Synthesis, characterization and antimycobacterial studies of ethyl 6-(4-chlorobenzoyl)-1,1-dioxo-3,5-diaryl-1,4-thiazinane-2-carboxylates using the green catalyst L-Proline

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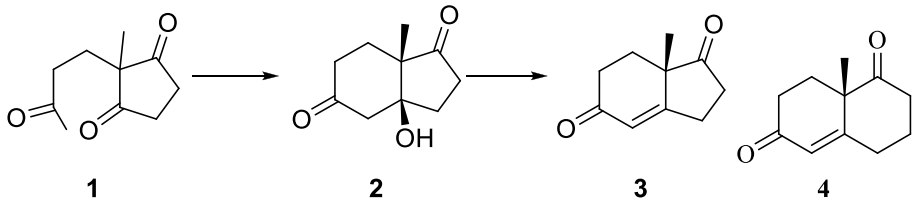
***Abstract*— The four component reaction of ethyl 2-[(2-oxo-2-arylethyl)sulfonyl]acetate, aromatic aldehyde and primary amine/ammonia in a 1:2:1 molar ratio in the presence of L-proline (30 mol %) in ethanol at room temperature for 2-4 hours afforded the [1,4]-thiazine in good yields (75-90 %) . Two [1,4]-thiazines described in the present work, have been previously reported by Reddy et al. albeit in lower yields (72 and 69% respectively) from the reaction of ethyl[(2-oxo-2-arylethyl)sulfonyl]acetate with aromatic aldehyde and ammonium acetate in ethanol, than that obtained in the present study employing (L)-proline (90 and 88% respectively).**

***Key words*- ethyl 2-[(2-oxo-2-arylethyl)sulfonyl]acetate, L-Proline, thiazine**

INTRODUCTION

Over the last decade, organocatalysis has become an area of active interest, and something as simple as proline has been shown to be effective as a catalyst. This amino acid has been lauded as the "simplest enzyme" due to its ability to catalyze reactions with high stereoselectivity. Proline was first investigated as a small molecule catalyst in the Hajos-Parrish-Eder-Sauer-Wiechert reaction. In the early 1970's, *L*-proline-catalyzed intramolecular aldol cyclizations were explored in the synthesis of optically pure starting materials for the CD rings of steroids.[2] Hajos and Parrish isolated the hydrindane dione **3** in an early proline-catalyzed intramolecular aldol cyclization. Experiments using 3 mole % *L*-proline in DMF gave 96.5:3.5 enantiomeric ratio (er) of aldol product **2** after 20 hours.[3]



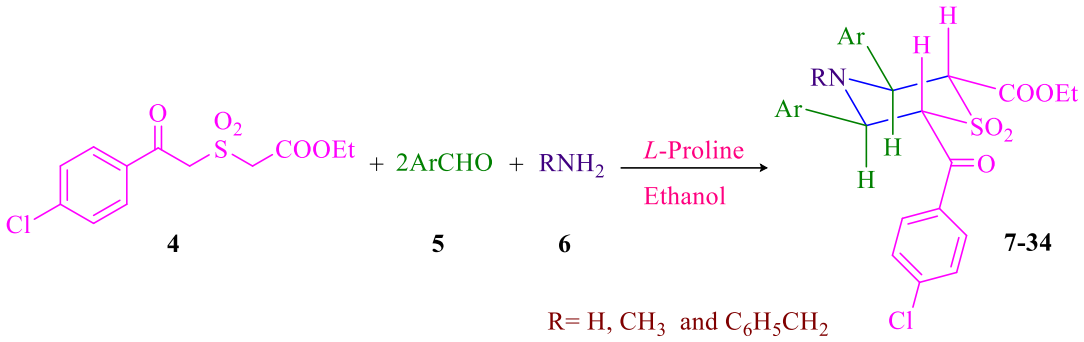
1 **2** **3** **4**

Despite these encouraging results, which were reported in 1974, the field did not expand, and it was not until the 1990's that a serious interest in proline as a catalyst was rekindled. Barbas and co-workers were interested in catalyzed intramolecular Robinson annulations when they started studying past syntheses of the Wieland-Miescher ketone (**4**).[4] In 2000, they described the first intermolecular direct asymmetric aldol reaction catalyzed with proline. This sparked intense interest from several groups in further investigating proline-catalyzed reactions.

This discloses that (*L*)-proline serves as an efficient catalyst and it can play diverse catalytic roles, *viz.* as either an acid or a base or both concurrently, its ability to form enamines upon reaction with carbonyl compounds, etc. It is pertinent to note that *L*-proline is an abundant and inexpensive amino acid which catalyses diverse organic transformations, both enantio- and non enantioselective ones such as aldol, [6] Mannich [6] Michael, [7] Diels Alder/Knoevenagel, [8] unsymmetric Biginelli [9] and tandem [10] reactions.

RESULTS & DISCUSSION

The four component reaction of ethyl 2-[(2-oxo-2-arylethyl)sulfonyl]acetate **4**, aromatic aldehyde **5** and primary amine/ammonia **6** in a 1:2:1 molar ratio in the presence of *L*-proline (30 mol %) in ethanol at room temperature for 2-4 hours afforded the [1,4]-thiazine in good yields (75-90 %) (**Scheme. 1**). Two [1,4]-thiazines described in the present work, **33** and **35**, have been previously reported by Reddy *et al.*[11] albeit in lower yields (72 and 69% respectively) from the reaction of ethyl[(2-oxo-2-arylethyl)sulfonyl]acetate **4** with aromatic aldehyde **5** and ammonium acetate in ethanol, than that obtained in the present study employing (*L*)-proline (90 and 88% respectively).



4 **5** **6** **7-34**

Scheme-1

Table 1. Synthesis of [1,4]-thiazines

Comp.	R	Ar	Yield (%)	m.p (°C)	Comp.	R	Ar	Yield (%)	m.p (°C)
7	$C_6H_5CH_2$	C_6H_5	76	163	**22**	H	4-ClC_6H_4	89	134
8	$C_6H_5CH_2$	4-ClC_6H_4	78	161	**23**	H	4-$CH_3C_6H_4$	88 (69)[a]	153
9	$C_6H_5CH_2$	4-FC_6H_4	72	139	**24**	H	4-$OCH_3C_6H_4$	90	128
10	$C_6H_5CH_2$	3-FC_6H_4	78	162	**25**	H	3- $NO_2C_6H_4$	87	151
11	$C_6H_5CH_2$	4-$CH_3C_6H_4$	76	168	**26**	H	2-thienyl	84	195
12	$C_6H_5CH_2$	4-$OCH_3C_6H_4$	79	102	**27**	H	4- $NO_2C_6H_4$	90	173
13	CH_3	C_6H_5	87	176	**28**	H	1-naphthyl	82	180
14	CH_3	4-ClC_6H_4	85	172	**29**	H	2-$OCH_3C_6H_4$	81	166
15	CH_3	2-$CH_3C_6H_4$	83	167	**30**	H	4-$N(Me)_2C_6H_4$	87	158
16	CH_3	2-BrC_6H_4	88	173	**31**	H	2- $NO_2C_6H_4$	85	178
17	CH_3	2-furyl	90	154	**32**	H	3-FC_6H_4	88	165
18	CH_3	3- $NO_2C_6H_4$	82	190	**33**	H	2-furyl	86	163
19	CH_3	4-$CH_3C_6H_4$	83	149	**34**	H	2,4-$Cl_2C_6H_3$	82	202
20	H	C_6H_5	90 (72)[a]	140					

[a]Yields in parentheses from reference **13**.

The structure of 1,4-thiazines was characterized by one- and two-dimensional NMR spectroscopic data. The ^{1}H NMR spectrum of thiazine **7** gives a doublet at 4.46 ppm assignable to H-2. This proton shows a H,H-COSY correlation with the doublet due to H-3 at 4.85 ppm (J = 10.8 Hz) . The H-2 and H-3 chemical shifts and C,H-COSY correlations assign C-2 and C-3 respectively to 72.5 and 67.5 ppm. These assignments are also supported by the HMBC correlations of: (i) H-2 with the ester carbonyl at 161.6 ppm, C-3 at 67.5 ppm and *ipso* carbon of the aryl ring at C-3, (ii) H-3 with the *ipso* and *ortho* carbons of the aryl ring attached to C-3. The J value (10.8 Hz) of H-2 and H-3 points to their axial orientations and, hence, equatorial orientations for the ester group at C-2 and aryl ring at C-3 . Another set of doublets at 5.03 and 5.29 ppm (J = 10.8 Hz) are assigned to H-5 and H-6 respectively, whose C,H-COSY correlations assign the signals at 66.8 and 71.6 ppm to C-5 and C-6 respectively. The 2H singlet at 3.58 ppm showing a C,H-COSY correlation with the carbon signal at 53.3 ppm is assigned to the benzylic protons. This assignment is evident from their HMBC correlations with: (i) the C-3 at 67.5 ppm, (ii) the C-5 at 66.8 ppm, and (iii) the *ipso* and *ortho* carbons of the benzylic phenyl ring. The triplet at 0.95 ppm (J = 7.1 Hz) and the multiplet at 3.89-4.02 ppm are assigned to the ester ethyl. The aromatic protons give a multiplet at 6.76-7.62 ppm. The other [1,4]-thiazines (**7-34**) also show similar spectroscopic features.

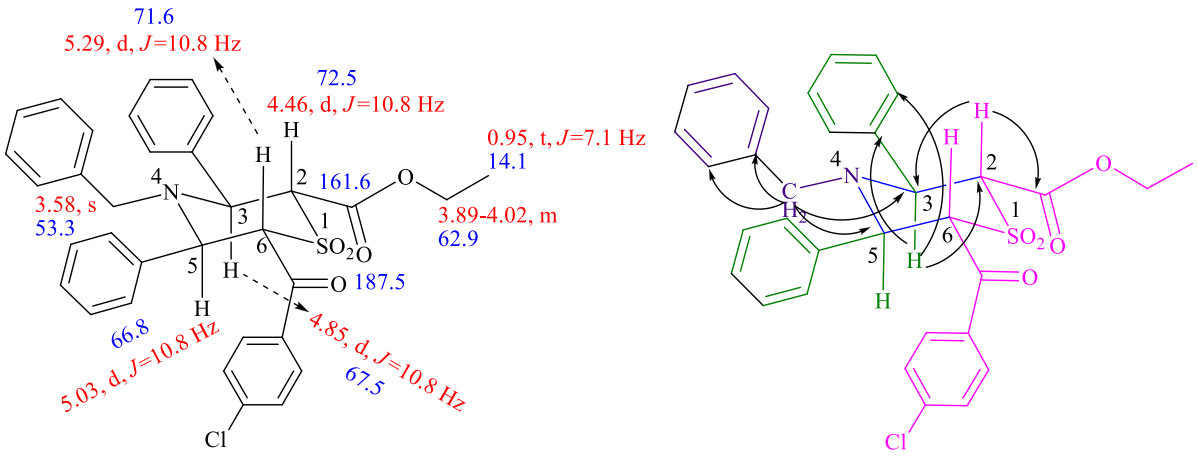


Figure 1. ^{1}H and ^{13}C chemical shifts and selected HMBC correlations of **7.**

ANTIMYCOBACTERIAL ACTIVITY

Tuberculosis (TB) is a contagious and potentially fatal disease that can affect almost any part of the body but manifests mainly as an infection of the lungs. It is caused by a bacterial microorganism, the *tubercle bacillus* or *Mycobacterium tuberculosis.* [12] Tuberculosis (TB) has become an important public health problem worldwide since the mid-1980s due to two major factors, the acquired immuno deficiency syndrome (AIDS) epidemic and the advent of multi-drug resistant strains (MDR). TB is responsible for 20% of all deaths in adults, and each year there are about 8.9–9 millions of new cases of which 15% are children, and 1.7–2 millions of deaths of which 450,000 are children. Globally, the number of TB cases is currently rising at 2% per year with an estimate of 32% of the world population, about 2 billion people, being infected by latent TB. In the case of patients with AIDS, TB is the most common opportunistic infection which causes the death 1 of every 3 patients.[13]

Single agent TB therapy rapidly leads to drug-resistant organisms, [14] while multi-drug treatment needs to be prolonged as *Mycobacterium tuberculosis* divides slowly and it is metabolically capable of becoming drug insensitive and/or bacilli may become sequestered. [15] Patient adherence is a major problem with such prolonged treatment regimens. Due to the increase of MDR-TB and AIDS cases worldwide and the lack of discovery of new drugs, there is an imperative need for discovery of short and effective TB drug regimens. In continuation of our efforts in discovering novel leads for antimycobacterial activities, we now report the synthesis of highly functionalized 1,4-thiazines and the results of their evaluation for *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv (MTB), multi-drug resistant *Mycobacterium tuberculosis* (MDR-TB) and *Mycobacterium smegmatis* (MC^2).

The 1,4-thiazines (**7-34)** were screened *in vitro* for their antimycobacterial activity against MTB, MDR-TB and MC^2 and the MIC values were determined in duplicate by agar dilution method.[16] The MDR-TB clinical isolate was resistant to isoniazid, rifampicin, ethambutol and ofloxacin. The MIC, defined as the minimum concentration of compound required to completely inhibit the bacterial growth, of the synthesized compounds and the standard drug isoniazid, for comparison, are reported.[17]

In the first phase of screening against MTB, all the compounds showed excellent *in vitro* activity with MIC ranging from 0.4–12.5 µg/ml. Only four compounds belonging to the NH-thiazines (**17, 18, 19** and **22**) were tested against MDR-TB, as they showed enhanced activity with respect to MTB. Among them, the compound with *para*-nitro group (**27**) showed the highest activity against MDR-TB, 4 times higher than that of isoniazid. The compounds (**11** and **12)** with *para*-methyl and *para*-methoxy groups in the phenyl ring were found to be 2 times more active than isoniazid and the compound (**14**) with a *para*-chlorophenyl ring showed half the activity of isoniazid. Most of the thiazines evaluated against MC^2 have MIC values ranging from 0.78–25 µg/ml.

The influence of structure on the antimycobacterial activity against MTB deserves mention. The results demonstrate that the NH-thiazines (**16-29**) displayed greater activity than either the NMe (**9-15**) or the N-CH_2Ph thiazines (**3-8**) suggesting that probably the hydrogen donor property of the NH-thiazines enhance the activity. Among *N*-Me and *N*-benzyl thiazines, three compounds (**10**, **13** and **15**) in the former series displayed a MIC of 3.13, while in the latter series only one compound (**5**) showed equal activity. In the NH thiazines, four compounds (**20**, **24, 27** and **28**) showed a MIC value of 3.13 and six compounds (**17-19**, **22**, **26** and **29**) showed a higher activity with MIC values ranging from 0.4 to 1.78. From the above results, it follows that the order of activity of NH-, NMe- and NCH_2Ph-thiazines is: NH > NMe > NCH_2Ph. This suggests that the activity decreases with enhanced steric congestion at nitrogen, which in turn could diminish the accessibility of lone pair of electrons on the nitrogen for hydrogen bonding interactions.

The compounds (**24)** and (**27),** belonging to the NH-thiazines, with *para*-methoxy and *para*-nitro group respectively in the phenyl ring showed highest activity with MIC value of 0.4. When the nitro group is at either the *ortho*- (**25**) or *meta*- (**18**) position of the phenyl ring of NH-thiazines, the activity is diminished with MIC values of 1.78 and 3.13 respectively relative to the *para*-nitro analog (**27**) with the MIC of 0.4 disclosing that the activity is sensitive to the position of the substituent in the aryl ring. The NH-thiazine with *para*-NMe_2 (**25**) group showed much less activity (MIC = 6.25) than that with either *para*-NO_2 (**24**) or *para*-MeO group (**27**), suggesting that besides electronic effects other factors also influence the activity. Among the halogenated compounds, it is found that the order of activity is: 2,4-dichloro > 4-chloro > 3-F with their MIC values respectively being 0.78, 1.56 and 3.13. Among the heteroaryl compounds, the 1,4-thiazine with 2-furyl group (**28:** MIC = 3.13) is found to be twice active relative to the 2-thienyl compound (**21:** MIC = 6.25). When the aryl ring is phenyl, 1-naphthyl or *para*-dimethyaminophenyl, the activity is reduced; the MIC value of these compounds is 6.25.

CONCLUSION

A series of ethyl 6-(4-chlorobenzoyl)-1,1-dioxo-3,5-diaryl-1,4-thiazinane-2-carboxylates were prepared in good yields (75-90 %) from the reaction of ethyl 2-[(2-oxo-2-arylethyl)sulfonyl]acetate, substituted aromatic aldehydes and amines in presence of green catalyst, (L)-proline. These compounds were evaluated for in vitro antimycobacterial activity against Mycobacterium tuberculosis H37Rv (MTB), multi-drug resistant Mycobacterium tuberculosis (MDR-TB) and Mycobacterium smegmatis (MC) using agar dilution method. Ethyl 6-(4-chlorobenzoyl)-3,5-di(4-nitrophenyl)-1,1-dioxo-1,4-thiazinane-2-carboxylate was found to be the most promising compound (MIC: 0.4 μg/mL) active against MTB and MDR-TB.

ACKNOWLEDGMENT

The author acknowledges the UGC for funding under the Major project (UGC letter No: 43-244(SR) and The Madura College Management for their constant support.

REFERENCES

[1]Movassaghi, M.; Jacobsen, E. N. *Science* **2002**, *298*, 1904.
[2] Eder, U.; Sauer, G.; Wiechert, R.; *Angew. Chem. Int. Ed*. **1971**, *10*, 496.
[3] Hajos, A. G.; Parrish, D. R.; *J. Org. Chem*. **1974**, *39*, 1615.
[4] Zhong, G.; Hoffmann, T.; Lerner, R.A.; Danishefsky, S.; Barbas, C. F., III. *J. Am. Chem. Soc*. **1997**, *119*, 8131.
[5] List, B.; Lerner, R. A.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.
[6] Alcaide, B.; Almendros, P.; Luna, A.; Rosario Torres, M. *J. Org. Chem*. **2006**, *71*, 4818.
[7] Janey, J. M.; Hsiao, Y.; Armstrong, J. D., III. *J. Org. Chem*. **2006**, *71*, 390.
[8] (a) Kotrusz, P.; Toma, S. *Molecules*, **2006**, *11*, 197; (b) Chen, H.; Wang, Y.; Wei, S.; Sun, J. *Tetrahedron: Asymmetry*, **2007**, *18*, 1308.
[9] (a) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III. *Angew. Chem*. **2003**, *115*, 4365.
[10] (a) Yadav, J. S.; Kumar, S. P.; Kondaji, G.; Rao, R. S.; Nagaiah, K. *Chem. Lett*. **2004**, *33*, 1168; (b) Mabry, J.; Ganem, B. *Tetrahedron Lett*. **2006**, *47*, 55.
[11] Srinivasan, M.; Perumal, S. *Tetrahedron*, **2007**, *63*, 2865.
[13]Reddy, D. B.; Reddy, M. M.; Reddy, P. V. R. *Indian J. Chem.* **1993**, *32B*, 1018.
[14](a) De Souza, M. V. N. *Recent Pat. Anti-Infect. Drug Discovery*, **2006**, *1*, 33. (b) De Souza, M. V. N. *Curr. Opin. Pulm. Med.* **2006**, *12*, 167.
[15] Honer zu Bentrup, K.; Russell, D. G. *Trends Microbiol*. **2001**, *9*, 597.
[16] (a) Agerton, T. B.; Valway, S. E.; Blinkhorn, R. J.; Shilkret, K. L.; Reves, R.; Schluter, W. W.; Gore, B.; Pozsik, C. J.; Plikaytis, B. B.; Woodley, C.; Onorato, I. M. *Clin. Infect. Dis*. **1999**, *29*, 85. (b) Dye, C.; Williams, B. G.; Espinal, M. A.; Raviglione, M. C. *Science*, **2002,** *295*, 2042.
[17] Sriram, D.; Yogeeswari, P.; Dinakaran, M.; Thirumurugan, R. *J. Antimicrob. Chemother*., **2007**, *59*, 1194.