Synthesis of Some 2-Oxo and 2-Thioxo Substituted Pyrimidines Using Solvent-free Conditions

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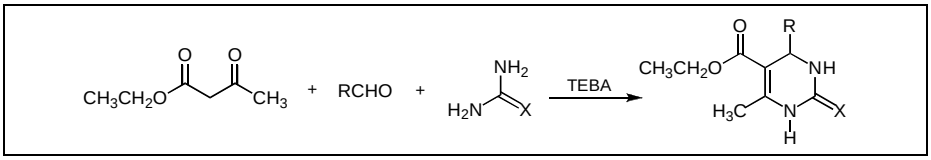

A series of oxo- and thioxopyrimidines **4(a-m)** were synthesized by one-pot three components cyclocondensation reaction of β-ketoester, aldehyde and urea/thiourea using benzyltriethylammonium chloride as a catalyst under solvent-free conditions. The yields of products following recrystallization from ethanol were of the order of 65-87%. IR and ^{1}HNMR spectroscopy and elemental analysis were used for identification of these compounds.

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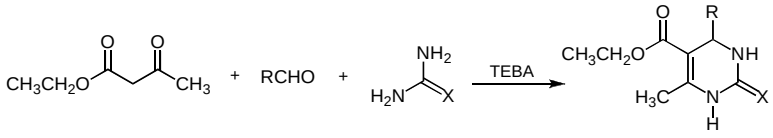
INTRODUCTION

Multicomponent reactions (MCRs) have received significant attention in organic and medicinal chemistry [1-4]. Multicomponent reactions are convergent reactions, in which three or more starting materials are generally combined together in a single event to form a final product displaying features of all components, thus offering greater possibilities for molecular diversity per step with a minimum of synthetic time. Biginelli reaction [5] is a multicomponent reaction of an aldehyde, ketoester and urea or thiurea in the presence of catalytic amount of acid to produce pyrimidine derivatives, which show various interesting pharmacological properties including antiviral [6], antibacterial [7], antitumor [8] and antihypertensive [9] effects. Biginelli reaction often suffers from low yileds, especially in the case of substituted aldehydes [10]. Several papers have been published for the synthesis of pyrimidines including classical conditions or solvent-free conditions with microwave irradiation [11-28]. However most of them use the procedure which concerned with enhancing of chemical safety and yields of products. Rarely attentions are paid to the fact that many of these methods involve use of highly toxic reagents, expensive catalyst or non-available materials [18] and strongly acidic conditions. Therefore, the development of a new catalyst which promotes the Biginelli reaction under simple conditions is required. In organic chemistry, the subject of green chemistry is becoming increasingly important and calls for clean procedures that can avoids the use of organic solvents, which also lead to safety and environmental respects. In view of this, we wish to report synthesis of some oxo- and thioxopyrimidines under solvent-free conditions using benzyltriethylammonium chloride (TEBA) as a transfer catalyst.

RESULTS AND DISCUSSIONS.

The cyclocondensation reaction for the preparation of substituted 3,4-dihydro-2*H*-pyrimidone, DHPMs, was first described by Biginelli in 1893 [5]. This multi-component synthesis involving the one-pot cyclocondensation of β-ketoester, **1**, with an aldehyde, **2**, and urea/thiourea, **3**, suffers from low yields. For example reaction of urea and ethyl acetoacetate with aliphatic aldehydes gives related pyrimidines in yields less than 30-40%. This led to the development of multi step methods to improve yields and reaction rates. However many of these methods involve expensive catalyst or materials that are not readily available. In view of this, we have developed a solvent-free strategy for the preparation of substituted 3,4-dihydropyrimidines by using benzyltriethylammonium chloride (TEBA), which is commonly used as a phase transfer catalyst in organic synthesis [29]. Here we wish to disclose our results employing this catalyst. This proposed method is general and involves Biginelli's one

Scheme 1



pot-condensation of three components, **1**, **2** and **3** in the present of TEBA to give **4** (Scheme 1 and Table 1).

This simple procedure gives the products in high yields (65-87%, Table 1) and avoids the use of highly toxic reagents or expensive catalyst. Furthermore, we have studied the reaction with different amounts of catalyst and found that use of just 10-mol % of TEBA is sufficient to carry out the reaction. At higher than 10-mol % of TEBA, there are no improvements in the reaction rate and yields.

Table 1

TEBA- Catalyzed Efficient Synthesis of DHMPs

Products	R	X	Time (h)	Yield (%)
4a	H	S	0.5	65
4b	methyl	S	1	65
4c	ethyl	S	2	85
4d	propyl	S	3	77
4e	isopropyl	S	1.5	86
4f	butyl	S	3	87
4g	isobutyl	S	3	82
4h	H	O	0.5	77
4i	methyl	O	1	86
4j	ethyl	O	2	74
4k	propyl	O	1	76
4l	butyl	O	3	81
4m	isobutyl	O	3	85

^{1}H NMR spectra of all synthesized compounds showed the two different broad signals at low field assigned to the resonance of two NHs of the pyrimidine ring. This was supported by IR spectra, which included signals in the region 3200-3400 cm^{-1}. Elemental analysis data of all compounds showed good agreement with those of calculated.

Conclusion.We have developed a solvent-free method for the Biginelli condensation of aldehydes with ethylacetoacetae and urea/thiourea. This mild and efficient catalytic method avoids the use of the more traditional heating method. Several pyrimidine derivatives can be easily prepared in good overall yields and purity under short reaction times and mild conditions using TEBA as a catalyst.

EXPERIMENTAL

Melting points were determined on an electrothermal digital melting point apparatus.^{1}H NMR spectra were recorded on a Bruker (300 MHz) Spectrometer using DMSO as a solvent. The IR spectra were recorded on Galaxy FT-IR 5000 Spectrometer. Reactions were monitored by thin layer chromatography. All chemicals were purchased from Merck Co.

General Procedure for Synthesis of 4(a-m). A mixture of the appropriate aldehyde (0.01 mol), thiourea/urea (0.015 mol), ethylacetoacetate (0.01 mol) and benzyltriethylammonium chloride (0.001 mol) was heated at 100 °C for the desired time. The reaction mixture was kept at room temperature overnight and then poured into 10 ml of ice-cooled water. The precipitate was collected by filtration and then recrystallizd from ethanol.

6-Methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (4a). Yield 65%, lit 87% [30], mp= 235-236 °C; IR (KBr): ν = 3205, 3160, 3026, 2987, 1714, 1658, 1612 cm^{-1}; ^{1}HNMR (DMSO-d_6): δ (ppm) = 1.19 (t, J=8.4 Hz, 3H, $CH_{3-ester}$), 2.17 (s, 3H, $CH_{3-pyrimidine}$), 3.88 (s, 2H, H-pyrimidine), 4.08 (q, J=8.4 Hz, 2H, $CH_{2-ester}$), 8.94 (bs, 1H, NH), 9.93 (bs, 1H, NH). *Anal.* Calcd. for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04; N, 13.99%. Found: C, 48.36; H, 5.96; N, 14.24%.

4,6-Dimethyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (4b). Yield 65%, lit %95 [30], mp= 189-191 °C; IR (KBr): ν = 3310, 3176, 3126, 2989, 1662, 1583 cm^{-1}; ^{1}H NMR (DMSO-d_6):δ (ppm)= :δ (ppm) =1.22-1.29 (m, 6H, $CH_{3-ester}$ and CH_{3-C4}), 2.23 (s, 3H, $CH_{3-pyrimidine}$), 4.12-4.40 (m, 3H, $CH_{2-ester}$ and $H_{-pyrimidine}$), 9.20 (bs, NH),10.09 (bs, NH). *Anal.* Calcd. for $C_9H_{14}N_2O_2S$: C, 50.44; H, 6.59; N, 13.07%. Found: C, 50.16; H, 6.68; N, 13.40%.

4-Ethyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (4c). Yield 85%, lit %74 [18], mp= 142-143 °C; IR (KBr): ν = 3321, 3182, 3119, 2982, 1660, 1577 cm^{-1}; ^{1}HNMR (DMSO-d_6): δ (ppm) = 0.77 (t, J=7.5 Hz, 3H, $CH_{3-ethyl}$), 1.18 (t, J=7 Hz, 3H, $CH_{3-ester}$), 1.42 (m, 2H, $CH_{2-ethyl}$), 2.20 (s, 3H, $CH_{3-pyrimidine}$), 4.02-4.13 (m, 3H, $CH_{2-ester}$ and $H_{-pyrimidine}$), 9.23 (bs, 1H, NH), 10.08 (bs, 1H, NH). *Anal.* Calcd. for $C_{10}H_{16}N_2O_2S$: C, 52.61; H, 7.06; N, 12.27%. Found: C, 52.83; H, 7.41; N, 12.11%.

6-Methyl-4-Propyl-2-thioxo -1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (4d). Yield 77%, mp= 168-169 °C; IR (KBr): ν = 3323, 3180, 3134, 2955, 1666, 1576 cm^{-1}; ^{1}HNMR (DMSO-d_6): δ (ppm) = 0.85 (t, J=7.8 Hz, 3H, $CH_{3-propyl}$), 1.17-1.38 (m, 7H, $CH_{3-ester}$ and 2 x $CH_{2-propyl}$), 2.20 (s, 3H, $CH_{3-pyrimidine}$), 4.07-4.13 (m, 3H, $CH_{2-ester}$ and $H_{-pyrimidine}$), 9.21 (bs, 1H, NH), 10.05 (bs, 1H, NH). *Anal.* Calcd. for $C_{11}H_{18}N_2O_2S$: C, 54.52; H, 7.49; N, 11.56%. Found: C, 54.12; H, 7.21; N, 11.51%.

4-Isopropyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (4e). Yield 86%, mp= 172-173 °C; IR (KBr): ν = 3323, 3186, 2960, 1662, 1581 cm^{-1}; ^{1}HNMR (DMSO-d6): δ (ppm) = 0.75 (dd, J=6.8Hz, 6H, 2 $CH_{3-isopropyl}$), 1.18 (t, J=7Hz, 3H, $CH_{3-ester}$), 1.65 (m, 1H, $CH_{-isopropyl}$), 2.21 (s, 3H, $CH_{3-pyrimidine}$), 3.96 (t, J=4.1 Hz, 1H, $H_{-pyrimidine}$), 4.06 (m, 2H, $CH_{2-ester}$), 9.22 (bs, 1H, NH), 10.08 (bs, 1H, NH). *Anal.* Calcd. for $C_{11}H_{18}N_2O_2S$: C, 54.53; H, 7.49; N, 11.56%. Found: C, 54.78; H, 7.31; N, 11.66%.

4-Butyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (4f). Yield 87%, mp= 180-181 °C; IR (KBr): ν = 3230, 3151, 2945, 1710, 1651, 1597 cm^{-1}; ^{1}HNMR (DMSO-d_6): δ =0.84 (t, J=6.8 Hz, 3H, $CH_{3-butyl}$), 1.38-1.63 (m, 9H, $CH_{3-ester}$ and 3 $CH_{2-butyl}$), 2.19(s, 3H, $CH_{3-pyrimidine}$), 4.02-4.12 (m, 3H, $CH_{2-ester}$ and $H_{-pyrimidine}$), 9.25 (bs, 1H, NH), 10.09 (bs, 1H, NH). *Anal.* Calcd. for $C_{12}H_{20}N_2O_2S$: C, 56.21; H, 7.86; N, 10.92%. Found: C, 56.48; H, 7.58; N, 11.12%.

4-Isobutyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (4g). Yield 82%, mp= 150-152 °C; IR (KBr): υ=3217, 3155, 2985, 1710, 1653, 1589 cm^{-1}; ^{1}HNMR (DMSO-d_6): δ (ppm) = 0.86 (t, J=6.3Hz, 6H, 2 $CH_{3-isobutyl}$), 1.03-1.21 (m, 4H, $CH_{3-ester}$ and $CH_{a-isobutyl}$), 1.19 (t, J=7 Hz, 3H), 1.33-1.48 (m, 1H, $CH_{b-isobutyl}$), 1.67 (m, 1H, $CH_{-isobutyl}$), 2.19 (s, 3H, $CH_{3-pyrimidine}$), 3.98-4.13 (m, 3H, CH_2-ester and $H_{-pyrimidine}$), 9.35 (bs, 1H, NH), 10.15 (bs, 1H, NH). *Anal.* Calcd. for $C_{12}H_{20}N_2O_2S$: C, 56.22; H, 7.86; N, 10.93%. Found: C, 56.29; H, 8.15; N, 10.78%.

6-Methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (4h). Yield 77%, mp= 23-255°C. IR (KBr): ν =3261, 3140, 2958, 1739, 1710, 1666 cm^{-1}. ^{1}HNMR (DMSO-

d_6): δ (ppm) = 1.17 (t, J=7Hz, 3H, $CH_{3\text{-ester}}$), 2.14 (s, 3H, $CH_{3\text{-pyrimidine}}$), 3.87 (d, 2H, $H_{\text{-pyrimidine}}$), 4.05 (q, J=7 Hz, 2H, $CH_{2\text{-ester}}$), 7.02 (bs, 1H, NH), 8.85 (bs, 1H, NH). *Anal.* Calcd. for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21%. Found: C, 52.28; H, 6.58; N, 15.46%.

4,6-Dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (4i). Yield 86%, lit 53% [31], mp= 240-242 °C; IR (KBr): ν = 3421, 3311, 3219, 2990, 1674, 1660, 1562 cm^{-1}; ^{1}HNMR (DMSO-d_6): δ (ppm) =1.11 (d, J=7.5 Hz, 3H, $CH_{3\text{-}C4}$), 1.19 (t, J= 6 Hz, 3H, $CH_{3\text{-ester}}$), 2.15 (s, 3H, $CH_{3\text{-pyrimidine}}$), 4.02-4.14 (m, 3H, $CH_{2\text{-ester}}$ and $H_{\text{-pyrimidine}}$), 7.18 (bs, 1H, NH), 8.95 (bs, 1H, NH). *Anal.* Calcd. for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13%. Found: C, 54.69; H, 6.86; N, 14.40%.

4-Ethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (4j). Yield 74%, lit 73% [18], mp= 179-181 °C. IR (KBr): ν = 3230, 3126, 2962, 1722, 1710, 1645, 1660 cm^{-1}. ^{1}HNMR (DMSO-d_6): δ (ppm) =0.78 (t, J=7.3 Hz, 3H, $CH_{3\text{-ethyl}}$), 1.17 (t, J= 7 Hz, 3H, $CH_{3\text{-ester}}$), 1.42 (m, 2H, $CH_{2\text{-ethyl}}$), 2.15 (s, 3H, $CH_{3\text{-pyrimidine}}$), 4.01-4.10 (m, 3H, $CH_{2\text{-ester}}$ and $H_{\text{-pyrimidine}}$), 7.29 (bs, NH), 8.92 (bs, 1H, NH). *Anal.* Calcd. for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20%. Found: C, 56.89; H, 7.44; N, 13.58%.

6-Methyl-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (4k). Yield 76%, lit 83% [10], mp= 183-185 °C; IR (KBr): ν = 3317, 3192, 3128, 2966, 1658, 1579 cm^{-1}; ^{1}HNMR (DMSO-d_6): δ (ppm) =0.84 (t, J=8.1Hz, 3H, $CH_{3\text{-propyl}}$), 1.16-1.43 (m, 7H, $CH_{3\text{-ester}}$ and 2 x $CH_{2\text{-propyl}}$), 2.16 (s, 3H, $CH_{3\text{-pyrimidine}}$), 4.01-4.11 (m, 3H, $CH_{2\text{-ester}}$ and $H_{\text{-pyrimidine}}$), 7.33 (bs, 1H, NH), 8.93 (bs, 1H, NH). *Anal.* Calcd. for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38%. Found: C, 58.68; H, 7.68; N, 12.47%.

4-Butyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (4l). Yield 81%, mp= 161-163 °C; IR (KBr): ν = 3256, 3119, 2950, 1724, 1710, 1651 cm^{-1}; ^{1}HNMR (DMSO-d_6): δ (ppm) =0.84 (t, J=6.5 Hz, 3H, $CH_{3\text{-butyl}}$), 1.15-1.39 (m, 9H, $CH_{3\text{-ester}}$ and 3 x $CH_{2\text{-butyl}}$), 2.15 (s, 3H, $CH_{3\text{-pyrimidine}}$), 3.99-4.11 (m, 3H, $CH_{2\text{-ester}}$ and $H_{\text{-pyrimidine}}$), 7.32 (bs, NH), 8.93 (bs, 1H, NH). *Anal.* Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66%. Found: C, 59.81; H, 8.40; N, 11.89%.

4-Isobutyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (4m). Yield 85%, mp= 187-189 °C; IR (KBr): ν = 3250, 3113, 2933, 1707, 1651, 1465 cm^{-1}; ^{1}HNMR (DMSO-d_6): δ (ppm) =0.83 (d, J=6.4 Hz, 6H, 2 x $CH_{3\text{-isobutyl}}$), 1.03-1.19 (m, 4H, $CH_{3\text{-ester}}$ and $CH_{a\text{-isobutyl}}$), 1.31-1.40 (m, 1H, $CHb_{\text{-isobutyl}}$), 1.66 (m, 1H, $CH_{a\text{-isobutyl}}$), 2.14 (s, 3H, $CH_{3\text{-pyrimidine}}$), 4.04 (m, 2H, $CH_{2\text{-ester}}$), 7.42 (bs, NH), 8.95 (bs, 1H, NH). *Anal.* Calcd. for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66%. Found: C, 60.24; H, 8.54; N, 11.76%.

REFERENCES

[1] C. O. Kappe, *Acc. Chem. Res*, **33**, 879 (2000).

[2] R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating, *Acc. Chem. Res*, **29**, 123 (1996).

[3] I. Ugi, A. Döming, W. Hort, *Endeavour*, **18**, 115 (1994).

[4] A. Domling, Comb. Chem. High Throughput Screening, **1**, 1 (1998).

[5] P. Biginelli, *Gazz. Chim. Ital.* **23**, 360 (1893).

[6] R. S. Varma, *Green. Chem*; 43 (1999).

[7] W. Xie, Y. Jin, P. G. Wang, *Chemtech*, **2**, 23 (1999).

[8] C. O. Kappe, W. M. F. Fabian and M. A. Semones, *Tetrahedron*, **53**, 2803 (1997).

[9] K. S. Atwal, B. N. Swanson, S. E. Unger, D. M. Floyd, S. Moreland, A. Hedberg, B. C. O'Reilly, *J. Med. Chem*; **34**, 806 (1991).

[10a] K. Folkers, H. J. Harwood, T. B. Johnson, *J. Am. Chem. Soc*., **54**, 3751 (1932); [b] P. Wipf, A. Cunningham, *Tetrahedron Lett*., **36**, 7819 (1995); [c] K. Folkers T. B. Johnson, *J. Am. Chem. Soc*., 1180 (1934).

[11] B. Schnell, W. Krenn, K. Faber, C. O. Kappe, *J. Chem. Soc. Perkin Trans. 1*, 4382 (2000).

[12] J. J. Vander, N. Hecq, O. Kataeva, C. O. Kappe, *Tetrahedron*, **57**, 1785 (2001).

[13] M. Kidwai, and A. D. Mishra, *Bull. Korean Chem. Soc*., **24**, 1038 (2003).

[14] C. O. Kappe and P. Roschge, *J. Heterocyclic Chem*., **26**, 55 (1989).

[15] H. Lin, J. Ding, X. Chen and Z. Zhang, *Molecules*, **5**, 1240 (2000).

[16] N. Foroughifar, A. Mobinikhaledi and H. Fathinejad Jirandehi, *Phosphorus*, *Sulfur*, *and Silicon*, **178**, 495 (2003).

[17] M. A. F. Sharaf, F. A. Abdel Aal, A. M. Abdel Fattah and A. M. R. Abdel Khalil, *J. Chem. Research (S)*, 354 (1996).

[18] A. D. Shutalev, E. A. Kishko, N. Sivova, A. Y. Kuznetsov, *Molecules*, **3**, 100 (1998).

[19] H. Lin, J. Ding, X. Chen and Z. Zhang, *Molecules*; **5**, 1240 (2000).

[20] N. Foroughifar, S. M. Shariatzadeh , A. Mobinikhaledi, E. Khasnavi and M. Masoudnia, *UltraScience*, **12**, 277 (2000).

[21] N. Foroughifar, A. Mobinikhaledi and H. Fathinejad Jirandehi, *Phosphorus*, *Sulfur*, *and Silicon*, **178**, 1241 (2003).

[22] D. S. Bose, R. K. Kishore and L. Fatima, *Synlett*, 279 (2004).

[23] G. Jender, *Tetrahedron Lett*., **45**, 6195 (2004).

[24] D. Russowsky, F. A. Lopes, V. S. S. da Silva, K. F. S. Canto, M. G. Montes D'Oca^{II}, M. N. Godoi^{II}, *J. Braz. Chem. Soc*., **15**, 165 (2004).

[25] M. Adharvana Chari, D. Shobha, T. Kiran Kumar, and P. K. Dubey, *Arkivoc, xv,* 74 (2005).

[26] Y. Ma, C. Qian, L. Wang, M. Yuang, *J. Org. Chem*., **65**, 3864 (2000).

[27] S. K. De, R. A. Gibbs, *Synthesis*, 1748 (2005).

[28] R. S. Varma, *Pure Appl. Chem*., **73**, 193 (2001).

[29] D. S. Bose and A. V. Narsaiah, *J. Chem. Research (S)*, 36 (2001).

[30] A. D. Shutalev, V. Kuksa, V. A. Khim, *Geterotsikl. Soedin*, **8**, 105 (1997).

[31] F. S. Falsone, C. O. Kappe, *Arkivoc*, **2**, 1234 (2001).