SYNTHESIS OF N-ARYLAZO PRODUCTS OF INDOLE AND PYRROLE ON POLYMERIC SUPPORT

In the previous chapters, methods have been described for carrying out the diazocoupling reactions in the "solid phase" by using diazonium ions immobilized on a cation exchanger. In chapter III, the solid phase diazocoupling reaction of indole was dealt with and it has been observed that the product was invariably the 3-arylanoldole. The "solid phase" synthesis of the 3-arylanoldoles offers certain advantages over the classical synthetic method as has already been discussed. The solid phase diazocoupling reaction, can, however, be extended to the synthesis of N-arylanoldoles also as the only product of reaction.

Review of Electrophilic Substitution Reaction at 1-position

A variety of theoretical reactivity indices, including total $\pi$-electron densities, localization energy, frontier electron densities and superdelocalizabilities, have been applied to the interpretation of electrophilic aromatic substitutions in indole and related $\pi$-excessive heteroaromatics. All these reactivity indices successfully predict C-3 to be the preferred site of substitution. The frontier electron density of indole for electrophilic substitution was studied by Fukui et al. (1) and the following pattern has been put forwarded.

![Frontier electron density of indole for electrophilic substitution](image)

From the above discussion, it follows that electrophilic substitution reaction would occur at the C-3 position in preference to all other positions. It has been observed in subsequent studies that the N-H proton can be substituted to give N-substituted products of indole by an indirect method wherein the usual procedure is to metallate the 1-position followed by reaction of the metalloindole with appropriate reagents.
Since indoles are relatively acidic they may readily be converted to the corresponding indolyl anion by treatment with strong bases. Nearly all indoles form salts when treated with sodium methoxide or even aqueous NaOH. These indolyl anions bear a formal negative charge on the nitrogen which causes this atom to become the most nucleophilic site in the molecule. The electron density calculations at different positions of the indolyl anion by the CNDO/2 method gives the following picture. This points to the fact that the 1-position of the indolyl anion is the preferred site of attack by an electrophile. It can thus be anticipated that indolyl anion should preferentially react on nitrogen when treated with an electrophile. Reports indicate that this is generally true under conditions where the free indolyl anion exists.

N-alkylation occurs when indolyl sodium in tetrahydrofuran(THF) is treated with alkylhalide (2). Preferential alkylation of the indole nitrogen of tryptamines may be carried out on the indolyl salt. Thus treatment of N,N-dimethyl-5-methoxy tryptamine with NaNH₂ in liq. NH₃ followed by methyl iodide afforded the 1-methyl derivative in good yield (3).

3-Methyl indolyl magnesium bromide in ether gave a mixture of 1- and 2-acyl derivatives with acylhalides at low temperature whereas at reflux temperature only the 2-acyl derivative was obtained (4). Treatment of indolyl magnesium iodide in ether with CO₂ afforded approximately equal amounts of 1- and 3-carboxylic acids (5) [Scheme IV A].

**SCHEME IV. A**

![Scheme IV A](image)
The above and the subsequent studies on the reactivity of indolyl anions revealed that in the indolyl ambident anion both C-3 substitution and N-substitution are competitive as shown in Scheme IV B.

The regioselectivity of N- and C-3 alkylation in particular and electrophilic attack in general of the indolyl metal salt was studied under various conditions. It has been observed that the effect of the counter metal ion is crucial in determining the regioselectivity. In THF, exclusive N-alkylation occurred with the potassium salt but the extent of C3-alkylation increased with the sodium and lithium salts and becomes predominant with MgBr salt. However, N-alkylation was favoured generally in more polar solvents and for alkyl toluene-p-sulphonates it was favoured even with MgBr salts.

To conclude, the reaction of the ambident indolyl anion is influenced delicately by many factors such as the structure of the anion itself, the metal counter ion, the alkylating reagent, and the reaction conditions such as the homogeneity of the system, solvent, concentration of the reagent and the temperature etc. (6-12).

Although several examples are available on the electrophilic N-substitution of indole and the related compound pyrrole, N-substitution by diazonium ions in the homogeneous phase is not possible. An attempt to carry out diazocoupling reaction at the 1-position of indole by using sodio indole as the substrate in the homogeneous phase failed.
to give the N-arylazoindole probably because of the fact that when the reaction is carried out in the homogeneous phase, two electrophilic species, namely the H⁺ ions and the diazonium ions compete with each other to attack at the electron rich 1-position of sodio indole. Under such conditions, H⁺ attacks the 1-position in preference to the weakly electrophilic diazonium ions. This gives back the indole which subsequently undergoes diazocoupling reaction in the usual C3-position which is shown in Scheme IV C.

**SCHEME IV. C**

[Diagram showing the homogeneous phase diazocoupling reaction of sodio indole]

In short, the homogeneous phase diazocoupling reaction of sodio indole gives the 3-arylazoindoles and not the N-arylazoindoles. Similarly, it has been observed that the homogeneous phase diazocoupling reaction of sodio pyrrole, a related π-excessive heteroaromatic also did not give the N-arylazopyrroles. Interestingly, N-arylazoindoles can indeed be synthesized successfully using the resin immobilized diazonium ions. In other words, if the diazocoupling reactions of sodio indole is carried out in a biphasic condition using resin immobilized diazonium ions, the reaction is regiospecific with respect to the formation of N-arylazoindoles.

In this study, the diazonium ions were prepared in the usual way by diazotizing aromatic amines with HNO₂ and then immobilized on to a cation exchanger. The immobilized diazonium ions were then brought into reaction with a solution of sodio indole prepared in anhydrous THF. In the absence of H⁺ ions in the reaction medium, the diazonium ions were the only species capable of attacking the 1-position of sodio indole to give exclusively the N-arylazoindoles. The synthesis of the N-arylazoindoles can also
be carried out by a "reverse" method. In the reverse method, the indolyl anions prepared in the usual way in anhydrous THF was immobilized in an anion exchanger, and the resin immobilized indolyl anions were then brought into reaction with a solution of an appropriate diazonium ions to give the N-arylazoindole as the major product. The two procedures adopted are as shown in the Scheme IV D and IV E.

**SCHEME IV. D**

\[
\text{Ar NH}_2 \xrightarrow{\text{HONO}} \text{Ar N}_2^+ \cdot \text{Cl}^-
\]

\[
\text{Ar N}_2^+ + \text{Resin-Na}^+ \rightarrow \text{Ar N}_2^+ \cdot \text{Resin}
\]

\[
\text{Resin- N}_2^+ \cdot \text{Ar} + \text{Resin-N}_2^+ \rightarrow \text{N-arylazoindole}
\]

N - coupling by the direct procedure using resin immobilized diazonium ions

**SCHEME IV.E**

\[
\text{N} \xrightarrow{\text{NaH, THF}} \text{Resin(Cl)} \rightarrow \text{N-arylazoindole}
\]

N - coupling by the reverse procedure using resin immobilized indolyl anion
However, in the 'reverse' procedure the reaction medium is not actually free of H⁺ ions. Consequently, the N-arylazoindoles obtained in this case was not entirely free of byproducts. To authenticate synthetic procedure, diazocoupling reaction under identical conditions were carried out with sodio pyrrole in anhydrous THF using resin immobilized diazonium ions and analytical studies conclusively indicate the formation of the N-arylazopyrrole. The reaction with pyrrole is shown in the Scheme IV F.

**SCHEME IV.F**

\[
\text{Resin} \quad \overset{\text{N}^+{\text{-Ar}}}{{\text{N coupling in pyrrole (using resin immobilized diazonium ions)}}}
\]

**EXPERIMENTAL**

Indole was purified by recrystallization from aqueous alcohol and the arylamines were purified by established procedure as mentioned earlier. Amberlite IRA-400 macroporous type according to Rohm & Haas specifications with type analysis strong base-quarternary-N-Me₂O₂⁻Cl⁻ 20-50 mesh, Cl⁻ form, styrene-DVB(8%) was chosen as the anion exchanger and the cation exchanger used was Amberlite IR-120 (Na⁺ form) and detail specification of which is given at the beginning of the experimental section of the previous chapter.

**Immobilization of diazonium ions on the cation exchanger**

The aromatic amines were diazotized in the usual way using NaNO₂ and conc. HCl and the diazonium ions obtained were immobilized in the cation exchanger by a procedure described in chapter I, page 27. The resin immobilized diazonium ions were washed and dried and average diazonium ion content was found to be 2.23 m.eqv. per gm. of the resin and detail procedure for the same is given in page 27.
Preparation of sodio indole (13,14)

A solution of 5 gm (0.043 mole) indole in 15 ml of anhydrous tetrahydrofuran (THF) was slowly added to the suspension of 2.05 gm of NaH, previously washed with hexane, in 20 ml of anhydrous THF. During the addition an instantaneous gas evolution occurred and then the mixture was refluxed for half an hour. The sodio indole thus obtained was used immediately.

Preparation of sodio pyrrole (13,14)

To a mixture of 4.6 gm NaH and 150 ml of anh. THF, 16.1 gm (0.23 mole) of pyrrole was added slowly. The reaction was complete after stirring continuously for 3 hrs. The sodio pyrrole obtained was readied for reaction immediately.

Immobilization of indolyl anions onto anion exchanger

The sodio indole prepared as above in THF solution was passed several times through a column of dry Amberlite IRA-400 (Cl− form). Consequently, the indolyl anions were immobilized onto the anion exchanger by replacement of the Cl− ions by the indolyl anions. The resin beads were washed with THF, removed from the column and dried. Some loaded resin were then treated with HCl and the indole liberated indicated the successful grafting of the indolyl anion on to the anion exchanger. The loaded resins were kept at ordinary temperature under nitrogen atmosphere.

Immobilization of pyrryl anions onto anion exchanger

The THF solution of sodio pyrrole was passed several times through a column packed with Amberlite-IRA-400 (Cl− form) resin, already purified. The pyrryl anions were immobilized on the anion exchanger by replacement of the Cl− ions by the pyrryl anions. The resin beads were washed with dry THF, removed from the column and finally dried. Some loaded resins were then treated with HCl and the pyrrole liberated indicated the successful grafting of the pyrryl anions onto the anion exchanger. The loaded resins were kept under nitrogen atmosphere at ordinary temperature.

General method of synthesis of N-arylazoindoles (Direct Method)

2.5 gm of the resin immobilized diazonium ions were taken in a flask and to it 20 ml of the solution of sodio indole was added dropwise with constant stirring under an atmosphere of N₂ gas. After the whole solution have been added, the reaction mixture was
stirred for a further period of 30 mins. Immediate appearance of a deep red colour indicated that the reaction had taken place. The resin beads were recovered, dried and extracted with ethanol in a soxhlet extraction apparatus to extract out the product from. On evaporation of the solvent under ambient temperature gave the N-arylazoidoles as dark coloured solid. TLC on prepared silica gel H plates in the appropriate eluents showed only one spot indicating the formation of only one product. Rf values and other relevant data of different products are given in Table IV.1.

General Method of synthesis of N-arylazopyrrole

In an similar fashion, N-arylazopyrroles were synthesized taking pyrryl sodium instead of indolyl sodium as in the previous case. The products were recovered from the beads by extraction with methanol in a soxhlet apparatus. TLC of the coloured solids in prepared silica gel H plates gave only one spot indicating the formation of only one product. Physical and spectral data of the products are given in Table IV.2.

General method of synthesis of N-arylazoindoles (Reverse Method)

In the "reverse" method of synthesis of the N-arylazoindoles, indolyl anions were immobilized onto Amberlite-IRA-400 (Cl⁻ form). 5 gms of dried resin immobilized indolyl anion were taken in a conical flask and to it was added with constant stirring 50 ml of a well cooled(0-5° C) solution containing 0.05 mole of the aromatic amine, 0.05 mole of NaNO₂, 5ml conc.HCl and the rest, water. Stirring was continued for a further period of half an hour. Change in the colour of the resin beads indicated that the reaction was instantaneous. The beads were recovered, washed with water to remove excess of diazonium ions(alkaline 2-naphthol test), then with cyclohexane to remove any indole that may have formed. The product obtained were then extracted from the resin beads with ethanol in a soxhlet apparatus and evaporation of the solvent gave the desired product. TLC on the prepared silica gel H plates in the appropriate eluents showed the formation of the N-arylazoindoles in predominant quantities. In this case, the by products were found to be present in small amounts. Physical and spectral characteristics of N-arylazoindole are shown in the Table IV.1.
### TABLE IV.1
Physical and spectral characteristics of N-arylazoindoles (IV)

![Structural formula of N-arylazoindole]

<table>
<thead>
<tr>
<th>Product X</th>
<th>Y</th>
<th>m.p. *</th>
<th>colour</th>
<th>λmax**</th>
<th>Rf</th>
<th>Nitrogen% *</th>
<th>ir (cm⁻¹) **</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVa</td>
<td>NO₂</td>
<td>93</td>
<td>red</td>
<td>302</td>
<td>0.41*</td>
<td>21.00</td>
<td>21.05</td>
</tr>
<tr>
<td>IVb</td>
<td>Cl</td>
<td>110</td>
<td>purple</td>
<td>285</td>
<td>0.40*</td>
<td>16.52</td>
<td>16.43</td>
</tr>
<tr>
<td>IVc</td>
<td>Br</td>
<td>133</td>
<td>brown</td>
<td>312</td>
<td>0.57*</td>
<td>13.90</td>
<td>14.00</td>
</tr>
<tr>
<td>IVd</td>
<td>NO₂</td>
<td>NO₂</td>
<td>brown</td>
<td>289</td>
<td>0.61*</td>
<td>22.27</td>
<td>22.50</td>
</tr>
<tr>
<td>IVe</td>
<td>Cl</td>
<td>Cl</td>
<td>red</td>
<td>290</td>
<td>0.40*</td>
<td>14.67</td>
<td>14.48</td>
</tr>
<tr>
<td>IVf</td>
<td>H</td>
<td>SO₃H</td>
<td>red</td>
<td>285</td>
<td>0.62c</td>
<td>13.65</td>
<td>13.95</td>
</tr>
<tr>
<td>IVg</td>
<td>NO₂</td>
<td>Cl</td>
<td>brownish</td>
<td>298</td>
<td>0.55b</td>
<td>18.33</td>
<td>18.63</td>
</tr>
<tr>
<td>IVh</td>
<td>H</td>
<td>CH₃</td>
<td>118</td>
<td>298</td>
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<td>17.66</td>
<td>17.87</td>
</tr>
</tbody>
</table>

* uncorrected, determined by open capillaries, ** solvent, ethanol

eluent, a:benzene-dioxan(3:1); b:ethanol; c:benzene-dioxan(8:2)

Nitrogen analysis carried out in Elemental Analyser Carbo Erba 1106 instrument.

characteristic of triazene frequency.

### TABLE IV.2
Physical and spectral characteristics of N-arylazopyrroles (IV')

![Structural formula of N-arylazopyrrole]

<table>
<thead>
<tr>
<th>Product</th>
<th>X= NO₂</th>
<th>Y= Cl</th>
<th>Z= H</th>
<th>m.p. * (°C)</th>
<th>Rf **</th>
<th>Y%</th>
<th>Nitrogen% ***</th>
<th>ir(cm⁻¹) ****</th>
<th>λmax*</th>
<th>'H-nmr</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVa'</td>
<td></td>
<td>Cl</td>
<td></td>
<td>57</td>
<td>0.77</td>
<td>52</td>
<td>22.18</td>
<td>22.35</td>
<td>1430</td>
<td>358</td>
</tr>
<tr>
<td>IVb'</td>
<td></td>
<td>NO₂</td>
<td></td>
<td>44</td>
<td>0.71</td>
<td>59</td>
<td>26.96</td>
<td>26.81</td>
<td>1423</td>
<td>364</td>
</tr>
<tr>
<td>IVc'</td>
<td></td>
<td>Cl</td>
<td></td>
<td>51-52</td>
<td>0.85</td>
<td>63</td>
<td>24.55</td>
<td>24.34</td>
<td>1437</td>
<td>360</td>
</tr>
<tr>
<td>IVd'</td>
<td></td>
<td>NO₂</td>
<td></td>
<td>45</td>
<td>0.85</td>
<td>50</td>
<td>17.59</td>
<td>17.50</td>
<td>1433</td>
<td>366</td>
</tr>
<tr>
<td>IVe'</td>
<td></td>
<td>Cl</td>
<td></td>
<td>42-43</td>
<td>0.85</td>
<td>68</td>
<td>24.33</td>
<td>24.34</td>
<td>1430</td>
<td>370</td>
</tr>
<tr>
<td>IVf'</td>
<td></td>
<td>CH₃</td>
<td></td>
<td>44</td>
<td>0.80</td>
<td>65</td>
<td>22.54</td>
<td>22.70</td>
<td>1436</td>
<td>358</td>
</tr>
</tbody>
</table>

* uncorrected, determined by open capillaries, ** eluent, benzene-ethyl acetate (7:3)

*** analysis carried out in Elemental analyser Carbo Erba 1106

**** characteristic of triazene frequency.
uv-vis spectra of compound IVa (in ethanol) showing absorption at 302nm.

uv-vis spectra of compound IVg (in ethanol) showing absorption at 298nm.
uv-vis spectra of compound IVa' (in ethanol) showing absorption at 358 nm.

uv-vis spectra of compound IVc' (in ethanol) showing absorption at 360 nm.
IR spectra of compound IVa in KBr, showing -OH str. at 1330 and 1500 cm\(^{-1}\), -N-H str. at 1400 cm\(^{-1}\) and showing the absence of N-H str. freq. of indole at 3400 cm\(^{-1}\).

IR spectra of compound IVh in KBr, showing -NH-N str. at 1422 cm\(^{-1}\) and absence of -NH str. of indole at 3400 cm\(^{-1}\).
$^1$H nmr spectra of compound IVa in 90 MHz instrument in Acetone-d$_6$ with TMS as internal standard (absence of a broad signal at 8.0-9.5 $\delta$, even at 5000 amplification, characteristic of N-H proton of indole)

$^1$H nmr spectra of compound IVh in 90 MHz instrument taking TMS as internal standard in acetone-d$_6$, broad signal at 9.4 $\delta$, absent at 2000 amplification (inset); characteristic of indole NH
uv-absorption spectra of compounds:

The uv-vis spectra of the compounds isolated were studied in a Hitachi U 3210 spectrophotometer in 95% v/v ethanol. Compounds showed λ max at around 300 nm for N-arylaizoindoles and 360 nm for N-arylaizopyrroles which were characteristic of the triazene (15).

Infrared spectra of compounds:

The ir spectra were taken in KBr pallets in a Perkin-Elmer 1600 FT IR spectrometer. The ir spectra have conclusively indicated the N-coupling of the diazonium ions. The free indole N-H stretching frequency appears in the region around 3400 cm⁻¹ and is fairly isolated and that for N-H in the case of pure pyrrole is similar. Substitution of the N-H proton should consequently be accompanied by the disappearance of the N-H stretching in the region mentioned. The ir spectra of the compounds obtained show the disappearance of the N-H stretching conclusively indicates the fact that substitution occurred at the 1-positions to give N-arylaizoindoles and N-arylaizopyrroles. Besides the absorption at around 1440-1430 cm⁻¹ indicate the presence of the triazene nitrogen triad (16).

¹H-nmr spectra:

In a similar fashion, ¹H-nmr spectra have also indicated that the coupling has occurred at the 1-positions of indole and pyrrole. The ¹H-nmr spectra of indole in acetone-d₆ showed a broad signal at 9.8 δ due to the N-H proton. The signal was observed to be absent in the ¹H-nmr spectra of the N-arylaizoindoles and broad and low intensity signal observed for pure pyrrole in DMSO-d₆ at c.a. 7.4 δ was found to be absent in the case of N-arylaizopyrroles. The absence of the N-H proton signal conclusively proves that diazocoupling reaction had taken place in the 1-positions of sodio indole and sodio pyrrole.

In conclusion it can be mentioned that ir and ¹H-nmr spectra were helpful in showing conclusively that the coupling of the diazonium ions occurred exclusively at the 1-position of sodio indole to give the N-arylaizoindole. Similarly, N-substitution of sodio pyrrole gives N-arylaizopyrroles.

CONCLUSION

From the study, it has been possible to emphasize the synthetic importance of resin immobilized diazonium ions. The method of carrying out diazocoupling reaction in the "solid phase" can be utilized to carry out the synthesis of N-arylaizoindoles/N-arylaizopyrroles which cannot be carried out otherwise in the homogeneous phase. Further, the products, N-arylaizoindoles and N-arylaizopyrroles are obtained as the only product of reaction.
IR spectra of compound IVc in KBr, showing characteristic \(-\text{NO}_2\)-str. at 1560 and 1360 cm\(^{-1}\) and \(-\text{N}-\text{N}-\text{N}\)-str. at 1423 cm\(^{-1}\).