

Solvent Free Synthesis of Pyrimidine, Quinazolinone and Diazatricyclo Derivatives via Phase-Transfer Catalysis Method

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Abstract: A simple and practical green chemistry procedure for the synthesis of some pyrimidine, quinazolinone and diazatricyclo derivatives is described. These compounds were synthesized in good to high yields by a Biginelli-like reaction of urea/thiourea, aldehyde and ketone under solvent free conditions in the presence of triethyl benzyl ammonium chloride (TEBAC) as a catalyst.

Keywords: Multicomponent, Biginelli, Solvent free, Catalyst, TEBAC

Introduction

Dihydropyrimidine-2-ones/thiones are an important class of heterocyclic compounds associated with a wide range of therapeutic and medicinal properties^{1,2} such as anti-microbial, antihypertensives, antiinflammatory^{3,4}, antifungal⁵. They have been reported to show moderate calcium channel blocking⁶⁻⁸ and sodium channel blockade activities⁹. Also several marine alkaloids with interesting biological activities containing the dihydropyrimidine core have been known in the past few years^{10,11}. Biginelli synthesized dihydropyrimidinones via a one-pot acid-catalyzed condensation reaction of β -ketoesters, aldehyds, and urea in refluxing ethanol¹². However, this simple reaction is associated with low yield of products and prolongs reaction times. The importance of multicomponent reactions, MCRs, reactions and the interesting biological activities associated with dihydropyrimidinones led to the development of various multistep reactions that produce products in higher yields but lake of simplicity¹³⁻¹⁶.

Recently, a considerable attention has been focused on the synthesis of dihydropyrimidinones using more efficient methods¹⁷⁻²⁴. In spite of their advantages, some of them need vigorous reaction conditions, expensive or unavailable catalyst, long reaction times and use of toxic solvents. Therefore, in order to overcome these limitations, the discovery and development of more practical and efficient protocols for the synthesis of

Biginelli-like reactions is still of special interest for chemists. More recently, much attention has been directed toward the solvent-free reaction in order to develop classical methods and make them more clean and practical to carry out^{25,26}.

In continuation of our work in synthesis of pyrimidines²⁷⁻³⁰ we wish to report the synthesis of pyrimidine, quinazolinone and diazatricyclo derivatives via a practical green chemistry procedure by using triethyl benzyl ammonium chloride (TEBAC) as a catalyst under solvent free conditions.

Experimental

All reagent and solvents used are commercially available. Melting points were measured with an Electrothermal apparatus. IR spectra were recorded with a Galaxy Series FT-IR 5000 spectrometer. The ¹H NMR and ¹³C NMR spectra were recorded with a Bruker Avance 300MHz spectrometer with DMSO-*d*₆ as the solvent and TMS as the internal standard. The NMR spectra were identical with those of authentic materias³⁰. Microanalyses were performed by the Elemental Analyzer (Elemental, Vario EL III) at the Arak University. Reactions were monitored by thin layer chromatography (TLC) using silica gel F₂₅₄ aluminum sheets (Merck).

General procedure for preparation of **4**

An equimolar amount of substituted aldehyde **1**, urea or thiourea **2**, ketone **3** and triethyl benzyl ammonium chloride (TEBAC, 5 mol%) was heated at 90 °C for an appropriate time. After completion of reaction, the reaction mixture was cooled to room temperature and ethanol was added (10-15 mL). The result solid was filtered, washed by hot water and ethanol and recrystallized from ethanol to give the pure product of **4a-n**.

Selected data

6-Methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**4a**)

Time: 130 min, Yield: 75%, M.p 305-306 °C. IR: ν 3303 (NH), 3223 (NH), 3068 (CH_{aromatic}), 2972 (CH_{aliphatic}), 1656 (C=O). ¹H NMR: δ 1.68 (s, 3H, CH₃), 4.92 (d, *J*= 9 Hz, 1H, H_{pyrimidine}), 5.06 (d, *J*= 9 Hz, 1H, CH), 6.61 (s, 1H, NH), 6.81 (s, 1H, NH), the NH protons disappeared on D₂O addition, 7.04-7.45 (m, 5H, H_{aromatic}). ¹³C NMR (DMSO-*d*₆, 75 MHz), δ (ppm) 43.8, 49.9, 126.7, 127.7, 128.0, 128.8, 142.0, 4H, 2CH₂), 4.77 (s, 1H, H_{pyrimidine}), 7.12-7.43 (m, 5H, H_{aromatic}), 8.76 (s, 1H, NH), 9.58 (s, 1H, NH), the NH protons disappeared on D₂O addition. ¹³C NMR: δ 23.8, 26.8, 54.2, 58.2, 125.3, 127.4, 128.3, 128.7, 129.0, 142.8, 143.0, 173.3. Anal calcd for: C₁₄H₁₄N₂OS, C, 65.09; H, 5.46; N, 10.84; S, 12.41%. Found: C, 65.23; H, 5.48; N, 10.99; S, 12.30%.

5-Bromo-6-hydroxy-4,6-diphenyl-tetrahydropyrimidin-2(1H)-one (**4e**)

Time: 100 min, Yield: 80%, M.p 220-223 °C. IR: ν 3217 (NH), 3190 (NH, OH), 3082 (CH_{aromatic}), 2980 (CH_{aliphatic}), 1682 (C=O). ¹H NMR: δ 3.69 (d, *J*= 5.6 Hz, 1H, H_{pyrimidine}), 5.04 (d, *J*= 5.6 Hz, 1H, CHBr), 7.25-7.51 (m, 11H, 10H_{aromatic}, 1H, OH), 8.16 (s, 1H, NH), 8.82 (s, 1H, NH), the NH and OH protons disappeared on D₂O addition. ¹³C NMR: δ 20.5, 55.5, 66.4, 123.9, 127.1, 128.0, 128.3, 128.9, 132.1, 132.8, 144.0, 153.7. Anal calcd for: C₁₆H₁₅BrN₂O₂, C, 55.35; H, 4.35; N, 8.07; Br, 23.01%. Found: C, 55.45; H, 4.44; N, 8.15; Br, 23.21%.

6-Hydroxy-4,6-diphenyl-tetrahydropyrimidine-2(1H)-thione (**4g**)

Time: 90 min, Yield: 90%, M.p 288-289 °C. IR: ν 3387 (NH), 3212 (NH, OH), 3063 (CH_{aromatic}), 2947 (CH_{aliphatic}). ¹H NMR: δ 3.15 (d, *J*= 5.6 Hz, 2H, CH₂), 4.15 (t, *J*= 5.6 Hz, 1H, H_{pyrimidine}), 6.97-6.99 (m, 5H, H_{aromatic}), 7.13-7.15 (m, 6H, 5H, H_{aromatic}, 1H, OH), 8.20 (1H, NH), 8.99 (1H,

NH), the NH and OH protons disappeared on D₂O addition. ¹³C NMR: δ 44.7, 55.4, 69.2, 126.9, 127.3, 127.8, 128.1, 128.4, 128.7, 139.3, 140.1, 175.8. Anal calcd for: C₁₆H₁₆N₂OS, C, 67.58; H, 5.67; N, 9.85; S, 11.28%. Found: C, 67.78; H, 5.65; N, 9.71; S, 11.12%.

9-Methyl-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-11-one (4h)

Time: 80 min, Yield: 90%, M.p 291-293 °C. IR: ν 3311 (NH), 3240 (NH), 3120 (CH_{aromatic}), 2891 (CH_{aliphatic}), 1687 (C=O). ¹H NMR: δ 1.58 (s, 3H, CH₃), 2.09 (d, J = 5.6 Hz, 2H, CH₂), 4.22 (t, J = 5.6 Hz, 1H, H_{pyrimidine}), 6.72-7.13 (m, 4H, H_{aromatic}), 7.28 (s, 1H, NH), 7.58 (s, 1H, NH), the NH protons disappeared on D₂O addition. ¹³C NMR: δ 26.7, 32.6, 44.9, 82.6, 116.9, 120.5, 126.0, 129.2, 129.5, 151.7, 155.7. Anal calcd for: C₁₁H₁₂N₂O₂, C, 64.69; H, 5.92; N, 13.72%. Found: C, 64.48; H, 6.04; N, 13.51%.

9-Phenyl-8-oxa-10,12-diazatricyclo [7.3.1.0^{2,7}]trideca-2,4,6-triene-11-one (4l)

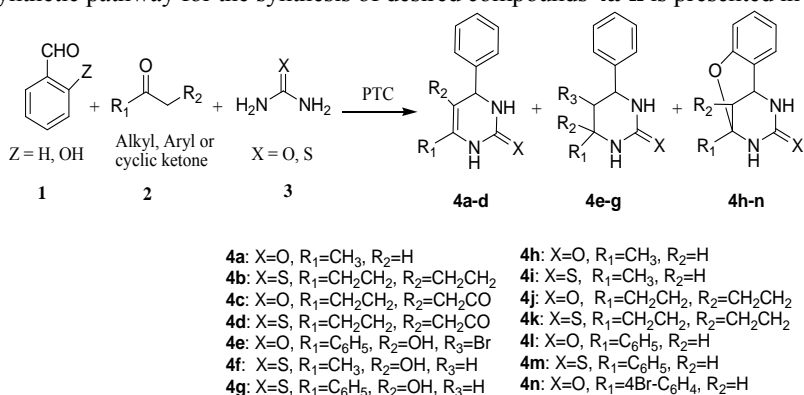
Time: 105 min, Yield: 87%, M.p 272-273 °C. IR: ν 3321 (NH), 3219 (NH), 3072 (CH_{aromatic}), 2982 (CH_{aliphatic}), 1687 (C=O). ¹H NMR: δ 2.20 (d, J = 5.6 Hz, 2H, CH₂), 4.32 (t, J = 5.6 Hz, 1H, H_{pyrimidine}), 6.80-7.88 (m, 9H, H_{aromatic}), 8.64 (s, 1H, NH), 9.71 (s, 1H, NH), the NH protons disappeared on D₂O addition. ¹³C NMR: δ 35.3, 49.9, 85.2, 121.0, 125.7, 126.2, 126.8, 128.3, 128.7, 129.5, 131.2, 134.6, 151.8, 156.3. Anal calcd for: C₁₆H₁₄N₂O₂, C, 72.16; H, 5.30; N, 10.52%. Found: C, 72.37; H, 5.25; N, 10.68%.

9-(4-Bromophenyl)-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-11-one (4n)

Time: 115 min, Yield: 86%, M.p 285-287 °C. IR: ν 3317 (NH), 3220 (NH), 3074 (CH_{aromatic}), 2914 (CH_{aliphatic}), 1682 (C=O). ¹H NMR: δ (ppm) 2.17 (d, J = 5.6 Hz, 2H, CH₂), 4.31 (t, J = 5.6 Hz, 1H_{pyrimidine}), 6.92-7.26 (m, 4H, H_{aromatic}), 7.40-7.62 (m, 4H, H_{aromatic}), 7.64 (s, 1H, NH), 7.90 (s, 1H, NH), the NH protons disappeared on D₂O addition. ¹³C NMR: δ 35.2, 45.1, 85.0, 121.1, 122.2, 126.0, 128.7, 129.4, 129.7, 131.5, 131.7, 141.3, 151.4, 156.1. Anal calcd for: C₁₆H₁₃BrN₂O₂, C, 55.67; H, 3.80; N, 8.12; Br, 23.15%. Found: C, 55.89; H, 3.85; N, 7.98; Br, 23.32%.

Results and Discussion

The synthetic pathway for the synthesis of desired compounds **4a-n** is presented in Scheme 1.



Scheme 1. Synthetic pathway of pyrimidine, quinazolinone and diazatricyclo derivatives **4a-n**

Reaction of substituted aldehyde **1** with urea or thiourea and corresponding ketone in the presence triethyl benzyl ammonium chloride (TEBAC) as a catalyst gave compounds **4a-n**. This Biginelli-like reaction was carried out with different ketones. In the case of salicylaldehyde as a

starting material, the Biginelli-like reaction is followed by a Michael addition and formation of an oxygen bridge with C-6 of the pyrimidine ring to produce diazatricyclo derivatives **4h-n**. The formation of this oxygen bridge may be due to the effective distance between the ortho-hydroxyl group of phenol group and the C-6 atom of pyrimidine ring³¹.

The good to high yields of reactions, use of safe and available catalyst and green reaction conditions are some advantages of this method for the synthesis of desired compounds. All synthesized compounds were identified using IR, NMR spectroscopy as well as elemental analysis and also by comparison with their authentic samples³¹. In the ¹H NMR spectrum of **4a-n**, the appearance of two broad singlets at ~ 6.60-9.70 ppm is related to the resonance of two NH protons (disappeared on D₂O addition). Also, in the IR spectra of these compounds the appearance of the absorption bond at ~3184-3421 cm⁻¹, the characteristic of the NH group, are good evidences in support of expected reactions

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