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ARYLHYDRAZONONITRILES AS BUILDING BLOCKS IN HETEROCYCLIC SYNTHESIS: SYNTHESIS OF NEW BENZOTHIAZOLYL-1,2,3-TRIAZOLE AMINES AND-1,2,3-TRIAZOL-4-YL-1,3,4-THIADIAZOLE-5-YLAMINES

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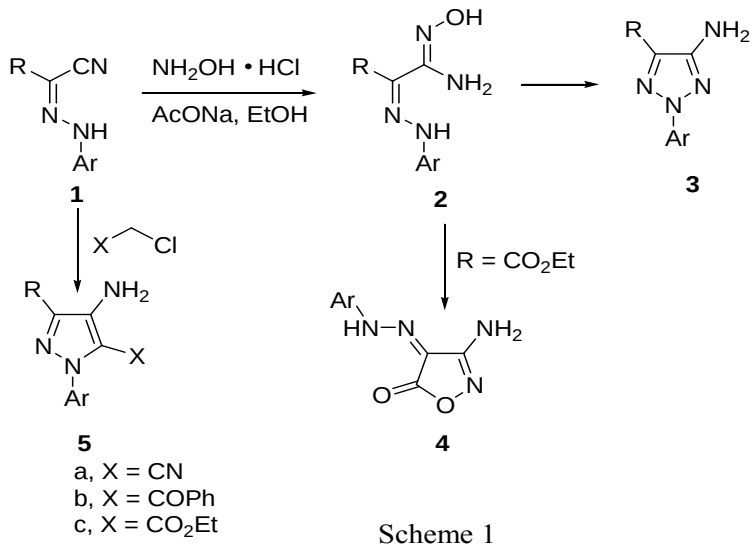
Abstract - Benzothiazole-2-ylacetonitriles **6a-b** and 5-benzoylamino-1,3,4-thiadiazol-2-ylacetonitrile **6c-d** coupled with aromatic diazonium salts to yield arylhydrazones **7a-d**. Compound **7a-d** reacted with hydroxylamine hydrochloride in ethanolic sodium acetate to yield the corresponding amidoximes **8a-d**. Compounds **8a-d** cyclized readily into the 1,2,3-triazole derivatives **9a-d** upon reflux in ethanolic DMF in the presence of anhydrous sodium acetate.

INTRODUCTION

Arylhydrazononitriles **1** are versatile reagents and their chemistry is now receiving considerable attention.[1-3] Recently Elnagdi *et al.*[1,2] have reported two new syntheses for 2,5-disubstituted 1,2,3-triazolyl-4-amines **3** and 1-aryl-3-substituted-4-aminopyrazole-5-carboxylic acids **5** utilizing **1** as starting materials. In previous work[4] we have reported successful synthesis of triazoles, however, attempted extending of **1(**R=CO_2Et) to the triazole synthesis, resulted in formation of the aminoisoxazolones **4** (Scheme 1). In the present article, the results of investigation aimed at extending these syntheses for azolylacetonitriles **5a,b** are reported.



Scheme 1

RESULTS AND DISCUSSION

Coupling **6a-d** with aromatic diazonium salts following previously reported literature has resulted in formation of **7a-d** in good yields. Although **7** may exist either in E or Z forms, X-ray crystal structure indicated that it exists exclusively at least in crystal in Z-form. Z-form is stabilized through hydrogen bonding.[5] All **7a-d** reacted with hydroxylamine hydrochloride in ethanolic sodium acetate to yield the amidoximes **8a-d**. Compounds **8a-d** cyclized smoothly via loss of water to yield products that can in theory be assigned to structure **9** or isomer **11**. Thus, direct cyclization of **8a-d** at hydrazone nitrogen would afforded **9** while if **8a-d** underwent a Tiemann rearrangement prior to cyclization as has been recently observed by Al-Matar *et al.*,[1] then **11** may be produced. X-Ray crystal structure determination confirmed that the reaction product is **9a-b** Figure 1, Figure 2 and Scheme 2.[6] Bond lengths and angles indicate effective delocalization of N-2 lone pair at benzimidazole ring, which contributes to the stability of **9**. X-ray data indicates that N-N bond is shorter than what may be expected for such bond and bond angles are more for sp^2 nitrogen (Table 1).

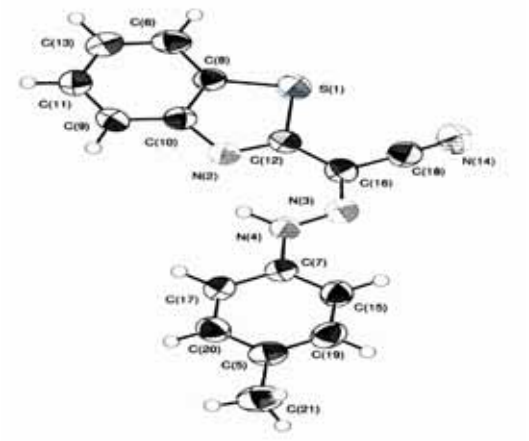


Figure 1. X-Ray crystal structure of compound 7b

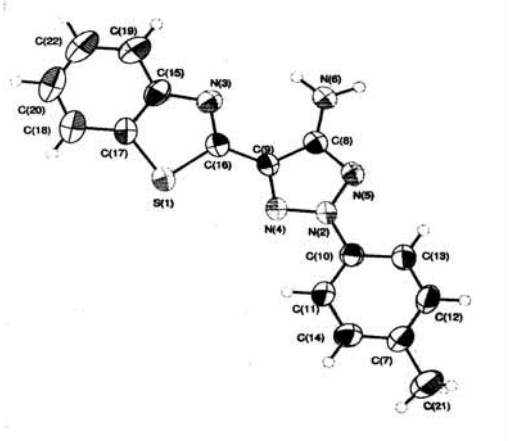
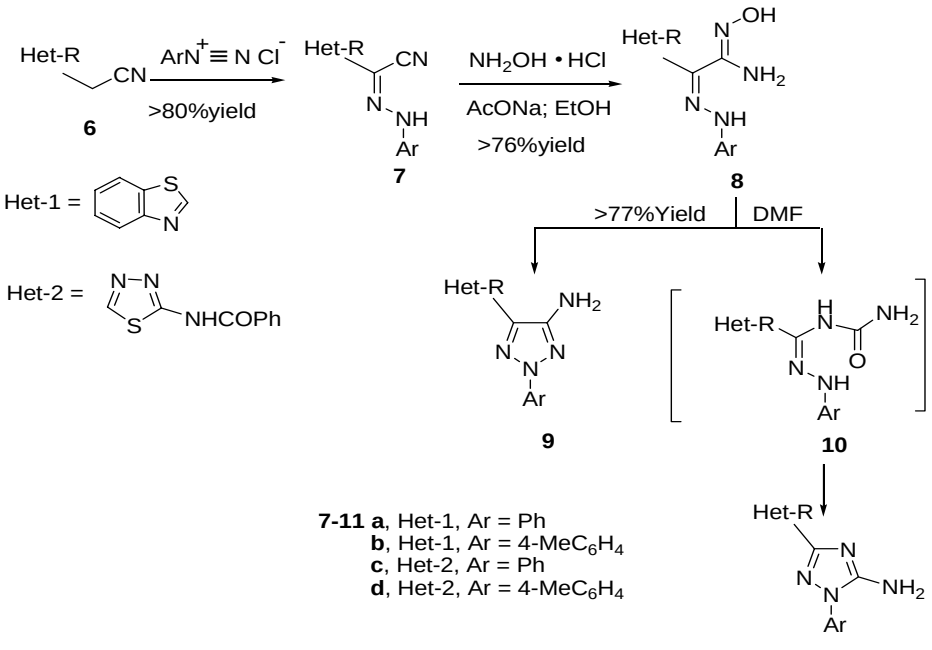


Figure 2. X-Ray crystal structure of compound 9b

Table 1. (Selected bond lengths and bond angles for compound **9b**)

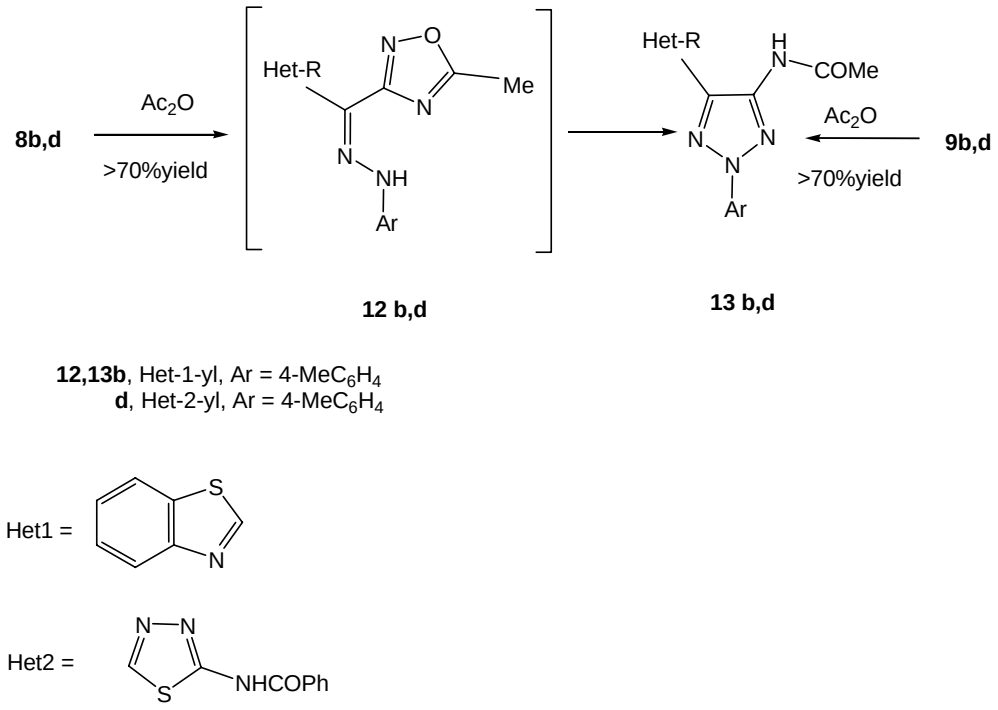
Bond	Bond Length	Bond	Bond Angle
N2-N5	1.356 A˚	N2-N5-C8	103.11˚
N2-N4	1.319 A˚	N2-N4-C9	103.81˚
N2-C10	1.419 A˚	N5-N2-N4	115.67˚
N5-C8	1.342 A˚	N5-N2-C10	121.83˚
N6-C8	1.350 A˚	N5-C8-N6	123.30˚
N4-C9	1.342 A˚	N4-N2-C10	122.50˚
C8-C9	1.404 A˚	N4-C9-C8	108.94˚



Scheme 2

Similar cyclization reaction could be effected for **7c,d**, however a single crystal suitable for X-ray could not be prepared to enable to assign either structure **9** or **11**. However, NOE difference experiments confirmed that the formed product is also a 1,2,3-triazole as irradiating NH_2 signal at δ 6.15 ppm did not enhance aryl protons. If the products **11** are formed the enhancement of aryl ortho protons should have been effected. In a trial to cyclize the amidoximes **8b,d** in acetic anhydride, a product of acylation and water elimination has been obtained. This can thus be assigned to structure **12** or the isomeric form **13**. Arylhydrazonothiadiazoles are reported to rearrange readily into 1,2,3-triazoles. The 1,2,3-triazoles structures **13b,d** could be established by their direct preparation via acylation of **9b,d**.

It is, however, difficult to exclude initial formation of **12** despite our inability to isolate such intermediates (Scheme 3).



Scheme 3

CONCLUSION

In conclusion presently reported synthesis of 1,2,3-triazoles is a general one and can be efficiently utilized for synthesis of biologically interesting heteroaromatic 2-substituted 1,2,3-triazoles.

EXPERIMENTAL

All melting points were determined on a Stuart melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra (300 MHz) were recorded on Varian Gemini NMR spectrometer. Chemical shifts (δ) are given from TMS (δ ppm) as internal standard for ^{1}H-NMR and ^{13}C-NMR. Mass spectra were measured on a Shimadzu GMMS -QP-1000 EX mass spectrometer at 70 eV. The elemental analyses were performed at the micro analytical center, Cairo University. The IR spectra were recorded in KBr using a FTIR unit Bruker-vector 22 spectrophotometer.

General method for preparation of Benzothiazol-2-yl-arylhydrazono acetonitrile (7a-b)

To a solution of **6a-b** (0.01 mol) and ethanolic dioxane (20 mL) aromatic diazonium salt (0.01 mol) was added dropwise in the presence of sodium acetate, after 15 min water was added to dissolve sodium

acetate, the solid product so formed was filtered off and crystallized from EtOH to afford **7a-b**.

Benzothiazol-2-yl-(phenylhydrazono)acetonitrile (7a)

Yield: 2.25g (80 %), mp 174-175 ˚C. IR (KBr, cm^{-1}): 3446 (NH), 2214 (CN); ^1H NMR (300 MHz, DMSO-d_6): δ 12.18 (s, 1H, NH), 7.10-8.26 (m, 9H, Ar-H); ^{13}C NMR (DMSO-d_6); δ 115.36, 116.72, 121.90, 123.66, 125.17, 126.5, 129.37, 133.57, 141.19, 152.15, 155.14, 156.89, 164.08; MS(EI); m/z : 278(M^+). *Anal*. Calcd for $C_{15}H_{10}N_4S$ (278.21):C, 64.74; H, 3.59; N, 20.14. Found: C, 64.78; H, 3.57; N, 20.03.

Benzothia-2-yl-(*p*-tolylhydrazono)acetonitrile (7b)

Yield: 2.5 g (86 %), mp 180-182 ˚C. IR (KBr, cm^{-1}): 3442 (NH), 2216 (CN); ^1H NMR (300 MHz, DMSO-d_6): δ 2.27 (s, 3H, CH_3), 12.2 (s, 1H, NH); 7.21-8.3 (m, 8H, Ar-H); ^{13}C NMR (DMSO-d_6): δ 20.9, 115.42, 116.72, 122.23, 123.66, 125.17, 126.55, 129.37, 130.14, 143.25, 152.15, 155.42, 156.11, 161.78; MS (EI): m/z : 292 (M^+). *Anal*. Calcd for $C_{16}H_{12}N_4S$ (292.32):C, 65.75; H, 4.10; N, 19.18. Found: C, 65.74; H, 3.99; N, 19.16.

General method for preparation of *N*-{5-[cyano(arylhydrazono)methyl][1,3,4]thiadizol-2-yl} benzamide (7c-d)

To a solution of **6c-d** (0.01 mol) and pyridine (20 mL), aromatic diazonium salt (0.01 mol) was added dropwise in the presence of sodium acetate, the solid product so formed was filtered and crystallized from EtOH/dioxane.

***N*-{5[-Cyano-(phenylhydrazono)-methyl]-[1,3,4]thiadiazol-2-yl}benzamide (7c)**

Yield: 2.8 g (80 %), mp 288-290 ˚C. IR (KBr, cm^{-1}): 3448 (NH), 3177 (NHCO), 2211 (CN), 1662(CO); ^1H NMR (300 MHz, DMSO-d_6): δ 7.03-8.12 (m, 10H, Ar-H), 11.9 (s, 1H, NH), 13.3 (s, 1H, NH CO); ^{13}C NMR (DMSO-d_6): δ 106.07, 110.03, 115.10, 115.33, 123.6, 128.49, 129.46, 131.129, 132.92, 142.23, 158.9, 159.6, 165.2; MS (EI): m/z : 348 (M^+). *Anal*. Calcd for $C_{17}H_{12}N_6SO$(348.16): C, 58.62; H, 3.45; N, 24.14. Found: C, 58.59; H, 3.35; N, 24.12.

***N*-{5-[Cyano(*p*-tolylhydrazono)methyl][1,3,4]thiadiazol-2-yl}benzamide (7d)**

Yield: 2.8 g (79 %), mp 264-265 ˚C. IR (KBr, cm^{-1}): 3442 (NH), 3147 (NHCO), 2204 (CN), 1667 (CO); ^1H NMR (300 MHz, DMSO-d_6): δ 2.3 (s, 3H, CH_3), 7.03-8.12 (m, 9H, Ar-H), 11.9 (s, 1H, NH), 13.11 (s, 1H, NHCO); ^{13}C NMR (DMSO-d_6); δ 20.39, 106.07, 110.03, 115.10, 115.33, 123.6, 128.49, 129.46, 131.12, 132.92, 142.23, 158.9, 159.6, 165.2; MS (EI): m/z : 362 (M^+). *Anal*. Calcd for $C_{18}H_{12}N_6SO$ (360.23): C, 60.01, H, 3.33; N 23.31. Found: C, 59.72; H, 3.23, N, 23.20.

General method for preparation of 2-benzothiazol-2-yl-*N*-hydroxy-2-(arylhydrazono)acetamidine (8a-b)

A mixture of arylhydrazononitrile **7a-b** (0.01 mol) and hydroxylamine hydrochloride (0.04 mol) was refluxed in EtOH (20 mL) in the presence of sodium acetate for 3 h. The solvent was evaporated under

vacuum and the crude product was collected and crystallized from EtOH/dioxane.

2-Benzothiazol-2-yl-N-hydroxy-2-(phenylhydrazono)acetamidine (8a)

Yield: 2.5 g (80 %), mp 184-186 ˚C. IR (KBr, cm^{-1}): 3445 (NH), 3358 and 3241 (NH_2), 3054 (OH); ^1H NMR (300 MHz, DMSO-d_6): δ 5.76 (s, 2H, NH_2), 7.03-8.2 (m, 9H, Ar-H), 13.56 (s, 1H, NH), 14.45 (s, 1H, NOH); ^{13}C NMR (DMSO-d_6): δ 114.45, 121.3, 122.13, 122.7, 125.3, 126.13, 129.14, 133.23, 142.84, 149.35, 152.68, 158.17, 169.39; MS (EI): m/z : 311 (M^+). *Ana*l. Calcd for $C_{15}H_{13}N_5SO$ (311.12): C, 57.87; H, 4.18; N, 22.50. Found : C, 57.65; H, 4.35; N, 22.36.

2-Benzothiazol-2-yl-*N*-hydroxy-2-*(p*-tolylhydrazono)acetamidine (8b)

Yield: 2.5 g (77 %), mp 194-194 ˚C. IR (KBr, cm^{-1}): 3445 (NH), 3350 and 3245 (NH_2), 3052 (OH); ^1H NMR (300 MHz, DMSO-d_6): δ 2.2 (s, 3H, CH_3), 5.76 (s, 2H, NH_2) 7.1-8.2 (m, 8H, Ar-H), 13.5 (s, 1H, NH), 14.46 (s, 1H, NOH); ^{13}C NMR (DMSO-d_6): δ 20.35, 114.6, 122.12, 122.66, 125.38, 126.16, 129.78, 130.06, 133.45, 140.73, 150.76, 152.88, 158.37, 169.67; MS (EI): m/z : 325 (M^+). *Anal.* Calcd for $C_{16}H_{15}N_5OS$ (325.21): C, 59.07; H, 4.61; N, 21.54. Found: C, 58.8; H, 4.41; N, 21.20.

General method for preparation of *N*-{5-[(*N*-hydroxycarbamimidoyl)(arylhydrazono)methyl]-[1,3,4]thiadiazol-2-yl}benzamide

A mixture of arylhydrazononitriles **7c-d** (0.01 mol) and hydroxylamine hydrochloride (0.04 mol) was refluxed in EtOH (20 ml) in the presence of sodium acetate for 3 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from EtOH/dioxane.

***N*-{5-[(*N*-Hydroxycarbamimidoyl)(phenylhydrazono)methyl][1,3,4]thiadiazol-2-yl}benzamide (8c)**

Yield: 3 g (78 %), mp 238-240 ˚C. IR (KBr, cm^{-1}) 3427 (NH), 3324 and 3200 (NH_2), 3164 (CONH), 3028 (OH), 1641 (CO); ^1H NMR (300 MHz, DMSO-d_6): δ 5.82 (s, 2H, NH_2), 7.0-8.15 (m, 10H, Ar-H), 10.46 (s, 1H, NH), 13.02 (s, 1H, CONH), 13.56 (s, 1H, NOH); ^{13}C NMR (DMSO-d_6): δ 114.28, 120.83, 121.62, 122.52, 128.54, 129.31, 142.66, 143.05, 149.02, 150.41, 154.87, 161.94, 165.37; MS(EI): m/z : 381 (M^+). *Ana*l. Calcd for $C_{17}H_{15}N_7O_2S$ (381.21): C, 53.54; H, 3.94; N, 25.75. Found: C, 53.34; H, 3.74; N, 25.20.

***N*-{5-[(*N*-Hydroxycarbamimidoyl)*(p*-tolylhydrazono)methyl][1,3,4]thiadiazol-2-yl}benzamide (8d)**

Yield: 3 g (76 %), mp 222-223 ˚C. IR (KBr, cm^{-1}) 3427 (NH), 3317 and 3200 (NH_2), 3156 (NHCO), 3018 (OH), 1640 (CO). ^1H NMR (300 MHz, DMSO-d_6): δ 2.27 (s, 3H, CH_3); 5.79 (s, 2H, NH_2), 7.14-8.15 (m, 9H, Ar-H), 10.2 (s, 1H, NH), 13.02 (s, 1H, NHCO), 13.53 (s, 1H, NOH). ^{13}C NMR (DMSO-d_6): δ 20.35, 114.26, 120.15, 120.65, 120.68, 128.43, 128.58, 130.07, 132.94, 148.99, 150.4, 154.88, 161.83, 165.34. MS(EI): m/z : 395 (M^+). *Anal*. Calcd for $C_{18}H_{17}N_7SO_2$ (395.23): C, 54.68; H, 4.30; N, 24.81: Found C, 54.48; H 4.10; N, 24.51.

General method for preparation of 5-benzothiazol-2-yl-2-aryl-2*H*-[1,2,3]triazol-4-ylamine (9a-b)

A mixture of arylhydrazono nitrile **7a-b** (0.01 mol) and hydroxylamine hydrochloride (0.04 mol) was refluxed in DMF (20 mL) in the presence of anhydrous sodium acetate for 8 h. The solvent was evaporated under vacuum and the crude was collected and crystallized from EtOH .

5-Benzothiazol-2-yl-2-phenyl-2*H*-[1,2,3]triazol-4-ylamine (9a)

Yield: 2.39 g (78 %), mp 180-182 ˚C. IR (KBr, cm^{-1}): 3404 and 3298 (NH_2); ^1H NMR (300 MHz, DMSO-d_6): δ 6.43 (s, 2H, NH_2); 7.3-8.1 (m, 9H, Ar-H). ^{13}C NMR (DMSO-d_6): δ 117.57, 122.13, 122.39, 125.39, 126.51, 126.95, 128.37, 129.51, 133.25, 138.714, 152.15, 153.012, 158.75. MS(EI): m/z : 293 (M^+). *Anal*. Calcd for $C_{15}H_{11}N_5S$ (293.21): C, 61.43; H, 3.75; N, 23.89 %. Found: C, 61.10; H, 3.65; N, 23.77.

5-Benzolthiazol-2-p-tolyl-2H[1,2,3]triazol-4-yl-amine (9b)

Yield: 2.49 g (78 %), mp 205-207 ˚C. IR (KBr, cm^{-1}); 3440 and 3329 (NH_2); ^1H NMR (300 MHz, DMSO-d_6): δ 2.3 (s, 3H, CH_3), 6.39 (s, 2H, NH_2), 7.2-8.09 (m, 8H, Ar-H). ^{13}C NMR (DMSO-d_6): δ 20.42, 117.46, 122.3, 123.21, 125.26, 126.43, 127.93, 129.82, 133.22, 136.47, 136.57, 152.01, 153.02, 158.82. MS(EI): m/z : 307 (M^+). *Anal.* Calcd For $C_{16}H_{13}N_5S$ (307.22): C, 62.54; H, 4.23; N, 22.80. Found: C, 62.20; H, 4.03; N, 22.60.

General method for preparation of *N*-[5-(5-Amino-2-aryl-2*H*-[1,2,3]triazol-4-yl)[1,3,4]thiadiazol-2-yl]benzamide

A mixture of **7c-d** (0.01 mol) and hydroxylamine hydrochloride (0.04 mol) was refluxed in DMF (20 mL) in the presence of unhydrous sodium acetate for 8 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from EtOH.

***N*-[5-(5-Amino-2-phenyl-2*H*-[1,2,3]triazol-4-yl)[1,3,4]thiadiazol-2-yl]benzamide (9c)**

Yield: 2.8 g (77 %), mp 278-280 ˚C. IR (KBr, cm^{-1}) 3459 and 3362 (NH_2), 1674 (CO); ^1H NMR (300 MHz, DMSO-d_6); δ 6.15 (s, 2H, NH_2), 7.26-8.11 (m, 10H, Ar-H), 13.03 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 117.45, 126.3, 126.8, 128.47, 129.3, 129.56, 131.36, 133.02, 138.84, 151.71, 154.56, 158.47, 165.29; MS (EI): m/z : 363 (M^+). *Anal*. Calcd for $C_{17}H_{13}N_7SO$ (363.22): C, 56.19; H, 3.58; N, 26.99. Found: C, 55.92; H, 3.43; N, 26.88.

***N*-[5-(5-Amino-2-p-tolyl-2*H*-[1,2,3]triazol-4-yl)[1,3,4]thiadiazol-2-yl]benzamide (9d)**

Yield: 3 g (79 %), mp 238-240 ˚C. IR (KBr, cm^{-1}) 3447 and 3363 (NH_2), 1673 (CO), ^1H NMR (300 MHz, DMSO-d_6): δ 2.3 (s, 3H, CH_3); 6.15 (s, 2H, NH_2) 7.28-8.14 (m, 9H, Ar-H). ^{13}C NMR (DMSO-d_6): δ 20.48, 117.40, 125.83, 128.42, 128.56, 129.88, 131.14, 132.95, 136.33, 136.73, 151.54, 154.56, 158.38, 165.3. MS(EI) m/z : 377 (M^+). *Anal.* Calcd for $C_{18}H_{15}N_7SO$ (377.23): C, 57.29; H, 3.97; N, 25.99. Found: C, 57.01; H, 3.78; N, 25.79.

***N*-(5-Benozthiazol-2-yl-2-*p*-tolyl-2*H*-[1,2,3]triazol-4-ylacetamide (13b)**

(0.01 mol) of [1,2,3]triazol **9b** was refluxed in acetic anhydride (20 mL) for 2 h. The solvent was

evaporated under vacuum and the crude product was collected and crystallized from EtOH.

Yield: 2.45 g (70 %), mp 190-191 ˚C. IR(KBr, cm^{-1}): 3280 (NH), 1681(CO); ^{1}H NMR (300 MHz, DMSO- d_6): δ 2.21 (s, 3H, CH_3), 2.50 (s, 3H, $COCH_3$), 7.43-8.20 (m, 8H, Ar-H), 10.30 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 20.40, 22.97, 122.92, 123.2, 125.8, 126.8, 126.23, 126.53, 126.74, 130.05, 130.09, 133.82, 136.15, 137.94, 138.76. 152.97, 171.5. MS(EI) m/z : 349 (M^+). *Anal*. Calcd for $C_{18}H_{15}N_5SO$ (349.23): C, 61.89; H; 4.29; N, 20.05. Found: C, 61.69; H, 4.05; N, 19.80.

***N*-[5-(5-Acetylamino-2-p-tolyl-2*H*-[1,2,3]triazol-4-yl)[1,2,3]triazol-4-yl)[1,3,4]thiadiazol-2-yl]benz-amide (13d)**

(0.01 mol) of [1,2,3]triazol **9d** was refluxed in acetic anhydride (20 mL) for 2 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from EtOH.

Yield: 3 g (71 %), mp 220-221 ˚C. IR (KBr, cm^{-1}) 1674 (COPh), 1717 ($COCH_3$); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.5(s, 3H, $COCH_3$), 2.32 (s, 3H, CH_3), 7.2-8.1 (m, 9H, Ar-H), 10.2 (s, H, NH), 12.75 (s, H, NH). ^{13}C NMR (DMSO-d_6); δ 20.58, 22.38, 118.75, 125.83, 128.42, 128.56, 129.88, 131.14, 132.95, 136.33, 136.73, 151.54, 154.56, 158.38, 165.81, 169.02. MS (EI) m/z : 419 (M^+).

Anal. Calcd for $C_{20}H_{17}N_7O_2S$ (419.24): C, 57.28; H, 4.05; N, 23.38. Found: C, 57.01; H, 3.98; N, 23.11.

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