SHORT PAPER

J. Chem. Research (S),
2003, 330–331

A convenient synthesis of 5-benzylidenethiazolidine-2,4-diones under microwave irradiation without solvent[†]

De-Hong Yang[b], Zhen-Chu Chen[a,b]*, Song-Ying Chen[b] and Qin-Guo Zheng[c]

[a]Ningbo Institute of Technology, Zhejiang University, Ningbo, 315104, P.R. China

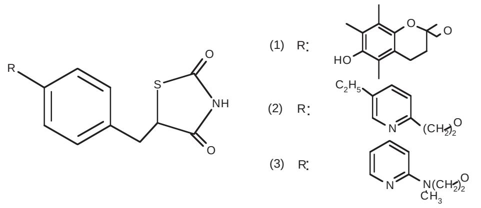
[b]Department of Chemistry, Zhejiang University (XiXi Campus), HangZhou, 310028, P.R. China

*[c]Pharmaceutical Sciences Research Institute, Aston University, Aston Triangle,
Birmingham B4 7ET, UK*

A series of 5-benzylidenethiazolidine-2,4-diones was synthesised by the Knoevenagel condensation of aromatic aldehydes with thiazolidine-2,4-dione in the presence of catalytic amounts of piperidine and acetic acid under microwave irradiation without solvent in good yields.

Keywords: 5-benzylidenethiazolidine-2,4-diones

5-Benzylidenethiazolidine-2,4-diones are useful versatile synthons. They can be used as intermediates in organic synthesis especially pharmaceutical synthesis.[1] For example, they are key intermediates for the synthesis of antidiabetic drugs, troglitazone (**1**), pioglitazone (**2**), and rosiglitazone (**3**)[2] *etc*. (Scheme 1).

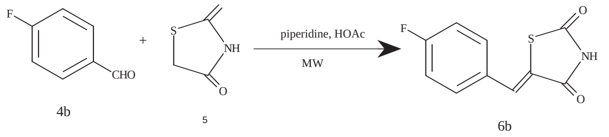


Scheme 1

The conventional synthesis of 5-benzylidenethiazolidine-2,4-diones involves the Knoevenagel condensation of aromatic aldehydes with thiazolidine-2,4-dione in the presence of catalytic amounts of organic base or acid or salt in toluene.[3] However, these reactions require long reaction times and use a toxic solvent and a tedious work-up procedure.

Microwave-assisted organic transformations, coupled with solvent-free conditions have attracted much attention due to their enhanced reaction rates, easier work-up, and in many cases, use of solvent-free conditions.[4] Herein we would like to report the synthesis of 5-benzylidenethiazolidine-2,4-diones by the Knoevenagel condensation of aromatic aldehydes with thiazolidine-2,4-dione with catalytic amount of piperidine and acetic acid under microwave irradiation without solvent. This method is simple, fast and affords good yields.

For this study, a commercial microwave oven was used for irradiation of the reaction mixture. At first, using the reaction of 4-fluorobenzaldehyde (**4b**) with thiazolidine-2,4-dione (**5**) as a representative we investigated the effects of the power and time of microwave irradiation for the formation of 5-(4’-fluorobenzylidene)thiazolidine-2,4-dione (**6b**) (Scheme 2).The results are summarised in Tables 1 and 2.



Scheme 2

Table 1 Effect of the power of microwave irradiation for the formation of (**6b**) [a]

Power/w	100	210	350	500	700
Yield/% [b]	14	66	95	30	tar

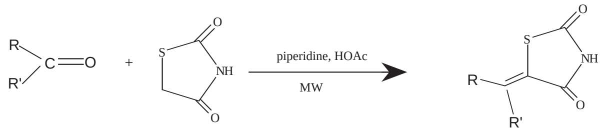
[a]All reactions were run with 4-fluorobenzaldehyde 1mmol, thiazolidine-2,4-dione 1mmol and catalytic amounts of piperidine and acetic acid under microwave irradiation for 1.5min.
[b]Isolated yields of pure products.

Table 2 Effect of the time of microwave irradiation for the formation of (**6b**)[a]

Time/min [b]	0.5	1	1.25	1.5	1.75	2
Yield/%[c]	15	59	80	95	71	42
Time/min [d]	0.25	0.5	1	1.25	1.5	2
Yield/%[c]	18	77	93	65	30	tar

[a]All reactions were run with substrate 1mmol, thiazolidine-2,4-dione 1mmol and catalytic amounts of piperidine and acetic acid under microwave irradiation [b]Power/W, 350; [c]Isolated yields of pure products; [d]Power/W, 350.

Then the scope of the Knoevenagel condensation of various aromatic aldehydes (**4**) with thiazolidine-2,4-dione (**5**) under microwave irradiation was investigated. We found the reaction occurred easily under microwave irradiation in the presence of catalytic amounts of piperidine and acetic to form the corresponding 5-benzylidenethiazolidine-2,4-diones (**6**) (Scheme 3).



Scheme 3

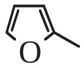
The reactions were completed within 1.5 min. The results are summarised in Table 3. The products were characterised by ^{1}HNMR, IR and melting points which were consistent with the literature data. As can be seen in Table 3, the reaction was found to be general applicable to various aromatic aldehydes. Cinnamaldehyde, furfural and acetophenone were also successfully reacted.

In conclusion, we have provided a simple, fast, convenient and efficient method for the preparation of 5-benzylidenethiazolidine-2,4-diones under microwave irradiation. Additionally, the solvent-free conditions make this procedure more economic and environmentally benign.

---

* To receive any correspondence. E-mail: zhenchuc@mail.hz.zj.cn
[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 3 Preparation of 5-benzylidenethiazolidine-2,4-diones **6a**-**n**[a]

Product	R	R′	Yield [b]/%	M.p./°C
6a	C_6H_5	H	88	245–247(lit.[5] 247–249)
6b	4-FC_6H_4	H	95	220–221(lit.[5] 219.5–220)
6c	4-ClC_6H_4	H	82	223–224(lit.[6] 224–225)
6d	4-$NO_2C_6H_4$	H	77	185–189(lit.[6] 189–190)
6e	3-$NO_2C_6H_4$	H	75	267–270(lit.[6] 268–269)
6f	4-OHC_6H_4	H	90	225–226(lit.[7] 226)
6g	2-OHC_6H_4	H	80	310–312(lit.[5] >300)
6h	4-$CH_3OC_6H_4$	H	92	217–218(lit.[5] 218)
6i	2,5-$(CH_3O)_2C_6H_3$	H	73	270–272
6j	3,4-$(CH_3O)_2C_6H_3$	H	70	208–210
6k	4-$CH_3C_6H_4$	H	89	225–226(lit.[8] 227)
6l	$C_6H_5CH{=}CH$	H	86	218–220
6m		H	64	230–233(lit.[9] 231–232)
6n	C_6H_5	CH_3	50	120–122

[a]All reactions were run with 4-fluorobenzaldehyde 1mmol, thiazolidine-2,4-dione 1mmol and catalytic amounts of piperidine and acetic acid under microwave irradiation for 1.5min. (Power/W, 350); [b]Isolated yields of pure products.

Experimental

Melting points were uncorrected. IR spectra were recorded as KBr pellets on an IR spectrophotometer. ^1H NMR spectra were recorded on a Bruker (400MHz) spectrometer in DMSO-d6 using TMS as an internal standard. Microwave irradiation was run in a commercial microwave oven (2450MHz, 350w) under atmospheric pressure. Elemental analysis was performed on a Carlo Erba EA 1106 instrument.

General procedure: Aldehyde (1mmol) and thiazolidine-2,4-dione (1mmol) were mixed with a few drops of piperidine and acetic acid at ambient temperature in a flask (10ml). The resulting mixture was subjected to microwave irradiation at 350w for 1.5min. Then the reaction mixture was washed with H_2O (5ml) and the crude product was purified by recrystallisation from EtOH to give **6**.

Reprensentative data for typical compounds **6i**, **6j**, **6l** *and* **6n**: **6i**: yellow solid; IR(cm-1) 3442, 3122, 3021, 1731, 1678, 1591; ^{1}HNMR δH 3.75(3H, s, OCH_3), 3.83 (3H, s, OCH_3), 6.92 (1H, m, ArH), 7.08–7.11 (2H, m, ArH), 7.92 (1H, s, =CHAr), 12.58 (1H, s, NH). Found: C, 54.0%; H, 4.2%; N, 5.5%; $C_{12}H_{11}NO_4S$ requires C, 54.3%; H, 4.2%; N, 5.3%.

6j: yellow solid; IR(cm^{-1}) 3441, 3022, 1737, 1688, 1581; ^{1}HNMR δH 3.82 (3H, s, OCH_3), 3.83(3H, s, OCH_3) 7.12-7.20 (3H, m, ArH), 7.76 (1H, s, =CHAr), 12.53 (1H, s, NH). Found: C, 54.0%; H, 4.1%; N, 5.5%; $C_{12}H_{11}NO_4S$ requires C, 54.3%; H, 4.2%; N, 5.3%.

6l: yellow brown solid; IR(cm^{-1}) 3192, 3027, 1719, 1684, 1610, 1585; ^{1}HNMR δH 6.90–6.97 (1H, t, J=11.6Hz, CH=CH*-CH=), 7.28–7.66 (5H, m, ArH), 7.679–7.683 (2H, b, *J*=1.6Hz, CH*=CH-CH*=), 12.42 (1H, bs, NH). Found: C, 62.7%, H, 4.0%, N, 5.9%; $C_{12}H_9NO_2S$ requires C, 62.3%; H, 3.9%; N, 6.1%.

6n: white solid; IR (cm^{-1}) 3163, 3044, 1735, 1678, 1582; ^{1}HNMR δH 2.65 (3H, s, CH_3), 7.41-7.49 (5H, m, ArH), 12.30 (1H, bs, NH). Found: C, 59.9%, H, 4.2%, N, 6.4%; $C_{11}H_9NO_2S$ requires C, 60.3%; H, 4.1%; N, 6.4%.

Received 7 October 2002; accepted 20 January 2003
Paper 02/1577

References

1 K. Meguro, T. Fuiita, C. Hatanaka and S. Oi, **EP 257 781**, CA 1988, 109: 6504h

2 S. Takashi, M. Katsutoshi, H. Takeo, M. Yoshitaka and K. Yutaka, *Chem. Pharm. Bull.*, 1983, **31**, 560

3 P.C. Unanst, D.T. Connor, W.A. Cetenko, R.J. Sorenson, C.R. Kostlan, J.C. Sircar, C.D. Wrighl, .D.J. Schrier and R.D. Dyer, *J. Med. Chem.*, 1994, **37**, 322

4 (a) S. Caddick, Tetrahedron, 1995, **51**, 10403; (b) R.A. Abramovitch, *Org. Prep. Proc. Int.*, 1991, **23**, 683; (c) A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacqualt and D. Mathe, *Synthesis*, 1998, 1213; (d) R.S. Varma, *Green Chem.*, 1999, **1**, 43; (e) D.M.P. Mingos and D.R. Baghurst, *Chem. Soc. Rev.*, 1991, **20**, 1

5 R.G. Giles, N.J. Lewis, J.K. Quick, M.J. Sasse, M.W.J. Urquhart and L. Youssef, *Tetrahedron*, 2000, **56**, 4531

6 I.B. Levshin, I.B. Tsurkan, K.A. V'yunov and A.I. Ginak, *Zh. Prikl. Khim.*, 1983, **56**, 1453

7 V.G. Zubenko, *Trudy L'vov. Med. Inst.*, 1957, **12**, 80, CA 1960,54:21059

8 L. Musial and J. Staniec, *Roczniki Chem.* 1965, **39**, 839, CA 1966, 64: 3516a

9 V.G. Zubenko, *Trudy L'vov. Med. Inst.*, 1957, **12**, 80, CA 1958, 55: 17623d