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# Convenient Acylation of Pyrimidine Derivatives Using Microwave Irradiation

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N-Acylated ethyl-6-methyl-4-aryl-2-oxo (or thioxo)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2a–f**) and 6-methyl-4-aryl-2-oxo (or thioxo)-1,2,3,4-tetrahydropyrimidine-5-methylketone (**2g–h**) were synthesized by the reaction of an appropriate pyrimidine derivative (**1**) and acetic anyhydride under microwave irradiation. Yields of products following recrystallization from ethanol were of the order of 60–85%.

**Key Words: Microwave, Pyrimidine, Carboxylate, Methylketone.**

## INTRODUCTION

Synthesis of compounds belonging to pyrimidines constitute an important area research due to their interesting diverse biological activities[1–11] including antiviral, antitumour, antibacterial[2, 3] and antihypertensive[4] effects. The most general method for the acylation of pyrimidines involves the reaction of these compounds with acetic anhydride using force conditions. Thus a simple and efficient method for acylation of these important heterocyclics is required.

In the last few years, there has been increased interest in the use of microwave heating in organic synthesis and it forms now the basis of a number of commercial systems. Some interesting features of this method are the rapid reaction rates, simplicity, being solvent-free, ease of work-up after a reaction and better selectivity[1, 12, 14]. Also microwave irradiation generates rapid intense heating of polar substances, which results in reduction of reaction time compared to conventional heating.

Hence continuing with our studies on the synthesis of pyrimidines using microwave irradiation[10, 15, 17], we have developed a simple and efficient route for the preparation of N-acylated pyrimidines.

## EXPERIMENTAL

Pyrimidine derivatives **1** were prepared according to our previous reports[10, 16, 17, 19, 20]. $^1$H NMR spectra were recorded on a Bruker 500 MHz spectrometer. Chemical shifts are reported in ppm relative to TMS (tetramethylsylan) as an internal standard. Spectra were acquired in DMSO. Reaction procedure was routinely monitored by thin layer chromatography (TLC) on silica gel plates. Reactions were performed in a Samsung microwave oven with a 230V-50Hz power source, 900W output and 2450 MHz operating frequency.

## General procedure

Appropriate pyrimidine derivative, **1** (0.001 mol) and acetic anhydride (0.02 mol) was quite mixed in a 25 mL beaker. The beaker was placed inside a larger container filled with potsherd and was then inserted into the microwave oven. The mixture was then subjected to microwave irradiation at 100% power level for the desired time. After cooling the reaction mixture, cold water (20 mL) was added and stirred at room temperature for 1–2 h. The crude product was filtered and recrystallized from ethanol or a mixture of ethanol and water to give the pure product.

**Ethyl-3-acetyl-6-methyl-4-(4-acetamidophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2a):** m.p. 202–203°C; $^1$H NMR (DMSO-$d_6$): δ (ppm): 1.25 (t, J = 7.2 Hz, 3H, $CH_3$), 2.15 (s, 3H, $CH_3$), 2.3 (s, 3H, $CH_3$), 2.50 (s, 3H, $CH_3$), 4.20 (q, 2H, $CH_2$), 6.50 (s, 1H, H-4), 7.25 (m, 4H, $H_{arom}$), 9.95 (bs, 1H, NH), 10.0 (bs, 1H, NH). Anal. (%) Calcd. for $C_{18}H_{21}N_3O_5$: C, 60.10; H, 5.00; N, 11.69; Found: C, 60.20; H, 4.95; N, 11.75.

**Ethyl-3-acetyl-6-methyl-4-(4-acetamidophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2b):** m.p. 165–166°C; $^1$H NMR (DMSO-$d_6$): δ (ppm): 1.20 (t, J = 7.2 Hz, 3H, $CH_3$), 2.10 (s, 3H, $CH_3$), 2.40 (s, 3H, $CH_3$), 2.50 (s, 3H, $CH_3$), 4.20 (q, 2H, $CH_2$), 6.55 (s, 1H, H-4), 7.30 (m, 4H, $H_{arom}$), 9.90 (bs, 1H, NH), 11.60 (bs, 1H, NH), Anal. (%) Calcd. for $C_{18}H_{21}N_3O_4S$: C, 57.54; H, 5.59; N, 11.19; Found: C, 57.31; H, 5.85; N, 12.21.

**Ethyl-3-acetyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2c):** m.p. 142–143°C; $^1$H NMR (DMSO-$d_6$): δ (ppm): 1.22 (t, J = 7.2 Hz, 3H, $CH_3$), 2.40 (s, 3H, $CH_3$), 2.80 (s, 3H, $CH_3$), 4.20 (q, 2H, $CH_2$), 6.70 (s, 1H, H-4), 7.20 (m, 5H, $H_{arom}$), 9.10 (bs, 1H, NH). Anal. (%) Calcd. for $C_{16}H_{18}N_2O_4$: C, 63.51; H, 5.95; N, 9.26; Found: C, 63.76; H, 4.80; N, 9.41.

**Ethyl-3-acetyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2d):** m.p. 145–146°C; $^1$H NMR (DMSO-$d_6$): δ (ppm): 1.20 (t, J = 7.2 Hz, 3H, $CH_3$), 2.33 (s, 3H, $CH_3$), 2.77 (s, 3H, $CH_3$), 4.23 (q, 2H, $CH_2$), 6.65 (s, 1H, H-4), 7.30 (m, 5H, $H_{arom}$), 8.70 (bs, 1H, NH). Anal. (%) Calcd. for $C_{16}H_{18}N_2O_3S$: C, 60.30; H, 5.65; N, 8.79; Found: C, 60.50; H, 5.54; N, 8.99.

**Ethyl-3-acetyl-6-methyl-4-(4-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2e):** m.p. 152–153°C; $^1$H NMR (DMSO-$d_6$): δ (ppm): 1.15 (t, J = 7.2 Hz, 3H, $CH_3$), 2.30 (s, 3H, $CH_3$), 2.70 (s, 3H, $CH_3$), 4.10 (q, 2H, $CH_2$), 6.60 (s, 1H, H-4), 7.30 (m, 4H, $H_{arom}$), 10.10 (bs, 1H, NH). Anal. (%) Calcd. for $C_{16}H_{17}N_2O_3SCl$: C, 54.42; H, 4.82; N, 7.94; Found: C, 54.61; H, 4.91; N, 7.71.

**Ethyl-3-acetyl-6-methyl-4-(4-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2f):** m.p. 159–160°C; $^1$H NMR (DMSO-$d_6$): δ (ppm): 1.13 (t, J = 7.2 Hz, 3H, $CH_3$), 2.35 (s, 3H, $CH_3$), 2.65 (s, 3H, $CH_3$), 4.15 (q, 2H, $CH_2$), 6.70 (s, 1H, H-4), 7.35 (m, 4H, $H_{arom}$), 10.00 (bs, 1H, NH). Anal. (%) Calcd. for $C_{16}H_{17}N_2O_4Cl$: C, 57.00; H, 5.05; N, 8.31; Found: C, 57.29; H, 5.30; N, 8.21.

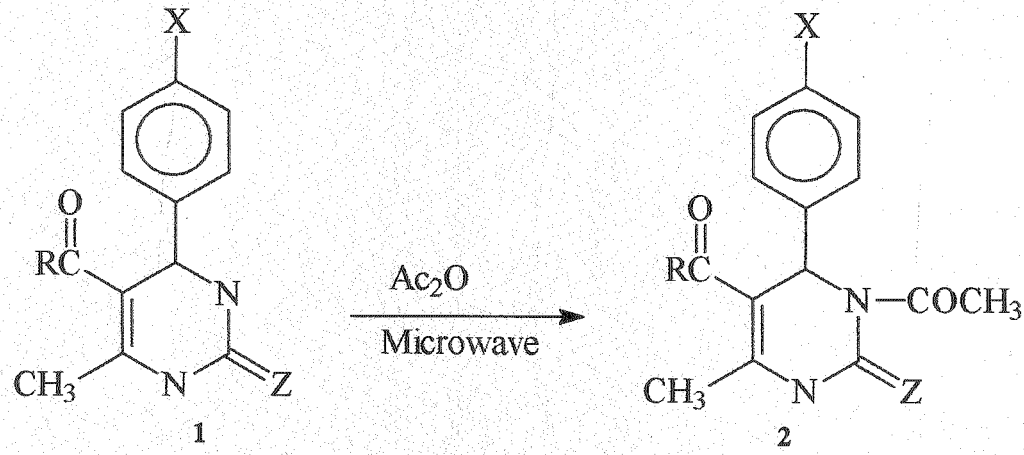
**3-Acetyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-methylketone (2g):** m.p. 138-139°C; $^1$H NMR (DMSO-$d_6$): δ (ppm): 2.13 (s, 3H, $CH_3$), 2.36 (s, 3H, $CH_3$), 2.72 (s, 3H, $CH_3$), 6.72 (s, 1H, H-4), 7.40 (m, 5H,

$H_{arom}$), 9.90 (bs, 1H, NH). Anal. (%) Calcd. for $C_{15}H_{16}N_2O_2S$: C, 62.42; H, 5.54; N, 9.71; Found: C, 62.30; H, 5.32; N, 9.40.

**3-Acetyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-S-methyl-ketone (2h):** m.p. 130-131°C; $^1$H NMR (DMSO-$d_6$): δ (ppm): 2.15 (s, 3H, $CH_3$), 2.35 (s, 3H, $CH_3$), 2.75 (s, 3H, $CH_3$), 6.74 (s, 1H, H-4), 7.40 (m, 5H, $H_{arom}$), 9.95 (bs, 1H, NH). Anal. (%) Calcd. for $C_{15}H_{16}N_2O_3$: C, 66,10; H, 5.88; N, 10.28; Found: C, 66.35; H, 5.62; N, 10.05%.

## RESULTS AND DISCUSSION

Pyrimidine derivative (**1**) and acetic anhydride were reacted under microwave irradiation to give the corresponding N-acyl pyrimidine **2** (**Scheme-1**).




**Scheme-1**

TABLE-1
N-ACYL PYRIMIDINE DERIVATIVES (**2a–h**)

| Entry | Z | X | R | Time (s) | Yield (%) |
|---|---|---|---|---|---|
| **2a** | O | —$NHCOCH_3$ | OEt | 35 | 85 |
| **2b** | S | —$NHCOCH_3$ | OEt | 37 | 75 |
| **2c** | O | —H | OEt | 40 | 66 |
| **2d** | S | —H | OEt | 50 | 60 |
| **2e** | O | —Cl | OEt | 80 | 73 |
| **2f** | S | —Cl | OEt | 77 | 75 |
| **2g** | O | —H | Me | 70 | 70 |
| **2h** | S | —H | Me | 70 | 77 |

The reaction of pyrimidine derivatives (**1**) with methyl iodide under reflux gives rise to formation of S-methylated compounds, which has been well documented[18]. However, reaction of **1** with acetic anhydride under reflux or microwave irradiation afforded N-acylated compounds. The $^1$H spectral data confirm the expected structures. In $^1$H NMR spectra two singlet signals at 2.50–2.80 and 2.33–2.40 ppm are due to the resonance of the —$NCOCH_3$ group and $CH_3$ of the pyrimidine ring respectively. The $CH_3$ of the ester group for **2a–f** resonates at 1.13-1.25 ppm as a triplet signal. However, the $CH_3$ of the acyl group (—$CCOCH_3$) for **2g–h** resonates

as a singlet at 2.13–2.15 ppm. The singlet and multiplet signals at 6.50–6.74 and 7.20–7.40 ppm are assigned to H-4 and aryl protons respectively. The $^1$H NMR spectrum of **2** shows a broad signal for the NH proton of pyrimidine ring at downfield which compares to $^1$H NMR spectrum of starting material **1** with two pyrimidine NH protons signal is in support of the acylation reaction.

Rapid heating induced by microwave irradiation using potsherd as a heat sink avoids the forcing classical conditions and the decomposition of materials. This leads to the formation of products under mild conditions with the consequent significant increases in yield (Table-1).

In conclusion, the present work offers a highly efficient microwave induced procedure for N-acylation of pyrimidine derivatives under mild conditions using a microwave oven as the irradiation source.

## REFERENCES

1. R.S. Varma, *Green Chem.*, **1**, 43 (1999).
2. C.O. Kappe, *Tetrahedron*, **49**, 6937 (1993).
3. W. Xie, Y. Jin and P.G Wang, *Chemtech.*, **2**, 23 (1999).
4. K.S. Atwal, B.N. Swanson, S.E. Unger, D.M. Floyd, S. Moreland, A. Hedberg and B.C. O'Reilly, *J. Med. Chem.*, **34**, 806 (1991).
5. C.G. Rovnyak, K.S. Atwal, A. Hedberg, S.D. Kimball, S. Moreland, J.Z. Gougoutas, B.C. O'Reilly, J. Schwartz and M.F. Malley, *J. Med. Chem.*, **35**, 3254 (1992).
6. K. Tsuji and H. Ishikawa, *Bioorg. Med. Chem.*, **4**, 1601 (1994).
7. J. Wichmann, A. Geo, S. Koclzewski, M. Vincent and T. Woletring, *Bioorg. Med. Chem. Lett.*, **9**, 1573 (1999).
8. G.J. Grover, S. Dzwonczyk, D.M. McMullen, C.S. Normadinam, P.G. Sleph and S.J. Moreland, *J. Cardiovasc. Pharmacol.*, **26**, 289 (1995).
9. A.K. Bose, B.K. Banik, N. Lavlinskaia, M. Jayaraman and M.S. Manhas, *Chemtech.*, **27**, 18 (1997).
10. N. Foroughifar, A. Mobinikhaledi, S.M. Shariatzadeh and M. Masoudnia, *Asian J. Chem.*, **14**, 782 (2002).
11. A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault and D. Math, *Synthesis*, 1213 (1998).
12. S. Caddick, *Tetrahedron*, **51**, 1043 (1995).
13. R. Laurent, A. Laporterie, J. Dubac, J. Berlan, S. Lefeuvre and M. Audhuy, *J. Org. Chem.*, **57**, 7099 (1992).
14. D.M.P. Mingos and D.R. Baghurst, *Chem. Soc. Rev.*, **20**, 1 (1991).
15. A. Mobinikhaledi and N. Foroughifar, *Phosphorus, Sulfur and Silicon*, **179**, 1175 (2004).
16. N. Foroughifar, A. Mobinikhaledi and H.F. Jirandehi, *Phosphorus, Sulfur and Silicon*, **178**, 1241 (2003).
17. A. Mobinikhaledi, N. Foroughifar and H.F. Jirandehi, *Phosphorus, Sulfur and Silicon*, **179**, 2259 (2004).
18. K.S. Atwal, B.C. O'Helly, J.Z. Cougoutas and M.F. Malley, *Heterocycles*, **26**, 1189(1987).
19. N. Foroughifar, A. Mobinikhaledi and H.F. Jirandehi, *Phosphorus, Sulfur and Silicon*, **178**, 495 (2003).
20. N. Foroughifar, A. Mobinikhaledi, H.F. Jirandehi and S. Memar, *Phosphorus, Sulfur and Silicon*, **178**, 1269 (2003).

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