

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

The structures of all new compounds **3a-e**, **4a-e** were established by analysis of their ^1H - and ^{13}C -NMR and mass spectra. The Z configuration of the exocyclic C=C bond was assigned on the basis of ^1H -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. ^1H -NMR spectra were recorded on a Bruker ARX 200 (^1H at 200 MHz) or Bruker AC 300P (^1H 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 Synthwave 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; ^1H -NMR ($\text{CDCl}_3/\text{CF}_3\text{COOH}$): δ 10.00 (bs, 2H, NH), 7.47 (m, 10H); ^{13}C -NMR ($\text{CDCl}_3/\text{CF}_3\text{COOH}$) δ : 178.89 (C=S), 137.23, 129.12, 126.65, 124.79. **1-(4-methylpyridin-2-yl)-3-phenylthiourea (1a')**: 94% yield; beige crystals; mp = 160°C; ^1H -NMR (CDCl_3) δ : 13.91 (bs, 1H, NH), 9.72 (bs, 1H, NH), 8.07 (d, 1H, $J=5.16\text{Hz}$), 7.36 (m, 5H), 6.82 (d, 1H, $J=6\text{Hz}$), 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 ($\varnothing = 1.5\text{cm}$). 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; $^1\text{H-NMR}$ (CDCl_3) δ : 7.88 (s, 1H, $\text{CH}=\text{C}_{5\text{rhod}}$), 7.6–7.04 (m, 15H); $^{13}\text{C-NMR}$ (CDCl_3) δ : 166.6 ($\text{C}=\text{O}$), 151.05 ($\text{C}=\text{N}$), 148.23, 134.77 ($\text{CH}=\text{C}_{5\text{rhod}}$), 134.51, 133.73, 133.28, 132.73, 131.58, 130.35, 129.46, 128.13, 127.36, 124.96, 121.37; 121.15 ($\text{C}_{5\text{rhod}}$); HRMS, m/z found 356.0982 (calc. for $\text{C}_{22}\text{H}_{16}\text{N}_2\text{OS}$: 356.09834)

5-(4-Methoxybenzylidene)-3-phenyl-2-(phenylimino)thiazolidin-4-one (3b): 50W (90°C); yellow powder; mp = 204°C; $^1\text{H-NMR}$ (CDCl_3) δ : 7.8 (s, 1H, $\text{CH}=\text{C}_{5\text{rhod}}$), 7.32 (m, 10H), 7.04 (d, 2H, $J=7.3\text{Hz}$), 6.9 (d, 2H, $J=8.76\text{Hz}$), 3.8 (s, 3H, CH_3O); $^{13}\text{C-NMR}$ (CDCl_3) δ : 166.70 ($\text{C}=\text{O}$), 160.99, 151.36 ($\text{C}=\text{N}$), 148.49, 134.89 ($\text{CH}=\text{C}_5$), 133.80, 133.12, 132.03, 129.29, 128.92, 127.12, 126.39, 124.88, 121.22, 121.27, 118.35 ($\text{C}_{5\text{rhod}}$), 114.77 ($\text{C}_{5\text{rhod}}$), 55.46 (CH_3); HRMS, m/z found 386.1072 (calc. for $\text{C}_{23}\text{H}_{19}\text{N}_3\text{O}_2\text{S}$: 386.10890)

5-(4-(Dimethylamino)benzylidene)-3-phenyl-2-(phenylimino)thiazolidin-4-one (3c): 50W (110°C); yellow crystals; mp = 208°C; $^1\text{H-NMR}$ (CDCl_3) δ : 7.82 (s, 1H, $\text{CH}=\text{C}_{5\text{rhod}}$), 7.58–7.06 (m, 10H), 7.03 (d, 2H, $J=8.03\text{Hz}$), 6.76 (d, 2H, $J=8.8\text{Hz}$), 3.02 (s, 6H, $(\text{CH}_3)_2$); $^{13}\text{C-NMR}$ (CDCl_3) δ : 167.03 ($\text{C}=\text{O}$), 151.92 ($\text{C}=\text{N}$), 151.15, 148.76, 135.19 ($\text{CH}=\text{C}_{5\text{rhod}}$), 134.51, 132.72, 132.46, 129.29, 128.72, 128.26, 127.50, 124.65, 121.35, 114.58 ($\text{C}_{5\text{rhod}}$), 112.01, 40.06 (CH_3); HRMS, m/z found 399.1406 (calc. for $\text{C}_{22}\text{H}_{21}\text{N}_3\text{OS}$: 399.1053).

5-(3-(4(Dimethylamino)phenyl)allylidene)-3-phenyl-2-(phenylimino)thiazolidin-4-one (3d): 30W (110°C); purple crystals; mp = 246°C; $^1\text{H-NMR}$ (CDCl_3) δ : 7.62–7.47 (m, 10H), 7.39 (d, 2H, $J=7.61\text{Hz}$), 7.20 (1H, dd, $J=6\text{Hz}$, $J=2\text{Hz}$), 7.02 (d, 2H, $J=7.57\text{Hz}$), 6.78 (d, 1H, $J=3\text{Hz}$), 6.57 (d, 1H, $J=3.4\text{Hz}$), 3.06 (s, 6H, $(\text{CH}_3)_2$); $^{13}\text{C-NMR}$ (CDCl_3) δ : 166.06 ($\text{C}=\text{O}$), 151.54 ($\text{C}=\text{N}$), 48.60, 142.96, 134.98 ($\text{CH}=\text{C}_5$), 134.77, 132.37, 131.31, 129.24, 129.20, 128.76, 128.09, 124.74, 121.25, 119.07 ($\text{C}_{5\text{rhod}}$), 112.74, 40.68 (CH_3); HRMS, m/z found 425.1567 (calc. for $\text{C}_{26}\text{H}_{23}\text{N}_3\text{OS}$: 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; $^1\text{H-NMR}$ (CDCl_3) δ : 7.90 (s, 1H, $\text{CH}=\text{C}_{5\text{rhod}}$), 7.76 (s, 1H, $\text{CH}=\text{C}_{5\text{rhod}}$), 7.57–6.85 (m, 20H), 7.3 (s, 1H), 7.18 (d, 1H, $J=8.0\text{Hz}$), 7.10 (d, 1H, $J=8.2\text{Hz}$), 7.03 (d, 1H, $J=8.3\text{Hz}$), 7.01 (s, 1H), 6.02 (s, 2H, CH_2), 6.01 (s, 2H, CH_2); $^{13}\text{C-NMR}$ (CDCl_3) δ : 167.22 ($\text{C}=\text{O}$), 166.58 ($\text{C}=\text{O}$), 151.54 ($\text{C}=\text{N}$), 150.99 ($\text{C}=\text{N}$), 149.91, 149.20, 148.78, 148.40, 148.65, 148.38, 148.33, 148.30, 134.87, 134.80 ($\text{CH}=\text{C}_{5\text{rhod}}$), 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 ($\text{C}_{5\text{rhod}}$), 119.02 ($\text{C}_{5\text{rhod}}$), 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; $^1\text{H-NMR}$ (CDCl_3) δ : 7.76 (s, 1H, $\text{CH}=\text{C}_{5\text{rhod}}$), 7.60–6.86 (m, 10H), 7.00 (s, 1H), 7.03 (d, 1H, $J=8.4\text{Hz}$), 6.86 (d, 1H, $J=8.07\text{Hz}$), 6.01 (s, 2H, CH_2); $^{13}\text{C-NMR}$ (CDCl_3) δ : 166.58 ($\text{C}=\text{O}$), 150.99 ($\text{C}=\text{N}$).

N), 149.20, 148.65, 148.38, 148.31, 134.81 (CH=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 (CH₂); HRMS, *m/z* found 400.0889 (calc. for C₂₃H₁₆N₂O₃S: 400.08816).

5-Benzylidene-3-(4-methylpyridin-2-yl)-2-(phenylimino)thiazolidin-4-one (4a): 50W (110°C); yellow solid; mp>260°C; ¹H-NMR (CDCl₃/CF₃COOH) 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, CH₃); ¹³C-NMR (CDCl₃) 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 (CH₃); HRMS, *m/z* found 371.1083 (calc. for C₂₂H₁₇N₃OS: 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; ¹H-NMR (CDCl₃/CF₃COOH) δ: 8.28 (d, 1H, *J* = 5.76Hz), 7.95 (s, 1H, CH=C5_{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, CH₃_{pyridine}), 2.54 (s, 3H, CH₃O); ¹³C-NMR (CDCl₃) 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 (CH₃O), 22.26 (CH₃_{pyridine}); HRMS, *m/z* found 401.1213 (calc. for C₂₃H₁₉N₃O₂S: 401.11980).

5-(4-(Dimethylaminobenzylidene)-3-(4-methylpyridin-2-yl)-2-(phenylimino)thiazolidin-4-one (4c): 30W (90°C); red crystals; mp = 230°C; ¹H-NMR (CDCl₃/CF₃COOH) 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 (CH₃)₂), 2.35 (s, 3H, CH₃_{pyridine}); ¹³C-NMR (CDCl₃/CF₃COOH) 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 (CH₃)₂, 22.52 (CH₃); HRMS, *m/z* = 414.1501 found (calc. for C₂₄H₂₂N₄OS: 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; ¹H-NMR (CDCl₃) 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, (CH₃)₂), 2.34 (s, 3H, CH₃_{pyridine}); ¹³C-NMR (CDCl₃) 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 (CH₃)₂, 20.79 (CH₃_{pyridine}); HRMS, *m/z* found 440.1657 (calc. for C₂₆H₂₄N₄OS: 440.16708).

5-((Benzo[d][1,3]dioxol-6-yl)methylene)-3-(4-methylpyridin-2-yl)-2-(phenylimino)thiazolidin-4-one (4e): 50W (90°C); yellow powder; mp = 217°C; ¹H-NMR (CDCl₃/CF₃COOH) 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, CH₂), 2.53 (s, 3H); ¹³C-NMR (CDCl₃) 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 (CH₃); HRMS, *m/z* found 415.099 (calc. for C₂₃H₁₇N₃O₃S: 415.09906).

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Sample Availability: Available from the authors.