 (s, 1H, NH), 10.4 (s, 1H, SH). ^{13}C NMR (DMSO d_6) δ_C: 36.12 (CH_2), 51.28 (CH_3), 51.92 (CH_3), 54.00 (CH), 101.96, 126.68, 127.89, 128.64, 141.77, 142.85, 165.19, 169.17, 173.97.

Methyl 6-methoxycarbonylmethyl-4-(3-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c). White powder, yield 81%, mp 184-186 °C. Spectrum data are shown in Figures 1 and 2, respectively.

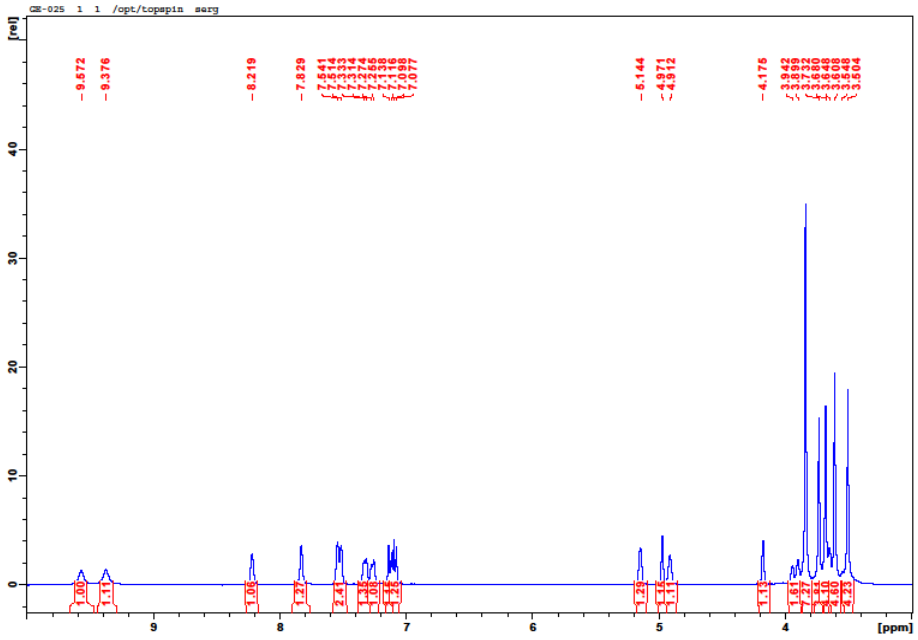


Fig 1. Spectrum ^{1}H NMR (DMSO d_6)

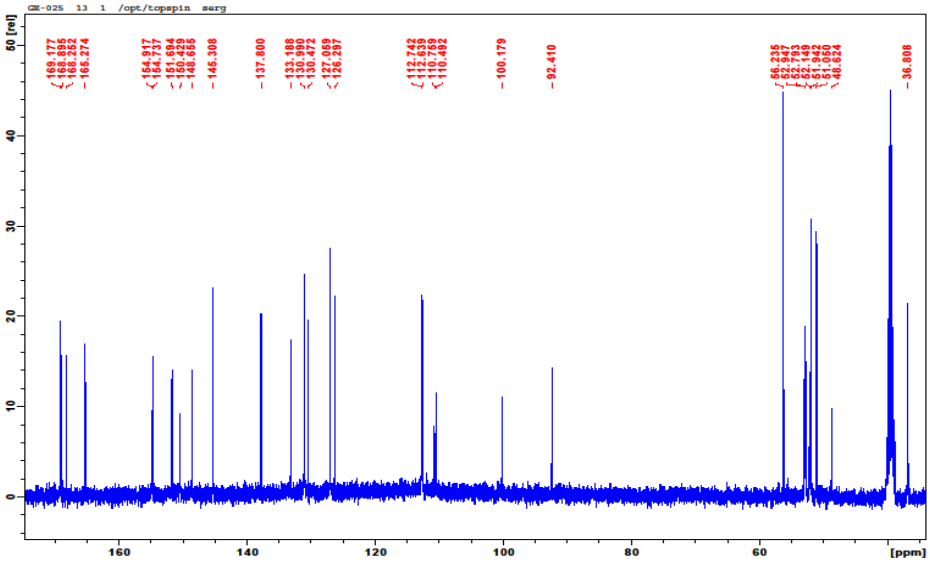


Fig 2. Spectrum ^{13}C NMR (DMSO d_6)

Methyl 6-methoxycarbonylmethyl-4-(3-bromo-4-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d). White powder, yield 86%, mp 139-141 °C. Spectrum data are shown in Figures 3 and 4, respectively.

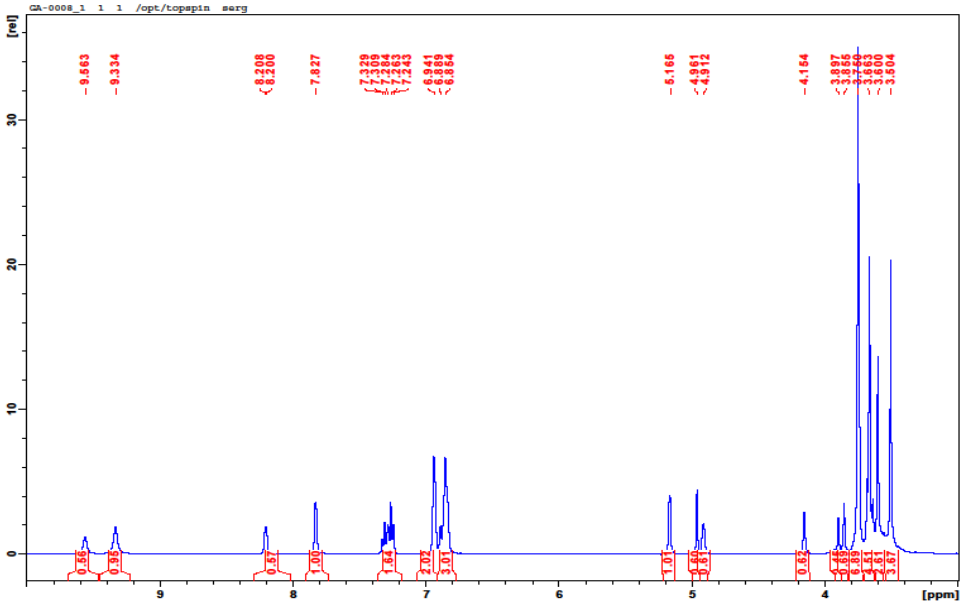


Fig 3. Spectrum ^{1}H NMR (DMSO d_6)

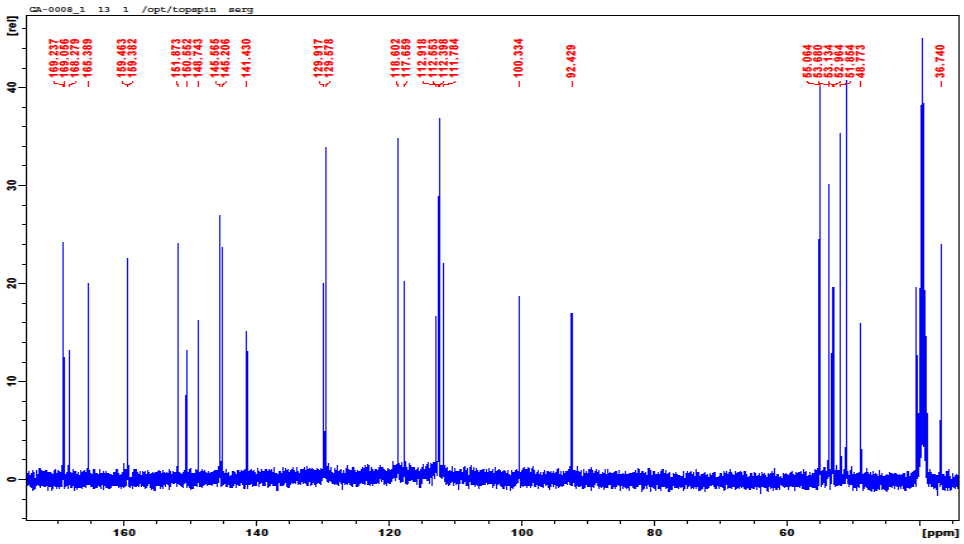


Fig 4. Spectrum ^{13}C NMR (DMSO d_6)

Methyl 6-methoxycarbonylmethyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i). White powder, yield 80%, mp 141-143 °C. ^{1}H NMR (DMSO d_6) δ_H: 3.50 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 3.70 (d, 1H, *J*=16.8 Hz, CH_2), 3.85 (d, 1H, *J*=16.8 Hz, CH_2), 5.32 (s, 1H, CH), 7.61 (d, 2H, *J*=8.4 Hz, CH), 8.00 (s, 1H, NH), 8.22 (d, 2H, *J*=8.4 Hz, CH), 9.49 (s, 1H, NH). ^{13}C NMR (DMSO d_6) δ_C: 36.76 (CH_2), 51.09 (CH_3), 51.94 (CH_3), 53.48 (CH), 99.62, 123.86, 127.80, 145.93, 146.88, 151.25, 151.56, 165.11, 169.12.

Methyl 6-methoxycarbonylmethyl-4-(4-nitrophenyl)-2-thio-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f) Yellow powder, yield 77%, mp 148-150 °C. . ^{1}H NMR (DMSO d_6) δ_H: 3.52 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 3.72 (d, 1H, *J*=16.8 Hz, CH_2), 3.86 (d, 1H, *J*=16.8 Hz, CH_2), 5.32 (s, 1H, CH), 7.63 (d, 2H, *J*=8.4 Hz, CH), 8.25 (d, 2H, *J*=8.4 Hz, CH), 9.03 (s, 1H, NH), 10.5 (s, 1H, SH). ^{13}C NMR (DMSO d_6) δ_C: 36.66 (CH_2), 51.11 (CH_3), 51.93 (CH_3), 53.60 (CH), 99.62, 125.86, 127.83, 145.96, 146.90, 151.21, 151.50, 164.11, 168.12.

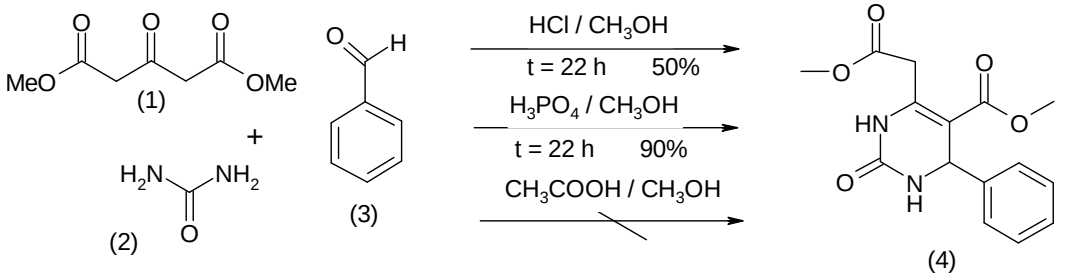
Methyl 6-methoxycarbonylmethyl-4-(4-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g). White powder, yield 84%, mp 210-213 °C. ^{1}H NMR (DMSO d_6) δ_H: 3.48 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 3.68 (d, 1H, *J*=16.8 Hz, CH_2), 3.80 (d, 1H, *J*=16.8 Hz, CH_2), 5.08 (s, 1H, CH), 6.71 (d, 2H, *J*=8.0 Hz, CH), 7.13 (d, 2H, *J*=8.0 Hz, CH), 7.72 (s, 1H, NH), 9.25 (s, 1H, OH)), 9.36 (s, 1H, NH). ^{13}C NMR (DMSO d_6) δ_C: 36.71 (CH_2), 50.93 (CH_3), 51.84 (CH_3), 53.31 (CH), 101.04, 115.07, 127.66, 134.76, 144.51, 151.96, 156.73, 165.48, 169.27.

RESULTS AND DISCUSSION

Here we describe a method of high-yield reaction Biginelli as ternary reaction of aldehydes, dimethyl 3-oxoglutarate and urea derivatives for the synthesis of 6-substituted DHPMs (4 a-g) by using phosphoric acid under mild conditions.

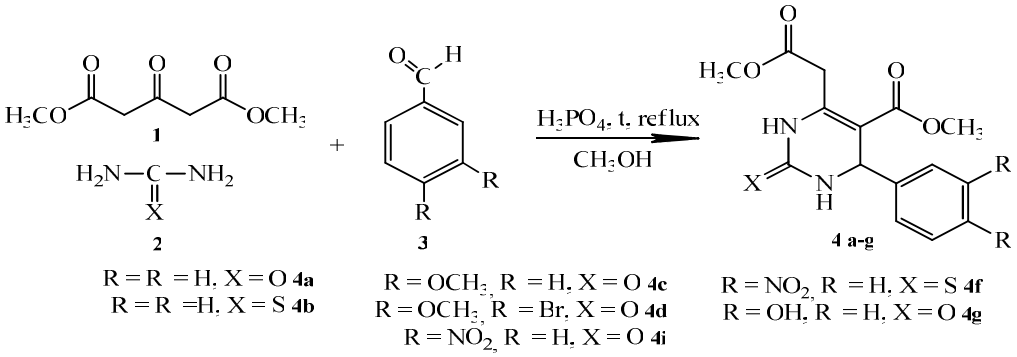
We found that an application of phosphoric acid as a catalyst, as opposed to hydrochloric acid provides a high output of pyrimidines (4 a-g). Thus, application of phosphoric acid gives a yield of product in the range 70-90% and the acetic - 40-50%. The application of acetic acid as the acid does not lead to the formation of the condensation product (Scheme 1).

Scheme 1



DHPMs **4a** was isolated in 90% yield from a mixture of dimethyl-3-oxoglutarate **1**(1,4 mmol), benzaldehyde **3** (1 mmol), urea **2** (1mmol), and H_3PO_4 (1 mmol) (Scheme 2).

Scheme 2



The reaction was carried out at 65 ºC for 22 h. Then the Biginelli reaction of other various aldehydes **3** under a established protocol wherein we used a 1:1,4:1:1 ratio of H_3PO_4, dimethyl-3-oxoglutarate, aldehyde, and urea derivatives, respectively, gives suitable DHPMs (4 b-g) with good yields.

Aromatization derived compounds, i.e. conversion into derivatives homophtalic acid is a major problem. We have used a number of oxidants: but in some, such as 68% solution of HNO_3, SeO_2, $K_2Cr_2O_7/CH_3COOH$) is the complete collapse of the heterocycle and in other S, $NaNO_2$, MnO_2, $(CH_3COO)_2Cu$ - oxidation occurs.

CONCLUSIONS

1. We have described a mild, convenient way to get some new 6-substituted DHPMs by Biginelli cyclocondensation three-component reaction of dimethyl 3-oxoglutarate, aldehyde and urea derivatives.
2. These reactions were carried out using a cheap, non-toxic, readily soluble in water and readily available catalyst H_3PO_4.
3. Additionally, this new reaction might be a useful tool for high-throughput organic synthesis.

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Николаев А.С. Синтез пиримидиновых аналогов гомофталевой кислоты на основе диметилового эфира ацетондикарбоновои кислоты по реакции Бидженелли / А.С.Николаев , А.А. Гелеверя , Е.В. Гуртовая, О.И. Харанеко, С.Л. Богза // Ученые записки Таврического национального университета им. В.И. Вернадского. Серия «Биология, химия». – 2013. – Т. 26 (65), № 4. – С.307-314.
Удобный способ получения пиримидиновых аналогов гомофталевои кислоты с диметилового эфира ацетондикарбоновои кислоты по реакции Биджинелли, которые могут служить основой для синтеза биологически активных веществ. Эти реакции проводили с использованием дешевого, нетоксичного, легко доступного катализатора H_3PO_4, легко растворяющегося в воде. Кроме того, эта новая реакция может быть полезным инструментом для высокорезультативного органического синтеза.
Ключевые слова: 3,4-дигидропиримидины-2(1Н)-оны, реакция Бидженелли, гомофталева кислота.

Ніколаєв О.С. Синтез піримідинових аналогів гомо фталевої кислоти на основі диметилового ефіру ацетондікарбонової кислоти за реакцією Бідженеллі / О.С.Ніколаєв, А.О. Гелеверя, К.В. Гуртова, О.І. Харанеко, С.Л. Богза // Вчені записки Таврійського національного університету ім. В.І. Вернадського. Серія „Біологія, хімія". – 2013. – Т. 26 (65), № 4. – С. 307-314.
Зручний спосіб отримання піримідинових аналогів гомофталевої кислоти з диметилового ефіру ацетондикарбонової кіслоти за реакцією Біджінеллі, які можуть служити основою для синтезу біологічно активних речовин. Ці реакції проводили з використанням дешевого, нетоксичного, легко доступного каталізатора H_3PO_4, що легко розчиняється у воді. Крім того, ця нова реакція може бути корисним інструментом для високорезультативного органічного синтезу.
Ключові слова: 3,4-дигідропіримідин-2(1Н)-они, реакція Бідженеллі, гомофталева кислота.

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