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Synthesis and Bioevaluation of Novel Thiazolidinones from Aromatic Azo-Aldehydes

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Abstract: ***Some novel substituted 4-Thiazolidinones (azo-dispersive dyes) were synthesized from azo-incorporated aromatic aldehydes (1a-1c) and heteryl hydrazides (2a-2b) in zinc chloride and DMF via synthesis of azomethines (Schiff bases) (4a-4e) conventionally by using mercaptoacetic acid, a very important precursor responsible for cyclization of azomethines.***

Keywords: 4-Thiazolidinones, azo-incorporated aromatic aldehydes, heteryl hydrazides, azomethines, mercaptoacetic acid.

1. Introduction

Heterocyclic compounds having atoms other than carbon in the ring, had been proved to have numerous bioactivities. Thiazolidinone is one of the most biologically important heterocyclic ring having an atom of sulfur at 1st position, nitrogen at position 3rd position. 4-Thiazolidinone is a wonder moiety and was reported to possess various biological activities such as anti-cancer [1, 2], antitumor [3, 4], antimicrobial [5], anti-inflammatory [6], anti-fungal [7], herbicidal [8], antiproliferative [9], anti-viral [10], urease inhibitors [11]. Compounds containing thiazolidinone nucleus have properties such as anti-HIV [12], antioxidant [13, 14], antitubercular [15, 16] and analgesic [17].

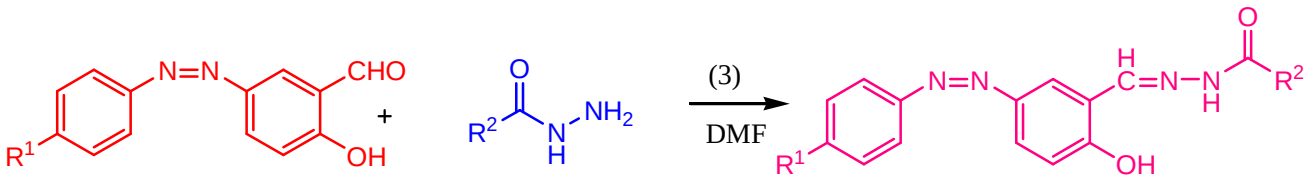
The most important intermediate required for synthesis of thiazolidinones are imines also known as azomethine. Conventionally, synthesis of thiazolidinone is a two-step process, acid catalyzed condensation of aromatic aldehydes with aromatic amines to get imines and further cyclization takes place with mercaptoacetic acid. The most interested fact found is removal of water during cyclization of mercaptoacetic acid with imine is one of the most important rate determining process. Various efforts have been taken to remove water by various catalyst and solvent-systems [18, 19].

Different protocols have been used to remove water such as molecular sieves [20] trimethylorthoformate [21], sodium sulfate [22], $ZnCl_2$ [23] and azeotropic distillation with benzene or toluene [24], DCC [25], ionic liquid such as tetrabutyl ammonium bromide [26], diisopropylethyl ammonium acetate [27], Urazolium diacetate [28] were also reported for synthesis of thiazolidinone. The main demerit of removal of water molecule had also been re-evaluated by using water as a greener solvent [29].

Considering the bio-significance of 4-Thiazolidinones and in continuation of our studies based on synthesis and its bioactivity [30], we report synthesis of novel 4-Thiazolidinones and its solvent screening for achieving efficient yields.

2. Result and Discussions

In this work, we report synthesis of some novel 4-Thiazolidinones by conventional route. In Scheme 1, various substituted azomethines (Schiff bases) were synthesized from aromatic substituted aldehydes incorporated with azo group **(1a-1c)**, heteryl hydrazides **(2a-2b)** and glacial acetic acid **(3)** in DMF. In Scheme 2, those azomethine **(4a-4e)** undergoes cyclization with mercaptoacetic acid **(5)** to obtain mentioned 4-Thiazolidinones **(6a-6e)**. Physical data listed in **Table no. 1 and 2**.

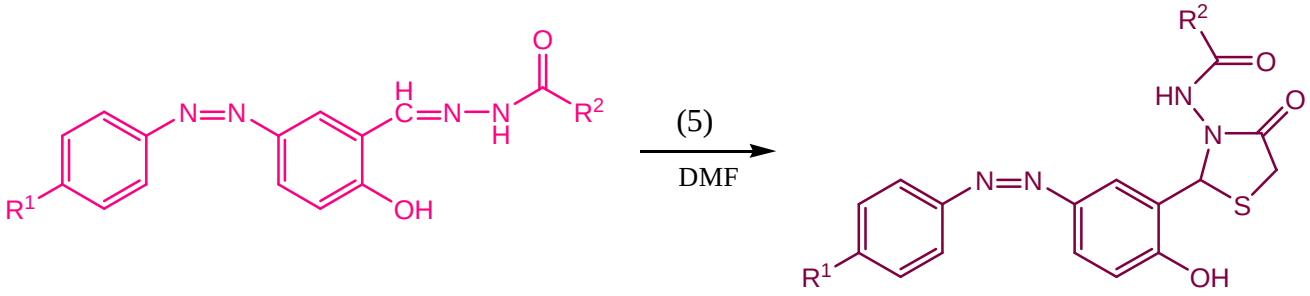


1a-1c **2a-2b** **4a-4e**

(3) Glacial acetic acid

R^1 = 2-OEt, 4-OEt, 4-Cl
R^2 = Isonicotinohydrazide, 1-phenyl-5-(thiophen-2-yl)pyrazole-3-carbohydrazide

Scheme 1



4a-4e **6a-6e**

(5) mercaptoacetic acid

R^1 = 2-OEt, 4-OEt, 4-Cl

R^2 = Isonicotinohydrazide, 1-phenyl-5-(thiophen-2-yl) pyrazole-3-carbohydrazide

Scheme 2

Table 1: Physical Data of Azomethines

Product	Time (hrs.)	% yield	Melting point
4a	8 hrs	82%	98°c
4b	9 hrs	74%	198°c
4c	10 hrs	85%	180°c
4d	6 hrs	71%	215°c
4e	6 hrs	69%	225°c

*Melting points are uncorrected.

Table 2: Physical Data of 4-Thiazolidinones

Product	Time (hrs.)	% yield	Melting point
6a	8 hrs	82%	230°c
6b	9 hrs	74%	238°c
6c	10hrs	85%	154°c
6d	6 hrs	71%	190°c
6e	6 hrs	69%	195°c

*Melting points are uncorrected

In order to scrutinize solvent for the efficiently high yield, cyclization was performed of **(6a)** with mercaptoacetic acid **(5)** in different solvent systems. Summarized data of scrutinizing of solvent is given in **Table no. 3**. DMF was found to be reasonable regarding time and yield

Table 3: Screening of solvents for efficient yield

Solvent	Time (for completion)	Yield (%)
Methanol	-	-
Ethanol	-	-
Water	24 hrs	30%
1,4-Dioxane	14 hrs	54%
DMF	12 hrs	79%
Benzene	10 hrs	49%
Toluene	20 hrs	52%

Anti-microbial activity

Compounds (**6a-6e)**were evaluated for antimicrobial activity by cup-plate agar diffusion method against E. coli (gram -ve) and S. aureus (gram +ve) species using ampicillin as standard compound. The antimicrobial screening data are presented in **Table no. 4**.

Table 4: Antimicrobial Screening of 4-Thiazolidinones

Sr. No.	Compound	Antimicrobial activity (Zone of inhibition in mm)	
		E.coli	S.aureus
1	6a	0	10
2	6b	12	12
3	6c	14	18
4	6d	13	13
5	6e	12	14
6	Ampicillin	16	18

3. Experimental Section

3.1 Materials and Methods

All the chemicals had been used in this were of Himedia, Aldrich, Merck and Loba. Derivatives of substituted aldehyde containing azo moiety were prepared in laboratory. All the reactions were completely monitored by TLC aluminum sheet silica $gel_{60}F_{254}$ and visualized in UV chamber. Purity of the product was also check by using TLC technique. Melting points were determined using melting point apparatus and are uncorrected. IR spectra were recorded on Shimadzu FT-IR spectrophotometer by using KBr discs. PMR and ^{13}C NMR spectra were recorded at 500 MHz using $CDCl_3$ as solvent. Chemical shift values were expressed in ppm and tetramethylsilane was used as an internal solvent.

3.2 Experimental Procedure:

3.2.1 Preparation of Azomethines:

Different substituted azo aldehydes (1 mole eq.) and substituted hydrazides (1 mole eq.) were taken in round bottomed flask in DMF as a solvent. 2-3 drops of glacial acetic acid were added and refluxed it for 6-8 hours. Reaction was monitored by thin-layer chromatography. After completion whole reaction mixture was poured on crushed ice. Solid separated out. Filtered on vacuum, dried. Crystallization was done by using 1,4-dioxane. Pure substituted Schiff bases were obtained **(4a-4e)**.

FT-IR data of azomethines:

2-(isonicotinyl imino)-4-[(4-ethoxyphenyl)diazinyl]phenol(4a):FT-IR (KBr cm^{-1}): 1482 cm^{-1}(aromatic C=C stretching), 3697 cm^{-1}(Phenolic OH stretching), 1665cm^{-1} (C=N stretching), 1222 cm^{-1} (C-S-C stretching), 896 cm^{-1} (C-S stretching), 1710 cm^{-1} (C=O aromatic stretching).

2-(isonicotinylimino)-4-[(2-ethoxyphenyl)diazinyl]phenol(4b):FT-IR (KBr cm^{-1}): 1461 cm^{-1}(aromatic C=C stretching), 3790 cm^{-1}(Phenolic OH stretching), 1659 cm^{-1} (C=N stretching), 1244 cm^{-1} (C-S-C stretching), 919cm^{-1} (C-S stretching), 1690 cm^{-1} (C=O aromatic stretching).

2-[1-phenyl-5-(thiophen-2-yl)-pyrazole-(3-amido) imino]-4-[(2-ethoxyphenyl)diazinyl]phenol(4c):FT-IR (KBr cm^{-1}): 1482 cm^{-1}(aromatic C=C stretching), 3520 cm^{-1}(Phenolic OH stretching), 1651cm^{-1} (C=N stretching), 1220 cm^{-1} (C-S-C stretching), 889 cm^{-1} (C-S stretching), 1690 cm^{-1} (C=O aromatic stretching).

2-[1-phenyl-5-(thiophen-2-yl)-pyrazole-(3-amido) imino]-4-[(4-ethoxyphenyl) diazinyl] phenol(4d):FT-IR (KBr cm^{-1}): 1497 cm^{-1}(aromatic C=C stretching), 3745 cm^{-1}(Phenolic OH stretching), 1609 cm^{-1} (C=N stretching), 1204 cm^{-1} (C-S-C stretching), 896 cm^{-1} (C-S stretching), 1693 cm^{-1} (C=O aromatic stretching).

2-[1-phenyl-5-(thiophen-2-yl)-pyrazole-(3-amido) imino]-4-[(4-chlorophenyl) diazinyl] phenol(4e):FT-IR (KBr cm^{-1}): 1503 cm^{-1}(aromatic C=C stretching), 3735 cm^{-1}(Phenolic OH stretching), 1654cm^{-1} (C=N stretching), 1250 cm^{-1} (C-S-C stretching), 864 cm^{-1} (C-S stretching), 1686 cm^{-1} (C=O aromatic stretching).

3.2.2 Preparation of novel 4-Thiazolidinones:

Prepared azomethine (1 mole eq.), mercaptoacetic acid (1 mole eq.) were dissolved in DMF. Pinch of anhydrous zinc chloride was added. Reaction mixture was refluxed for 12 hours. Reaction was monitored by thin-layer chromatography. After reaction completion, reaction mixture was poured on crushed ice. Filter and dried. Crystallization were done by using 1,4-dioxane and DMF (8:2). Pure substituted 4-Thiazolidinones were obtained **(6a-6e)**.

2-{1-[(4-ethoxyphenyl) diazinyl(2-hydroxy) phenyl]}-3-isonicotinamido-thiazolidin-4-one(6a):FT-IR (KBr cm^{-1}): 1765 cm^{-1} (aliphatic C=O stretching), 1665 cm^{-1} (aromatic C=O stretching), 1601cm^{-1} (aromatic C=O stretching), 692 cm^{-1} and 1207cm^{-1} (C-S and C-O stretching respectively), 1065 cm^{-1} (C-N stretching), 3539 cm^{-1} (phenolic OH stretching).

2-{1-[(2-ethoxyphenyl) diazinyl(2-hydroxy) phenyl]}-3-isonicotinamido-thiazolidin-4-one(6b):FT-IR (KBr cm^{-1}): 1756 cm^{-1} (aliphatic C=O stretching), 1659 cm^{-1} (aromatic C=O stretching), 1601cm^{-1} (aromatic C=O stretching), 690 cm^{-1} and 1245cm^{-1} (C-S and C-O stretching respectively), 1047 cm^{-1} (C-N stretching), 3663 cm^{-1} (phenolic OH stretching).

2-{1-[(4-ethoxyphenyl) diazinyl(2-hydroxy) phenyl]}-3-[1-phenyl-5-(thiophen-5-yl)pyrazole-3-amido] thiazolidin-4-one(6c):FT-IR (KBr cm^{-1}): 1778 cm^{-1} (aliphatic C=O stretching), 1665 cm^{-1} (aromatic C=O stretching), 1591cm^{-1} (aromatic C=O stretching), 693 cm^{-1} and 1255cm^{-1} (C-S and C-O stretching respectively), 1207 cm^{-1} (C-N stretching), 3683 cm^{-1} (phenolic OH stretching).

2-{1-[(4-ethoxyphenyl) diazinyl(2-hydroxy) phenyl]}-3-[1-phenyl-5-(thiophen-5-yl)pyrazole-3-amido] thiazolidin-4-one(6d):FT-IR (KBr cm^{-1}): 1750 cm^{-1} (aliphatic C=O stretching), 1642 cm^{-1} (aromatic C=O stretching), 1590cm^{-1} (aromatic C=O stretching), 693 cm^{-1} and 1237 cm^{-1} (C-S and C-O stretching respectively), 1222 cm^{-1} (C-N stretching), 3683 cm^{-1} (phenolic OH stretching). **H^{1}NMR (CDCl$_3$, 500 MHz)**: 3.70 and 3.80 ppm (s, 2H), 5.15 ppm (s, 1H), 3.88 (s, 1H). **C^{13} NMR (ppm)**: 114.16, 166.16, 39.7, 55.78, 131.94, 128.66.

2-{1-[(4-chlorophenyl) diazinyl(2-hydroxy) phenyl]}-3-[1-phenyl-5-(thiophen-5-yl)pyrazole-3-amido] thiazolidin-4-one(6e):FT-IR (KBr cm^{-1}): 1765 cm^{-1} (aliphatic C=O stretching), 1678 cm^{-1} (aromatic C=O stretching), 1600cm^{-1} (aromatic C=O stretching), 693 cm^{-1} and 1278 cm^{-1} (C-S and C-O stretching respectively), 1210 cm^{-1} (C-N stretching), 3683 cm^{-1} (phenolic OH stretching).

4. Conclusion

In this work, we synthesized novel 4-thiazolidinones by conventional pathway. And screening of various solvents for betterment of yields was done. And also evaluate their bio-significance listed in Table no. 4.

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