Studies With 2-Arylhydrazononitriles: A Novel Simple, Efficient Route To 5-Acyl-2-Substituted-1,2,3-Triazol-4-Amines

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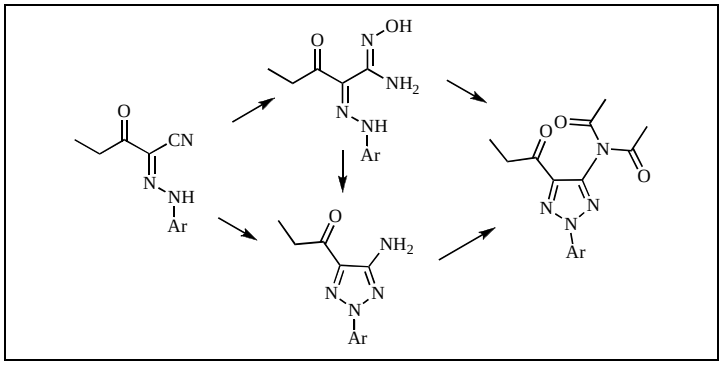

Efficient route to 5-acyl-2-substituted-1,2,3-triazol-4-amines *via* reaction of 3-oxo-2-(arylhydrazono)-pentanenitrile with hydroxylamine hydrochloride is reported. X-ray crystal structure has been made to confirm the structure of reaction products.

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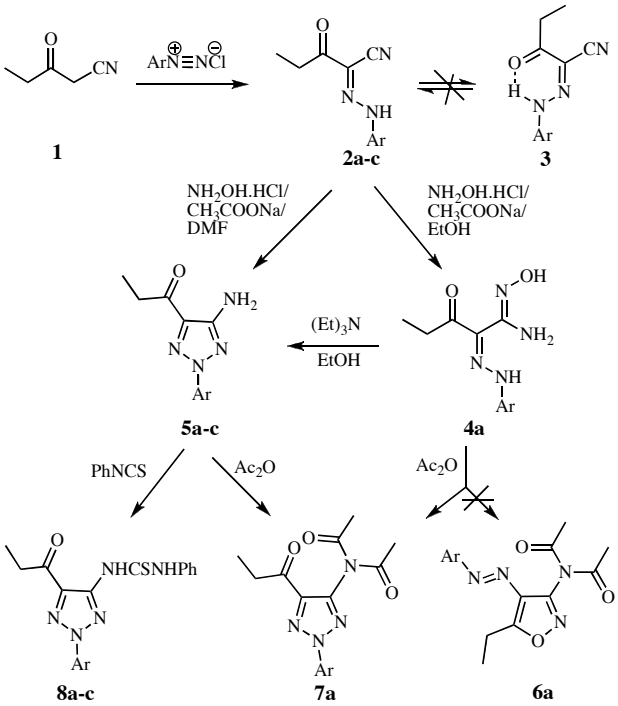
INTRODUCTION

Arylhydrazononitriles are readily obtainable materials [1-3] and their chemistry has been extensively investigated in our laboratories [4-6]. The utility of some of the arylhydrazononitriles by several other authors in published [7] and patent [8,9] literature prompted us to explore further interesting synthetic potentials of such compounds as precursors for heteroaromatic amines that could be utilized as intermediates in dye and pharmaceutical industries [10]. In the present article we report a novel route for 5-acyl-2-aryl-1,2,3-triazole-4-amines that may be interesting as precursors for the synthesis of the potentially biologically active condensed 1,2,3-triazole ring. The biological importance of Zaprinast [11], Tazobactam [12] and some anti-HIV agents [13,14] that incorporate such ring in their structures has been well established.

RESULTS AND DISCUSSION

Reaction of 2-oxopentanenitrile (**1**) with aromatic diazonium salts afforded the corresponding coupling products (Scheme 1). Although these can be represented as **2** or **3**, several authors [15,16] have assumed the predominance of **3** to account for the deshielding of NH. However, X-ray crystal structure (*cf*. Figure 1 and Table 1 for selected bond lengths and bond angles), clearly indicates that these compounds exit in the antiform **2a**. Thus deshielding of hydrazone NH may be due to the creation of positive charge on hydrazone NH through lone pair delocalization. Similar assumption has been recently made by El-Dusouqui *et al* [16]. Possible deschielding *via* hydrogen bonding with NMR solvent (DMSO) cannot be



a, Ar= *p*-Cl-C_6H_4
b, Ar=*o*-Cl-C_6H_4
c, Ar=*p*-CH_3-C_6H_4

Scheme 1

over looked as in $CDCl_3$ the hydrazone NH resonance appears at 9.23 ppm.

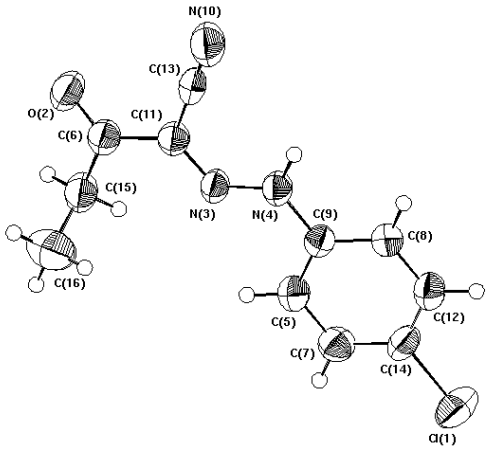


Figure 1. X-ray crystal structure for compound **2a**.

Table 1 selected bond lengths and bond angles. *Geometric parameters (Å, °.)*, for compound **2a**

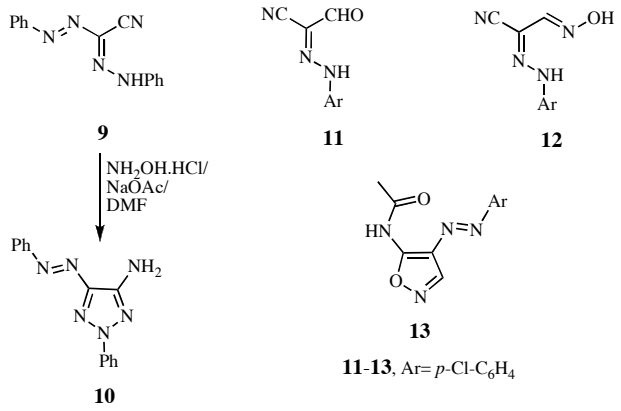
Bond	**Bond lengths**
$O_2—C_6$	1.213
$N_3—N_4$	1.301
$N_3—C_{11}$	1.313
$N_4—C_9$	1.415
$C_6—C_{11}$	1.475
Bond	**Bond angles**
$N_4—N_3—C_{11}$	121.47
$N_3—N_4—C_9$	118.97
$O_2—C_6—C_{11}$	118.5
$O_2—C_6—C_{15}$	122.2
$C_{11}—C_6—C_{15}$	119.3
$N_4—C_9—C_5$	121.2
$N_4—C_9—C_8$	118.5
$N_3—C_{11}—C_6$	118.8
$N_3—C_{11}—C_{13}$	123.9
$C_6—C_{11}—C_{13}$	117.3

El-Bannany *et al* [17] have earlier reported the formation of 1,2,3-triazoles from reaction of some hydrazononitriles with phenylhydrazine. This synthesis however is rather atom non economic as it involves elimination of aniline. We thus believe that the utility of hydroxylamine in these transformations is more attractive approach.

Compound **2a**, reacted readily with hydroxylamine hydrochloride in ethanolic sodium acetate to yield amidoxime **4a**, in 91 % yield. This was cyclized on reflux with acetic anhydride to yield diacylated dehydration products. At first glance we assumed formation of isoxazoles **6a** in analogy to well established structures suggested for the products of cyclization of amidoximes in acid and base media [18]. However, we noted in ^{13}C NMR the presence of low field carbonyl carbon at δ 195.7 ppm. We thus considered the possibility that the cyclization has afforded the 1,2,3-triazole **7a**. Later, this was confirmed by X-ray crystal structure (*cf.* Figure 2 and Table 2 for selected bond lengths and bond angles), which indicates that the N-2 lone pair is extensively delocalized at both N-1 and N-3. Although routes to amino-1,2,3-triazoles are well established [19], but these routes could not be adapted for the preparation of 2-substituted-1,2,3-triazol-4-amines (Scheme 1).

In an earlier study, the formation of N-oxide on cyclizing amidoxime has normally been observed [19]. In this work, when the amidoxime **4a** was refluxed in DMF in the presence of excess of triethylamine, the 1,2,3-triazole-4-amine **5** was produced. Typical for heteroaromatic amines, the amino function in **5a-c** reacted with phenylisothiocyanate yielding the thiourea derivative **8a-c**. However, attempts to diazotize this amino function failed.

Similar to the behaviour of **2** the nitrile **9**, recently obtained in our laboratories via reacting **11** with benzenediazonium chloride [3], reacted with hydroxylamine hydrochloride in DMF solution to yield the arylazo-1,2,3-triazoleamime **10**. In addition, when compound **11** reacted with hydroxylamine hydrochloride, the amidoxime **12** was produced and then cyclized in Ac_2O into acetylamino-isoxazole **13** (Scheme 2). These results agree with our earlier report [3], but contradict our findings shown above.



Scheme 2

In conclusion we succeeded to offer a new and efficient general route to synthesize substituted 1,2,3-triazole amines that could be of importance for utility in dyes, pharmaceutical and agrochemical industries.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr disks using a Pye-Unicam SP-3000 IR spectrophotometer and Testscan Shimadzu FT-IR 8000 series. ^1H and ^{13}C NMR spectra were measured in DMSO-d_6 at 400/100 and 300/75 MHz on a Varian Gemini relative to DMSO (2.50 ppm for ^1H and 39.5 ppm for ^{13}C); chemical shifts are reported in δ (ppm). Mass spectra were measured on a GCMS-QP 1000-EX Shimadzu.

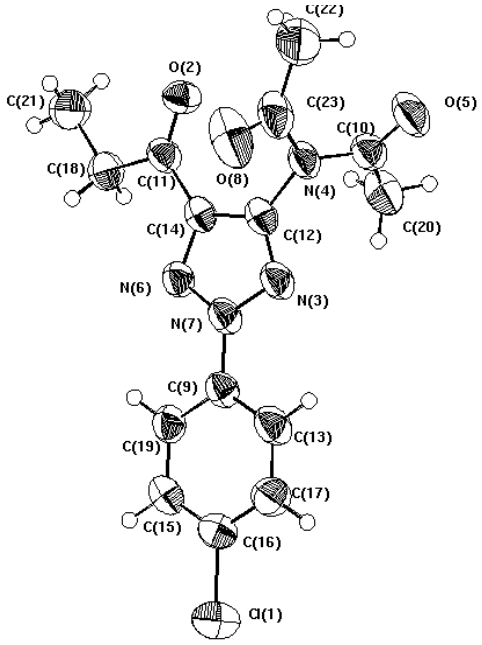


Figure 2. X-ray crystal structure for compound **7a.**

Table 2 selected bond lengths and bond angles. *Geometric parameters (Å, °.)*, for compound **7a**

Bond	**Bond lengths**
N_3—N_7	1.346
N_3—C_{12}	1.323
N_4—C_{12}	1.423
N_4—C_{23}	1.422
O_5—C_{10}	1.210
N_6—N_7	1.322
N_6—C_{14}	1.335
N_7—C_9	1.428
Bond	**Bond angles**
N_7—N_3—C_{12}	101.8
C_{10}—N_4—C_{12}	120.8
C_{10}—N_4—C_{23}	124.1
C_{12}—N_4—C_{23}	115.2
N_7—N_6—C_{14}	104.2
N_3—N_7—N_6	116.1
N_3—N_7—C_9	121.7
N_3—C_{12}—N_4	121.3
N_6—N_7—C_9	122.2

Crystal structures were performed using Envaf Nonius 591 Kappa CCD single crystal diffraction. Elemental analyses were carried out by the Microanalytical Center of Cairo University, Giza, Egypt. 3-Oxo-pentanenitrile **1** [15], phenylhydrazono(phenylazo)-acetonitrile **9** [3, 20] were prepared as previously reported.

Structural date have been deposited at Cambridge Crystallographic Data Centre, deposition number for **2a** and **7a** CCDC 612931 and 612930.

General procedure for the preparation of 2-aryl-hydrazono-3-oxo-pentanenitrile (2b-d). To a mixture of **1** (9.70 g, 0.1 mol) in ethanol (100 ml), sodium acetate (20 g, 0.24 mol) was added. The mixture was then added gradually with stirring at room temperature to a cold solution of the appropriate aryldiazonium salt (prepared from 0.1 mol of aromatic amine and appropriate quantities of hydrochloric acid and sodium nitrile) the product was separated on standing, collected by filtration and crystallized from ethanol.

2-[(4-Chloro-phenyl)-hydrazono]-3-oxo-pentanenitrile (2a). This compound was obtained as yellow crystals, (yield 72%, 17.0 g) mp 153-154°C; ir (KBr): ν_{max} 3436 (NH), 2212 (CN) 1667 cm^{-1} (CO); ^{1}H nmr (400 MHz, DMSO-d_6): δ 1.05 (t, 3H, J = 7.3 Hz, CH_3), 2.89 (q, 2H, J = 7.3 Hz, CH_2), 7.48 (d, 2H, J = 8.9 Hz, Ar-H), 7.54 (d, 2H, J = 8.9 Hz, Ar-H), 12.28 ppm (brs, 1H, NH); ^{13}C nmr (100 MHz; DMSO-d_6): δ 196.3, 142.0, 130.6, 130.4, 129.7, 119.2, 118.8, 114.6, 111.9, 30.5, 9.0 ppm; ms (70 eV) m/z 235 (M^+, 40%), 111 (p-$ClC_6H_4^+$). Anal. calcd. for $C_{11}H_{10}ClN_3O$: (235.67) C, 57.35; H, 4.28; N, 17.83. Found: C, 57.35; H, 4.51; N, 17.34.

2-[(2-Chloro-phenyl)-hydrazono]-3-oxo-pentanenitrile (2b). This compound was obtained as yellow crystals, (yield 66%, 15.5 g) mp 128-130°C; ir (KBr): ν_{max} 3420 (NH), 2217 (CN) 1654 cm^{-1} (CO); ^{1}H nmr (300 MHz, DMSO-d_6): δ 1.07 (t, 3H, J = 7.2 Hz, CH_3), 2.87 (q, 2H, J = 7.2 Hz, CH_2), 7.22-7.27 (m, 1H, Ar-H), 7.42-7.76 (m, 3H, Ar-H), 11.00 ppm (brs, 1H, NH); ms (70 eV) m/z 235 (M^+, 39 %), 111 (o-$ClC_6H_4^+$). Anal. calcd. for $C_{11}H_{10}ClN_3O$: (235.67) C, 56.06; H, 4.28; N, 17.83. Found: C, 56.18; H, 4.20; N, 18.21.

3-Oxo-2-(*p*-tolyl-hydrazono)-pentanenitrile (2c). This compound was obtained as yellow crystals, (yield 76%, 16.3 g) mp 110-111°C; ir (KBr): ν_{max} 3240 (NH), 2215 (CN) 1683 cm^{-1} (CO); ^{1}H nmr (300 MHz, DMSO-d_6): δ 1.05 (t, 3H, J = 7.5 Hz, CH_3), 2.92 (s, 3H, CH_3), 2.85 (q, 2H, J = 7.5 Hz, CH_2), 7.20 (d, 2H, J = 8.4 Hz, Ar-H), 7.42 (d, 2H, J = 8.4 Hz, Ar-H), 12.12 ppm (brs, 1H, NH); ms (70 eV) m/z 215 (M^+, 44%), 91 ($C_7H_7^+$). Anal. calcd. for $C_{12}H_{13}N_3O$: (215.25) C, 66.96; H, 6.09; N, 19.52. Found: C, 66.32; H, 6.34; N, 19.89.

2-[(4-Chloro-phenyl)-hydrazono]-N-hydroxy-3-oxo-pentan-amidine (4a). A mixture of **2a** (0.235 g, 1 mmol) in 20 ml EtOH, hydroxylamine hydrochloride (0.069 g, 1 mmol) and sodium acetate (1 mmol) was heated under reflux for 2 hrs. the reaction mixture was then poured into water, collected by filtration and recrystallized from ethanol to give red crystal, (yield 91%, 0.244 g) mp 110-112°C; ir (KBr): ν_{max} 3496 (NH), 3379 (NH_2, OH) 1647 cm^{-1} (CO); ^{1}H nmr (400 MHz, DMSO-d_6): δ 1.04 (t, 3H, J = 7.3 Hz, CH_3), 2.97 (q, 2H, J = 7.3 Hz, CH_2), 6.53 (brs, 2H, NH_2), 7.32 (d, 2H, J = 8.7 Hz, Ar-H), 7.45 (d, 2H, J = 8.7 Hz, Ar-H), 10.21 (brs, 1H, NH), 13.68 ppm (s, 1H, OH); ^{13}C nmr (100 MHz; DMSO-d_6): δ 201.9, 151.9, 142.5, 129.5, 128.1, 127.3, 117.4, 31.6, 9.8 ppm; ms (70 eV) m/z 268 (M^+, 34%) 251(M^+- 17), (M^+- p-ClC_6H_4), 111 (p-$ClC_6H_4^+$). Anal. calcd. for $C_{11}H_{13}ClN_4O_2$: (268.70) C, 49.17; H, 4.88; N, 20.85. Found: C, 49.65; H, 4.69; N, 20.40.

General procedure for the preparation of 1-(5-Amino-2-aryl-2*H*-[1,2,3]triazol-4-yl)-propan-1-one (5a-c). *Method A*: A mixture of **2a-c** (1 mmol) in 15 ml DMF, hydroxylamine hydrochloride (0.069 g, 1 mmol) and sodium acetate (1 mmol) was heated under reflux for 40 min. the reaction mixture was then poured into water, the solid collected by filtration and recrystallized from ethanol to give **5a-c** in 72, 63, 69 % yield, respectively. *Method B*: A mixture of **4a** (0.27 g, 1 mmol) and 5 ml triethylamine in 10 ml absolute EtOH was heated under reflux for 3 hrs, left to cool, then poured into H_2O, neutralized by HCl. The solid product, so formed, was collected by filtration and crystallized from EtOH to give **5a** in 83 % yield.

1-[5-Amino-2-(4-chloro-phenyl)-2*H*-[1,2,3]triazol-4-yl]-propan-1-one (5a). This compound was obtained as red crystals, mp 135-137°C; ir (KBr): ν_{max} 3468, 3367 (NH_2), 1667 cm^{-1} (CO); ^{1}H nmr (300 MHz, DMSO-d_6): δ 1.11 (t, 3H, J = 7.2

Hz, CH_3), 2.97 (q, 2H, J = 7.2 Hz, CH_2), 6.22 (brs, 2H, NH_2) 7.55 (d, 2H, J = 8.5 Hz, Ar-H), 7.90 ppm (d, 2H, J = 8.5 Hz, Ar-H); ^{13}C nmr (75 MHz; DMSO-d_6): δ 195.69, 154.49, 137.49, 131.75, 131.47, 129.50, 119.67, 31.65, 7.78 ppm; ms (70 eV) m/z 250 (M^+, 37%), 221 (M^+- 29), 139 (M^+- *p*-ClC_6H_4), 111 (*p*-$ClC_6H_4^+$). Anal. calcd. for $C_{11}H_{11}ClN_4O$: (250.68) C, 52.70; H, 4.42; N, 22.35. Found: C, 52.08; H, 4.67; N, 21.94.

1-[5-Amino-2-(2-chloro-phenyl)-2*H*-[1,2,3]triazol-4-yl]-propan-1-one (5b). This compound was obtained as red crystals, mp 135-136°C; ir (KBr): ν_{max} 3422, 3289 (NH_2), 1627 cm^{-1} (CO); ^{1}H nmr (300 MHz, DMSO-d_6): δ 1.31 (t, 3H, J = 7.5 Hz, CH_3), 3.12 (q, 2H, J = 7.5 Hz, CH_2), 6.47 (brs, 2H, NH_2) 7.41-7.48 (m, 2H, Ar-H), 7.66-7.71 ppm (m, 2H, Ar-H); ^{13}C nmr (75 MHz; DMSO-d_6): δ 176.4, 155.5, 147.2, 133.1, 131.9, 130.4, 128.0, 125.2, 116.7, 19.1, 11.2 ppm; ms (70 eV) m/z 250 (M^+, 48%), 221 (M^+- 29), 139.(M^+- *o*-ClC_6H_4), 111 (*o*-$ClC_6H_4^+$). Anal. calcd. for $C_{11}H_{11}ClN_4O$: (250.68) C, 52.70; H, 4.42; N, 22.35. Found: C, 52.31; H, 4.13; N, 22.52.

1-(5-Amino-2-*p*-tolyl-2*H*-[1,2,3]triazol-4-yl)-propan-1-one (5c). This compound was obtained as red crystals, mp 148-149°C; ir (KBr): ν_{max} 3204 (NH_2), 1708 cm^{-1} (CO); ^{1}H nmr (300 MHz, DMSO-d_6): δ 1.25 (t, 3H, J = 8.4 Hz, CH_3), 2.29 (s, 3H, CH_3) 2.66 (q, 2H, J = 8.4 Hz, CH_2), 6.30 (brs, 2H, NH_2) 7.23 (d, 2H, J = 9.8 Hz, Ar-H), 7.51 ppm (d, 2H, J = 9.8 Hz, Ar-H); ^{13}C nmr (75 MHz; DMSO-d_6): δ 205.0, 163.4, 13.9.0 135.7, 129.8, 118.9, 116.8, 30.6, 20.48, 10.4 ppm; ms (70 eV) m/z 231 (M^++1, 20%), 202 (M^+-29), 140 (M^+- *p*-$CH_3C_6H_4$). Anal. calcd. for $C_{12}H_{14}N_4O$: (230.27) C, 62.59; H, 6.13; N, 24.33. Found: C, 62.22; H, 6.42; N, 23.98.

N-Acetyl-N-[2-(4-chloro-phenyl)-5-propionyl-2*H*-[1,2,3]-triazol-4-yl]-acetamide (7a). *Method A*: A mixture of **4a** (0.27 g, 0.01 mol) and 15 ml of acetic anhydride was refluxed for 4.5 hrs then poured into H_2O. The solid formed was collected by filtration and crystallized from ethanol to yield 2.6 g (78 %). *Method B*: A mixture of **5a** (0.25 g, 0.01 mol) and 15 ml of acetic anhydride was refluxed for 2 hrs then poured into H_2O. The solid that formed was collected by filtration and crystallized from ethanol to yield 2.8 g (84 %). This compound was obtained as red crystals, X-ray crystal structure figure 2, mp 154-155°C; ir (KBr): ν_{max} 1722 (CO), 1672 cm^{-1} (CO); ^{1}H nmr (300 MHz, DMSO-d_6): δ 1.10 (t, 3H, J = 7.2 Hz, CH_3), 2.14 (s, 6H, $2CH_3$), 2.99 (q, 2H, J = 7.2 Hz, CH_2), 7.60 (d, 2H, J = 9.0 Hz, Ar-H), 7.97 ppm (d, 2H, J = 9.0 Hz, Ar-H); ^{13}C nmr (75 MHz; DMSO-d_6): δ 194.66, 171.40, 144.36, 137.22, 132.78, 129.72, 120.20, 32.86, 23.11, 7.38 ppm; ms (70 eV) m/z 291 (M^+- CH_3CO), 248 (291-43). Anal. calcd. for $C_{15}H_{15}ClN_4O_3$: (334.76) C, 53.82; H, 4.52; N, 16.74. Found: C, 54.09; H, 4.31; N, 16.43.

General procedure for the preparation of 1-(2-aryl-5-propionyl-2*H*-[1,2,3]triazol-4-yl)-3-phenyl-thiourea (8a-c). A mixture of **5a-c** (1 mmol) in DMF (10 ml), phenylisothiocyanate (0.135 g, 1 mmol) and KOH (0.056 g, 1 mmol) was stirred at room temperature for 24 hrs. the reaction mixture was then poured into ice water, and neutralize by HCl, the solid so formed was collected by filtration and recrystallized from ethanol to give **8a-c**.

1-[2-(4-Chloro-phenyl)-5-propionyl-2*H*-[1,2,3]triazol-4-yl]-3-phenyl-thiourea (8a). This compound was obtained as orange crystals, (yield 83%, 0.32 g) mp 190-191°C; ir (KBr): ν_{max} 3483 (NH), 3365 (NH), 1672 cm^{-1} (CO); ^{1}H nmr (300 MHz, DMSO-d_6): δ 1.09 (t, 3H, J = 8.7 Hz, CH_3), 2.96 (q, 2H, J = 8.7 Hz, CH_2), 6.24 (brs, 1H, NH), 7.21-7.41 (m, 3H, phenyl-H), 7.53 (d, 2H, J = 10.5 Hz, Ar-H), 7.59-7.62 (m, 2H, phenyl-H), 7.87 (d, 2H, J = 10.5 Hz, Ar-H) 9.70 ppm (brs, 1H, NH); ^{13}C nmr (75 MHz; DMSO-d_6): δ 195.7, 154.5, 137.5, 131.8, 131.7 131.5, 129.7, 129.5, 128.6, 124.8, 120.5, 119.7, 31.7, 7.8 ppm; ms (70 eV) m/z 385 (M^+, 33%), 249 (M^+- PhNHCS), 111 (*p*-$ClC_6H_4^+$). Anal. calcd. for $C_{18}H_{16}ClN_5OS$: (385.87) C, 56.03; H, 4.18; N, 18.15. Found: C, 55.81; H, 4.39; N, 18.57.

1-[2-(2-Chloro-phenyl)-5-propionyl-2*H*-[1,2,3]triazol-4-yl]-3-phenyl-thiourea (8b). This compound was obtained as red crystals, (yield 75%, 0.29 g) m.p.175-177 °C; ir (KBr): ν_{max} 3472, 3325 (NH_2), 1678 cm^{-1} (CO); ^{1}H nmr (300 MHz, DMSO-d_6): δ 1.15 (t, 3H, J = 8.7 Hz, CH_3), 3.11 (q, 2H, J = 8.7 Hz, CH_2), 6.80 (brs, 1H, NH), 7.10-7.84 (m, 8H, phenyl-H and Ar-H) 14.57 ppm (brs, 1H, NH); ms (70 eV) m/z 385 (M^+, 48%), 249 (M^+- PhNHCS), 111 (*o*-$ClC_6H_4^+$). Anal. calcd. for $C_{18}H_{16}ClN_5OS$: (385.87) C, 56.03; H, 4.18; N, 18.15. Found: C, 56.31; H, 4.27; N, 17.91.

1-Phenyl-3-(5-propionyl-2-*p*-tolyl-2*H*-[1,2,3]triazol-4-yl)-thiourea (8c). This compound was obtained as dark red crystals, (yield 77%, 0.28 g) mp 215-216 °C; ir (KBr): ν_{max} 3456, 3195 (NH_2), 1682 cm^{-1} (CO); ^{1}H nmr (300 MHz, DMSO-d_6): δ 1.17 (t, 3H, J = 8.7 Hz, CH_3), 2.27 (s, 3H, CH_3), 3.05 (q, 2H, J = 8.7 Hz, CH_2), 7.14-7.17 (m, 4H, phenyl-H and Ar-H), 7.40-7.42 (m, 5H, phenyl-H and Ar-H), 8.10 (brs, 1H, NH), 9.71 ppm (brs, 1H, NH); ms (70 eV) m/z 365 (M^+, 46%), 91 ($C_7H_7^+$). Anal. calcd. for $C_{19}H_{19}N_5OS$: (365.45) C, 62.44; H, 5.24; N, 19.16. Found: C, 62.47; H, 5.03; N, 18.87.

2-Phenyl-5-phenylazo-2*H*-[1,2,3]triazol-4-ylamine (10). A mixture of **9** (0.25 g, 1 mmol) in DMF (10 ml), hydroxylamine hydrochloride (0.069 g, 1 mmol) and sodium acetate (1 mmol) was heated under reflux for 40 min. The reaction mixture was then poured into water, the solid collected by filtration and recrystallized from ethanol to give red crystal, (yield 68%, 0.18 g) mp 205°C; ir (KBr): ν_{max} 3472, 3355 (NH_2), 1612 cm^{-1} (CO); ^{1}H nmr (300 MHz, DMSO-d_6): δ 6.75 (brs, 2H, NH_2), 7.54-7.56 (m, 6H, Ar-H), 7.97-8.00 ppm (m, 4H, Ar-H); ms (70 eV) m/z 264 (M^+, 20%), 187 (M^+- Ph), 105 ($PhNN^+$), 77 (Ph^+). Anal. calcd. for $C_{14}H_{12}N_6$: (264.28) C, 63.62; H, 4.58; N, 31.80. Found: C 63.48; H, 4.29; N, 31.96.

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