Studies with 1-Functionally Substituted Alkyl Azoles: Novel Synthesis of Functionally Substituted Azolylbenzimidazoles and Functionally Substituted Azolyl-1,2,4-Triazoles

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ω-Azolylacetophenones **1** and **2** react with dimethylformamide dimethylacetal to yield enaminones **7,8** that were converted into azolylazoles *via* reaction with hydrazine and with hydroxylamine. Compounds **1,2** also coupled with aromatic diazonium salts to yield arylhydrazones and reacted with nitrous acid to yield corresponding oximes.

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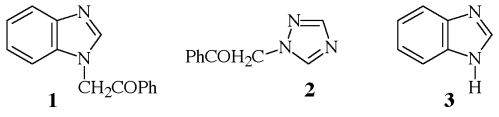
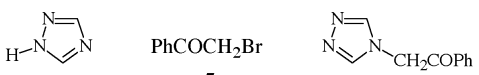
The ability of the benzotriazole ring to stabilise acyl carbanions directly attached to the ring N-1 by effectively attracting negative charge has attracted considerable attention in recent years[1-5]. Recently we have demonstrated that the pyrazole function in pyrazolylacetone also stablise adjacent carbanions[6]. Although N-1 functionally substituted alkyl benzimidazoles and N-1 functionally substituted 1,2,4-triazoles are also capable of stabilising negative charges on carbons adjacent to the ring N, the carbanionic chemistry of these species has attracted only very limited interest [7]. As part of biological chemistry programmes in our laboratory, samples of functionally substituted benzimidazoles and 1,2,4-triazoles were required. We have therefore investigated the carbanionic chemistry of **1** and **2** as an easy route to required compounds. In the present article we report on the synthesis of **1** and **2** and their utility for the preparation of the desired derivatives. The work has resulted in the synthesis of a number of derivatives of **1** and **2**, some of which carry latent functional substituents useful for further chemical transformations.

Thus **1** and **2** were prepared in good yields by reacting benzimidazole and 1,2,4-triazole **4** with phenacyl bromide **5** in refluxing acetone in the presence of equivalent amounts of triethyl amine. Although reaction of **4** with **5** may also yield **6**, structure **2** was established for the reaction product based on ^{1}H NMR spectroscopy which revealed the two triazolyl ring protons at δ 8.08 and 8.56 ppm,. If the reaction product is **6** the triazolyl protons should give one nmr signal as the molecule is symmetrical.

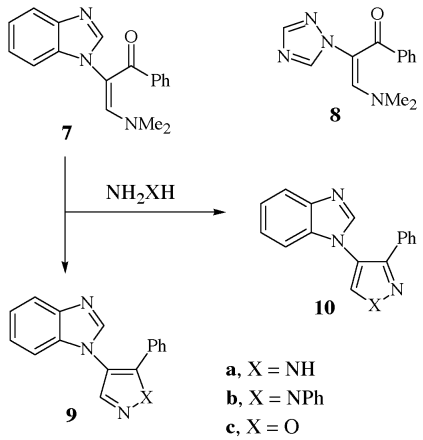


1 **2** **3**



4 **5** **6**

Compounds **1** and **2** condensed readily with dimethylformamide dimethylacetal (DMFDMA) to yield the enaminones **7** and **8**. Compound **7** reacted with hydrazine hydrate and with phenylhydrazine to yield pyrazole derivatives which may be formulated as **9a,b** or isomeric **10a,b**. Structure **9a,b** could be established for these products based on the non-identity of reaction of **7** with phenylhydrazine with a sample of **10b**, prepared *via* initial condensation of **1** with phenylhydrazine and subsequent reaction of the formed phenylhydrazone **11a** with DMFDMA. Compound **7** also reacted with hydroxylamine to yield a product that may be formulated also as **9c** or **10c**. Attempt to prepare a sample of **10c** from the reaction of oxime **11b** with DMFDMA failed. However, structure **9c** could be established for the reaction product based on its conversion into the nitrile **12**, which was also prepared *via* direct cyanation of **1** with *N*-cyanobenzotriazole **13** : a new synthetic equivalent of $^+$CN [8].



7 **8**

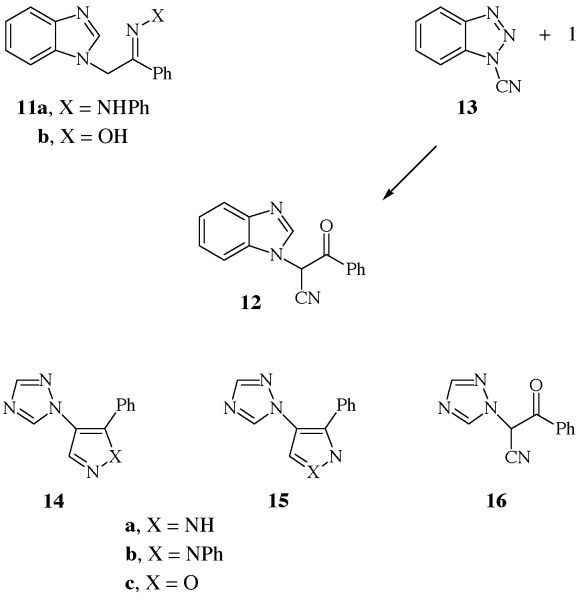
10

9

a, X = NH
b, X = NPh
c, X = O

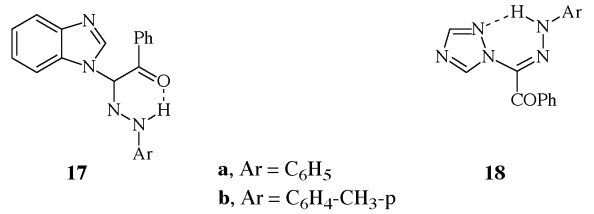
Like **7,** compound **8** reacted with hydrazines to yield the pyrazole derivatives **14a,b** and with hydroxylamine to yield isoxazole **14c**. The isomeric pyrazole **15b** could be

prepared by condensing **2** with phenylhydrazine and subsequent condensation of the formed phenylhydrazone with DMFDMA.

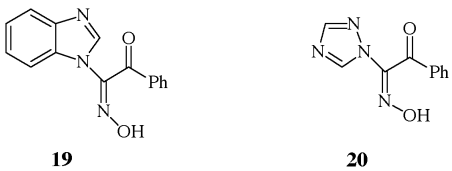


Likewise, the isoxazole **14c** was converted into the oxoalkanenitrile **16** on refluxing in dioxane in the presence of NaH. Alternatively **16** was directly prepared from reaction of **2** with **13**.

Compound **1** and **2** coupled with aromatic diazonium salts to yield the corresponding arylhydrazones **17a,b** and **18a,b** (or possible steric isomers), respectively.



Compounds **1** and **2** also reacted with sodium nitrite in acetic acid solution to yield oximes **19** and **20**.



EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded as KBr discs using a FTIR unit Bruker-Vector 22 spectrophotometer. The ^{1}H NMR spectra were recorded on a Bruker AC-80 spectrometer with, DMSO-d_6 as solvent and TMS as internal standard. Chemical shifts are reported in δ units (ppm). Mass spectra were measured on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Microanalyses were performed at the microanalytical center, Cairo University.

ω-(Benzimidazol-1-yl)acetophenone (**1**).

A mixture of **3** (0.01 mol) and **5** (0.011 mol) in acetone (20 ml) was treated with triethylamine (0.01 mol) and refluxed for 2 hours. The solid product, so formed, was collected by filtration and crystallized from DMF to give **1** as colourless crystals; mp 240-1 °C; yield (92 %); ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.6 (s, 2H, $COCH_2$), 6.8-7.6 (m, 10H, Ar-H); IR (KBr): ν 2970 (aliphatic CH) and 1690 (CO)cm^{-1}; MS (EI, 70 eV): m/z (%), 236 [M$^+$ (7)], 213(7), 199(7), 185(7).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C 76.27; H, 5.08; N 11.86%. Found: C 76.50; H 5.0; N 11.80%.

ω-(1,2,4-Triazol-1-yl)acetophenone (**2**).

A mixture of **4** (0.01 mol) and **5** (0.011 mol) in acetone (20 ml) was treated with triethylamine (0.01 mol) and refluxed for 8 hours. The solid obtained upon heating was collected by filtration and crystallized from ethanol to give **2** as colourless crystals; mp 195-6 °C; yield 86%. ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.6 (s, 2H, $COCH_2$), 6.9-7.6 (m, 5H, Ar-H), 8.08 and, 8.50 (2s, 2H, H-3 and H-5); IR (KBr): ν 2920 (aliphatic CH) and 1680 (CO) cm^{-1}; MS (EI, 70 eV): m/z (%), 187 [M$^+$, (5)], 167(26), 150(12), 149(100), 129(12).

Anal. Calcd. for $C_{10}H_9N_3O$: C 64.17; H 4.81; N 22.45%. Found: C 64.40; H, 5.00 ; N 22.50%.

Formation of Enaminones **7** and **8**.

A mixture of **1** or **2** (0.01 mol) and DMFDMA (0.012 mol) in xylene (30 ml) was refluxed for 12 hours. The reaction mixture was evaporated *in vacuo* to give enaminone **7** or **8** as a yellow oil.

Reaction of Enaminones 7 with Hydrazines: Formation of Pyrazoles (**9a,b**).

A mixture of **7** (0.01 mol) and hydrazine hydrate or phenylhydrazine (0.012 mol) was heated under reflux in absolute ethanol for 4 hours, then allowed to cool to room temperature and poured into cold water. The solid product, so formed, was collected by filtration and crystallized from the appropriate solvent to give **9a,b**.

2-(Benzimidazol-1-yl)-5-phenyl-1*H*-pyrazole (**9a**).

Compound **9a** was obtained as yellow crystals from ethanol/water(1:1), mp 168-170 °C; yield 68%. ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.8-7.6 (m, 11H, Ar-H and pyrazolyl H-4), 11.0 (s, 1H, NH); IR (KBr): ν 3400 (NH), 1630 (C=N) cm^{-1}; MS (EI, 70 eV): m/z (%) = 260 [M$^+$, (6)], 257(7), 255(5), 250(50), 237(15).

Anal. Calcd. for $C_{16}H_{12}N_4$: C 73.84; H 4.61; N 21.53%. Found: C 74.00; H 4.50; N 21.50%.

4-(Benzimidazol-1-yl)-1,5-diphenyl pyrazole (**9b**).

Compound **9b** was obtained as yellow crystals from acetic acid, mp 185-6 °C; yield 72%. ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.8-7.4 (m, 16H, Ar-H and pyrazolyl H-3); IR (KBr): ν 3050 (CH), 640 (C=N) cm^{-1}.

Anal. Calcd. for $C_{22}H_{16}N_4$: C 78.57; H 4.76; N 16.66%. Found: C 78.80; H 4.60; N 16.50%.

4-(Benzimidazol-1-yl)-5-phenylisoxazole (**9c**).

A mixture of **7** (0.01 mol) and hydroxyl amine (0.012 mol) in absolute ethanol (20 ml) containing fused sodium acetate (1.0 g) was refluxed for 5 hours, then allowed to cool at room temperature and poured into cold water. The solid product obtained was collected by filtration and crystallized from dioxane to give **9c** as yellow crystals, mp 176-8 °C; yield 72%. ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.8-7.6 (m, 11H, Ar-H and isoxazolyl H-3); MS (EI, 70 eV): m/z (%)= 261 [M$^+$, (5)], 257(6), 233(4), 222(88). %); IR (KBr): ν 3058 (CH), 1645 (C=N) cm^{-1}.

Anal. Calcd. for $C_{16}H_{11}N_3O$: C 73.56; H 4.21; N 16.09%. Found: C 73.80; H 4.40; N 16.00%.

ω-(Benzimidazol-1-yl)acetophenonephenylhydrazone (**11a**).

A mixture of **1** (0.01 mol) and phenyl hydrazine (0.012 mol) in absolute ethanol (30 ml) containing a few drops of acetic acid was refluxed for 6 hours, after which the reaction mixture was cooled and poured into cold water. The solid product obtained was collected by filtration and crystallized from ethanol/water (1:1) to give **11a** as yellow crystals, mp 142-3 °C; yield 68%. ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.6 (s, 2H, -NCH$_2$C=N-), 6.8-7.4 (m, 15H, Ar-H), 10.2 (s, 1H, NH); IR (KBr): ν 3210 (NH), 1640 (C=N) cm^{-1}.

Anal. Calcd. for $C_{21}H_{18}N_4$: C 77.30; H 5.52; N 17.17%. Found: C 77.50; H 5.50; N 17.40%.

ω-(Benzimidazol-1-yl)acetophenoneoxime (**11b**).

A mixture of **1** (0.01 mol) and hydroxylamine (0.012 mol) in pyridine (20 ml) was refluxed for 6 hours. The solid obtained on evaporating excess solvent was collected by filtration and crystallized from ethanol to give **11b** as colourless crystals, mp 192-4 °C; yield 55%. IR (KBr): ν 3450 (OH), 1645 (C=N) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.8 (s, 2H, NCH$_2$C=N), 6.8-7.6 (m, 10H, Ar-H), 11.0 (s, 1H, OH).

Anal. Calcd. for $C_{15}H_{13}N_3O$: C 71.71; H 5.17; N 16.73%. Found: C 72.0; H 5.40; N 16.50%.

4-(Benzimidazol-1-yl)-1,3-diphenylpyrazole (**10b**).

A mixture of **11a** (0.01 mol) and DMFDMA (0.012 mol) in xylene (20 ml) was refluxed for 18 hours. The solid obtained on evaporating excess solvent was collected by filtration and crystallized from ethanol to give **10b**, mp 200-2 °C; yield 62%.^{1}H NMR (200 MHz, DMSO-d_6): δ 6.7-7.2 (m, 16H, Ar-H and pyrazolyl H-5); IR (KBr): ν 3045 (CH),1645 (C=N) cm^{-1}.

Anal. Calcd. for $C_{22}H_{16}N_4$: C 78.57; H 4.76; N 16.66%. Found: C 78.50 ; H 4.90; N 16.90%.

ω-(Benzimidazol-1-yl)ω-acetophenone (**12**).

Method A.

A mixture of **9c** (0.01 mol) and sodium hydride (0.012 mol) in dioxane (20 ml) was refluxed for 8 hours. The solid so formed during heating was collected by filtration and the reaction mixture was poured into cold water. The solid obtained was isolated by filtration and crystallized from acetic acid to give **12**, mp 210 °C; yield 62%.

Method B.

A mixture of **1** (0.01 mol) and **13** (0.01 mol) in dioxane (20 ml) containing sodium hydride was refluxed for 6 hours. The solid so formed was collected by filtration and crystallized from acetic acid to give **12**, mp 210-12 °C; yield 82%. ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.8-7.7 (m, 10H, Ar-H), 11.5 (s, 1H, OH); IR (KBr): ν 3320 (OH), 2922 (CH), 2171(CN), 1670 (CO) cm^{-1}; MS (EI, 70 eV): m/z (%) = 261 [M$^+$, (1)], 236(2), 235(11), 194(3), 178(6).

Anal. Calcd. for $C_{16}H_{11}N_3O$: C 73.56; H 4.21; N 16.09%. Found: C 73.70; H 4.50; N 16.00%.

1-Cyanobenzotrizole (**13**).

The titled compound was prepared according to the reported method [8].

4-(1,2,4-Triazol-1-yl)-5-phenyl-1*H*-pyrazole (**14a**).

Compound **14a**, was obtained by the same manner used for preparation of **9a** using **2** instead of **1**. The solid so formed was crystallized from ethanol to give **14a**, as pale yellow crystals, mp 182-4 °C; yield 87%. ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.7-7.6 (m, 6H, Ar-H and pyrazole H-3), 8.1, 8.49 (2s, 2H, triazole H-3 and H-5), 10.6 (s, 1H, NH); IR (KBr): ν 3420 (NH), 1630(C=N) cm^{-1}; MS (EI, 70 eV): m/z (%) = 211 [M$^+$, (10)], 185(10), 167(14), 149(5).

Anal. Calcd. for $C_{11}H_9N_5$: C 62.55; H 4.26; N 33.17%. Found: C 62.80; H 4.40; N 33.50%.

4-(1,2,4-Triazol-1-yl)-1,5-diphenylpyrazole (**14b**).

Compound **14b**, was formed on applying the same method used for the preparation of **9b** using **2** instead of **1**. The solid so formed was crystallized from dioxane to give **14b**, as yellow crystals, mp 211-12 °C; yield 78%. ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.6-7.4 (m, 11H, Ar-H and pyrazole H-3), 8.08, 8.50 (2s, 2H, triazole H-3 and H-5); IR (KBr): ν 3030 (CH), 1645 (C=N) cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}N_5$: C 71.08; H 4.52; N 24.39%. Found: C 71.00; H 4.50; N 24.50%.

4-(1,2,4-Triazol-1-yl)-5-phenylisoxazole (**14c**).

Compound **14c**, was prepared by the same method as used for **9c** using **2** instead of **1**. The solid so formed was crystallized from ethanol to give **14c** as colourless crystals, mp 185-6 °C; yield 72%. ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.8-7.2 (m, H, Ar-H and pyrazole H-3), 8.0, 8.50 (2s, 2H, triazole H-3 and H-5); IR (KBr): ν 3025 (CH), 1640 (C=N) cm^{-1}.

Anal. Calcd. for $C_{11}H_8N_4O$: C 62.26; H 3.77; N 26.41%. Found: C 62.50; H 4.00; N 26.50%.

4-(1,2,4-Triazol-1-yl)-1,3-diphenyl pyrazole (**15b**).

Compound **15b**, was obtained by the same manner used for the preparation of **10b** using phenylhydrazone produced from the reaction of **2** with phenylhydrazine. The solid so formed was crystallized from acetic acid to give **15b**, mp 178-80 °C; yield 87%. ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.8-7.6 (m, 11H, Ar-H and pyrazole H-5), 8.08, 8.49 (2s, 2H, triazole H-3 and H-5); IR (KBr): ν 3045 (CH), 1635 (C=N) cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}N_5$: C 71.08; H 4.52; N 24.39%. Found: C 71.20; H 4.50; N 24.50%.

ω-(1,2,4-Triazol-1-yl)ω-cyanoacetophenone (**16**).

This compound was obtained from the two method (a and b) used for the preparation of **12** using **14c** instead of **9c** in Method A and **2** instead of **1** in Method B. Compound **15b**, was crystallized from ethanol, mp 240-2 °C; yield 86%. ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.8-7.5 (m, 5H, Ar-H), 8.08, 8.50 (2s, 2H, triazole H-3 and H-5), 11.2 (s, 1H, OH); IR (KBr): ν 3340 (OH), 2210 (CN), 1665 (CO) cm^{-1}.

Anal. Calcd. for $C_{11}H_8N_4O$: C 62.26; H 3.77; N 26.41%. Found: C 62.50; H 3.60; N 26.60%.

General Procedure for the Preparation of Arylhydrazones **17a,b** and **18a,b**.

Compound **1** or **2** (0.01 mol) was dissolved in ethanol (50 ml) and treated with sodium acetate (5.0 g), then gradually treated under stirring with a solution of aryldiazonium chloride (prepared from the corresponding aromatic amine (0.01 mol) and the appropriate quantities of both hydrochloric acid and sodium nitrite). The solid product, so formed, was collected by filtration and crystallized from the proper solvent to give **17a,b** or **18a,b**.

ω-(Benzimidazol-1-yl)ω-phenylhydrazonoacetophenone (**17a**).

Compound **17a** was obtained as yellow crystals, mp 178-9 °C; yield 78%. ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.9-7.5 (m, 15H, Ar-H), 10.6 (s, 1H, NH); MS (EI, 70 eV): m/z (%) 340 [M$^+$, (32)], 237(2), 207(10), 193(55); IR (KBr): ν 3390 (NH), 2920 (CH), 1695 (CO) cm^{-1}.

Anal. Calcd. for $C_{21}H_{16}N_4O$: C 74.11; H 4.70; N 16.47%. Found: C 74.40 ; H 4.50; N 16.50%.

ω-(Benzimidazol-1-yl)ω-tolylhydrazonoacetophenone (**17b**).

Compound **17b** was obtained as yellow crystals, mp 186-8 °C; yield (82%).- IR (KBr): ν 3390 (NH), 2922 (CH), 1700 (CO) cm^{-1}; MS (EI, 70 eV): m/z (%) 354 [M$^+$, (46)], 264(13), 259(49), 242(53).

Anal. Calcd. for $C_{22}H_{18}N_4O$: C 74.57; H 5.08; N 15.81%. Found: C 74.50; H 5.00; N 15.80%.

ω-(1,2,4-Triazol-1-yl)ω-phenylhydrazonoacetophenone (**18a**).

Compound **18a** was obtained as yellow crystals, mp 110-2 °C; yield (62%). IR (KBr): ν 3390 (NH), 2924 (CH), 1670 (CO) cm^{-1}; MS (EI, 70 eV): m/z (%) 291 [M$^+$, (41)], 255(25), 249(13), 232(5).

Anal. Calcd. for $C_{16}H_{13}N_5O$: C 65.97; H 4.46; N 24.05%. Found: C 66.10; H 4.50; N 24.20%.

ω-(1,2,4-Triazol-1-yl)ω-tolylhydrazonoacetophenone (**18b**).

Compound **18b** was obtained as yellow crystals, mp 165-7 °C; yield (78%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.5 (s, 3H, CH_3), 7.0-7.6 (m, 9H, Ar-H), 8.1, 8.50 (2s, 2H triazolyl H-2 and H-5), 11.0 (s, 1H, NH); IR (KBr): ν 3390 (NH), 2920 (CH), 1675 (CO) cm^{-1}; MS (EI, 70 eV): m/z (%) = 305 [M$^+$, (3)], 269(13).

Anal. Calcd. for $C_{17}H_{15}N_5O$: C 66.88; H 4.91; N 22.95%. Found: C 67.00; H 5.00; N 22.60%.

Action of Nitrous Acid on **1** and **2**; Formation of Oximes **19** and **20**.

To an ice-cold solution of **1** or **2** (0.01 mol) in acetic acid (30 ml), sodium nitrite (0.015 mol) was added dropwise with stirring, then the reaction mixture left overnight. The solid obtained was isolated by filtration and crystallized from ethanol to give **19** or **20**.

1-(Benzimidazol-1-yl)-2-phenyl-1-glyoxalmonooxime (**19**).

Compound **19** was obtained as yellow crystals, mp 126-8 °C; yield (76%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.8-7.2 (m, 10H, Ar-H), 10.6 (s, 1H, OH); IR (KBr): ν 3450 (OH), 2920 (CH), 1670 (CO) cm^{-1}; MS (EI, 70 eV): m/z (%) 265 [M$^+$, (3)], 239(3), 236(3), 228(2).

Anal. Calcd. for $C_{15}H_{11}N_3O_2$: C 67.92; H 4.15; N 15.85%. Found: C 67.70; H 4.40; N 15.90%.

1-(1,2,4-Triazol-1-yl)-2-phenyl-1-glyoxalmonooxime (**20**).

Compound **20** was obtained as yellow crystals, mp 68-70 °C; yield (65%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.8-7.6 (m, 5H, Ar-H), 8.08, 8.49 (2s, 2H triazolyl H-3 and H-5), 11.0 (s, 1H, OH); IR (KBr): ν 3390 (OH), 1695 (CO) cm^{-1}.

Anal. Calcd. for $C_{10}H_8N_4O_2$: C 55.5; H 3.70; N 25.92%. Found: C 55.50 ; H 3.60; N 26.00%.

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