MICROWAVE-INDUCED ONE-POT FACILE SYNTHESIS OF THIAZOLO-PYRIMIDINES USING SILICA GEL AS SOLID SUPPORT

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ABSTRACT

An efficient one-pot rapid synthesis of thiazolo-pyrimidines was carried out via Biginelli three component condensation reaction under microwave irradiations in a solvent-free media using Silica gel as solid support. The present method provides a high speed, efficient, environmentally benign modification of classical Biginelli reaction without using an expensive reagent.

INTRODUCTION

In 1893, Pietro Biginelli reported[1] the first synthesis of 3,4-dihydropyrimidin-2(1H)-ones by a very simple one-pot condensation reaction of an aromatic aldehyde, urea and ethyl acetoacetate in ethanolic solution through thermal heating. Later on, lots of structural variations2 were carried out in dihydropyrimidines because of their resemblance to commercially used Hantzsch pyridines as antihypertensive agents. The present paper describes the synthesis of their bicyclic derivatives viz. thiazolo-pyrimidines.

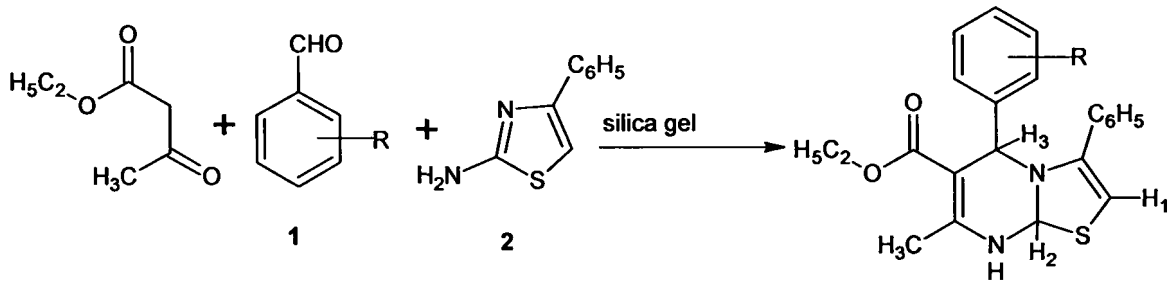
Thiazoles and pyrimidines individually[3] or in combination[4] are involved with a wide range of biological activities. They can act as antiviral, antitumoral, antimalarial, antifungal, antihypertensive, analgesic and anti-inflammatory agents. The wider therapeutic application of thiazolo-pyrimidines derivatives prompted us to synthesize this class of compounds. Several[5] conventional and non-conventional methods have been reported for the synthesis of thiazolo-pyrimidines. However, these methods are associated with many drawbacks like multistep synthetic route, longer reaction time with drastic conditions, difficult work up, low yield and use of expensive and hazardous chemicals. But, as the concept of one-pot multicomponent reaction[6] and Microwave-induced organic reaction enhancement technique using dry media[7] is gaining importance, due to increasing environmental and economical concerns, we have modified the synthetic route of the title compounds to one-pot multicomponent cyclocondensation reaction under microwave irradiations using solid support. As the solution phase microwave reaction have some limitations, like superheating of the solvent may result in explosion. The solid supports viz. alumina, silica gel, montmorillonite, etc. provide acidic, basic and neutral environment and they reduce the amount of toxic wastes and byproducts in chemical transformations. Through this modification, precious solvents can be saved, reaction time can be reduced and overall yield can be improved by reducing the no. of steps. Thus, it is a step towards green chemistry.

RESULTS AND DISCUSSION

The multicomponent reactions under microwave irradiation using dry media develop a facile protocol to generate library of several heterocyclic compounds in an environmentally benign fashion. In view of this, the synthesis of the title compounds was carried out using these techniques. For this, thiazole was reacted with ethylacetoacetate and aromatic aldehydes using silica gel as solid support (**Scheme 1**). The reaction was completed in 1-6 min. A variety of

aromatic aldehydes carrying either electron donating or electron withdrawing substituents reacted very well, giving products in high purity.

Scheme 1



1 2

R = 2-OH; 3-OH; 4-OH; 2-NO_2; 3-NO_2; 4-NO_2; 4-Br; 2,4-(Cl), 4-OCH_3; 2,3-(O-CH_2-O); 4-OH,3-OCH_3; 4-N(CH_3); H

EXPERIMENTAL

Melting points are uncorrected and were determined in open end capillaries. Thin layer chromatography was performed on Silica gel G (Merck).^{1}H NMR spectra were recorded on BRUKER ADVANCE II 400 NMR Spectrometer. The IR spectra were recorded on Perkin-Elmer spectrum RX IFT-IR System. The mass spectra were obtained on a JEOL 5 x 102/DA-6000 mass spectrometer. All the compounds gave satisfactory elemental analysis within $\pm$ 0.4% of theoretical values. The microwave-irradiated reactions were performed in domestic household microwave oven Samsung M177N.

General procedure

Synthesis of Ethyl 5-[substituted phenyl]-7-methyl-3-phenyl-8,8a-dihydro-5*H*-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate: A mixture of aromatic/heterocyclic aldehyde(**1**, 0.01 mole), 4-phenyl-1,3-thiazol-2-amine(**2**, 0.01 mole), and ethylacetoacetate was taken. To this, silica gel as solid support was added and stirred vigorously. The dry powder was irradiated in a microwave oven for the appropriate time (**Table 1**) at 320 W. After completion of the reaction (followed by TLC) , the product was eluted with ethanol. Removal of the solvent under reduced pressure yielded the product which was recrystallized from ethanol. The structures of the prepared compounds, were elucidated on the basis of IR, NMR, Elemental and Mass spectral data.

Table 1: Synthesis of Ethyl 5-[substituted phenyl]-7-methyl-3-phenyl-8,8a-dihydro-5*H*-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate

Entry	R	Time(sec..)	Product	m.p(^{0}C)	Yield(%)
1.	2-OH	360	1a	216-218	66
2.	3-OH	240	1b	220-221	35
3.	4-OH	50	1c	192-193	49
4.	2-NO_2	180	1d	236-238	28
5.	3-NO_2	180	1e	244-245	26
6.	4-NO_2	180	1f	235-237	28
7.	4-Br	180	1g	268-270(d)	38
8.	2,4-(Cl)	180	1h	278-280	36
9.	4-OCH_3	180	1i	247-250(d)	67
10.	2,3-(O-CH_2-O)	300	1j	225-226(d)	35
11.	4-OH,3-OCH_3	30	1k	185-187	53
12.	4-N(CH_3)	90	1l	191-193	28
13.	H	180	1m	239-240(d)	29

Table 2: Characterization data of the synthesized compounds

Comp	^{1}H(δ,ppm), Mass, IR, Elemental analysis
1a	PMR (δ,ppm): 9.01(s,1H, OH); 7.33 (s, 1H, NH); 6.79-7.30 (m, 10H, Ar-H & H_1); 5.68 (s, 1H, H_3) ; 3.31 O$\underline{CH_2}CH_3$); 2.29 (s, 3H, CH_3); 2.11 (s, 1H, H_2); 1.29 (t, 3H, $OCH_2\underline{CH_3}$), also OH and NH protons got exchanged with D_2O. IR (KBr,cm^{-1}) :3436.5; 2924.3; 2857; 1637; 1590.5; 1489 Anal. Cald. for $C_{22}H_{22}N_2SO_3$: C 72.93; H 6.07; N 7.73. Found: C 72.56; H 6.00; N 7.25%
1b	PMR (δ,ppm): 9.16(s,1H, OH); 7.43 (s, 1H, NH); 6.69-7.35 (m, 10H, Ar-H & H_1); 5.70 (s, 1H, H_3) ; 3.25(q, 2H,-O$\underline{CH_2}CH_3$); 2.23 (s, 3H, CH_3); 2.19 (s, 1H, H_2); 1.25 (t, 3H, $OCH_2\underline{CH_3}$), also OH and NH protons got exchanged with D_2O. IR (KBr,cm^{-1}) :3423; 2962; 2840; 1634; 1562.1; 1495 Anal. Cald. for $C_{22}H_{22}N_2SO_3$; C 72.93; H 6.07; N 7.73. Found: C 72.35; H 6.01; N 7.61%
1c	PMR (δ,ppm): 9.10(s,1H, OH); 7.39 (s, 1H, NH); 6.92-7.40 (m, 10H, Ar-H & H_1); 5.72 (s, 1H, H_3) ; 2H,-O$\underline{CH_2}CH_3$); 2.30 (s, 3H, CH_3); 2.20 (s, 1H, H_2); 1.35 (t, 3H, $OCH_2\underline{CH_3}$), also OH and NH protons got exchanged with D_2O. IR (KBr,cm^{-1}) :3423; 2962; 2840; 1634; 1562.1; 1495 Anal. Cald. for $C_{22}H_{22}N_2SO_3$: C 72.93; H 6.07; N 7.73. Found: C 72.12;

	H 5.92; N 7.34%
1d	IR (KBr,cm^{-1}) : 3285; 2922.4; 2839; 1646.2; 1592; 1479.1 Anal. Cald. for $C_{22}H_{21}N_3SO_4$: C 67.52; H 5.37; N 10.74. Found: C 67.49; H 5.25; N 10.80%
1e	IR (KBr,cm^{-1}): 3290; 2926.1; 2830; 1634.2; 1595; 1499.1 Anal. Cald. for $C_{22}H_{21}N_3SO_4$: C 67.52; H 5.37; N 10.74. Found: C 67.59; H 5.20; N 10.68%
1f	IR (KBr,cm^{-1}): 3402.4; 2924.3; 2845; 1636.2; 1590.2; 1480.7 Anal. Cald. for $C_{22}H_{21}N_3SO_4$: C 67.52; H 5.37; N 10.74. Found: C 67.34; H 5.42; N 10.62%
1g	IR (KBr,cm^{-1}): 3278; 2920.3; 2834; 1638.2; 1599.2; 1485.7 Anal. Cald. for $C_{22}H_{21}N_2SO_2Br$: C 62.12; H 4.94; N 6.58. Found: C 62.01; N 6.23%
1h	PMR (δ,ppm): 7.59 (s, 1H, NH); 7.19-7.37 (m, 9H, Ar-H & H_1); 5.91 (s, 1H, H_3) ; 3.26(q, 2H,-O$\underline{CH_2}CH_3$); 1.99 (s, 3H, CH_3); 2.16 (s, 1H, H_2); 1.20 (t, 3H, $OCH_2\underline{CH_3}$), also NH protons got exchanged with D_2O. Anal. Cald. for $C_{22}H_{20}N_2SO_2Cl_2$: C 63.79; H 4.83; N 6.76. Found: C 63.87; H 4.56; N 6.82%
1i	IR (KBr,cm^{-1}): 3299; 2930; 2854; 1631.8; 1582.9; 1478.2 Anal. Cald. for $C_{23}H_{24}N_2SO_3$: C 73.40; H 6.38; N 7.45. Found: C 73.29; H 6.46; N 7.33%
1j	PMR (δ,ppm): 7.63 (s, 1H, NH); 6.69-7.40 (m, 9H, Ar-H & H_1); 5.66 (s, 1H, H_3); 6.00(s, 2H, O-CH_2-O ; 3.41(q, 2H,-O$\underline{CH_2}CH_3$); 2.45 (s, 3H, CH_3); 2.19 (s, 1H, H_2); 1.19 (t, 3H, $OCH_2\underline{CH_3}$), alsoNH protons got exchanged with D_2O. IR (KBr,cm^{-1}): 3293.2; 1630.4, 1534.5, 1480 Anal. Cald. for $C_{23}H_{22}N_2SO_4$: C 70.77; H 5.64; N 7.18. Found: C 70.67; H 5.52; N 7.27%
1k	IR (KBr,cm^{-1}) : 3361, 3275, 1635.8, 1519, 1462 Anal. Cald. for $C_{23}H_{24}N_2SO_4$: C 70.41; H 6.12; N 7.14. Found: C 70.52; H 5.98; N 7.23%
1l	PMR (δ,ppm) : 7.43 (s, 1H, NH): 7.09-7.28 (m, 10H, Ar-H & H_1); 5.66 (s, 1H, H_3) ; 3.34(q, 2H,O$\underline{CH_2}CH_3$); 2.96 (s, 6H, $N(CH_3)_2$);2.34 (s, 3H, CH_3); 2.16 (s, 1H, H_2); 1.22 (t, 3H, $OCH_2\underline{CH_3}$), protons got exchanged with D_2O. Anal. Cald. for $C_{24}H_{27}N_3SO_2$: C 74.03; H 6.94; N 10.79. Found: C 73.91; H 6.86; N 10.65%

1m	PMR (δ,ppm) : 7.79 (s, 1H, NH); 7.16-7.39 (m, 11H, Ar-H & H_1); 5.75 (s, 1H, H_3) ; 3.60(q, 2H,-O$\underline{CH_2}CH_3$); 2.58 (s, 3H, CH_3); 2.15 (s, 1H, H_2); 1.15 (t, 3H, $OCH_2\underline{CH_3}$), also NH protons got exchanged with D_2O. IR (KBr,cm^{-1}) : 3282, 1631, 1540.7, 1492.6 Anal. Cald. for $C_{22}H_{22}N_2SO_2$: C 69.84; H 5.82; N 7.41. Found: C 69.78; H 5.62; N 7.54% Mass (m/z): 276; 176; 134; 132; 104.1; 32

REFERENCES

1. P. Biginelli, *Gazz. Chem. Ital.*, 1893, **23**, 360.
2. (a) C.O.Kappe, P. Roschger, *J. Heterocyclic Chem.* 1989, **26**, 55 (b) A. Saini, S. Kumar, J. S. Sandhu, *J. Indian Chem. Soc.*, 2007, ***84***, 959.
3. (a) P. Pevarello, R.Amici, G. Traquandi, M. Villa, A. Vulpetti, A.Isacchi, U.S.Patent, 2006, 7,037,929 B1.(b) G.C.Rounyak, 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. (c) P.Pathak, R.Kaur, B.Kaur, *ARKIVOC*, 2006, **xvi**, 160.
4. (a) F.Debarre, J.L.Fabre, D.Farge, C.James, *U.S.Patent*, 1983, 4,419,356.(b) J.P.Beck, *U.S.Patent*, 2000, 6,107,294.
5. M. Kidwai, S.Bala, A.D. Mishra, *Indian J. Chem*, 2004, 43B, 2485.(b) M.M. Kurbanova, *Russian J. Org. Chem.* 2006, 42, 1871.(c) G. Doria, C. Passarotti, M.L. Corno, *U.S. Patent.* 1985, 4,558,046.
6. H. Bienayme, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* 2000, 6, 3321.
7. (a) Todda F, *Acc Chem Res*,1995, 480. (b) Tanaka K and Todda F, *Chem Rev*, 2000,1024. (c) Dittmer D C, *Chem Ind*, 1997, 779.(d) Bram G, Loupy A, Villemin D, Ellis Harwood, London, 1992.

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