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Research Article

Difference in Rate of Reaction of Some Thiazolidinone Derivatives with Synthesis and Spectral Characterization

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ABSTRACT

A series of substituted 5-ethylidene-2-(phenylimino) thiazolidin-4-ones were prepared by using phenylthiourea **(I)** as a starting material. Phenylthiourea on reaction with ethylchloroacetate in presence of ethanol (95%) and fused sodium acetate gives 2-(phenylimino) thiazolidin-4-one **(II)**, 2-(phenylimino) thiazolidin-4-one on further reaction with substituted benzaldehyde gives substituted 5-ethylidene-2-(phenylimino) thiazolidin-4-one **(III-XI)**. Synthesized compounds were authenticated on the basis of elemental analysis, IR and ^{1}H NMR and Mass spectral analysis

Keywords: Thiazole, Thiazolidinone, Synthesis, Heterocyclic, Substitution

1. INTRODUCTION

Medicinal chemistry deals with the design, synthesis and production of molecules having therapeutic value. During the past few decades growth in areas like combinatorial chemistry and heterocyclic chemistry has lead to development of many privileged structure with proven utility in medicinal chemistry [1]. Thiazolidinone, a saturated form of thiazole with carbonyl group on fourth carbon, has been considered as a magic moiety (wonder nucleus) which posses almost all types of biological activities. It belongs to an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring [2]. This biologically active scaffold has encouraged our interest in synthesizing several new compounds by using several substitutions at different positions, attached to 4-thiazolidinone moieties. Our aim is to search for biologically active heterocyclic compounds containing sulfur and nitrogen, we have now synthesized a series of substituted 5-ethylidene-2-(phenylimino) thiazolidin-4-one. Substitution can be done at 2, 3 and 5 positions. The carbonyl group present is highly unreactive. Substituent at 2-, 3- and 5- positions may be varied, but the greatest difference in structure and properties is exerted by the group attached to the carbon atom in the 2-position [3]. Tetrahydro derivative of thaiazole is known as thiazolidine and the oxo derivative of thiazolidine is known as thiazolidinone.

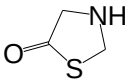


Figure 1: Thiazolidinone

The 3-unsubstituted thiazolidinone are usually solids, often melting with decomposition, but the attachment of an alkyl group to the nitrogen lowers the melting point. The thiazolidinone that do not contain aryl or higher alkyl substituents are somewhat soluble in water [4]. Thiazolidinones are known to exhibit antitubercular [5], antibacterial [6], anticonvulsant [7], antifungal [8] and antithyroid activities [9]. Some of thiazoline derivatives were found to show interesting anti-HIV and anticancer activities [10]. Thiazolidinone, with carbonyl group at 2, 4 or 5 position have been subjected to extensive study in the recent years. Numerous reports have appeared in the literature, which highlights their chemistry and use [11]. It was observed that reaction with cyclizing reagents like α-halocarbonyl compounds such as $ClCH_2COCl$, $BrCH_2COCl$, $BrCH_2COOEt$ and $ClCH_2COCH_2COOEt$ in boiling ethanol with fused sodium acetate have better biological profiles as thiazolidinone [12].

2. EXPERIMENTAL

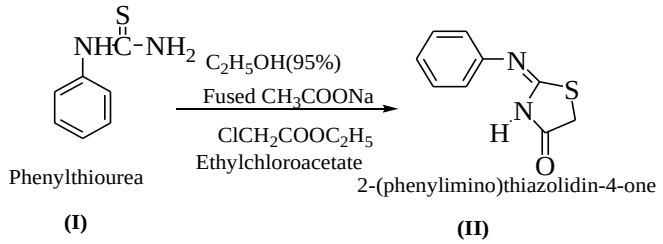
All the chemicals and reagents were obtained from Sigma (Germany) and CDH (India) and were recrystallized/ redistilled as necessary. Melting points were determined by open capillary tube method and are uncorrected. Purity of the compounds was checked on thin layer chromatography (TLC) plates precoated. With silica gel G using solvent system toluene: ethyl acetate: formic acid (5:4:1). The spots were located under iodine vapors and UV light. IR spectra were recorded using KBr on FTIR Shimadzu 8400S IR spectrophotometer (Japan). A JEOL AL300 FTNMR 300 MHz spectrometer was used to acquire ^{1}H-NMR spectra with $CDCl_3$ as solvent and TMS as internal standard. Chemical shift values are expressed in δ ppm. Mass spectra were obtained using Kratos-AEI MS-902S instrument. Elemental analyses were carried out with a Perkin Elmer Model 240-C apparatus (CDRI, Lucknow). The results of the elemental analysis (C, H, and N) were within ± 0.4% of the calculated amounts.

2.1 Reaction Scheme

Step 1

General Procedure for synthesis of 2-phenyliminothiazolidin-4-one (II)

Phenyl thiourea (I) 8g (0.04 moles) was dissolved in 16.45ml ethanol (95%). The resulting mixture was refluxed with fused sodium acetate 4.31g (0.052 moles) and ethylchloroacetate 6.46 g (5.65 mL) for 4hr. The reaction mixture was then poured in to water. Keep the reaction mixture overnight for complete precipitation. The precipitate obtained was filtered and dried at room temperature. The compound was recrystallised in ethanol (95%).



(I) **(II)**

Scheme 1: Synthesis of 2-(phenylimino) thiazolidin-4-one

Table 1: Physical property of synthesized compound (II)

Compd	R	Mol. Formula	M.Wt	R_f Value	%Yield	Rea Time (hr)
II	H	$C_9H_8N_20S$	192.24	0.755	80.79	3-4

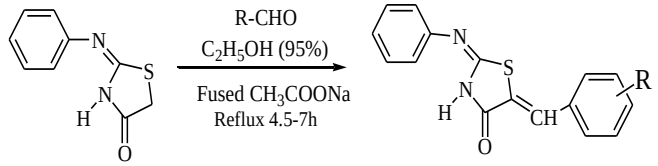
2-phenyliminothiazolidin-4-one (II)

Yield: 80.79% (solid); M.p: 175–177 °C; R_f value (T: E: F; 5:4:1): 0.755**;** IR (KBr): 3415, 2978, 1745, 1610 cm^{-1}**;** ^1H NMR ($CDCl_3$): δ = 3.21 (s, 2H, CH_2), 6.98– 7.34 (m, 5 H, phenyl), 11.82 (s, 1H, NH)**;** MS m/z: 192 (M^+)**;** Anal. Calcd for $C_9H_8N_2OS$: C, 55.26; N, 14.10; S, 16.60.

Step-2

General Procedure for the preparation of substituted Thiazolidinone Derivatives (III-XI)

2-phenyliminothiazolidin-4-one **(II)** (0.01 mole) was reacted with different aromatic aldehyde (0.01mole) with fused sodium acetate (0.01mole) in ethanol (8 ml) for 6-7 hr. The reaction mixture then cool to room temperature, poured in to ice cold water and kept overnight. The precipitate obtained was filtered and washed with water to remove unreacted aldehyde and then dried the precipitate at room temperature. The product obtained was recrystallied from dimethyl formamide.



(II) **(III-XI)**

Scheme 2: Synthesis of substituted 5-ethylidene-2-(phenylimino) thiazolidin-4-one

Table 2: Physical properties of synthesized compounds (III-XI)

Compound	R	Molecular Formula	M. Wt.	(%) yield	Reaction Time(hr)
III	2-Nitro	$C_{16}H_{11}N_3O_3S$	325.34	41.2	4- 6.30
IV	4-Niro	$C_{16}H_{11}N_3O_3S$	325.34	54.5	1.0- 2.30
V	2,4-dinitro	$C_{16}H_{10}N_4O_5S$	370.34	51.4	3-5.0
VI	4-Methoxy	$C_{17}H_{14}N_2O_2S$	310.37	93.75	2.5-3.0
VII	3,4di-Methoxy	$C_{18}H_{16}N_2O_3S$	340.4	80.56	3-4.30
VIII	3,4,5-trimethoxy	$C_{19}H_{18}N_2O_4S$	370.42	62.16	4.5-6
IX	4-chloro	$C_{16}H_{11}ClN_2OS$	314.79	76.19	2.5-4.0
X	2-chloro	$C_{16}H_{11}ClN_2OS$	314.79	82.8	3.5-4.30
XI	2,4-dichloro	$C_{16}H_{10}C_{12}N_2S$	349.23	87.9	4.0-5

2.2 Spectral Data of the synthesized compounds

5-(2-nitrobenzylidene)-2-(phenylamino) thiazolidin-4-one (III)

Yield: 41.2% (solid); M.p: 297-300°C, R_f value (T: E: F; 5:4:1): 0.765**;** IR (KBr): 3420, 3031, 1660, 1600, 1492 cm^{-1}**;** ^1H NMR ($CDCl_3$) δ: 6.90-7.32 (m, 5H, phenyl); 7.60 (s, 1H, C=CH); 7.70-8.24 (m, 4H, 3-nitrobenzylidene); 8.7 (s, 1H, NH)**;** MS m/z: 325.04 (M^+)**;** Anal. Calcd for $C_{16}H_{11}N_3O_3S$: C, 59.06; N, 12.90; S, 9.82.

5-(4-nitrobenzylidene)-2-(phenylamino) thiazolidin-4-one (IV)

Yield: 54.5%, M.p: 320-322, R_f value (T: E: F; 5:4:1): 0.730**;** IR (KBr): 1510, 1674, 1335 cm^{-1}**;** ^1H NMR ($CDCl_3$) δ: 6.90-7.32 (m, 5H, phenyl; 7.60 (s, 1H, C=CH); 7.52 (m, 2H, 4-nitrobenzylidene); 8.14 (m, 2H, 4-nitrobenzylidene); 8.2 (s, 1H, NH)**;** MS m/z: 325.04 (M^+)**;** Anal. Calcd for $C_{16}H_{11}N_3O_3S$: C, 59.07; N, 12.90; S, 9.80.

5-(2, 4-dinitrobenzylidene)-2-(phenylamino) thiazolidin-4-one (V)

Yield: 51.4%, M.p: 242-244, R_f value (T: E: F; 5:4:1): 0.72**;** IR (KBr): 1664, 1160, 670, 1340, 1608 cm^{-1}**;** ^1H NMR ($CDCl_3$), δ: 6.99-7.00 (m, 5H, phenyl); 7.32 (s, 1H, C=CH); 8.2 (s, 1H, NH); 7.80-9.00 (Ar C-H benzylidene)**;** MS (m/z) 370.02 (M^+)**;** Anal. Calcd for $C_{16}H_{10}N_4O_5S$: C, 51.89; N, 15.12; S, 8.60.

5-(4-methoxybenzylidene)-2-(phenylamino) thiazolidin-4-one (VI)

Yield: 93.75% (solid); M.p: 195-197°C, R_f value (T: E: F; 5:4:1): 0.638**;** IR (KBr): 1638, 1332, 1220 cm^{-1}**;** ^1H NMR ($CDCl_3$) δ ppm: 7.00-7.15 (m, 9H, phenyl and benzylidene); 7.35 (m, 1H, C=CH); 8.2 (s, 1H, NH)**;** MS (m/z): 312.08 (M^+)**;** Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C 65.30, N 8.97, S, 10.25.

5-(3, 4-dimethoxybenzylidene)-2-(phenylamino) thiazolidin-4-one (VII)

Yield: 80.56% (solid); Mp: 189-191°C, R_f value (T: E: F; 5:4:1):0.65**;** IR (KBr): 1670, 670, 1220 cm^{-1}**;** ^1H NMR ($CDCl_3$, δ ppm): 6.60-7.15 (m, 9H, phenyl and benzylidene); 6.30 (m, 1H, C=CH); 8.0(s, 1H, NH)**;** MS (m/z): 342.08 (M^+)**;** Anal. Calcd for $C_{18}H_{18}N_2O_3S$: C 64.30, N 8.07, S, 9.25.

5-(3, 4, 5-trimethoxybenzylidene)-2(phenylamino) thiazolidin-4-one (VIII)

Yield: 62.16% (solid); m.p: 210-212°C, R_f value (T: E: F; 5:4:1): 0.70**;** IR (KBr): 1660, 1180, 1220 cm^{-1}**;** ^1H NMR ($CDCl_3$, δ ppm): 3.82 (s, 9H, OCH_3); 8.14 (s, 1H, C=CH); 8.01 (s, 1H, NH)**;** MS (m/z): 370.09 (M^+)**;** Anal. Calcd for $C_{19}H_{18}N_2O_4S$: C, 61.61; N, 7.54; S, 8.60.

5-(4-chlorobenzylidene)-2-(phenylamino) thiazolidin-4-one (IX)

Yield: 76.19%, M.p: 285-287°C; R_f value (T: E: F; 5:4:1): 0.80**;** IR (KBr): 1674, 1240, 1190 cm^{-1}**;** ^1H NMR ($CDCl_3$, δ ppm): 6.9-7.2 (m, 5H, phenyl); 7.20 (d, 2H, benzylidene); 7.22 (d, 2H, benzylidene); 6.70 (s, 1H, C=CH); 8.38 (s, 1H, NH)**;** MS (m/z): 314.02 (M^+)**;** Anal. Calcd for $C_{16}H_{11}ClN_2OS$: C, 61.02; N, 8.70; S, 10.19.

5-(2-chlorobenzylidene)-2-(phenylamino) thiazolidin-4-one (X)

Yield: 82.8%, M.p: 200-202, R_f value (T: E: F; 5:4:1): 0.673**;** IR (KBr): 1520, 1670, 1070 cm^{-1}**;** ^1H NMR ($CDCl_3$, δ ppm): 6.99-7.0 (m, 5H, phenyl); 7.20 (s, 1H, C=CH); 7.00-7.20 (m, 4H, chlorobenzylidene); 8.2 (s, 1H, NH)**;** MS (m/z): 314.02 (M^+)**;** Anal. Calcd for $C_{16}H_{11}ClN_2OS$: C, 61.04; N, 8.80; S, 10.19.

5-(2, 4-dichlorobenzylidene)-2-(phenylamino) thiazolidin-4-one (XI)

Yield 87.9% (solid); M.p 186-188°C, R_f value (T: E: F; 5:4:1): 0.679**;** IR (KBr): 3461, 3037, 2953, 1671 cm^{-1}**;** ^1H NMR ($CDCl_3$, δ ppm) 6.99-7.20 (m, 10H, phenyl and benzylidene); 7.60 (s, 1H, C=CH); 8.2 (s, 1H, NH)**;** MS (m/z): 347.98 (M^+)**;** Anal. Calcd for $C_{16}H_{10}C_{12}N_2OS$: C, 55.0; N, 8.00; S, 9.10.

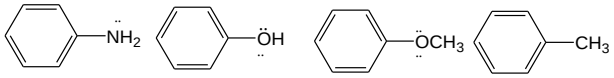
3. RESULTS AND DISCUSSION

It was observed that substitution in 5-ethylidene-2-(phenylimino)thiazolidin-4-one ring by elecrophilic group (electron withdrawing groups) e.g. Nitro groups usually takes longer reaction time as compared to Nucleophilic groups (electrons donating groups) like methoxy or substitution by methyl group. As presence of nitro substituted benzaldehye deactivates the ring and thus increase the rate of reaction time duration while substitution by methoxy (an electron donating group) causes activation of ring towards eletrophilc substitution and thus time duration of the reaction decreases. Within the compounds of nitro substituted series of compound, shows lesser reaction time duration as in case of nitro group para position is most active as compared to ortho and meta position. In case of methoxy substituted derivatives Para position is most active but trisubstituted like 3, 4, 5 trimethoxy takes longer time because of the hinderence provided by the bulky groups. For chloro substituted derivatives maximum effect is observed at ortho and para postions.

Comparison of reaction time for substitution by different electrophilic and nucleophilic groups

The reaction generally takes place in acidic medium in presence of ethanol (95%) and fused sodium acetate reaction of intermediates (1) with different benzaldehyde and cyclising reagents like $ClCH_2COCl$, $BrCH_2COCl$, $BrCH_2COOEt$ and $ClCH_2COCH_2COOEt$ in boiling absolute ethanol containing anhydrous sodium acetate afforded the substituted 4- thiazolidinones derivatives. The reaction involves cyclization and complete anhydrous condition is maintained thought the reaction. Substitution by electron withdrawing groups takes longer reaction time duration as comparison to nucleophilic groups. In case of electophilic substitution at Meta position takes place easily as comparison to para position which takes longer time duration. Below are given some examples of activating and deactivating groups.

Activating Substituent's



Deactivating Substituent's

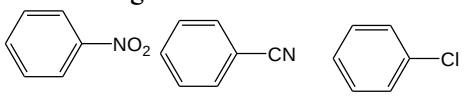


Table 3: Reaction and % of product obtained at different substituted position

Compd	Reaction	% Ortho-Product	% Meta-Product	% Para-Product
$-O-CH_3$	Nitration	30–40	0–2	60–70
$-O-CH_3$	F-C Acylation	5–10	0–5	90–95
$-NO_2$	Nitration	5–8	90–95	0–5
$-CH_3$	Nitration	55–65	1–5	35–45
$-CH_3$	Sulfonation	30–35	5–10	60–65
$-CH_3$	F-C Acylation	10–15	2–8	85–90
–Br	Nitration	35–45	0–4	55–65
–Cl	Chlorination	40–45	5–10	50–60

4. CONCLUSION

The structures of the synthesized compounds were confirmed by IR spectra, mass spectra, ^1H NMR spectral analysis and elemental analysis. The IR spectra of **(III-XI)** exhibited some characteristic band due to =C-H str. (3100-3000cm^{-1}), C=C str. (1635-1495 cm^{-1}), C-H bending (900-860 cm^{-1}), C-H bending (substituted aryl (840-800 cm^{-1}), C-S-C str. (700-600cm^{-1}), C=N (ring) (1650-1580 cm^{-1}) stretching vibration band, C=O (1674 cm^{-1}, 4-thiazolidinone moiety). In the ^1H NMR spectrums the signal appears between δ 5.1- 6.1 indicates the thiazolidinone.

5. ACKNOWLEDGEMENTS

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