Synthesis of syn-\(N\)-aryl sulfonyl-4-substituted phenyl-2-oxo-1,3-oxazolidine-5-carboxylates and their conversion to \(ant\)-form using DBU†

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Received 2 September 2003; accepted (revised) 17 September 2004

Novel syn-\(N\)-arylsulfonyl-4-substituted phenyl-2-oxo-1,3-oxazolidine-5-carboxylates have been synthesized from the corresponding \(\beta\)-azido alcohols and converted to their \(ant\)-form by epimerizing C-2 proton using DBU. Studies on the stabilization energies are done to evaluate conversion from syn-to \(ant\)-and not the vice-versa. All the compounds have been tested for their in vitro anti-bacterial activity against \(S.\) aureus, \(E.\) faecalis and \(E.\) faecium.

IPC: Int.Cl.7 C 07 D 263/00 // A 61 P 31/04

The increasing incidence of bacterial resistance to large number of antibacterial agents makes it necessary to develop new antibacterial drugs. In this direction oxazolidinone moiety has emerged as very important class of antibacterial agent. The oxazolidinones, exemplified by DUP-721 1 (ref. 1) and Linezolid 2, (ref. 2) are a new class of synthetic antibiotic agents.

Combination of active pharmacophores into one molecule is one of the novel drug designing techniques used in drug discovery programme3. In this purview, structure 4 was designed, which has structural features of both Linezolid and Sulfamethaxazole4. Sulfamethaxazole is a wide-spectrum anti-bacterial agent and Linezolid is a new class of anti-bacterial agent active against Gram-positive bacteria by inhibiting their protein synthesis at an early stage.

Results and Discussion

Racemic azido alcohols 5 (Scheme 1) were prepared5 from racemic \(anti\)-glycidic esters, which are obtained by Darzens’ condensation. Reaction of 5 with phenyl chloroformate in the presence of pyridine gave corresponding carbonate derivative 6. The compounds 6 were reductively cyclized using Pd/C or
Ph3P/THF-H2O as we reported earlier to get the corresponding 2-oxazolidinone derivatives. 2-Oxazolidinones, thus obtained, were converted into their 4-methylphenylsulfonamide derivatives by reacting with 4-methylphenylsulfonyl chloride, in CH3CN and K2CO3 as base. The reaction time was greatly reduced by using TEBAC as a PTC catalyst. Debenzylation of 4d over Pd/C gave the required 4e, which on acetylation gave 4f as shown in Scheme I.

During preparation of sulfonamides 4a without using PTC, we observed formation of a new compound in trace quantities on prolonged reflux in CH3CN, which was close to the required compound in TLC. This compound was isolated by flash chromatography and was found to have same mass in mass spectrum. The 1H NMR was also very much similar except the chiral protons. It was now obvious for us to judge that the compound obtained was an anti-isomer anti-4a, which was obtained due to prolonged heating of syn-isomer syn-4a. This made us to visualize complete transformation of the syn-compounds to anti-compounds by epimerization of the slightly acidic C-5 proton. In an attempt to make complete conversion of syn-4a to anti-4a, various bases like NaH, KOH, LiOH, tBuOK and guanidine base 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) were tried. Among these bases complete conversion was achieved only with DBU at reflux temperature in toluene by carrying out the epimerisation at C-5 proton as shown in Scheme II. Different syn-4 have been converted to anti-4 using this procedure. It is found that only syn-compounds could be converted to anti-and not the vice-versa under these conditions.

Energy minimization data was studied to understand the conversion from syn-to anti-but not the vice-versa using Silicon Graphics Octane 2 workstation software. The energy minimization studies were carried out for all syn-4 and anti-4. (4R, 5R) and (4R, 5S) configurated structures (Figures 1 and 2) are taken for energy minimization and energy studies were done. The molecules were sketched and optimized by using MMFF94 force field. Distance dependent dielectric constant for calculation of energy data was taken as unity (1). The minimization energies and heat of formation calculated for both syn- and anti-isomers is summarized in Table I. It is evident from the energy data that anti-compounds are of much lower energy than the syn-compounds. The heat of formation for the anti-compounds is also

![Diagram](attachment:image.png)
much lower than *syn*-compounds. Thus, we can conclude that the *anti*-form is much stable than the *syn*-form and hence the conversion of *syn*-to *anti*-and not the vice-versa.

**Structural confirmation of *syn*-and *anti*-4**

The compounds *anti*-4 and *syn*-4 gave same protonated molecular ion in the mass spectrum by chemical ionization method and showed the different $^1$H NMR spectra. In $^1$H NMR, chemical shift values for vicinal protons 4H and 5H for compounds *syn*-4 and *anti*-4 were found to be at $\delta$ 5.3-5.65 and 4.75-5.45, respectively. This is in accordance with reported trends and was further supported by correlation of dihedral angle calculated using energy minimization of structures *syn*-4 and *anti*-4 using Chem Draw software (Chem3D Pro Version 3.5.1) and the Karplus curve. According to the Karplus curve the coupling constant $J$ should be $\approx 8.6$ Hz for a *syn*-and $\approx 2.5$ Hz for *anti*-configuration as observed for *syn*-4 and *anti*-4. This confirms the configuration assigned to *syn*-4 and *anti*-4. The other spectral details (IR, $^1$H NMR and mass) were in confirmation for the structures of *syn*-4 and *anti*-4.

**in vitro Antibacterial results**

All *anti* and *syn* sulfonamide derivatives of ethyl 2-oxo-4-substituted phenyl-1,3-oxazolane-5-carboxylates were tested for the antibacterial activity against *Staphylococcus aureus*, *Enterococcus faecalis* and *Enterococcus faecium*. The results confirm that the compounds synthesized are of much lower antibacterial activity against the reference compounds Linezolid 2 and Ciprofloxacin. Their minimum inhibitory concentrations (MIC, $\mu$g/mL) are shown in Table II.

In conclusion *syn*-oxazolidinones can be prepared from easily available *anti* glycidic esters. The *syn*-compounds thus obtained can be efficiently converted to the *anti*-form by DBU catalyzed epimerization at hydroxy center.

**Experimental Section**

Melting points were determined on Buchi 535 melting point apparatus and are uncorrected. IR spectra were recorded in KBr/CHCl$_3$ on a Perkin-Elmer 1650 Spectrometer; $^1$H NMR and $^{13}$C NMR were recorded in CDCl$_3$/DMSO using 200 MHz.
Varian Gemini spectrometer (chemical shifts in δ, ppm) with TMS as internal standard; and mass spectra on a HP-5989A spectrometer. The Analytical Research Department of Dr. Reddy’s Research Foundation carried out all analytical work. All the organic extracts were dried over Na2SO4 after work-up. The dry reactions were carried out under nitrogen with magnetic/mechanical stirring. Unless otherwise mentioned all the solvents and reagents used were of LR grade. TLC was performed on precoated silica-gel plates, which were visualized using UV light and sulphuric acid-ethanol (5:95) charring. Flash column chromatography was carried out on silica gel (230-400 mesh) unless otherwise stated.

**General procedure for the preparation of ethyl syn-3-(4-methyl-phenylsulfonyl)-2-oxo-4-substituted phenyl-1,3-oxazolane-5-carboxylate 4a-d.** A mixture of oxazolidinone 7 (4.25 mmoles), potassium carbonate (10.64 mmoles), tosylchloride (4.68 mmoles) and TEBAC (0.425 mmoles) in acetonitrile (10 mL) was refluxed for 10 hr. The mixture was then allowed to cool to RT and filtered. The residue was washed with acetonitrile (10 mL) and the combined filtrates and washings were evaporated. The residue was taken into water (20 mL) and it was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with water (2 × 5 mL), brine (5 mL) and dried over Na2SO4. After evaporation of the solvent under reduced pressure, the residue was stirred in IPA solvent. The fine solid thus obtained, was filtered and dried in a hot oven at 60°C.

**Compound syn-4a:** Yield 91%, m.p. 133-35°C; IR (KBr): 3440, 2981, 1776, 1750, 1377, 1174 cm⁻¹; ¹H NMR (CDCl3): δ 0.8 (t, 3H, -CH₂-C₃H₃), 2.4 (s, 3H, PhC₃H₃), 3.8 (q, 2H, -CH₂CH₃), 5.3 (d, 1H, -COCH-, J=8.59 Hz), 5.65 (d, 1H, PhC₃H₃-, J=8.59 Hz), 7.05-7.45 (m, 9H, Ar-H); Mass (m/z): (M++1) 390.

**Compound syn-4b:** Yield 92%, m.p. 138-41°C; IR (KBr): 3425, 2971, 1799, 1771, 1171 cm⁻¹; ¹H NMR (CDCl3): δ 0.9 (t, 3H, -CH₂-C₃H₃), 2.4 (s, 3H, PhC₃H₃), 3.8 (q, 2H, -CH₂CH₃), 5.3 (d, 1H, -COCH-, J=8.59 Hz), 6.85-7.45 (m, 9H, Ar-H); Mass (m/z): (M++1) 408.

**Compound syn-4c:** Yield 92.3%, m.p. 176-78°C; IR (KBr): 2995, 1789, 1766 cm⁻¹; ¹H NMR (CDCl3): δ 0.85 (t, 3H, -CH₂-C₃H₃), 2.35 (s, 3H, PhCH₃), 3.75 (s, 3H, -OCH₃), 3.8 (q, 2H, -CH₂CH₃), 5.25 (d, 1H, -COCH-, J=8.59 Hz), 6.75 (d, 2H, Me adjacent Ar-H, J=8.59 Hz), 7.1 (d, 2H, oxazolidinone adjacent Ar-H, J=8.05 Hz), 7.4 (d, 2H, -OCH₃ adjacent Ar-H, J=8.05 Hz); Mass (m/z): (M++1) 420.

**Compound syn-4d:** Yield 91.5%, m.p. 112-14°C; IR (KBr): 3440, 2981, 1776, 1750, 1377, 1174 cm⁻¹; ¹H NMR (CDCl3): δ 0.85 (t, 3H, -CH₂-C₃H₃), 2.35 (s, 3H, PhCH₃), 3.8 (q, 2H, -CH₂CH₃), 5.05 (s, 2H, -CH₂Ph), 5.3 (d, 1H, -COCH-, J=8.59 Hz), 5.6 (d, 1H, PhCH₃, J=8.59 Hz), 6.75-7.45 (m, 13H, Ar-H); Mass (m/z): (M++1) 496.

**Preparation of ethyl syn-4-(4-hydroxyphenyl)-3-(4-methylphenylsulfonyl)-2-oxo-1,3-oxazolane-5-carboxylate, syn-4e.** A mixture of compound syn-4d

<table>
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<td></td>
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<tr>
<td></td>
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</tr>
<tr>
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<tr>
<td>anti-4f</td>
<td>&gt;256</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.5</td>
</tr>
<tr>
<td>Linezolid</td>
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</table>
(1.0 g, 2.02 mmoles) in 1,4-dioxane (10 mL) was hydrogenated over 5% Pd/C (200 mg) at 5-10 psi at RT for 12 hr. The catalyst was filtered off and the filtrate was concentrated. The residue was triturated with diisopropyl ether to get a solid that was filtered to afford syn-4e as a white solid, yield 97%, m.p. 173-75°C; IR (KBr): 3437, 1757, 1380, 1171 cm⁻¹; ¹H NMR (CDCl₃): δ 0.85 (t, 3H, -CH₂-C₃), 2.3 (s, 3H, PhCH₃), 3.8 (q, 2H, -CH₂-CH₃), 5.35 (d, 1H, -COCH-, J=8.59 Hz), 5.65 (d, 1H, PhCH-, J=8.59 Hz), 6.9-7.2 (m, 8H, Ar-H); Mass (m/z): (M⁺+1) 448.

**Preparation of ethyl syn-4-(4-benzyloxyphenyl)-3-(4-methylphenylsulfonyl)-2-oxo-1,3-oxazolane-5-carboxylate, syn-4f.** To a cooled solution of syn-4e (500 mg, 1.234 mmoles), DCM (10 mL) and TEA (187.38 mg, 1.851 mmoles), acetyl chloride (116.29 mg, 1.481 mmoles) was added dropwise and stirred at 0°C for 1 hr, then the reaction mixture was washed with water (2 × 4 mL) to get a residue which was stirred in IPA to obtain a solid which was filtered to give syn-4f, yield 95.5%, m.p. 183-85°C; IR (KBr): 3456, 2976, 1800, 1760, 1735, 1202, 1167 cm⁻¹; ¹H NMR (CDCl₃): δ 1.3 (t, 3H, -CH₂-C₃), 2.4 (s, 3H, PhCH₃), 3.8 (q, 2H, -CH₂-CH₃), 4.3 (q, 2H, -CH₂-CH₃), 4.75 (d, 1H, -COCH-, J=2.4 Hz), 6.8 (d, 2H, Me adjacent Ar-H), J=8.32 Hz), 6.8-7.5 (m, 13H, Ar-H); Mass (m/z): (M⁺+1) 496.

**General procedure for the conversion of syn-to anti-ethyl 3-(4-methylphenylsulfonyl)-2-oxo-4-substitutedphenyl-1,3-oxazolane-5-carboxylate, anti-4a-f.** A solution of syn-sulfonamides syn-4 (1.285 mmoles) and DBU (0.254 mmoles) in toluene (5 mL) was refluxed for 7-10 hr. The reaction mass was concentrated under reduced pressure to give a residue. This residue was purified by flash chromatography on 230-400 mesh silica gel (ethyl acetate-pet. ether; 60-80°; 4:6) to afford the anti-sulfonamides, anti-4.

**Compound anti-4a:** Yield 90%, m.p. 141-43°C; IR (KBr): 2987, 1789, 1751, 1378, 1171 cm⁻¹; ¹H NMR (CDCl₃): δ 1.3 (t, 3H, -CH₂-C₃), 2.4 (s, 3H, PhCH₃), 4.3 (q, 2H, -CH₂-CH₃), 4.75 (d, 1H, -COCH-, J=2.68 Hz), 5.45 (d, 1H, PhCH-, J=2.68 Hz), 7.1-7.5 (m, 9H, Ar-H); Mass (m/z): (M⁺+1) 390.

**Compound anti-4b:** Yield 89.5%, m.p. 127-29°C; IR (KBr): 3488, 2997, 1806, 1757, 1365, 1171 cm⁻¹; ¹H NMR (CDCl₃): δ 1.3 (t, 3H, -CH₂-C₃), 2.4 (s, 3H, PhCH₃), 4.3 (q, 2H, -CH₂-CH₃), 4.75 (d, 1H, -COCH-, J=2.68 Hz), 5.45 (d, 1H, PhCH-, J=2.68 Hz), 7.0-7.55 (m, 9H, Ar-H); Mass (m/z): (M⁺+1) 408.

**Compound anti-4c:** Yield 89%, m.p. 104-06°C; IR (KBr): 2995, 1800, 1755 cm⁻¹; ¹H NMR (CDCl₃): δ 1.3 (t, 3H, -CH₂-C₃), 2.4 (s, 3H, PhCH₃), 3.8 (s, 3H, OCH₃), 4.3 (q, 2H, -CH₂-CH₃), 4.75 (d, 1H, -COCH-, J=2.44 Hz), 5.45 (d, 1H, PhCH-, J=2.44 Hz), 6.85 (d, 2H, Me adjacent Ar-H), J=8.54 Hz), 7.15 (m, 4H, sulfonamide adjacent Ar-H and oxazolidinone adjacent Ar-H), 7.5 (d, 2H, OCH₃ adjacent Ar-H), J=8.30 Hz); Mass (m/z): (M⁺+1) 420.

**Compound anti-4d:** Yield 88%, m.p. 114-16°C; IR (KBr): 1805, 1757, 1366, 1173 cm⁻¹; ¹H NMR (CDCl₃): δ 1.3 (t, 3H, -CH₂-C₃), 2.4 (s, 3H, PhCH₃), 4.3 (q, 2H, -CH₂-CH₃), 4.75 (d, 1H, -COCH-, J=2.44 Hz), 5.1 (s, 2H, -CH₂-CH₂Ph), 5.4 (d, 1H, PhCH₃, J=2.44 Hz), 6.9-7.5 (m, 13H, Ar-H); Mass (m/z): (M⁺+1) 496.

**Compound anti-4e:** Yield 46%, m.p. 177-79°C; IR (KBr): 3482, 1772, 1752, 1367, 1174 cm⁻¹; ¹H NMR (CDCl₃): δ 1.3 (t, 3H, -CH₂-C₃), 2.4 (s, 3H, PhCH₃), 4.3 (q, 2H, -CH₂-CH₃), 4.75 (d, 1H, -COCH-, J=2.4 Hz), 5.4 (d, 1H, PhCH-, J=2.4 Hz), 6.8 (d, 2H, Me adjacent Ar-H), J=8.32 Hz), 7.0 (d, 2H, sulfonamide adjacent Ar-H, J=8.32 Hz), 7.2 (d, 2H, oxazolidinone adjacent Ar-H, J=8.05 Hz), 7.45 (d, 2H, OCH₃ adjacent Ar-H, J=8.05 Hz), 9.0 (s, 1H, -OH, D₂O exchangeable); Mass (m/z): (M⁺+1) 406.

**Compound anti-4f:** Yield 82%, m.p. 112-14°C; IR (KBr): 2992, 1792, 1765, 1375, 1209, 1170 cm⁻¹; ¹H NMR (CDCl₃): δ 1.35 (t, 3H, -CH₂-C₃), 2.35, 2.4 (2s, 6H, PhCH₃ and CH₃CO-), 3.8 (q, 2H, -CH₂-CH₃), 5.35 (d, 1H, -COCH-, J=8.59 Hz), 5.65 (d, 1H, PhCH-, J=8.59 Hz), 6.9-7.2 (m, 8H, Ar-H); Mass (m/z): (M⁺+1) 448.

**Acknowledgement**

The authors are thankful to Dr. Reddy’s Group of Companies for supporting this work. Co-operation extended by all the colleagues of the analytical R&D and Pharmacology Divisions is gratefully acknowledged. Discussions with Dr J Moses Babu, Dr B Gopalakrishnan and Mr Pankaj Daga of Discovery Research, for the dihedral angle and for energy minimization data are also gratefully acknowledged.

**References**


2. (a) Brickner S J, Hutchinson D K, Barbachyn M R, Garmon S A, Grega K C, Hendges S K, Manninen P R, Toops D S,


3 Many such examples are known in literature. To cite a few, Acedapsone (anti-malarial and anti-bacterial), Acefylline (diuretic, cardiotonic and bronchodilator), Beclomethasone (anti-allergic, anti-asthmatic and anti-inflammatory), Benactyzine (anti-depressant and anti-cholinergic), Xylazine (sedative, analgesic and muscle relaxant), Zileuton (anti-asthmatic and anti-inflammatory), etc.