Studies with 2-arylhydrazononitriles: a new convenient synthesis of 2, 4-disubstituted- 1,2,3-triazole-5-amines

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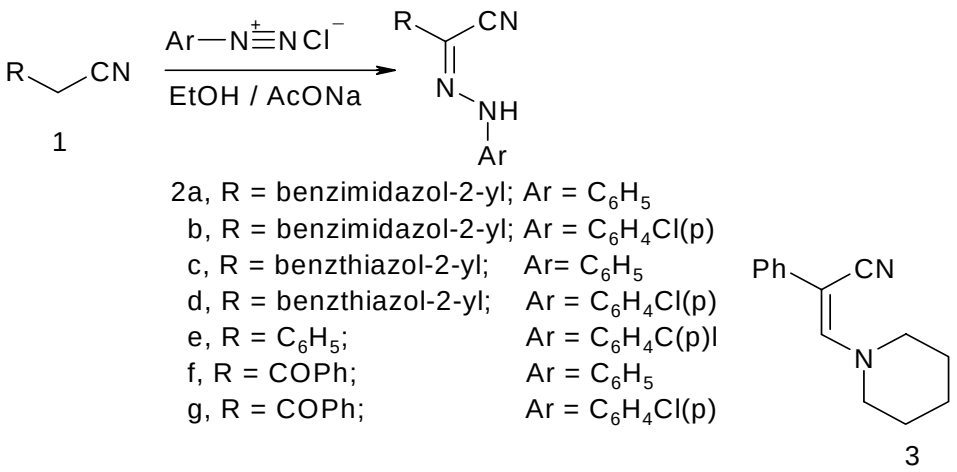
Abstract

A new simple and efficient approach to 2,4-disubstituted 1,2,3-triazoles-5-amines from the reaction of 2-arylhydrazononitriles and hydroxylamine is described. Investigation of behavior of 3-phenyl-3oxo-2-arylhydrazonopropane nitriles has been undertaken. In addition to readily reported formation of aminoisoxazoles, 4-benzoyl-1-aryl-1,2,3-triazole-5-amines **5f,g** were prepared via cyclising products of reacting **2f,g** with hydroxylamine in basic medium.

Keywords: Hydrazononitriles, 1,2,3-triazoles, aminoisoxazoles

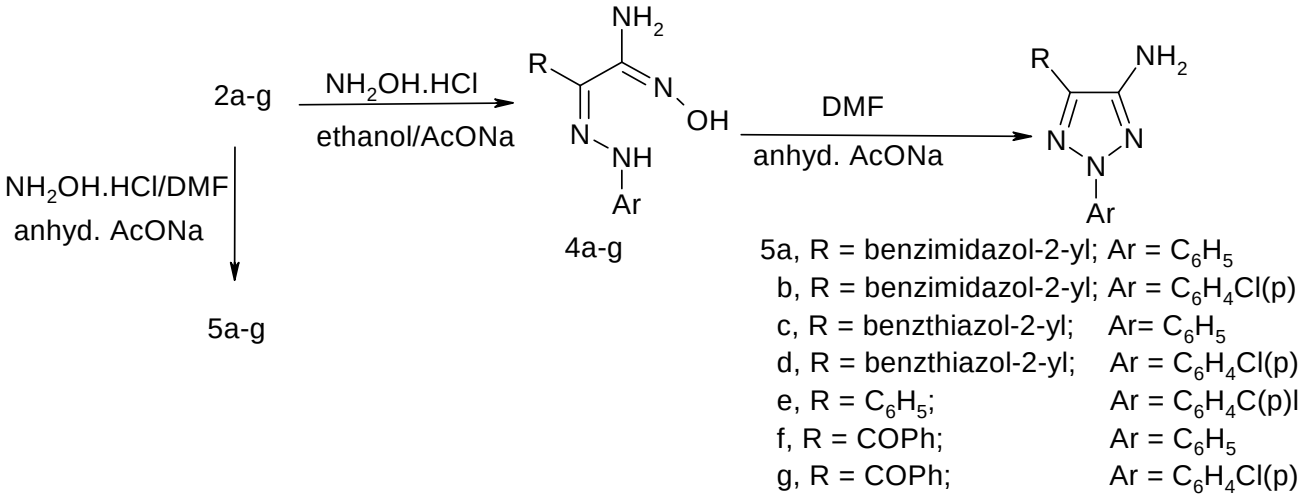
Results and Discussion

1,2,3-triazoles constitute a class of compounds which have attracted considerable attention in industry, agricultural and medicinal chemistry[1-4]. Owing to their importance an impressive number of work has been published on the chemistry and synthesis of 1,2,3-triazoles [5-16]. However, literature inspection indicated lack of efficient synthetic approach to 2-substituted-1,2,3-triazoleamines [15]. Cyclization of 2-arylhydrazonooximes into 1,2,3-triazole oxides has been reported some time ago [15]. Moreover the acetylated derivative of Mesoaldehyde 1,3-dioxime-2-arylhydrazone has been reported to cyclise in acetic acid in presence of $CsCO_3$ into 1,2,3-triazole[17]. We have looked into possible utility of a modification of this approach as a route for synthesis of amino-1,2,3-triazoles. Thus the arylhydrazononitriles **2a-g** were prepared via coupling appropriate active methylene nitriles **1** with aromatic diazonium salts. Compound **2e** has been prepared via reacting **3** with aryldiazonium salts as has been recently described [18] (cf. scheme 1).



Scheme 1

The arylhydrazones **2a-e** reacted smoothly with hydroxylamine hydrochloride in ethanol/sodium acetate to afford amidooximes **4a-e** in excellent yields (cf. scheme 2). The ^{13}C NMR of compounds **4c,d** revealed expected 13 carbon signals. However ^{1}H NMR revealed expected two signals for an oxime OH with the relative intensities of 1 : 1.2, other two signals for hydrazone NH and amino protons appear also at two different positions. This may be interpreted by assuming that amidooximes **4c,d** exists at least in DMSO as a mixture of **4c,d (I)** and **4c,d (II)** (cf. fig. 1). However, when **4a-e** were refluxed in DMF in presence of anhydrous sodium acetate 1,2,3-triazoles **5a-e** were obtained in 75-85% yields (cf. scheme 2). Compounds **5a-e** were directly obtained from reaction of **2a-e** with hydroxylamine hydrochloride in refluxing DMF in presence of anhydrous sodium acetate.



Scheme 2

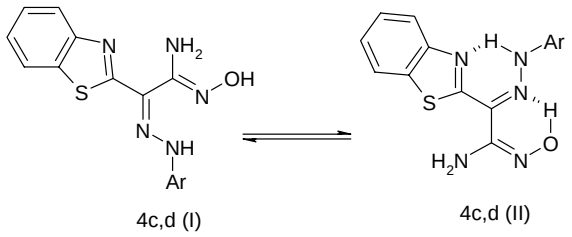


Figure 1. Stereoisomeric conformers of compounds **4c,d**.

In accordance with literature [19] compound **2f** reacted with hydroxylamine hydrochloride in ethanol/sodium acetate solution to yield amidooxime **4f** which then cyclised smoothly via loss of water in DMF and in presence of anhydrous sodium acetate. At first we thought that this product is then the arylazoisoxazole **6**. However, physical data of the reaction product were found different from those reported in literature [19] for **6**. Compound **6** has been prepared from cyclization of amidooxime **4f** in Conc. H_2SO_4 and was found to be really different than our cyclization product **5f** (cf. scheme 3). However at this stage it seemed quite probable that may be our cyclization product is that isoxazole and literature product is really the 1,2,3-triazole. This possibility seemed in fact however, least likely as ^{13}C NMR of cyclization product in DMF revealed carbonyl carbon at δ 185.99 ppm. Conclusive evidence for structure has been obtained via inspection of X-ray structure of compound **5g** (C.f. fig 2 and table 1) for bond angles and bond lengths. X-ray data [20] clearly indicate that the triazole ring is almost planer with extensive delocalization of nitrogen lone pair N-2 at exocyclic carbonyl function such resonance stabilization may be behind readily formation of the triazole ring in this case. Such delocalization can also be envisioned for other derivatives of **5**.

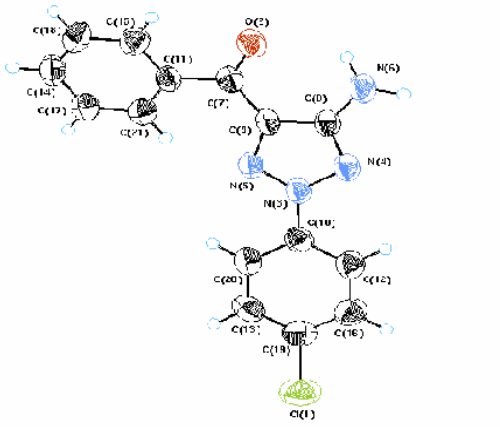


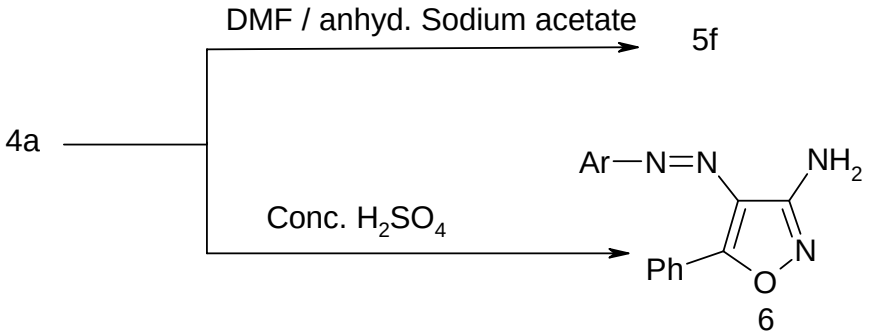
Figure 2. X-ray crystal structure of compound **5g**.

It was found also that on refluxing triazole **5f** in acetic anhydride it gave the acetylated product **8**. This same product was obtained via refluxing **4f** in acetic anhydride for long time, where **4f** is firstly acetylated to 1,2,4-oxadiazole intermediate **7** which readily rearranges into the

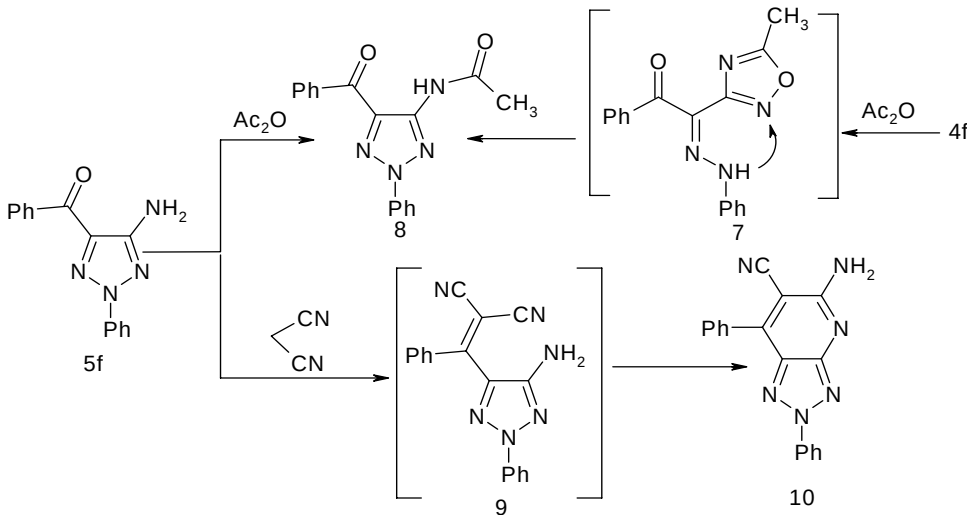
acetyl product 8 . The triazole **5f** also condensed with malononitrile yielding **10** most likely via intermediate **9**.

Table 1. Bond lengths and bind angles of compound **5g**

Bond	Bond length	Bond	Bond angle
N3-N4	1.358	N3-N4-C8	102.80
N3-N5	1.324	N3-N5-C9	104.0
N3-C10	1.416	N4-N3-N5	115.88
N4-C8	1.338	N4-N3-C10	122.5
N6-C8	1.356	N4-C8-N6	122.2
N5-C9	1.340	N5-N3-C10	121.6
C8-C9	1.417	N5-C9-C8	108.3



Scheme 3



Scheme 4

Conclusions

In conclusion a new simple approach to 1,2.3-triazoles amine from 2-arylhydrazononitriles have been achieved. Utility of triazole amines for synthesis of triazolo[4,5-b]pyridine-6-carbonitrile is also achieved.

Experimental

General Procedures. Melting points were determined on a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded in KBr using a FTIR unit Bruker-vector 22 spectrophotometer. The ^{1}H and $^{13}CNMR$ spectra were recorded in DMSO-d_6 as solvent at 300 MHz on Varian Gemini NMR spectrometer using TMS as internal standard. Chemical shifts are reported in δ units (ppm). Mass spectra were measured on a Shimadzu GMMS -QP-1000 EX mass spectrometer at 70 eV. The crystal structure was determined by the X-ray unit at the National Research Center, Dokki, Cairo.

Crystallographic analysis for compound 5g. The crystals were mounted on a glass fiber. All measurements were performed on an ENRAF NONIUNS FR 590. The data were collected at temperature 20 ± 1 ^{o}C using the ω scanning technique to a maximum of 20 of 27.12^{o}. The temperature was solved by direct method using SIR 92 and full-matrix least squares. Non hydrogen atoms were refined anisotropically. Hydrogen atoms were located geometrically and were refined isotropically.

Crystal data

$C_{15}H_{11}N_4O$, M = 298.733, monoclinic, *a* = 12.1876 (4), *b*= 7.8561 (2), c= 17.7250 (7) Å, α = γ = 90.00^{o}, β = 13.(18) *10^{1o} space group: $P2_1/c$. Z = 4, D_x = 1.426 Mg m^{-3}, reflection 5739 measured, θ_{max} = 27.50^{o} , ωR factor = 0.097

General procedures for compounds 4a-g

A mixture of arylhydrazononitriles **2** (10 mmol), and hydroxyl amine was refluxed in ethanol (20 ml) in presence of sodiumacetate for 2 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from ethanol.

2-(*1H*-Benzoimidazol-2-yl)-*N*-hydroxy-2-(phenyl-hydrazono)-acetamidine (4a). Yield: 2.23 g (76%), mp: 232 ^{o}C. *Anal.* Calcd. for $C_{15}H_{14}N_6O$ (294.32): C, 61.22; H, 4.79; N, 28.55. Found: C, 61.34; H, 4.74; N, 28.64. IR (KBr, cm^{-1}): 3455.9, 3358.5, 3255.2 (NH_2, NH, OH); ^{1}H MNR (300 MHz, DMSO-d6): δ, ppm 5.89 (s, 2H, NH_2), 6.96-7.84 (m, 9H, Ar-H) 9.98 (s, 1H, OH), 12.42 (s, 1H, benzimidazole-NH), 14.33 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d6) : δ, ppm 112.47, 113.93, 118.77, 119.15, 121.68, 122.36, 123.94, 129.33, 131.56, 140.96, 143.28, 145.64, 150.69; MS (EI): m/z (%) = 294 (M^+).

2-Benzothiazol-2-yl-*N*-hydroxy-2-(phenyl-hydrazono)-acetamidine (4c). Yield: 2.39 g (77%), mp: 168-170 ^{o}C. *Anal.* Calcd. for $C_{15}H_{13}N_5OS$ (311.37): C, 57.86; H, 4.21; N, 22.49. Found: C,

57.92; H, 4.32; N, 22.38. IR (KBr, cm^{-1}): 3445.6, 324.6, 3054.2 (NH_2, NH, OH); ^1H MNR (300 MHz, DMSO-d6) : δ, ppm 5.80 (s, 1H, NH_2), 7.26 (br s, 1H, NH_2), 7.04 – 8.30 (m, 9H, Ar–H), 10.09 (s, 0.46 H, OH), 10.43 (s, 0.54 H, OH), 13.58 (s, 0.56 H, NH), 14.48 (s, 0.44 H, NH); MS (EI): m/z (%) = 311 (M^+).

2-Benzothiazol-2-yl) -2-[(4-chloro-phenyl)-hydrazono)]-*N*-hydroxy-acetamidine (4d). Yield: 2.70 g (78%), mp: 299-201 °C. *Anal.* Calcd. for $C_{15}H_{12}ClN_5OS$ (345.81): C, 52.10; H, 3.50; N, 20.25. Found: C, 52.23; H, 3.41; N, 20.33. IR (KBr, cm^{-1}): 3425.4, 3354.3, 3266.5, 3057.4 (NH_2, NH, OH); ^1H MNR (300 MHz, DMSO-d6) : δ, ppm 5.83 (s, 1H, NH_2), 7.27 (br s, 1H, NH_2), 7.30-8.32 (m, 8H, Ar-H), 10.12 (s, 0.52 H, OH), 10.44 (s, 0.48 H, OH), 13.57 (s, 0.48 H, NH), 14.48 (s, 0.52 H, NH); MS (EI): m/z (%) = 345 (M^+).

General procedures for compounds 5a-g

A mixture of arylhydrazononitriles **2** (10 mmol), and hydroxyl amine was refluxed in DMF (20 ml) in presence of anhydrous sodiumacetate (2g) for 8 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from proper solvent.

5-(*1H*-Benzoimidazol-2-yl)-2-phenyl-*2H*-[1,2,3]triazol-4-ylamine (5a). Yield: 2.24 g (81%), mp: 248-250 °C. *Anal.* Calcd. for $C_{15}H_{12}N_6$ (276.30): C, 65.21; H, 4.38; N, 30.42. Found: C, 65.37; H, 4.29; N, 30.53. IR (KBr, cm^{-1}): 336.3, 3278.8, 3151.5 (NH_2, NH); ^1H MNR (300 MHz, DMSO-d6): δ, ppm 6.32 (s, 2H, NH_2), 7.23 – 7.98 (m, 9H, Ar-H), 13.05 (s, 1H, NH); MS (EI): m/z (%) = 276 (M^+).

5-(*1H*-Benzoimidazol-2-yl)-2-(4-chloro-phenyl-*2H*-[1,2,3]triazol-4-ylamine (5b). Yield: 2.36 g (76%), mp: 278-280 °C. *Anal.* Calcd. for $C_{15}H_{11}ClN_6$ (310.75): C, 57.98; H, 3.57; N, 27.04. Found: C, 57.86; H, 3.42; N, 27.13. IR (KBr, cm^{-1}): 3360.8, 3273.1, 3191.2 (NH_2, NH); ^1H MNR (300 MHz, DMSO-d6) : δ, ppm 6.38 (s, 2H, NH_2), 7.25 (d, 2H, Ar-H), 7.55-7.65 (m, 4H, benzimidazole-H), 7.96 (d, 2H, Ar-H), 13.08 (s, 1H, benzimidazole-NH); MS (EI): m/z (%) = 310 (M^+).

5-Benzothiazol-2-yl)-2-phenyl-*2H*-[1,2,3]triazol-4-ylamine (5c). Yield: 2.17 g (74%), mp: 205-207 °C. *Anal.* Calcd. for $C_{15}H_{11}N_5S$ (293.35): C, 61.42; H, 3.78; N, 23.87. Found: C, 61.53; H, 371; N, 23.96. IR (KBr, cm^{-1}): ν 3401.4, 3294.4 (NH_2); ^1H MNR (300 MHz, DMSO-d6) : δ, ppm 6.45 (s, 2H, NH_2), 7.37-7.57 (m, 5H, Ph-H), 7.93-8.14 (m, 4H, benzothiazol-H); MS (EI): m/z (%) = 293 (M^+).

5-Benzothiazol-2-yl)-2-(4-chloro-phenyl)-*2H*-[1,2,3]triazol-4-ylamine (5d). Yield: 2.56 g (78%), mp: 230-232 °C. *Anal.* Calcd. for $C_{15}H_{10}ClN_5S$ (327.80): C, 54.96; H, 3.07; N, 21.36. Found: C, 54.89; H, 3.18; N, 21.42. IR (KBr, cm^{-1}): 3303.7, 3150.4 (NH_2); ^1H MNR (300 MHz, DMSO-d6) : δ, ppm 6.91 (s, 2H, NH_2), 7.46-8.16 (m, 8H, Ar-H); ^{13}C NMR (DMSO-d6) : δ, ppm 122.26, 123.18, 125.49, 125.81, 126.54, 129.46, 132.14, 134.46, 135.45, 153.42, 154.27, 155.77, 159.17; MS (EI): m/z (%) = 327 (M^+).

2-(4-Chlorophenyl)-5-phenyl-2*H*-[1,2,3]triazole-4-ylamine (5e). Yield: 2.19 g (81%), mp: 165 °C. *Anal.* Calcd. for $C_{14}H_{11}ClN_4$ (270.72): C, 62.11; H, 4.10; N, 20.71. Found: C, 62.31; H, 4.12; N, 20.83. IR (KBr, cm^{-1}): 3331.3, 3170.4 (NH_2); ^1H MNR (300 MHz, DMSO-d6) : δ, ppm 5.86 (s, 2H, NH_2), 7.36-7.78 (m, 9H, Ar-H); MS (EI): m/z (%) = 270 (M^+).

5-Amino-2-phenyl-*2H*-[1,2,3]triazole-4-yl)-phenyl-methanone (5f). Yield: 1.95 g (74%), mp: 102-103 °C. *Anal.* Calcd. for $C_{15}H_{12}N_4O$ (264.29): C, 68.17; H, 4.58; N, 21.20. Found: C, 68.23; H, 4.38; N, 21.26. IR (KBr, cm^{-1}): 3426.9, 3295.1 (NH_2), 1632.5 (CO); ^{1}H MNR (300 MHz, DMSO-d6) : δ, ppm 6.56 (s, 2H, NH_2), 7.38-8.32 (m, 10H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d6) : δ, ppm 118.39, 127.83, 128.38, 129.58, 129.62, 130.84, 132.76, 136.87, 138.71, 156.71, 185.98; MS (EI): m/z (%) = 264 (M^+).

5-Amino-2-(4-chloro-phenyl)-*2H*-[1,2,3]triazol-4-yl]-phenyl-methanone (5g). Yield: 2.24 g (75%), mp: 158-160 °C. *Anal.* Calcd. for $C_{15}H_{11}ClN_4O$ (298.73): C, 60.31; H, 3.71; N, 18.75. Found: C, 60.43; H, 3.67; N, 18.69. IR (KBr, cm^{-1}): 3458.1, 3352.7 (NH_2), 1627.8 (CO); ^{1}H MNR (300 MHz, DMSO-d6): δ, ppm 6.58 (s, 2H, NH_2), 7.55 – 8.29 (m, 9H, Ar-H); MS (EI): m/z (%) = 298 (M^+).

Preparation of *N*-(5-Benzoyl-2-phenyl-2*H*-[1,2,3]azol-4-yl)acetamide (8)

Method A. 10 mmol of triazole 5f was refluxed in acetic anhydride (20 ml) for 1.5 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from ethanol.

Method B. 10 mmol of amidoxime **4f** was refluxed in acetic anhydride (20 ml) for 4 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from ethanol.

Yield: 2.27 g (74%), mp: 138-140 °C. *Anal.* Calcd. for $C_{17}H_{14}N_4O_2$ (306.33): C, 66.66; H, 4.61; N, 18.29. Found: C, 66.42; H, 4.73; N, 18.26. IR (KBr, cm^{-1}): 3324.5 (NH), 1692.8, 1636.7 (CO); ^{1}H MNR (300 MHz, DMSO-d6): δ, ppm 2.07 (s, 3H, CH_3), 7.43-8.08 (m, 10H, Ar-H), 10.71 (s, 1H, NH); ^{13}C NMR (DMSO-d6): δ, ppm 22.81, 118.56, 128.26, 128.47, 129.64, 129.69, 133.40, 136.32, 137.26, 138.58, 144.85, 168.05, 185.99; MS (EI): m/z (%) = 306 (M^+).

Preparation of 5-Amino-2,7-diphenyl-2*H*-[1,2,3]triazolo[4,5-b]pyridine-6-carbonitrile (10)

A mixture of triazole **5f** (10 mmol), and malononitrile (10mmol) was refluxed in ethanol (20 ml) in presence of piperidine (0.5 ml) for 4 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from ethanol.

Yield: 2.12 g (68%), mp: 285-287 °C. *Anal.* Calcd. for $C_{18}H_{12}N_6$ (312.34): C, 69.22; H, 3.87; N, 26.91. Found: C, 69.31; H, 3.84; N, 27.01. IR (KBr, cm^{-1}): 3409.5, 3333.3 (NH_2), 2213.9 (CN); ^{1}H MNR (300 MHz, DMSO-d6): δ, ppm 4.10 (s, 2H, NH_2), 7.28-7.46 (m, 10H, ph-H); MS (EI): m/z (%) = 312 (M^+).

References

1. Kadaba, P. U. *J. Med. Chem.* **1988**, *31*, 196.
2. Wamhoff, H. In *Comprehensive Heterocyclic Chemistry*, K. T. Potts, Ed., Pergamon: Oxford, 1984; pp 669.
3. Ferrarini, P. L.; Livi, O. *Il Farmaco ed. Sci.* **1981**, *83*, 243.

4. Matloubi, H.; Shafiee, A.; Saemian, N.; Shirvani, G.; Daha, F. J., *Applied Radiation and Isotopes* **2004**, *60*, 665.
5. Invidiata, F. Paolo; Aiello, S.; Furno, G.; Aiello, E. *J. Heterocycl. Chem.* **2000**, *30*, 355.
6. Lalezari, I.; Gomez, L. A.; Khorshidi, M. *J. Heterocycl. Chem.* **1990**, *27*, 687.
7. Molteni, G.; Del Buttero, P. *Tetrahedron* **2005**, *61*, 4983.
8. Zhao, Y.-B.; Yan, Z.-Y.; Liang, Y.-M. *Tetrahedron Lett.* **2006**, *47*, 1545.
9. Chittaboina, S.; Xie, F.; Wang, Q. *Tetrahedron Lett.* **2005**, *46*, 2331.
10. Kiselyou, A. S. *Tetrahedron Lett.* **2006**, *47*, 2631.
11. Batori, S.; Gacs-Baitz, E.; Bokotey, S.; Messmer, A. *Tetrahedron* **2003**, *59*, 4297.
12. IJsselstijn, M.; Cintrat, J.-C. *Tetrahedron,* Science direct online, Click chemistry with ynamides.
13. Huisgen, R.; Knorr, R.; Mobius, L.; Szeimies, *Chem. Ber* **1965**, *98*, 4014.
14. Businelli, S.; Martino, E. D.; Zanirato, P. *Arkivoc* **2001**, *(i),* 131.
15. Fan, W. Q.; Katritzky, A. R. *Comprehensive Heterocyclic Chemistry II*, Elsevier: New York, 1996; Vol 4.
16. Rai, B; Lakhan, R. Indian *J. Chem., Sect. B* **1989**, *28B*(7), 595.
17. Swartz, D. L.; Karash, A. R.; Berry, L. A. and Jaeger, D. L. *Journal of Heterocycl. Chem.* **1983**, *20*, 1561.
18. Elnagdi, N. M., Ph.D. Thesis, Cairo University, **2006**.
19. Elnagdi, M. H.; Elmoghayer, M. R. H.; Hafez, E. A.; Almina, H. H. *J. Org. Chem.* **1975**, *40*, 2604.
20. Further details of the crystal structure of **5g** will be available in the Cambridge Crystallographic Data center under deposit nos. CCDC 613081.