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Research Article

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Design, Synthesis of Novel Benzylidenehydrazone Derivatives

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Abstract This article describes the synthesis of new benzylidenehydrazone derivatives (**4a-c**). These compounds were synthesized by first designing N-substituted benzaldehyde derivatives (**3a-c**) through the action of cyclic amine with 2-chloro-5-nitrobenzaldehyde (**2**). Condensation of these aldehydes (**3a-c**) with tosylhydrazine led to hydrazones derivatives (**4a-c**). The structures of these compounds were characterized by ^{1}H, ^{13}C Nuclear Magnetic Resonance (NMR) spectroscopy, and High-Resolution Mass Spectrometry (HRMS) analysis. Three of them were identified by X-ray crystallography.

Keywords: Hydrazone, tosylhydrazine, nitration, nucleophilic substitution, X-ray crystallography
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Introduction

Hydrazones are special organic compounds derived from the family of Schiff bases and comprising the chain -C=N-N-. They are an important class of chemical intermediates, which can act as electrophiles or nucleophiles in Mannich-type reactions [1], Mitsunobu reactions [2], asymmetric hydroxycyanations [3], and allylations [4-6]. Hydrazone-based compounds possess a wide range of biological and pharmacological properties such as anticonvulsant [7-9], antimalarial [10,11], antimicrobial [12-15], antitumor [15-18], antiviral including anti-HIV [15,19] and anti-inflammatory and analgesic [20,21] activity. For example, 4-hydroxybenzoic acid [(5-nitro-2-furyl)methylene]-hydrazide (nifuroxazide) is an intestinal antiseptic, and isonicotinic acid hydrazide (isoniazid) has a very high *in vivo* inhibitory activity against tuberculosis strains. Hydrazones' wide range of biological, pharmacological applications and also in the continuation of our previous work [22-25] on this kind of scaffold, has

encouraged us to synthesize new derivatives. This work presents the synthesis of new hydrazones from functionalized aromatic aldehydes.

2. Material and Methods

2.1 Material

The solvents and reagents are of high quality and come 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, 254 nm, and/or 365 nm). 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), m (multiplet), br (broad). The mass spectra were recorded on a JEOL JMS DX300 spectrometer in ESI mode (electrospray/quadripolar ionization or ESI mass).

2.2. Methods

2.2.1. Method for the synthesis of 2-chloro-5-nitro benzaldehyde 2

To 2-chlorobenzaldehyde (**1)** (1 eq, 71.4 mmol), a mixture of H_2SO_4 (40 mL) and HNO_3 (40 mL) was added dropwise at 0°C for about 10 min using a dropping funnel. After stirring at room temperature for 24 hours, the reaction mixture was poured slowly into 1 L of ice water and left to crystallize overnight at room temperature. The crystals obtained were filtered, washed, and recrystallized in an ethanol/water mixture (80/20). Compound **2** was obtained as white crystals (11.42 g, 71.4 mmol) in 86 % yield. m.p = 76-78 °C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 10.50 (s, 1H, CHO), 8.71 (d, 1H, H_{Ar}, J = 2.7 Hz), 8.37 (dd, 1H, H_{Ar}, J = 2.7 Hz, J = 9Hz), 7.68 (d, 1H, H_{Ar}, J = 9 Hz). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 187.39, 147.03, 140.80, 138.70, 132.20, 130.15, 124.00. HRMS (ESI) Calc. for $C_7H_5NO_3Cl$ ($M+H^+$) = 186.996 Found = 186.998.

2.2.2. General method for the synthesis of N-substituted 5-nitrobenzaldehyde 3a-c

To 2-chloro-5-nitrobenzaldehyde (**2)** (1 eq, 43 mmol) dissolved in 120 mL of distilled ethanol were added cyclic amine pyrrolidine, piperidine and morpholine (1.5 eq, 64.5 mmol), and sodium hydrogen carbonate (1.5 eq, 64.5 mmol). The mixture was allowed to stay under reflux of ethanol for 24 hours. After cooling, the mixture was poured into 150 mL of dichloromethane, and washed with water (2 x 50 mL). 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).

2.2.2.1. 5-nitro-2-pyrrolidin-1-yl-benzaldehyde 3a

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.

2.2.2.2. 5-nitro-2-piperidin-1-yl-benzaldehyde 3b

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.

2.2.2.3. 2-morpholin-4-yl-5-nitro benzaldehyde 3c

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.

2.2.3. General method for the synthesis of arylhydrazones

To compounds (**3a-c)** (1 eq, 22 mmol) suspended in 150 mL of distilled ethanol, tosylhydrazine (1 eq, 22 mmol) was added and the mixture was allowed to stay under reflux of ethanol. After one hour, the mixture was cooled to room temperature. The precipitate obtained was filtered and then washed several times with ethanol. The crude was recrystallized in ethanol.

2.2.3 1. (E)-5-nitro-2-pyrrolidinobenzylidene paratoluenesulfonylhydrazone 4a

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.

2.2.3 2. (E)-5-nitro-2-piperidinobenzylidene paratoluene sulfonylhydrazone 4b

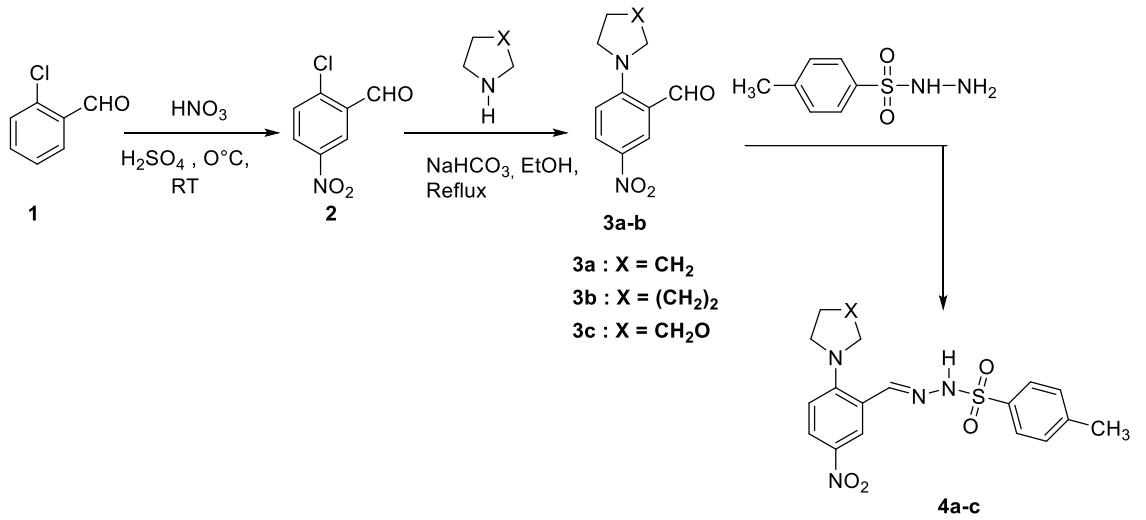
Yellow crystals, yield = 82 % (7.25 g, 18.04 mmol), m.p = 186-188 °C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm) : 11.40 (brs,1H, NH), 8.21 (d, 1H, H_{Ar}, J = 2,7 Hz), 8.14 (dd,1H, H_4, J = 2.7 Hz, J = 9 Hz), 7.98 (s, 1H, HC=N), 7.73 (d, 2H, H_{Ar}, J = 8.4 Hz), 7.40 (d, 2H, H_{Ar}, J =8.1 Hz), 7.13 (d, 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.

2.2.3 3. (E)-2-morpholino-5-nitro benzilidene paratoluene sulphonylhydrazone 4c

Yellow crystals, yield = 80 % (7.13 g, 17.64 mmol), 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 = 9Hz), 8.02 (s, 1H, HC=N), 7.73 (d, 2H, H_{Ar}, J = 8.4 Hz), 7.40 (d, 2H, H_{Ar}, J = 9Hz), 7.16 (d, 1H, H_3, J = 9Hz), 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.

3. Results and Discussion

The new arylhydrazones (**4a-c)** were synthesized by first preparing three N-substituted benzaldehyde derivatives (**3a-c)**. The precursor of these compounds, 2-chloro-5-nitro benzaldehyde **2**, was previously synthesized from 2-chloro benzaldehyde **1.** The latter reacted in a mixture of nitric acid (HNO_3) and sulfuric acid (H_2SO_4) at 0 °C and then at room temperature to give 2-chloro-5-nitro benzaldehyde **2** in 86% yield. Attaching a nitro group (NO_2) to the -4 position of benzene allowed the substitution of chlorine easily in the benzene ring. Thus, the reaction of 2-chloro-5-nitrobenzaldehyde **2** with various heterocyclic amines (morpholine, piperidine and pyrrolidine) in a basic medium lead to compounds **3a-c** in yields ranging from 67% to 86%. Their condensation of these with tosylhydrazine under reflux of ethanol afforded hydrazones (**4a-c)** in yields between 80 and 87% (Scheme 1).



Scheme 1: Synthesis route of hydrazones

The structures of the various compounds were confirmed by ^{1}H, ^{13}C NMR spectroscopy, and HRMS analysis. Compounds 3a-c were characterized by the presence of pyrrolidine, piperidine, and morpholine scaffolds. This is because these rings provide new chemical shifts compared to their precursor 2-chloro-5-nitro benzaldehyde 2. Indeed, in the ^{1}H NMR spectra, we saw the presence of signals between 1.70 - 3 ppm, which are characteristic of the methylene protons of compounds 3a and 3b. Those linked to nitrogen are more deshielded and come out to about 3 ppm. For compound 3c, the methylene protons linked to nitrogen appear around 3.3 ppm, and those bound to oxygen appear around 3.7 ppm. As for compounds 4a-c, they were characterized by the presence of a hydrazone chain (-CH=N-NH-) and a methyl present on the tosyl group. The ^{1}H NMR spectra show a singlet around 8 ppm characteristic of the imine proton (HC=N-). Another one appears around 11.40 to 11.70 ppm characteristic of the NH proton and, finally one around 2.35 ppm characteristic of methyl group.

Three of the synthesized compounds, 3a, 3b, and 4b, have been subject of crystallographic data. This study not only confirmed the structure of the compounds but also showed the arrangement of the various atoms in space. The crystal structure of compound 3a (Figure 1) shows, that the pyrrolidine moiety is disordered, as is usual [26,27]. The atoms of this ring are disordered at two positions, except for the N2 nitrogen, giving rise to two conformers. The pyrrolidine ring adopts a shell conformation in both conformers with respect to the C91 and C92 carbon atoms lying out of the plane formed by the remaining four atoms.

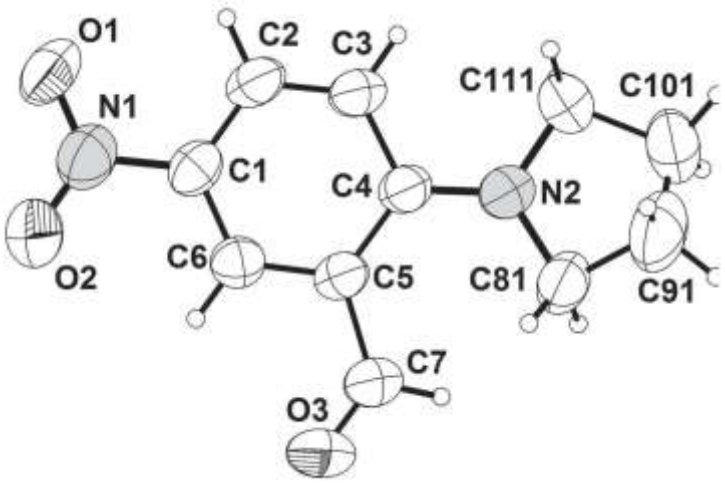


Figure 1 : ORTEP diagramme of molecular structure of compund 3a

In the structure of compound **3b**, the piperidine ring adopts a chair conformation and the aryl substituent defined by (C1C2C3C4C5C6) occupies an equatorial position and is essentially planar. The C4 atom is equatorial to the piperidine ring (Figure 2).

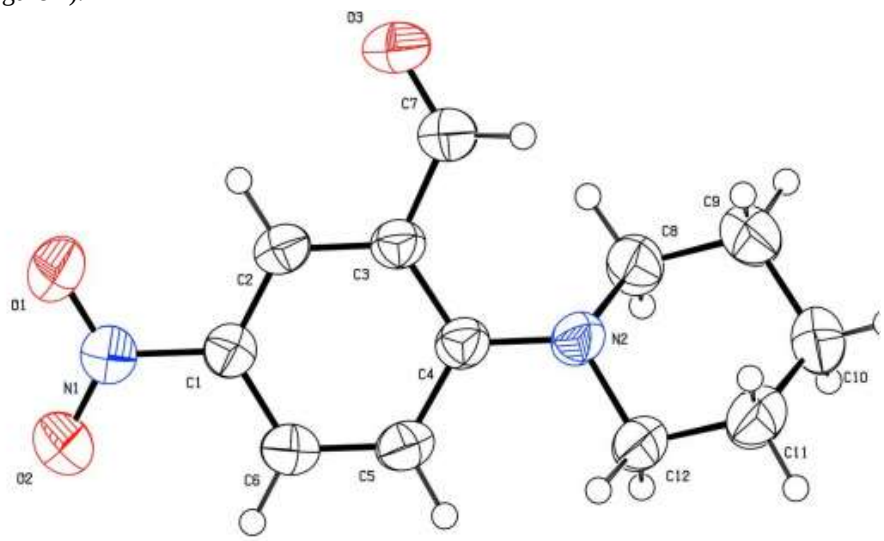


Figure 2 : ORTEP diagramme of molecular structure of compund 3b

In the crystal structure of compound **4b**, the arrangement of substituents around the C=N bond indicates that the isolated compound **4b** is E-shaped (Figure 3). The piperidine ring, represented by the chain of N4C7C8C9C10C11 atoms has a chair conformation. The N4 nitrogen and the C9 carbon deviate from the plane, defined by the C7C8C10C11 atoms, by -0.6822 to - 0.6540 Å, respectively. The plane of the piperidine ring forms an angle of 41.62 °C with the plane of the aromatic ring (C1C2C3C4C5C6).

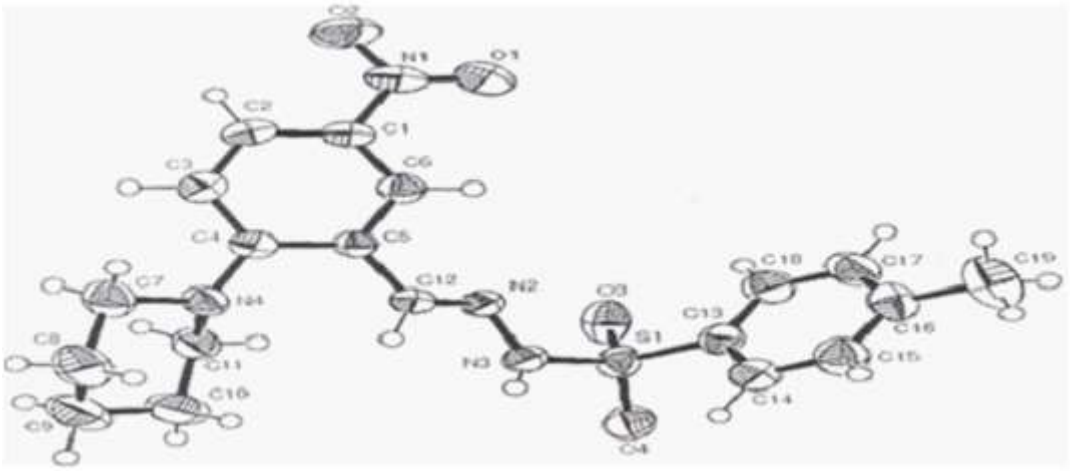


Figure 3 : ORTEP diagramme of molecular structure of compund 4b

4. Conclusion

In this work, benzyldenehydrazone derivatives were prepared from previously synthesized precursors, functionalized aldehydes. All compounds were obtained in good yields and their structures were confirmed by ^{1}H NMR, ^{13}C NMR and mass spectroscopic analyses. Three compounds were subjected to X-ray structure determination, which revealed their spatial arrangement and confirmed the E-conformation of hydrazone **4b**.

Conflicts of interest

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

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