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DESIGN, SYNTHESIS OF NEW INDOLES BY INTRAMOLECULAR CYCLIZATION OF BENZYLIDENE HYDRAZONE DERIVATIVES

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ABSTRACT

Indoles are essential compounds due to their wide biological and pharmacological applications. Here, we describe the synthesis of indoles by intramolecular cyclization of benzylidene hydrazone derivatives following the method of Meth-Cohn and Sushitzky. These compounds were obtained by first designing benzylidene hydrazone derivatives (3a-c) by condensation reaction of N-substituted aldehydes (2a-c) with tosylhydrazine. N-substituted aldehydes (2a-c) were obtained by the action of cyclic amine on 2-chloro-5-nitrobenzaldehyde (1). Finally, sodium methanoate reacts on benzylidene hydrazones (3a-c) under ethanol reflux and led to the indoles (4a-c). The structures of these compounds were determined by ^{1}H, ^{13}C Nuclear Magnetic Resonance (NMR) spectroscopy, and High-Resolution Mass Spectrometry (HRMS) analysis. The structure of compound 4b was determined by X-ray crystallography.

KEYWORDS

Indoles, Benzylidene hydrazone, Intramolecular cyclization and X-ray crystallography.

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INTRODUCTON

Indole chemistry began in the mid-19th century with extensive studies on the natural dye indigo, whose structure was determined by Baeyer in 1866[1]. Many biologically active natural products contain an indole or indoline scaffold. These compounds are important sources of pharmaceuticals. Molecules such as the antihypertensive drug reserpine, the

anticancer drug vincristine, and the neurotransmitter serotonin, contain these heterocycles in their structures. Indole derivatives possess a variety of therapeutic properties such as oxidative[2-6], antibacterial[7-12], anticancer[13-18], antiviral including anti-HIV[19-26] and anti-inflammatory activity[27-30]. These wide range of biological and pharmacological applications of indoles motivate us to synthesize new indole derivatives. Hence, various synthetic routes exist to prepare indoles, both intramolecular and intermolecular[31-33]. Therefore, we realize the synthesis of new indoles by designing an intramolecular cyclization of benzylidene hydrazone derivatives from functionalized aromatic aldehydes.

MATERIAL AND METHODS

Material

The solvents and reagents were purchased with any other purifications from Aldrich Chemical or Fischer Scientific (France). The reactions were followed by TLC on pre-coated Merck 60 F254 silica gel plates and revealed using a UV lamp (6 W, 254nm, and/or 365nm). The purification of the products was carried out on a Merck G60 silica gel column. Melting points (m.p °C) were determined using a temperature gradient (40-265°C) Kofler bench. For all compounds, the Nuclear Magnetic Resonance (NMR) spectra of proton ^{1}H and carbon ^{13}C were recorded on a Brucker 300 advance device. Tetramethylsilane (TMS) was used as a reference for chemical displacements expressed in ppm. The NMR spectra description uses the following symbols: s (singlet), d (doublet), dd (double doublet), q (quadruplet), m (multiplet), br (broad). The mass spectra were recorded on a JEOL JMS DX300 spectrometer in ESI mode (electrospray/quadripolar ionization or ESI mass).

Methods

General method for the synthesis of N-substituted 5-nitrobenzaldehyde 2a-c

To 2-chloro-5-nitrobenzaldehyde (1**)** (1 eq, 43mmol) dissolved in 120mL of distilled ethanol were added cyclic amine pyrrolidine, piperidine and morpholine (1.5 eq, 64.5mmol) and sodium hydrogencarbonate (1.5 eq, 64.5mmol). The mixture was allowed to stay under reflux of ethanol for 24 hours. After cooling, the mixture was poured into 150mL of dichloromethane, and washed with water (2 x 50mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: dichloromethane / hexane: 40/60).

5-nitro-2-pyrrolidin-1-yl-benzaldehyde 2a

Yellow crystals, yield = 86 %, m.p = 138-140°C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 10.00 (s, 1H, CHO), 8.15 (dd, 1H, H_{Ar}, J = 2.7 Hz, J = 9.3 Hz), 6.79 (d, 1H, H_{Ar}, J = 9.3 Hz), 3.46-3.42 (m, 4H, 2 NCH_2), 2.15- 2.05 (m, 4H, 2 CH_2). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 187.85, 151.82, 136.74, 131.32, 128.69, 120.87, 114.29, 50.39, 25.17 HRMS (ESI) Calc. for $C_{11}H_{13}N_2O_3$ ($M+H^+$) = 221.093 Found = 221.095.

5-nitro-2-piperidin-1-yl-benzaldehyde 2b

Yellow crystals, yield = 82 %, m.p = 114-116°C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 10.03 (s, 1H, CHO), 8.60 (d,1H, H_{Ar}, J = 2.7 Hz), 8.26 (dd, 1H, H_{Ar}, J = 2.7 Hz, J = 9.3 Hz), 7.06 (d, 1H, H_{Ar}, J = 9.3 Hz), 3.30-3.27 (m, 4H, 2 NCH_2), 1.81-1.66 (m, 6H, 3 CH_2). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 188.58, 158.98, 140.28, 129.17, 127.67, 125.68, 118.18, 54.63, 25.85, 23.74 HRMS (ESI) Calc. for $C_{12}H_{15}N_2O_3$ ($M+H^+$) = 235.108 Found = 235.110.

2-morpholin-4-yl-5-nitro benzaldehyde 2c

Yellow crystals, yield = 67 %, m.p = 118-120°C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 10.25 (s, 1H, CHO), 8.48 (d, 1H, H_{Ar}, J = 2,7 Hz), 8.30 (dd, 1H, HAr, J = 3 Hz, J = 9.3 Hz), 7.28 (d, 1H, H_{Ar}, J = 9Hz), 3.76-3.39 (m, 4H, 2 NCH_2), 3.33-3.30 (m, 4H, 2 OCH_2). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 188.98, 156.94, 139.43, 129.09, 128.56, 124.67, 118.67, 65.82, 52.47. HRMS (ESI) Calc. for $C_{11}H_{13}N_2O_4$ ($M+H^+$) = 237.088 Found = 237.091.

General method for the synthesis of arylhydrazones 3a-c

To arylhydrazone compounds (3a-c) (1 eq, 22mmol) suspended in 150mL of distilled ethanol, tosylhydrazine (1 eq, 22mmol) was added. The mixture was then allowed to stay under reflux of ethanol. After one hour, the mixture was cooled to

room temperature. The precipitate obtained was filtered and washed several times with ethanol. The crude was recrystallized in ethanol.

5-nitro-2-pyrrolidinobenzylidene paratoluene sulfonylhydrazone 3a

Yellow crystals, yield = 87%, m.p = 226-228°C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm) : 11.70 (brs, 1H, NH), 8.21 (d, 1H, H_{Ar}, J = 2.7Hz), 8.13 (dd, 1H, H_{Ar}, J= 2.7 Hz, J = 9 Hz), 7.98 (s, 1H, HC=N), 7.75 (d, 2H, H_{Ar}, J = 8.10 Hz), 7.42 (d, 2H, H_{Ar}, J = 7.8 Hz), 7.30 (d, 1H, H_{Ar}, J = 9 Hz), 3.39-3.76 (m, 4H, 2 NCH_2), 3.33-3.30 (m, 4H, 2 CH_2), 2.37 (s, 3H, CH_3). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm) : 156.94, 150.00, 140.09, 139.43, 129.56, 129.09, 128.80, 128.56, 124.67, 118.67, 116.67, 55.82, 28.47, 20.25. HRMS (ESI) Calc. for $C_{18}H_{21}N_4O_4S$ ($M+H^+$) = 389.128 Found = 389.131.

5-nitro-2-piperidinobenzylidene paratoluene sulfonylhydrazone 3b

Yellow crystals, yield = 82% (7.25g, 18.04mmol), m.p = 186-188°C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm) : 11.40 (brs,1H, NH), 8.21 (d, 1H, H_{Ar}, J = 2,7 Hz), 8.14 (dd,1H, H_4, J = 2.7 Hz, J = 9 Hz), 7.98 (s, 1H, HC=N), 7.73 (d, 2H, H_{Ar}, J = 8.4 Hz), 7.40 (d, 2H, H_{Ar}, J = 8.1 Hz), 7.13 (d, 1H, H_{Ar}, J = 9Hz), 2.68-2.92 (m, 4H, H_{Ar}), 2.35 (s, 3H, CH_3), 1.53-1.63 (m, 6H, 3 CH_2). NMR ^{13}C (DMSO d_6, 75 MHz) δ (ppm): 157.43, 143.95, 141.13, 139.43, 132.12, 130.56, 129.80, 128.67, 119.19, 116.67, 53.04, 29.30, 20.93, 23.24. HRMS (ESI) Calc. for $C_{19}H_{23}N_4O_4S$ ($M+H^+$) = 403.144 Found = 403.142.

2-morpholino-5-nitro benzilidene paratoluene sulfonylhydrazone 3c

Yellow crystals, yield = 80% (7.13g, 17.64mmol), m.p = 220-222°C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm) : 11.40 (s, 1H, NH), 8.22-8.24 (d, 1H, H_{Ar}, J =2.7 Hz), 8.11-8.16 (dd, 1H, H4, J = 2.7 Hz, J = 9 Hz), 8.02 (s, 1H, HC=N), 7.73 (d, 2H, H_{Ar}, J = 8.4 Hz), 7.40 (d, 2H, H_{Ar}, J = 9 Hz), 7.16 (d, 1H, H_3, J = 9 Hz), 3.70-3.72 (m, 4H, H_{Ar}), 2.93 (m, 4H, H_{Ar}), 2.35 (s, 3H, CH_3). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 156.25, 143.67, 140.13, 138.40, 130.15, 129.42, 128.56, 127.32, 126.60, 115.15, 110.29, 65.66, 52.03, 20.91. HRMS (ESI) Calc. for $C_{18}H_{21}N_4O_5S$ ($M+H^+$) = 405.123 Found = 405.125.

General method for the synthesis of tricyclic indolines 4a-c

To a mixture of MeONa (2.5 eq, 37.5mmol) in 25mL of dioxane, were added arylhydrazone derivatives 3a-c (1 eq, 15mmol) in small portions over 15 minutes. The mixture was stirred under reflux for 1 hour it magnetic stirring. After cooling, the reaction mixture was poured onto celite and then washed several times with acetone. The filtrate obtained was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate (90/10).

2, 3, 9, 9a-tetrahydro-7-nitro-1H-pyrrolo [1, 2-a] indole 4a

Yellow crystals, yield = 72%, m.p = 64-66°C. NMR ^{1}H ($CDCl_3$, 300 MHz) δ (ppm) : 8.03 (dd, 1H, H_{Ar}, J = 9 Hz, J = 2.1 Hz), 7.88-7.89 (d, 1H, H_{Ar}, J = 2.1 Hz), 6.42 (d, 1H, H_{Ar}, J = 8.7 Hz), 2.94-4.05 (m, 5H, 2 x CH_2, 1 CH), 1.30-1,50 (m, 4H, 2 x CH_2). NMR ^{13}C ($CDCl_3$, 75 MHz) □ (ppm) : 159.81, 139.72, 130.89, 126.08, 121.05, 107.79, 66.21, 49.70, 32.32, 31.73, 25.88. HRMS (ESI) Calc. for $C_{11}H_{13}N_2O_2$ ($M+H^+$) = 205.090 Found = 205.092.

6, 7, 8, 9, 9a, 10-hexahydro-2-nitropyrido [1, 2-a] indole 4b

Red crystals, yield = 80%, m.p = 120-122°C. NMR ^{1}H ($CDCl_3$, 300 MHz) δ (ppm) : 8.03 (dd, 1H, H_{Ar}, J = 9 Hz, J = 2.1 Hz), 7.84-7.85 (d, 1H, H_{Ar}, J = 2,1 Hz), 6.23 (d, 1H, H_{Ar}, J = 9 Hz), 2.63-3.62 (m, 5H, 2 x CH_2, 1 CH), 1.46-1.91 (m, 6H, 3 x CH_2). NMR ^{13}C ($CDCl_3$, 75 MHz) δ (ppm): 156.13, 137.49, 128.84, 126.74, 120.75, 102.76, 63.54, 43.92, 34.26, 31.73, 24.61, 23.78. HRMS (ESI) Calc. for $C_{12}H_{15}N_2O_2$ ($M+H^+$) = 219.106 Found = 219.109.

3, 4, 10, 10a-tetrahydro-8-nitro-1H-[1, 4]oxazino [4, 3-a]indole 4c

Red crystals, yield = 76%, m.p = 120-122°C. NMR ^{1}H ($CDCl_3$, 300 MHz) δ (ppm): 8.03 (dd, 1H, H_{Ar}, J = 9 Hz, J = 2.1 Hz), 7.88-7.89 (d, 1H, H_{Ar}, J = 2.1 Hz), 6.42 (d, 1H, H_{Ar}, J = 8.7 Hz), 2.94-4.05 (m, 5H, 2 x CH_2), 1.30-1.50 (m, 4H, 2 x CH_2). NMR ^{13}C ($CDCl_3$, 75 MHz) δ (ppm): 159.81, 139.72, 130.89, 126.08, 121.05, 107.79, 66.21, 49.70, 32.32,

31.73, 25.88. HRMS (ESI) Calc. for $C_{11}H_{13}N_2O_3$ ($M+H^+$) = 221.085 Found = 221.087.

RESULTS AND DISCUSSION

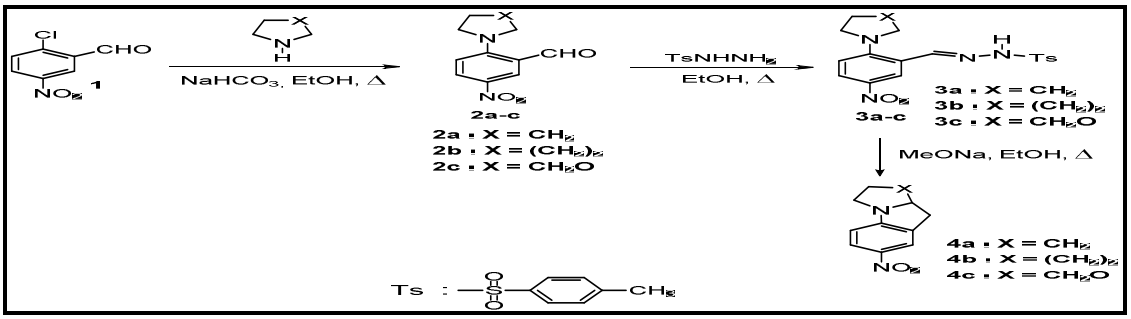
The indole derivatives (4a-c) were obtained *via* intramolecular cyclization of the hydrazones (3a-c). The precursors of these compounds, N-substituted aldehydes (2a-c), were previously obtained by an aromatic substitution reaction between 2-chloro-5-nitrobenzaldehyde (1) and various heterocyclic amines (morpholine, piperidine and pyrrolidine) in the presence of base ($NaHCO_3$) in yields ranging from 67% to 86%. Condensation of these N-substituted aldehydes with tosylhydrazine under refluxing of ethanol afforded to the hydrazones (3a-c) in yields between 80 and 87%. The action of sodium methanoate (MeONa) on these hydrazones led to the indole derivatives (4a-c) in 72-80% yields (Scheme No.1).

As shown in Scheme No.2, the MeONa used in the indole formation deprotonated the hydrazone, followed by loss of the tosylate group yielding to an intermediate A. It can then evolve through two ways: *via* a carbene pathway and/or a cationic pathway. The first route involves a similar mechanism as the Bamford-Stevens reaction[34] forming carbene B after diazo (N_2) elimination. A[1,5] hydrogen migration then leads to an indoline. In the second route, the[1,5] hydrogen migration is followed by diazo removal.

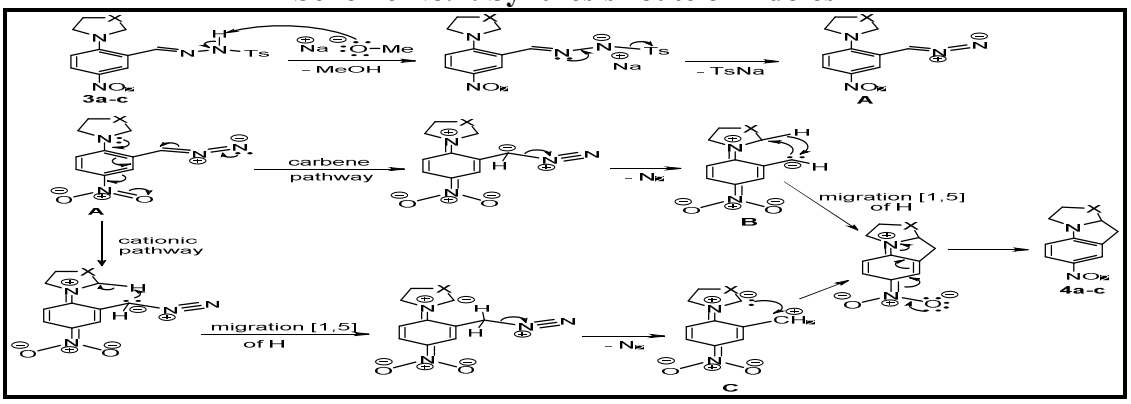
The structures of the various compounds were confirmed by ^1H, ^{13}C NMR spectroscopy, and HRMS analysis. Compounds 2a-c were characterized by the presence of pyrrolidine, piperidine, and morpholine scaffolds. The reason is due to the fact that these rings provide new chemical shifts compared to their precursor, 2-chloro-5-nitro benzaldehyde. Indeed, in the ^1H NMR spectra, we note the presence of signals between 1.70 - 3ppm, characteristic of the methylene protons of compounds 2a and 2b. Methylene linked to nitrogen are more deshielded and come out to about 3ppm. For compound 2c, the methylene protons linked to nitrogen appear around 3.3ppm and those bound to oxygen appear around 3.7ppm. Substrates 3a-c, were characterized by the presence of a hydrazone chain (-CH=N-NH-) and a methyl (CH_3) present on the tosyl group. The ^1H NMR spectra show a singlet around 8ppm characteristic of the imine proton (HC=N-). Another one appears around 11.40 to 11.70ppm characteristic of the NH proton and, finally one around 2.35ppm characteristic of methyl group.

Formation of indoles 4a-c (Figure No.1) was characterized in the ^1H NMR spectra by the disappearance of protons signals of the hydrazones chain (HC=N-NH-), around 8ppm for the HC=N-proton, and between 11.40 and 11.70ppm for the NH proton. We also note the disappearance of the methyl protons signal around 2.35ppm present in the tosyl group lost during the reaction. The characteristic methylene protons signal of the indole ring formed appear between 1.20 and 2ppm.

Compound 4b was subjected to crystallographic data. This study not only confirmed the structure of the compound but also showed the various arrangements of atoms in space[35]. This indicates that the molecule is not planar and the piperidine ring adopts a chair conformation (Figure No.1). This configuration therefore involves coupling of protons at axial and equatorial positions, which explains the presence of various peaks in the ^1H NMR spectra between 1.4 and 3.7ppm characteristic of the eleven non-aromatic protons of the tricycle.



Scheme No.1: Synthesis route of indoles



Scheme No.2: Mechanism of indole formation

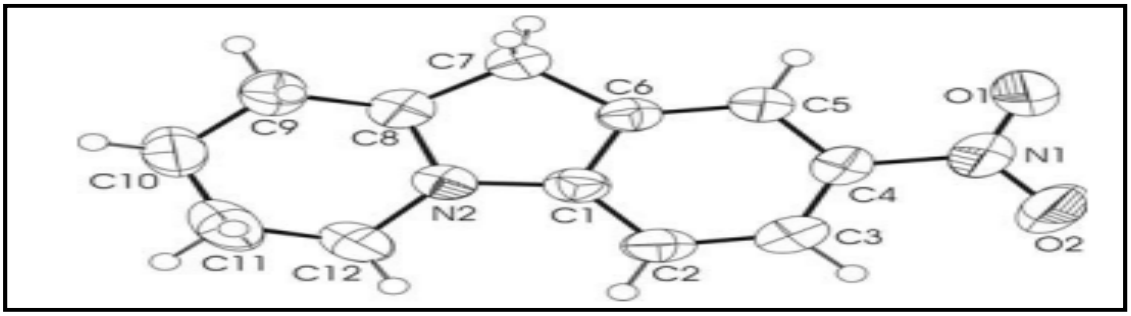


Figure No.1: ORTEP diagramme of molecular structure of compund 4a

CONCLUSION

In this work, indole derivatives were synthesized by intramolecular cyclization of benzylidene hydrazone derivatives. All compounds were obtained in good yields and their structures were confirmed by ^{1}H NMR, ^{13}C NMR and mass spectroscopic analyses. One indole derivative 4b was subjected to X-ray structure determination, which explained the presence of various peaks in the proton NMR spectrum between 1.4 and 3.7ppm.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest regarding the publication of this paper.

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