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# Solid Phase Synthesis of N-arylazoindoles

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***Abstract :*** Diazonium ions have been immobilized onto an ion-exchange resin support and were subsequently reacted with sodioindole in dry tetrahydrofuran to give the N-arylazoindole. The solid phase diazocoupling reaction appears to be the only method for the preparation of the target molecules.
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## INTRODUCTION

Polymeric reagents and reagents immobilized on polymer supports have been extensively used in organic synthesis. Solid phase organic synthesis offers several advantages which includes easy work up, mild experimental conditions, high turnover of products. It also offers possibility of carrying out site specific reactions[1,2,3].

Diazonium ions have been immobilized onto an ion-exchange resin support and diazocoupling reactions in the solid phase have been carried out to synthesize the usual azo compounds[4] and the triazenes[5] In the 'solid phase' technique, diazocoupling reaction could be carried out in organic solvents in the absence of acids unlike the homogeneous phase diazocoupling reactions. The homogeneous phase diazocoupling reactions involves the generation of diazonium ions in aqueous solution by the action of $NaNO_2$ and HCl on an aromatic amine and the subsequent reaction of the diazonium ions with the substrate in an water-miscible organic solvent. The presence of $H^+$ ions in the reaction medium is at times a disadvantage specially when the substrate and/or the target compounds are acid labile.

Diazocoupling reaction of indole has been extensively studied. It has been reported that the homogeneous phase diazocoupling reaction of indole gives poor yield of the expected 3-arylazoindoles because of the autocatalytic side reactions and acid catalyzed decomposition of the 3-arylazoindoles[6-9]. However, it has been possible to synthesize the 3-arylazoindole in good yield by carrying out the diazocoupling reaction of indole in the 'solid phase', in organic solvents and in the absence of acids[10].

## DISCUSSION AND RESULTS

The technique of 'solid phase' diazocoupling reaction is here extended to the synthesis of the N-arylazoindoles. A variety of theoretical reactivity indices of indole indicates $C_3$-position to be the preferred site of electrophilic substitution [11,12]. Conversion of indole to metalloindole drastically alters the electron density pattern at different positions [13] as shown in Figure I .

**FIGURE I**

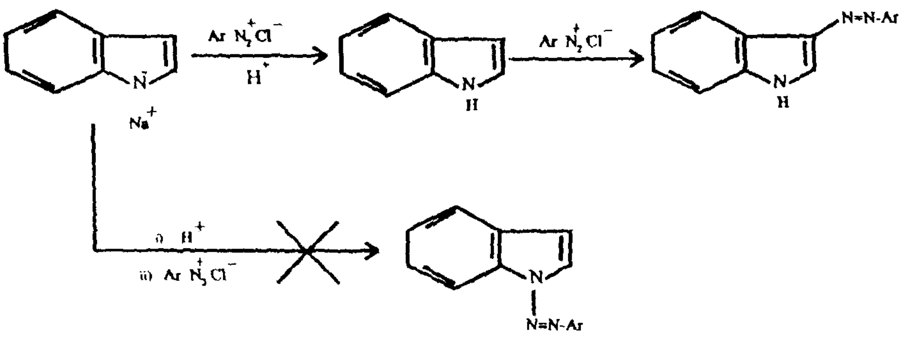
Electron density at $N_1$,$C_2$ & $C_3$ of indole

Electron density at $N_1$, $C_2$ & $C_3$ of indolyl anion

In metalloindoles, the electron density is found to be the highest at $N_1$ , and this position is, therefore, the preferred site of attack by an electrophile. Electrophilic substitution on metalloindoles was studied and the results indicated the presence of both $C_3$ - and $N_1$ -substituted products. The indolyl moiety is an ambident anion and regioselectivity of an electrophilic substitution reaction on sodioindole is found to be dependent on both the solvent and the metal counterion [13].

In the present study , the diazocoupling reaction of sodioindole was carried out in the homogeneous phase by adding an acidic (aqueous HCl) solution of diazonium ions to sodioindole in anhydrous tetrahydrofuran(THF). Contrary to expectation , the N-arylazoindoles were not obtained at all and instead 3-arylazoindoles were obtained in small amounts besides other by products. This observation can be rationalized by the fact that in the homogeneous phase diazocoupling reaction of sodioindole, the $H^+$ ions in the reaction medium attacks the $N_1$ - position in preference to the weakly electrophilic diazonium ions giving back indole which subsequently undergoes diazocoupling reaction at the $C_3$-position (Scheme1).

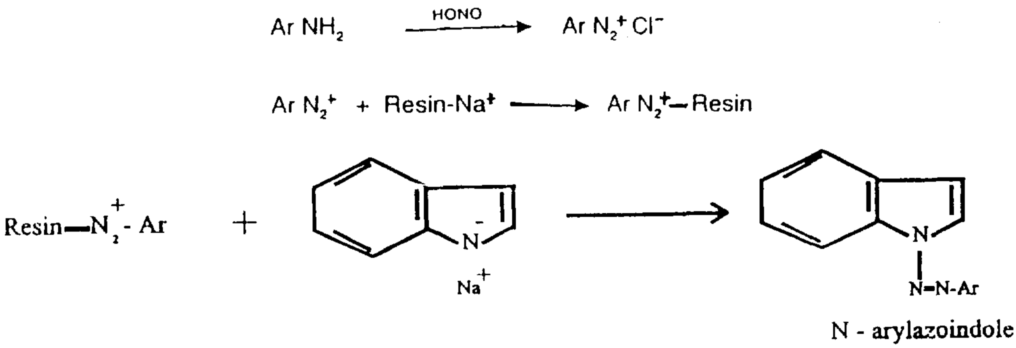
**SCHEME 1**



Homogeneous phase diazocoupling reaction of sodio indole

In order to carry out diazocoupling reaction of sodioindole in the absence of $H^+$ ions, the reaction was carried out in the ' solid phase ' using resin immobilized diazonium ions. In a typical run, a solution of sodioindole in dry THF was added to resin immobilized diazonium ions with constant stirring, at room temperature and under an atmosphere of nitrogen. The reaction was performed in the absence of $H^+$ ions and diazonium ions being the only electrophile present in the reaction medium and being a weak electrophile, exclusively attacked the electron dense $N_1$ -position to give only the N-arylazoindoles. $N_1$ -coupling 'solid phase ' diazocoupling reaction appears to be the only method for the synthesis of N -arylazoindoles (Scheme 2). Physical and spectral characteristics of the products isolated are given in Table 1 .

SCHEME 2

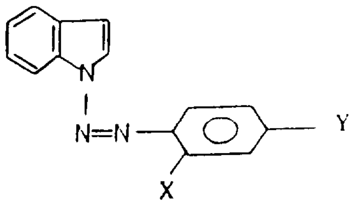


N-coupling in indole using resin immobilized diazonium ions

The uv spectra of the compounds in 95% ethanol recorded in a Hitachi U3210 spectrophotometer showed $\lambda_{max}$ at around 300 nm characteristics of cyclic-acyclic triazenes[14]. The ir spectra in KBr pallets taken in Perkin-Elmer 1600 FT-IR spectrophotometer showed the absence of N-H stretching frequency at 3400 $cm^{-1}$. Absence of this absorption indicates reaction to have taken place at the $N_1$-position of indole, another absorption at around 1430 $cm^{-1}$ indicates the presence of the triazene nitrogen triad[15]. The $^1H$ nmr spectra of indole in acetone $d_6$ shows a broad N-H signal at 9.8 $\delta$ and the proton at $C_3$ appears at 6.2 $\delta$ . In the N-arylazoindoles obtained, $^1H$ nmr in acetone $d_6$ showed the absence of the signal at 9.8 $\delta$ but $C_3$ proton appeared at 6.4-6.5 $\delta$ indicating that reaction occurred at $N_1$ -position and not at the $C_3$ -position . $^1H$ nmr were recorded in 90MHz instrument taking TMS as an internal standard and elemental analysis were carried out in Carbo Erba 1106 instrument.

## TABLE I

***Physical and spectral properties of N-arylazoindoles (1)***



| Product | X | Y | m.p.* (°C) | colour | $\lambda_{max}$** (nm) | Rf *** | Nitrogen% $^{i}$ found | Nitrogen% $^{i}$ Calc. | ir$^{ii}$ (cm$^{-1}$) |
|---|---|---|---|---|---|---|---|---|---|
| **1a** | H | $NO_2$ | 93 | red | 302 | 0.14$^{a}$ | 21.00 | 21.05 | 1400 |
| **1b** | H | Cl | 110 | purple | 285 | 0.40$^{a}$ | 16.52 | 16.43 | 1418 |
| **1c** | H | Br | 133 | brown | 312 | 0.57$^{b}$ | 13.90 | 14.00 | 1417 |
| **1d** | $NO_2$ | $NO_2$ | 158 | brown | 289 | 0.61$^{a}$ | 22.27 | 22.50 | 1414 |
| **1e** | Cl | Cl | 120 | red | 290 | 0.40$^{a}$ | 14.67 | 14.48 | 1418 |
| **1f** | H | $SO_3H$ | 109 | red | 285 | 0.62$^{c}$ | 13.65 | 13.95 | 1416 |
| **1g** | $NO_2$ | Cl | 98 | brownish | 298 | 0.55$^{b}$ | 18.33 | 18.63 | 1410 |
| **1h** | H | $CH_3$ | 118 | red | 298 | 0.62$^{c}$ | 17.66 | 17.87 | 1422 |

* determined in open capillaries, uncorrected

** solvent, ethanol

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

*i* nitrogen analysis carried out in Elemental Analyser Carbo Erba 1106 instrument.

*ii* characteristic of triazene frequency.

## EXPERIMENTAL

Aromatic amines, indole were purified before use. Amberlite - IR-120 ($Na^+$ form), macroporous type according to Rohm & Haas specification with type analysis $SO_3^=$ , 20-50 mesh , $Na^+$ form , styrene-DVB 8% was choosen as the cation exchanger. The resin was washed several times with deionized water before use. THF was dried according to established procedure.

### *1. Immobilization of diazonium ions onto cation exchanger*

Aromatic amine (0.01 mole) was dissolved in 50 mL of conc. HCl and diazotized with a solution of sodium nitrite at 0-5°C . The diazonium salt solution was filtered through Celite-545 filter aid and the filtrate passed through a column slurry packed with 15 gms of the cation exchanger, Amberlite-IR-120 ($Na^+$ form) at the rate of 2mL/min. The resin was recovered and washed several times with distilled water till free of diazonium ions (alkaline β -naphthol test). The loaded resin was then dried over $P_2O_5$ at 50°C under reduced pressure ( 50 mm Hg).

The dried resin was analyzed for diazonium ion content by reductometric titration procedure using 57% hydroiodic acid [16,17] where the liberated iodine was titrated with sodium thiosulphate solution using starch as indicator. The average capacity was found to be 2.4 m. mol of $ArN^+_2$/gm of the resin. This experiment was done with the diazonium ions obtained from p-toluidine and may be taken as representative. The dry resin was stored at room temperature and diazonium ion capacity was found to remain constant over a period of 12 weeks. Immobilization of diazonium ions on cation exchange resin is in fact an excellent procedure for their stabilization.

### 2. *Preparation of sodioindole* [18,19]

A solution of 5 gms (0.043 mole) of indole in 30 mL of anhydrous THF was slowly added to a suspension of 2.05 gms of NaH (previously washed with petroleum ether, 60-80 ) in 30 mL of anhydrous THF. The mixture was refluxed for 1 hour. The sodioindole thus obtained was used immediately.

### 3. *General procedure for the synthesis of N-arylazoindole*

20 mL of the above solution of sodioindole was added dropwise with constant stirring to 10 gms of resin immobilized diazonium ions under nitrogen atmosphere and at room temperature. Immediate change in colour of the resin beads to dark red indicated that the reaction had taken place instantaneously. The mixture was stirred for further 30 minutes. The resin beads were recovered, dried and extracted with 95% ethanol in a soxhlet extraction apparatus to separate out the product from the beads. Removal of the solvent under reduced pressure gave the N-arylazoindoles as coloured solids. TLC on prepared silica gel H plates with the appropriate eluent gave only one spot indicating the formation of only one product.

## CONCLUSION

The study establishes the fact that 'solid phase' diazocoupling reaction of sodioindole is $N_1$-substitution regiospecific and gives the N-arylazoindoles whereas the homogeneous phase diazocoupling reaction fails to give the desired products.

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