Studies on 2-Arylhydrazononitriles: Synthesis of 3-Aryl-2-arylhydrazopropanenitriles and Their Utility as Precursors to 2-Substituted Indoles, 2-Substituted-1,2,3-Triazoles, and 1-Substituted Pyrazolo[4,3-d]pyrimidines

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Abstract: Coupling of 2-benzylmalononitrile with aromatic diazonium salts afforded 3-phenyl-2-arylhydrazopropanenitriles 4a,b, which were rearranged into 2-cyanoindoles 5a,b upon heating with ZnCl2 in the presence of glacial acetic acid. The produced indole derivatives 5a,b can be successfully used as valuable precursors to synthesize 1,2,4-oxadiazolylindoles 8a,b. The reaction of arylhydrazononitriles 4a,b with hydroxylamine afforded amidoximes 9a,b that could be cyclized into 1,2,3-triazole-4-amines 10a,b. In addition, 4a,b could be converted into 4-aminopyrazoles 12a,b via condensation with chloroaacetonitrile in the presence of triethylamine as a basic catalyst. Finally, compounds 12a,b were refluxed with dimethylformamide dimethylacetal (DMFDMA) to afford amidines 13a,b that were readily cyclized to the corresponding pyrazolo[4,3-d]pyrimidines 14a,b when refluxed with ammonium acetate.

Keywords: benzylidenemalononitrile; 2-arylhydrazononitrile; amidoxime; cyanoindole; dimethylformamide dimethylacetal; 1,2,3-triazole
1. Introduction

2-Arylhydrazononitriles 4a,b are versatile reagents and their chemistry has recently attracted considerable interest [1–8]. In previous recent work we have established the utility of these compounds as precursors for 1,2,4-triazoles [5], 1,2,3-triazoles [6], and pyrazolo[1,5-a]pyrimidines [7,8]. In conjunction to that work we report herein an easy route to the title compounds and their utility as precursors for synthesis of various heterocycles. 1,2,3-Triazine derivatives are an important class of heterocyclic compounds that are considered useful precursors in organic synthesis and as pharmaceuticals (e.g., as antimalarials) [9–11]. In this article, we enabled development of an easy approach to 1,2,4-oxadiazolylindole [12,13], and pyrazolo[4,3-d]pyrimidine derivatives of notable biological and pharmaceutical importance [14–16].

2. Results and Discussion

The hydrazononitriles 4a,b were synthesized by reducing benzylidenemalononitrile (1) with sodium borohydride as recently described, to yield 2 [17]. Coupling of compound 2 with aromatic diazonium salts afforded intermediates 3. It is believed that the initially formed 3a,b readily undergo Japp-Klingmann cleavage [18] yielding the final isolable products 4a,b in 75%, and 70% yield respectively. Compounds 4a,b afforded the 2-cyanoindoles 5a,b upon treatment with zinc chloride and glacial acetic acid. This is an example of the utility of the Fisher indole synthesis in the synthesis of 2-cyanoindoles (Scheme 1).

Scheme 1. Synthesis of indole-2-carbonitriles 5a,b.

The 3-phenylindole-2-carbonitriles 5a,b reacted with hydroxylamine hydrochloride to yield amidoximes 6a,b. Reacting these products with dimethylformamide dimethylacetal (DMFDMA)
afforded products 8a,b in 68%, and 65% yield respectively, rather than 7, as indicated by a NOE experiment that showed an interaction between the indole-H-1, at 10.4 ppm and indole-H-7, at 6.8–7.3 ppm (Scheme 2).

Scheme 2. Synthesis of 1,2,4-oxadiazolylindole derivatives 8a,b.

![Scheme 2](image)

Our attention then shifted to explore the utility of 2-arylhydrazonals as efficient precursors to 1,2,3-triazoles. Compounds 4a,b reacted with hydroxylamine hydrochloride to yield amidoximes 9a,b that could be cyclized into 10a,b or the isomeric 11a,b upon reflux in DMF. From the previously reported findings concerning this reaction, the structure of the product is not clear, where the 1,2,3-triazole 10a,b found a parallel in results reported for similar reactions under similar conditions [1–3]. Although cyclization into isoxazoles has been reported by either refluxing of amidoximes in acidic medium [4] or refluxing an ester derivative of an amidoxime in dimethylformamide [19], cyclization to a 1,2,4-triazole via a Tiemann-like rearrangement has been reported by us in one case [5]. Structures 11a,b could be excluded due to the absence of any interaction between the NH 2 protons and the aryl protons in a NOE experiment (Scheme 3). Moreover, we successfully confirmed that the correct structures are the 1,2,3-triazoles 10a,b based on the obtained single crystal X-ray crystallography results recently reported by our group [6].

Compounds 4a,b was refluxed with chloroacetonitrile to yield 12a,b that were then refluxed with DMFDMA to give the expected amidines 13a,b. The amidines, so formed, were then cyclized in the presence of NH 4OAc and glacial acetic acid to give pyrazolo[4,3-d]pyrimidines 14a,b (cf. Scheme 3). The structure of the products 14a,b was confirmed by the spatial interaction between the NH 2 protons, at 5.87 ppm, and aryl protons, at 7.08–7.17 ppm, in the NOE experiment.
Scheme 3. Synthesis of 1,2,3-triazoles and pyrazolo[4,3-d]pyrimidines.

![Scheme 3](image)

3. Experimental

3.1. General Procedures

Melting points were recorded on a Gallenkamp apparatus and are uncorrected. Infrared spectra (KBr) were determined on a Jasco FT/IR-6300 FT-IR instrument. NMR measurements were determined on a Bruker DPX spectrometer at 600 MHz for $^1$H-NMR and 125 MHz for $^{13}$C-NMR, in DMSO-$d_6$ as solvent and using TMS as internal standard. Mass spectra were measured on GC MS DFS-hermo spectrometers. Elemental analyses were measured by means of an Elementar Vario Micro Cube. Microwave heating was carried out with a single mode cavity Explorer Microwave Synthesizer (CEM Corporation, NC, USA), producing continuous irradiation and equipped with simultaneous external air–cooling system.
3.2. Synthesis of 2-Benzylidenemalononitrile (2)

This was prepared by the literature procedure [17]. A mixture of benzaldehyde (10 mmol) and malononitrile (0.66 g, 10 mmol) was dissolved in aqueous ethanol (1:4, 25 mL) and stirred overnight. The reaction was followed to completion by TLC. To the pre-cooled reaction mixture, an equivalent amount of NaBH4 was added portionwise with stirring at 0 °C for 15 min. The mixture was acidified with aqueous HCl and the product was extracted with CH2Cl2. The clear filtrate was evaporated under reduced pressure, and the remaining solid was collected by filtration. The solid product was then recrystallized from ethanol to give a colorless powder (82%); mp 85–86 °C (lit. mp 86–88 °C [20]); IR (KBr): \( \nu = 2188.4 \) (CN), 2198 (CN) cm\(^{-1}\); \(^1\)H-NMR: \( \delta = 3.28 \) (d, \( J = 7.0 \) Hz, 2H), 3.88 (t, \( J = 7.0 \) Hz, 1H), 7.32–7.44 (m, 5H, phenyl); \(^13\)C-NMR: \( \delta = 25.2 \) (CH), 37.1 (CH2), 112.0 (2 CN), 128.6, 129.0, 129.2, 132.8 (aromatic carbons); MS, \( m/z \) (%): 156.07 (M\(^+\), 100), 77 (53); Anal. Calcd. for C\(_{10}\)H\(_8\)N\(_2\): C, 76.90; H, 5.16; N, 17.94. Found: C, 76.77; H, 5.09; N, 17.72.

Coupling of 2 with aryl diazonium chlorides. A cold solution of the appropriate aryl diazonium salt was prepared by adding sodium nitrite solution (1.4 g dissolved in 10 mL water) to a pre-cooled solution of the corresponding arylamine hydrochloride (p-chloroaniline or p-toluidine, 10 mmol of arylamine in 6 mL 6 M HCl) with continuous stirring. The resulting aryl diazonium salt solutions were then added carefully to a cold ethanolic solution (50 mL) of benzylidenemalononitrile (2, 10 mmol) and sodium acetate trihydrate (2.8 g, 20 mmol). The mixture was stirred at room temperature for 1 h and the solid product formed was collected by filtration, washed with water and recrystallized from ethanol.

2-[(4-Chlorophenyl)hydrazono]-3-phenylpropionitrile (4a). This compound was obtained as pale yellow solid (75%); mp ~148 °C; IR (KBr): \( \nu = 3300 \) (br. NH), 2185 (CN) cm\(^{-1}\); \(^1\)H-NMR: \( \delta = 2.61 \) (s, 2H, CH\(_2\)), 7.02 (d, 2H, \( J = 8 \) Hz, aryl), 7.34 (d, 2H, \( J = 8 \) Hz, aryl), 7.44 (m, 5H, phenyl), 8.9 (s, 1H, NH); \(^13\)C-NMR: \( \delta = 30.2 \) (CH\(_2\)), 113.6, 117.6 (CN), 119.5, 125.3, 126.8, 128.0, 129.8, 133.0, 135.9 (aromatic carbons), 159.1 (C=N); MS, \( m/z \) (%): 269.1 (M\(^+\), 100), 77 (66); Anal. Calcd. for C\(_{15}\)H\(_{12}\)ClN\(_3\): C, 66.79; H, 4.48; Cl, 13.14; N, 15.58. Found: C, 66.68; H, 4.40; Cl, 13.05; N, 15.46.

3-Phenyl-2-(p-tolylhydrazono)propionitrile (4b). This compound was obtained as a yellow solid (70%); mp ~126 °C; IR (KBr): \( \nu = 3320 \) (br. NH), 2189 (CN) cm\(^{-1}\); \(^1\)H-NMR: \( \delta = 1.71 \) (s, 3H, CH\(_3\)), 2.66 (s, 2H, CH\(_2\)), 7.13 (d, 2H, \( J = 8 \) Hz, aryl), 7.18 (d, 2H, \( J = 8 \) Hz, aryl), 7.22 (m, 5H, phenyl), 11.5 (s, 1H, NH); \(^13\)C-NMR: \( \delta = 36.2 \) (CH\(_3\)), 38.6 (CH\(_2\)), 117.4 (CN), 118.9, 123.5, 127.3, 129.2, 132.4, 134.6 (aromatic carbons), 157.5 (C=N); MS, \( m/z \) (%): 249.31 (M\(^+\), 100), 77 (54); Anal. Calcd. for C\(_{16}\)H\(_{15}\)N\(_3\): C, 77.08; H, 6.06; N, 16.85. Found: C, 76.97; H, 5.98; N, 16.77.

Cyclization of 4\(a,b\) in the presence of ZnCl\(_2\) and glacial acetic acid. A mixture of 4\(a,b\) (10 mmol), zinc chloride (1.34 g, 10 mmol), and glacial acetic acid (50 mL) was refluxed and followed by TLC till completion after 24 h. The reaction mixture was poured into an ice/water mixture and the solid product, thus formed, was then collected by filtration and recrystallized from ethanol.

5-Chloro-3-phenyl-1H-indole-2-carbonitrile (5a). This compound was obtained as a yellow solid (60%); mp ~212 °C; IR (KBr): \( \nu = 3300 \) (br. NH), 2206 (CN) cm\(^{-1}\); \(^1\)H-NMR: \( \delta = 7.03–7.26 \) (m, 8H,
aryl & phenyl), 11.1 (s, 1H, NH); $^{13}$C-NMR: $\delta = 117.6$ (CN), 119.8, 121.4, 122.9, 124.7, 128.4, 129.6, 130.5, 133.0, 137.9 139.1, 142.2 (aromatic carbons); MS, $m/z$ (%): 252.05 (M$^+$, 100), 77 (51); Anal. Calcd. for C$_{13}$H$_8$ClN$_2$: C, 71.29; H, 3.59; Cl, 13.84; N, 10.97.

5-Methyl-3-phenyl-1H-indole-2-carbonitrile (5b). This compound was obtained as a colorless solid (70%); mp $\sim$168 °C; IR (KBr): $\nu$ = 3320 (br. NH), 2189 (CN) cm$^{-1}$; $^1$H-NMR: $\delta$ = 1.81 (s, 3H, CH$_3$), 6.87–7.33 (m, 8H, phenyl), 10.8 (s, 1H, NH); $^{13}$C-NMR: $\delta$ = 35.2 (CH$_3$), 117.6 (CN), 120.6, 122.3, 122.6, 123.4, 127.0, 128.7, 129.4, 132.7, 132.8, 134.6, 139.8 (aromatic carbons); MS, $m/z$ (%): 232.1 (M$^+$, 100), 77 (48); Anal. Calcd. for C$_{16}$H$_{12}$N$_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.68; H, 5.14; N, 11.95.

### 3.3. Synthesis of 1,2,4-Oxadiazolyl-indoles 8a,b

A mixture of 5a,b (10 mmol), hydroxylamine hydrochloride (0.69 g, 10 mmol), and sodium acetate (3 g, 25 mmol) in ethanol (25 mL) was refluxed for 5 h. The reaction mixture was poured into ice/water with stirring while a yellow solid separated and was then collected by filtration. The crude product was refluxed with DMFDMA for 6 h. The pure products 8a,b were purified by recrystallization from ethanol.

3-(5-Chloro-3-phenyl-1H-indol-2-yl)-1,2,4-oxadiazole (8a). Obtained as a pale yellow powder (68%); mp $\sim$142 °C; IR (KBr): $\nu$ = 1586 (aromatic C=C) cm$^{-1}$; $^1$H-NMR: $\delta$ = 6.84–7.31 (m, 9H, aromatic), 10.4 (s, 1H, NH, imidazole); $^{13}$C-NMR: $\delta$ = 112.3, 115.2, 121.2, 122.8, 123.4, 124.0, 127.9, 128.5, 129.1, 131.4, 133.8, 134.7, 137.9, 148.6 (aromatic carbons); MS, $m/z$ (%): 295.1 (M$^+$, 56), 77 (100); Anal. Calcd. for C$_{16}$H$_{10}$ClN$_3$O: C, 64.98; H, 3.41; Cl, 11.99; N, 14.21. Found: C, 64.91; H, 3.36; Cl, 11.91; N, 14.13.

3-(5-Methyl-3-phenyl-1H-indol-2-yl)-1,2,4-oxadiazole (8b). Obtained as a yellow solid (65%); mp $\sim$124 °C; IR (KBr): $\nu$ = 3100 (aromatic CH) cm$^{-1}$; $^1$H-NMR: $\delta$ = 2.69 (s, 3H, CH$_3$), 6.72–7.28 (m, 9H, aromatic), 10.1 (s, 1H, NH, imidazole); $^{13}$C-NMR: $\delta$ = 36.3 (CH$_3$), 110.6, 112.7, 119.3, 121.7, 122.6, 122.9, 123.9, 127.4, 128.9, 129.6, 131.2, 132.6, 134.8 142.6 (aromatic carbons); MS, $m/z$ (%): 275.1 (M$^+$, 83), 77 (100); Anal. Calcd. for C$_{17}$H$_{13}$N$_3$O: C, 74.17; H, 4.76; N, 15.26. Found: C, 74.09; H, 4.66; N, 15.13.

### 3.4. Synthesis of 1,2,3-Triazole Derivatives 10a,b

A mixture of 4a,b (10 mmol), hydroxylamine hydrochloride (0.69 g, 10 mmol), and sodium acetate (3 g, 25 mmol) was dissolved in ethanol (25 mL). The mixture was refluxed for 4 h. The reaction mixture was poured into ice/water with stirring while a yellow solid separated and was then collected by filtration. The crude product, so formed, was then refluxed in DMFDMA for 5 h and the reaction mixture was poured into cold water. The products 10a,b were purified by crystallization from ethanol.

5-Benzyl-2-(4-chlorophenyl)-2H-1,2,3-triazol-4-amine (10a). It was obtained as a yellow solid (75%); mp >250 °C; IR (KBr): $\nu$ = 3330 (br. NH$_2$) cm$^{-1}$; $^1$H-NMR: $\delta$ = 3.65 (s, 2H, CH$_2$), 6.87 (s, 2H, NH$_2$), 7.01–7.23 (m, 9H, aromatic); $^{13}$C-NMR: $\delta$ = 33.1 (CH$_2$), 104.8, 121.3, 122.7, 122.9, 125.7, 128.3,
129.1, 132.0, 134.6, 141.0 (aromatic carbon); MS, m/z (%): 284.08 (M⁺, 65), 77 (84); Anal. Calcd. for C₁₅H₁₃ClN₄: C, 63.27; H, 4.60; Cl, 12.45; N, 19.68. Found: C, 63.18; H, 4.53; Cl, 12.34; N, 19.62.

5-Benzyl-2-(4-tolyl)-2H-1,2,3-triazol-4-amine (10b). It was obtained as a yellow solid (70%); mp ~197 °C; IR (KBr): ν = 3340 (br. NH₂) cm⁻¹; ¹H-NMR: δ = 2.44 (s, 3H, CH₃), 3.61 (s, 2H, CH₂), 5.82 (s, 2H, NH₂), 7.01–7.24 (m, 9H, aromatic); ¹³C-NMR: δ = 30.8 (CH₃), 32.6 (CH₂), 106.4, 119.6, 121.2, 122.7, 124.3, 128.1, 128.4, 131.8, 133.2, 139.1 (aromatic carbons); MS, m/z (%): 264.14 (M⁺, 46), 77 (100); Anal. Calcd. for C₁₆H₁₆N₄: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.57; H, 6.02; N, 21.13.

3.5. Cyclization of 4a,b with Chloroacetonitrile in the Presence of Et₃N

A mixture of 4a,b (10 mmol), chloroacetonitrile (0.75 g, 10 mmol), and triethylamine (0.5 mL) was irradiated at 80 W for 5 min (final temperature 140 °C). The reaction mixture was poured into a HCl/water mixture and the solid product, so formed, was then collected by filtration and recrystallized from ethanol.

4-Amino-3-benzyl-1-(4-chlorophenyl)-1H-pyrazole-5-carbonitrile (12a). This compound was obtained as a yellow solid (67%); mp ~227 °C; IR (KBr): ν = 3350 (br. NH₂), 2210 (CN) cm⁻¹; ¹H-NMR: δ = 3.86 (s, 2H, CH₂), 6.87 (s, 2H, NH₂), 7.01–7.26 (m, 9H, aromatic); ¹³C-NMR: δ = 31.6 (CH₂), 117.8 (CN), 119.9, 121.5, 122.3, 125.1, 125.4, 127.2, 129.8, 132.6, 133.8, 135.1, 138.7 (aromatic carbons); MS, m/z (%): 308.08 (M⁺, 27), 77 (100); Anal. Calcd. for C₁₇H₁₃ClN₄: C, 66.13; H, 4.24; Cl, 11.48; N, 18.15. Found: C, 66.04; H, 4.07; Cl, 11.33; N, 18.05.

4-Amino-3-benzyl-1-p-tolyl-1H-pyrazole-5-carbonitrile (12b). This compound was obtained as a yellow solid (70%); mp ~204 °C; IR (KBr): ν = 3330 (br. NH₂), 2190 (CN) cm⁻¹; ¹H-NMR: δ = 2.27 (s, 3H, CH₃), 3.62 (s, 2H, CH₂), 6.41 (s, 2H, NH₂), 6.94–7.21 (m, 9H, aromatic); ¹³C-NMR: δ = 35.9 (CH₃), 38.1 (CH₂), 117.7 (CN), 119.2, 121.1, 121.7, 124.2, 127.9, 128.6, 129.7, 131.2, 132.4, 134.0, 136.4 (aromatic carbons); MS, m/z (%): 288.14 (M⁺, 62), 77 (100); Anal. Calcd. for C₁₈H₁₆N₄: C, 74.98; H, 5.59; N, 19.43. Found: C, 74.88; H, 5.47; N, 19.27.

3.6. Synthesis of Pyrazolopyrimidine Derivatives

A mixture of 12a,b (10 mmol) and dimethylformamide dimethylacetal (1.8 g, 15 mmol) in dry xylene (50 mL) was refluxed for 6 h. The reaction mixture was cooled and then the product, so formed, was refluxed with ammonium acetate (1.54 g, 20 mmol) and glacial acetic acid (25 mL) for 4 h. The reaction mixture was cooled and treated with petroleum ether whereby a yellowish solid precipitated and was collected by filtration. The pure product was obtained by crystallized from ethanol.

3-Benzyl-1-(4-chlorophenyl)-1H-pyrazolo[4,3-d]pyrimidin-7-amine (14a). This compound was obtained as a yellow solid (72%); mp >250 °C; IR (KBr): ν = 3350 (br. NH₂) cm⁻¹; ¹H-NMR: δ = 3.36 (s, 2H, CH₂), 5.87 (s, 2H, NH₂), 7.08–7.17 (m, 9H, aromatic), 8.98 (s, 1H, CH pyrimidine); ¹³C-NMR: δ = 34.6 (CH₂), 104.7, 110.4, 114.0, 119.1, 121.4, 123.9, 124.2, 127.3, 128.7, 130.2, 131.7, 134.3, 139.7 (aromatic carbons); MS, m/z (%): 335.09 (M⁺, 48), 77 (100); Anal. Calcd. for C₁₈H₁₄ClN₅: C, 64.38; H, 4.20; Cl, 10.56; N, 20.86. Found: C, 64.26; H, 4.06; Cl, 10.39; N, 20.67.
3-Benzyl-1-p-tolyl-1H-pyrazolo[4,3-d]pyrimidin-7-amine (14b). This compound was obtained as a yellow solid (65%); mp >250 °C; IR (KBr): $\nu = 3330$ (br. NH$_2$) cm$^{-1}$; $^1$H-NMR: $\delta = 2.84$ (s, 3H, CH$_3$), 3.17 (s, 2H, CH$_2$), 5.61 (s, 2H, NH$_2$), 6.86–7.19 (m, 9H, aromatic), 8.62 (s, 1H, CH pyrimidine); $^{13}$C-NMR: $\delta = 36.4$ (CH$_3$), 38.6 (CH$_2$), 105.2, 112.4, 119.1, 119.7, 122.1, 124.9, 128.2, 128.6, 130.9, 132.3, 134.6, 135.0, 137.8 (aromatic carbons); MS, m/z (%): 315.1 (M$^+$, 53), 77 (100); Anal. Calcd. for C$_{19}$H$_{17}$N$_5$: C, 72.36; H, 5.43; N, 22.21. Found: C, 72.25; H, 5.31; N, 22.08.

4. Conclusions

2-Arylhydrazono-3-propanenitriles are readily obtainable versatile intermediates in the syntheses of a diversity of heterocycles, especially indoles, pyrazoles, 1,2,3-triazole, and pyrazolo[4,3-d]pyrimidines, thus proving the general scope of our newly reported findings on the reactions of 2-aryl-hydrazoneonitriles.

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Sample Availability: Samples of the compounds 5, 8, 10, and 14 are available from the authors.

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