

Article

Studies with Azinylacetonitriles: 2-Pyridylacetonitrile as a Precursor to Functionally Substituted Pyridines

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Abstract: 2-Pyridylacetonitrile (**1**) couples with aromatic diazonium salts to yield arylhydrazones **2a-c**, that were shown to exist in the *syn*-form **2** rather than the *anti*-form **4**. Compounds **2a,c** reacted with hydroxylamine in refluxing DMF to yield the interesting 1,2,3-triazolylpyridines **6**. Attempts to cyclize **2** to give the corresponding fused pyrazolopyridines **9** failed. On the other hand, compound **1** condensed with dimethylformamide dimethyl acetal to yield enaminonitrile **10** that could be converted into pyrazolylpyridine **11**.

Keywords: 2-pyridylacetonitrile; enaminonitrile; arylhydrazones

Introduction

It is well accepted that the methylene moieties in heteroaromatic substituted acetonitriles are reactive toward electrophiles under mild conditions [1–3]. This reactivity has been utilized for synthesis of a variety of functionally substituted azoles [4,5] and condensed azoles [6,7]. However, little has been reported on the utility of azinylacetonitriles for synthesis of functionally substituted azines [8].

Results and Discussion

In conjunction with our interest in using aromatic and heteroaromatic substituted acetonitriles as precursors for the synthesis of heteroaromatics, we report herein the reactivity of 2-pyridylacetonitrile (**1**) as a good precursor to several azolypyridines. Thus, compound **1** coupled with aromatic diazonium salts to yield arylhydrazones **2a-c**. Although a mixture of the two geometrical isomers was expected based on an earlier report [9], the existence of only the *syn*-structure **2** could be established, at least in the solid state, based on X-ray crystal structure determination [10] (cf. Figure 1 and Table 1 for bond angles and bond lengths).

Scheme 1. Syntheses of hydrazones.

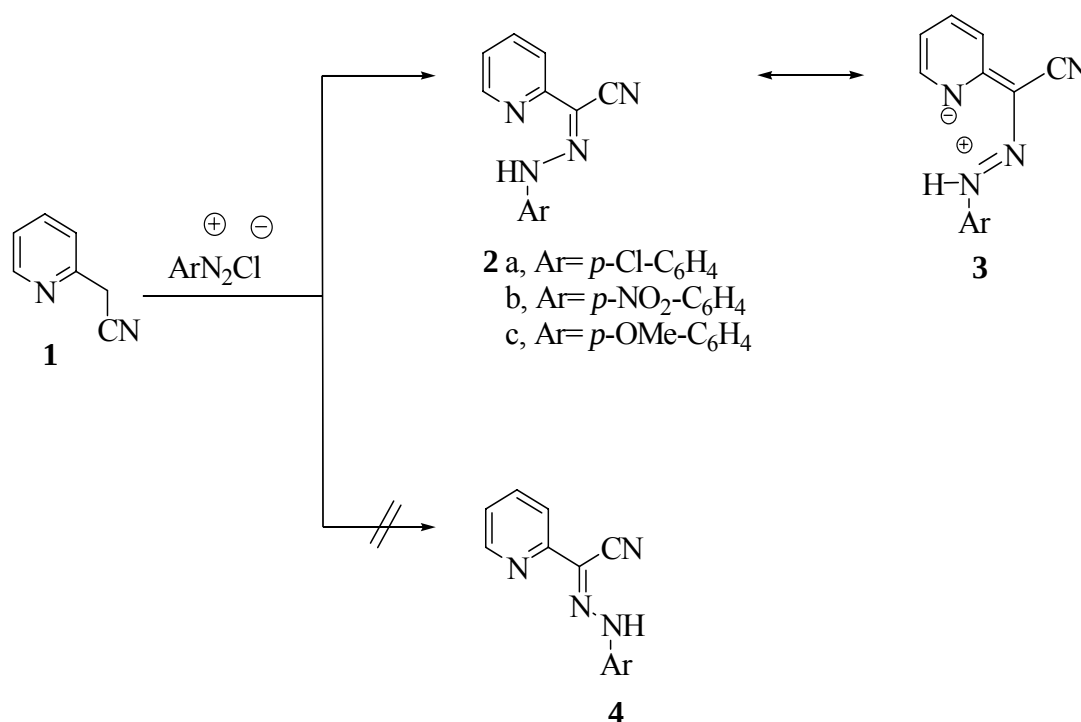


Figure 1. X-ray crystal structure of compound **2a**.

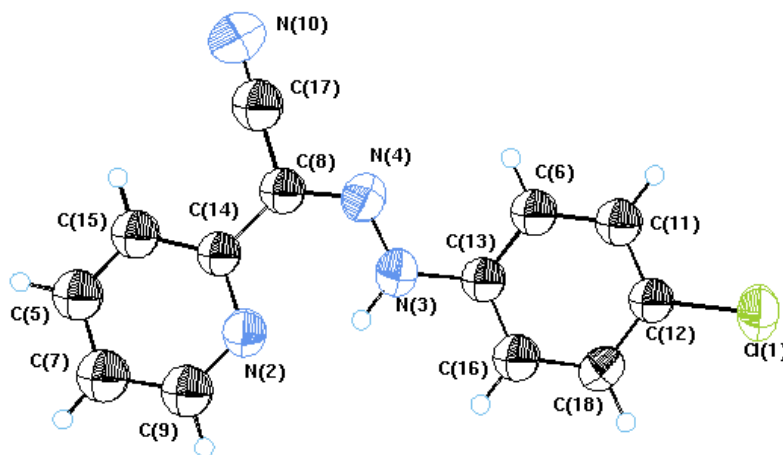


Table 1. Crystal data and structure refinement for compound **2a**.

Parameter	2a
Empirical Formula	C ₁₃ H ₉ N ₄ Cl
Formula weight	256.696
Crystal System	Monoclinic
Space group	P2 ₁ /c
Unit cell parameters	
a [Å]	8.4969(3)
b [Å]	13.5879(6)
c [Å]	12.8704(6)
alpha	90.00
B ^o	12.(18) 10 ¹⁰
gamma	90.00
Unit cell volume	1228.62(9)
Z	4
Temperature (K)	298
Radiation type	Mo Ka
Dx Mg/m ³	1.388
F(000)	528 loop
Absorption coefficient (mm ⁻¹)	0.30
Parameters	103
R factor	0.061

Bond lengths		Bond lengths	
N4 C8	1.320(4)	N3 N4	1.326(4)
N2 C9	1.326(5)	N3 C13	1.412(5)
N2 H3	1.906(3)	C6 C13	1.363(5)
C8 C17	1.449(5)	Cl 1 C12	1.742(3)
N2 C14	1.349(4)	N10 C17	1.143(4)
N4 H3	1.985(3)	C13 C16	1.377(4)

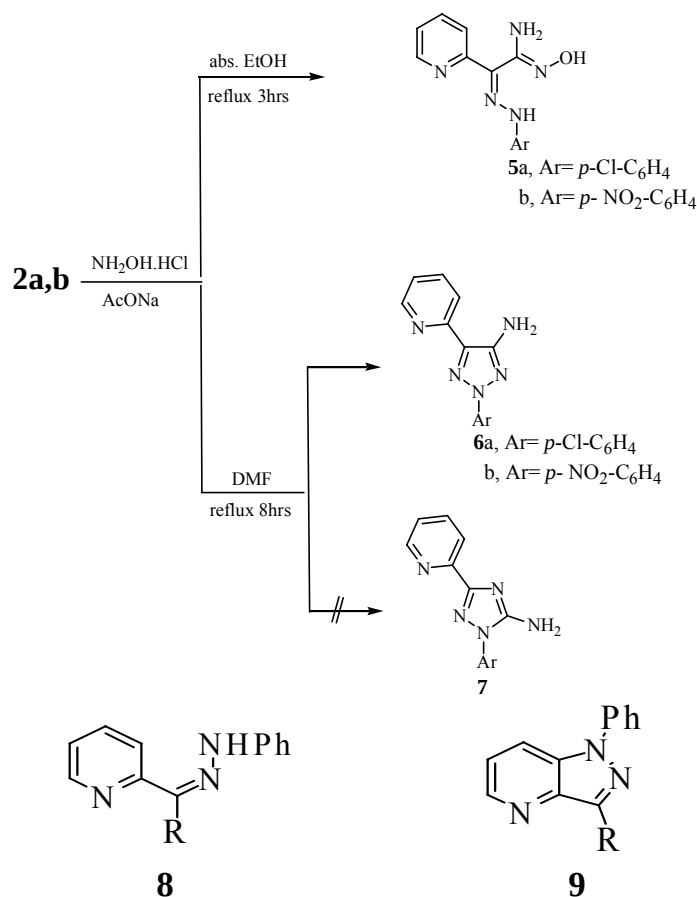
Bond angles		Bond angles	
N3 N4 C8	118.6(3)	N2 C14 C8	116.9(3)
C14 C8 C17	118.5(3)	N2 H3 N3	132.7(2)
N2 C9 C7	124.3(4)	N3 H3 N4	35.4(2)
C8C17 N10	179.3(4)	C8 C14C15	122.1(3)
N3C13 C6	122.2(3)	N4 C8 C14	130.4(3)
N4 N3 C13	118.4(3)	N3 C13C16	117.6(3)

Inspection of Table 1 indicates that the acetonitrile N4-C8-C14 bond angle is larger than a typical sp² bond angle (120°), perhaps to reduce the steric interaction between hydrogen NH, and the pyridyl ring N3-N4 bond length is more like a double bond. We assume that nitrogen lone pair is delocalized at the ring nitrogen and that electrostatic attraction between the positively charged hydrazone moiety and the negatively charged ring nitrogen holds the molecule in the *syn*-form. It is thus concluded that charge separation in **2** contributes significantly to the actual structure [10-12].

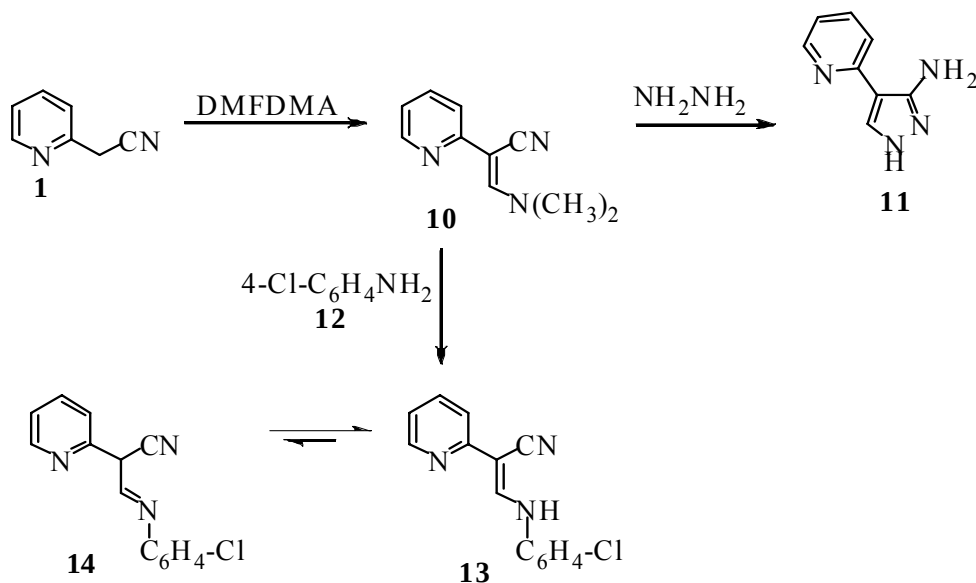
Compounds **2a,b** reacted with hydroxylamine hydrochloride in refluxing DMF and in the presence of sodium acetate to yield the products of addition and water elimination which can thus be formulated as 1,2,3-triazoles **6a,b** or their isomeric structures 1,2,4-triazoles **7**, and are assumed to be formed *via* the intermediately formed amidoximes **5a,b** that could be isolated (Scheme 2). NOE difference spectra enabled the assignment of structure **6** for the products as irradiation of the NH₂ protons at δ = 6.3 ppm did not enhance the aryl protons. If the reaction product were **7** enhancement of these aryl protons should have been observed. The behavior of **2** towards hydroxylamine is thus similar to that of other hydrazononitriles and differs from that of 2-*p*-nitrophenyl-2-arylhydrazonoacetonitrile where rearrangement preceded cyclization affording 1,2,4-triazoles **7**. Although 2-arylhydrazono-2-acetylpyridine **8** has been recently reported to afford **9** when heating in dichlorobenzene at 190 °C, in our hands, compounds **2a-c** have been recovered unaffected under these conditions [13]. It seems that replacing a methyl by a cyano group affects the HOMO-LUMO energy of the cyclised 6π electron system as this cyclization is believed to proceed by a pericyclic rule. Next, compound **1** was reacted

with DMFDMA to yield the corresponding enaminonitrile **10**, for which exact stereochemistry could not be established. Reacting **10** with hydrazine hydrate afforded aminopyrazole derivative **11**, in good yield (cf. Scheme 3). The ^1H -NMR of compound **11** revealed three singlets at $\delta = 5.60$, 7.90 and 11.76 ppm for the exocyclic NH_2 , pyrazole CH and pyrazole NH protons, respectively.

Scheme 2. Syntheses of 1,2,3-triazoles.



Scheme 3. Reactions of the enaminonitrile **10**.



Compound **10** reacted with *p*-chloroaniline **12** to give compound **13**. Structure **14** was excluded based on ^1H -NMR and ^{13}C -NMR that revealed the absence of signals for a sp^3 carbon or protons linked to such a carbon (Scheme 3). It can thus be concluded that while compound **1** is a versatile precursor to azolylpyridines, conversion of compound **2** to pyrazolo[4,3-*b*]pyridine via a route similar to that reported for converting **8** into **9** could not be effected, at least under the conditions reported in the published work [13].

Experimental

General

All melting points were measured on Gallenkamp electrothermal melting point apparatus and are uncorrected. Microwave synthesis were carried out in SJO390W microwave oven. IR spectra were recorded as KBr pellets on a Pye Unicam SP 3-300 spectrophotometer. ^1H -NMR spectra were recorded in deuterated dimethylsulfoxide ($\text{DMSO}-d_6$) at 300 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane (TMS) as an internal reference and results are expressed as δ values. Mass spectra were performed on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were performed by the Microanalytical Center at Cairo University. The crystal structure was determined by the X-ray unit at the National Research Center, Dokki, Cairo.

General procedure for the synthesis of arylhydrazones **2a-c**

A cold solution of aryldiazonium salt (10 mmol), prepared by adding a solution of sodium nitrite (10 mmol in 10 mL of water) to a cold solution of arylamine hydrochloride (10 mmol of arylamine in 6 mL of HCl) with stirring, was added to a cold solution of 2-pyridylacetonitrile (**1**, 10 mmol) in ethanol (50 mL) containing sodium acetate trihydrate (10 mmol). The mixture was then stirred at room temperature for 1 h and the resulting solid product was collected by filtration, washed well with water, dried and recrystallized from ethanol.

[(4-Chlorophenyl)hydrazono]pyridine-2-yl-acetonitrile (2a): Orange crystals (92%); mp. 147-148 °C; IR (cm^{-1}): 3258 (NH), 2212 (CN), ^1H -NMR: δ = 7.50-8.10 (m, 4H, pyr-H), 8.58 (d, 2H, J = 7.2 Hz, Ar-H), 8.70 (d, 2H, J = 7.2 Hz, Ar-H), 15.03 (s, 1H, NH); Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{ClN}_4$ (256.69): C, 60.83; H, 3.53; N, 21.83. Found: C, 60.64; H, 3.60; N, 21.64. MS (EI): m/z (%) = 255 (M^+ -1).

[(4-Nitrophenyl)hydrazono]pyridine-2-yl-acetonitrile (2b): Orange crystals (90%); mp. 217-219 °C; IR (cm^{-1}): 3241 (NH), 2218 (CN); ^1H -NMR: δ = 7.40-8.20 (m, 4H, pyr-H), 8.63 (d, 2H, J = 7.3 Hz, Ar-H), 8.65 (d, 2H, J = 7.3 Hz, Ar-H), 15.25 (s, 1H, NH); Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{N}_5\text{O}_2$ (267.24): C, 58.43; H, 3.39; N, 26.21. Found: C, 58.27; H, 3.29; N, 25.91. MS (EI): m/z (%) = 267 (M^+).

[(4-Methoxyphenyl)hydrazono]pyridine-2-yl-acetonitrile (2c): Yellow crystals (81%); mp. 181-182 °C; IR (cm^{-1}): 3250 (NH), 2216 (CN); ^1H -NMR: δ = 3.70 (s, 3H, CH_3), 6.90-8.07 (m, 4H, pyr-H), 8.60 (d, 2H, J = 7.0 Hz, Ar-H), 8.70 (d, 2H, J = 7.0 Hz, Ar-H), 15.03 (s, 1H, NH); ^{13}C -NMR: δ = 156.1, 151.9, 150.0, 147.7, 139.1, 136.2, 123.2, 121.1, 119.1 (CN), 116.8, 114.8, 55.3 (OCH_3); Anal. Calcd. for

C₁₄H₁₂N₄O (252.27): C, 66.65; H, 4.79; N, 22.21. Found: C, 66.72; H, 4.82; N, 22.28. MS (EI): *m/z* (%) = 252 (M⁺).

General procedure for the synthesis of compounds 5a,b

To a mixture of arylhydrazononitriles **2a,b** (10 mmol) and hydroxylamine hydrochloride (10 mmol) in absolute ethanol (20 mL), anhydrous sodium acetate (2g) was added and the reaction mixture was then refluxed for 3 hrs. After cooling to room temperature, the mixture was poured into water and the resulting precipitate collected by filtration, washed with water, dried and recrystallized from ethanol.

2-[(4-Chlorophenyl)hydrazono]-N-hydroxy-2-yl-acetamidine (5a): Yellow crystals (80%); mp.164-165 °C; IR (cm⁻¹): 3495 (OH), 3390, 3273 (NH₂), 3185 (NH); ¹H-NMR: δ = 5.60 (s, 2H, NH₂), 7.20-8.0 (m, 4H, pyr-H), 8.50 (d, 2H, *J* = 7.1 Hz, Ar-H), 8.70 (d, 2H, *J* = 7.1 Hz, Ar-H), 10.17 (s, 1H, NH), 12.8 (s, 1H, OH); Anal. Calcd. for C₁₃H₁₂ClN₅O (289.73): C, 53.89; H, 4.17; N, 24.17. Found: C, 53.79; H, 3.99; N, 24.20. MS (EI): *m/z* (%) = 288 (M⁺-1).

2-[(4-Nitrophenyl)hydrazono]-N-hydroxy-2-yl-acetamidine (5b): Orange crystals (80%); mp.284-285 °C; IR (cm⁻¹): 3495 (OH), 3382, 3270 (NH₂), 3179 (NH); ¹H-NMR: δ = 5.20 (s, 2H, NH₂), 7.40-8.0 (m, 4H, pyr-H), 8.30 (d, 2H, *J* = 7.0 Hz, Ar-H), 8.70 (d, 2H, *J* = 7.0 Hz, Ar-H), 8.90 (s, 1H, NH), 15.2 (s, 1H, OH); Anal. Calcd. for C₁₃H₁₂O₃N₅ (300.27): C, 52.0; H, 4.03; N, 27.99. Found: C, 52.10; H, 3.98; N, 28.02. MS (EI): *m/z* (%) = 300 (M⁺).

General procedure for the synthesis of compounds 6a,b

To a mixture of arylhydrazononitriles **2a,b** (10 mmol) and hydroxylamine hydrochloride (10 mmol) in DMF (20 mL), anhydrous sodium acetate (2 g) was added. Then, the reaction mixture was refluxed for 8 hrs. The solvent was evaporated under vacuum and the crude product was collected by filtration, washed with ethanol, dried and recrystallized from ethanol/dioxane.

2-(4-Chlorophenyl)-5-pyridin-2-yl-2H-[1,2,3]triazol-4-ylamine (6a): Yellow crystals (80%); mp.167-169°C; IR (cm⁻¹): 3303, 3155 (NH₂); ¹H-NMR: δ = 6.30 (s, 2H, NH₂), 7.30-8.0 (m, 4H, pyr-H), 8.02 (d, 2H, *J* = 7.2 Hz, Ar-H), 8.6 (d, 2H, *J* = 7.2 Hz, Ar-H); ¹³C-NMR: δ = 152.8, 150.7, 148.8, 137.9, 137.2, 132.1, 130.3, 129.4, 122.3, 119.7, 118.7; Anal. Calcd. for C₁₃H₁₀ClN₅ (271.70): C, 57.47; H, 3.71; N, 25.78. Found: C, 57.31; H, 3.68; N, 25.89. MS (EI): *m/z* (%) = 271 (M⁺).

2-(4-Nitrophenyl)-5-pyridin-2-yl-2H-[1,2,3]triazol-4-ylamine (6b): Orange crystals (79%); mp. 280 °C; IR (cm⁻¹): 3336, 3278 (NH₂); ¹H-NMR: δ = 6.50 (s, 2H, NH₂), 7.30-8.11 (m, 4H, pyr-H), 8.30 (d, 2H, *J* = 7.3 Hz, Ar-H), 8.68 (d, 2H, *J* = 7.3 Hz, Ar-H); ¹³C-NMR: δ = 157.1, 150.0, 148.4, 137.7, 135.0, 132.1, 130.0, 129.0, 124.0, 122.0, 119.0, Anal. Calcd. for C₁₃H₁₀N₆O₂ (282.26): C, 55.32; H, 3.57; N, 29.77. Found: C, 55.20; H, 3.46; N, 29.69. MS (EI): *m/z* (%) = 282 (M⁺).

Synthesis of 3-dimethylamino-2-pyridin-2-yl-acrylonitrile (10): A mixture of compound **1** (10 mmol) and dimethylformamide dimethylacetal (DMFDMA) (10 mmol) was irradiated in a domestic

microwave oven for 1 minute at 240 W. The mixture was left standing overnight and the resulting solid product was collected by filtration, washed with ethanol, dried and recrystallized from ethanol to give compound **10** as brown crystals (80%), mp. 116–118 °C; IR (cm⁻¹): 2221 (CN); ¹H-NMR: δ = 2.48 (s, 6H, 2CH₃), 6.90–8.60 (m, 4H, pyr-H), 8.07 (s, H, olefinic CH); Anal. Calcd. for C₁₀H₁₁N₃ (173.21): C, 69.34; H, 6.40; N, 24.26. Found: C, 69.41; H, 6.41; N, 24.17. MS (EI): *m/z* (%) = 173 (M⁺).

Synthesis of 4-pyridin-2-yl-2H-pyrazol-3-yl-amine (11): A mixture of compound **10** (10 mmol) and hydrazine hydrate (80%, 10 mmol) was irradiated in a domestic microwave oven for 2 minutes. The resulting solid product was collected by filtration, washed with ethanol, dried and recrystallized from ethanol to give compound **11** as brown crystals (75%); mp. 120–121 °C; ¹H-NMR: δ = 5.60 (s, 2H, NH₂), 6.90–8.40 (m, 4H, pyr-H), 7.90 (s, 1H, pyrazole H-5), 11.76 (s, 1H, NH); ¹³C-NMR: δ = 155.1, 151.1, 148.8, 136.8, 133.4, 119.0, 118.7, 103.0; Anal. Calcd. for C₈H₈N₄ (160.20): C, 59.99; H, 5.03; N, 34.98. Found: C, 60.01; H, 4.98; N, 34.87. MS (EI): *m/z* (%) = 160 (M⁺).

Synthesis of 3-(4-chlorophenylamino)-2-pyridin-2-ylacrylonitrile (13): To a mixture of *p*-chloroaniline **12** (10 mmol) and compound **10** (10 mmol), a drop of AcOH was added, then the mixture was irradiated in a domestic microwave oven for 2 minutes at 280 W. The resulting solid product was collected by filtration, washed with ethanol, dried and recrystallized from ethanol to give compound **13** as colourless crystals (86%); mp. 179–180 °C; IR (cm⁻¹): 3387 (NH), 2202 (CN); ¹H-NMR: δ = 7.1–8.2 (m, 4H, pyr-H), 8.40 (d, 2H, *J* = 7.2 Hz, Ar-H), 8.50 (s, H, olefinic CH), 8.60 (d, 2H, *J* = 7.2 Hz, Ar-H), 12.60 (brs, 1H, NH); ¹³C-NMR: δ = 156.0, 150.0, 149.0, 144.0, 137.0, 130.0, 123.0, 122.0, 121.0, 119.0 (CN), 116.0, 103.0; Anal. Calcd. for C₁₄H₁₀ClN₃ (255.7): C, 65.76; H, 3.94; N, 16.43. Found: C, 65.59; H, 3.99; N, 16.52. MS (EI): *m/z* (%) = 254 (M⁺-1).

Conclusions

In conclusion, a new simple approach to 2,5-disubstituted-1,2,3-triazole-5-amines from 2-arylhydrazononitriles has been achieved.

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Sample Availability: Samples of the compounds **1–13** are available from the authors.

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