A Convenient Synthesis of 5- and 6-Substituted 2-Phenyl-3H-pyrimidin-4-ones

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Abstract: A simple and convenient one-pot procedure for the synthesis of 5- and 6-substituted 2-phenyl-3H-pyrimidin-4-ones by the condensation of 4-alkoxy-1,1,1-trichloroalk-3-en-2-ones with benzamidine hydrochloride is described.

Key words: pyrimidines, 2-phenylpyrimidin-4-ones, trichloromethylated enones, benzamidine hydrochloride, Sildenafil

The 2-phenyl(aryl)-substituted pyrimidine-4-ones moiety is present in important biological active compounds such as azapurine,1 an efficient anti-allergic substance, and Sildenafil2 used for men’s dysfunction erection. Since the discovery of the biological properties of Sildenafil and its analogues, there was an increasing interest to develop shorter and more reliable synthetic method to obtain these molecules to search for new biological active compounds.

2-Phenyl-3H-pyrimidin-4-ones have been synthesized by the reaction of: i) acetylacetone, acetylacetophenone, and ethyl acetoacetate with amidoximes catalyzed by ruthenium carbon monoxide under a carbon monoxide pressure of 5 kg cm–2;3 ii) ethylacetophenones with benzamidine hydrochloride in the presence of DMF and potassium hydroxide or potassium tert-butoxide;4 iii) acetylacetone, methylacetonate, and dimethyl malonate with benzamidine;5 iv) ethyl α-bromocinnamates with benzamidine in the presence of an excess of triethylamine in anhydrous benzene;6 and v) 3-aminocrotonamide with benzonitrile in methanol and sodium methoxide.7 2-Phenylpyrimidin-4-ones have also been synthesized by the derivatization and chemical transformation of the substituents from other pyrimidines.8–10

One can observe from the examples cited above that there are only few methods available for the synthesis of 5- or 6-substituted 2-phenyl-3H-pyrimidin-4-ones. In addition, some of these methods are of restricted scope,3,5 result in low yields,6,11 or entail a multi-step synthesis.12 Furthermore, the synthetic potential of 4-alkoxy-1,1,1-trichloroalk-3-en-2-ones 1a–l as precursors of 2-phenyl-3H-pyrimidin-4-ones has not been tested yet. Enones 1a–l have the following advantage over the traditional methods to prepare 2-phenyl-3H-pyrimidin-4-ones: i) they are easily prepared by acylation of enol ethers13 and acetalts;14 ii) the reactions are more regioselective than 1,3-dicarbonyl compounds; iii) they allow one to introduce a wider range of substituents on the final product than compared with most of the methods cited above; iv) the yields are usually higher; and v) uses milder reaction conditions. Thus, in this study we report a simple and efficient one-pot method to obtain a wide scope of 5- and 6-substituted 2-phenyl-3H-pyrimidin-4-ones from the reaction of the readily available 4-alkoxyvinyl trichloromethyl ketones and benzamidine hydrochloride. To our knowledge, 4-alkoxyvinyl trichloromethyl ketones have not been used for the synthesis of 2-phenyl-3H-pyrimidin-4-ones. The synthetic versatility of 4-alkoxyvinyl trichloromethyl ketones has been recently demonstrated by the preparation of 3-aminoethylenedihydrofuran-2-ones,15 pyrazoles and pyrazolium chlorides,16 fural-3-carboxylic acids and derivatives,17 pyrazolecarboxamide,18 azolymethylpyrimidin-2-ones,19 and 4-trichloromethyl-2-methanesulfonyl pyrimidines.20 The synthesis and applications of 4-alkoxy-1,1,1-trichloroalk-3-en-2-ones have also been the subject of a recent review.21

Scheme 1 outlines the synthesis of a series of 5- or 6-substituted 2-phenyl-3H-pyrimidin-4-ones from the reactions of the enones 1a–l with benzamidine hydrochloride. In order to obtain better yields, three methods were tested (Scheme 1). Table 1 presents the optimized results obtained after each reaction was carried out by the three methods. It is important to mention that method A was the method of choice for most reactions, because it furnished better yields and purity and allowed for an easier isolation of the products than the other methods studied. We speculate that method B was not adequate because sodium methoxide is a base strong enough to decompose the enones 1.22 Method C exhibited better results only for the reaction of enone 1b with benzamidine hydrochloride to furnish 2h. Product 2h is important, because the bromomethyl substituent on the 6-position of the pyrimidine ring allows for further derivatizations.23 It was observed that the reaction of the 4-aryl-substituted enones 1i–l with benzamidine hydrochloride furnished the desired pyrimidin-4-ones 2i–l as the major compound (55–90%), but minor amounts (5–8%) of 4-trichloromethyl pyrimidine 3i–l, were also obtained. The major compounds 2i–l were separated from their corresponding minor compounds 3i–l by recrystallization.
The reaction of enones 1m–o, which bear a substituent at the α-carbonyl position, with benzamidine hydrochloride furnished 2-phenyldihydropyrimidin-4-ones 4m–o, in good yields. The presence of a substituent at the 5-position of the pyrimidine ring stabilizes the dihydropyrimidine probably due to the steric effect between the 5-substituent and the trichloromethyl group. The elimination of the 6-alkoxy and 4-hydroxy groups can be achieved by using dehydrating agents such as sulfuric acid or phosphorous pentoxide. Compounds obtained in this study were analyzed by 1H and 13C NMR, GC-MS, and elemental analysis.

The mechanism of formation of 2-phenyl-3H-pyrimidin-4-ones 2 probably involves the addition of a nitrogen atom from benzamidine to the β-carbon of the β-alkoxyvinyl ketones 1 (Structure I, Scheme 2) followed by the τautomerization of the hydroxyl hydrogen with the α-carbon and restoration of the carbonyl group (Structure II, Scheme 2). The ether function (OR2) is stable under basic condition. In the second step, the other nitrogen of benzamidine undergoes intramolecular nucleophilic addition to the carbonyl group generating a quaternary carbon and closing a six-membered pyrimidine ring (Structure III).

On the presence of a base, the carbonyl is restored and the trichloromethyl group is eliminated to furnish the dihydropyrimidines 4m–o. Next, the base removes the H-5, causing the elimination of the alkoxy group leading to the 2-phenyl-3H-pyrimidin-4-ones 2 according to Scheme 2.

In conclusion, we have described a simple and convenient one-pot procedure for the synthesis of 5- or 6-substituted 2-phenyl-3H-pyrimidin-4-ones 2 from the condensation reaction of 4-alkoxy-1,1,1-trichloroalk-3-en-2-ones with benzamidine hydrochloride, under mild conditions and in good yields. In addition, a simple method to obtain the 6-bromomethylpyrimidine, which is an important intermediate for further derivatizations, has been presented.
The syntheses of compounds 1a–o are reported in the literature. All melting points were determined on a Kofler Reichert Thermovar or on a QMAGP-301 apparatus and are uncorrected. The CHN microanalyses were performed on a PerkinElmer 2400 elemental analyzer from the Department of Chemistry of the São Paulo University (USP), São Paulo, SP, Brazil. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC. The GC was equipped with a split-splitless injector, auto-sampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and helium was used as the carrier gas. H and 13C NMR spectra were acquired on a Bruker DPX200 or DPX400 spectrometer in DMSO-d6 with TMS as the internal reference.

5- and 6-Substituted 2-Phenyl-3H-pyrimidin-4-ones 2 and 4; General Procedure

Method A: A solution of enone 1 (1.0 mmol) in CHCl3 (0.5 mL) was added to a vigorously stirred mixture of hexane–CHCl3 (1:3). The mixture of compounds 2a–g and 4m–o were recrystallized from a mixture of hexane–CHCl3 (1:3). The mixture of compounds 2i–l and 3i–l were recrystallized from a mixture of CHCl3–MeOH (5:1). By this recrystallization, the major products 2l–i crystallized and were recovered by filtration and the minor products 3l–i were recovered from the mother liquor.

2-Pyrimidin-4(3H)-one (2a)

Mp 205–207 °C (hexane–CHCl3, 1:3). 1H NMR (200 MHz, DMSO-d6): δ = 6.34 (d, J = 6.6 Hz, 1 H, H-5), 7.45–7.62, 7.09–8.13 (m, 5 H, C6H5), 8.05 (d, J = 6.6 Hz, 1 H, H-6), 12.69 (br s, 1 H, NH). 13C NMR (50 MHz, DMSO-d6): δ = 112.7 (C-5), 127.7, 128.6, 131.6, 132.7 (C6H5), 154.5 (C-6), 158.1 (C-2), 163.4 (C-4).

GC-MS (EI 70 eV): m/z (%): 172 (M+*, 100), 144 (17), 104 (86), 69 (46).


2-Phenyl-6-propylpyrimidin-4(3H)-one (2d)

Mp 146–148 °C (hexane–CHCl3, 1:3).

1H NMR (200 MHz, CDCl3): δ = 1.00 (t, J = 7.4 Hz, 3 H, CH3), 1.78 (sext, J = 7.4 Hz, 2 H, CH2), 2.59 (t, J = 7.4 Hz, 2 H, CH2), 6.29 (s, 1 H, H-5), 7.49–7.53, 8.21–8.26 (m, 5 H, C6H5), 13.36 (br s, 1 H, NH).

13C NMR (50 MHz, CDCl3): δ = 13.6 (CH3), 21.1 (CH3), 39.6 (CH3), 110.2 (C-5), 127.8, 128.7, 131.7, 132.3 (C6H5), 156.4 (C-2), 165.6 (C-4), 169.8 (C-6).

GC-MS (EI 70 eV): m/z (%): 214 (M+, 10), 186 (100), 158 (23), 104 (43), 77 (25).


6-Butyl-2-phenylpyrimidin-4(3H)-one (2c)

Mp 218–220 °C (hexane–CHCl3, 1:3).

1H NMR (200 MHz, CDCl3): δ = 0.89 (t, J = 7.4 Hz, 3 H, CH3), 1.35 (sext, J = 7.0 Hz, 2 H, CH2), 1.66 (quint, J = 7.6 Hz, 2 H, CH2), 2.55 (t, J = 7.6 Hz, 2 H, CH2), 6.22 (s, 1 H, H-5), 7.45–7.48, 8.12–8.17 (m, 5 H, C6H5), 13.07 (br s, 1 H, NH).

13C NMR (50 MHz, CDCl3): δ = 13.8 (CH3), 22.2 (CH3), 30.0 (CH3), 37.3 (CH3), 109.9 (C-5), 127.8, 128.7, 131.6, 132.6 (C6H5), 156.7 (C-2), 166.0 (C-4), 170.0 (C-6).

GC-MS (EI 70 eV): m/z (%): 229 (M+, 100), 156 (42), 104 (42), 77 (23).

Anal. Calcd for C13H12N2O: C, 73.66; H, 7.06; N, 12.20. Found: C, 73.47; H, 7.02; N, 11.99.

6-Isobutyloxy-phenylpyrimidin-4(3H)-one (2f)

Mp 163–168 °C (hexane–CHCl3, 1:3).

1H NMR (400 MHz, CDCl3): δ = 0.95 (d, J = 6.5 Hz, 6 H, 2 CH3), 1.24 (m, 1 H, CH), 2.37 (d, J = 7.0 Hz, 2 H, CH2), 5.90 (s, 1 H, H-5), 7.36–7.56, 7.77–8.10 (m, 5 H, C6H5), 9.28 (br s, 1 H, NH).

13C NMR (100 MHz, DMSO-d6): δ = 22.4 (2 CH3), 27.2 (CH3), 46.2 (CH3), 108.3 (C-5), 127.5, 127.8, 138.4 (C6H5), 161.9 (C-2), 165.0 (C-4), 172.7 (C-6).

GC-MS (EI 70 eV): m/z (%): 229 (M+, 9), 186 (100), 158 (21), 104 (34), 77 (21).

Anal. Calcd for C13H13NO: C, 73.66; H, 7.06; N, 12.20. Found: C, 73.51; H, 7.01; N, 11.95.

2,6-Diphenylpyrimidin-4(3H)-one (2g)

Mp 299–300 °C (hexane–CHCl3, 1:3).

1H NMR (400 MHz, DMSO-d6): δ = 6.92 (s, 1 H, H-5), 7.51–7.62, 8.17–8.28 (m, 10 H, C6H5), 12.76 (br s, 1 H, NH).

13C NMR (100 MHz, DMSO-d6): δ = 106.6 (C-5), 126.9, 127.9, 128.6, 128.7, 130.5, 131.6, 132.9, 136.3 (C6H5), 157.3 (C-2), 160.8 (C-6), 164.2 (C-4).

GC-MS (EI 70 eV): m/z (%): 248 (M+, 100), 220 (19), 149 (48), 104 (64), 77 (43).


6-(4-Bromophenyl)-2-phenylpyrimidin-4(3H)-one (2i)


1H NMR (400 MHz, DMSO-d6): δ = 6.94 (s, 1 H, H-5), 7.54–7.71, 8.11–8.24 (m, 9 H, C6H5), 12.80 (br s, 1 H, NH).

4-(4-Chlorophenyl)-2-phenyl-6-(trichloromethyl)pyrimidine (4j), 127 (72), 104 (103), 77 (93), 75 (33).

2-Phenyl-4-(p-tolyl)-6-(trichloromethyl)pyrimidine (3k) Mp 151–154 °C (CHCl₃–MeOH, 5:1).

1H NMR (400 MHz, DMSO-d₆): δ = 2.44 (s, 3 H, CH₃), 6.88 (s, 1 H, H-5), 7.31–7.85 (m, 9 H, C₆H₅), 10.42 (br s, 1 H, NH).

1H NMR (100 MHz, CDCl₃): δ = 55.5 (OCH₃), 96.0 (CCl₃), 107.6 (C-5), 127.6, 127.9, 128.8, 129.2, 131.2, 136.0, 162.3 (2 C=O), 163.2 (C=O), 165.8 (C=O), 166.0 (C=O).

GC-MS (EI 70 eV): m/z (%) = 232 (M⁺, 100), 203 (64), 143 (22), 138 (68), 104 (47), 76 (17).

6-Ethoxy-5-methyl-2-phenyl-5,6-dehydropyrimidin-4(3H)-one (4m) Mp 120–124 °C (hexane–CHCl₃, 1:3).

1H NMR (400 MHz, CDCl₃): δ = 3.89 (s, 3 H, OCH₃), 7.16 (s, 1 H, H-5), 7.57–7.61, 8.33–8.57 (m, 9 H, C₆H₅).

1H NMR (100 MHz, CDCl₃): δ = 3.89 (s, 3 H, OCH₃), 7.16 (s, 1 H, H-5), 7.57–7.61, 8.33–8.57 (m, 9 H, C₆H₅).

GC-MS (EI 70 eV): m/z (%) = 214 (M⁺, 5), 188 (100), 160 (76), 143 (22), 104 (47), 76 (17).

6-Ethoxy-5-methyl-2-phenyl-5,6-dehydropyrimidin-4(3H)-one (3l) Mp 110–115 °C (hexane–CHCl₃, 1:3).

1H NMR (400 MHz, CDCl₃): δ = 3.89 (s, 3 H, OCH₃), 7.16 (s, 1 H, H-5), 7.57–7.61, 8.33–8.57 (m, 9 H, C₆H₅).

1H NMR (100 MHz, CDCl₃): δ = 3.89 (s, 3 H, OCH₃), 7.16 (s, 1 H, H-5), 7.57–7.61, 8.33–8.57 (m, 9 H, C₆H₅).

GC-MS (EI 70 eV): m/z (%) = 214 (M⁺, 5), 188 (100), 160 (76), 143 (22), 104 (47), 76 (17).


1H NMR (400 MHz, CDCl₃): δ = 1.30 (t, J = 7.2 Hz, 3 H, CH₃), 1.46 (m, 2 H, H-6), 2.24 (m, 2 H, H-6a), 4.17 (dq, J = 12.0, 7.2 Hz, 1 H, CH₂), 4.67 (d, J = 11.2 Hz, 2 H, H-7), 4.72–4.75, 7.89–7.90 (m, 9 H, C₆H₅), 9.36 (br s, 1 H, NH).

1H NMR (100 MHz, CDCl₃): δ = 10.3 (CH₃), 15.0 (OCH₃), 39.6 (C-5), 63.2 (OCH₃), 90.6 (C-6), 126.4, 128.6, 130.2, 132.9 (CH₃), 149.1 (C-2), 174.7 (C-4).

GC-MS (EI 70 eV): m/z (%) = 232 (M⁺, 3), 203 (64), 143 (22), 138 (68), 104 (47), 76 (17).

Anal. Calcd for C₁₃H₁₆N₂O₂: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.22; H, 6.94; N, 12.06.
Anal. Calcd for C11H9BrN2O: C, 49.84; H, 3.42; N, 10.57. Found: (38), 51 (21).

127.8, 128.3, 131.6, 131.9 (C₆H₅), 157.5 (C-6), 163.9 (C-2), 167.1

GC-MS (EI 70 eV):

149.4 (C-2), 172.6 (C-4).

4a), 66.2 (C-7), 89.2 (C-8a), 127.3, 128.3, 131.1, 132.6 (C₆H₅),

13C NMR (100 MHz, DMSO-


References


