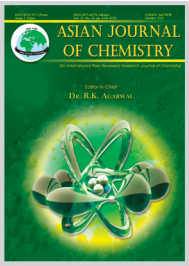
Asian Journal of Chemistry; Vol. 24, No. 4 (2012), 1421-1424

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in



Microwave-Assisted Synthesis of *Bis*(dihydropyrimidinone)benzenes

BEHROOZ MIRZA[1,*], MOHSEN SARGORDAN[2] and REZA FAZAELI[1]

[1]Department of Chemistry, Faculty of Science, South Tehran Branch, Islamic Azad University, Tehran, Iran
[2]Department of Chemistry, Faculty of Science, Shar-e-Rey Branch, Islamic Azad University, Shar-e-Rey, Iran

*Corresponding author: E-mail: behrooz.mirza@yahoo.com

(*Received*: 1 January 2011; *Accepted*: 15 November 2011) AJC-10680

Bis(dihydropyrimidinonoe)benzenes were synthesized in good to high yields by a pseudo four-component reaction of a dialdehyde such as terephthalic aldehyde or isophthalic aldehyde, (thio)urea and 1,3-dicarbonyl compounds using reusable nanosilica (average particle size *ca.* 50 nm, BET specific surface area (SSA) > 200 m^2/g as catalyst), under microwave irradiation in solvent-free conditions. Inexpensive reusable catalyst, low energy consumption, high yields of the products and simple work-up are attractive features of this green protocol.

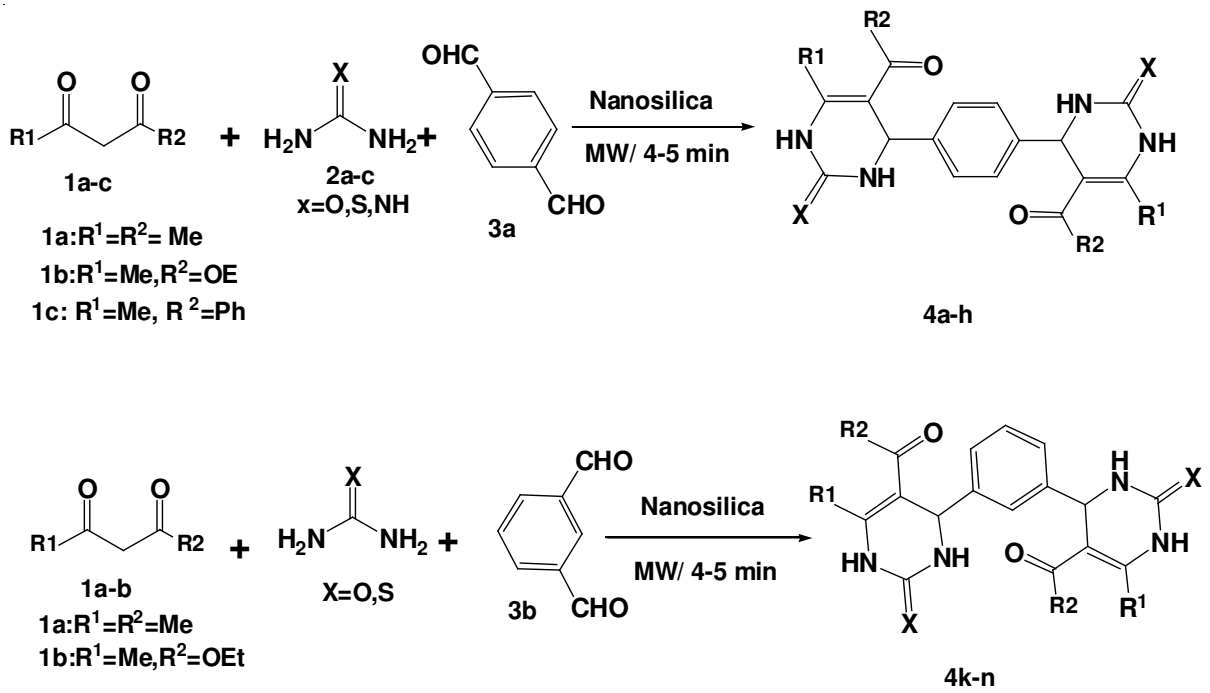
Key Words: Biginelli reaction, Dihydropyrimidinone, Nanosilica, Microwave irradiation, Terephthalic aldehyde, Multicomponent.

INTRODUCTION

In recent years, the multicomponent reactions (MCRs) are of increasing importance in organic and speed, diversity and efficiency in the drug discovery process[1,2], multicomponent reaction strategies offer significant advantages over conventional linear-type syntheses. Multicomponent reaction condensations involve three or more compounds reacting in a single event, but consecutively to form a new product, which contains the essential parts of all the starting materials. The search and discovery for new multicomponent reaction's on one hand[3] and the full exploitation of already known multicomponent reactions on the other hand, is therefore of considerable current interest. One such multicomponent reactions that belongs in the latter category is the Biginelli dihydropyrimidine synthesis. In 1893, Italian chemist Pietro Biginelli reported on the acid-catalyzed cyclocondensation reaction of an aldehyde, a β-ketoester and urea (thiourea), a procedure known as the Biginelli reaction[4]. More than a century ago, Biginelli anticipated the synthetic potential of multicomponent reactions by combining in a single flask the reactants of two different reactions having one component in common[5]. The result of the three-component reaction was a new product that was correctly characterized as a substituted 3,4-dihydropyrimidine-2(1*H*)-one (DHPM). Over the past decade, dhydropyrimidin-2(1*H*)-ones and their derivatives have attracted considerable attention in organic and medicinal chemistry as the dihydropyrimidine scaffold displays a fascinating array of pharmacological and therapeutic properties[6]. They have emerged as integral backbones of several calcium channel blockers, antihypersentive agents, α-1a-antagonists and neuropeptide Y (NPY) antagonists[7]. Moreover, several alkaloids containing the dihydropyrimidine core unit have been isolated from marine sources, which also exhibit interesting biological properties. Most notably, among these are the batzelladine alkaloids, which were found to be potent HIV gp-120-CD4 inhibitors[8]. In the frame work of our program to develop the chemistry of heterocyclic compounds and in connection with our ongoing interests in multicomponent reactions[11-15], we would like to introduce a facile procedure for the synthesis of *bis*(dihydropyrimidinone)benzenes *via* one-pot condensation of terephthalic aldehyde or isophthalic aldehyde with (thio)urea, guanidine and 1,3- dicarbonyl compounds (**Scheme-I**). The reaction proceeds at 100 ºC under solvent-free microwave irradiation conditions using catalytic amount of nanosilica to afford the title compounds in short time periods with high yields. Microwave-promoted solvent-free heterogeneous reactions are well known as environmentally benign methods that also usually provide improved selectively, enhanced reaction rates, cleaner products and manipulative simplicity[13].

EXPERIMENTAL

The reactions under microwaves were performed in a Milstone microwave reactor. Melting points was measured on the Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Bomem FT-IR-MB 100 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured with a Bruker DRX-300 Avance spectrometer at 300 MHz and 75 MHz using TMS as internal standard. Chemical shifts are



Scheme-I

reported (δ) relative to TMS and coupling constant (*J*) is reported in hertz (Hz). Mass spectra were recorded on a MS model 5973 Network apparatus at ionization potential of 70 eV. Elemental analysis for C, H and N were performed using a Thermo Finnigan Flash EA 1112 instrument. All other reagents were purchased from commercial sources and were freshly used after being purified by standard procedures.

Typical procedure for the preparation of (4a-4n): A mixture of dialdehyde (1 mmol), 1,3-dicarbonyl compounds (2 mmol), (thio)urea or guanidine (3 mmol) and nanosilica catalyst (0.2 g nano SiO_2) were mixed and sealed with a cap containing a septum. The loaded vial was then placed into the cavity of the microwave reactor and heated at 100 ºC for 3-4 min. After completion of the reaction (monitored by TLC, the ethyl acetate/*n*-hexane), the contents were cooled to room temperature and mixed thoroughly with 3 × 10 mL of acetone. The solid catalyst was fitered off. After separation of solid, the solvent was evaporated under reduced pressure. The resulting solid residue was purified by recrystallization from acetone-water (9:1 v:v). Products were characterized by analyzing their ^{1}H NMR and ^{13}C NMR and mass spectra and their purity was confirmed by elemental analysis.

4'-(1,4-Phenylene)*bis*[5-acetyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one] (4a): Yield 93 %, m.p. 315-317 °C (decomp.). IR (KBr, ν_{max}, cm^{-1}): 3279, 3103, 2923, 1706, 1601, 1326. ^{1}H NMR (DMSO-d_6) δ: 9.17 (s, br, 2H, NH), 7.78 (s, br, 2H, NH), 7.18 (s, 4H, Ar), 5.21 (d, *J* = 3 Hz, 2H, CH), 2.27 (s, 6H, COMe), 2.10 (s, 6H, Me). ^{13}C NMR (DMSO-d_6) δ: 195.0, 152.9, 148.9, 144.3, 127.4, 110.5, 54.3, 31.3, 19.7. MS: (m/z) (%) 382 (M$^+$, 7), 354(10), 259(17), 183(100), 155(45), 43(95).

1,1'-[4,4'-(1,4-Phenylene)*bis*(6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5,4-diyl)]diethanone (4b): Yield 91 %, m.p. 310-312 °C (decomp.). IR (KBr, ν_{max}, cm^{-1}): 3384, 3176, 2981, 1615, 1447. ^{1}H NMR (DMSO-d_6) δ: 10.23 (s, 2H, NH), 9.66 (s, 2H, NH), 7.17 (s, 4H, Ar), 5.24 (s, 2H, CH), 2.29 (s, 6H, COM), 2.16 (s, 6H, Me). ^{13}C NMR (DMSO-d_6) δ: 193.5, 174.6, 148.9, 144.2, 127.4, 110.6, 54.5, 31.2, 19.80. MS: (m/z) (%) 414 (M$^+$, 6), 325(11), 314(17), 274(19), 140(94), 59(100).

1,1'-[4,4'-(1,4-Phenylene)*bis*(2-imino-6-methyl-1,2,3,4-tetrahydropyrimidine-5,4-diyl)]diethanone (4c): Yield 85 %, m.p. 298-300°C (decomp.). IR (KBr, ν_{max}, cm^{-1}): 3353, 3220, 2973, 1694, 1606, 1374. ^{1}H NMR (DMSO-d_6) δ: 9.99 (s, br, 2H, NH), 7.95 (s 2H, NH), 7.21 (s, 4H, Ar), 6.28 (s, br, 2H, NH), 5.23 (s, 2H, CH), 2.23 (s, 6H, COMe), 2.06 (s, 6H, Me). ^{13}C NMR (DMSO-d_6) δ: 193.4, 178.2, 154.3, 144.6, 127.6, 109.5, 53.2, 31.1, 20.1. MS: (m/z) (%) 380 (M$^+$, 9), 351(11), 307(19), 267(25), 183(78), 59(81), 43(100). Anal. calcd. (%) for $C_{20}H_{24}N_6O_2$: C, 63.14; H, 6.36; N, 22.09. Found: C, 63.41, H, 6.71; N, 21.97.

Diethyl 4,4'-(1,4-phenylene)*bis*(6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate) (4d): Yield 90 %, m.p. 315-317 °C (decomp.). IR (KBr, ν_{max}, cm^{-1}): 3326, 3105, 2975, 1702, 1236. ^{1}H NMR (DMSO-d_6) δ: 9.97 (s, 2H, NH), 7.71 (s, 2H, NH), 7.18 (s, 4H, Ar), 5.11 (d, *J* = 3.1 Hz, 2H, CH), 3.97 (q, *J* = 7.1 Hz, 4H, OCH_2CH_3), 2.83 (s, 6H, Me), 1.11 (t, *J* = 7.1 Hz, 6H, OCH_2CH_3). ^{13}C NMR (DMSO-d_6) δ: 165.3, 152.1, 148.3, 143.9, 127.1, 99.2, 59.2, 53.7, 17.8, 14.1. MS: (m/z) (%) 442 (M$^+$, 7), 398(9), 296(21), 256(54), 183(73), 59(100).

Diethyl 4,4'-(1,4-phenylene)*bis*(6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate) (4e): Yield 91 %, m.p. 312-315 °C (decomp.). IR (KBr, ν_{max}, cm^{-1}): 3308, 3169, 2987, 1667, 1451. ^{1}H NMR (DMSO-d_6) δ: 10.23 (s, 2H, NH), 9.54 (s, br, 2H, NH), 7.15 (s, 4H, Ar), 5.14 (d, *J* = 3.5 Hz, 2H, CH), 3.92 (q, *J* = 6.6 Hz, 4H, OCH_2CH_3), 2.25 (s, 6H, Me), 1.06 (t, *J* = 6.6 Hz, 6H, OCH_2CH_3). ^{13}C NMR (DMSO-d_6) δ: 175.1, 165.9, 145.9, 143.8, 127.5, 101.4, 60.5, 54.6, 18.1, 14.8. MS: (m/z) (%) 474 (M$^+$, 5), 304(31), 199(50), 84(54), 60(39), 59(100). Anal. calcd. (%) for $C_{22}H_{26}N_4O_4S_2$:

C, 55.68; H, 5.52; N, 11.81. Found: C, 55.71; H, 5.63; N, 11.59.

Diethyl-4,4'-(1,4-phenylene)*bis*(2-imino-6-methyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate) (4f): Yield 81 %, m.p. 295-297 °C (decomp.). IR (KBr, ν_{max}, cm^{-1}): 3366, 3175, 2978, 1699, 1186. ^{1}H NMR (DMSO-d_6) δ: 9.96 (s, 2H, NH), 7.86 (s, br, 2H, NH), 7.17 (s, 4H, Ar), 6.01 (s, 2H, NH), 5.21 (s, 2H, CH), 3.95 (q, *J* = 6.7 Hz, 4H, OCH_2CH_3), 2.23 (s, 6H, Me), 1.06 (t, *J* = 6.7 Hz, 6H, OCH_2 CH_3). ^{13}C NMR (DMSO-d_6) δ: 166.8, 165.3, 154.8, 142.3, 127.6, 101.3, 59.6, 53.1, 18.9, 18.1. MS: (m/z) (%) 440 (M^+, 8), 396(11), 350(17), 290(51), 263(54), 210(61), 57(100). Anal. calcd. (%) for $C_{22}H_{28}N_6O_4$: C, 59.99; H, 6.41; N, 19.08. Found: C, 60.05; H, 6.87; N, 18.95

4,4'-(1,4-Phenylene)*bis*(6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5,4-yl))*bis*(phenylmethanone) (4g): Yield 86 %, m.p. 295-298 °C (decomp.). IR (KBr, ν_{max}, cm^{-1}): 3312, 3110, 2923, 1702, 1667. ^{1}H NMR (DMSO-d_6) δ: 9.15 (s, 2H, NH), 7.75 (s, br, 2H, NH), 7.49-7.38 (m, 10H, COPh), 7.13 (s, 4H, Ar), 5.23 (d, *J* = 2.5 Hz, 2H, CH), 1.64 (s, 6H, Me). ^{13}C NMR (DMSO-d_6) δ: 195.1, 152.9, 146.5, 144.1, 141.9, 132.3, 129.4, 128.5, 127.2, 110.2, 55.7, 19.3. MS: (m/z) (%) 506 (M^+, 5), 450(7), 410(100), 318(71), 242(85), 126(31), 116(41), 57(26). Anal. calcd. (%) for $C_{30}H_{26}N_4O_4$: C, 71.13; H, 5.17; N, 11.06. Found: C, 71.49; H, 5.11; N, 11.13.

4,4'-(1,4-Phenylene)*bis*(6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5,4-diyl))*bis*(phenylmethanone) (4h): Yield 85 %, m.p. 301-303 °C (decomp.), IR (KBr, ν_{max}, cm^{-1}): 3268, 3167, 2993, 1610, 1574, 1460. ^{1}H NMR (DMSO-d_6) δ: 10.23 (s, 2H, NH), 9.58 (s, br, 2H, NH), 7.49-7.39 (m, 10H, COPh), 7.13 (s, 4H, Ar), 5.23 (d, *J* = 2.3 Hz, 2H, CH), 1.66 (s, 6H, Me). ^{13}C NMR (DMSO-d_6) δ: 195.3, 175.1, 143.3, 142.8, 140.9, 132.7, 129.5, 128.7, 127.5, 110.8, 55.8, 18.8. MS: (m/z) (%) 538 (M^+, 5), 523(9), 509(12), 442(75), 418(23), 398(37), 298(100), 116(51), 106(31). Anal. calcd. (%) (%) for $C_{30}H_{26}N_4O_2S_2$: C, 66.89; H, 4.86; N, 10.40. Found: C, 66.61; H, 5.02; N, 10.25.

4,4'-(1,4-Phenylene)*bis*(5-acetyl-6-(trifluoromethyl)-3,4-dihydropyrimidin-2(1*H*)-one) (4i): Yield 81 %, m.p. 328-330 °C (decomp.). IR (KBr, ν_{max}, cm^{-1}): 3324, 2962, 1710, 1645, 1231. ^{1}H NMR (DMSO-d_6) δ: 9.48 (s, 2H, NH), 7.76 (s, 2H, NH), 7.31 (s, 4H, Ar), 5.14 (s, 2H, CH), 2.25 (s, 6H, Me). ^{13}C NMR (DMSO-d_6) δ: 193.9, 152.6, 144.4, 132.5, 129.1, 125.9, 107.8, 50.5, 27.6. MS: (m/z) (%) 490 (M^+, 11), 256(100), 69(85), 57(81), 43(63). Anal. calcd. (%) for $C_{20}H_{16}N_4O_4F_6$: C, 48.99; H, 3.29; N, 11.43. Found: C, 49.76; H, 3.21; N, 11.51.

4,4'-(1,4-Phenylene)*bis*(5-(thiophene-2-carbonyl)-6-(trifluoromethyl)-3,4-dihydropyrimidin-2(1*H*)-one) (4j): Yield 82 %, m.p. 218-220 °C (decomp.). IR (KBr, ν_{max}, cm^{-1}): 3157, 3089, 2912, 1658, 1603, 1205. ^{1}H NMR (DMSO-d_6) δ: 9.92 (s, 2H, NH), 7.89 (d, *J* = 4.5 Hz, 2H, thienyl), 7.78 (d, *J* = 3.9 Hz, 2H, thienyl), 7.69 (s, 2H, NH), 7.50 (s, 4H, Ar), 7.16 (dd, *J* = 3.9, 4.5 Hz, 2H, thienyl), 5.61 (s, 2H, CH). ^{13}C NMR (DMSO-d_6) δ: 182.3, 154.5, 146.1, 142.4, 140.9, 138.9, 137.0, 130.7, 129.3, 123.2, 104.5, 54.6. MS: (m/z) (%) 626 (M^+, 5), 542(11), 446(15), 397(21), 350(50), 268(71), 222(55), 111(100), 69(91). Anal. calcd. (%) for $C_{26}H_{16}N_4O_4S_2F_6$: C, 49.84; H, 2.57; N, 8.94. Found: C, 49.89; H, 2.69; N, 9.09.

1,1'-[4,4'-(1,3-Phenylene)*bis*(6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5,4-diyl)]diethanone (4k): Yield 83 %, m.p. 298-300 °C (decomp.). IR (KBr, ν_{max}, cm^{-1}): 3338, 3145, 2958, 1685, 1614, 1201. ^{1}H NMR (DMSO-d_6) δ: 9.17 (s, 2H, NH), 7.85 (s, br, 2H, NH), 7.30 (t, *J* = 7.2 Hz, 1H, Ar), 7.17 (s, 1H, Ar), 7.14 (d, *J* = 7.2 Hz, 2H, Ar), 5.21 (d, *J* = 3 Hz, 2H, CH), 2.27 (s, 6H, COMe), 2.08 (s, 6H, Me). ^{13}C NMR (DMSO-d_6) δ: 194.9, 152.9, 148.9, 145.3, 129.5, 126.4, 125.1, 110.3, 54.5, 31.3, 19.7. MS: (m/z) (%) 382 (M^+, 6), 368(40), 353(21), 236(71), 183(25), 57(100).

1,1'-[4,4'-(1,3-Phenylene)*bis*(6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5,4-diyl)] tetrahydropyrimidine-5,4-diyl))diethanone (4l): Yield 81 %, m.p. 298-301 °C (decomp.). IR (KBr, ν_{max}, cm^{-1}): 3266, 3192, 2920, 1612, 1561, 1449. ^{1}H NMR (DMSO-d_6) δ: 10.26 (s, br, 2H, NH), 9.76 (s, br, 2H, NH), 7.42-7.26 (m, 4H, Ar), 5.25 (s, 2H, CH), 2.32 (s, 6H, COMe), 2.15 (d, *J* = 5.4 Hz, 6H, Me). ^{13}C NMR (DMSO-d_6) δ: 195.5, 174.8, 145.4, 130.1, 126.9, 125.6, 111.3, 54.4, 31.3, 19.1. MS: (m/z) (%) 414 (M^+, 11), 369(9), 232(12), 183(95), 156(3), 59(100). Anal. calcd. (%) for $C_{20}H_{22}N_4O_2S_2$: C, 57.95; H, 5.35; N, 13.52. Found: C, 57.38; H, 5.49; N, 13.21.

Diethyl-4,4'-(1,3-phenylene)*bis*(6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate) (4m): Yield 82 %, m.p. 303-305 °C (decomp.). IR (KBr, ν_{max}, cm^{-1}): 3428, 3258, 2923, 1642, 1458. ^{1}H NMR (DMSO-d_6) δ: 9.18 (s, br, 2H, NH), 7.75 (s, br, 2H, NH), 7.28 (t, *J* = 7.5 Hz, 1H, Ar), 7.14 (s, 1H, Ar), 7.11 (d, *J* = 7.5 Hz, 2H, Ar), 5.10 (d, *J* = 3 Hz, 2H, CH), 3.96 (q, *J* = 6.5 Hz, 4H, OCH_2CH_3), 2.23 (s, 6H, Me), 1.10 (t, *J* = 6.5 Hz, 6H, OCH_2CH_3). ^{13}C NMR (DMSO-d_6) δ: 166.1, 152.9, 149.2, 145.9, 129.3, 126.1, 124.9, 100.1, 60.1, 54.7, 18.6, 14.9. MS: (m/z) (%) 442 (M^+, 19), 396(15), 353(29), 183(100), 43(52).

Diethyl-4,4'-(1,3-phenylene)*bis*(6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5- carboxylate) (4n): Yield 81 %, m.p. 297-300 °C (decomp.), IR (KBr, ν_{max}, cm^{-1}): 3466, 3254, 2981, 1694, 1652, 1462. ^{1}H NMR (DMSO-d_6) δ: 10.11 (s, 2H, NH), 9.35 (s, br, 2H, NH), 7.41-7.27 (m, 4H, Ar), 5.14 (d, *J* = 3.3 Hz, 2H, CH) 4.05 (q, *J* = 7.2 Hz, 4H, OCH_2CH_3), 36 (s, 6H, Me), 1.12 (t, *J* = 7.2 Hz, 6H, OCH_2CH_3). ^{13}C NMR (DMSO-d_6) δ: 175.3, 165.4, 145.8, 137.3, 133.5, 130.5, 127.2, 101.2, 60.5, 54.7, 18.1, 14.8. MS: (m/z) (%) 474 (M^+, 11), 368(81), 353(33), 230(70), 183(61), 59(100). Anal. calcd. (%) for $C_{22}H_{26}N_4O_4S_2$: C, 55.68; H, 5.52; N, 11.81. Found: C, 55.23; H, 5.68; N, 12.01.

RESULTS AND DISCUSSION

The original Biginelli protocol for the preparation of the 3,4-dihydropyrimidine-2-(1*H*)-ones (DHMPs) consisted of heating a mixture of the three components (aldehyde, β-keto-ester and urea) in ethanol containing a catalytic amount of HCl[6]. The major drawback associated with this protocol is the low yields, particularly for substituted aromatic and aliphatic aldehydes[14]. This has led to the development of multi-step synthetic strategies[15], involving combinations of Lewis acids and transition metal salts, *e.g.* $BF_3.OEt_2$, polyphosphate esters and reagents like CuI, $InCl_3$, $Mn(OAc)_3$, trimethylsilyltriflate, $LaCl_3{\cdot}7H_2O$, TMSCl, I_2, $CeCl_3{\cdot}7H_2O$, $LiClO_4$, $KHSO_4$ $Yb(OTf)_3$, clays, *etc*. However, many of these methods involve expensive reagents, long reaction times and stoichiometric

TABLE-1
NANOSILICA CATALYZED ONE-POT SYNTHESIS OF COMPOUNDS (**4**) UNDER MICROWAVE IRRADIATION CONDITIONS

Compound[a]	OHC-Ar-CHO	R^1	R^2	X	Time (min)	Yields[c] (%)
4a	1,4-$(CHO)_2$-C_6H_4	Me	Me	O	3	93
4b	1,4-$(CHO)_2$-C_6H_4	Me	Me	S	4	91
4c	1,4-(CHO)-C_6H_4[b]	Me	Me	NH	3	85
4d	1,4-$(CHO)_2$-C_6H_4	Me	OEt	O	3	90
4e	1,4-$(CHO)_2$-C_6H_4	Me	OEt	S	4	91
4f	1,4-$(CHO)_2$-C_6H_4[b]	Me	OEt	NH	4	81
4g	1,4-$(CHO)_2$-C_6H_4[b]	Me	Ph	O	4	86
4h	1,4-$(CHO)_2.C_6H_4$[b]	Me	Ph	S	4	85
4i	1,4-$(CHO)_2$-C_6H_4[b]	CF_3	Me	O	3	81
4j	1,4-$(CHO)_2$-C_6H_4[b]	CF_3	2-thienyl	O	3	82
4k	1,3-$(CHO)_2$-C_6H_4	Me	Me	O	3	83
4l	1,3-$(CHO)_2$-C_6H_4[b]	Me	Me	S	3	81
4m	1,3-$(CHO)_2$-C_6H_4	Me	OEt	O	3	82
4n	1,3-$(CHO)_2$-C_6H_4[b]	Me	Oet	S	4	81

[a]Reaction conditions: Dialdehyde (1 mmol), (thio)urea or guanidine (3 mmol) and 1,3-dicarbonylcompounds (2 mmol), acetic acid/nano SiO_2, under microwave irradiation conditions, no solvent. [b]All new products were fully characterized by ^{1}H NMR and ^{13}C NMR, IR, mass spectroscopy, and elemental analysis. [c]Isolated yields.

amount of catalysts and difficult to handle especially on a large scale. Therefore, the discovery of a new and an inexpensive catalyst for the preparation of dihydropyrimidin-2(1*H*)-ones under mild and efficient conditions is of prime importance. For the increasing environmental and economical concerns in recent years, it is now essential for chemists to search environmentally benign catalytic reactions as many as possible. Here we wish to report the use of a catalytic agent, phosphoric acid in the Biginelli's reaction under microwave- assisted solvent-free conditions. Table-1 summarizes the results for reactions of terephthalic aldehyde or isophthalic aldehyde with various derivatives of (**1**) and (**2**). We initially examined the reaction of ethyl acetoacetate (**1b**) with thiourea (**2b**) and terephthalic aldehyde (**3a**) in the presence of nano SiO_2 as an inexpensive and effective catalyst under microwave irradiation conditions at 100 °C (**Scheme-I**). The structure of product **4e** in 91 % yield was elucidated by spectroscopy methods and its purity was confirmed by elemental analysis. The procedure is shown to be equally efficient when thiourea is replaced urea or guanidine. Microwave is a very convenient energy source and is becoming more and more commonly used in synthetic organic chemistry[16]. In addition, it can be concluded from both ^{1}H NMR and ^{13}C NMR spectra of the product that the reaction is stereospecific loading to exclusive formation of one the meso or dl diastereoproducts from which the meso product is shown here for the simplicity.

Conclusion

An efficient and important catalytic activity of nanosilica (cheap, non-corrosive, easily available and reusable catalyst) has been studied for synthesis of *bis*(dihydropyrimidin-ones or thiones)benzenes under microwave irradiation (MWI) conditions. The present procedure describes useful improvement in the protocol condition for the Biginelli condensation. High to excellent yields, ease of workup, mild reaction conditions, short reaction times, environmentally friendly procedure, survival of different functional groups and the ability to tolerate a variety of substituents in all three components are features of this new procedure. This method not only preserved the simplicity of Biginelli's one-pot condensation but also remarkably improved the yields (> 81 %) of dihydropyrimidinones in shorter reaction times (3-4 min). The catalyst is reusable and can be applied several times without any decrease in the yield of the reactions.

ACKNOWLEDGEMENTS

The authors gratefully acknowledged the financial support from the Islamic Azad University-South Tehran Branch.

REFERENCES

1. (a) J. Zhu and H. Bienaym, Multicomponent Reactions, Wiley-VCH, Weinheim (2005); (b) H. Bienayme, C. Hulme, G. Oddon and P. Schmitt, *Chem. Eur. J.*, **6**, 3321 (2000).
2. (a) S.L. Schreiber, *Science*, **287**, 1964 (2000); (b) R.E. Dolle and K.H. Nelson, *J. Comb. Chem.*, **1**, 235 (1999).
3. L. Weber, K. lllgen and M. Almstetter, *Synlett*, **3**, 366 (1999).
4. P. Biginelli, *Gazz. Chim. Ital.*, **23**, 360 (1893).
5. Biginelli stated (ref 4) that his research was inspired by the earlier work of R. Behrend on the urea-ketoester coupling and U. Schiff on the urea-aldehyde coupling.
6. (a) C.O. Kappe, *Tetrahedron*, **49**, 6937 (1993) and references cited therein; (b) C.O. Kappe, *Acc. Chem. Res.*, **33**, 879 (2000).
7. (a) C.O. Kappe, *J. Med. Chem.*, **35**, 1043 (2000); (b) G.C. Rovnyak, S.D. Kimball, B. Beyer, G. Cucinotta, J.D. DiMarco, J.Z. Gougoutas, A. Hedberg, M.F. Malley, J.P. McCarthy, R. Zhang and S. Moreland, *J. Med. Chem.*, **38**, 119 (1995) and references therein.
8. (a) B.B. Snider, J. Chen, A.D. Patil and A. Freyer, *Tetrahedron Lett.*, **37**, 6977 (1996); (b) A.V. Rama Rao, M.K. Gujar and J. Vasudevan, *J. Chem. Soc., Chem. Commun.*, 1369 (1995).
9. D. Nematollahi, J. Azizian, M. Sargordan-Arani, M. Hesari and B. Mirza, *J. Heterocycl. Chem.*, **46**, 1000 (2009).
10. J. Azizian, B. Mirza, M.M. Mojtahedi, M.S. Abaee and M. Sargordan, *J. Fluorine Chem.*, **129**, 1083 (2008).
11. J. Azizian, A.A. Mohammadi, M. Kohshari, A.R. Karimi and M.R. Mohammadizadeh, *J. Heterocycl. Chem.*, **44**, 455 (2007).
12. J. Azizian, F. Hatamjafari, A.R. Karimi and M. Shaabanzadeh, *Synthesis*, 765 (2006).
13. S.A. Galema, *Chem. Soc. Rev.*, **26**, 233 (1997).
14. (a) K.S. Atwal, G.C. Rovnyak, B.C. O'Reilly and J. Schwartz, *J. Org. Chem.*, **54**, 5898 (1989).
15. (a) H.R. Kalita and P. Phukan, *Catal. Commun.*, **8**, 179 (2007); (b) A.D. Dilman and S.L. Loffe, *Chem. Rev.*, **103**, 733 (2003).
16. S. Caddick, *Tetrahedron*, **51**, 10403 (1995).