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### A CONVENIENT SYNTHESIS OF 5-ARYLIDENETHIAZOLIDINE-2,4-DIONES ON POTASSIUM FLUORIDE-ALUMINIUM OXIDE

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**A CONVENIENT SYNTHESIS OF 5-ARYLIDENETHIAZOLIDINE-  
2,4-DIONES ON POTASSIUM FLUORIDE-ALUMINIUM OXIDE**

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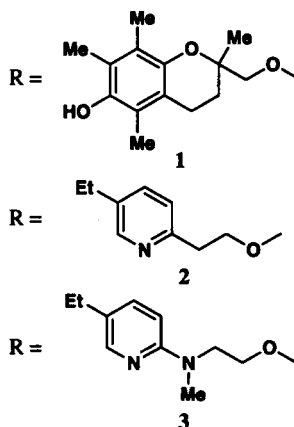
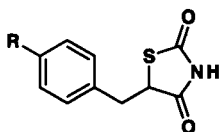
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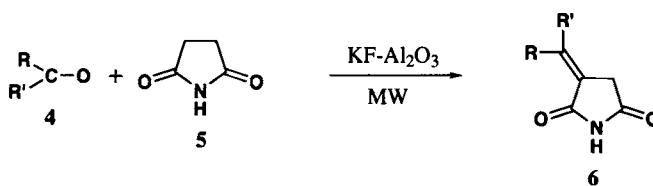
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5-Arylidene-thiazolidine-2,4-diones (**6**) are versatile synthons which are useful as intermediates especially in the synthesis of anti-diabetic drugs such as *trogli-tazone* (**1**), *pioglitazone* (**2**), and *rosiglitazone* (**3**).<sup>1,2</sup>



The conventional synthesis of 5-arylidene-thiazolidine-2,4-diones involves the condensation of aromatic aldehydes with thiazolidine-2,4-dione in the presence of catalytic amounts of an organic base or acid or salt in toluene.<sup>3</sup> However, these reactions require long reaction times, the use of toxic solvents and tedious work-up procedures. Recently, there has been increased interest in the use of environmentally benign reagents and conditions<sup>4</sup> and particularly in solvent-free procedures,<sup>5a-5d</sup> thus avoiding the need for organic solvents. Villemin *et al.*<sup>5e-5g</sup> have used  $\text{KF-Al}_2\text{O}_3$  without solvent in palladium-catalyzed reactions (Suzuki, Heck, Stille, Trost-Tsuji) under microwave irradiation. We now report a facile, efficient and environmentally benign method for the synthesis of 5-arylidene-thiazolidine-2,4-diones (**6**) by the condensation of aromatic aldehydes with thiazolidine-2,4-dione (**5**) on  $\text{KF-Al}_2\text{O}_3$ <sup>6</sup> under microwave irradiation without solvent (see *Scheme*).



- a) R = C<sub>6</sub>H<sub>5</sub>, R' = H; b) R = 4-FC<sub>6</sub>H<sub>4</sub>, R' = H; c) R = 4-ClC<sub>6</sub>H<sub>4</sub>, R' = H; d) R = 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, R' = H; e) R = 3-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, R' = H; f) R = 4-HOC<sub>6</sub>H<sub>4</sub>, R' = H; g) R = 2-OHC<sub>6</sub>H<sub>4</sub>, R' = H; h) R = 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>, R' = H; i) R = 2, 5-(CH<sub>3</sub>O)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, R' = H; j) R = 3,4-(CH<sub>3</sub>O)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, R' = H; k) R = 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, R' = H; l) R = C<sub>6</sub>H<sub>5</sub>CH=CH, R' = H; m) R = 2-furfuryl, R' = H; n) R = C<sub>6</sub>H<sub>5</sub>, R' = CH<sub>3</sub>; o) R, R' = cyclohexyl

## Scheme

We initially chose the reaction of benzaldehyde (**4a**) with thiazolidine-2,4-dione (**5**) as a representative example to investigate the effects of the power, time of microwave irradiation, different catalysts and different amounts of KF-Al<sub>2</sub>O<sub>3</sub> on the formation of 5-arylidene-thiazolidine-2,4-dione (**6a**). The results are summarized in *Table 1*.

**Table 1.** Effect of Power, Time, Catalyst and Amount of Catalyst on the Yield of **6a**

Power <sup>b</sup> (watt)	Yield <sup>a</sup> (%)	Time <sup>c</sup> (min.)	Yield (%)	Catalyst <sup>d</sup>	Yield (%)	Amount <sup>e</sup> of KF-Al <sub>2</sub> O <sub>3</sub>	Yield (%)
100	56	5	49	KF-Al <sub>2</sub> O <sub>3</sub>	96	0.02	95
210	96	8	78	KF	64	0.1	96
350	80	10	96	Basic Al <sub>2</sub> O <sub>3</sub>	60	0.16	92
500	55	12	86	Pipd.-HOAc	88	0.2	90
750	40	15	60	Pipd.	81	0.26	85
----	----	----	----	HOAc	19	0.3	83
----	----	----	----	----	15	----	----

a) Yields of pure product; all reactions were run on 1 mmol of benzaldehyde and thiazolidine-2,4-dione. b) Irradiation 10 min. with 0.1 g of KF-Al<sub>2</sub>O<sub>3</sub>. c) With 0.1 g of KF-Al<sub>2</sub>O<sub>3</sub>. d) With 0.1 g of catalyst for 10 min. e) At 210 watts for 10 min.

As can be seen from *Table 1*, the presence of catalyst is necessary for the reaction of **4a** with **5** to afford **6a**, from among the tested catalysts, such as KF-Al<sub>2</sub>O<sub>3</sub>, KF, basic alumina, piperidine acetate, piperidine and acetic acid, the KF-Al<sub>2</sub>O<sub>3</sub> combination gave the best results. Additionally, variation of the ratios of substrate (mmol) to KF-Al<sub>2</sub>O<sub>3</sub> (g) from 1:0.02 to 1:0.1 did not affect the yield. It was shown that when the power of microwave irradiation was higher (>350 w), and the time of microwave irradiation was longer (>10 min), lower yields were obtained along with formation of black and viscous tars. The scope of the reaction of various aromatic aldehydes (**4**) with thiazolidine-2,4-dione (**5**) under microwave irradiation was investigated. The reaction proceeded easily on KF-Al<sub>2</sub>O<sub>3</sub> under microwave irradiation (210 w) for 10min to form the corresponding 5-arylidene-thiazolidine-2,4-diones (**6**) in good yields (50-96%).

**A CONVENIENT SYNTHESIS OF 5-ARYLIDENETHIAZOLIDINE-2,4-DIONES**

The results are summarized in *Table 2*. The products were characterized by <sup>1</sup>H NMR, IR, and melting points which were consistent with the literature data. The reaction is generally applicable to aromatic aldehydes containing various substituents, such as fluoro, chloro, nitro, hydroxy, methyl and methoxy. Reactions with cinnamaldehyde and furfural were also successful. Although acetophenone, and cyclohexanone underwent condensation, lower yields of **6n** and **6o** were obtained possibly because of aldol condensation side-reaction; under the same conditions, benzophenone (steric hindrance), *n*-heptanal, and acetone (volatility). Additionally, *n*-heptanal is readily to be oxidized to the carboxylic acid. The reactions proceed by heating in an oil bath but required much longer time; the condensation of *p*-fluorobenzaldehyde with **5** in toluene (with azeotropic removal of water) gave a 90% yield of **6b** in 18 hrs while an 80% yield was obtained in dimethyl sulfoxide after 15 hrs.

**Table 2.** 5-Arylidene-thiazolidine-2,4-diones<sup>a</sup>

Cmpd	Yield (%)	Color	mp. (°C)	lit. mp. (°C)	Reference
<b>6a</b>	96	pale yellow	245-247	247-249	7
<b>6b</b>	91	orange	220-221	219.5-220	7
<b>6c</b>	90	pale yellow	223-224	224-225	8
<b>6d</b>	86	yellow	267-270	268-269	8
<b>6e</b>	83	yellow	185-190	189-190	8
<b>6f</b>	85	yellow	310-312	>300	7
<b>6g</b>	77	orange	225-226	226	9
<b>6h</b>	93	yellow	217-218	218	7
<b>6i</b>	70	yellow	270-272	---- <sup>b</sup>	----
<b>6j</b>	70	yellow	208-210	---- <sup>c</sup>	----
<b>6k</b>	92	pale yellow	225-226	227	10
<b>6l</b>	82	yellow brown	218-220	---- <sup>d</sup>	----
<b>6m</b>	71	pale reddish brown	230-233	231-232	9
<b>6n</b>	57	white	120-122	---- <sup>e</sup>	----
<b>6o</b>	50	pale yellow	140-142	139-142	11

a) All reactions were run with carbonyl compounds (1 mmol), thiazolidine-2,4-dione (1 mmol) and KF-Al<sub>2</sub>O<sub>3</sub> (0.1 g) under microwave irradiation (210 w) for 10 min. b) *Anal.* Calcd for C<sub>12</sub>H<sub>11</sub>NO<sub>4</sub>S: C, 54.34; H, 4.15; N, 5.28. Found: C, 54.15; H, 4.19; N, 5.41. c) *Anal.* Calcd for C<sub>12</sub>H<sub>11</sub>NO<sub>4</sub>S: C, 54.34; H, 4.15; N, 5.28. Found: C, 54.03; H, 4.12; N, 5.47. d) *Anal.* Calcd for C<sub>12</sub>H<sub>9</sub>NO<sub>2</sub>S: C, 62.34; H, 3.90; N, 6.06. Found: C, 62.67; H, 4.01; N, 5.92. e) *Anal.* Calcd for C<sub>11</sub>H<sub>9</sub>NO<sub>2</sub>S: C, 60.27; H, 4.11; N, 6.39. Found: C, 59.98; H, 4.15; N, 6.44.

In conclusion, KF-Al<sub>2</sub>O<sub>3</sub> is an economical and efficient catalyst for the condensation of aromatic aldehydes with thiazolidine-2,4-dione. The use of dry reaction techniques coupled with microwave irradiation provide a clean, efficient and economical technology for preparation of

the pharmaceutically useful intermediates 5-arylidene-thiazolidine-2,4-diones. The present method has some obvious advantages including environmentally more benign, the simplicity of the methodology, the ease of product isolation shorter reaction times and higher yields.

**Table 3.** IR and NMR Spectra of Compounds **6a-o**

Cmpd	IR (cm <sup>-1</sup> )	<sup>1</sup> H NMR (δ)
<b>6a</b>	3461, 1738, 1689	7.46-7.61 (5H, m, ArH), 7.80 (1H, s, = CHAr), 12.64 (1H, bs, NH)
<b>6b</b>	3447, 1700	7.36-7.40 (2H, m, ArH), 7.65-7.68 (2H, m, ArH), 7.80 (1H, s, = CHAr), 12.61 (1H, s, NH)
<b>6c</b>	3447, 1720	7.59-7.64 (4H, m, ArH), 7.80 (1H, s, = CHAr), 12.68 (1H, bs, NH)
<b>6d</b>	3459, 1714, 1679	7.84-7.89 (2H, m, ArH), 7.95 (1H, s, = CHAr), 8.33-8.35 (2H, m, ArH), 12.77 (1H, bs, NH)
<b>6e</b>	3477, 1700	7.81-7.83 (1H, m, ArH), 7.92 (1H, s, = CHAr), 8.01-8.03 (1H, m, ArH), 8.27-8.29 (1H, m, ArH), 8.44 (1H, s, ArH), 12.73 (1H, bs, NH)
<b>6f</b>	3410, 1725, 1675	6.90-6.92 (2H, m, ArH), 7.44-7.47 (2H, m, ArH), 7.70 (1H, s, = CHAr), 10.33 (1H, s, OH), 12.47 (1H, s, NH)
<b>6g</b>	3419, 1724, 1673	6.92-6.97 (2H, m, ArH), 7.28-7.38 (2H, m, ArH), 7.99 (1H, s, = CHAr), 10.48 (1H, s, OH), 12.46 (1H, s, NH)
<b>6h</b>	3138, 1734, 1687	3.82 (3H, s, OCH <sub>3</sub> ), 7.10-7.12 (2H, m, ArH), 7.56-7.58 (2H, m, ArH), 7.76 (1H, s, = CHAr), 12.54 (1H, bs, NH)
<b>6i</b>	3442, 1731, 1678	3.75 (3H, s, OCH <sub>3</sub> ), 3.83 (3H, s, OCH <sub>3</sub> ), 6.92-6.97 (1H, m, ArH), 7.08-7.11 (2H, m, ArH), 7.92 (1H, s, = CHAr), 12.58 (1H, s, NH)
<b>6j</b>	3441, 1737, 1688	3.82 (3H, s, OCH <sub>3</sub> ), 3.83 (3H, s, OCH <sub>3</sub> ), 7.12-7.20 (3H, m, ArH), 7.76 (1H, s, = CHAr), 12.53 (1H, s, NH)
<b>6k</b>	3168, 1736, 1685	2.36 (3H, s, CH <sub>3</sub> ), 7.34-7.36 (2H, m, ArH), 7.48-7.50 (2H, m, ArH), 7.76 (1H, s, = CHAr), 12.57 (1H, bs, NH)
<b>6l</b>	3192, 1719, 1684	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)
<b>6m</b>	3144, 1733, 1684	6.74 (1H, s, furanyl 3-H), 7.08-7.09 (1H, d, J = 4Hz, furanyl 4-H), 7.61 (1H, s, furanyl 5-H), 8.05 (1H, s, = CH), 12.46 (1H, bs, NH)
<b>6n</b>	3163, 1735, 1678	2.65 (3H, s, CH <sub>3</sub> ), 7.41-7.49 (5H, m, ArH), 12.30 (1H, bs, NH)
<b>6o</b>	3173, 1728, 1688	1.58-1.66 (6H, m, cyclohexyl H), 2.19-2.22 (2H, m, cyclohexyl H), 3.04-3.05 (2H, m, cyclohexyl H), 12.13 (1H, bs, NH)

## EXPERIMENTAL SECTION

Melting points measured on BeiGuang X<sub>4</sub> apparatus are uncorrected. IR spectra were recorded as KBr pellets on VECTOR-22 IR spectrophotometer. <sup>1</sup>H NMR spectra were determined on Bruker (400 MHz) spectrometer in DMSO-d<sub>6</sub> using TMS as an internal standard. Microwave irradiation was performed in a commercial microwave oven (2450 MHz) under atmospheric pressure. Elemental analyses were performed on Carlo Erba EA 1106 instrument. The IR and NMR spectra of compounds **6a-o** are shown in *Table 3*. The catalyst was prepared according to the literature procedure.<sup>6</sup>

**General Procedure for Synthesis of 5-Arylidene-thiazolidine-2,4-diones (6).**- The aldehyde (1 mmol) and thiazolidine-2,4-dione (1 mmol, 0.12 g) and  $\text{KF-Al}_2\text{O}_3$  (0.1 g) were mixed in a round bottom flask (10 mL) at room temperature. The mixture was then subjected to microwave irradiation (210 watts) for 10 min. After cooling, DMF (5 mL) was added to the reaction mixture, and it was stirred for a while, then filtered to remove insoluble solids. The filtrate was diluted with  $\text{H}_2\text{O}$  (50 mL) to precipitate the product which was purified by recrystallization from EtOH.

## REFERENCES

1. K. Meguro, T. Fuiita, C. Hatanaka and S. Oi, *Eur. Pat. Appl. EP 257,781*; *Chem. Abstr.*, **109**:6504 (1988).
2. S. M. Takashi, H. Katsutoshi, M. Takeo, and K. Yutaka, *Chem. Pharm. Bull.*, **31**, 560 (1983).
3. P. C. Unanist, D. T. Connor, W. A. Cetenko, R. J. Sorenson, C. R. Kostlan, J. C. Sircar, C. D. Wrihl, D. J. Schrier and R. D. Dyer, *J. Med. Chem.*, **37**, 322 (1994).
4. (a) J. H. Clark, S. R. Cullen, S. J. Barlow and T. W. Bastock, *J. Chem. Soc. Perkin Trans. 2*, 1117 (1994); (b) D. Villemin and M. Hammadi, *Synth. Commun.*, **26**, 4337 (1996); (c) R. S. Varma, R. Dahiya and R. K. Saini, *Tetrahedron Lett.*, **38**, 7029 (1997).
5. (a) A. Loupy, G. Bram and J. Sansoulet, *New J. Chem.*, **16**, 223 (1992); (b) A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullett and P. Jacquault and D. Mathe, *Synthesis*, 1213 (1988); (c) R. S. Varma, *Green Chemistry*, **1**, 43 (1999); (d) R. S. Varma, *Pure Appl. Chem.*, **73**, 193 (2001); (e) D. Villemin and A. B. Alloum, *Synth. Commun.*, **21**, 63 (1991); (f) D. Villemin, B. Matin, and B. Garrigues, *Synth. Commun.*, **23**, 2251 (1993); (g) D. Villemin and F. Caillot, *Tetrahedron Lett.*, **42**, 639 (2001) and references cited.
6. Preparation of  $\text{KF/Al}_2\text{O}_3$ : (a) T. Ando, J. Yamawaki, T. Kawate and S. Sumi, *Bull. Chem. Soc. Jpn*, **55**, 2504 (1982); (b) Y. Nakano, S. Niki, S. Kinouchi, H. Miyamae and M. Igarashi, *Bull. Chem. Soc. Jpn*, **65**, 2934 (1992).
7. R. G. Giles, N. J. Lewis, J. K.Quick, M. J. Sasse, M. W. J. Urquhart and L. Youssef, *Tetrahedron*, **56**, 4531 (2000).
8. I. B. Levshin, I. B. Tsurkan, K. A. V'yunov and A. I. Ginak, *Zh. Prikl. Khim.*, **56**, 1453 (1983); *Chem. Abstr.*, **99**:158338v (1983).
9. V. G. Zubenko, *Trudy L'vov. Med. Inst.*, **12**, 80 (1957); *Chem. Abstr.*, **55**:17623d (1958).
10. L. Musial and J. Staniec, *Roczniki Chem.*, **39**, 839 (1965); *Chem. Abstr.*, **64**:3516a (1966).
11. W. J. Croxall, C. Pen and E. Y. Shropshire, *J. Am. Chem. Soc.*, **75**, 5419 (1953).

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