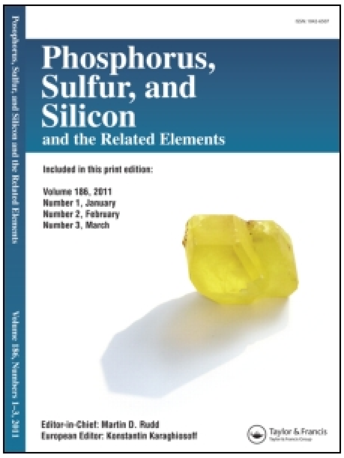

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Microwave Assisted Synthesis of Some Pyrimidine Derivatives Using Polyphosphate Ester (PPE) in Ceramic Bath

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To cite this Article Foroughifar, N. , Mobinikhaledi, A. and FathinejadJirandehi, H.(2003) 'Microwave Assisted Synthesis of Some Pyrimidine Derivatives Using Polyphosphate Ester (PPE) in Ceramic Bath', Phosphorus, Sulfur, and Silicon and the Related Elements, 178: 6, 1241 — 1246

To link to this Article: DOI: 10.1080/10426500307892

URL: http://dx.doi.org/10.1080/10426500307892

Phosphorus, Sulfur, and Silicon, 178:1241–1246, 2003

ISSN: 1042-6507 print
DOI: 10.1080/10426500390200512

MICROWAVE ASSISTED SYNTHESIS OF SOME PYRIMIDINE DERIVATIVES USING POLYPHOSPHATE ESTER (PPE) IN CERAMIC BATH

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(Received September 10, 2002; accepted October 15, 2002)

*Pyrimidine derivatives, **4a–4m**, were synthesized in high yield using a newly developed microwave-assisted cyclocondensation reaction of β-ketoester, aryl aldehyde, and (thio)urea. In all of these Biginelli reactions, a mixture of the appropriate β-ketoester, aryl aldehyde, and (thio)urea were subjected to microwave irradiation by using polyphosphate ester (PPE) as a reaction moderator. ^{1}H NMR and IR spectroscopies were used for characterization of compounds **4a–4m**.*

Keywords: Microwave irradiation; polyphosphate ester; 1,2,3,4-tetrahydro-pyrimidine-5-carboxylate

Pyrimidines have been subjected to large number of different modifications in order to obtain derivatives having different biological properties. Several groups have studied the chemistry and pharmacological properties of pyrimidine derivatives.[1–14] Pyrimidines have been found to have a broad range of biological effects including antiviral, antitumor, antibacterial, anti-inflammatory,[1] antihypertensive,[2] cardiovascular agents,[3] calcium channel blocking[4] (e.g., nifedipine), and neuropeptide Y (NPY) antagonists.[15] Microwave irradiation is a nonconventional energy source which has been of special interest in organic chemistry in recent years.[16–19] Some interesting features of this method are the rapid reaction rates, simplicity, and cleaner reaction conditions.[5,13,16] The versatile biological properties of pyrimidine derivatives prompted us to take up this project for synthesizing some novel derivatives by using a newly developed microwave-assisted cyclocondensation reaction of β-ketoester, aryl aldehyde, and (thio)urea.

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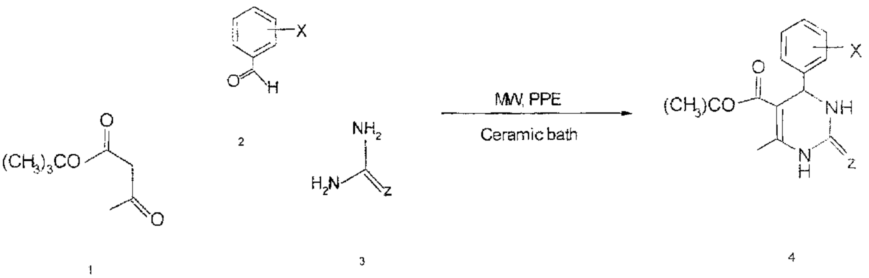
RESULTS AND DISCUSSION

β-Ketoester **1**, aryl aldehyde **2**, (thio)urea **3**, and polyphosphate ester (PPE) were reacted under microwave irradiation to give the corresponding pyrimidine derivative **4** (Scheme 1).



SCHEME 1

In all experiments a molar ratio 1.1:1.1:1.5 of the three components, **1, 2**, and **3**, were used as reactants.[21] This method is very easy and it can be utilized for different aldehydes **2** and (thio)ureas **3** depending on X and Z groups to prepare entries **4a–4m** (see Table I).

The advantage of PPE as a moderate in this reaction may be due to specific interaction of PPE with N-acyliminium ion intermediate which may formed from the aldehyde **2** and urea **3** in the initial reaction step.[22] Yields of these one-pot protocol reactions following recrystallization in ethanol were of the order of 68–90% (see Table I), which is very favorable as compared with the multistep method.[23] ^{1}H NMR

TABLE I Pyrimidine Derivatives **4a–4m**

Entry	Z	X	Yield%
4a	O	H	85
4b	O	2,5-$(MeO)_2$	90
4c	O	4-$N(Me)_2$	83
4d	O	4-Cl	75
4e	O	4-MeO	69
4f	O	2-Me	70
4g	O	3-NO_2	78
4h	O	4-Me	68
4i	S	H	85
4j	S	2,5-$(MeO)_2$	90
4k	S	4-$N(Me)_2$	80
4l	S	4-Cl	83
4m	S	4-MeO	70

(500 MHz) measurements of these compounds confirmed their purity to be more than 95%. In the ^{1}H NMR spectra the sharp singlet signal at 1.20–1.30 ppm with integrating 9 protons is assigned to the t-Bu group. The singlet signal at 2.20–2.25 ppm with integrating 3 protons is assigned to the resonance of the $-CH_3$ group on the pyrimidine ring. Resonances at 6.87–8.00 ppm are attributed to aromatic protons of the phenyl and pyrimidine rings. The protons of the pyrimidine ring resonate at higher field compared to those of the phenyl ring. The two different broad signals at low field are due to resonance of the two NHs of the pyrimidine ring. This was supported by IR spectra, which included signals in the region 3126–3425 cm^{-1}. Also, the IR spectra of all compounds show absorption at 1698–1709 cm^{-1}, which is characteristic of the carbonyl group. In conclusion we have found that using PPE is an efficient medium for the preparation of pyrimidine derivatives by using microwave irradiation in solvent free conditions.

EXPERIMENTAL

All chemicals (β-ketoester, arylaldehyde, (thio)urea) were of reagent grade quality and used without further purification. PPE was prepared using the method of Cava and coworkers[20] (yield 85%, d = 1.503 g/ml). Melting points were determined on an electrothermal digital melting point apparatus. H^1 NMR spectra were recorded on a Brucker 500 MHz spectrometer. TMS was used as internal standard. IR spectra were performed on a Galaxy FT-IR 500 spectrophotometer. Reaction progress was monitored routinely by thin layer chromatography on silica gel (Merck) plates. Reactions were performed in a Samsung microwave oven of household with a 230V-50Hz power source, 900W output, and 2450 MHz operating frequency.

General Procedure

β-Ketoester (2.2 mmol), aryl aldehyde (3.0 mmol), (thio)urea (3.0 mmol), along with PPE (300 mg) were placed in a 25 ml glass beaker and stirred for 3 min with a magnetic stirrer. This beaker was placed inside a ceramic bath and was then inserted into a microwave oven. The mixture was subjected to microwave irradiation at 50% power level 3 times for 30 s (total irradiation time 90 s). The mixture was cooled for 1 and 2 min after first and second irradiation respectively. After cooling the reaction mixture, water (5 ml) was added and stirred at room temperature for 2 h. The crude products were filtered and recrystallized from ethanol to give compounds **4a–4m**.

tert-Butyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydro Pyrimidine-5-carboxylate (4a)

Yield 85%, m.p. 215–216°C

IR (KBr): $\nu = 3240, 3090, 1705, 1680, 1650\ \mathrm{cm}^{-1}$

^{1}H NMR (DMSO-d_6); δ (ppm) = 1.31 (s, 9H, t-Bu), 2.21 (s, 3H, CH_3), 5.10 (d, 1H, j = 3.0 Hz), H-4), 6.87–7.21 (m, 5H, arom), 7.69 (brs, 1H, NH), 9.01 (brs, 1H, NH)

tert-Butyl-6-methyl-4-(2,5-dimetothxy Phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b)

Yield 90%, m.p. 200–202°C

IR (KBr): $\nu = 3294, 3182, 3045, 1708, 1654.8, 1600\ \mathrm{cm}^{-1}$

^{1}H NMR (DMSO-d_6); δ (ppm) = 1.22 (s, 9H, t-Bu), 2.24 (s, 3H, CH_3), 5.39 (d, j = 3.0 Hz, 1H, H-4), 6.87 (m, 2H, arom), 7.10 (m, 1H, arom), 7.35 (brs, 1H, NH), 8.94 (brs, 1H, NH)

tert-Butyl-6-methyl-4-(4-dimethyl Amino Phenyl)-2-oxo-1,2,3,4-tetrahydro Pyrimidine-5-carboxylate (4c)

Yield 83%, m.p. 213–214°C

IR (KBr): $\nu = 3126.8, 3010, 1701, 1650, 1618\ \mathrm{cm}^{-1}$

H^1 NMR (DMSO-d_6); δ (ppm) = 1.29 (s, 9H, t-Bu), 2.24 (s, 3H, CH_3), 4.97 (d, j = 3.0 Hz, 1H, H-4), 6.71 (m, 2H, arom), 6.97 (m, 2H, arom), 8.46 (brs, 1H, NH), 9.10 (brs, 1H, NH)

tert-Butyl-6-methyl-4-(4-chloro Phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d)

Yield 75%, m.p. 195–197°C

IR (KBr): $\nu = 3247, 3103.9, 1701.1, 1651\ \mathrm{cm}^{-1}$

H^1 NMR (DMSO-d_6); δ (ppm) = 1.28 (s, 9H, t-Bu), 2.22 (s, 3H, CH_3), 5.07 (d, j = 3.0 Hz, 1H, H-4), 7.25–7.35 (m, 4H, arom), 7.69 (brs, 1H, NH), 9.11 (brs, 1H, NH)

tert-Butyl-6-methyl-4-(4-methoxy Phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e)

Yield 69%, m.p. 212–213°C

IR (KBr): $\nu = 3236, 3111, 1705, 1648, 1603\ \mathrm{cm}^{-1}$

H^1 NMR (DMSO-d_6); δ (ppm) = 1.25 (s, 9H, t-Bu), 2.22 (s, 3H, CH_3), 5.08 (d, j = 3.0 Hz, 1H, H-4), 6.83–7.01 (m, 4H, arom), 8.01 (brs, 1H, NH), 9.30 (brs, 1H, NH)

tert-Butyl-6-methyl-4-(2-methyl Phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f)

Yield 70%, m.p. 200–201°C

IR (KBr): $\nu = 3236.3, 3109, 1701.1, 1678\ \mathrm{cm}^{-1}$

^{1}H NMR (DMSO-d_6); δ (ppm) = 1.30 (s, 9H, t-Bu), 2.24 (s, 3H, CH_3), 5.12 (d, j = 3.0 Hz, 1 H, H-4), 6.90–7.10 (m, 4H, arom), 7.66 (brs, 1H, NH), 8.66 (brs, 1H, NH)

tert-Butyl-6-methyl-4-(3-nitro Phenyl)-2-oxo-1,2,3,4-tetrahhydropyrimidine-5-carboxylate (4g)

Yield 78%, m.p. 195–196.5°C

IR (KBr): $\nu = 3240, 3105, 1705, 1674, 1535, 1350\ cm^{-1}$

^{1}H NMR (DMSO-d_6); δ (ppm) = 1.29 (s, 9H, t-Bu), 2.24 (s, 3H, CH_3), 5.10 (d, J = 3.0 Hz, 1H, H-4), 7.25 (m, 2H, arom), 7.90 (brs, 1H, NH), 8.10 (m, 2H, arom), 9.34 (brs, 1H, NH)

tert-Butyl-6-methyl-4-(4-methyl Phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4h)

Yield 68%, m.p. 206–207°C

IR (KBr): $\nu = 3186, 3080, 1705, 1655, 1634\ cm^{-1}$

^{1}H NMR (DMSO-d_6); δ (ppm) = 1.27 (s, 9H, t-Bu), 2.21 (s, 3H, CH_3), 5.01 (d, j = 3.0 Hz, 1H, H-4), 6.85–6.98 (m, 4H, arom), 7.25 (brs, 1H, NH), 8.35 (brs, 1H, NH)

tert-Butyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i)

Yield 85%, m.p. 206–207°C

IR (KBr): $\nu = 3165, 3050, 1703.2, 1562\ cm^{-1}$

^{1}H NMR (DMSO-d_6); δ (ppm) = 1.27 (s, 9H, t-Bu), 2.25 (s, 3H, CH_3), 5.10 (d, j = 3.0 Hz, 1H, H-4), 7.24 (m, 5H, arom), 9.55 (brs, 1H, NH), 10.19 (brs, 1H, NH)

tert-Butyl-6-methyl-(2,5-dimethoxy Phenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4j)

Yield 90%, m.p. 201–202°C

IR (KBr): $\nu = 3176, 3010, 1709, 1655\ cm^{-1}$

^{1}H NMR (DMSO-d_6); δ (ppm) = 1.31 (s, 9H, t-Bu), 2.22 (s, 3H, CH_3), 5.25 (d, j = 3.0 Hz, 1H, H-4), 6.98 (m, 2H, arom), 7.35 (m, 1H, arom), 7.85 (brs, 1H, NH), 8.90 (brs, 1H, NH)

tert-Butyl-6-methyl-4-(4-dimethylamino Phenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4k)

Yield 80%, m.p. 206–207°C

IR (KBr): $\nu = 3425, 3169.6, 1701.1, 1650\ cm^{-1}$

^{1}H NMR (DMSO-d_6); δ (ppm) = 1.30 (s, 9H, t-Bu), 2.24 (s, 3H, CH_3), 5.01 (d, j = 3.0 Hz, 1H, H-4), 6.99 (m, 2H, arom), 7.40 (m, 2H, arom), 9.46 (brs, 1H, NH), 10.10 (brs, 1H, NH)

tert-Butyl-6-methyl-4-(4-chloro Phenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4l)

Yield 83%, m.p. 214–215°C
IR (KBr): $\nu = 3250, 3105, 1703, 1680\ \text{cm}^{-1}$
^{1}H NMR (DMSO-d$_6$); δ (ppm) = 1.32 (s, 9H, t-Bu), 2.23 (s, 3H, CH_3), 5.20 (d, j = 3.0 Hz, 1H, H-4), 7.40–7.80 (m, 4H, arom), 7.95 (brs, 1H, NH), 8.90 (brs, 1H, NH)

tert-Butyl-6-methyl-4-(4-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4m)

Yield 70%, m.p. 183–185°C
IR (KBr): $\nu = 3313.5, 3170.8, 3105, 1698, 1666\ \text{cm}^{-1}$
^{1}H NMR (DMSO-d$_6$); δ (ppm) = 1.28 (s, 9H, t-Bu), 2.25 (s, 3H, CH_3), 5.01 (d, j = 3.0 Hz, 1H, H-4), 7.20 (m, 2H, arom), 7.40 (m, 2H, arom), 7.65 (brs, 1H, NH), 9.01 (brs, 1H, NH)

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