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Research Article

Catalyst-Free Synthesis of Highly Biologically Active 5-Arylidene Rhodanine and 2,4-Thiazolidinedione Derivatives Using Aldonitrones in Polyethylene Glycol

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A green, efficient synthesis of 5-arylidene rhodanine and 2,4-thiazolidinedione derivatives without using any external catalyst in polyethylene glycol (PEG) at 80°C has been described. Reaction procedure is very simple, short, and obtained yields are very high.

1. Introduction

Rhodanines and thiazolidinediones both are aprivileged class of molecule, and they show large number of biological activities. The most significant position of these molecules seems to be as they are asubset of commercially employed noninsulin-dependent diabetes mellitus (NIDDM), insulin sensitizing agents (Figure 1) such as epalrestat, ciglitazone, AD-5061, pioglitazone, rosiglitazone, and so forth.

Furthermore, rhodanine derivatives possess anticonvulsant, antibacterial, antiviral, and antidiabetic activities [1–3] Some of rhodanine-based derivatives act as hepatitis C virus (HCV) protease inhibitor [4], uridine diphospho-*N*-acetylmuramate/L-alanine ligase inhibitor [5], aldose reductase [6], β-lactamase [7], and JNK-stimulating phosphatase-1 (JSP-1) [8], while some of its derivatives are used for the analysis of certain noble metal ions [9]. Therefore, the synthesis of rhodanine derivatives currently is of much importance and a variety of methods and catalysts have been used [10–12].

Unlike rhodanine, 2,4-thiazolidinedione derivatives also have remarkable biological activities like antidiabetic [13], antibacterial [14], antifungal [15], antiproliferative effect on vascular smooth muscle [16], aldose reductase inhibitors [17], 15-hydroxyprostaglandin dehydrogenase inhibitors [18] instead of these biological activities 5-benzylidene-thiazolidine-2,4-dione derivatives act as inhibitors of MurD ligase [19]. In the literature several methods have been reported to synthesize these privileged molecules [20–24]. Therefore, significant biological activities prompt us to synthesize thiozolidine derivatives.

Nitrones (imine oxides) are reputed as 1,3-dipoles and are extensively explored for the synthesis of five membered heterocycles by combining them with several types of multiple bonds [25–27]. Apart from this major utility their general chemistry is little studied.[27] There are few reports of successful 1,3-additions of nitrones [28, 29]. Yousif et al. reported reactions of heterocyclic N-oxides under acidic conditions and obtained only condensed products [30]. In contrast, their counterpart imines are extensively explored to expose their utility as aldehyde equivalent [31–33]. Present protocol is the environment benign synthesis of 5-arylidene rhodanine and 2,4-thiazolidinedione derivatives using aldonitrones in polyethylene glycol (PEG). The reaction proceeds via addition-elimination way and afforded the desire products in very good to excellent yield (Scheme 1).

2. Results and Discussion

First of all, a series of nitrones was prepared using a variety of aldehyde and hydroxyl amine as per already reported method [34]. A mixture of freshly prepared N-phenyl-N-phenylmethylidenamine oxide (10 mmol) **1a** and rhodanine

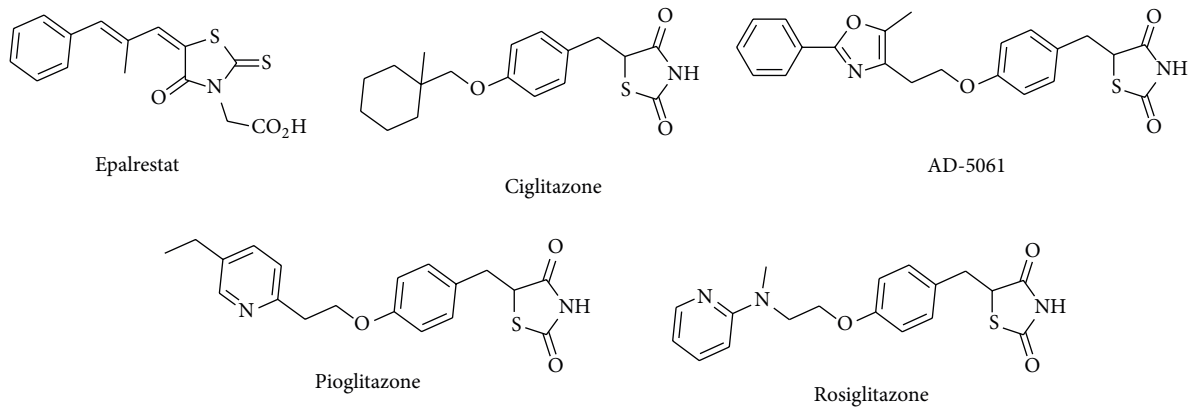
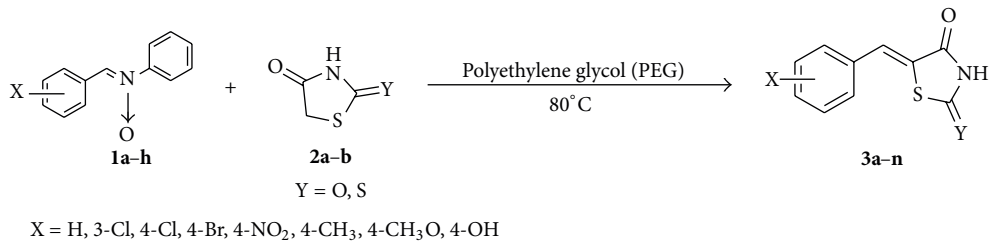


Figure 1: Clinically used molecules having 5-arylidene rhodanines and 2,4-thiazolidenediones.



Scheme 1: Synthesis of 5-arylidene thiazolidinediones.

(10 mmol) **2a** was stirred at 80°C in polyethylene glycol (PEG) for 20 min to afford corresponding arylidene rhodanine **3a** *via* addition-elimination process.

To check the effect of the solvent, a set of reactions was performed using different solvents such as MeOH, EtOH, H_2O, THF, PEG, DMF, and so forth and in absence of solvent. Conclusively, in case of PEG best results were obtained with high yields in minimum reduced time. Keeping optimized reaction conditions, a variety of aldehydes with rhodanine/2,4-thiazolidinedione were reacted to afford 5-arylidenerhodanines **3a–g** and 5-arylidene-2,4-thiazolidinediones **3h–n** with excellent yields (Table 1).

Active methylene compounds **2a–b** afforded the Knoevenagel products **3a–n** selectively with exo-double bond without the formation of other side-products/bis-products as shown in Scheme 2 via addition-elimination process. Electron withdrawing and donating groups on aromatic *N*-oxides showd slightly diversion in rate of reaction and yields; that is, electron withdrawing group containing aromatic *N*-oxides afforded arylidene compounds with better yields in shorter reaction time (Table 1).

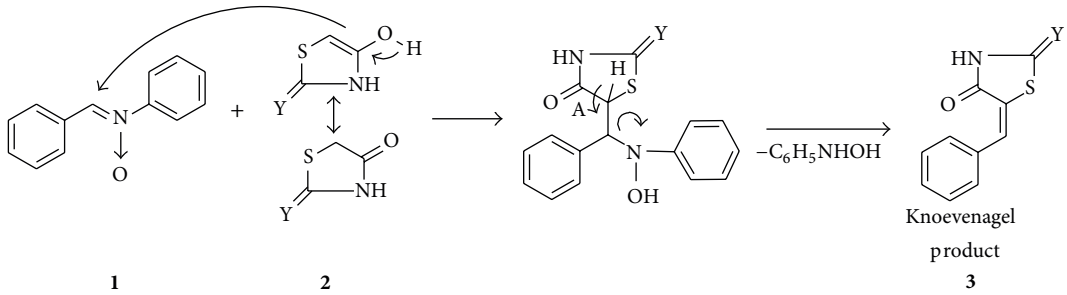
Next, the recyclability of the solvent was studied by using **1a** and **2a** as the model substrates. We observed that PEG could be recovered by under vacuum filtration of products obtained on cooling. PEG recovered as filtrate and was successfully recycled and reused for five runs.

As far as mechanism is concerned, reaction proceeds via nucleophilic addition of **2** on **1** with subsequent elimination of amine part of aromatic N-oxides to afford arylidene products **3** (Scheme 2).

Table 1: Synthesis of 5-arylidine rhodanine and 2,4-thiazolidinedione derivatives using aldonitrones in polyethylene glycol (PEG).

Entry	X	Y	Product[a]	Time (min)	Yield (%)[b]	Melting point (°C) reference
1	H	S	**3a**	20	85	202-203 [11]
2	4-Cl	S	**3b**	20	93	230–232 [11]
3	4-Br	S	**3c**	20	89	229-230 [3]
4	4-NO_2	S	**3d**	25	94	254-255 [11]
5	4-CH_3	S	**3e**	30	78	224-225 [11]
6	4-CH_3O	S	**3f**	30	83	250-251 [11]
7	4-OH	S	**3g**	30	79	184-185 [35]
8	H	O	**3h**	25	92	240-241 [36]
9	3-Cl	O	**3i**	25	88	270-271 [36]
10	4-Cl	O	**3j**	25	85	224-225 [37]
11	4-NO_2	O	**3k**	25	75	260–262 [37]
12	4-CH_3	O	**3l**	25	86	224-225 [37]
13	4-CH_3O	O	**3m**	35	88	234-235 [36]
14	4-OH	O	**3n**	35	90	280-281 [36]

[a]Reaction conditions: **1a–h** (10 mmol), **2a-b** (10 mmol), and polyethylene glycol (PEG) 5 mL were heated at 80°C on magnetic stirrer. The products were characterized by spectral techniques like IR, ^{1}H NMR. [b]Isolated yields after recrystallization.



Scheme 2: Plausible reaction mechanism.

3. Conclusion

In summary, the present protocol is an efficient and environmentally benign procedure for the synthesis of drug intermediate 5-arylidine rhodanine and 2,4-thiazolidinedione derivatives using aldonitrones in polyethylene glycol (PEG) *via* simple addition-elimination process. Present protocol does not need any external catalyst, and it is applicable on a variety of nitrones. This method produces good to excellent yields in shorter reaction time, and it seems that reaction is autocatalyzed because eliminatingpart of nitrone acts as catalyst.

4. Experimental Section

4.1. General. Reagent-grade chemicals were purchased from a commercial source and used without further purification. Yields refer to the yield of the isolated products. Melting points were determined in open capillaries in paraffin bath and are uncorrected. Infrared (IR) spectra were recorded in KBr discs on a Perkin-Elmer 240C analyzer. ^{1}H NMR spectra were recorded on a BRUKER AVANCE II 400 NMR Spectrometer using tetramethylsilane (TMS) as internal standard. The progress of the reaction was monitored by thin layer chromatography (TLC) using silica gel G (Merck).

*4.2. General Method for the Synthesis of 5-Arylidene Rhodanine and 2,4-Thiazolidinedione (**3a–n**).* A mixture-nitrone (10 mmol) 1, rhodanine or 2,4-thiazolidinedione (10 mmol) 2, and polyethylene glycol (5 mL) was stirred at 80°C temperature for appropriate time (see Table 1). Reaction progress was monitored via TLC. After reaction completion, crude product was precipitated out on cooling. Obtained product was filtered, dried, and for further purification recrystallized from ethanol-DMF.

4.3. Spectral Data of Reprehensive Compounds. (5Z)-5-Benzylidene-2-thioxo-1,3-thiazolidine-4-one (**3a**): IR (KBr): 3390, 1709, 1669, 1600, 1429, 1200 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ_H: 13.57 (s, 1H, NH), 7.68 (s, 1H, =CH), 7.48–7.79 (m, 5H, Ar–H).

(5Z)-5-(4-Methoxybenzylidene)-2-thioxo-1,3-thiazolidine-4-one (**3f**): ^{1}H NMR (300 MHz, DMSO-d$_6$) δ_H: 13.71 (s, 1H, NH), 7.61 (s, 1H, =CH), 7.52 (d, 2H, j = 8.2 Hz, Ar–H), 7.08 (d, 2H, j = 8.2 Hz, Ar–H), 3.09 (s, 3H, OCH$_3$).

(5Z)-5-Benzylidene-1,3-thiazolidine-2,4-dione (**3h**): IR (KBr) cm^{-1}: 3155 (NH), 3049, 879 (CH; aromatic), 2868 (CH; aliphatic), 1739, 1691 (C=O). ^{1}H NMR (300 MHz, DMSO-d$_6$) δ_H: 8.27 (1H, s, NH), 7.86 (1H, s, CH), 7.26 (5H, m, aromatic protons). MS m/z (%): 206 (M + 1).

(5Z)-5-(4-Methylbenzylidene)-1,3-thiazolidine-2,4-dione (**3m**): IR (KBr) 3211, 1725, 1689 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ_H: 12.50 (s, 1H, br, NH), 7.69 (s, 1H, =CH), 7.50 (d, 2H, j = 8.3 Hz, Ar–H), 7.11 (d, 2H, j = 8.3 Hz, Ar–H), 3.49 (s, 3H, OCH$_3$).

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