Studies With Enamines: Synthesis and Reactivity of 4-Nitrophenyl-1-piperidinostyrene. Synthesis of Pyridazine, Oxadiazole, 1,2,3-Triazole and 4-Aminopyrazole Derivatives

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4-Nitrophenyl-1-piperidinostyrene (**4**) reacts with an aromatic diazonium salt to afford the arylhydrazonal **6**. The latter condenses with active methylene compounds to yield pyridazine derivatives, and with hydroxylamine hydrochloride to produce oxadiazole and 1,2,3-triazole derivatives. Compound **12** was reacted with chloroacetonitrile to afford 4-aminopyrazoles **15**.

Key words: 2-Arylhydrazononitriles, Pyridazinimine, Oxadiazole, 1,2,3-Triazole, 4-Aminopyrazoles

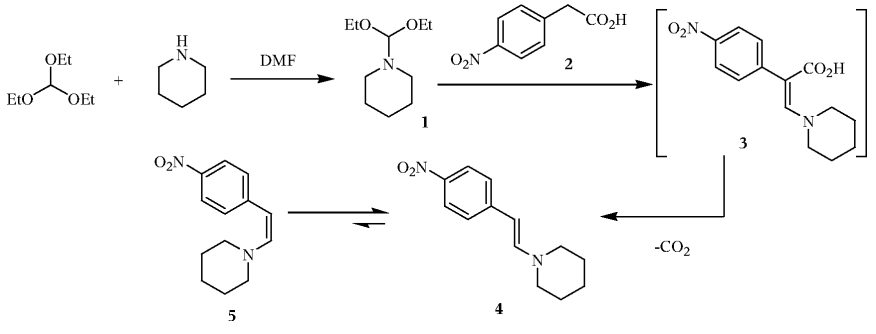
Introduction

Enamines are versatile reagents that are currently utilized extensively as synthetic equivalents of aldehydes [1 – 5]. In earlier work we have shown that functionally substituted enamines are versatile precursors to otherwise not readily obtainable active methylene aldehydes [6 – 8]. In conjunction with this work, we report here a synthesis of the title compound **4** and its use as a 4-nitrophenylacetaldehyde equivalent for the synthesis of different heteroaromatic compounds such as pyridazines, 4-aminopyrazoles and 1,2,3-triazoles (Scheme 1). The strategy adopted herein for the synthesis of the target compound **4** is based on the use of 4-nitrophenylacetic acid (**2**).

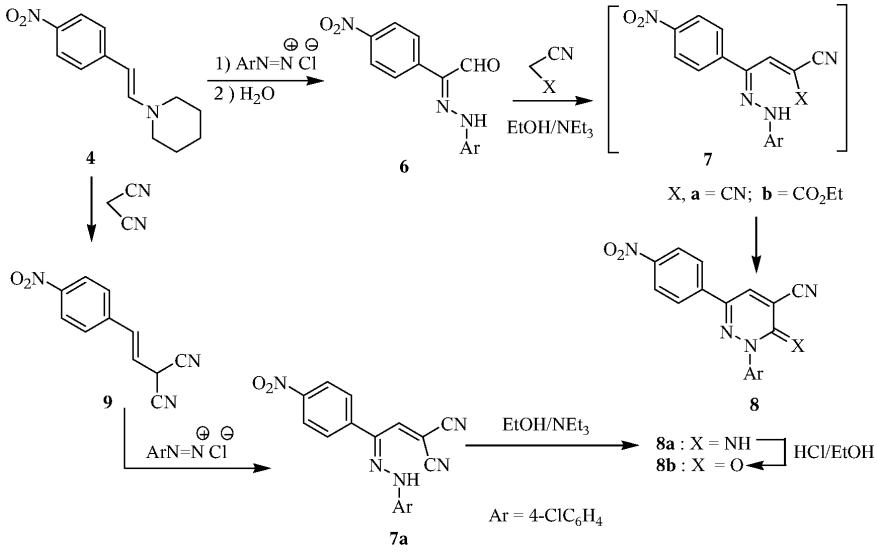
Result and Discussion

The reaction of 4-nitrophenylacetic acid (**2**) with triethyl orthoformate and piperidine in DMF solution afforded the enamine **4** in good yield. Utilization of triethyl orthoformate and piperidine in DMF solution was found more economic and safer than using DMFDMA. It is believed that piperidine reacts with acetal **1** which then condenses with **2** to yield **3**, which is readily decarboxylated into the final isolated product **4** as depicted in Scheme 1.

The possibility that decarboxylation preceded condensation was ruled out based on the failure of attempts to condense 4-nitrotoluene with orthoformate under the same reaction conditions. Although it was earlier reported that nitrotoluenes condense with DMFDMA to yield enamines [9], we failed to repeat this work. The ^{1}H NMR spectrum of compound **4** showed two singlet signals for the piperidinyl protons at δ = 1.64 (3 CH_2) and 3.20 (2 CH_2) ppm and two doublets at δ = 5.30 and 6.96 ppm for the two olefinic protons. The olefinic coupling constant (^3J = 14 Hz) indicated that the reaction product exists solely in the *E*-form **4**. The



Scheme 1.



Scheme 2.

Z-isomer **5** was not detected by NMR. ^{13}C NMR and mass spectra of compound **4** are in accordance with the proposed structure.

The considerable biological activities of pyridazine derivatives have incited considerable interest in developing efficient synthetic approaches for differently substituted pyridazine derivatives [10 – 13]. Compound **4** proved to be a perfect synthetic equivalent for 4-nitrophenylacetaldehyde to produce pyridazine derivatives. Thus, it coupled readily with aromatic diazonium salts to yield the arylhydrazonals **6**. It reacted with malononitrile and ethyl cyanoacetate to afford compounds **8a, b**. Establishing of their structures was based on the elemental analyses and spectral data. Compound **8a** was converted quantitively into pyridazinone **8b** by treatment with ethanolic hydrochloric acid solution as shown in Scheme 2 [14, 15].

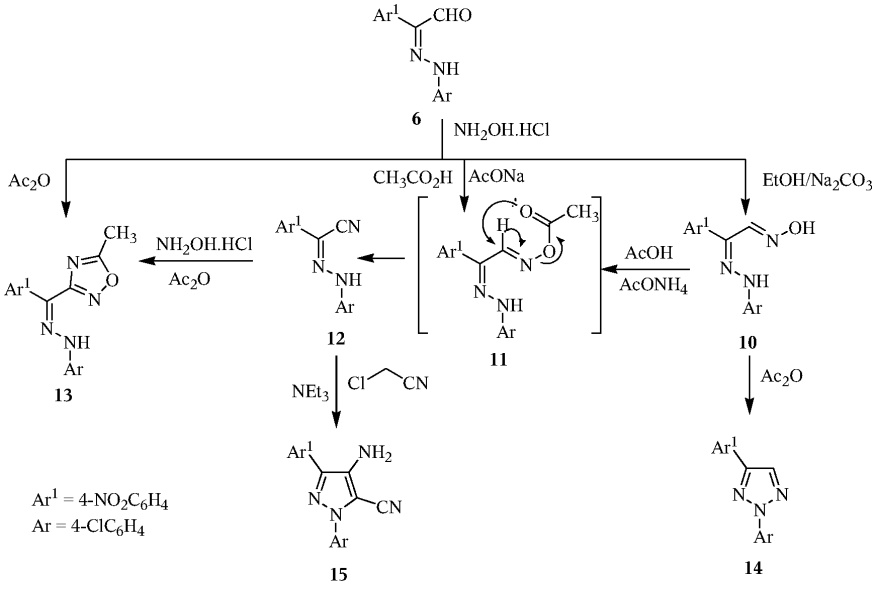
Establishing of structure **8** was based on the spectral analysis. For example, the IR spectra of compound **8a** showed an NH stretching band at 3363 cm^{-1} and a strong band at 2196 cm^{-1} for the CN group. In case of **8b**, a C=O absorption band at 1681 cm^{-1} in addition to a CN band at 2235 cm^{-1} was found. The ^{1}H NMR spectra of compound **8a** revealed, in addition to the aromatic protons, the presence of a singlet at δ = 7.63 ppm corresponding to pyridazinimine 4-H and a singlet at δ = 8.58 ppm corresponding to NH. The mass spectra of the products are in accordance with the proposed structure (*cf*. Experimental Section).

The structures of compounds **8a, b** were confirmed by their alternative synthesis *via* refluxing compound **4** with malononitrile in ethanol in the presence of a catalytic amount of triethylamine to yield compound **9** which was coupled with an aromatic diazonium salt to afford compound **7a**. Compound **7a** was cyclized into the pyridazinimine **8a** by heating in ethanolic triethylamine solution (m. p., mixed m. p. and TLC control). Compound **8a** could be converted into **8b** by refluxing compound **8a** in ethanolic hydrochloric acid as indicated in Scheme 2 [14, 15].

The utility of 2-arylhydrazonoaldehydes in heterocyclic synthesis has received a considerable interest in the past decade [7, 8]. Compound **6** reacted with hydroxylamine hydrochloride in ethanol in the presence of triethylamine to afford the oxime **10**, similar to an earlier report on arylhydrazonals [7]. In refluxing aqueous acetic acid and in the presence of sodium acetate, compound **6** reacted with hydroxylamine hydrochloride to yield 2-arylhydrazononitrile **12**, formed *via* intermediacy of the oxime acetate **11**.

Compound **12** has also been obtained from treatment of oxime **11** with acetic acid/ammonium acetate solution. It is believed that **11** was acylated in acetic acid solution and that the acylated compound **11** derivative underwent thermal elimination of acetic acid to yield **12** (Scheme 3).

Treatment of compound **6** with acetic anhydride at reflux afforded the oxadiazole derivative **13**, whereas refluxing of **10** in acetic anhydride yielded the 1,2,3-triazole derivative **14**. The structures of **13** and **14** were established based on their elemental analysis and spectral data. For example, the ^{1}H NMR spectrum of com-



Scheme 3.

pound **13** revealed the presence of a singlet at δ = 2.66 ppm corresponding to a CH_3 group, a multiplet at δ = 7.30 – 8.35 ppm corresponding to aromatic protons and a singlet at δ = 9.86 ppm corresponding to NH. The mass spectrum of the product was consistent with these results. Again compound **13** could also be obtained by refluxing the 2-aryl-hydrazononitrile **12** with hydroxylamine hydrochloride in acetic anhydride for 4 h (m. p., mixed m. p. and TLC control). The ^{1}H NMR spectrum of compound **14** revealed in addition to the aromatic protons a singlet at δ = 8.15 ppm corresponding to the triazole proton 5-H.

Compound **12**, so formed, proved to be a valuable precursor to arylazoles. For example, reacting **12** with chloroacetonitrile afforded 4-aminopyrazole **15**, relatives of which have been described recently [16].

Experimental Section

All melting points were measured with a Gallenkamp electrothermal melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets with a Pye Unicam SP 3-300 Spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in deuterated dimethylsulfoxide [D_6]DMSO or deuterated chloroform ($CDCl_3$) at 300 MHz with 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 carried out at the Microanalytical Center of Cairo University.

*4-Nitrophenyl-1-piperidinostyrene (**4**)*

A mixture of 4-nitrophenyl acetic acid (0.5 mol), triethyl orthoformate (0.5 mol) and piperidine (0.5 mol) was treated with 50 mL of DMF and refluxed for 72 h. The reaction mixture was then cooled to r. t. and poured onto water. The solid product, so formed, was collected by filtration and crystallized from ethanol. M. p. 98 – 99 °C. Yield: 75 %. – IR (KBr): ν = 2853 (CH aliphatic), 1629 (C=C) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.64 (s, 6H, $3CH_2$), 3.20 (s, 4H, $2CH_2$), 5.30 (d, J = 14 Hz, 1H, CH), 6.94 (d, J = 14 Hz, 1H, CH), 7.16 (d, J = 9 Hz, 2H, Ar-H), 8.04 (d, J = 9 Hz, 2H, Ar-H). – ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 23.8, 25.2, 48.9, 94.7 (H*C*=CH), 122.2, 124.2, 141.1 (HC=*C*H), 144.7, 149.0. – MS (EI, 70 eV): *m/z* (%) = 232 (36) [M$^+$]. – $C_{13}H_{16}N_2O_2$ (232.27): calcd. C 67.22, H 6.94, N 12.06; found C 66.95, H 6.80, N 12.22.

*2-[2-(4-Chlorophenyl)hydrazono]-2-(4-nitrophenyl)-acetaldehyde (**6**)*

A cold solution of arenediazonium chloride (10 mmol) was prepared by adding a solution of sodium nitrite (10 mmol in 2 mL of H_2O) to a cold solution of the aromatic amine hydrochloride with stirring. The resulting solution of the arenediazonium chloride was added to a cold solution of 1-(4-nitrostyryl)piperidine (**4**) in ethanol (50 mL) containing sodium acetate (5 g). The reaction mixture was stirred at r. t. for 30 min. The solid product, so formed, was collected by filtration, washed with water and crystallized from ethanol. M. p. 210 – 212 °C. Yield: 70 %. – IR (KBr): ν = 3423 (NH), 1700 (C=O) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 7.16 (d, J = 9 Hz, 2H, Ar-H), 7.41 (d,

J = 9 Hz, 2H, Ar-H), 7.66 (d, *J* = 9 Hz, 2H, Ar-H), 8.32 (d, *J* = 9 Hz, 2H, Ar-H), 9.56 (s, 1H, CHO), 11.0 (s, 1H, NH). – MS (EI, 70 eV): *m/z* (%) = 303 (72) [M^+], 305 (23) [M^++2]. – $C_{14}H_{10}ClN_3O_3$ (303.7): calcd. C 55.37, H 3.32, N 13.84, Cl 11.67; found C 55.26, H 3.10, N 13.75, Cl 11.60.

*2-[2-[(4-Chlorophenyl)hydrazono]-2-(4-nitrophenyl) ethylidene]malononitrile (**7a**)*

A cold solution of arenediazonium chloride (10 mmol) was prepared by adding a solution of sodium nitrite (10 mmol in 2 mL of H_2O) to a cold solution of the aromatic amine hydrochloride with stirring. The resulting solution of the arenediazonium chloride was added to a cold solution of **9** in ethanol (50 mL) containing sodium acetate (5 g). The reaction mixture was stirred at r. t. for 30 min. The solid product, so formed, was collected by filtration, washed with water and crystallized from ethanol. M. p. 130 – 132 °C. Yield: 72 %. – IR (KBr): ν = 3340 (NH), 2220, 2208 (CN), 1610 (C=C) cm^{-1}. – MS (EI, 70 eV): *m/z* (%) = 351 (36) [M^+], 353 (11) [M^++2]. – $C_{17}H_{10}ClN_5O_2$ (351.74): calcd. C 58.05, H 2.87, N 19.91, Cl 10.08; found C 57.95, H 3.05, N 19.77, Cl 10.18.

*General procedure for the preparation of pyridazine derivatives **8a, b***

Method A: a mixture of 2-arylhydrazonal **6** (10 mmol) and malononitrile or ethyl cyanoacetate (10 mmol of each) was refluxed in ethanol (50 mL) for 3 h in the presence of triethylamine. The solvent was evaporated *in vacuo* and the solid residue was collected by filtration and crystallized from ethanol.

Method B: To a solution of **7a** (10 mmol) in 30 mL of ethanol was added 1 mL of triethylamine, and the solution was refluxed for 1 h. After cooling to r. t. the reaction mixture was diluted with cold water and neutralized with hydrochloric acid. The precipitate was collected by filtration and crystallized to afford a product, which was identical to **8a** in all respects.

*Transformation of **8a** to **8b***

To a solution of 3.03 g (10 mmol) of **8a** in 30 mL of ethanol was added conc. HCl (5 mL) and the solution was refluxed for 1 h. After cooling to r. t. the reaction mixture was diluted with cold water and neutralized with ammonia. The precipitate was collected by filtration and crystallized to afford a product, which was identical to **8b** in all respects.

*2-(4-Chlorophenyl)-2,3-dihydro-3-imino-6-(4-nitrophenyl)pyridazine-4-carbonitrile (**8a**)*

M. p. 175 – 177 °C. Yield: 70 %. – IR (KBr): ν = 3363 (NH), 2196 (CN) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 7.20 – 7.53 (m, 4H, Ar-H), 7.63 (s, 1H, 5-H), 7.85 – 8.27 (m, 4H, Ar-H), 8.58 (s, 1H, NH). – MS (EI, 70 eV): *m/z* (%) = 351 (100) [M^+], 353 (33) [M^++2]. – $C_{17}H_{10}ClN_5O_2$ (351.7): calcd. C 58.05, H 2.87, N 19.91, Cl 10.08; found C 57.80, H 2.80, N 20.17, Cl 10.30.

*2-(4-Chlorophenyl)-2,3-dihydro-6-(4-nitrophenyl)-3-oxopyridazine-4-carbonitrile (**8b**)*

M. p. 270 – 272 °C (EtOH/DMF, 3 : 1). Yield: 74 %. – IR (KBr): ν = 2235 (CN), 1681 (C=O) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 7.56 (d, *J* = 9 Hz, 2H, Ar-H), 7.92 (d, *J* = 9 Hz, 2H, Ar-H), 8.19 (d, *J* = 9 Hz, 2H, Ar-H), 8.35 (d, *J* = 9 Hz, 2H, Ar-H), 9.08 (s, 1H, 5-H). – MS (EI, 70 eV): *m/z* (%) = 352 (75) [M^+], 354 (23) [M^++2]. – $C_{14}H_{10}ClN_3O_3$ (352.73): calcd. C 57.89, H 2.57, N 15.88, Cl 10.05; found C 57.66, H 2.70, N 15.75, Cl 10.30.

*2-[2-(4-Nitrophenyl)vinyl]malononitrile (**9**)*

A mixture of **4** (2.32 g, 10 mmol), malononitrile (0.66 g, 10 mmol) and triethylamine (1.01 g, 10 mmol) in ethanol (25 mL) was refluxed for 3 h. The solvent was evaporated under vacuum, and the crude product was collected and crystallized from ethanol. M. p. 80 – 81 °C. Yield: 80 %. – IR (KBr): ν = 2201 (CN), 1601 (C=C) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 4.44 (s, 1H, CH), 7.25 (d, *J* = 9 Hz, 1H, CH), 7.80 (d, *J* = 9 Hz, 1H, CH), 7.90 – 8.35 (m, 4H, Ar-H). – MS (EI, 70 eV): *m/z* (%) = 213 (31) [M^+]. – $C_{11}H_7N_3O_2$ (213.19): calcd. C 61.97, H 3.31, N 19.71; found C 61.65, H 3.35, N 19.75.

*2-(4-Chlorophenylhydrazono)-2-(4-nitrophenyl)ethanal-1-oxime (**10**)*

A warm solution of hydroxylamine hydrochloride (0.69 g, 10 mmol) and sodium carbonate (1.26 g, 12 mmol) in water (10 mL) was added to a stirred solution of the arylhydrazonoethanal (**6**) (10 mmol) in ethanol (4 mL). The reaction mixture was stirred at r. t. for 4 h. The oximes soon separated as semisolid crystals that were solidified by cooling in crushed ice. The solid product, so formed, was collected by filtration and crystallized from ethanol/DMF (3 : 1). M. p. 270 – 272 °C. Yield: 77 %. – IR (KBr): ν = 3365 (OH), 3206 (NH) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 7.05 (d, *J* = 9 Hz, 2H, Ar-H), 7.20 (s, 1H, CH), 7.44 (d, *J* = 9 Hz, 2H, Ar-H), 7.60 (d, *J* = 10 Hz, 2H, Ar-H), 8.16 (d, *J* = 10 Hz, 2H, Ar-H), 8.24 (s, 1H, NH), 8.88 (s, 1H, OH). – MS (EI, 70 eV): *m/z* (%) = 318 (80) [M^+], 320 (26) [M^++2]. – $C_{14}H_{11}ClN_4O_3$ (318.75): calcd. C 52.76, H 3.48, N 17.58, Cl 11.12; found C 52.89, H 3.35, N 17.75, Cl 11.22.

*(4-Chlorophenyl)hydrazono-(4-nitrophenyl)acetonitrile (**12**)*

Method A: A mixture of hydroxylamine hydrochloride (0.69 g, 10 mmol), sodium acetate (3 g) and arylhydrazo-

noethanal (**6**) (10 mmol) was refluxed in acetic acid (20 mL) for 4 h. The solvent was removed under vacuum and the residue was poured onto water. The solid product was collected by filtration and crystallized from ethanol.

Method B: The oxime **10** (10 mmol) was refluxed in acetic acid (10 mL) and ammonium acetate (3 g) for 4 h, and then left to cool at r. t. The solvent was reduced under vacuum and the residue was poured onto water. The solid product was collected by filtration and crystallized from ethanol. M. p. 200 – 201 °C. Yield: 80 %. – IR (KBr): ν = 3380 (NH), 2208 (CN) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 6.99 – 7.25 (m, 4H, Ar-H), 7.30 (s, 1H, NH), 7.75 (d, J = 10 Hz, 2H, Ar-H), 8.22 (d, J = 10 Hz, 2H, Ar-H). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 157.2 (*C*=N), 155.2, 144.1, 137.4, 130.2, 129.1, 124.5, 123.4, 120.2, 117.2 (*C*N). – MS (EI, 70 eV): *m/z* (%) = 300 (25) [M$^+$], 302 (8) [M$^+$+2]. – $C_{14}H_9ClN_4O_2$ (300.70): calcd. C 55.92, H 3.02, N 18.63, Cl 11.79; found C 55.75, H 2.90, N 18.90, Cl 11.94.

*2-(4-Chlorophenyl)-1-(5-methyl-1,2,4-oxadiazol-3-yl)-(4-nitrophenyl)methylene hydrazine (**13**)*

Method A: A mixture of hydroxylamine hydrochloride (0.69 g, 10 mmol), and arylhydrazonoethanal (**6**) (10 mmol) was refluxed in acetic anhydride (20 mL) for 6 h. The solvent was removed under vacuum and the residue was poured onto water. The solid product was collected by filtration and crystallized from ethanol.

Method B: A mixture of hydroxylamine hydrochloride (0.69 g, 10 mmol) and arylhydrazononitrile **12** (10 mmol) was refluxed in acetic anhydride (10 mL) for 4 h, and then left to cool at r. t. The solvent was removed under vacuum and the residue was poured onto water. The solid product was collected by filtration and crystallized from ethanol.

M. p. 120 – 122 °C. Yield: 55 %. – IR (KBr): ν = 3396 (NH) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.66 (s, 3H, CH_3), 7.30 – 7.60 (m, 4H, Ar-H), 7.69 – 8.35 (m, 4H, Ar-H), 9.86 (s, 1H, NH). – MS (EI, 70 eV): *m/z* (%) = 357 (13) [M$^+$]. – $C_{16}H_{12}ClN_5O_3$ (357.75): calcd. C 53.72, H 3.38, N 19.58, Cl 9.91; found C 53.60, H 3.40, N 19.38, Cl 9.60.

*2-(4-Chlorophenyl)-4-(4-nitrophenyl)-2H-[1,2,3]triazole (**14**)*

The oxime **11** (10 mmol) was refluxed in acetic anhydride (10 mL) for 4 h, and then left to cool at r. t. The solid product separated was collected by filtration and crystallized from ethanol. M. p. 150 – 152 °C. Yield: 55 %. – IR (KBr): ν = 2925 (CH-Ar), 1601 (C=N) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.48 (d, J = 9 Hz, 2H, Ar-H), 7.61 (d, J = 9 Hz, 2H, Ar-H), 8.04 (d, J = 9 Hz, 2H, Ar-H), 8.32 (d, J = 9 Hz, 2H, Ar-H), 8.15 (s, 1H, triazole 5-H). – MS (EI, 70 eV): *m/z* (%) = 300 (69) [M$^+$], 302 (24) [M$^+$+2]. – $C_{14}H_9ClN_4O_2$ (300.75): calcd. C 55.92, H 3.02, N 18.63, Cl 11.79; found C 55.70, H 3.17, N 18.51, Cl 11.95.

*4-Amino-2-(4-chlorophenyl)-5-(4-nitrophenyl)-2H-pyrazole-3-carbonitrile (**15**)*

To a solution of **12** (3.0 g, 10 mmol) in dioxane (25 mL) and triethylamine (1.01 g, 10 mmol), chloroacetonitrile (1 mL, 0.016 mol) was added. The reaction mixture was refluxed for 3 h and then the solvent evaporated *in vacuo*; the solid product was filtered off and crystallized from ethanol. M.p. 187 – 188 °C. Yield: 85 %. – IR (KBr): ν = 3451, 3348 (NH_2), 2217 (CN) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 6.49 (s, 2H, NH_2), 7.25 – 7.48 (m, 4H, Ar-H), 7.55 (d, J = 10 Hz, 2H, Ar-H), 8.20 (d, J = 10 Hz, 2H, Ar-H). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 145.2, 143.0 (C-3), 141.6, 139.3, 137.6, 135.9 (C-4), 134.6, 128.8, 124.5, 122.2, 119.7 (C-5), 117.9 (CN). – MS (EI, 70 eV): *m/z* (%) = 339 (37) [M$^+$], 341 (11) [M$^+$+2]. – $C_{16}H_{10}ClN_5O_2$ (339.74): calcd. C 56.56, H 2.97, N 20.61, Cl 10.44; found C 56.42, H 3.10, N 20.30, Cl 10.50.

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