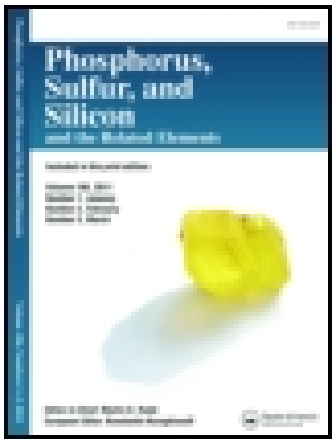


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Synthesis of Some Biginelli Compounds in Solvent Medium Using a Photochemistry Method

N. Foroughifar [a] , A. Mobinikhaledi [a] & H. Fathinejad Jirandehi [a]

[a] Arak University , Arak, Iran

Published online: 27 Oct 2010.

To cite this article: N. Foroughifar , A. Mobinikhaledi & H. Fathinejad Jirandehi (2003) Synthesis of Some Biginelli Compounds in Solvent Medium Using a Photochemistry Method, Phosphorus, Sulfur, and Silicon and the Related Elements, 178:3, 495-500

To link to this article: http://dx.doi.org/10.1080/10426500307928

Phosphorus, Sulfur and Silicon, 2003, Vol. 178:495–500

1042-6507/03 $12.00 + .00
DOI: 10.1080/10426500390170624

SYNTHESIS OF SOME BIGINELLI COMPOUNDS IN SOLVENT MEDIUM USING A PHOTOCHEMISTRY METHOD

N. Foroughifar, A. Mobinikhaledi, and H. Fathinejad Jirandehi
Arak University, Arak, Iran

(Received August 13, 2002)

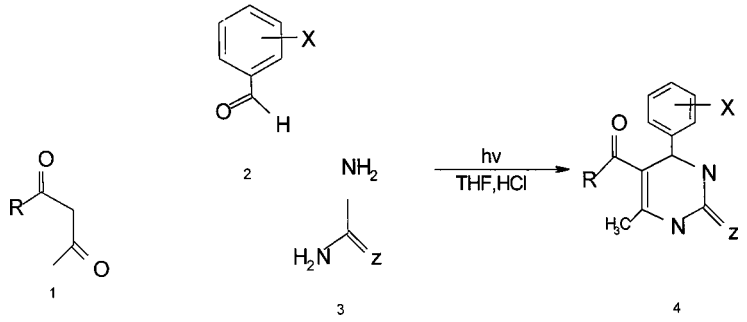
Some Biginelli compounds were synthesized by using a photochemistry method. The Biginell three-component cyclocondensation reactions in THF medium using a mixture of β-ketoester or β-diketone, arylaldehyde and (thio)urea under irradiation with a Wolframe lamplight gave 1,4-dihydropyrimidine-2(1H)-ones, DHPMs, in 70–95% yield after workup.

Keywords: 1,4-Dihydropyrimidine-2(1H)-ones; DHPM; photochemistry

INTRODUCTION

The first Biginelli compound was synthesized in 1893.[1] Recently this reaction has been extended for preparation of a large number of DHPMs.[2] It is well established that various derivatives of pyrimidines, DHPMs, exert interesting pharmacological efficiencies such as antitumor, antiviral, and antibacterial activities.[2–11] In the past decade DHPMs with appropriate functional groups have emerged as antihypertensive agents[6–9] and potent calcium channel blockers.[3–5] Thus, it seemed of interest for us to prepare 1,4-dihydropyrimidine-2(1H)-ones, DHPMs, with an improved procedure and in high yield. The most convenient method for preparation of these compounds is condensation of a β-ketoester or β-diketone **1**, arylaldehyde **2**, and (thio)urea **3** under acidic conditions giving a low to moderate yield, in particular when substituted aromatic aldehydes or thioureas are used as starting materials. The purpose of the present work is to extend the method of preparation of pyrimidine derivatives of type **4** by using the photochemistry method (Scheme 1).

Address correspondence to N. Foroughifar, Arak University, Chemistry Department, Dr. Beheshti Avenue, Arak, Iran. E-mail: N_Foroughifar@yahoo.com



SCHEME 1

RESULTS AND DISCUSSION

Reaction of the β-ketoester or β-diketone **1**, appropriate aldehyde **2**, and (thio)urea 3 in THF under irradiation with a 100 W electrical lamp afforded **4a–4m** in high yields (see Table I). In each experiment a molar ratio 1.1:1:1.5 of the three components, **1**, **2**, and **3** were used as reactants.[12] The method is very simple and it can be used for different β-ketoesters or β-diketones **1**, appropriate aldehydes **2**, and (thio)ureas **3** depending on Z, X, R groups to prepare various compounds. Substituted aldehydes or (thio)ureas can be used with no loss of yield (**4a–4g**, **4h–4m**, see Table I) which is the advantage of this method as compared with other methods.[2,12–16] Solubility of impurities in THF as a solvent is another advantage of this method, which distinguishes it from the

TABLE I 1,4-Dihydropyrimidine-2(1H)-ones, DHPMs (**4a–4m**)

DHPMs	Z	X	R	Required time (h)	Yield (%)
4a	O	H	Me	2.5	88
4b	O	4-Cl	Me	2	75
4c	O	4-$N(Me)_2$	Me	3	86
4d	O	H	EtO	2.5	85
4e	O	4-Cl	EtO	5	79
4f	O	4-NO_2	EtO	4	80
4g	O	2,5-$(MeO)_2$	EtO	3	95
4h	S	4-Me	EtO	4	85
4i	S	4-$N(Me)_2$	EtO	4	80
4j	S	H	EtO	3	81
4k	S	4-$N(Me)_2$	t-BuO	4	85
4l	S	4-Cl	t-BuO	5	75
4m	S	4-MeO	t-BuO	4	81

microwave-promoted preparation.[12] Reactions were usually carried out for 2 to 4 h. Yields of these one-pot protocol reactions following recrystallization in ethanol were of the order of 70–95%, which is very favorable as compared with a multistep method.[17] Based on ^{1}H NMR (500 MHz) spectra these products exhibited high purity. In the ^{1}H NMR spectra of these compounds the two different broad signals at low field were assigned to resonance of two NHs of the pyrimidine ring. This was supported by IR spectra, which included signals in the region 3200–3300 cm^{-1}.

In conclusion we have developed a simple and efficient practical method for preparation of 1,4-dihydropyrimidine-2(1H)-ones, DHPMs, in high yield, by using a 100 W electrical lamp.

EXPERIMENTAL

Melting points were determined on an electrothermal digital melting point apparatus. ^{1}H NMR spectra were recorded on a Bruker (500 MHz) Spectrometer. The IR spectra were recorded on Galaxy FT-IR 5000 Spectrophotometer. Reactions were monitored by thin layer chromatography. All commercial materials were used without purification.

General Procedure

A mixture of the β-ketoester or β-diketone (2.2 mmol) **1**, appropriate aldehyde **2** (2 mmol), (thio)urea (3 mmol) **3**, and THF (25 ml) was stirred while the set-up was irradiated from the top by a 100 W electrical lamp for the desired time. For compounds **4a–4m**, the clear solution converted to a turbid solution after the required time. Then the mixture was kept at room temperature for 5 h. The crude product was filtered off and recrystallized from ethanol to give pure product in 70–95% yields (Table I).

5-Acyl-6-methyl-4-phenyl-2-oxo-1,2,3, 4-tetrahydropyrimidine (4a)

Yield 88%, m.p. 219–221°C. IR (KBr): $\nu = 3260$, 3050, 1700, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d$_6$): δ (ppm) = 2.1 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 5.1 (d, J = 2.4 Hz, 1H, H_4), 7.2 (m, 5H, H_{arom}), 7.9 (brs, 1H, NH), 8.7 (brs, 1H, NH).

5-Acyl-6-methyl-4-(4-chlorophenyl)-2-oxo-1,2,3, 4-tetrahydropyrimidine (4b)

Yield 75%, m.p. 223–225°C. IR (KBr): $\nu = 3289$, 3050, 1699, 1619 cm^{-1}. ^{1}H-NMR (DMSO-d$_6$): δ (ppm) = 2.1 (s, 3H, CH_3), 2.3 (s, 3H,

CH_3), 5.2 (d, J = 2.4 Hz, 1H, H_4), 7.3 (m, 2H, H_{arom}), 7.8 (brs, 1H, NH), 9.2 (s, 1H, NH).

5-Acyl-6-methyl-4-(4-dimethylaminophenyl)-2-oxo-1,2,3, 4-tetrahydropyrimidine (4c)

Yield 86%, m.p. 235–237°C. IR (KBr): $\nu = 3265$, 3130, 3020, 1699, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 2.1 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 5.3 (d, J = 2.4 Hz, 1H, H_4), 7.2 (m, 2H, H_{arom}), 7.4 (m, 2H, H_{arom}), 7.7 (brs, 1H, NH), 8.5 (brs, 1H, NH).

Ethyl-6-methyl-4-phenyl-2-oxo-1,2,3, 4-tetrahydropyrimidine-5-carboxylate (4d)

Yield 86%, m.p. 202–204°C. IR (KBr): $\nu = 3245$, 3120, 3040, 1730, 1710 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 1.1 (t, J = 7.2 Hz, 3H, CH_3), 2.3 (s, 3H, CH_3), 4.0 (q, 2H, J = 7.5, $-OCH_2$), 5.2 (d, J = 3.4 Hz, 1H, H-4), 7.4 (m, 2H, H_{arom}), 7.7 (brs, 1H, NH), 8.5 (brs, 1H, NH).

Ethyl-6-methyl-4-(4-chlorophenyl)-2-oxo-1,2,3, 4-tetrahydropyrimidine-5-carboxylate (4e)

Yield 79%, m.p. 214–216°C. IR (KBr): $\nu = 3242$, 3118, 1724, 1702, 1648 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 1.1 (t, J = 7.2 Hz, 3H, CH_3), 2.3 (s, 3H, CH_3), 4.0 (q, J = 7.2 Hz, 2H, —OCH_2), 5.2 (d, J = 3.4 Hz, 1H, H_4), 7.4 (m, 4H, H_{arom}), 7.8 (brs, 1H, NH), 9.2 (brs, 1H, NH).

Ethyl-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3, 4-tetrahydropyrimidine-5-carboxylate (4f)

Yield 80%, m.p. 175–177.5°C. IR (KBr): $\nu = 3244$, 3117, 1726, 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 1.0 (t, 3H, CH_3), 2.2 (s, 3H, CH_3), 4.0 (q, J = 7.2 Hz, 2H, OCH_2), 5.3 (d, J = 3.6 Hz, 1H, H_4), 7.5 (m, 2H, H_{arom}), 7.9 (brs, 1H, NH).

Ethyl-6-methyl-4-(2,5-dimethoxyphenyl)-2-oxo-1,2,3, 4-tetrahydropyrimidine-5-carboxylate (4g)

Yield 95%, m.p. 187–188.5°C. IR (KBr): $\nu = 3240$, 3112, 1705, 1680 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 1.0 (t, J = 7.2 Hz, 3H, CH_3), 2.3 (s, 3H, CH_3), 3.8 (s, 6H, OCH_3), 4.0 (q, 2H, OCH_2), 5.2 (d, J = 3.6 Hz, 1H, H_4), 7.2 (s, 1H, H_{arom})), 7.5 (m, 2H, H_{arom}), 8.1 (brs, 1H, NH), 9.2 (brs, 1H, NH).

Ethyl-6-methyl-4-(4-methylphenyl)-2-thioxo-1,2,3, 4-tetrahydropyrimidine-5-carboxylate (4h)

Yield 85%, m.p. 185–187°C. IR (KBr): $\nu = 3325$, 3177, 1674 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 1.1 (t, J = 7.2 Hz, 3H, CH_3), 2.3 (s, 6H,

$2CH_3$), 4.0 (q, J = 7.2 Hz, 2H, $-OCH_2$), 5.2 (d, J = 3.6 Hz, 1H, H_4), 7.2 (m, 4H, H_{arom})), 9.5 (brs, 1H, NH), 10.2 (brs, 1H, NH).

Ethyl-6-methyl-4-(4-dimethylaminophenyl)-2-thioxo-1,2,3, 4-tetrahydropyrimidine-5-carboxylate (4i)

Yield 80%, m.p. 248–250°C. IR (KBr): $\nu = 3240$, 3100, 1730, 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 1.1 (t, J = 7.2 Hz, 3H, CH_3), 2.2 (s, 3H, CH_3), 2.8 (s, 6H, $N(CH_3)_2$), 4.0 (q, J = 7.2 Hz, 2H, OCH_2), 5.0 (d, J = 3.6 Hz, 1H, H_4), 6.5 (m, 2H, H_{arom}), 7.1 (m, 2H, H_{arom}), 7.5 (brs, 1H, NH).

Ethyl-6-methyl-4-phenyl-2-thioxo-1,2,3, 4-tetrahydropyrimidine-5-carboxylate (4j)

Yield 80%, m.p. 206–208°C. IR (KBr): $\nu = 3340$, 3180, 1703, 1675 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 1.1 (t, J = 7.2 Hz, 3H, CH_3), 2.3 (s, 3H, CH_3), 4.0 (q, J = 7.2 Hz, 2H, OCH_2), 5.3 (d, J = 3.6 Hz, 1H, H_4), 7.3 (m, 5H, H_{arom}), 9.6 (brs, 1H, NH), 10.3 (brs, 1H, NH).

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

Yield 85%, m.p. 214–216°C. IR (KBr): $\nu = 3330$, 3160, 3050, 1720, 1662 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 1.3 (s, 9H, $3CH_3$), 2.24 (s, 3H, CH_3), 2.8 (s, 6H, $N(CH_3)_2$), 5.12 (d, J = 3 Hz, 1H, H_4), 6.8 (m, 2H, H_{arom}), 7.3 (m, 2H, H_{arom}), 7.5 (brs, 1H, NH), 9.0 (brs, 1H, NH).

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

Yield 75%, m.p. 209–211°C. IR (KBr): $\nu = 3220$, 3180, 3010, 1705 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 1.3 (s, 9H, $3CH_3$), 2.24 (s, 3H, CH_3), 5.3 (d, J = 3.0 Hz, 1H, H_4), 7.3 (m, 4H, H_{arom}), 8.0 (brs, 1H, NH), 9.8 (brs, 1H, NH).

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

Yield 81%, m.p. 185–187°C. IR (KBr): $\nu = 3280$, 3150, 3045, 1705 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) = 1.3 (s, 9H, $3CH_3$), 2.25 (s, 3H, CH_3), 5.2 (d, J = 3.0 Hz, 1H, H_4), 7.1 (m, 2H, H_{arom}), 7.5 (m, 2H, H_{arom}), 8.2 (brs, 1H, NH), 9.5 (brs, 1H, NH).

REFERENCES

[1] P. Biginelli, *Gazz. Chim. Itall.*, **23,** 360 (1893).
[2] C. O. Kappe, *Tetrahedron*, **49,** 6937 (1993).

[3] H. Cho et al., *J. Med. Chem.*, **32,** 2399 (1989).
[4] S. K. Atwal et al., *J. Med. Chem.*, **33,** 2629 (1990).
[5] G. C. Rovnyak et al., *J. Med. Chem.*, **38,** 119 (1995).
[6] K. S. Atwal, B. N. Swanson, S. E. Unger, D. M. Floyed, S. Moreland, A. Hedberg, and B. C. O'Reilly, *J. Med. Chem.*, **34,** 806 (1991).
[7] G. C. Rovnyak, K. S. Atwal, A. Hedberg, S. D. Kimball, S. Moreland, J. Z. Gougoutas, B. C. Oreilly, J. Schwartz, and F. M. Malley, *J. Med. Chem.*, **35,** 3254 (1992).
[8] G. J. Grover, S. Dzwonczyk, D. M. McMullen, C. S. Normadinam, P. G. Sleph, and S. J. Moreland, *Pharm.*, **26,** 289 (1995).
[9] C. O. Kappe and F. S. Falsone, *Synlett.*, 718 (1998).
[10] W. C. Wong, B. Lagu, D. Nagarathnam, M. R. Marzabadi, and C. Gluchowskj, PCT Int. Appl. WO 98 51, 311.
[11] M. A. Bruce, G. S. Pointdexter, and G. Johnson, PCT Int. Appl. WO 98 33, 791.
[12] C. O. Kappe, D. Kumar, and R. S. Varma, *Synthesis*, 1799–1803 (1999).
[13] F. Bigi, S. Carloni, B. Frullanti, R. Maggi, and G. Sartori, *Tetrahedron Lett.*, **40,** 3465 (1999).
[14] P. Wipf and A. Cunningham, *Tetrahedron Lett.*, **36,** 7819 (1995).
[15] A. Studer, S. Hadida, R. Ferrito, S. Y. Kim, P. Jeger, P. Wipf, and D. P. Curran, *Science*, **275,** 823 (1997).
[16] A. Studer, P. Jeger, P. Wipf, and D. P. Curran, *J. Org. Chem.*, **62,** 2917 (1997).
[17] B. C. O'Reilly and K. S. Atwal, *Heterocycles*, **26,** 1185 (1987).