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5-phosphonato-3,4-dihydropyrimidin-2(1*H*)-ones: Zinc triflate-catalyzed one-pot multi-component synthesis, X-ray crystal structure and anti-inflammatory activity

Idris Essid [a, *], Karima Lahbib [a], Werner Kaminsky [b], Cherif Ben Nasr [c], Soufiane Touil [a]

[a] Laboratory of Heteroatom Organic Chemistry, University of Carthage, Faculty of Sciences of Bizerte, 7021, Jarzouna, Tunisia
[b] Department of Chemistry, BOX 351700, University of Washington Seattle, WA, 98195, USA
[c] Laboratoire de Chimie des Matériaux, Université de Carthage, Faculté des Sciences de Bizerte, 7021, Jarzouna, Tunisia

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ABSTRACT

Herein we report a simple and efficient one-pot three-component synthesis of 5-phosphonato-3,4-dihydropyrimidin-2(1*H*)-ones, through the zinc triflate-catalyzed Biginelli-type reaction of β-ketophosphonates, aldehydes and urea. The compounds obtained were characterized by various spectroscopic tools including IR, NMR (^{1}H, ^{31}P, ^{13}C) spectroscopy, mass spectrometry and single crystal X-ray diffraction. All the synthesized compounds were screened, for the first time, for anti-inflammatory activity by carrageenan-induced hind paw edema method, using female Wister rats and they showed significant anti-inflammatory activity in some cases higher than the standard indomethacin.

1. Introduction

3,4-Dihydropyrimidin-2(1*H*)-ones and their derivatives are an important class of compounds in medicinal chemistry with a wide range of biological properties, including antitumoral [1], antimalarial [2], anti-inflammatory [3] and anti-HIV [4] activities; some are also medicinally important as calcium channel modulators and α_{1a}-adrenergic receptor antagonists [5]. The introduction of a phosphonate functionality on 3,4-dihydropyrimidinones, may be very interesting for the enhancement of the biological properties of these molecules, in a similar way to that reported for other pharmaceuticals [6,7]. It is also known that phosphonate and phosphonic acid moieties regulate important biological functions by mimicking carboxylic acid groups [8].

With this in mind, and in the continuation of our interest to develop efficient protocols for the synthesis of heterocyclic phosphonates with possible biological properties [9–11], we report herein a simple and efficient one-pot multi-component synthesis of 5-phosphonato-3,4-dihydropyrimidin-2-ones, through the zinc triflate-catalyzed Biginelli-type reaction [12–17] of β-ketophosphonates, aldehydes and urea.

To the best of our knowledge, there are only two reports on the use of β-ketophosphonates as substrates in the Biginelli reaction, which employed ytterbium triflate [18] or *p*-toluenesulfonic acid [19] as catalyst. However, in spite of their potential utility, these procedures suffer from one or the other drawbacks such as the unsatisfactory yields, tedious work-up or long reaction time.

By comparison with these existing strategies, our method offers significant advantages such as efficiency, short reaction time, easy work-up and high yields. In addition, the zinc triflate catalyst used is known for its low toxicity, low cost, and environmentally benignity. This is very beneficial for safely obtaining phosphonodihydropyrimidinone derivatives of pharmacological interest.

All the synthesized compounds were screened for anti-inflammatory activity by carrageenan-induced hind paw edema method [20], using female Wister rats and they showed significant anti-inflammatory activity in some cases higher than the standard indomethacin.

* Corresponding author.
E-mail address: idris_essid@hotmail.fr (I. Essid).

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2. Experimental

2.1. Methods and materials

^{1}H, ^{31}P and ^{13}C NMR spectra were recorded with $CDCl_3$ or DMSO-d_6 as the solvent, on a Bruker AC-300 spectrometer operating at 300.1 MHz for ^{1}H, 121.5 MHz for ^{31}P and 75.5 MHz for ^{13}C. The chemical shifts are reported in ppm relative to TMS (internal reference) for ^{1}H and ^{13}C NMR and relative to 85% H_3PO_4 (external reference) for ^{31}P NMR. The coupling constants are reported in Hz. For the ^{1}H NMR, the multiplicities of signals are indicated by the following abbreviations: s: singlet; d: doublet; t: triplet; q: quartet; m: multiplet and br s: broad singlet. Mass spectra were determined on an Agilent 5975B spectrometer, under electronic impact (EI) conditions. FT-IR spectra were recorded on a Nicolet IR200 spectrometer, the number of scans was 32, the scanning range was 4000–400 cm^{-1} and the resolution 4 cm^{-1}. The progress of the reactions was monitored by TLC. Purification of products was performed by column chromatography using silica gel (Fluka). The starting β-ketophosphonates **1** were synthesized by literature procedures [21].

2.2. General procedure for the synthesis of 5-phosphonato-3,4-dihydropyrimidin-2(1H)-ones (**3**)

A mixture containing the β-ketophosphonate (2 mmol), aldehyde (2 mmol), urea (3 mmol) and $Zn(OTf)_2$ (15 mol%) in toluene (8 mL), was refluxed for 3 h. After completion of the reaction, as indicated by TLC, the solvent was removed under reduced pressure, then $CHCl_3$ (30 mL) was added. The organic phase was washed with H_2O (2 × 10 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude obtained was purified by chromatography on a silica gel column, using EtOAc as eluent.

2.2.1. 5-Diethoxyphosphoryl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**3a**)

White Solid; mp 169–170 °C. IR (neat): $\nu_{P=O}$ = 1235 cm^{-1}; $\nu_{C=O}$ = 1703 cm^{-1}; ν_{NH} = 3116-3224 cm^{-1}. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 18.8. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (t, 3H, $^{3}J_{HH}$ = 6.0 Hz, C*H*$_3$–CH$_2$–O); 1.11 (t, 3H, $^{3}J_{HH}$ = 6.0 Hz, C*H*$_3$–CH$_2$–O); 2.12 (d, 3H, $^{4}J_{PH}$ = 3.0 Hz, C*H*$_3$); 3.49–3.83 (m, 4H, 2 CH$_3$–C*H*$_2$–O); 5.05 (dd, 1H, $^{3}J_{PH}$ = 9.0 Hz, $^{3}J_{HH}$ = 3.0 Hz, C*H*–NH); 6.14 (br s, 1H, N–*H*) 7.18–7.30 (m, 5H, arom-H); 8.73 (d, 1H, $^{3}J_{HH}$ = 3.0 Hz, N–*H*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.0 (d, $^{3}J_{CP}$ = 7.5 Hz, *C*H$_3$–CH$_2$–O); 16.3 (d, $^{3}J_{CP}$ = 6.0 Hz, *C*H$_3$–CH$_2$–O); 18.2 (d, $^{3}J_{CP}$ = 3.7 Hz *C*H$_3$); 56.6 (d, $^{2}J_{CP}$ = 15.7 Hz, *C*H–NH); 61.3 (d, $^{2}J_{CP}$ = 5.1 Hz, CH$_3$–*C*H$_2$–O); 61.4 (d, $^{2}J_{CP}$ = 5.1 Hz, CH$_3$–*C*H$_2$–O); 96.0 (d, $^{1}J_{CP}$ = 206.8 Hz, P–*C*=C); 147.0 (d, $^{2}J_{CP}$ = 20.6 Hz, P–C=*C*); 154.23 (s, C=O); phenyl carbons: δ 126.9, 128.2, 128.7, 143.8; EI-HRMS: calculated for $C_{15}H_{21}N_2O_4P$: 324.1239 (M^+); Found: 324.1238.

2.2.2. 5-Dimethoxyphosphoryl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**3b**)

White Solid; mp 198–200 °C. IR (neat): $\nu_{P=O}$ 1236 cm^{-1}; $\nu_{C=O}$ 1700 cm^{-1}; ν_{NH} = 3119-3258 cm^{-1}. ^{31}P NMR (121.5 MHz, DMSO-d_6): δ = 22.9. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.15 (d, 3H, $^{4}J_{HP}$ = 2.7 Hz, C*H*$_3$); 3.34 (d, 3H, $^{3}J_{PH}$ = 11.3 Hz, C*H*$_3$–O); 3.46 (d, $^{3}J_{PH}$ = 11.5 Hz, C*H*$_3$–O); 4.89 (dd, 1H, $^{3}J_{PH}$ = 8.6 Hz, $^{3}J_{HH}$ = 3.2 Hz, C*H*–NH); 7.32–7.40 (m, 5H, arom-H); 7.77 (br s, 1H, N–H); 9.28 (d, 1H, $^{3}J_{HH}$ = 3.1 Hz, N–H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 17.3 (d, $^{3}J_{CP}$ = 3.5 Hz, *C*H$_3$); 51.3 (d, $^{2}J_{CP}$ = 4.9 Hz, CH$_3$–O); 51.4 (d, $^{2}J_{CP}$ = 5.2 Hz, CH$_3$–O); 54.9 (d, $^{2}J_{CP}$ = 15.2 Hz, *C*H–NH); 92.5 (d, $^{1}J_{CP}$ = 205.8 Hz, P–*C*=C); 148.8 (d, $^{2}J_{CP}$ = 20.7 Hz, P–C=*C*); 152.5 (s, C=O); phenyl carbons: 126.5, 127.4, 128.4, 144.5; EI-HRMS: calculated for $C_{13}H_{17}N_2O_4P$: 296.0926 (M^+); Found: 296.0922.

2.2.3. 5-Diethoxyphosphoryl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (**3c**)

Yellow Solid; mp 219–220 °C. IR (neat): $\nu_{P=O}$ = 1225 cm^{-1}; $\nu_{C=O}$ = 1700 cm^{-1}; ν_{NH} = 3120-3232 cm^{-1}. ^{31}P NMR (121.5 MHz, DMSO-d_6): δ = 19.2. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.00 (t, 3H, $^{3}J_{HH}$ = 7.0 Hz, C*H*$_3$–CH$_2$–O); 1.13 (t, 3H, $^{3}J_{HH}$ = 7.0 Hz, C*H*$_3$–CH$_2$–O); 2.12 (d, 3H, $^{4}J_{PH}$ = 2.2 Hz, C*H*$_3$); 3.59–3.84 (m, 4H, 2 CH$_3$–C*H*$_2$–O); 5.01 (dd, 1H, $^{3}J_{PH}$ = 8.5 Hz, $^{3}J_{HH}$ = 3.4 Hz, C*H*–NH); 7.53–8.25 (m, 4H,, arom-H); 7.81 (d, 1H, $^{4}J_{PH}$ = 1.7 N–*H*); 9.31 (d, 1H, $^{3}J_{HH}$ = 3.0 Hz, N–*H*). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 15.7 (d, $^{3}J_{CP}$ = 6.6 Hz, *C*H$_3$–CH$_2$–O); 16.0 (d, $^{3}J_{CP}$ = 6.2 Hz, *C*H$_3$–CH$_2$–O); 17.4 (d, $^{3}J_{CP}$ = 3.4, *C*H$_3$); 54.6 (d, $^{2}J_{CP}$ = 15.1 Hz, *C*H–NH); 60.6 (d, $^{2}J_{CP}$ = 5.1 Hz, CH$_3$– *C*H$_2$–O); 60.7 (d, $^{2}J_{CP}$ = 5.2 Hz, CH$_3$–*C*H$_2$–O); 92.7 (d, $^{1}J_{CP}$ = 206.4 Hz, P–*C*=C); 149.1 (d, $^{2}J_{CP}$ = 20.6 Hz, P–C=*C*); 152.2 (s, C=O); phenyl carbons: 123.7, 127.8, 146.7, 151.6; EI-HRMS: calculated for $C_{15}H_{20}N_3O_6P$: 369.1090 (M^+); found: 369.1092.

2.2.4. 5-Dimethoxyphosphoryl-6-méthyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (**3d**)

Yellow Solid; mp 235–237 °C. IR (neat): $\nu_{P=O}$ = 1228 cm^{-1}; $\nu_{C=O}$ = 1701 cm^{-1}; ν_{NH} = 3142-3232 cm^{-1}. ^{31}P NMR (121.5 MHz, DMSO-d_6): δ = 22.3. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.16 (d, 3H, $^{4}J_{PH}$ = 2.2 Hz, C*H*$_3$); 3.41 (d, 3H, $^{3}J_{PH}$ = 11.2 Hz, C*H*$_3$–O); 3.50 (d, 3H, $^{3}J_{PH}$ = 11.4 Hz, C*H*$_3$–O); 5.05 (dd, 1H, $^{3}J_{PH}$ = 8.5 Hz, $^{3}J_{HH}$ = 3.4 Hz, C*H*–NH); 7.59–8.30 (m, 4H, arom-H); 7.90 (d, 1H, $^{4}J_{PH}$ = 1.7 Hz, N–H); 9.42 (d, 1H, $^{3}J_{HH}$ = 3.0 Hz, N–H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 17.3 (d, $^{3}J_{CP}$ = 3.5 Hz, *C*H$_3$); 51.5 (d, $^{2}J_{CP}$ = 5.1 Hz, *C*H$_3$–O); 51.6 (d, $^{2}J_{CP}$ = 5.3 Hz, *C*H$_3$–O); 54.5 (d, $^{2}J_{CP}$ = 15.3 Hz, *C*H–NH); 91.5 (d, $^{1}J_{CP}$ = 206.9 Hz, P–*C*=C); 149.7 (d, $^{2}J_{CP}$ = 20.5 Hz, P–C=*C*); 152.1 (s, C=O); phenyl carbons: 123.8, 127.8, 146.7, 151.5; EI-HRMS: calculated for $C_{13}H_{16}N_3O_6P$: 341.0777 (M^+); found: 341.0776.

2.2.5. 5-Diethoxyphosphoryl-6-méthyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (**3e**)

White Solid; mp 120–122 °C. IR (neat): $\nu_{P=O}$ = 1227 cm^{-1}; $\nu_{C=O}$ = 1700 cm^{-1}; ν_{NH} = 3127-3243 cm^{-1}. ^{31}P NMR (121.5 MHz, DMSO-d_6): δ = 19.1. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.03 (t, 3H, $^{3}J_{HH}$ = 7.0 Hz, C*H*$_3$–CH$_2$–O); 1.13 (t, 3H, $^{3}J_{HH}$ = 7.0 Hz, C*H*$_3$–CH$_2$–O); 2.12 (d, 3H, $^{4}J_{PH}$ = 2.1 Hz, C*H*$_3$); 3.57–3.86 (m, 4H, 2 CH$_3$–C*H*$_2$–O); 5.02 (dd, 1H, $^{3}J_{PH}$ = 8.1 Hz, $^{3}J_{HH}$ = 2.8 Hz, C*H*–NH); 7.07 (br s, 1H, N–H), 7.17–7.27 (m, 4H, arom-H); 9.00 (br s, 1H, N–H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 15.0 (d, $^{3}J_{CP}$ = 7.0 Hz, *C*H$_3$–CH$_2$–O); 15.2 (d, $^{3}J_{CP}$ = 6.7 Hz, *C*H$_3$–CH$_2$–O); 16.9 (d, $^{3}J_{CP}$ = 3.6 Hz, *C*H$_3$); 54.5 (d, $^{2}J_{CP}$ = 15.6 Hz, *C*H–NH); 60.2 (d, $^{2}J_{CP}$ = 5.2 Hz, 2 CH$_3$–*C*H$_2$–O); 93.7 (d, $^{1}J_{CP}$ = 207.4 Hz, P–*C*=C); 146.9 (d, $^{2}J_{CP}$ = 20.6 Hz, P–C=*C*); 152.8 (s, C=O); phenyl carbons: 127.4, 127.5, 132.2, 141.8. EI-HRMS calculated for $C_{15}H_{20}ClN_2O_4P$: 358.0849 (M^+); found: 358.0811.

2.2.6. 5-Dimethoxyphosphoryl-6-méthyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (**3f**)

White Solid; mp 226–227 °C. IR (neat): $\nu_{P=O}$ = 1227 cm^{-1}; $\nu_{C=O}$ = 1702 cm^{-1}; ν_{NH} = 3128-3251 cm^{-1}. ^{31}P NMR (121.5 MHz, DMSO-d_6): δ = 22.7. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.14 (d, 3H, $^{4}J_{PH}$ = 2.0 Hz, C*H*$_3$); 3.39 (d, 3H, $^{3}J_{PH}$ = 11.3 Hz, C*H*$_3$–O); 3.48 (d, 3H, $^{3}J_{PH}$ = 11.4 Hz, C*H*$_3$–O); 4.91 (dd, 1H, $^{3}J_{PH}$ = 8.6 Hz, $^{3}J_{HH}$ = 3.4 Hz, C*H*–NH); 7.33–7.48 (m, arom-H); 7.80 (d, 1H, $^{4}J_{PH}$ = 1.6 Hz N–H); 9.33 (d, 1H, $^{3}J_{HH}$ = 3.1 Hz, N–H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 17.3 (d, $^{3}J_{CP}$ = 3.5 Hz, *C*H$_3$); 51.4 (d, $^{2}J_{CP}$ = 5.0 Hz, *C*H$_3$–O); 51.5 (d, $^{2}J_{CP}$ = 5.3 Hz, *C*H$_3$–O); 54.3 (d, $^{2}J_{CP}$ = 15.3 Hz, *C*H–NH); 92.1(d, $^{1}J_{CP}$ = 206.3 Hz, P–*C*=C); 149.1 (d, $^{2}J_{CP}$ = 20.7 Hz, P–C=*C*); 152.3 (s, C=O); phenyl carbons: 128.4, 131.9, 143.4.

2.2.7. 5-Diethoxyphosphoryl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (**3g**)

White Solid; mp 138–140 °C. IR (neat): $\nu_{P=O}$ = 1229 cm^{-1}; $\nu_{C=}$