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Polyethylene Glycol Mediated One-Pot Three-Component Synthesis of New 4-Thiazolidinones

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ABSTRACT: *An efficient one-pot three-component cyclocondensation of 4-(p-toulyl sulfonoxy) benzaldehyde, aryl amines, and mercaptoacetic acid in polyethylene glycol 400 (PEG-400) was conducted to obtain new 2,3-disubstituted-4-thiazolidinones. This route is economical and ecofriendly.* © 2011 Wiley Periodicals, Inc. Heteroatom Chem 23:166–170, 2012; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20766

INTRODUCTION

Thiazolidinone and its derivatives are an important class of heterocyclic compounds. They have a wide range of biological and pharmacological activities [1], such as antiinflammatory [2], anti-HIV [3], anticancer [4], antimalarial [5], antitubercular [6], anticonvulsant [7], antibacterial [8], and antiarrythmic [9]. Moreover, agents bearing sulfonyl moieties have also been found to display diverse therapeutic activities, such as hypoglycemia [10], anticancer [11], and antiinflammation [12].

The literature reveals that 4-thiazolidinones with heteryl derivatives/moieties have shown potential biodynamic activity [13]. It has also been observed that there is scanty information on the thiazolidinones with toluene sulfonoxy phenyl and aryl/heteryl moieties.

Keeping the significance of 4-thiazolidinones and sulfonoxy bioisosteres in mind, it was planned to synthesize new 4-thiazolidinones with the above-referred pharmacophoric systems by providing an efficient/convenient synthetic protocol.

Several synthetic methods are reported to prepare 4-thiazolidinones. The two widely used methods are cyclocondensation of thioureas with α-halo acid derivatives [14] and cyclocondensation of azomethines (Schiff bases) with mercaptoacetic acid [15] or its derivatives. The first method has been widely used to obtain 2-imino thiazolidinones, whereas 2,3-disubstituted value-added 4-thiazolidinones have been synthesized by using the second method. Attempts are also being made to accelerate the rate of the cyclocondensation of Schiff's bases and mercaptoacetic acid and to conduct the reactions using volatile aprotic organic solvents and catalysts/dececants such as anhydrous $ZnCl_2$[16], sodium sulfate [17], KSF montmorillonite [18], *N,N′*-dicyclohexylcarbodiimide [19], activated fly ash [20], and ionic liquid, [bmim][PF_6] [21]. Solvent-free synthesis has also been reported for 4-thiazolidinones [22].

However, these reported methods still have one or more limitations such as requiring hazardous solvents, expensive catalysts, prolonged heating or tedious workup procedures. In our group, Lingampalle et al. [23], Mali et al. [15], and Pratap

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et al. [24] have also tried to provide convenient synthetic routes for value-added 4-thiazolidinones using ionic liquid, heterogeneous catalysts such as silica chloride, and biocatalyst baker's yeast, respectively. These routes have certain advantages along with few limitations. To circumvent these difficulties and to speed up the synthesis, we focused on developing an alternate route for the synthesis of 4-thiazolidinones.

The use of environment-friendly catalysts and solvents in organic and medicinal chemistry is an area of considerable importance. From both an economical and environmental point of view, the use of nonvolatile solvents and green catalysts enhances various value-added organic transformations [25].

In this connection, polyethylene glycols (PEGs) have attracted much attention with organic chemists as a result of their inexpensive, ecofriendly nature, high thermal stability, biodegradability, and the ability to act as phase transfer catalysts [26]. PEGs are widely used as a medium and catalysts for carrying out various organic transformations [27] such as Heck, asymmetric dihydroxylation, Baylis–Hillman, Biginelli, Stille cross coupling, Wacker, and asymmetric Aldol reactions.

Considering the above-mentioned significance of PEGs and 4-thiazolidinones and in continuation of our earlier endeavors [15,23,24] toward the development of ecofriendly synthetic routes for 4-thiazolidinones, it was thought worthwhile to develop a facile, greener, and expeditious synthetic route for new 2,3-disubstituted 4-thiazolidinones.

RESULTS AND DISCUSSION

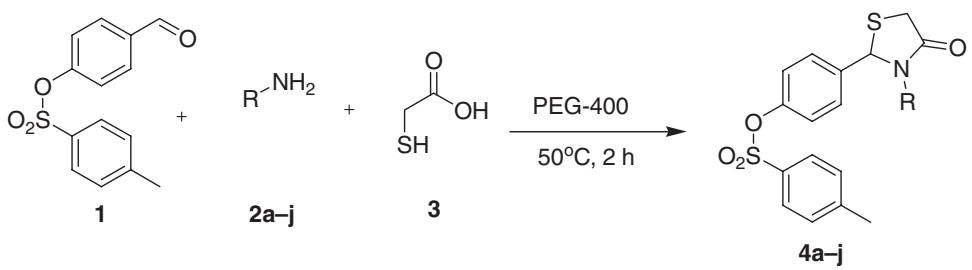
In this article, we report the synthesis of known and some new 4-thiazolidinones. The one-pot three-component cyclocondensation of 4-(*p*-toulylsulfonoxy) benzaldehyde (**1**), aryl/heteryl amines (**2a–j**), and mercaptoacetic acid (**3**) in PEG-400 was performed to obtain the titled 4-thiazolidinones (**4a–j**) (Scheme 1).

In the initial optimization studies, the synthesis of 4-thiazolidinones was conducted in two steps. In first step, intermediate azomethine was prepared by condensing 4-(*p*-toulylsulfonoxy) benzaldehyde (**1**) and 4-chloroaniline (**2a**) in ethanol as a model reaction. Subsequently, the azomethine was cyclocondensed in the second step with mercaptoacetic acid in toluene/benzene/THF under reflux for more than 4 h and less than 50% yield of titled 4-[3-(chloro)-4-oxothiazolidin-2-yl] phenyl-4-methyl benzene sulfonate (**4a**) was obtained. It was noticed that none of the approaches was convenient to afford the desired 4-thiazolidinones with high yields.

Considering the synthetic utilities of PEG-400 as a green reaction catalyst and a safe medium, it was therefore considered worthwhile to use PEG-400 to carry out the cyclocondensation, leading to the desired 4-thiazolidinones.

Using these results, an effort was made to carry out the cyclocondensation in PEG-400 in two steps, leading to more knowledge about 4-thiazolidinones. In the first step, anisaldehyde and 4-chloroaniline (**2a**) were condensed in PEG-400 at room temperature for 15 min and azomethine with 92% yield was obtained. Then, the cyclocondensation of the azomethine was carried out with mercaptoacetic acid in PEG-400 at 50°C for 2 h. It was noticed that this gave 69% yield of the 3-(4-chlorophenyl)-2-(4-methoxyphenyl)thiazolidin-4-one (a reported molecule) [28]. From the above results, it was confirmed that PEG-400 promotes the formation of the intermediate, azomethine, as well as the subsequent cyclization of azomethine and mercaptoacetic acid, leading to the desired 4-thiazolidinone.

Next, we synthesized 4-thiazolidinones in one pot. The one-pot three-component cyclocondensation of anisaldehyde, 4-chloroaniline (**2a**), and mercaptoacetic acid was carried out to obtain 4-thiazolidinone at 50°C. It was observed that the reaction has smoothly produced 3-(4-chlorophenyl)-2-(4-methoxyphenyl)thiazolidin-4-one with 78% yield.



SCHEME 1 Synthesis of 4-[3-(substituted)-4-oxothiazolidin-2-yl]phenyl-4-methyl benzene sulfonates.

TABLE 1 Screening of Reaction Medium for the Synthesis of Compound **4a**[a]

Entry	*PEG-400*	*Isolated Yields (%)*
1	0·2 mL	76
2	0·4 mL	79
3	0·6 mL	80
4	0·8 mL	84
5	1·0 mL	89
6	1·2 mL	87
7	1·4 mL	86
8	Ionic liquid (1 mL)	61
9	Deep eutectic solvent (1 mL)	59

[a]All the reactions were carried out at 50°C for 2 h.

TABLE 2 Synthesis of 4-[3-(Substituted)-4-oxothiazolidin-2-yl]phenyl-4-methyl Benzene Sulfonates[a]

Entry	*R*	*Product*	*Yield (%)*[b]	*Melting Point (°C)*
1	*p*-Cl C_6H_4	**4a**	89	177–179
2	C_6H_5	**4b**	82	122–123
3	*p*-F C_6H_4	**4c**	79	154–156
4	*p*-$CH_3C_6H_4$	**4d**	85	118–120
5	*p*-OCH_3 C_6H_4	**4e**	87	183–184
6	*p*-OCH_2CH_3 C_6H_4	**4f**	92	139–140
7	*p*-NO_2 C_6H_4	**4g**	74	190–192
8	2-Pyridinyl	**4h**	69	150–152
9	5-*p*-Tolylthiazole	**4i**	58	162–163
10	4-(4-Chlorophenyl)thiazole	**4j**	65	167–169

[a]Reaction conditions: Aldehyde (2 mmol), amine (2 mmol), and mercaptoacetic acid (2 mmol) in PEG-400 (1 mL) stirred for 2 h at 50°C.
[b]Isolated yields.

To study the effect of the solvent on the model reaction, the environmentally acceptable media such as ionic liquid and deep eutectic solvents (choline chloride:urea) were used. It was noticed that in these media this cyclocondensation was accomplished after prolonged reaction time and gave moderate yields of the product.

All the efforts confirmed that PEG-400 has the potential to act as a safe medium and catalyst while performing the one-pot cyclocondensation of aldehydes, amines, and mercaptoacetic acid, leading to 4-thiazolidinones. Prompted by these observations, we used PEG-400 to conduct the one-pot cyclocondensation of 4-(*p*-toulylsulfonoxy) benzaldehyde (**1**), 4-chloroaniline (**2a**), and mercaptoacetic acid (**3**) and obtained better yields of the desired 4-thiazolidinone (**4a**) within 2 h at 50°C.

To optimize the quantity of PEG-400, various attempts were made to use different amounts of PEG-400, i.e., 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, and 1.4 mL for 2 mmol of the substrates (Table 1), and the best results were achieved when 1 mL of PEG-400 was employed for the model reaction (Table 1, entry 5). The reaction was completed within 2 h, yielding 89% of 4-thiazolidinone (**4a**). When we used PEG-400 in an amount more than 1 mL for 2 mmol of the substrate, there was no improvement in the yield of the product.

For further optimization, PEG-400 was used in combination with various solvents. However, the use of solvents in combination with PEG-400 for the reaction failed to improve the product yields and the rate of the reaction. One milliliter of PEG-400 for 2 mmol of the substrates was found to promote the reaction without need for any additional catalysts/solvents. Using these optimized conditions, the other 4-thiazolidinenones (**4a–j**) were synthesized and results are presented in Table 2.

The success of PEG-400 could be due to the following reasons: PEG-400 possesses two active site free hydroxyl groups and ethereal oxygen linkages. These hydroxyl groups via hydrogen bonding with carbonyl oxygen of aldehydes might increase the electrophilic character of carbonyl carbon of aldehyde, thereby accelerating the rate of addition of amines on aldehydes, generating intermediate azomethines. Ethereal oxygen linkages might be responsible for enhancing nucleophilicity of the mercapto group of mercaptoacetic acid, resulting in its facile addition on the imino intermediates (azomethines), generated in situ. These factors might be responsible for acceleration of the cyclocondensation.

CONCLUSION

In summary, the use of PEG-400 to promote the one-pot cyclocondensation of aldehydes, amines, and mercaptoacetic acid to obtain 4-thiazolidinones has been well explored for the first time. The developed synthetic route is simple, ecofriendly, and high yielding.

EXPERIMENTAL

The chemicals used were of laboratory grade. Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded on a Varian USA 400 MHz NMR spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard and chemical shift in δ (in ppm). Mass spectra were recorded on a Sciex model API 3000 LCMS/MS instrument. The purity of each compound was checked by thin layer chromatography (TLC) using silica-gel, 60F254 aluminum sheets as an adsorbent, and visualization was accomplished by iodine/ultraviolet

light. 4-(*p*-Toulylsulfonoxy) benzaldehyde (**1**) was synthesized by using the procedure discussed in the literature[29].

General Procedure for the Synthesis of 4-[3-(Substituted)-4-oxothiazolidin-2-yl] phenyl-4-methyl Benzene Sulfonates **(4a–j)**

A mixture of 4-(*p*-toulylsulfonoxy) benzaldehyde (**1**) (2 mmol), aryl/heteryl amines (**2a–j**) (2 mmol), and mercaptoacetic acid (**3**) (2–3 mmol) in PEG-400 (1 mL) was stirred at 50°C. The progress of the reaction was monitored by TLC using ethyl acetate: hexane (3:7) as solvent. After 2 h of stirring, the reaction mass was poured onto cold water, washed with $NaHCO_3$, and extracted with ethyl acetate (2 × 50 mL). Ethyl acetate was removed under reduced pressure, and the obtained crude products were crystallized from ethanol. The physical characterization of compounds **4a–j** is presented in Table 2, and their synthesis route is shown in Scheme 1.

Spectral Data of a Few Representative Thiazolidin-4-ones

Compound **1**. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.45 (s, 3H), 7.18 (d, 2H, J = 7.89 Hz), 7.33 (d, 2H, J = 7.89 Hz), 7.82(d, 2H, J = 7.88 Hz), 7.84 (d, 2H, J = 7.89 Hz), and 9.96 (s, 1H). MS (m/z): 276 (M^+).

Compound **4a**. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.45 (s, 3H), 3.87 (d, 1H, J = 9.6 Hz), 3.97 (d, 1H, J = 10.0 Hz), 6.02 (s, 1H, methine), 6.9 (d, 2H, J = 7.2 Hz), 7.1 (d, 2H, J = 7.1 Hz), 7.3 (m, 6H), and 7.6 (d, 2H, J = 7.1 Hz). MS (m/z): 450 (M^+).

Compound **4b**. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.44 (s, 3H), 3.79(d, 1H, J = 10.1 Hz), 3.92(d, 1H, J = 10.1 Hz), 6.05 (s, 1H, methine), 6.90 (d, 2H, J = 7.9 Hz), 7.09 (d, 2H, J = 7.9 Hz), 7.12 (d, 2H, J = 7.5 Hz), 7.23–7.52 (m, 5H), and 7.6 (d, 2H, J = 7.7 Hz). MS (m/z): 412 (M^+).

Compound **4f**. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.37 (t, 3H), 2.44 (s, 3H), 3.88–3.90 (d, 2H, –CH_2–S–, overlapped, J = 9.9 Hz), 3.96 (q, 2H, J = 7.9 Hz), 5.94 (s, 1H, methine), 6.77 (d, 2H, J = 7.9 Hz), 6.90 (d, 2H, J = 7.8 Hz), 7.20 (d, 2H, J = 7.7 Hz), 7.22 (d, 2H, J = 7.7 Hz), 7.27 (d, 2H, J = 7.8 Hz), and 7.58 (d, 2H, J = 7.8 Hz). MS (m/z): 460 (M^+).

Compound **4h**. ^{1}H NMR (400 MHz, $CHCl_3$, δ ppm): 2.42 (d, 3H, J = 8.23 Hz), 3.77 (d, 1H, J = 10.2 Hz), 3.94 (d, 1H, J = 10.2 Hz), 6.4 (s, 1H, methine), 6.87 (d, 2H, J = 7.8 Hz), 7.24–7.36 (m, 4H), 7.61 (d, 2H, J = 7.2 Hz), 7.68 (d, 2H, J = 7.9 Hz), 8.02 (d, 1H, J = 7.8 Hz), and 8.18 (d, 1H, J = 7.8 Hz). MS (m/z): 427 (M^+).

Compound **4i**. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.26 (s, 6H), 3.80 (d, 1H, J = 10.0 Hz), 4.04 (d, 1H, J = 10.0 Hz), 5.91 (s, 1H), 6.80 (s, 1H, methine), 7.08 (d, 2H, J = 8.5 Hz), 7.22 (d, 2H, J = 8.5 Hz), 7.25 (m, 6H), and 7.61 (d, 2H, J = 7.9 Hz). MS (m/z): 522 (M^+).

Compound **4j**. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.35 (s, 3H), 3.77 (d, 1H, J = 10.1 Hz), 4.01 (d, 1H, J = 10.1 Hz), 5.74 (s, 1H,), 6.45 (s, 1H, methine), 6.89 (d, 2H, J = 7.2 Hz), 7.14 (d, 2H, J = 7.9 Hz), 7.19 (m, 6H), and 7.60 (d, 2H, J = 7.9 Hz). MS (m/z): 543 (M^+).

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