DIRECT AMINATION. Part 4.[1] REACTIONS OF INDOLES WITH PRIMARY AROMATIC AMINES AND IODOSOBENZENE DIACETATE

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Abstract - Indole, 2-methylindole, 2-phenylindole, and primary aromatic amines react with iodosobenzene diacetate leading both to 2-arylamino-3-arylimino-3*H*-indole in the case of indole and 2-methylindole, and to 2-phenyl-3-arylimino-3*H*-indole in the case of 2-phenylindole. The reaction is believed to proceed through the formation of a nitrenium ion formed by the interaction of iodosobenzene diacetate and primary aromatic amines and the mechanism is supported by experimental evidences. The methyl elimination from 2-methylindole is explained on the basis of the isolation of the possible intermediate and the formation of an aminal, whose decomposition leads to the reaction products. The intermediate aminal is proposed on the basis of the bis-(2-methylindol-3-yl)methane formation.

Direct amination of aromatic substrates has been obtained by hydrazoic acid in the presence of $AlCl_3$ or H_2SO_4.[2] Tertiary aromatic amines were synthesized by reacting aromatic hydrocarbons with dialkylamino radical cations originated in acidic medium by treating *N*-chlorodialkylamines with metal cations in their

lowest oxidation state.[3] Secondary aromatic amines have been obtained by treatment of activated aromatic hydrocarbons with arylazides[4] or with arylhydroxylamines in the presence of acids.[5]

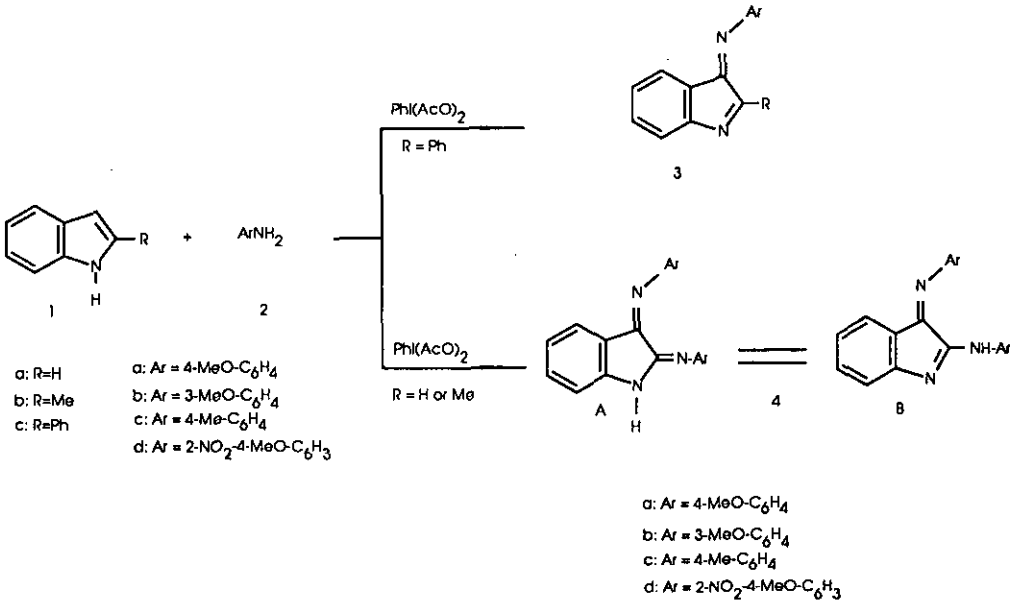
No examples of direct amination by primary aromatic amines forming secondary amines have been reported in the literature. Recently we have described the arylamination of indoles by reacting them with primary aromatic amines and either lead tetraacetate, *N*-chlorobenzotriazole, or *N*-chloroisatine.[1,6]

In this paper we report the results obtained working with iodosobenzene diacetate. The use of this reagent has been suggested by its oxidative peculiarities,[7] and by the need to obtain further information in order to understand the reaction product formation between indoles and primary aromatic amines, and first of all the demethylation of 2-methylindole.

RESULTS

Indoles (**1a-c**) and primary aromatic amines were added to iodosobenzene diacetate in $CHCl_3$ at room temperature using the reagents in 1:1:1.5 (in the case of 2-phenylindole (**2c**) and 1:1:3 (in the cases of indole (**2a**) and 2-methylindole (**2b**)) molar ratio, respectively. The reaction products were compounds (**3**) or (**4**), depending on the starting indole. (Scheme 1)

Scheme 1



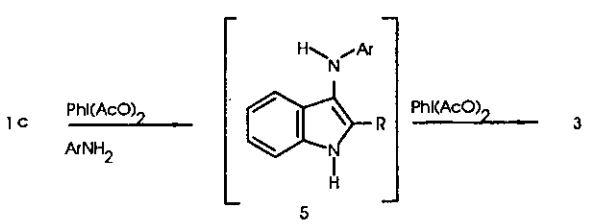
Compounds (**3**) were isolated starting from 2-phenylindole (**1c**), whereas compounds (**4**) were obtained from indoles (**1a**) and (**1b**). In the reaction of 2-methylindole (**1b**), bis-(2-methylindol-3-yl)methane (**12**) was also isolated in traces. Products (**3**) and (**4**) were isolated in 22-45% yields. When the reaction of 2-methylindole (**1b**) with *p*-toluidine (**2c**) and iodosobenzene diacetate was performed with 1:2:6 molar ratio, no improvement in **4c** yield was observed; on this basis we did not look further for the best reagents ratio. Compounds (**3a**),[8] (**3c**)[8] and (**3d**)[6] were identified by comparison with authentic samples. Compound (**3c**) showed ^{1}H nmr (δ, ppm) and ir (ν, cm^{-1}) spectra similar to those obtained for compound (**3b**). In fact all these compounds show in their ^{1}H nmr spectrum a multiplet at δ ca 8.3-8.5 due to the *ortho* hydrogens of the phenyl group at C-2, and in their ir (ν, cm^{-1}) spectrum absorptions at *ca.* 1640 cm^{-1}, typical of the indolenine system. [8]

Compounds (**4a**) and (**4c**) were also identified by comparison with authentic samples, whereas **4b** and **4d** were identified by comparing their ^{1}H nmr (δ, ppm) and ir (ν, cm^{-1}) spectra with those of **4a** and **4c**. Ir data show absorptions at 3340-25 (NH), 1675-50 (C=N in the position 3) and 1650-30 (C=N in the position 2) cm^{-1}. The di-indolylmethane (**12**) was identified by comparison with a sample obtained by an independent way and examined by X-ray analysis.

DISCUSSION

The concept of direct amination is justified by the fact that the first product formed is the intermediate (**5**), which is easily oxidized[8] to compound (**3**) in the reaction medium according to Scheme 2. In fact, in an independent experiment, the intermediate (**5**) was quantitatively transformed into **3** by iodosobenzene diacetate. (see experimental)

Scheme 2



5

Compounds (**5**) were never detected owing to their low oxidation potentials,[9] which justify their conversion to **3**. The formation of compounds (5) could be explained by the interaction of the amino radical cation formed by oxidation of primary aromatic amines with iodosobenzene diacetate. However, this route may be

discarded since amino radical cations of primary aromatic amines originated by anodic oxidation in the presence of indoles do not afford compounds (**3**) and (**4**).[6]

$$ArNH_2 + PhI(AcO)_2 \longrightarrow \overset{+\cdot}{ArNH_2} + PhI + AcO^- + Me^{\cdot} + CO_2 \quad (1)$$

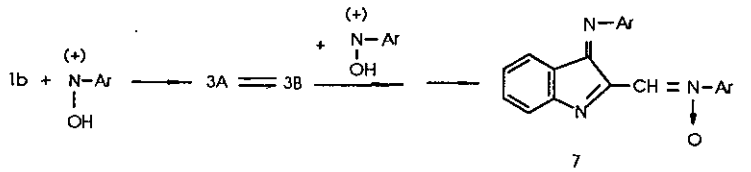
$$\overset{+\cdot}{ArNH_2} + AcO^- + Me^{\cdot} \longrightarrow ArNHOAc + MeH \quad (2)$$

$$ArNHOAc \longrightarrow \overset{+}{Ar\text{-}N\text{-}H} + AcO^- \quad (3)$$

$$Ar\text{-}NO + H^+ \longrightarrow \overset{+}{Ar\text{-}N\text{-}OH} \quad (4)$$

Taking into account the literature reports[10] we suppose that the operating species is a nitrenium ion formed as pointed out in eqs. 1-3. This supposition is also supported by the fact that nitroso compounds in the presence of acids give, with 2-methylindole (**1b**), compound (**7**) involving the nitrenium ion as shown in eq. 4 and in Scheme 3.

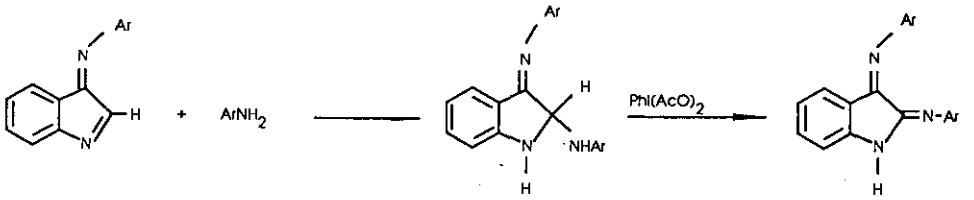
Scheme 3



Our experimental results on the reactivity of activated nitrosoarenes and the literature data[11-14] seem to agree with our proposal on the formation of a nitrenium ion as shown in eq. 3.

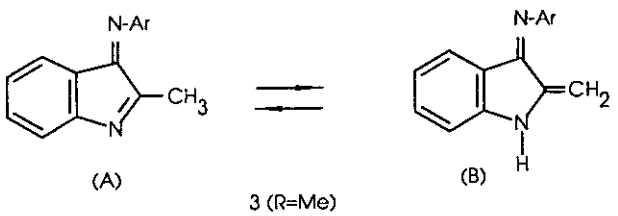
Starting from indoles (**1a**) and (**1b**), compounds (**3**) may be regarded as intermediates to **4**. In addition, starting from **1a**, compounds (**3**) could be transformed into **4** by nucleophilic addition of primary aromatic amines to the indolenine system leading to **6**, according to Scheme 4 and the literature reports,[15,16] which could be likely oxidized to compound (**4**) in the reaction medium.

Scheme 4



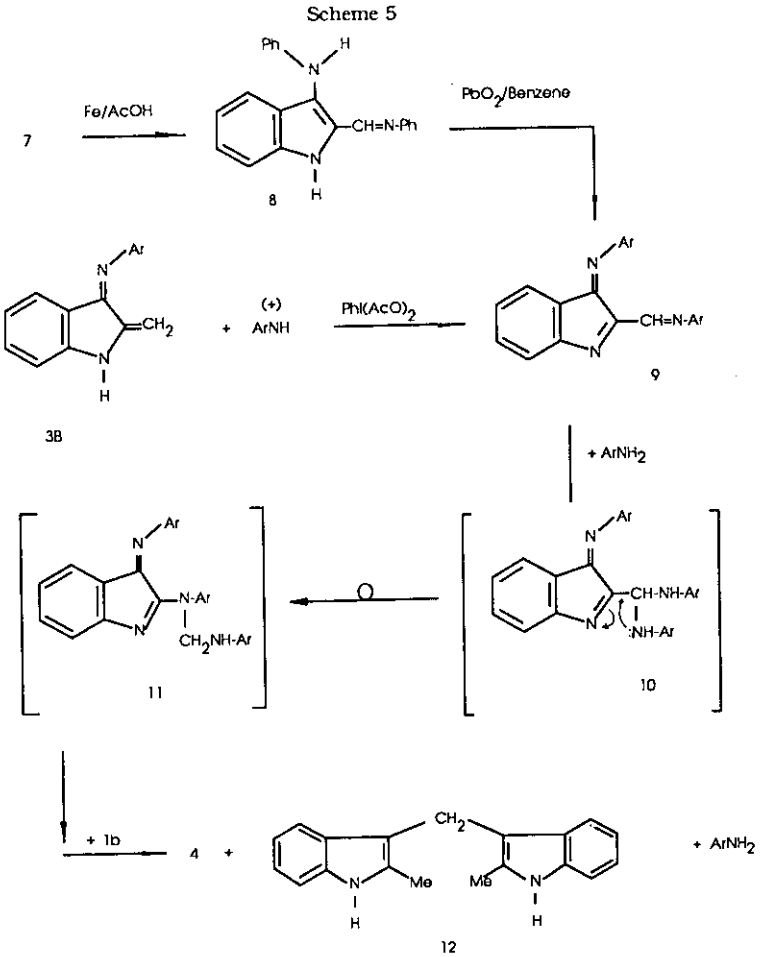
The substitution of the methyl group from C-2 in the case of 2-methyl-3-aryliminoindolenine (**3**; R=Me) involves a more complicated mechanism for which we obtained some experimental evidence.

It is well known that the 2-methylindolenine (**3**; R=Me) gives rise to the following tautomeric equilibrium:[17]



The tautomeric form B contains an enamine function which can further react with another molecule of nitrenium ion forming compound (**9**) as described in Scheme 5.

Scheme 5



The mechanism, reported in Scheme 5 to explain the formation of compounds (**4**), is supported by the fact that compound (**9**) could react with another molecule of aromatic amine affording compound (**4**) through the aminal (**10**)[18] and its evolution as shown in Scheme 5. Compound (**9**; Ar=Ph) was prepared from **8** by iron/acetic acid reduction and oxidation of the reaction product with PbO_2 in benzene; but, even though we had the comparison we were unable to identify intermediate (**9**) in the reaction medium probably owing to its high reactivity towards primary aromatic amines. From the mechanistic point of view, since amino radical cations do not react with indoles forming compounds (**3**) and (**4**) and nitrosoarenes activated by acids lead to the formation of compounds (**3**) and (**4**), it may be concluded that the reacting species is a nitrenium ion rather than a nitrene.[19] Even if we did not succeed in identifying the intermediate (**9**) in the reaction mixture, having demostrated that it reacts leading to the formation of compound (**4**) as reported in Scheme 5, may be considered satisfactory. In fact, a molecule of primary aromatic amine may add to the $\geq C{=}N-$ exocyclic double bond to form the intermediate (**10**). Subsequent rearrangement of **10** to **11** could occur through the formation of an aziridine which then rearranges under the reaction conditions leading to the aminal (**11**). This decomposes to form **4**, the corresponding aniline and formaldehyde. This latter compound could be considered the responsible species forming **12** with the starting indole (**1b**). The reaction of indole (**1b**) with formaldehyde to give the di-indolylmethane (**12**) is reported in the experimental section, even though such a reaction was already known.[20]

The complicated mechanism of the ipso-substitution of the C-2 methyl group on compound (**3**; R=Me) reported in Scheme 5 is justified first by the fact that the supposed intermediate (**9**) reacts with primary aromatic amine leading to the formation of compounds (**4**) and secondly by the fact that the di-indolylmethane (**12**) may be explained only by admitting the presence of formaldehyde, which could be likely formed in the decomposition of the proposed aminal (**11**). We were unable to give no other explanation involving the intermediate formation of formaldehyde.

In general, these reactions are not clean involving the formation of non identified products. Thus, the formation of iodonium salts as reported in the literature[21-22] cannot be excluded, even if no evidences were obtained in this way.

EXPERIMENTAL

Melting points were measured on an Electrothermal Melting Point Apparatus and are uncorrected. Ir spectra were recorded using a Nicolet Fourier Transform Infrared 20-SX Spectrophotometer equipped with a Spec.

Tech "DRIFT" Collector (1% of sample in KBr). ^{1}H Nmr (δ, ppm) spectra were recorded in $CDCl_3$ on a Varian Gemini 200 at 200 MHz and chemical shifts were reported downfield from TMS. Mass spectra were recorded on a Carlo Erba QMD 1000 spectrometer. Indoles and aromatic amines were Fluka and Aldrich commercial products. All solvents were Fluka RP-ACS grade.

Reaction of **1a-b** *with* **2a-d** *and iodosobenzene diacetate* (1:1:3).- Iodosobenzene diacetate (966 mg, 2 mmol) was added dropwise at room temperature and under stirring to a solution of indole (**1a-b**; 0.66 mmol) and amine (**2a-b**; 0.66 mmol) in chloroform (5 ml). After 3 h the brown reaction mixture was shaken with 10% aqueous $NaHCO_3$ (15 ml) and extracted with benzene (2 x 20 ml). The organic layer was dried (Na_2SO_4), evaporated to a small volume and then chromatographed on silica gel (cyclohexane/ethyl acetate from 9:1 to 8:2 ratio as eluant). From the red fraction, compounds (**4a-d**) were isolated.

2,3-bis(4'-methoxyphenylimino)-2H-indole **4a**.- (64 mg, 27%*): mp 166 °C (lit., [1] 166 °C).

2,3-bis(3'-methoxyphenylimino)-2H-indole **4b**.- (59 mg, 25%*): mp 170 °C from ethanol (Found: C, 73.2; H, 5.1; N, 11.9. $C_{22}H_{19}N_3O_2$ requires C, 73.9; H, 5.4; N, 11.8); δ_H 3.8 (3 H, s, OCH_3), 3.9 (3 H, s, OCH_3), 6.6 (6 H, m, ArH), 7.27 (6 H, m, ArH), 7.9 (1 H, br s, NH); ν, cm^{-1} 3297, 1660, 1640; m/z 219 (15), 326 (100) and 357 (44, M^+).

2,3-bis(4'-tolylimino)-2H-indole **4c**.- (75 mg, 35% *): mp 173-5 °C (lit., [1] 175 °C).

2,3-bis(2'-nitro-4'methoxyphenylimino)-2H-indole **4d**.- (88 mg, 30%*): mp 191 °C (Found: C, 59.4; H, 4.1; N, 15.3. $C_{22}H_{17}N_5O_6$ requires C, 59.0; H, 3.8; N, 15.7); δ_H 3.9 (3 H, s, OCH_3), 3.95 (3 H, s, OCH_3), 6.7 (2 H, m, ArH), 7.05 (1 H, d, J 8.8 H_z, ArH), 7.25 (1 H, dd, J 8.8 and 2.8 H_z, ArH), 7.3 (2 H, m, ArH), 7.38 (2 H, dd, J 9.3 and 3.0 H_z, ArH), 7.75 (2 H, dd, J 8.8 and 2.8 H_z, ArH), 9.25 (0.57 H (B), broad, NH aminic), 11.15 (0.434 H (A), broad, NH indolic)**, ν, cm^{-1} 3267, 1658, 1620; m/z 429 (23), 401 (8), 355 (95), 281 (84) and 447 (13, M^+).

Reaction of **1c** *with* **2a-d** *and iodosobenzene diacetate* (1:1:1.5).- Iodosobenzene diacetate (966 mg, 3 mmol) was added dropwise at room temperature and under stirring to a solution containing indole (**1c**; 386 mg, 2 mmol) and amine (**2a-d**; 2 mmol) in chloroform (5 ml). After 2 h the brown-red solution was shaken with 10% aqueous $NaHCO_3$ (15 ml) and extracted with benzene (2 x 20 ml). The organic layer was dried (Na_2SO_4), evaporated to a small volume and then chromatographed on silica gel (cyclohexane/ethyl acetate from 9:1 to 8:2 ratio as eluant). From the red fraction, compounds (**3a-d**) were isolated and crystallized from ethanol. Compounds (**3a, 3c-d**) were identified by comparison with authentic samples.

*Evaluated with respect to the starting indole.

** Compound (**4d**) is an equilibrium of two tautomeric forms (A and B) as shown in Scheme 1.

2-Phenyl-3-(4'-methoxyphenylimino)-3H-indole **3a.**- (218 mg; 35% yield): mp 166-8 °C (lit., [8] 169 °C).

2-Phenyl-3-(3'-methoxyphenylimino)indoline **3b.**- (137 mg, 22%) : mp 150 °C from ethanol (Found: C, 80.9; H, 5.3; N, 9.1. $C_{21}H_{16}N_2O$ requires C, 80.7; H, 5.2; N, 9.0); δ_H 3.9 (3 H, s, OCH_3), 7.3 (11 H, m, ArH), 8.4 (2 H, broad, m, ArH); ν, cm^{-1} 1675, 1576; m/z 191 (100), 297 (15), 312 (35, M^+).

2-Phenyl-3-(4'-tolylimino)-3H-indole **3c.**- (237 mg, 40%): mp 148 °C (lit.,[8] 148 °C).

2-Phenyl-3-(2'-nitro-4'-methoxyphenylimino)-3H-indole **3d.**- (321 mg, 45%): mp 193 °C (lit., [6] 193 °C).

Oxidation of 2-phenyl-3-phenylaminoindole **5** *with iodosobenzene diacetate*- A solution of the iodosobenzene diacetate (15 mg, 0.046 mmol) in CH_2Cl_2 (5 ml) was added at room temperature to a solution containing 2-phenyl-3-arylaminoindole (7 mg, 0.024 mmol) in CH_2Cl_2 (10 ml). After a few minutes the solution mixture became yellow-orange and 2-phenyl-3-phenylimino-3*H*-indole (**3**) was isolated by preparative tlc: mp 156 °C (ethanol) (lit., [8] 156 °C).

Reduction of 2-(phenyliminocarboxaldehyde-N-oxide)-3-phenylimino-3H-indole **7** *with iron and acetic acid*- To a solution of **7** (324 mg, 1 mmol) in acetic acid (10 ml), iron (112 mg; 2 mmol) was added under stirring at room temperature. After 2 h the colour turned from orange to red-brown. The reaction mixture was then filtered, the filtrate was neutralized with 10% aqueous sodium carbonate and extracted with benzene. The organic layer was dried (Na_2SO_4) and evaporated under vacuum. The residue was chromatographed on silica gel (cyclohexane/ethyl acetate from 9:1 to 8:2 ratio as eluant). The main fraction was constituted by 2-phenyliminocarboxaldehyde-3-phenylaminoindole (**8**) (148 mg, 48%): mp 177-80 °C (Found: C, 80.8; H, 5.6; N, 13.3.$C_{21}H_{17}N_3$ requires C, 81.0; H, 5.5; N, 13.5); δ_H 5.59 (1 H, broad, NH aminic), 6.83 (3 H, m, ArH), 7.05 (2 H, ddd, J 1.3, 6.7 and 8.0 H_z), 7.3 (9 H, m, ArH), 8.6 (1 H, s, -CH=N-Ph), 8.9 (1 H, broad, NH indolic); ν, cm^{-1} 3333 (NH_{exo}), 3309 (NH_{endo}), 1579 (CH=N); m/z 215 (33), 269 (52) and 311 (100, M^+).

Oxidation of **8** *with lead dioxide and further reaction with aniline*- To a solution of **8** (308 mg, 1 mmol), in benzene (10 ml), lead dioxide (717 mg, 3 mmol) was added at room temperature under stirring. The solution was stirred for an additional hour and then filtered off. Aniline (140 mg, 1.5 mmol) dissolved in benzene (2 ml) was added to the filtrate and the solution was left standing for 1 h at room temperature. The reaction mixture was evaporated under vacuum to give, after crystallization from ethanol, the dianil (**4**; 119 mg, 40%): mp 220 °C (Found: C, 80.8; H, 4.7; N, 14.0. $C_{20}H_{14}N_3$ requires C, 81.0; H, 4.8; N, 14.2); m/z 193, 208, 221, 296, 297 (M^+). [1]

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