International Journal of Scientific Research in Biological Sciences **Research Paper**
Vol.5, Issue.4, pp. 61-65, August (2018) **E-ISSN:** 2347-7520

Tosyl ester(s) of α-hydroxy acid(s) – Synthesis and antimicrobial studies

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Available online at: www.isroset.org

Accepted: 18/Aug/2018, Online: 30/Aug/ 2018

Abstract –Tosyl ester(s) of α-hydroxy acid(s) were prepared by treating the acid with *p*-toluenesulfonyl chloride (TsCl) in the presence of pyridine. The products were isolated, identified by TLC and characterized by IR, ^{1}H-NMR and ^{13}C-NMR spectral techniques. Anti microbial activity of the synthesized compounds were studied by Agar well diffusion method against two bacterial (*Escherichia Coli* and *Staphylococus Aureus*) and two fungal (*Candida albicans* and *Aspergillus Niger*) species using Ciprofloxacin against the bacterial strains, Nystatin against *Candida albicans* and Amphotericin against *Aspergillus niger* as standard antibiotics. The results infer that the tosyl ester(s) of α- hydroxy acid(s) are potentially active against bacterial and fungal strains.

Keywords – *Tosyl esters, α-hydroxy acids, Sulfonyl sulfur, TLC technique, Antimicrobial activity, Agar well diffusion method*

I. INTRODUCTION

Tosyl esters are sulfonyl esters synthesized by treating *p*-toluenesulfonyl chloride (known as tosyl chloride and abbreviated as TsCl) with phenols / aliphatic alcohols or carboxylic acids in the presence of base. Formation of tosyl ester is a nucleophilic substitution reaction in which the oxygen of the alcohol/acid displaces the chloride ion from the tosyl chloride. Base catalyzes the reaction and neutralizes the HCl that formed in the reaction [1, 2].

II. RELATED WORK

Organo Sulfur compounds find a wide range of chemical, medicinal, biomedical and industrial applications due to their low cost and useful properties such as solubility in aqueous and organic solvents, metal complexing ability, biological compatibility and ease of chemical modification [3-5]. The various methods of preparation of tosyl esters from aliphatic alcohols, aromatic acids, sulfonic acids and phenols have been reported [6-11].

Sulfur containing drugs such as sulfonamides, sulfonyl ureas, 2-thio uracil, 6-mercapto purines etc., have extensive therapeutic usage. Some sulfur containing agrochemicals have useful biological activity. They used as insecticides, herbicides, fungicides and agaricides [12]. Sulfonyl medicines and their antibiotics are commonly used for the treatment of infections occurred by microbes [13]. Various metal complexes of indole acetic acid [14], tosyl esters of indole aceticacid and naphthalene aceticacid [15] were studied for their antimicrobial activity.

With the development of new applications in medical and other applied areas, there is a growing demand for improved and versatile methods for the synthesis and characterization of sulfonyl derivatives. Hence, we synthesized few tosyl ester(s) of α- hydroxy acid(s), characterized by spectral techniques and studied their microbiological activities against pathogenic microbes.

III. METHODOLOGY

Materials

All the chemicals such as *p*- toluenesulfonyl chloride, glycolic acid, lactic acid, mandelic acid, pyridine and acetonitrile were purified before use by recrystallization or distillation until their physical constants (melting/boiling) agreed well with the literature values [16,17]. FT-IR (KBr) spectra were recorded on Perkin Elmer RXI spectrophotometer and H^{1} & C^{13} –NMR spectra were recorded on a Bruker AMX 400 MHz & 200 MHz NMR spectrometer respectively using TMS as an internal reference.

Synthesis of tosyl esters

***p*-toluenesulfonyl glycolate (PTSG)**

Equal volumes of equimolar solutions of *p*-toluenesulfonyl chloride (25ml, 0.05 mol dm^{-3}) and mixture of Glycolic acid – Pyridine (25ml, 0.05 mol dm^{-3}) in acetonitrile were mixed

with constant stirring and kept at about 30 ˚C for overnight. The solid product obtained was treated with ether. The ether layer was separated and kept under vacuum for evaporation to get residue and dried over anhydrous Na_2SO_4. The solid product obtained was recryslallized from toluene [Yield 0.387g, melting point 106 ˚C]. The product was identified as *p*-toluenesulfonyl glycolate from IR (KBr), ^{1}H NMR (200MHz, $CDCl_3$) and ^{13}C- NMR (DMSO-d_6) spectral data [18].

The same procedure was adopted for the synthesis of *p*-toluenesulfonyl lactate (Yield 0.294g) and *p*-toluenesulfonyl mandalate (Yield 0.302g).

Characterization of the synthesized compounds

Compound I: *p*-toluenesulfonyl glycolate (PTSG)

The spectral data are,

IR: 3417 υ$_{–OH\ (H\text{-}bonded)}$, 3063 υ $_{C\text{-}H\ (aromatic)}$, 2924 υ $_{C\text{-}H\ (aliphatic)}$, 1730 υ $_{C=O}$, 1375 υ $_{S\text{-}O\ (asy.)}$, 1182 υ $_{S\text{-}O\ (sym.)}$, 693 υ $_{S\text{-}O\text{-}C}$ cm^{-1}

^{1}H NMR: 2.31(s, 3H, C**H$_3$**-C_6H_5), 3.18 (s, 2H, C**H$_2$**), 7.22-7.20 (d, 2H, C_3- and C_5-H, -SO_2C_6**H$_4$**CH_3), 7.68-7.66 (d, 2H, C_2- and C_6-H, -SO_2C_6**H$_4$**CH_3), 3.69 (s, 1H, -O**H**) ppm

^{13}C NMR: 175, 140,138,129,126, 77 and 22ppm.

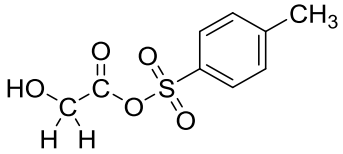


Figure 1: *p*-toluenesulfonyl glycolate

Compound II: *p*-toluenesulfonyl lactate (PTSL)

IR: 3411 υ $_{–OH\ (H\text{-}bonded)}$, 3097 υ C-H $_{(aromatic)}$, 2925 υ $_{C\text{-}H\ (aliphatic)}$, 1733 υ $_{C=O}$, 1339 υ $_{S\text{-}O(asy.)}$, 1166 υ $_{S\text{-}O\ (sym.)}$, 682 $_{\upsilon\ S\text{-}O\text{-}C}$ cm^{-1}

^{1}H NMR: 1.20 (d, 3H, C**H$_3$**-CH), 2.30 (s, 3H, C**H$_3$**-C_6H_5), 3.11-3.19 (q, 1H, CH_3-C**H**), 7.22-7.19 (d, 2H, C_3- and C_5-H, -SO_2C_6**H$_4$**CH_3), 7.69-7.66 (d, 2H, C_2- and C_6-H, -SO_2C_6**H$_4$**CH_3), 4.05(s, 1H, -O**H**) ppm

^{13}C NMR: 174, 140,128,126,125, 76 and 20ppm.

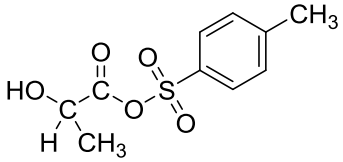


Figure 2: *p*-toluenesulfonyl lactate

Compound III: *p*-toluenesulfonyl mandalate (PTSM)

IR: 3402 υ $_{–OH\ (H\text{-}bonded)}$, 3040 υ C-H $_{(aromatic)}$, 2918 υ $_{C\text{-}H\ (aliphatic)}$, 1737 υ $_{C=O}$, 1314 υ $_{S\text{-}O\ (asy.)}$, 1158 υ $_{S\text{-}O\ (sym.)}$, 728 $_{\upsilon\ S\text{-}O\text{-}C}$ cm^{-1}

^{1}H NMR: 2.28 (s, 3H, C**H$_3$**-C_6H_5), 2.48 (s, 1H, HOC_6H_5-C**H**), 7.49 (d, 2H, C_3- and C_5-H, -SO_2C_6**H$_4$**CH_3), 7.11 (d, 2H, C_2- and C_6-H, -SO_2C_6**H$_4$**CH_3), 7.44-7.25 (m, 5H, C_6**H$_5$**CH-) 5.03 (s, 1H, -O**H**) ppm

^{13}C NMR: 169, 141,136, 135, 133, 124,123, 122, 121,120, 72 and 16 ppm.

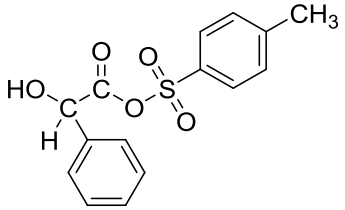


Figure 3: *p*-toluenesulfonyl mandalate

Antimicrobial Screening

Antimicrobial agent either kills microorganisms or stops their growth. Antimicrobial agents may be antibacterial, antifungal or antiviral. They all have different modes of action by which they act to suppress the infection [19]. Various groups of microorganisms have different extent of sensitivity towards antimicrobials. Microbes may develop drug resistance on continuous use of particular antimicrobial agent. So, antimicrobial studies have significant role to find the activity of particular chemical compound against microorganisms[20- 22].

In the present study Agar well disc diffusion technique has been used for determining the susceptibility of the bacterial (*Escherichia Coli* and *Staphylococus Aureus*) and fungal (*Candida albicans* and *Aspergillus Niger*) species on the test compounds. Nutrient Agar medium and Rose Bengal Chloramphenicol agar medium were used for culturing bacterial and fungal species respectively. The Agar media were inoculated with test organism and various concentrations (25, 50, 75 and 100 µg/ml in sterile DMSO) of the test solution of the compounds synthesized.

Then a standard antibiotic Ciprofloxacin against the bacterial strains *S. Aureus* and *E. Coli*, Nystatin against *Candida albicans* and Amphotericin against *Aspergillus niger* was placed at the center of the agar plate. The plate with bacterial organism was incubated at 35-37 °C for about 24 hours and the plate with fungal organism was incubated at the same temperature for 48 hours. After incubation the zone of inhibition was measured in mm scale. The results of antibacterial and antifungal screening on the test compounds are furnished in Table 1 and Figure 4 -7.

IV. RESULTS AND DISCUSSION

Tosyl esters of α - hydroxy acid(s) were prepared via a direct nucleophilic substitution reaction. α- hydroxy acid(s) react with tosyl chloride in the presence of pyridine in acetonitrile at room temperature for overnight to give the desired compounds (compound I to III). The schematic route of

synthesis of *p*-toluenesulfonyl glycolate is given in **Scheme 1**. The base pyridine abstracts the acidic hydrogen from glycolic acid and produces the nucleophile (glycolate anion) which displaces chlorine atom in tosyl chloride to form the corresponding tosyl ester.

The structure of the synthesized tosyl ester(s) of α - hydroxy acid(s) are characterized and confirmed by spectral measurements.

Antimicrobial activities on the synthesized compounds have been studied by Agar well diffusion method [23]. Antibacterial activities of the synthesized compounds were tested on gram positive *Staphylococcus aureus* and gram negative *Escherichia coli*, and antifungal activities were tested using *Aspergillus niger* and *Candida albicans*. The activities of the compounds were determined by measuring the zone of inhibition in mm around the test material and the results obtained were given in Table 1.

The results of the antimicrobial activity shows that the growth of *Staphylococcus aureus* is equally inhibited by both the compounds PTSG and PTSM. All the three esters synthesized show better activity against *Escherichia coli* and *Candida albicans.* PTSM shows excellent activity against *Aspergillus niger*.

From the results, it is clear that the synthesized compounds produced much larger zones of inhibition against bacterial and fungal strains and infers that the synthesized compounds have more antimicrobial activities towards the microorganism with minimum inhibitory concentration when compared to standard antibiotics. The synthesized compounds are able to interfere with the metabolic process that are essential for the growth of the micro-organisms and hence inhibit their growth significantly. It means that the compounds are active against bacterial and fungal strains. The effect of concentration of the test samples has also been studied. The result shows that antimicrobial activity of the test samples increases with increase of their concentrations. As the concentration of the sample solution increases the diameter of the zone of inhibition also increases in case of all the compounds tested against both bacterial and fungal strains. The results highlight the medicinal importance and drug activities of these sulfur compounds.

V. CONCLUSION AND FUTURE SCOPE

Tosyl ester(s) of α- hydroxy acid(s) were synthesized and characterized by FT-IR, ^{1}H-NMR and ^{13}C-NMR. From the spectral data the structure of the compound(s) were established. The synthesized tosyl esters (I to III) were screened for their antimicrobial activities against two bacterial and two fungal strains using standard antibiotics. From the zone of inhibition value it is clear that the antimicrobial activity of the synthesized samples increases with increase of their concentrations. The compounds (I to III) are highly active against both bacterial and fungal strains at minimum concentration. In future we have planned to conduct in-vivo studies on synthesized tosyl esters.

Figures and Tables

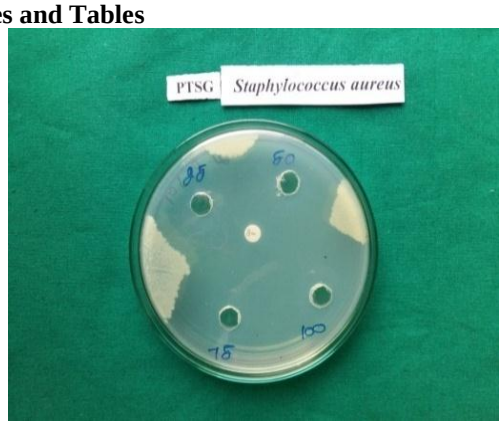


Figure 4: Antibacterial activity of *p*-toluenesulphonyl glycolate against *S. Aures*

Figure 5: Antibacterial activity of *p*-toluenesulphonyl glycolate against *A. niger*

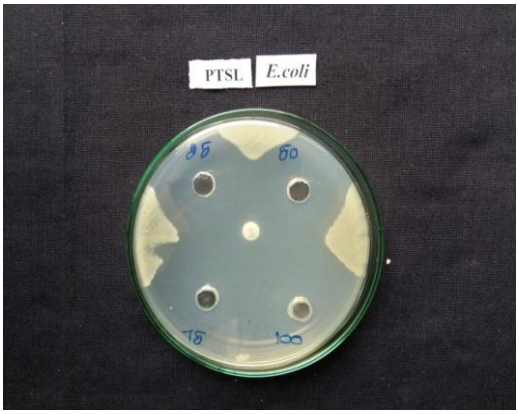


Figure 6: Antibacterial activity of *p*-toluenesulphonyl lactate against *E. coli*

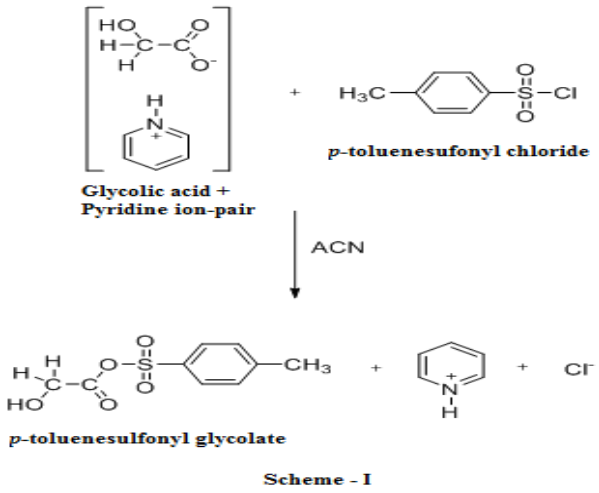
Figure 7: Antifungal activity of *p*-toluenesulphonyl mandalate against *C. albicans*

Table 1: Antimicrobial activity of tosyl ester(s) of α-hydroxyacid(s)

Test sample	Micro organism tested	Zone of inhibition (mm) produced by different sample concentrations				
		25 µg/ml	*50 µg/ml*	*75 µg/ml*	*100 µg/ml*	*Std.*
I PTSG	*S. aureus*	40	42	46	50	28
	E.coli	36	38	41	44	15
	C. albicans	40	42	46	50	25
	A.niger	40	42	46	50	30
II PTSL	*S. aureus*	36	38	41	44	28
	E.coli	38	40	43	47	15
	C. albicans	40	42	46	50	25
	A.niger	40	42	46	50	30
III PTSM	*S. aureus*	40	43	46	50	28
	E.coli	38	40	43	47	15
	C. albicans	40	43	46	50	25
	A.niger	41	44	47	50	30

STANDARD ANTIBIOTIC

Bacteria : Ciprofloxacin antibiotic disc
C. albicans : Nystatin antibiotic disc
A.niger : Amphotericin B antibiotic disc



Scheme - I

ACKNOWLEDGMENT

The authors are thankful to Dr. P. Senthil, Microbiologist, Eumic analytical lab, Trichy, for providing help in taking antibacterial and antifungal assays. The author R. Kavitha thanks M. Priyanka, Lab Assistant, Urumu Dhanalakshmi College, for her technical support.

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