ULTRASOUND PROMOTED $Cu(ClO_4)_2$ CATALYZED RAPID SYNTHESIS OF SUBSTITUTED 1,2,3,4-TETRAHYDROPYRIMIDINE-2-ONES & HANTZSCH 1,4-DIHYDROPYRIDINES IN DRY MEDIA

Saurabh Puri[1], Balbir Kaur[1], Anupama Parmar and Harish Kumar*
*Department of Chemistry, Sant Longowal Institute of Engineering & Technology, Longowal
[1]Department of Chemistry, Punjabi University, Patiala-147 002 (Pb.), India

Abstract

Copper perchlorate supported on bentonite clay as catalyst at room temperature gives 6-methyl-4-substituted-phenyl-2-oxo(thioxo)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl esters & diethyl 2,6-dimethyl-4-substitutedphenyl-1,4-dihydropyridine-3,5-dicarboxylate proficiently in high yields in solvent-less media under ultrasonic irradiation.

Introduction

Green chemistry protocols have shown significant potential as truly eco-friendly methodologies (1-2). Biginelli Compounds have exhibited pharmaceutical activities (3-6) whereas the 1,4-DHP motifs has been used as chemotherapeutic agents (7). The first synthetic method for the synthesis of 1,2,3,4-tetrahydropyrimidine-2-ones (THPMs) was reported by Biginelli (8) under strongly acidic conditions producing THPMs, though in low yields. In view of the pharmaceutical significance of these compounds, many improved catalytic methods have been developed (9-13). In continuation of our studies (14) we wish to report an expedient procedure for the synthesis of 1,2,3,4-tetrahydropyrimidine-2-one derivatives and Hanstzch 1,4 dihydropyridines from three-component condensation of aryl aldehydes, ethylacetoacetate and urea or thiourea or ammonium carbonate in solvent-less dry media (bentonite clay) supported-copper perchlorate as catalyst at room temperature under ultrasonic irradiation.

Experimental

Materials and Apparatus

All melting points recorded are uncorrected, open capillary measurements, using sulphuric acid bath. IR spectra were recorded using KBr pellets on a Perkin-Elmer spectrophotometer, NMR spectra on AL-300F (Bruker) FT NMR spectrophotometer. Sonication was performed in ELMA, Transsonic T 310/H Ultrasonic cleaner (with a frequency of 35 KHz), Hans Schmidbauer GmbH & Co., Germany. The reactions were performed in open vessels.

General procedure

Synthesis of 1,2,3,4-tetrahydropyrimidine-2-one derivatives 1a-f & Hantzsch 1,4 dihydropyridine derivatives 2a-f in solvent-less media: A mixture of aldehyde (0.010 mole), ethyl acetoacetate (0.015 mole) and urea or thiourea (0.012 mole) or ammonium carbonate (0.015 mole), in the presence of copper perchlorate (10% mmol) adsorbed on bentonite clay (5 gm) was placed in a sonicator under ultrasonic irradiation (completion of the reactions was monitored by TLC). To this crude reaction mixture was added ethyl alcohol (50 mL) and distilled water (5 mL). The mixture was stirred for 1 minute and then suction filtered. The spent reagent was washed twice with ethyl alcohol (10 mL each). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure. The solid separated was dried and recrystallized from 95% hot Ethanol. The formation of products was confirmed by comparing the melting points, IR and NMR data with authentic samples and literature data.

Selected Spectral and Physical Data of products

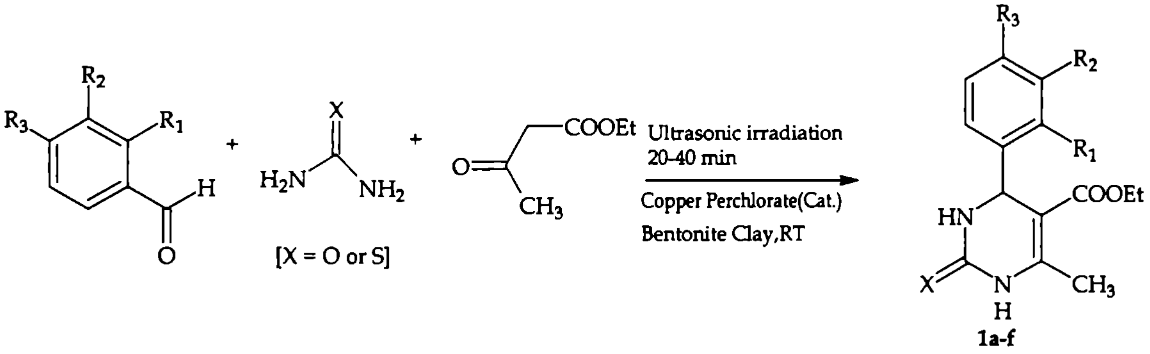
Product (1b). M. p. 204^0C. **^{1}H-NMR ($CDCl_3$):** δ: 9.1 (brs, 1H, NH); 7.9 (brs, 1H, NH); 6.9-7.2 (m, 5H, Ar-H); 5.3 (s,1H,-4CH) ; 4.0(q, 2H,$-OCH_2CH_3$); 2.4 (s, 3H, 6-CH_3);1.1(t,3H,$-OCH_2CH_3$). IR (Nujol): □: 3245, 3110, 2985, 1720, 1700, 1648.

Product (2d). M. p. 156^0C. **^{1}H-NMR ($CDCl_3$):** δ: 7.28–7.09 (brs, 5H, Ar-H), 5.71 (brs, 1 H), 4.98 (s, 1H), 4.08 (m, 4H), 2.31 (s, 6H), 1.22 (t, 6H). IR (Nujol): □: 3340, 1688, 1650, 1298, 1120, 1092, 1015, 825.

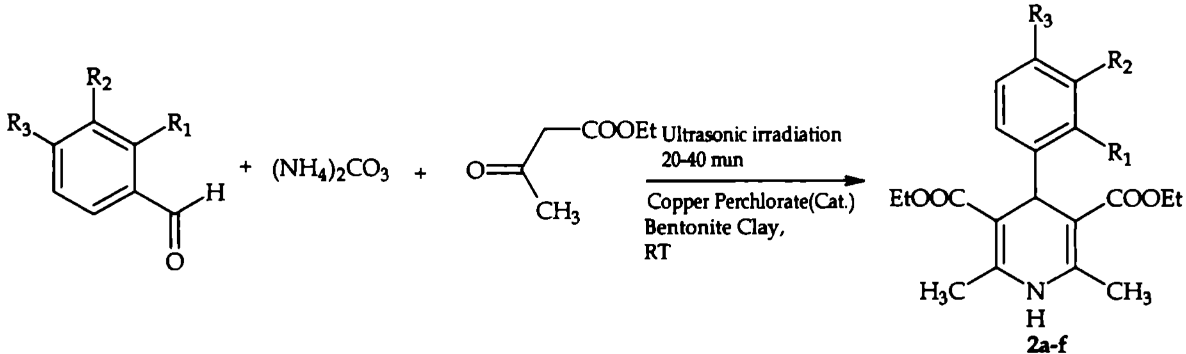
Results and Discussions

The synthesis of **1a-f & 2a-f** has been achieved in solvent-less dry media (bentonite clay) supported - 10% mmol copper perchlorate as catalyst at room temperature under ultrasonic irradiation **(Scheme 1 & 2).**

The structure of the products **1a-f & 2a-f** formed has been confirmed by elemental analyses, NMR, IR.The different catalyst concentrations (5 % mmol, 10 % mmol and 15 % mmol) were tried and it was found that 10 % mmol gave the maximum yield of the products. In the absence of catalyst, the yields of the products **1a-f & 2a-f** at room temperature were found to be very low. The reactions were also tried in the presence of catalyst at room temperature in the absence of ultrasound irradiation. The comparison of reaction time and yield of products in presence and absence of ultrasound irradiation is given in **Table 2 & 4.**



Scheme 1



Scheme 2

Table 1

Synthesis of 1,2,3,4 THPMs 1a-f at room temperature under sonication

Entry	Product	R_1	R_2	R_3	X	Product m.p. (Lit. m.p.)°C	Yield (%)
1.	**1a**	H	H	NO_2	O	210(208-211)	76
2.	**1b**	H	H	H	O	204 (202-204)	95
3.	**1c**	H	H	Cl	O	215 (213-215)	92
4.	**1d**	H	H	F	O	186 (185-187)	88
5.	**1e**	H	NO_2	H	S	195 (195-196)	73
6.	**1f**	H	H	H	S	199 (199-200)	91

Table 2
Comparison of reaction time and yields with or without sonication for the Synthesis 1a-f.

Entry	Product	Reaction time		Yield (%)	
		With sonication	With out sonication	With sonication	With out sonication
1.	**1a**	45 min	3 hr	76	74
2.	**1b**	20 min	2 hr	95	95
3.	**1c**	30 min	3 hr	92	89
4.	**1d**	30 min	3 hr	88	85
5.	**1e**	40 min	3 hr	73	69
6.	**1f**	25 min	2.5 hr	79	77

Table 3
Synthesis of 1,4 DHPs 2a-f at room temperature under sonication

Entry	Product	R_1	R_2	R_3	Product m.p. (Lit. m.p.)°C	Yield (%)
1.	**2a**	H	NO_2	H	126(128-134)	49
2.	**2b**	H	H	NO_2	131(129-131)	43
3.	**2c**	H	H	OCH_3	159(159-160)	48
4.	**2d**	H	H	H	156(158-160)	44
5.	**2e**	H	H	Cl	145(144-146)	41
6.	**2f**	H	H	F	155(151-155)	43

Table 4
Comparison of reaction time and yields with or without sonication for 2a-f

Entry	Product	Reaction Time		Yield (%)	
		With sonication	With out sonication	With sonication	With out sonication
1.	**2a**	45 min	3 hr	49	45
2.	**2b**	30 min	2.5 hr	43	40
3.	**2c**	20 min	2 hr	48	44
4.	**2d**	20 min	2 hr	44	42
5.	**2e**	25 min	2 hr	41	39
6.	**2f**	25 min	2 hr	43	37

Conclusion

In conclusion, the synthesis of 1,2,3,4-tetrahydropyrimidine-2-one and 1,4 DHP derivatives was successfully carried out in solvent-less dry media (bentonite clay) supported– copper perchlorate as catalyst under ultrasonic irradiation. The method offers several significant advantages, such as, high yields, easy handling, and cleaner green reaction profile which makes it a useful and attractive method for the efficient synthesis of 1,2,3,4-tetrahydropyrimidine-2-one and 1,4 DHPderivatives.

Acknowledgement

The authors are grateful to Head, Department of Chemistry, Sant Longowal Institute of Engineering & Technology, Longowal for providing laboratory facilities.

References

1. (a) R.S.Verma, Green Chem., 1999, 43-55 (b) Using chemical reagents on porous carriers, Akt.-Ges. FurChemiewerte, Br. Pat., 1924, 231,901; Chem. Abstr., 1925, **19**, 3571.

2. (a) A. Kumar, R. A. Maurya, J. Mol. Cat. A: Chem., 2007, **272**, 53-56; (b) F. Shirini, K.Marjani, H. T. Nahzomi, ARKIVOC, 2007 (i), 51-57.
3. A. D. Patil, N. V. Kumar, W. C. Kokke, M. F. Bean, A. J. Freyer, C. Debrosse, S. Mai, A. Trunch, D. J. Faulkner, B. Carte, A. L. Been, R. P. Herzberg, R. K. Johnson, J. W. Wastly, B. C. M. Ports, J. Org. Chem. 1995, **6**, 1182.
4. (a) K. S. Atwal, B. N. Swanson, S. E. Unger, D. M. Floyd, S. Moreland, A. Hedberg, B. C. O'Reilly, J. Med. Chem. 1991, **34**, 806. (b) K. S. Atwal, G. C. Rovnyak, S. D. Kimball, D. M. Floyd, S. Moreland, B. N. Swanson, J. Z. Gougoutas, J. Schwartz, K. M. Smillie, M. F. Malley, J. Med. Chem. 1990, **33**, 2629.
5. (a) G. C. Rovnyak, S. D. Kimball, B. Beyer, G. Cucinotta, J. D. Dimarco, J. Z. Gougoutas, A. Hedberg, M. Malley, J. P. McCarthy, R. Zhang, S. Moreland, J. Med. Chem. 1995, **38**, 119. (b) G. C. Rovnyak, K. S. Atwal, A. Hedberg, S. D. Kimball, S. Moreland, J. Z. Gougoutas, B. C. O'Reilly, J. Schwartz, M. F. Malley, J. Med. Chem. 1992, **35**, 3254.
6. B. B. Snider, Z. P. Shi, J. Org. Chem. 1993, **58**, 3828 and references cited therein.
7. S. F. Flaim, R. Zelis, Fed. Proc. 1981, **40**, 2877.
8. P. Bignelli, Gazz Chim Ital, 1893, **23**, 360.
9. (a) M. M. Khodaei, A. R. Khosropour, M. Beygzadeh, Synth. Commun. 2004, **34**, 1551. (b) S. Tu, F. Fang, S. Zhu, T. Li, X. Zhang, Q. Zhuang, Synlett 2004, 537. (c) M. Gohain, D. Prajapati, J. S. Sandhu, Synlett 2004, 235. (d) D. S.Bose, R. K. Kumar, L. Fatima, Synlett 2004, 279. (e) Z.T. Wang, L.W. Xu, C.G. Xia, H.Q. Wang, Tetrahedron Lett. 2004, **45**, 7951.
10. (a) P. Salehi, M. Dabiri, M. A. Zolfigol, M. A. Bodagh Ford, Tetrahedron Lett. 2003, **44**, 2889. (b) K. Kiran, G. S. Reddy, Ch. Srinivas Reddy, J. S. Yadav, G. Sabitha, Synlett 2003, 858. (c) R. Varala, M. M. Alam, S. R. Adapa, Synlett 2003, 67. (d) K. R. Reddy, C. V. Reddy, M. Mahesh, P. V. K. Raju, V. V. N. Reddy, Tetrahedron Lett. 2003, **44**, 8173. (e) S. Tu, F. Fang, C. Miao, H. Jiang, Y. Feng, D. Shi, X. Wang, Tetrahedron Lett. 2003, **44**, 6153.
11. (a) A. S. Paraskar, G. K. Dewkar, A. Sudalai, Tetrahedron Lett. 2003, **44**, 3305. (b) D. Subhas Bose, L. Fatima, H. B. Mereyala, J. Org. Chem. 2003, **68**, 587.
12. (a) C. V. Reddy, M. Mahesh, P. V. K. Raju, T. R. Babu, V. V. N. Reddy, Tetrahedron Lett. 2002, 43, 2657. (b) J. Lu, Y. Bai, Synthesis 2002, 466. (c) T. Jin, S. Zhang, J. Guo, T. Li, J. Chem. Res. (S) 2002, 37.
13. (a) B. Kumar, B. Kaur, J. Kaur, A. Parmar, R. D. Anand, H. Kumar, Indian J. Chem. 2002, **41**, 1526. (b) C. O. Kappe, J. Org. Chem. 1997, **62**, 7201 (c) J. Lu, Y. Bai, Z. Wang, B. Yang, H. Ma, Tetrahedron Lett. 2000, **41**, 9075.
14. A. Parmar, H. Kumar, Synth. Commun. 2007, **37**, 2321-29.

Received on May 24, 2008.