Anusaya S. Chavan, Arun S. Kharat, Manisha R. Bhosle and Ramrao A. Mane*

Baker's yeast catalyzed one-pot synthesis of bioactive 2-[benzylidene(or pyrazol-4-ylmethylene)hydrazono]-1,3-thiazolidin-4-one-5-yl-acetic acids

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Abstract: An efficient and simple one-pot protocol has been developed for synthesis of substituted derivatives of 2-hydrazono-4-thiazolidinone-5-acetic acids **4a–j** and **6a–g** by cyclocondensation of aryl/pyrazolyl aldehyde, thiosemicarbazide and maleic anhydride in acetonitrile in the presence of readily available whole cell biocatalyst, baker's yeast (*Saccharomyces cerevisiae*). The reaction is enhanced by ultrasonication.

Keywords: baker's yeast; 2-hydrazono-4-thiazolidinon-5-yl-acetic acids; one-pot multicomponent reaction; ultrasonication.

Introduction

Thiazolidinone ring system is a core component of penicillins and cephalosporins and many derivatives display a wide spectrum of therapeutic activities [1] including antibacterial [2, 3], anti-inflammatory [4, 5], anticancer [6–9], antitubercular [10], anticonvulsant [11], analgesic [12], antimicrobial [12–15], and COX-2 inhibitory properties [16]. 1,3-Thiazolidine-2,4-dione is an essential component of clinical antidiabetic agents ciglitazone and pioglitazone and others bioactive compounds [17–20] (Figure 1). In search for an efficient antidiabetic agent, chemists are paying attention to synthesis of new 1,3-thiazolidin-4-ones developing efficient synthetic protocols. Due to the therapeutic significance of hydrazono-4-thiazolidinone derivatives, several protocols have been reported [17–21] for their synthesis. A two-step synthesis is usually used for obtaining 2-hydrazono-4-thiazolidinone-5-acetic acids starting from aldehydes [18, 19]. The aldehyde is condensed with thiosemicarbazide and the resultant thiosemicarbazone is then allowed to react with maleic anhydride by thia-Michael addition to furnish the desired hydrazonothiazolidinone. Many hydrazonothiazolidinones have been prepared by carrying one-pot tandem cyclocondensation of aldehyde, maleic acid and thiosemicarbazide in toluene in the presence of *p*-toluenesulfonic acid as catalyst under microwave assisted irradiation at 100–120°C [18]. Hydrazonothiazolidinone acetic acids with a pyrazolyl scaffold have been synthesized in a similar manner starting from a pyrazolecarbaldehyde [17].

Enzymes are well explored as biocatalysts. Baker's yeast, one of the widely used whole cell source of biocatalysts [22–24] has been used to aid Hantzsch dihydropyridine synthesis [25], synthesis of polyhydroquinoline [26], Biginelli reaction for synthesis of dihydropyrimidinones [27], aldol condensation and Knoevenagel condensation [28]. It has been reported that biocatalysts display their catalytic behavior even in organic solvents, making way to easy solubilization of organic substrates [29–33].

Considering the information discussed above and in continuation of our earlier work on biocatalysis [28, 34–38], in this report we describe the use of activated baker's yeast as a source of a biocatalyst for accelerating the synthesis of substituted 2-hydrazono-4-thiazolidinone-5-acetic acids [17–21]. This report described an improved approach to the synthesis of the desired products.

Results and discussion

A one-pot multi-component cyclocondensation protocol was developed for synthesis of aryl-substituted 2-hydrazono-4-thiazolidine-1,3-one-5-acetic acids **4a–j** (Scheme 1) and pyrazol-4-yl substituted analogs **6a–g** (Scheme 2). The cornerstone of this work was finding that baker's yeast catalyzes these preparations. Initially, the cyclocondensation of benzaldehyde (**1a**), thiosemicarbazide (**2**) and maleic anhydride (**3**) in ethanol was run as a two-step model reaction. In the first step, a mixture of benzaldehyde and thiosemicarbazide was stirred in ethanol at room temperature in the presence of baker's yeast for 4 h to furnish the intermediate

***Corresponding author: Ramrao A. Mane,** Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004, India, e-mail: manera2011@gmail.com
Anusaya S. Chavan and Manisha R. Bhosle: Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004, India
Arun S. Kharat: Department of Biotechnology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Sub-Campus, Osmanabad, India

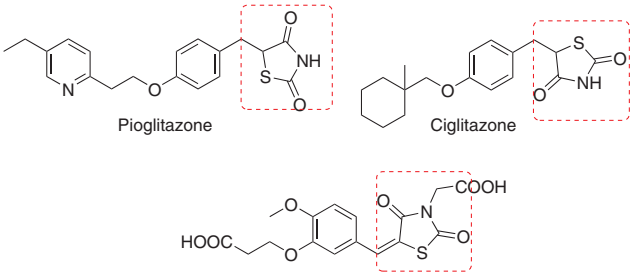
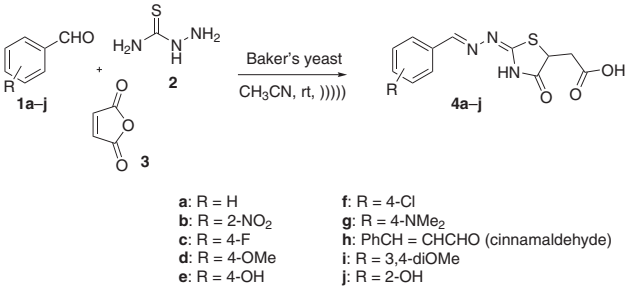


Figure 1 Selected bioactive agents with a thiazolidine-2,4-dione scaffold.



Scheme 1 Synthesis of compounds **4a–j**.

thiosemicarbazone in 76% yield. Then the intermediate thiosemicarbazone was allowed to react with maleic anhydride in ethanol in the presence of yeast at room temperature. This treatment gave the desired product **4a** in 65% yield after 48 h. It was found that both steps are catalyzed by baker's yeast. This finding prompted us to undertake cyclocondensation leading to **4a** by the reaction of benzaldehyde (**1a**), thiosemicarbazide (**2**) and maleic anhydride (**3**) in ethanol in the presence of baker's yeast at room temperature as a one-step procedure. This reaction furnished the desired product **4a** after 48 h with an enhanced yield of 70%.

The use of ultrasonication for organic transformations is well explored [37]. The ultrasonication is also used for disruption of the biological cells for the release of their interiors [39–41]. In this work, ultrasonication was used to disrupt baker's yeast cells for the release of intracellular enzymes that catalyze the reaction. The use of ultrasonication at room temperature resulted in a remarkable decrease of the reaction time from 48 h to 4 h. Interestingly, an attempted reaction under ultrasonication but in the absence of baker's yeast did not produce any product **4a** even after 40 h.

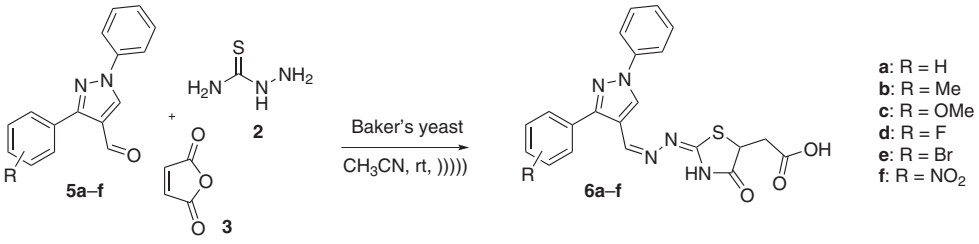
The model reaction was also screened using different solvents and varying the temperature. It was found that the reaction is best conducted in acetonitrile at room temperature. The optimized conditions are given in Experimental. Overall, products **4a–j** (Scheme 1) were obtained under the optimized conditions in the yields varying from 82% to 93%. In a similar way, the pyrazole analogs **6a–g** (Scheme 2) were synthesized in the yields of 71%–96%.

Conclusion

An alternative environmentally friendly baker's yeast-catalyzed synthetic route to known 2-hydrazono-1,3-thiazolidin-4-ones-5-carboxylic acids **4a–j** and **6a–g** was developed. Sonication-assisted disruption of the baker's yeast cell wall provides the intracellular enzymes that catalyze the reaction. The synthesis is operationally simple, is conducted at room temperature, and the desired product is obtained in short reaction time and with high yield.

Experimental

Melting points were determined in an open capillary tube and are uncorrected. ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker AvIII HD-300 spectrometer operating at 75 MHz. The purity of products was checked by TLC using silica gel-coated aluminum sheets, and visualization was accomplished by treatment with iodine or exposure to ultraviolet light. The ultrasonication-assisted reactions were carried out in a Bandelin Sonorexbath reactor operating at a frequency of 35 kHz and a nominal power of 200 W.



Scheme 2 Synthesis of compounds **6a–f**.

General procedure for synthesis of compounds 4a–j

A mixture of baker's yeast (1 g) and acetonitrile (15 mL) was sonicated at 35 kHz at room temperature for 30 min. After addition of a benzaldehyde **1a–j** or a pyrazol-4-carbaldehyde **5a–f** (5 mmol), thiosemicarbzide (5.5 mmol) and maleic anhydride (5.5 mmol) the mixture was stirred at room temperature for an additional 3.5 h. The progress of the reaction was monitored by thin layer chromatography on silica gel using ethyl acetate/petroleum ether (2:8) as eluent. The mixture was treated with ethyl acetate (30 mL), filtered through a pad of Celite (1 g), and the filtrate was concentrated under reduced pressure. The residue of product **4a–j** was crystallized from ethanol. The mp's and spectral data for all compounds **4a–j** are virtually identical with those reported previously [1, 2].

2-(*N*-Benzylidenehydrazono)-1,3-thiazolidin-4-one-5-acetic acid (4a) Yield 93%; off-white powder; mp 252–254°C; ^{13}C NMR: δ 36.7, 43.6, 127.7, 128.8, 130.7, 134.2, 156.3, 164.3, 171.7, 175.5. HRMS (ESI). Calcd for $C_{12}H_{11}N_3O_3S$ (M + H)$^+$: *m/z* 278.0677. Found: *m/z* 278.0676.

2-(*N*-2-Nitrobenzylidene)2-hydrazono-1,3-thiazolidin-4-one-5-acetic acid (4b) Yield 92%; pale yellow powder; mp 270–271°C; ^{13}C NMR: δ 36.8, 43.7, 120.5, 127.8, 128.9, 130.7, 156.3, 164.8, 171.6, 175.6. HRMS (ESI). Calcd for $C_{12}H_{10}N_4O_5S$ (M + H)$^+$: *m/z* 322.0411. Found: *m/z* 322.0410.

2-(4-Flurobenzylidenehydrazono)-4-thiazolidinone-5-acetic acid (4c) Yield 90%; off-white powder; mp 276–278°C; ^{13}C NMR: δ 36.8, 43.6, 115.8, 116.1, 129.8, 129.9, 130.8, 130.9, 155.1, 165.2, 161.9, 171.8, 175.5. HRMS (ESI). Calcd for $C_{12}H_{10}FN_3O_3S$ (M + H)$^+$: *m/z* 296.0499. Found: *m/z* 296.0499.

2-(4-Methoxybenzylidenehydrazono)-1,3-thiazolidin-4-one-5-acetic acid (4d) Yield 93%; off-white powder; mp 254–256°C; ^{13}C NMR: δ 36.7, 43.6, 55.2, 127.6, 128.9, 130.7, 134.3, 156.3, 164.3, 171.8 and 175.4. HRMS (ESI). Calcd for $C_{13}H_{13}N_3O_4S$ (M + H)$^+$: *m/z* 307.1356. Found: *m/z* 307.1356.

2-(4-Hydroxybenzylidenehydrazono)-1,3-thiazolidin-4-one-5-carboxylic acid (4e) Yield 85%; off-white powder; mp 255–257°C; ^{13}C NMR: δ 36.7, 43.6, 126.3, 127.8, 134.3, 155.2, 164.4, 170.9 and 175.3. HRMS (ESI). Calcd for $C_{12}H_{11}N_3O_4S$ (M + H)$^+$: *m/z* 293.1230. Found: *m/z* 293.1220.

2-(4-Chlorobenzylidenehydrazono)-1,3-thiazolidin-4-one-5-acetic acid (4f) Yield 87%; off-white powder; mp 273–274°C; ^{13}C NMR: δ 36.6, 43.5, 127.6, 128.8, 131.6, 133.2, 154.3, 164.3, 171.6 and 175.5. HRMS (ESI). Calcd for $C_{12}H_{10}ClN_3O_3S$ (M + H)$^+$: *m/z* 311.0131. Found: *m/z* 311.0131.

2-(4-*N,N*Dimethylaminobenzylidenehydrazono)-1,3-thiazolidin-4-one-5-acetic acid (4g) Yield 82%; off-white powder; mp 278–279°C; ^{13}C NMR: δ 36.9, 39.3, 43.6, 118.7, 119.4, 128.3, 130.7, 156.3, 164.4, 171.8, 175.5. HRMS (ESI). Calcd for $C_{14}H_{16}N_4O_3S$ (M + H)$^+$: *m/z* 320.0943. Found: *m/z* 320.0944.

2-(Cinnamylidenehydrazono)-1,3-thiazolidin-4-one-5-acetic acid (4h) Yield 84%; white powder; mp 192–194°C; ^{13}C NMR: δ 36.7, 43.5, 119.4, 127.6, 128.7, 130.7, 134.3, 138.3, 156.3, 164.3, 171.6, 175.5. HRMS (ESI). Calcd for $C_{14}H_{13}N_3O_3S$ (M + H)$^+$: *m/z* 304.0791. Found: *m/z* 304.0790.

2-(3,4-Dimethoxybenzylidene)hydrazono)-1,3-thiazolidin-4-one-5-acetic acid (4i) Yield 90%; off-white powder; mp 232–234°C; ^{13}C NMR: δ 38.4, 44.5, 56.2, 114.4, 115.4, 122.5, 127.1, 149.5, 149.9, 152.1, 177.0, 177.3. HRMS (ESI). Calcd for $C_{14}H_{15}N_3O_5S$ (M + H)$^+$: *m/z* 337.0732. Found: *m/z* 337.0732.

2-(2-Hydroxybenzylidenehydrazono)-1,3-thiazolidin-4-one-5-acetic acid (4j) Yield 82%; off-white powder; mp 236–238°C; ^{13}C NMR: δ 38.4, 44.5, 115.0, 118.2, 121.8, 130.3, 135.2, 149.5, 158.6, 163, 177.0, 177.3. HRMS (ESI). Calcd for $C_{12}H_{11}N_3O_4S$ (M + H)$^+$: *m/z* 293.0470. Found: *m/z* 293.0460.

General procedure for synthesis of compounds 6a–f

A mixture containing a pyrazole-4-carbaldehyde **5a–f** and other reagents as described above in acetonitrile (20 mL) was allowed to react for 8 h. Workup was conducted as described above.

2-[(1,3-Diphenylpyrazol-4-yl)methylenehydrazono]-1,3-thiazolidin-4-one-5-yl-acetic acid (6a) Yield 82%; off-white powder; mp 263–265°C; ^{13}C NMR: δ 36.8, 43.7, 116.7, 118.8, 127.1, 128.5 (2C), 128.6 (2C), 128.8 (2C), 129.5 (2C), 129.6, 132.0, 138.9, 149.1, 151.6, 171.7, 175.4; MS (ESI): *m/z* 420 (M + H)$^+$. Anal. Calcd for $C_{21}H_{17}N_5O_3S$: C, 60.13; H, 4.09; N, 16.70; S, 7.64. Found: C, 60.33; H, 4.04; N, 16.57; S, 7.61.

2-{[1-Phenyl-3-(4-methylphenyl)pyrazol-4-yl]methylenehydrazono}-1,3-thiazolidin-4-one-5-yl-acetic acid (6b) Yield 96%; off-white powder; mp 230–232°C; ^{13}C NMR: δ 20.9, 36.8, 43.7, 116.6, 118.8, 127.0, 128.5 (2C), 129.1 (2C), 129.6 (2C), 130.8, 138.0, 138.9, 149.2, 151.7, 162.7, 166.7, 171.8, 175.4; MS (ESI): *m/z* 434 (M + H)$^+$. Anal. Calcd for $C_{22}H_{19}N_5O_3S$: C, 60.96; H, 4.42; N, 16.16; S, 7.40. Found: C, 61.00; H, 4.48; N, 16.20; S, 7.35.

2-{[1-Phenyl-3-(4-methoxyphenyl)pyrazol-4-yl]methylenehydrazono}-1,3-thiazolidin-4-one-5-yl-acetic acid (6c) Yield 80%; off-white powder; 242–243°C; ^{13}C NMR: δ 36.9, 43.7, 55.2, 113.9, 114.3, 116.4, 118.8 (2C), 124.4 (2C), 126.9 (2C), 139.6, 130.0, 138.9, 149.3, 151.5, 159.6, 162.7, 171.8, 175.5; MS (ESI): *m/z* 450 (M + H)$^+$. Anal. Calcd for $C_{22}H_{19}N_5O_4S$: C, 58.79; H, 4.26; N, 15.58; S, 7.13. Found: C, 58.60; H, 4.30; N, 15.52 and S, 7.20.

2-{[1-Phenyl-3-(4-flurophenyl)pyrazol-4-yl]methylenehydrazono}-1,3-thiazolidin-4-one-5-yl-acetic acid (6d) Yield 82%; off-white powder; mp 249–250°C; ^{13}C NMR: δ 36.7, 43.7, 114.2, 115.2, 115.4, 117.2 (2C), 127.1 (2C), 128.6 (2C), 129.6, 130.8, 130.9, 138.8, 150.4, 162.8, 163.5, 171.8 and 175.4; MS (ESI): *m/z* 438 (M + H)$^+$. Anal. Calcd for $C_{21}H_{16}FN_5O_3S$: C, 57.66; H, 3.69; 4.34; N, 16.01; S, 7.33. Found: C, 57.60; H, 4.00; N, 16.08; S, 7.29.

2-{[1-Phenyl-3-(4-nitrophenyl)pyrazol-4-yl]methylenehydrazono}-1,3-thiazolidin-4-one-5-yl-acetic acid (6e) Yield 78%; off-white powder; mp 260–262°C; ^{13}C NMR: δ 36.7, 43.8, 117.5, 117.9, 118.7, 118.9 (2C), 123.9 (2C), 127.4 (2C), 128.9, 129.7, 131.4, 134.4, 138.8, 148.9, 163.2, 171.7 and 175.4; MS (ESI): *m/z* 465 (M + H)$^+$. Anal. Calcd for $C_{21}H_{16}N_6O_5S$: C, 54.31; H, 3.47; N, 18.09; S, 6.90. Found: C, 54.60; H, 3.40; N, 18.04; S, 6.89.

2-{[1-Phenyl-3-(4-bromophenyl)pyrazol-4-yl]methylenehydrazono}-1,3-thiazolidin-4-one-5-yl-acetic acid (6f) Yield 71%; off-white powder; mp 200–202°C; ^{13}C NMR: δ 38.4, 44.8, 106.1,

177.5, 177.9, 163.7, 118.9 (2C), 123.9 (1C), 132.4 (2C), 126.4, 128.9, 129.7 (2c), 131.4, 134.3, 138.8, 148.9, 163.2, 171.7 and 175.4; MS (ESI) *m/z* 465 $(M+H)^+$. Anal. Calcd for $C_{21}H_{16}BrN_5O_3S$: C, 50.61; H, 3.24; N, 14.05; S, 6.43. Found: C, 50.63; H, 3.19; N, 14.04; S, 6.39.

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