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Catalyst-free and environment friendly synthesis of 2-aryl-3-substituted-4-thiazolidinones in water

Manoj P. Thakare,† Rahimullah Shaikh* and Dipak Tayade

A simple, efficient, eco-friendly, and cost-effective method has been developed for three component one pot synthesis of 2-aryl-3-substituted-4-thiazolidinones is described. The method provides rapid and easy access to thiazolidinone compounds in good to excellent yields.

Introduction:

Sulphur containing compounds are found in a number of natural products and are of particular importance regarding pharmaceutically active substances (1). In recent years, 4-thiazolidinones are the most extensively investigated compounds and have fascinated organic and medicinal chemists. Thiazolidinones have emerged as an important class of compound because of their biological importance and have shown interesting biological activity profiles such as antibacterial (2), antitubercular (4), anti HIV (6), COX-1 inhibitor (7), anti HIV (8), anti-histaminic (9) agents and potent in vitro anti-urease agents (10).

Formation in the first step followed by attack of sulphur nucleophile on the imine carbon and finally intramolecular cyclization with the elimination of water. Variations have been made in the removal of water during cyclization. Different protocols have been used to affect the loss of water in final step such as molecular sieves (12), trimethylorthoformate (13), sodium sulphate (14), ZnCl₂ (15), and azeotropic distillation with benzene or toluene (16). The most recently used methods for the synthesis of thiazolidinones include DCC (17), Saccharomyces cerevisiae (18), HBTU (19), [bmim][PF6] (20), Bi(SCH₂COOH)₃ (21) silica chloride (22), mesoporous MCM-41 supported Schiff base and CuSO₄⋅5H₂O (23) and alum (24). However, the use of these reagents have some limitations such as high temperature, longer reaction time, corrosive, expensive, hazardous reaction condition and purification issues due to formation of by-products. Therefore, it is desired to develop a new method which can eliminate these difficulties. In this article, we report catalyst free and environment friendly synthesis of thiazolidinones via three component one pot condensation of aldehyde, amine and thioglycolic acid in water (scheme 1). The reactions are quick and no work up procedure is involved which makes it clean and green alternative to other reported procedures and is feasible for parallel synthesis of large number of compounds.

Results and discussion:

Treatment of aromatic aldehyde, amine and thioglycolic acid in water afforded the corresponding thiazolidinone derivatives under catalyst free in short reaction time with good yields. The model reaction was performed using benzaldehyde, 3-methylbenzylamine and thioglycolic acid in water keeping in mind that thiazolidinone compound form in the first step of condensation without using any catalyst. We have developed excellent and quicker method for the synthesis of thiazolidinones without any catalyst in water. This type of selectivity could be useful in synthesizing a small library of thiazolidinones in moderate to excellent yields. To the best of our knowledge, there are no earlier reports on the preparation of thiazolidinones without using any catalyst in water. This method...
avoids the use of toxic, expensive, hazardous chemicals and provides an easy and rapid access to pharmaceutically important thiazolidinone derivatives. The method offers many advantages over the reported methods such as shorter reaction time, cleaner reaction profile, easy isolation without any work up and excellent yield of the products. This method suggests that thiazolidinones formation without any catalyst in water is also faster like other methods. There is no requirement of extraction in organic solvents and purification by chromatography. We believe that our new protocol in water will find widespread applications in academic laboratories and industry.

In order to standardize the reaction, benzaldehyde (99 mg, 0.93 mmol) was added to a stirred solution of benzylamine (100 mg, 0.93 mmol) in water (5 mL) at room temperature and the mixture was stirred for 5 min. Thiglycolic acid (86 mg, 0.93 mmol) was then added to the above reaction mixture and stirring was continued for another 4 h whereupon water was removed under reduced pressure and the residue was stirred in diethyl ether at 0°C to afford solids. Solids were collected by filtration and washed with ice cooled diethyl ether to afford the pure product (220 mg, 87%) (Table 1, Entry 1).

Scheme 1. Reagent and condition: aromatic aldehyde (1.0 eq), amine (1.0 eq), thiglycolic acid (1.0 eq), water (5 mL), rt, 4-7h.

To establish the generality of the method, this condition was employed for other aromatic aldehydes and aromatic as well as aliphatic amines. The experimental procedure is very simple and proceeds very smoothly under catalyst-free condition in water and gives the title compound 4a-j in good to excellent yields which are summarized in Table 1 and the proposed reaction mechanism is shown in scheme 2. As shown in Table 1, the reaction worked well with variety of aryl aldehydes including those dearing electron-donating and electron-withdrawing groups such as OMe, Cl and CN and the desired compound obtained in good to excellent yields.

Table 1: Synthesis of 2-aryl-3-substitued-4-thiazolidinones using aldehyde, amine and thioglycolic acid in water at room temperature

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
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<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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*Isolated yields obtained using 1.0 mmol of aromatic aldehyde, 1.0 mmol of aromatic/aliphatic amine, 1.0 mmol of thiglycolic acid in water (5 mL) at room temperature. *Ref 17

Figure 2. Some different methods to assemble 4-thiazolidinine derivatives.
Products were characterized by $^1$H NMR, $^{13}$C NMR and LCMS.

In summary, an efficient synthesis of thiazolidinones derived from diverse aromatic aldehydes, amines and thioglycolic acid is reported. We know that the use of different reagents or catalysts for the synthesis of 4-thiazolidines have some limitations such as high temperature, longer reaction time, corrosive, expensive, hazardous reaction condition and purification issues due to formation of by-products. The method offers many advantages over the reported methods such as shorter reaction time, cleaner reaction profile, avoids the use of corrosive, expensive, hazardous chemicals as a reagent or catalyst, no high temperature, easy isolation and excellent yield of the products without any chromatographic purification. Without the need for any catalyst or reagent, this reaction condition eliminates solvent waste and is both green and cost-efficient to access pharmaceutically important thiazolidinone derivatives.

**General procedure for the synthesis of 2-aryls-3-substituted-4-thiazolidinones (4a-j):**

Aromatic aldehyde (1.0 mmol) was added to a stirred solution of amine (1.0 mmol) in water (5 mL) at room temperature and the suspension was stirred for 5 min to formed new type of partially soluble reaction mixture. Thioglycolic acid (1.0 mmol) was then added to the above reaction mixture and stirring was continued for another 4-7 h. As soon as the reaction proceeds, the reaction mixture become cloudy because of the formation of 4-thiazolidinones observed in the reaction mixture. The progress of reaction was monitored by thin layer chromatography. The mixture became clear because of the addition of thioglycolic acid on first intermediate imine. After some time, the clear reaction mixture became cloudy because of the formation of cyclosed product. After completion, the partially soluble cyclosed product i.e. 4-thiazolidinones observed in the reaction mixture. The progress of reaction was monitored by thin layer chromatography. The reaction mixture became clear at 50°C to remove water and the residue was triturated in diethyl ether at 0°C to afford solids which was then collected by filtration and washed with ice cooled diethyl ether to afford the pure product 4a-j.

**3-Benzyl-2-phenylthiazolidin-4-one (4a):** (217 mg, 87%) white solid; $^1$H NMR (400 MHz, CDCl$_3$): 7.380-7.419 (3H, m), 7.293-7.353 (3H, m), 7.22-7.243 (2H, m), 7.090-7.108 (2H, m), 7.386 (1H, s), 5.164 (1H, d, $J=14.8$ Hz), 3.907 (1H, d, $J=15.6$ Hz), 3.769 (1H, d, $J=15.6$ Hz), 3.537 (1H, d, $J=14.8$ Hz); $^{13}$C NMR (400 MHz, DMSO-d$_6$): 170.83, 139.83, 135.71, 128.86, 128.74, 128.56, 127.63, 127.46, 126.91, 61.78, 45.60, 31.72. LCMS calcd for C$_{16}$H$_{15}$NOS (M$^+$) 270.09, found 270.16.

**3-(3-methylbenzyl)-2-phenylthiazolidin-4-one (4b):** (217 mg, 93%) white solid; $^1$H NMR (400 MHz, DMSO-d$_6$): 7.354-7.391 (3H, m), 7.309 (2H, d, $J=7.6$ Hz), 7.197 (1H, t, $J=7.6$ Hz), 7.083 (1H, d, $J=7.6$ Hz), 6.875 (2H, s), 5.553 (1H, s), 4.817 (1H, d, $J=15.2$ Hz), 3.958 (1H, d, $J=15.2$ Hz), 3.782 (1H, d, $J=15.6$ Hz), 3.558 (1H, d, $J=15.2$ Hz), 2.257 (3H, s); $^{13}$C NMR (400 MHz, DMSO-d$_6$): 170.78, 139.88, 137.73, 135.59, 128.84, 128.73, 128.44, 128.26, 128.13, 126.92, 124.77, 61.79, 45.57,
3-(5-methylfuran-2-yl)methyl)-2-phenylthiazolidin-4-one (4c): (194 mg, 79%) brown solid; $^1$H NMR (400 MHz, DMSO-d$_6$): 7.340-7.417 (3H, m), 7.289-7.308 (2H, m), 5.974 (1H, d, J=2.8 Hz), 5.851 (1H, d, J=2.0 Hz), 5.558 (1H, s), 4.943 (1H, d, J=15.2 Hz), 3.860 (1H, d, J=15.6 Hz), 3.735 (1H, d, J=15.6 Hz), 3.606 (1H, d, J=15.6 Hz), 2.252 (3H, s). LCMS calcd for C$_{15}$H$_{17}$NOS (M$^+$) 284.39, found 284.13.

3-(2-(4-chlorophenyl)-3-(3-methylbenzyl)thiazolidin-4-one (4d): (239 mg, 91%) off white solid; $^1$H NMR (400 MHz, CDCl$_3$): 7.786 (2H, d, J=8.4 Hz), 7.578 (2H, d, J=8.0 Hz), 5.942 (1H, s), 3.903 (1H, d, J=15.2 Hz), 3.682 (1H, d, J=15.2 Hz), 3.508-3.581 (1H, m), 2.500-2.566 (1H, m), 1.021-1.141 (4H, m), 0.805 (3H, t, J=7.6 Hz); $^{13}$C NMR (400 MHz, DMSO-d$_6$): 170.79, 139.13, 137.72, 135.60, 133.18, 128.89, 128.81, 128.46, 128.32, 128.11, 124.83, 61.11, 45.70, 31.66, 20.93. LCMS calcd for C$_{16}$H$_{15}$ClNO$_2$S (M$^+$) 318.08, found 318.13.

2-(4-chlorophenyl)-3-cyclobutylthiazolidin-4-one (4e): (338 mg, 90%) light brown solid; $^1$H NMR (400 MHz, CDCl$_3$): 7.344 (2H, d, J=8.4 Hz), 7.181 (2H, d, J=8.8 Hz), 5.697 (1H, s), 4.184-4.228 (1H, m), 3.799 (1H, d, J=15.6 Hz), 3.610 (1H, d, J=15.6 Hz), 2.725-2.350 (1H, m), 2.175-2.220 (1H, m), 2.017-1.941 (1H, m), 1.818-1.774 (1H, m), 1.520-1.634 (1H, m); $^{13}$C NMR (400 MHz, DMSO-d$_6$): 170.83, 142.16, 132.58, 128.85, 127.54, 59.99, 48.99, 31.82, 27.91, 27.41, 15.03. LCMS calcd for C$_{14}$H$_{15}$ClNO$_2$S (M$^+$) 268.05, found 268.15.

3-cyclobutyl-2-(2-methoxyphenyl)thiazolidin-4-one (4f): (355 mg, 96%) brown solid; $^1$H NMR (400 MHz, CDCl$_3$): 7.306 (1H, t, J=7.6 Hz), 7.053 (2H, d, J=8.0 Hz), 6.930 (1H, t, J=7.6 Hz), 6.043 (1H, s), 4.108-4.195 (1H, m), 3.840 (3H, s), 3.669 (1H, d, J=15.2 Hz), 3.520 (1H, d, J=15.2 Hz), 2.215-2.314 (1H, m), 2.018-2.072 (1H, m), 1.869-1.970 (1H, m), 1.641-1.685 (1H, m), 1.473-1.537 (1H, m); $^{13}$C NMR (400 MHz, DMSO-d$_6$): 171.27, 155.84, 129.84, 129.32, 125.53, 120.40, 111.39, 55.66, 48.95, 32.00, 27.90, 27.46, 14.99. LCMS calcd for C$_{16}$H$_{15}$ClNO$_2$S (M$^+$) 264.10, found 264.15.


