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Communication

One-Pot Synthesis of 5-Arylidene-2-Imino-4-Thiazolidinones under Microwave Irradiation

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Abstract: A rapid and easy solvent free one-pot synthesis of 5-arylidene-2-imino-4-thiazolidinones by condensation of the thioureas with chloroacetic acid and an aldehyde under microwave-irradiation is described.

Keywords: 5-Arylidene-2-imino-4-thiazolidinones; one-pot synthesis, microwave-irradiation.

Introduction

4-Thiazolidinone derivatives constitute an important class of heterocyclic compounds for their potential pharmaceutical applications [1-8]. Consequently, a large number of synthetic protocols leading to these compounds have been reported in the literature [9]. Recently, 5-arylidene-2-imino-4-thiazolidinones [10] were synthesized by the reaction of 2-imino-4-thiazolidinones and appropriate aldehydes under basic conditions in ethanol at reflux for about 24 hours. The 2-imino-thiazolidinones in turn were obtained by condensation of thiourea with chloroacetyl chloride in the presence of

triethylamine in $CHCl_3$ at room temperature. We have previously reported the synthesis of iminothiazolines [11] by Hantzsch cyclisation using microwave-irradiation. In similar fashion and following the same strategy, we describe herein the one-pot three component solvent-free reaction of the thioureas **1a,a'**, chloroacetic acid and an appropriate aldehydes **2a-e** under microwave-irradiation according to Scheme 1. Yields and reaction conditions are given in Table 1.

Scheme 1. Synthesis of 5-arylidene-2-imino-4-thiazolidinones **3a-e, 4a-e.**

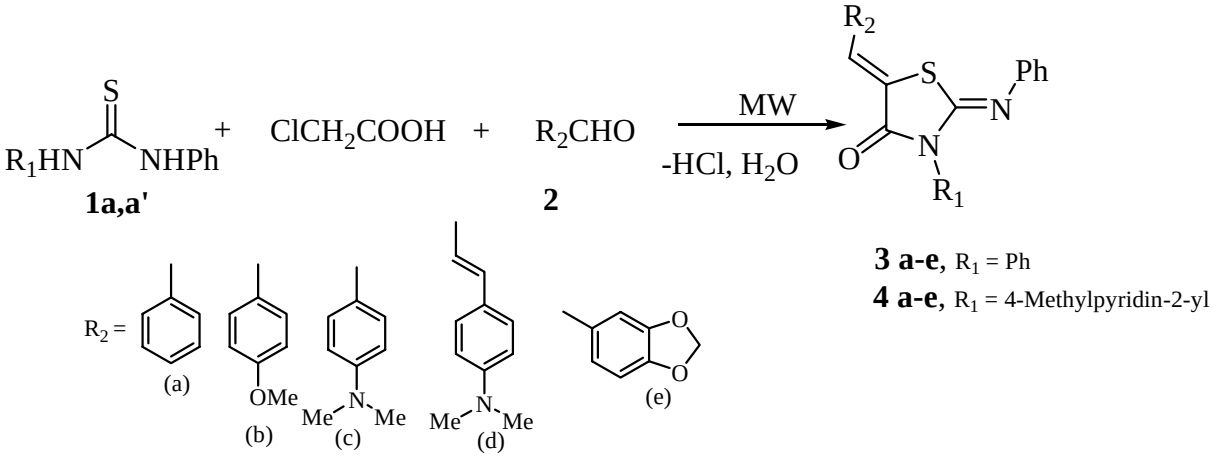

Table 1. Yields and reaction conditions used for the microwave syntheses of **3a-e** and **4a-e**

Compounds 3	R_1	Time (min)	Yields(%)[a]
3a	Ph	20	89
3b	Ph	15	64
3c	Ph	20	73
3d	Ph	20	71
3e, 3e'	Ph	20	75[b]
4a	4-methylpyridin-2-yl	20	79
4b	4-methylpyridin-2-yl	20	68
4c	4-methylpyridin-2-yl	10	77
4d	4-methylpyridin-2-yl	10	74
4e	4-methylpyridin-2-yl	15	61

[a] Isolated product yields

[b] 3:1 mixture of isomers 3e/3e'

The structures of all new compounds **3a-e, 4a-e** were established by analysis of their ^{1}H- and ^{13}C-NMR and mass spectra. The *Z* configuration of the exocyclic C=C bond was assigned on the basis of ^{1}H-NMR spectroscopy, according to literature data for analogous 4-thiazolidinones [3,10,12]. The methine proton deshielded by the adjacent C=O was detected at 7.76-8.30 ppm, except for **3d** and **4d.** In the case of the reaction with aldehyde **2e** a 3:1 mixture of two isomers **3e** and **3e'** was obtained. When the synthesis was performed in EtOH at reflux, the major and the most stable isomer **3e** was obtained. The ^{13}C-NMR spectra of all compounds were characterized by the presence of the rhodanine C_2 C=N at 150.99-154.90 ppm and C=O at the rhodanine C_4 at 165.20-167.25 ppm.

Conclusions

A solvent-free synthesis coupled with focused microwave irradiation appears to be a simple, fast and high yielding method for the preparation of 5-arylidene-2-imino-4-thiazolidinones.

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Experimental

General

Melting points were determined on a Koffler melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker ARX 200 (^{1}H at 200 MHz) or Bruker AC 300P (^{1}H and ^{13}C at 300 and 75 MHz, respectively) spectrometers. Chemical shifts are expressed in parts per million downfield from tetramethylsilane used as an internal standard. The mass spectra were recorded on a Varian MAT 311 at a ionizing potential of 70eV at the "Centre de Mesures Physiques de l'Ouest" (CRMPO, Rennes). Reactions under microwaves were performed in a PROLABO Synthewave 402 (2.45 GHz) microwave reactor with a single focused system. All solvents and reagents were purchased from Acros Organics and Aldrich Chemical and used without further purification.

Preparation of Thioureas **1a,a'**

A mixture of the appropriate amine (0.1 mol) and phenylisothiocyanate (0.12 mol) was stirred in CH_2Cl_2 at room temperature for 24 h. The crude product was concentrated under vacuum and recrystallized from ethanol. *1.3-diphenylthiourea* (**1a**): 93% yield; beige crystals; mp = 157°C; ^{1}H-NMR ($CDCl_3/CF_3COOH$): δ 10.00 (bs, 2H, NH), 7.47 (m, 10H); ^{13}C-NMR ($CDCl_3/CF_3COOH$) δ: 178.89 (C=S), 137.23, 129.12, 126.65, 124.79. *1-(4-methylpyridin-2yl)-3-phenylthiourea* (**1a'**): 94% yield; beige crystals; mp = 160°C; ^{1}H-NMR ($CDCl_3$) δ: 13.91 (bs, 1H, NH), 9.72 (bs, 1H, NH), 8.07 (d, 1H, *J*=5.16Hz), 7.36 (m, 5H), 6.82 (d, 1H, *J*=6Hz), 6.80 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 178.73 (C=S), 153.5 (C=N), 150.59, 150.09, 138.38, 128.73, 126.19, 125.02, 119.82, 112.72, 21.33 (CH_3).

General procedure for the preparation of 5-arylidene-2-imino-4-thiazolidinones **3a-e**, **4a-e.**

The appropriate thiourea **1a-a'** (3 mmol), chloroacetic acid (3.6 mmol) and the aldehyde **2** (3 mmol) were placed successively in a cylindrical quartz tube (Ø = 1.5cm). Then the tube was introduced into the Synthwave ® 402 Prolabo microwave reactor and irradiated at 90-110°C for 10-20 min. The microwave is monitored by a computer which allows the temperature of the reaction mixture to be adjusted. After, cooling down to room temperature; the mixture was extracted with CH_2Cl_2. After elimination of the solvent under vacuum, the residue was purified by recrystallisation from

EtOH/water. Reaction times and yields are listed in Table 1, while microwave power settings and reaction temperatures are given under each entry.

5-Benzylidene-3-phenyl-2-(phenylimino)thiazolidin-4-one (**3a**): 50W (110°C); yellow solid; mp = 216°C; ^{1}H-NMR ($CDCl_3$) δ: 7.88 (s, 1H, CH=$C5_{rhod}$), 7.6-7.04 (m, 15H); ^{13}C-NMR ($CDCl_3$) δ: 166.6 (C=O), 151.05 (C=N), 148.23, 134.77 (CH=$C5_{rhod}$), 134.51, 133.73, 133.28, 132.73, 131.58, 130.35, 129.46, 128.13, 127.36, 124.96, 121.37; 121.15 ($C5_{rhod}$); HRMS, *m/z* found 356.0982 (calc. for $C_{22}H_{16}N_2OS$: 356.09834)

5-(4-Methoxybenzylidene)-3-phenyl-2-(phenylimino)thiazoldin-4-one (**3b**): 50W (90°C); yellow powder; mp = 204°C; ^{1}H-NMR ($CDCl_3$) δ: 7.8 (s, 1H, CH=$C5_{rhod}$), 7.32 (m, 10H), 7.04 (d, 2H, *J*= 7.3Hz), 6.9 (d, 2H, *J*=8.76Hz), 3.8 (s, 3H, CH_3O); ^{13}C-NMR ($CDCl_3$) δ: 166.70 (C=O), 160.99, 151.36 (C=N), 148.49, 134.89 (CH=C_5), 133.80, 133.12, 132.03, 129.29, 128.92, 127.12, 126.39, 124.88, 121.22, 121.27, 118.35 ($C5_{rhod}$), 114.77 ($C5_{rhod}$), 55.46 $(CH_3)_2$); HRMS, *m/z* found 386.1072 (calc. for $C_{23}H_{19}N_3O_2S$: 386.10890)

5-(4-(Dimethylamino)benzylidene)-3-phenyl-2-(phenylimino)thiazolidin-4-one (**3c**): 50W (110°C); yellow crystals; mp = 208°C; ^{1}H-NMR ($CDCl_3$) δ: 7.82 (s, 1H, CH=$C5_{rhod}$), 7.58 -7.06 (m, 10H), 7.03 (d, 2H, *J* =8.03Hz), 6.76 (d, 2H, *J*=8.8Hz), 3.02 (s, 6H, $(CH_3)_2$); ^{13}C-NMR ($CDCl_3$) δ: 167.03 (C=O), 151.92 (C=N), 151.15, 148.76, 135.19 (CH=C_5rhod), 134.51, 132.72, 132 .46, 129.29, 128.72, 128.26, 127.50, 124.65, 121.35, 114.58 (C_5rhod), 112.01, 40.06 ($CH_3)_2$); HRMS, *m/z* found 399.1406 (calc. for $C_2H_{21}N_3OS$: 399.1053).

5-(3-(4(Dimethylamino)phenyl)allylidene)-3-phenyl-2-(phenylimino)thiazolidin-4-one (**3d**): 30W (110°C); purple crystals; mp = 246°C; ^{1}H-NMR ($CDCl_3$) δ: 7.62-7.47 (m, 10H), 7.39 (d, 2H, *J*= 7.61Hz), 7.20 (1H, dd, *J*=6Hz, *J*=2Hz), 7.02 (d, 2H, *J*=7.57Hz), 6.78 (d, 1H, *J*=3Hz), 6.57 (d, 1H, *J*= 3.4Hz), 3.06 (s, 6H, $(CH_3)_2$); ^{13}C-NMR ($CDCl_3$) δ: 166.06 (C=O), 151.54 (C=N), 48.60, 142.96, 134.98 (CH =C_5), 134.77, 132.37, 131.31, 129.24, 129.20, 128.76, 128.09, 124.74, 121.25, 119.07 ($C5_{rhod}$); 112.74, 40.68 $(CH_3)_2$); HRMS, *m/z* found 425.1567 (calc. for $C_{26}H_{23}N_3OS$ 425.15618).

5-((Benzo[d][1,3]dioxol-6-yl)methylene)-3-phenyl-2-(phenylimino)thiazolidin-4-one (**3e, 3e'**): 50W (110°C); a 3:1 mixture of **3e**/**3e'**; yellow solid; mp = 218°C, after crystallisation with EtOH/water; ^{1}H-NMR ($CDCl_3$) δ: 7.90 (s, 1H, CH=$C5_{rhod}$), 7.76 (s, 1H, CH=$C5_{rhod}$), 7.57-6. 85 (m, 20H), 7.3 (s, 1H), 7.18 (d, 1H, *J*=8.0Hz), 7.10 (d, 1H, *J* = 8.2Hz), 7.03 (d, 1H, *J* = 8.3Hz), 7.01 (s, 1H), 6.02 (s, 2H, CH_2), 6.01 (s, 2H, CH_2); ^{13}C-NMR ($CDCl_3$) δ: 167.22 (C=O), 166.58 (C=O), 151.54 (C=N), 150.99 (C=N), 149.91, 149.20, 148.78, 148.40, 148.65, 148.38, 148.33, 148.30, 134.87, 134.80 (CH=$C5_{rhod}$), 132.80, 131.42, 129.93, 129.34, 129.31, 129.22, 128.90, 126.15 , 127.51, 126.83 , 126.13, 124.90, 121.12, 119.04 ($C5_{rhod}$), 119.02 ($C5_{rhod}$), 109.80, 109.24, 109.20, 109.16, 109.10, 108.98, 102.02 (CH_2), 101.80 (CH_2). Isomer **3e** is obtained in 80% yield after reflux in EtOH for 5 hours; yellow solid; mp = 265°C; ^{1}H-NMR ($CDCl_3$) δ: 7.76 (s, 1H, C*H*=$C5_{rhod}$), 7.60-6.86 (m, 10H), 7.00 (s, 1H), 7.03 (d, 1H, *J*=8.4Hz), 6.86 (d, 1H, *J*=8.07Hz), 6.01 (s, 2H, CH_2); ^{13}C-NMR ($CDCl_3$) δ: 166.58 (C=O), 150.99 (C=

N), 149.20, 148.65, 148.38, 148.31, 134.81 (*C*H=C5$_{rhod}$), 131.43, 129.93, 129.31, 128.90, 126.14, 124.90, 121.12, 119.02 (C5$_{rhod}$), 109.20, 109.16, 108.98, 101.79 (*C*H$_2$); HRMS, *m/z* found 400.0889 (calc. for $C_{23}H_{16}N_2O_3S$: 400.08816).

5-Benzylidene-3-(4-methylpyridin-2-yl)-2-(phenylimino)thiazolidin-4-one (**4a**): 50W (110°C); yellow solid; mp>260°C; ^{1}H-NMR ($CDCl_3/CF_3COOH$) δ: 8.45 (d, 1H, *J*=6.7Hz), 8.17 (s, 1H, CH=C5$_{rhod}$), 7.60 (s, 1H), 7.53 (m, 10H), 7.46 (d, 1H, *J*=5.7Hz), 2.70 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ: 167.25 (C=O), 160.58, 153.05 (C=N), 148.75, 148.20, 139.10, 138.90, 135.90 (CH=C5$_{rhod}$), 132.09, 130.58, 129.90, 129.56, 127.84, 122.96, 118.61 (C5$_{rhod}$), 117.00, 116.9, 112.42, 22.54 (CH_3); HRMS, *m/z* found 371.1083 (calc. for $C_{22}H_{17}N_3OS$: 371.10923).

5-(4-Methoxybenzylidene)-3-(4-methyl-3-(4-methylpyridin-2-yl)-2-(phenylimino)thiazolidin-4-one (**4b**): 50W (90°C); yellow powder; mp = 207°C; ^{1}H-NMR ($CDCl_3/CF_3COOH$) δ: 8.28 (d, 1H, *J* = 5.76Hz), 7.95 (s, 1H, CH=C$_5$rhod), 7.9 (m, 5H), 7.3 (d, 2H, *J*=8.3Hz), 7.23 (d, 1H, *J*=5.6Hz), 7.19 (s, 1H), 6.97 (d, 2H, *J*=8.3Hz), 3.85 (s, 3H, CH$_{3pyridine}$), 2.54 (s, 3H, CH_3O); ^{13}C-NMR ($CDCl_3$) δ: 165.63 (C=O), 160.18, 154. 06 (C=N), 139.53, 136.14 (CH=C5$_{rhod}$), 133.72, 132.52, 129.68, 127.89, 125.16, 122.42, 121.27, 118.53 (C5$_{rhod}$), 117.45, 115.01, 113.63, 109.81, 55.51 (CH_3O), 22.26 (CH$_{3pyridine}$); HRMS, *m/z* found 401.1213 (calc. for $C_{23}H_{19}N_3O_2S$: 401.11980).

5-(4-(Dimethylaminobenzylidene)-3-(4-methylpyridin-2-yl)-2-(phenylimino)thiazolidin-4one (**4c**): 30W (90°C); red crystals; mp = 230°C; ^{1}H-NMR ($CDCl_3/CF_3COOH$) δ: 8.45 (d, 1H, *J*=5.74Hz), 7.96 (s, 1H, CH=C5$_{rhod}$), 7.62 (s, 1H), 7.58-7.50 (m, 5H), 7. 47 (d, 1H, *J*=4.12Hz), 7.33 (d, 2H, *J*=5.33Hz), 7.26 (d, 2H, *J*=5.43Hz), 3.10 (s, 6H $(CH_3)_2$), 2.35 (s, 3H, CH$_{3pyridine}$); ^{13}C-NMR ($CDCl_3/CF_3COOH$) δ: 165.20 (C=O), 159.65, 153.99 (C=N), 146.33, 139.67, 134.33 (CH=C5$_{rhod}$), 133.21, 132.28, 130.20, 129.90, 129. 62, 127.77, 122.51, 118.72 (C5$_{rhod}$), 118.63, 117.22, 113.41, 44.52 $(CH_3)_2$), 22.52 (CH_3); HRMS, *m/z* = 414.1501 found (calc. for $C_{24}H_{22}N_4OS$: 414.15143).

5-(3-(4-(Dimethylamino)phenyl)allylidene)-3-(4-methylpyridin-2-yl)-2-(phenylimino)thiazolidin-4-one **(4d)**: 30W (90°C); red crystals; mp> 260°C; ^{1}H-NMR ($CDCl_3$) δ: 8.43 (d, 1H, *J* =5.74Hz), 7.58 (d, 1H, *J*=5.21Hz), 7.53 (t, 1H, *J*=3.91Hz), 7.47 (m, 5H), 7.04 (s, 1H), 6.94 (d, 2H, *J*=6.28Hz), 6.90 (d, 1H, *J*=3.23Hz), 6.83 (d, 1H, *J*=3.83Hz), 6.74 (d, 2H, *J*=8.7Hz), 3.08 (s, 6H, $(CH_3)_2$, 2.34 (s, 3H, CH$_{3pyridine}$); ^{13}C-NMR ($CDCl_3$) δ: 165.96 (C=O), 158.01, 153.25 (C=N), 151.25, 149.28, 146.33, 143.34, 135.63, 133.59, 129.30, 129.05, 128.4, 124.10, 122.15, 121.2, 118.78 (C5$_{rhod}$), 112.03, 40.23 $(CH_3)_2$), 20.79 (CH$_{3pyridine}$); HRMS, *m/z* found 440.1657 (calc. for $C_{26}H_{24}N_4OS$: 440.16708).

5-((Benzo[d][1,3]dioxol-6-yl)methylene)-3-(4-methylpyridin-2yl)-2-(phenylimino)thiazolidin-4-one (**4e**): 50W (90°C); yellow powder; mp = 217°C; ^{1}H-NMR ($CDCl_3/CF_3COOH$) δ: 8.40 (d, 1H, *J*= 5.97Hz), 8.3 (s, 1H, CH=C5$_{rhod}$), 7.86 (s, 1H), 7.5 (d, 1H, *J*=3Hz), 7.20 (m, 8H), 6.04 (s, 2H, CH_2), 2.53 (s, 3 H); ^{13}C-NMR ($CDCl_3$) δ: 165.50 (C=O), 160.67, 154.9 (C=N), 150.15, 148.64, 141.07, 135.08 (CH=C5$_{rhod}$), 133.67, 129.52, 127.98, 127.92, 127.13, 127.04, 122.22, 118.81 (C5$_{rhod}$), 117.77, 116.44, 113.94, 108.99, 102.06, 22.26 (CH_3); HRMS, *m/z* found 415.099 (calc. for $C_{23}H_{17}N_3O_3S$: 415.09906)

References

1. Doran, W. J.; Shonle, H. A. Dialkyl thiazolidinones. *J. Org. Chem.* **1938**, *3*, 193-197.
2. Troutman, H. D.; Long, L. M. The synthesis of 2,3-disubstituted-4-thiazolidinones. *J. Am. Chem. Soc.* **1948**, *70*, 3436-3439.
3. Vicini, P.; Geronikaki, A.; Anastasia, K.; Incerti, M.; Zani, F. Synthesis and antimicrobial activity of novel 2-thiazolylimino-5-arylidene-thiazolidinones. *Bioorg. Med. Chem*. **2006**, *14*, 3859-3864.
4. El-Gendy, Z.; Abdel-Rahman, R. M.; Fawzy, M. M.; Mahmoud, M. B. Biologically active thiazolidinone. Part II. Synthesis and fungitoxicities of isolated and fused thiazolidinones derived from thiosemicarbazones. *J. Indian Chem. Soc.* **1990**, *67*, 927-929.
5. Zervosen, A.; Lu, W. P.; Chen, Z.; White, R. E .; Demuth, Jr, T.P.; Frère, J.M. Interaction between Penicillin- Binding Proteins (PBPs) and two novel classes of PBP inhibitors, aryl-alkylidene rhodanines and arylalkylidene iminothiazolidin-4-ones. *Antimicrob. Agents Chemother*. **2004**, *48*, 961- 969.
6. Diurno, M. V.; Mazzoni, O.; Piscopo, E.; Calignano, A.; Giordano, F.; Bolognese, A. Synthesis and antihistaminic activity of some thiazolidin-4-ones. *J. Med. Chem.* **1992**, *35*, 2910- 2912.
7. Bhargava, P. N.; Prakash, S.; Lakhan, R. Synthesis of 2- (4´,5´-disubstituted thiazol-2´-ylimino)-3-(methylphenyl)-5-methyl (or H)-thiazolidin-4-ones and their fungicidal activity. *Indian J. Chem.* **1981**, *20B*, 927-929.
8. Liu, H-L.; Li, Z.; Anthonsen, T. Synthesis and Fungicidal Activity of 2-Imino-3-(4-aryl-thiazol-2-yl)-thiazolidin-4-ones and their 5-Arylidene Derivatives. *Molecules* **2000**, *5*, 1055- 1061.
9. (a) Kandeel, K. A. Synthesis and structures of some new thiazolidin-4-ones and thiazolin-4-one of anticipated biological activity. *Arkivoc* **2006**, 1-6; (b) D'hooge, M.; De Kimpe, N. Synthetic approaches towards 2-iminothiazolidines: an overview. *Tetrahedron* **2006**, *62*, 513-535; (c) Laurent, D. R. St.; DedongWu, Q.G.; Serrano-Wu, H. Regioselective synthesis of 3-(hetero-aryl)-iminothiazolidin-4-ones. *Tetrahedron Lett*. **2004**, *45*, 1907-1910.
10. Ottana, R.; Maccari, R.; Barreca, M.L.; Bruno, G.; Rotondo, A.; Rossi, A.; Chiricosta, G.; Di-Paola, R.; Sautebin, L.; Cuzzocrea, S.; Vigorita, M.G. 5-Arylidene-2-imino-4-thiazolidinones: Design and synthesis of novel anti-inflammatory agents. *Bioorg. Med. Chem.* **2005**, *13*, 4243-4252.
11. Kasmi, S.; Hamelin, J.; Benhaoua, H. Microwave-assisted solvent free synthesis of imino-thiazolines. *Tetrahedron Lett*. **1998**, *39*, 8093-8096.
12. Bruno, G.; Costantino, L.; Curinga, C.; Maccari, R.; Monfore, F.; Nicolo, F.; Ottana, R.; Vigorita, M.G. *Bioorg. Med. Chem.* **2002,** *10*, 1077-1084.

Sample Availability: Available from the authors.