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An Efficient Synthesis for Novel 2, 3-Disubstituted -4-Thiazolidones and Antimicrobial Evaluation

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Abstract: ***Novel 2-Methyl (2'-hydroxy-3'/5'-chloro-5'/3'-chloromethyl phenyl)- 3-(3'/4'-sustitutedphenyl)-4-thiazolidones are synthesized from 2-Hydroxy-3/5-chloro-5/3-chloromethyl acetophenone in good yield with purity. The structure of these compounds are confirmed by IR, ^{1}H NMR and Mass spectra of a representative member from the series .These novel derivatives are then screened for antibacterial and antifungal activities against S.aureus, E.coli, X.citri, E.carotovora, C.albicans, T.rubrum, A.solani and H.turcicum.***

Keywords: 2-Hydroxy-3/5-chloro-5/3-chloromethyl acetophenone , 2,3-Disubstituted-4-thiazolidones , Antibacterial , Antifungal

1. Introduction

4-Thiazolidinones chemistry was reviewed in depth by F.C. Brown[1] in 1962, G.R. Newkome A. Nayak[2] in 1977. The potential of 4-Thiazolidones as drug is under consideration by the Pharmaceutical Science since the beginning of the XX century. During recent years a new phase has been seen in this field. Centerian history[3] of synthetic research possibilities of these heterocycles lead to diversity in modeling biologically active compounds using 4-Thiazolidone scaffolds. Modification of the 4-Thiazolidone cycle on 2-, 3- ,4- or 5-position is successful to achieve synthetic products with a wide spectrum of pharmacological activity and has received considerable attention in this review.

A wide range of Biological activities of thiazole containing compounds has been reported. Further reports regarding their synthesis, properties, reactions and applications have led to an increased interest in related thiazolidones[4]. Thiazole, Thiazolidone and 4-Thiazolidones or 4-Thiazolidinones substituted at 2- and 3-position showed a wide variety of biological activities. The frequent occurrence of group –NH-CS-NH or its tautomer in compounds possess and evaluated in vitro tuberculostatic activity by E. Frolich et al[5]. The various biological properties exhibited by these compounds are as anthelmintics[6,8], cardiovascular[7], antiviral[9], mosquito repellent[10], hypnotic[11-13], antifungal[14,15,29], antiulcer[16,18], antitumour[17], local angesthetic[19], analgesic[20], antimicrobial[21,24,37,39,41], antitubercular[22,27], antibacterial[23,25], antidiabetic[28], insecticidal[30], herbicidal[31], cardiotonic[32], antiinflammatory[33,39], analgesic and antithermic[34] antiprotozal[35,38], anticonvulsant[36] and anticancer[26,40] properties among others.

Various 4-Thiazolidones with substitutents like alkyl, aryl, furyl, cyclohexyl etc. moieties at 2-position have been synthesized. However, there are no reports on the synthesis of 4-Thiazolidones with trisubstituted aryl moiety having chloromethyl (-CH_2Cl) group as one of the substituent. V.M. Gurav, K.G. Huge et al[42] have synthesized 4-Thiazolidones with trisubstituted aryl moiety having hydroxymethyl (-CH_2OH) group.

Therefore, it was thought of interest to synthesize some new 4-Thiazolidones having chloromethyl (-CH_2Cl) group to evaluate their biological activities.

In the present study 2-Methyl (2'-hydroxy-3'/5'-chloro-5'/3'-chloromethyl phenyl)- 3-(3'/4'-sustitutedphenyl)-4-thiazolidones are synthesized from 2-Hydroxy-3/5-chloro-5/3-chloromethyl acetophenones (trisubstituted acetophenones having chloromethyl [-CH_2Cl] group) [CMA-A/B] with substituted amines and thioglycollic acid in the presence of Zinc chloride in dry Benzene (Scheme-I).

This method was selected for the synthesis of 4-Thiazolidones as the starting materials are readily available, the reaction conditions are mostly moderate, reaction products can be easily obtained in pure from , the yields are comparatively better.

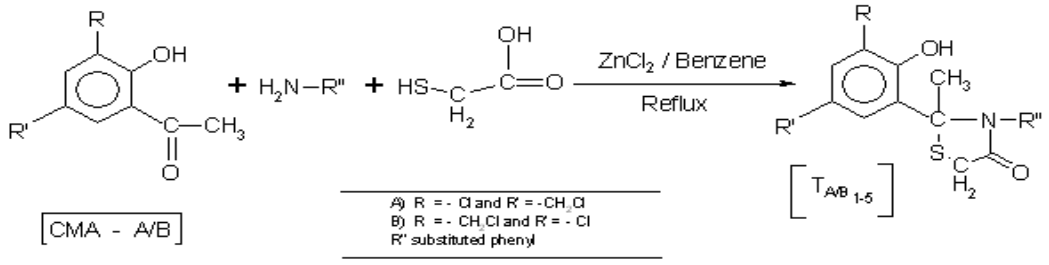
2. Experimental

The purity of compounds was checked by TLC on silica gel. The melting points were determined in open capillary tubes and are uncorrected. IR spectra of the representative member i.e. T_{A-2} from the series was recorded in KBr on a Shimadzu FTIR spectrometer- 8400. ^{1}H-NMR spectra was recorded in $CDCl_3$ with an mercury plus(varion 400 MHz) using TMS as an internal standard $CDCl_3$ (Chemical Shifts are given in δ ppm). Mass spectra was recorded on Schimadzu mass spectrometer - LCMS system.

General procedure

Equimolar mixture of 2-Hydroxy-3/5-chloro-5/3-chloromethyl acetophenones (trisubstituted acetophenone), thiogycollic acid and monosubstituted amines in dry benzene (20 ml) with pinch of zinc chloride and few drops of piperidine were refluxed on water bath for 10-12 hours. After completion of reaction (monitored by TLC) benzene was removed by evaporation and the solid obtained was washed by dilute solution of 10% Na_2CO_3, followed by dil. HCl to remove unreacted acid and amine respectively present in the compound. Recrystallize the product with

proper solvent. The general reaction can be represented in Scheme-I.



SCHEME - I

3. Result and Discussion

The formation of compounds was confirmed by IR, ^{1}H NMR and Mass spectral data of representative member [T_{A-2}] from the series and elemental analysis. The melting points, yield and elemental analysis were recorded in Table-I .

IR : 3302 cm^{-1} (O – H stretch, phenolic OH), 3078 cm^{-1} (Ar – H stretch), 2920 cm^{-1} (C – H stretch if $–CH_3$), 2862 cm^{-1} (C – H stretch if $–CH_2$), 1637 cm^{-1} (C = O stretch), 1612 cm^{-1} (C – N stretch), 1429, 1504, 1585 cm^{-1} (aromatic ring stretch), 893-983 cm^{-1} (1,2,3,5-tetra substituted benzene vibrations) and 659 cm^{-1} (C – Cl stretch).

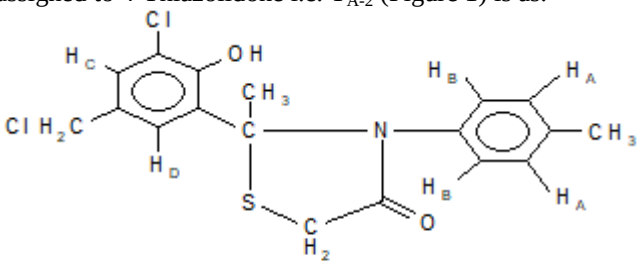
^{1}H NMR : ^{1}H NMR spectra of 4-Thiazolidone i.e. T_{A-2} studied in showed following peaks : δ 1.68 [s, 3H, C–CH_3], δ 2.34 [s, 3H, Ar–CH_3], δ 3.45 [s, 2H, – S– CH_2–C= O] , δ 4.64 [s,2H (-CH_2Cl)], δ 6.80 [s, $2H_A$], δ 7.44 [s, $2H_B$], δ 7.24 [s, $1H_C$], δ 7.62 [s, $1H_D$], δ 12.45 [s, 1H, Phenolic OH].

MASS : ($M^{+\bullet}$) peak at m/z = 381 with (M + 2) at m/z = 383 and (M + 4) at m/z = 385 in 9:6:1 ratio. The molecular ion peak is in agreement with molecular weight of the compound T_{A-2} and the (M + 2) peak at m/z = 383 and (M + 4) at m/z = 385 respectively confirms the presence of two chlorine atoms in the molecule.

Table I

[A] Characterization data of 2-Methyl(2'-hydroxy-3'-chloro-5'-chloromethyl phenyl)-3-(3'/4'-substituted phenyl)-4-thiazolidones.					
Sr. No.	Compound No.	R"	M.P. (^{0}C)	Yield (%)	Analysi % of Cl (Calcd/found)
1	T_{A-1}	p-Nitrophenyl	91	68	17.19/17.24
2	T_{A-2}	p-Methylphenyl	118	75	18.58/18.63
3	T_{A-3}	m-Methylphenyl	123	85	18.58/18.53
4	T_{A-4}	p-Chlorophenyl	138	80	26.45/26.50
5	T_{A-5}	m-Chlorophenyl	132	70	26.45/26.40
[B] Characterization data of 2-Methyl(2'-hydroxy-5'-chloro-3'-chloromethyl phenyl)-3-(3'/4'-substituted phenyl)-4-thiazolidones.					
1	T_{B-1}	p-Nitrophenyl	97	85	17.19/17.15
2	T_{B-2}	p-Methylphenyl	115	75	18.58/18.55
3	T_{B-3}	m-Methylphenyl	127	70	18.58/18.63
4	T_{B-4}	p-Chlorophenyl	136	75	26.45/26.40
5	T_{B-5}	m-Chlorophenyl	131	80	26.45/26.50

Hence, on the basis of above spectral data the structure assigned to 4-Thiazolidone i.e. T_{A-2} (Figure 1) is as.



2-Methyl(2-hydroxy-3'-chloro-5'-chloromethylphenyl)-3-(4'-methylphenyl or p-toulyl)-4-thiazolidone i.e. [T_{A-2}]

Figure 1

Antimicrobial activity

Antibacterial activities of synthesized compounds was carried out by using two human and two plant pathogenic bacterial cultures viz. *Staphylococcus aureus*, *Escherichia coli* and *Xanthomonas citri*, *Erwinia caratovora* respectively which was done by Cup plate method. The activity is reported in terms of zone of inhibition (in mm) and results are standardized against Tetracycline antibiotic. The antifungal activity of synthesized compounds was also carried out by using two human and two plant pathogenic fungal cultures such as *Candida albicans*, *Trichophyton rubrum* and *Alternaria solani*, *Helminthosporium turcicum* respectively.

Antifungal activity for *Candida albicans* and *Trichophyton rubrum* was done by Cup plate method, which is reported in terms of zone of inhibition (in mm) where as spore germination method was used for *Alternaria solani* and *Helminthosporium turcicum*, where the activity is reported in terms of percentage inhibition of Spore germination. The results are standardized against *Amphotericin-B*. The antimicrobial and antifungal activity of these compounds are given in Table-II.

Table II

Compound	R"	Antibacterial Activity				Antifungal Activity			
		Zone of inhibition (in mm)				Zone of inhibition (in mm)		% Spore inhibition of germination	
		S. aureus	*E. coli*	*X. citri*	*E. carotovora*	*C. albicans*	*T. rubrum*	*A.solani*	*H.turcicum*
T_{A-1}	p-Nitrophenyl	13	10	16	17	10	11	82	76
T_{A-2}	p-Methylphenyl	14	12	17	16	11	10	83	72
T_{A-3}	m-Methylphenyl	13	13	17	17	12	13	85	76
T_{A-4}	p-Chlorophenyl	15	12	16	18	12	12	84	76
T_{A-5}	m-Chlorophenyl	14	14	15	16	10	14	83	75
T_{B-1}	p-Nitrophenyl	13	15	12	14	11	13	85	76
T_{B-2}	p-Methylphenyl	15	12	14	15	12	12	85	78
T_{B-3}	m-Methylphenyl	14	13	16	17	13	10	86	78
T_{B-4}	p-Chlorophenyl	13	12	15	15	14	11	85	74
T_{B-5}	m-Chlorophenyl	12	15	12	13	12	13	86	74
Control (5% DMF)		1	0	0	1	0	1	0	1
Antibiotic (Tetracyclin)		20	18	22	21				
Fungicide (Amphotericin-B)						19	18	100	100

4. Conclusions

In the present study the synthesis of 2,3-Disubstituted-4-Thiazolidones [$T_{A/B,1-5}$] has been carried out successfully from the starting material 2-hydroxy-3/5-chloro-5/3-chloromethyl acetophenone (CMA-A/B). It was found that the the 2,3-Disubstituted-4-Thiazolidones [$T_{A/B,1-5}$] synthesized by the reaction of 2-hydroxy-3/5-chloro-5/3-chloromethyl acetophenone (trisubstituted acetophenones) [CMA-A/B] with substituted amines and Thioglycolic acid in the presence of Zinc chloride in dry Benzene also gave good to excellent yield with high purity.The structures of all these compounds was confirmed by elemental analysis and by taking IR, ^{1}H NMR and Mass spectra of representative member from the series .All these compounds possess antibacterial and antifungal properties.

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