Infrared, $^1$H and $^{13}$C NMR spectral studies of some 4-([1,1′-biphenyl]-4-y1)-6-(substituted phenyl)-5,6-dihydro-4H-1,3-oxazine-2-amines: Assessment of substituent effects


$^1$Department of Chemistry, Annamalai University, Annamalainagar-608 002, India  
$^2$Department of Chemistry, Sourashtra College, Madurai-625 004, India  
$^3$PG and Research department of Chemistry, Government Arts College, C-Muttur-608 102, Chidambaram, India

E-mail address: thirunarayanan.g.10313@annamalaiuniversity.ac.in; drgtnarayan@gmail.com

Keywords: Environmentally benign synthesis, Oxazine-2-amine, IR spectra, NMR spectra, Spectral LFER, Swain-Lupton's correlation

ABSTRACT. About ten titled compounds were prepared by microwave assisted silica-phosphoric acid catalysed cyclization of substituted styril 4-biphenyl ketones and urea under solvent-free conditions. The infrared frequencies (ν, cm$^{-1}$) of NH$_2$, C=N, COC stretches, NMR spectral chemical shifts (δ, ppm) of NH$_2$, H$_4$-$\alpha$, C=N, and C$_4$-$\alpha$ were assigned and correlated with Hammett substituent constants, F and R parameters using single and multi-regression analysis. From the results of statistical analysis, the effect of substituents on the infrared frequencies (ν, cm$^{-1}$) and NMR chemical shifts (δ, ppm) has been studied.

1. INTRODUCTION

The 1, 3-oxazine 2-amine are six membered heterocyclic compounds with oxygen and nitrogen as hetero atoms and are occupied alternative arrangement in the six membered cyclic structures [1]. These oxazine derivatives possess significant biological activities such as antimicrobial [2], anti-plasmodial [3], anti-cancer [4], anti-depressants [5], anti-tumour [6], cytotoxicity [7], anti-oxidant [8], anti-infectants [9], PTB-1B inhibition and IKB kinase beta inhibitions[10]. Numerous synthetic methods of oxazine derivatives were reported in literature such as solvent-free and solvent-assisted methods [11]. Correlation analysis was useful for prediction of reaction speeds, structural conformations of alkenes [12], alkynes [13], α,β-unsaturated aldehydes[14], ketones[15], ω-substituted ketones[16] and its esters, halo acyl bromides[17], 1H pyrazoles[18] and its derivatives. Infrared spectroscopic frequencies were applied for s-cis and s-trans conformations of ground state equilibrium of unsaturated carbonyl systems with respect to carbonyl and vinyl groups [19]. Proton nuclear magnetic resonance spectroscopic data were applied for prediction of E- and Z- conformations of unsaturated systems and spatial arrangements of cyclic systems [20]. Thirunarayanan et al., have studied the infrared and NMR spectral correlations of phenazine and quinoxaline derivatives [21, 22]. Mayavel et al., have studied the spectral correlation of some E-IMe [23]. The Qs and Qpr spectral correlation of some dihyroisoxazoles were reported by Thirunarayanan and Sathiyendiran [24]. From the complete literature survey, the similar study was not available with biphenyl based 1,3-oxazine-2-amines. Hence, the authors have taken efforts for the study of spectral correlation of the titled compounds by IR and NMR spectra.
2. EXPERIMENTAL

2.1. General

In this present work, all chemicals used were purchased from Sigma-Aldrich Company Bangalore, India. Melting points were determined using Mettler FP51 melting-point apparatus and are uncorrected. Infrared spectra (KBr, 4000–400 cm\(^{-1}\)) were recorded on a Bruker (Thermo Nicolet) Fourier transform spectrophotometer. The NMR spectra of all pyrazolines were recorded on a Bruker AV400 spectrometer operating at 400 MHz to record \(^1\)H and 100 MHz for \(^{13}\)C spectra in CDCl\(_3\) solvent with TMS as internal standard.

2.2. synthesis of the 4-([1,1′-biphenyl]-4-yl)-6-(substituted phenyl)-5,6-dihydro-4H-1,3-oxazine-2-amine derivatives.

In this present study, the titled compounds were synthesised and characterized by literature method[25]. The general structure of the 4-([1,1′-biphenyl]-4-yl)-6-(substituted phenyl)-5,6-dihydro-4H-1,3-oxazine-2-amines are shown in Fig.1.

![General structure of 4-([1,1′-biphenyl]-4-yl)-6-(substituted phenyl)-5,6-dihydro-4H-1,3-oxazine-2-amines](image)

\(X=H, 3-NH_2, 3-Cl, 4-Cl, 4-N(CH_3)_2, 4-OH, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2\)

Fig. 1. General structure of 4-([1,1′-biphenyl]-4-yl)-6-(substituted phenyl)-5,6-dihydro-4H-1,3-oxazine-2-amines

3. RESULTS AND DISCUSSION

3.1. Single parameter correlation

3.1.1. Correlation analysis with IR spectral data

From the infrared spectra of synthesized oxazine derivatives, the characteristic stretches (\(\nu, \text{cm}^{-1}\)) of NH\(_2\), C=N and C-O-C were assigned and tabulated in Table 1. Using Hammett equation and single and multi-regression analysis[2, 15-24] of these data with Hammett substituent constants and Swain-Lupton’s [26] parameters, the obtained statistical results are tabulated in Table 2. From the Table 2, the NH\(_2\) stretches (\(\nu, \text{cm}^{-1}\)) gave satisfactory correlations with positive \(\rho\) values. This \(\rho\) value indicates that, the normal substituent effects operate in all systems. The CN stretches (\(\nu, \text{cm}^{-1}\)) of the oxazine derivatives were produced satisfactory correlation with Hammett \(\sigma\) and \(\sigma^+\) constants. The Hammett \(\sigma_p\), \(\sigma_R\) constants, F and R parameters were failing in correlations. The failure in correlation was the inability of prediction of effects of substituents on the stretches and attributed with the resonance-conjugative structure as illustrated in Fig. 2.
Table 1. Infrared frequencies (ν, cm⁻¹) and NMR chemical shifts (δ, ppm) spectral data of 4-((1,1’-biphenyl)-4-yl)-6-(substituted phenyl)-5,6-dihydro-4H-1,3-oxazine-2-amines

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Substituent (X)</th>
<th>IR NH₂ C=N C-O-C</th>
<th>¹H NMR</th>
<th>¹³C NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NH₂</td>
<td>C=N</td>
<td>C-O-C</td>
</tr>
<tr>
<td>1</td>
<td>H</td>
<td>3550</td>
<td>1613</td>
<td>1248</td>
</tr>
<tr>
<td>2</td>
<td>3-NH₂</td>
<td>3550</td>
<td>1398</td>
<td>1211</td>
</tr>
<tr>
<td>3</td>
<td>3-Cl</td>
<td>3552</td>
<td>1993</td>
<td>1221</td>
</tr>
<tr>
<td>4</td>
<td>4-Cl</td>
<td>3555</td>
<td>1610</td>
<td>1212</td>
</tr>
<tr>
<td>5</td>
<td>4-N(CH₃)₂</td>
<td>3545</td>
<td>1614</td>
<td>1219</td>
</tr>
<tr>
<td>6</td>
<td>4-OH</td>
<td>3545</td>
<td>1398</td>
<td>1212</td>
</tr>
<tr>
<td>7</td>
<td>4-CH₃</td>
<td>3545</td>
<td>1613</td>
<td>1215</td>
</tr>
<tr>
<td>8</td>
<td>4-CH₃</td>
<td>3540</td>
<td>1612</td>
<td>1215</td>
</tr>
<tr>
<td>9</td>
<td>3-NO₂</td>
<td>3552</td>
<td>1615</td>
<td>1213</td>
</tr>
<tr>
<td>10</td>
<td>4-NO₂</td>
<td>3552</td>
<td>1612</td>
<td>1258</td>
</tr>
</tbody>
</table>

Table 2. Results of statistical analysis of IR and NMR spectral data of 4-((1,1’-biphenyl)-4-yl)-6-(substituted phenyl)-5,6-dihydro-4H-1,3-oxazine-2-amines with Hammett σ, σ⁺, σᵣ constants, F and R parameters.
<table>
<thead>
<tr>
<th></th>
<th>σ_R</th>
<th>F</th>
<th>R</th>
<th>2-NO₂, 4-NO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>δH₅(ppm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>σ</td>
<td>0.904</td>
<td>2.132</td>
<td>0.095</td>
<td>0.09</td>
</tr>
<tr>
<td>σ⁺</td>
<td>0.833</td>
<td>2.112</td>
<td>0.041</td>
<td>0.09</td>
</tr>
<tr>
<td>σ₁</td>
<td>0.907</td>
<td>0.701</td>
<td>0.268</td>
<td>0.07</td>
</tr>
<tr>
<td>σ_R</td>
<td>0.841</td>
<td>2.095</td>
<td>0.149</td>
<td>0.09</td>
</tr>
<tr>
<td>F</td>
<td>0.907</td>
<td>2.213</td>
<td>0.303</td>
<td>0.06</td>
</tr>
<tr>
<td>R</td>
<td>0.815</td>
<td>2.093</td>
<td>0.101</td>
<td>0.09</td>
</tr>
<tr>
<td>δH₆(ppm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>σ</td>
<td>0.836</td>
<td>4.566</td>
<td>0.104</td>
<td>0.13</td>
</tr>
<tr>
<td>σ⁺</td>
<td>0.841</td>
<td>4.566</td>
<td>0.104</td>
<td>0.13</td>
</tr>
<tr>
<td>σ₁</td>
<td>0.823</td>
<td>4.580</td>
<td>0.040</td>
<td>0.13</td>
</tr>
<tr>
<td>σ_R</td>
<td>0.843</td>
<td>4.506</td>
<td>0.225</td>
<td>0.13</td>
</tr>
<tr>
<td>F</td>
<td>0.815</td>
<td>4.587</td>
<td>0.068</td>
<td>0.14</td>
</tr>
<tr>
<td>R</td>
<td>0.842</td>
<td>4.501</td>
<td>0.238</td>
<td>0.12</td>
</tr>
<tr>
<td>δC₂(ppm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>σ</td>
<td>0.908</td>
<td>165.14</td>
<td>0.081</td>
<td>0.48</td>
</tr>
<tr>
<td>σ⁺</td>
<td>0.801</td>
<td>165.14</td>
<td>0.030</td>
<td>0.48</td>
</tr>
<tr>
<td>σ₁</td>
<td>0.823</td>
<td>165.04</td>
<td>0.415</td>
<td>0.46</td>
</tr>
<tr>
<td>σ_R</td>
<td>0.701</td>
<td>165.16</td>
<td>0.031</td>
<td>0.48</td>
</tr>
<tr>
<td>F</td>
<td>0.823</td>
<td>125.01</td>
<td>0.0505</td>
<td>0.46</td>
</tr>
<tr>
<td>R</td>
<td>0.707</td>
<td>165.13</td>
<td>0.089</td>
<td>0.48</td>
</tr>
<tr>
<td>δC₄(ppm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>σ</td>
<td>0.905</td>
<td>52.62</td>
<td>0.477</td>
<td>0.41</td>
</tr>
<tr>
<td>σ⁺</td>
<td>0.901</td>
<td>52.71</td>
<td>0.331</td>
<td>0.39</td>
</tr>
<tr>
<td>σ₁</td>
<td>0.809</td>
<td>52.60</td>
<td>0.175</td>
<td>0.47</td>
</tr>
<tr>
<td>σ_R</td>
<td>0.917</td>
<td>52.92</td>
<td>1.131</td>
<td>0.31</td>
</tr>
<tr>
<td>F</td>
<td>0.806</td>
<td>52.61</td>
<td>0.116</td>
<td>0.47</td>
</tr>
<tr>
<td>R</td>
<td>0.907</td>
<td>52.93</td>
<td>0.859</td>
<td>0.32</td>
</tr>
<tr>
<td>δC₅(ppm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>σ</td>
<td>0.837</td>
<td>47.58</td>
<td>0.510</td>
<td>0.63</td>
</tr>
<tr>
<td>σ⁺</td>
<td>0.838</td>
<td>47.56</td>
<td>0.317</td>
<td>0.63</td>
</tr>
<tr>
<td>σ₁</td>
<td>0.812</td>
<td>47.52</td>
<td>0.321</td>
<td>0.67</td>
</tr>
<tr>
<td>σ_R</td>
<td>0.905</td>
<td>47.88</td>
<td>0.1236</td>
<td>0.58</td>
</tr>
<tr>
<td>F</td>
<td>0.810</td>
<td>47.53</td>
<td>0.280</td>
<td>0.68</td>
</tr>
<tr>
<td>R</td>
<td>0.848</td>
<td>47.88</td>
<td>0.807</td>
<td>0.59</td>
</tr>
<tr>
<td>δC₆(ppm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>σ</td>
<td>0.843</td>
<td>66.59</td>
<td>0.449</td>
<td>0.46</td>
</tr>
<tr>
<td>σ⁺</td>
<td>0.905</td>
<td>66.67</td>
<td>0.319</td>
<td>0.41</td>
</tr>
<tr>
<td>σ₁</td>
<td>0.825</td>
<td>66.48</td>
<td>0.452</td>
<td>0.50</td>
</tr>
<tr>
<td>σ_R</td>
<td>0.846</td>
<td>66.29</td>
<td>0.867</td>
<td>0.46</td>
</tr>
<tr>
<td>F</td>
<td>0.814</td>
<td>66.52</td>
<td>0.305</td>
<td>0.51</td>
</tr>
<tr>
<td>R</td>
<td>0.905</td>
<td>66.84</td>
<td>0.682</td>
<td>0.43</td>
</tr>
</tbody>
</table>

r=correlation coefficient; I= intercept; ρ=slope; s=standard deviation; n=number of correlated derivatives
The correlation of νCOC (cm⁻¹) stretches with Hammett σ, σ⁺, σₐ, σₐR constants and R parameters gave satisfactory correlations. The Hammett σ₁ constant and F parameters were produced poor correlations. The reasons for the poor correlation was the inductive and field effects were absent for prediction of the reactivity on the νCOC(cm⁻¹) stretches and is associated with the resonance-conjugative structure as illustrated in Fig. 2.

3.1.2. ¹H NMR spectral correlation

From ¹H NMR spectra, the chemical shifts (δ, ppm) of NH₂, H₄₋₆ protons were assigned and are tabulated in Table 1. These chemical shifts were correlated with Hammett σ, σ⁺, σᵢ, σᵢR constants F and R parameters using single and multi-parameter regression analysis[2, 15-24]. The statistical analyses results are presented in Table 2. From Table 2, chemical shifts(δ, ppm) of NH₂ protons gave satisfactory correlations with Hammett σ, σ⁺, σᵢR constants and R parameters gave satisfactory correlations. The Hammett σᵢ constant and F parameters were produced poor correlations. The chemical shifts (δ, ppm) of H₄ protons gave poor correlations with Hammett σ, σ⁺, σᵢ, σᵢR constants and R parameters were fail in correlation. The chemical shifts (δ, ppm) of H₅ protons gave satisfactory correlations with Hammett σᵢ constant F parameters. Hammett σ, σ⁺, σᵢ constants and R parameters were fail in correlation. The chemical shifts (δ, ppm) of H₆ protons gave poor correlations with Hammett σ, σ⁺, σᵢR, σᵢ constants F and R parameters. All correlations gave with positive ρ values. These ρ values indicates that the normal substituent effects operates in all systems. The reasons for failure in correlations of the proton chemical shifts (δ, ppm) was already stated and associated with resonance-conjugative structure as illustrated in Fig. 2.

3.1.3. ¹H NMR spectral correlation

From ¹³C NMR spectra, the chemical shifts (δ, ppm) of C=N, and C₄₋₆ carbons were assigned and are tabulated in Table 1. These chemical shifts were correlated with Hammett σ, σ⁺, σᵢ, σᵢR constants F and R parameters using single and multi-parameter regression analysis[2, 15-24]. The results of single and multi-parameter statistical analyses are presented in Table 2. From Table 2, chemical shifts(δ, ppm) of C₂ carbons gave satisfactory correlation with Hammett σ constant only. The chemical shifts(δ, ppm) of C₄ carbons gave satisfactory correlation with σ, σ⁺, σᵢR constants and R parameters. The chemical shifts(δ, ppm) of C₅ carbons gave poor correlations with Hammett σ, σ⁺, σᵢ, σᵢR constants F and R parameters. The chemical shifts(δ, ppm) of C₆ carbons gave poor correlations with Hammett σ⁺ constant and R parameters. The rest of other correlations of these carbon chemical shifts gave poor correlation coefficients. All correlations gave with positive ρ values. This ρ value indicates that the normal substituent effects operates in all systems.
The failure in correlations for the carbon chemical shifts (δ, ppm) was already stated and associated with resonance-conjugative structure as illustrated in Fig. 2.

3.2. Multi-parameter correlations

Some of the single parameter correlations of infrared frequencies (ν, cm⁻¹) of NH₂, C=N, COC stretches, NMR spectral chemical shifts (δ, ppm) of NH₂, H₄, C=N, and C₄₋ gave poor correlations. When these are subjected to multi-parameter correlations, they gave satisfactory correlations with σᵣ, σᵣ constants, Swain-Lupton’s F and R parameters[26]. The generated multi-parameter equations are as follows (1-24):

\[\nu_{\text{NH}_2}(\text{cm}^{-1}) = 3545.48(\pm2.629) + 12.015(\pm5.471)\sigma_1 + 0.319(\pm0.057)\sigma_R (R=0.970, n = 10, P > 95\%)
\]

\[\nu_{\text{NH}_2}(\text{cm}^{-1}) = 3546.89(\pm2.694) + 9.292(\pm0.117)F + 2.371(\pm0.304)R (R = 0.962, n = 10, P > 95\%)
\]

\[\nu_{\text{CN}}(\text{cm}^{-1}) = 1601.03(\pm97.277) + 133.766(\pm20.258)\sigma_1 + 38.254(\pm19.973)\sigma_R (R=0.925, n = 10, P > 90\%)
\]

\[\nu_{\text{CN}}(\text{cm}^{-1}) = 1633.53(\pm100.830) + 74.714(\pm21.153)F + 24.458(\pm12.997)R (R = 0.919, n = 10, P > 90\%)
\]

\[\nu_{\text{COC}}(\text{cm}^{-1}) = 1235.17(\pm11.044) + 13.270(\pm2.298)\sigma_1 + 42.924(\pm2.262)\sigma_R (R=0.959, n = 10, P > 95\%)
\]

\[\nu_{\text{COC}}(\text{cm}^{-1}) = 1233.08(\pm11.932) + 8.871(\pm2.500)F + 24.478(\pm15.381)R (R = 0.952, n = 10, P > 95\%)
\]

\[\delta_{\text{NH}_2}(\text{ppm}) = 2.248(\pm0.055) + 0.014(\pm0.001)F + 0.239(\pm0.113)\sigma_R (R = 0.967, n = 10, P > 95\%)
\]

\[\delta_{\text{NH}_2}(\text{ppm}) = 2.257(\pm0.052) + 0.021(\pm0.001)F + 0.171(\pm0.062)R (R = 0.971, n = 10, P > 95\%)
\]

\[\delta_{\text{H}_4}(\text{ppm}) = 2.231(\pm0.028) + 0.017(\pm0.006)F + 0.024(\pm0.005)\sigma_R (R = 0.915, n = 10, P > 90\%)
\]

\[\delta_{\text{H}_4}(\text{ppm}) = 2.230(\pm0.029) + 0.027(\pm0.006)F + 0.013(\pm0.003)\sigma_R (R = 0.941, n = 10, P > 90\%)
\]

\[\delta_{\text{H}_5}(\text{ppm}) = 2.203(\pm0.045) + 0.218(\pm0.095)\sigma_1 + 0.112(\pm0.002)\sigma_R (R = 0.965, n = 10, P > 95\%)
\]

\[\delta_{\text{H}_5}(\text{ppm}) = 2.177(\pm0.037) + 0.237(\pm0.073)F + 0.091(\pm0.004)\sigma_R (R = 0.979, n = 10, P > 95\%)
\]

\[\delta_{\text{H}_5}(\text{ppm}) = 2.198(\pm0.005) + 0.259(\pm0.114)\sigma_1 + 0.016(\pm0.001)\sigma_R (R = 0.972, n = 10, P > 95\%)
\]

\[\delta_{\text{H}_5}(\text{ppm}) = 2.207(\pm0.052) + 2.825(\pm0.109)F + 0.109(\pm0.067)\sigma_R (R = 0.976, n = 10, P > 95\%)
\]

\[\delta_{\text{H}_6}(\text{ppm}) = 4.483(\pm0.099) + 0.263(\pm0.020)\sigma_1 + 0.606(\pm0.023)\sigma_R (R = 0.944, n = 10, P > 90\%)
\]

\[\delta_{\text{H}_6}(\text{ppm}) = 4.466(\pm0.101) + 0.286(\pm0.021)F + 0.063(\pm0.013)\sigma_R (R = 0.945, n = 10, P > 90\%)
\]

\[\delta_{\text{C}_2}(\text{ppm}) = 164.95(\pm0.362) + 0.545(\pm0.072)\sigma_1 + 0.246(\pm0.076)\sigma_R (R = 0.926, n = 10, P > 90\%)
\]

\[\delta_{\text{C}_2}(\text{ppm}) = 164.84(\pm0.366) + 0.724(\pm0.078)F + 0.297(\pm0.046)\sigma_R (R = 0.934, n = 10, P > 90\%)
\]

\[\delta_{\text{C}_4}(\text{ppm}) = 53.21(\pm0.205) + 0.708(\pm0.042)\sigma_1 + 1.681(\pm0.042)\sigma_R (R = 0.983, n = 10, P > 95\%)
\]

\[\delta_{\text{C}_4}(\text{ppm}) = 53.20(\pm0.221) + 0.677(\pm0.047)F + 1.053(\pm0.297)\sigma_R (R = 0.980, n = 10, P > 95\%)
\]

\[\delta_{\text{C}_5}(\text{ppm}) = 48.06(\pm0.450) + 0.472(\pm0.093)\sigma_1 + 1.152(\pm0.092)\sigma_R (R = 0.953, n = 10, P > 95\%)
\]
\[ \delta C_5(\text{ppm}) = 48.04(\pm 0.471) + 0.409(\pm 0.098)F + 0.924(\pm 0.064)R \]  
\( (R = 0.950, n = 10, P > 95\%) \) \hspace{1cm} (22)

\[ \delta C_6(\text{ppm}) = 66.79(\pm 0.359) + 0.103(\pm 0.073)\sigma_I + 0.886(\pm 0.073)\sigma_R \]  
\( (R = 0.946, n = 10, P > 90\%) \) \hspace{1cm} (23)

\[ \delta C_6(\text{ppm}) = 66.94(\pm 0.334) + 0.267(\pm 0.072)F + 0.759(\pm 0.044)R \]  
\( (R = 0.955, n = 10, P > 95\%) \) \hspace{1cm} (24)

4. CONCLUSIONS

About ten biphenyl based oxazine compounds were prepared by microwave assisted silica-phosphoric acid catalysed cyclization of substituted styryl 4-biphenyl ketones and urea under solvent-free conditions. The infrared frequencies (\( \nu, \text{cm}^{-1} \)) of NH\(_2\), C=N, COC stretches, NMR spectral chemical shifts(\( \delta, \text{ppm} \)) of NH\(_2\), H\(_4\)-6, C=N, and C\(_4\)-6 were assigned and correlated with Hammett substituent constants, F and R parameters using single and multi-regression analysis. From the results of statistical analysis, the effect of substituents on the infrared frequencies (\( \nu, \text{cm}^{-1} \)) and NMR chemical shifts(\( \delta, \text{ppm} \)) has been studied. More than 25 single parameter correlations and all multi-regressions gave satisfactory correlation-coefficients.

References


