# Efficient Microwave Enhanced Synthesis of 4-Thiazolidinones

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**Abstract:** A microwave-enhanced, rapid, three-component one-pot condensation method has been developed for the synthesis of 4-thiazolidinones using environmentally benign solvent ethanol in open vessels at atmospheric pressure. Applying this methodology ten different 4-thiazolidinones were synthesized in good yields.

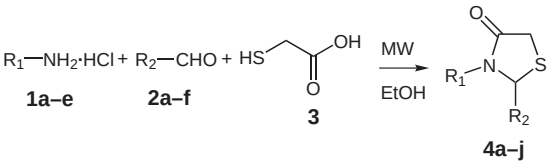
**Key words:** microwave, heterocycles, condensation, 4-thiazolidinones, synthesis

Experience has shown that compounds with biological activity are often derived from heterocyclic structures. Indeed, one of the richest sources of diversity for the medicinal chemist is small heterocyclic rings, which in addition to often exhibiting biological activity, may serve as rigid scaffolds for further display of functionalities. Thiazolidinones are one such class of heterocycles, which attracted much attention as they have been reported to possess a wide range of biological activities including antifungal, antibacterial, antihistaminic, antimicrobial and anti-inflammatory activities.[1]

As part of our endeavor to discover new anticancer agents we designed and synthesized highly cytotoxic thiazolidinone scaffold containing compounds for prostate cancer (undisclosed results). During this process we were seeking a rapid and efficient method for the synthesis of 4-thiazolidinones. Literature survey shows that many different protocols have been developed for the synthesis of 4-thiazolidinones. Most commonly employed methods[2] involve a one-pot three-component condensation of a primary amine, an aldehyde and mercaptoacetic acid with simultaneous azeotropic distillation of water formed in the reaction. Alternatively, a recent report[3] describes carbodiimide (DCC) mediated three-component reaction for the synthesis of 4-thiazolidinones. In either case the reaction is believed to proceed via imine formation followed by attack of sulfur on the imine carbon and final intramolecular cyclization with the elimination of water. However, the general applicability of the above-mentioned methods are limited, as the reactions require prolonged heating with continuous removal of water, and in some cases the reaction is performed in sealed vessels in the presence of a desiccant like anhydrous $ZnCl_2$[4] or sodium sulfate[5] or molecular sieves, and the use of stoichiometric amounts of DCC. In order to circumvent these difficulties and to speed up the synthesis we focused on developing an alternate method for the synthesis of 4-thiazolidinones.

Initially introduced in 1986,[6] the chemical application of microwaves has now become an area of interest for the synthesis of a wide variety of compounds. The advantages of microwave-expedited chemical synthesis are cleaner reactions, shorter reaction times and the ease of manipulation. Parekh[7] has described microwave-mediated synthesis of 4-thiazolidinones. However, this method[7] involves separate preparation of a hydrazone from the corresponding aldehyde and hydrazine, which was then mixed with thioglycolic acid and exposed to high power microwave irradiation.

In this communication we report microwave enhanced three-component one-pot condensation of a primary amine, an aldehyde and mercaptoacetic acid for the synthesis of a diverse set of 4-thiazolidinones (Scheme 1).




**Scheme 1**

A range of primary amines and aldehydes were condensed with mercaptoacetic acid in the presence of Hünig's base and molecular sieves under microwave irradiation (Figure 1). To optimize the method, initially we examined the condensation in toluene and observed that desired product was formed in low yield. Furthermore, all our attempts to improve the yield at elevated temperature, microwave power and longer reaction times were met with unsuccessful results. This may be due to poor microwave absorbing nature of toluene. In microwave mediated organic synthesis one of the most important characteristics of a solvent is its polarity. The more polar a solvent, the greater its ability to couple with the microwave energy, the faster the temperature of the reaction mixture increases that leads to faster reaction rates. To increase the efficiency we decided to perform the condensation in a more polar and high microwave absorbing solvent like ethanol. However, most of the reported methods[2] involve use of either high boiling hydrocarbons like toluene or benzene, or aprotic solvent tetrahydrofuran for this type of condensations. To check the feasibility of condensation in a protic solvent, a pilot experiment was carried out using glycine,

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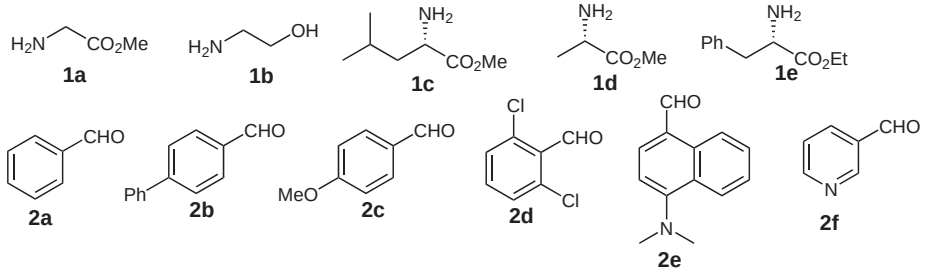


**Figure 1** Various amines and aldehydes used for the condensation

benzaldehyde and mercaptoacetic acid (Table 1, entry 1) in ethanol and observed that the reaction proceeded uneventfully forming the desired product in good yield. Interestingly, no product was formed when the reaction was carried out in ethanol in the absence of microwaves.

Encouraged by this result and to understand the general applicability of this protocol, we have synthesized a variety of 4-thiazolidinones. For this purpose five different amines and five different aldehydes were selected and condensed with mercaptoacetic acid (Table 1). With a chiral center in the amine component (Table 1, entries 8–10) as one might expect, formation of diastereomeric products was observed. The diastereomeric ratio was determined by NMR and LC-MS analysis [**4h** (1:1.8), **4i** (1:1), **4j** (1:1.7)]. It was observed that the ratios of reactants at 1:2:3 for amine, aldehyde and mercaptoacetic acid, respectively, gave best yields. This is in agreement with the earlier observation by Holmes et al.[2] Accordingly, the optimized procedure[8] involves microwave irradiation (power: 100 W) of a mixture of amine, aldehyde and mercaptoacetic acid (1:2:3) in presence of 1.25 equivalents of Hünig's base in ethanol at 120 °C for 30 minutes at atmospheric pressure and after standard workup gave the desired 4-thiazolidinones in good to high yields (Table 1).

**Table 1** Isolated Yields of 4-Thiazolidinones

| Entry | Amine·HCl | Aldehyde | Mercapto acid | 4-Thiazolidinone | Yield (%) |
|---|---|---|---|---|---|
| 1 | **1a** | **2a** | **3** | **4a** | 80 |
| 2 | **1a** | **2b** | **3** | **4b** | 83 |
| 3 | **1a** | **2c** | **3** | **4c** | 90 |
| 4 | **1a** | **2d** | **3** | **4d** | 65 |
| 5 | **1a** | **2e** | **3** | **4e** | 80 |
| 6 | **1a** | **2f** | **3** | **4f** | 91 |
| 7 | **1b** | **2a** | **3** | **4g** | 76 |
| 8 | **1c** | **2a** | **3** | **4h** | 55 |
| 9 | **1d** | **2a** | **3** | **4i** | 68 |
| 10 | **1e** | **2a** | **3** | **4j** | 63 |

In conclusion, we have developed a convenient three-component one-pot microwave rate enhanced efficient method for the synthesis of 4-thiazolidinones. It is noteworthy to mention that all reactions were carried out at atmospheric pressure in open vessels using environmentally benign solvent ethanol. The simplicity of this short procedure and generally satisfactory yields render this method particularly attractive for the rapid synthesis of 4-thiazolidinones.

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(8) **Typical Procedure for the Synthesis of 4-Thiazolidinones:** A mixture of glycine methyl ester hydrochloride (**1a**, 0.50 g, 4.00 mmol), aldehyde (**2e**, 1.66 g, 8.30 mmol), mercaptoacetic acid (0.83 mL, 12.00 mmol), di*iso*propylethylamine (0.85 mL, 4.83 mmol), and molecular sieves (4 Å, 0.10 g) in EtOH (10 mL) was irradiated with microwaves (power: 100 W) at 120 °C for 30 min, following which the sample was cooled using compressed air. The reaction mixture was diluted with $CHCl_3$ (75 mL), sequentially washed with sat. $NaHCO_3$, $H_2O$, brine, dried ($Na_2SO_4$) and solvent was removed in vacuo to get crude product that was purified by column chromatography (silica gel, hexanes–EtOAc) to afford **4e** (1.00 g, 80%). $^1H$ NMR (300 MHz, $CDCl_3$): δ = 2.85–2.86 (m, 1 H), 2.92 (s, 6 H), 3.50–3.63 (s, 3 H), 3.83 (br s, 2 H), 4.64 (d, *J* = 17.1 Hz, 1 H), 6.67 (br s, 0.6 H), 7.07 (br s, 0.7 H), 7.34 (d, *J* = 9.0 Hz, 1 H), 7.55 (d, *J* = 3.3 Hz, 2 H), 7.90 (br s, 1 H), 8.31 (m, 1 H). $^{13}C$ NMR (300 MHz, $CDCl_3$): δ = 31.94, 43.75, 44.53, 51.76, 58.47, 76.72, 112.97, 121.63, 122.69, 124.83, 124.94, 126.18, 131.33, 168.09. MS (ESI): *m/z* = 345 [M + H].