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AN EFFICIENT SINGLE STEP SYNTHESIS OF PYRIDAZINE, PYRAZOLO[5,1-*c*]-1,2,4-TRIAZINE, 1,2,4-TRIAZOLO[5,1-*c*]-1,2,4-TRIAZINE AND 1,2,4-TRIAZINO[4,3-*a*]BENZIMIDAZOLE DERIVATIVES

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Abstract – Coupling of *E*-1-(1-methylbenzimidazol-2-yl)-3-(*N*,*N*-dimethylamino)prop-2-enone **(1)** with the arenediazonium salt gave hydrazonopropanal **5** which underwent cyclocondensation with active methylene compounds to afford substituted pyridazin-6-imine **8** and **11**. The enaminone **1** coupled also with the diazonium salts prepared from aminopyrazole, aminotriazole and 2-amino-*1H*-benzimidazole to afford pyrazolo[5,1-*c*]-l,2,4-triazine **15**, 1,2,4-triazolo[5,1-*c*]-1,2,4-triazine **19**, 1,2,4-triazino[4,3-*a*]benzimidazole **23** derivatives, respectively.

INTRODUCTION

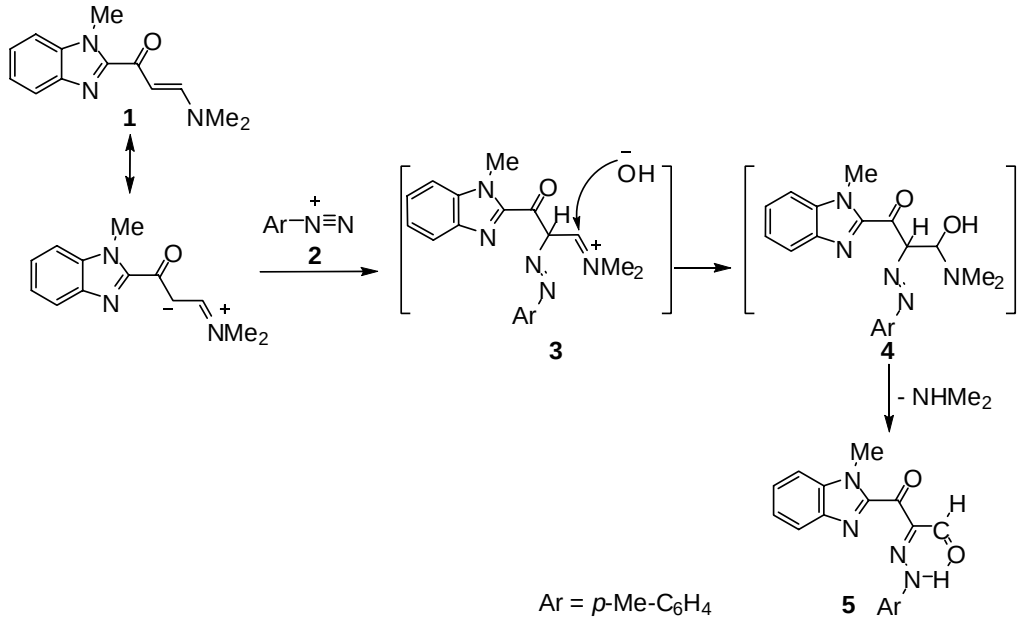
The synthesis of benzimidazole derivatives has attracted a great deal of interest due to their potent biological and pharmacological activities. For example, many benzimidazole derivatives have anthelmintic,[1,2] antiviral,[3] antibacterial,[4] antifungal,[5] anti-parasitic,[6] anticancer,[7] and antihistaminic activities.[8] Moreover, benzimidazole derivatives are also well known as anti-HIV,[9] anticoagulative[10] agents, analgesic,[11] anti-inflammatory,[11] antihypertensive,[12] antineoplastic,[13] anxiolytic agents,[14,15] and for treatment of cardiovascular disease.[16] In continuation of our studies on the chemistry of *E*-1-(1-methylbenzimidazol-2-yl)-3-*N*,*N*-dimethylaminoprop-2-enone **(1)**[17,18] and as part of our ongoing program directed towards developing efficient methods for the synthesis of a variety of heterocyclic systems incorporating benzimidazole moiety for biological evaluation,[19-22] we report here on the utility of the *E*-1-(1-methylbenzimidazol-2-yl)-3-(*N*,*N*-dimethylamino)prop-2-enone **(1)** and hydrazonopropanal **5** as versatile building blocks for the synthesis of the title compounds.

RESULTS AND DISCUSSION

E-1-(1-methylbenzimidazol-2-yl)-3-(*N*,*N*-dimethylamino)prop-2-enone **(1)** coupled with the arene-

diazonium salt **2** to afford the corresponding hydrazonopropanal derivative **5** (Scheme 1).

The ^{1}H NMR spectrum of the hydrazonopropanal **5** revealed characteristic signals at δ 9.56 and 12.53 due to formyl and hydrazone protons, respectively. These chemical shifts indicate that the hydrazone **5** exists in the (*E*) configuration which is stabilized by intramolecular hydrogen bonding as shown in Scheme 1.



Scheme 1

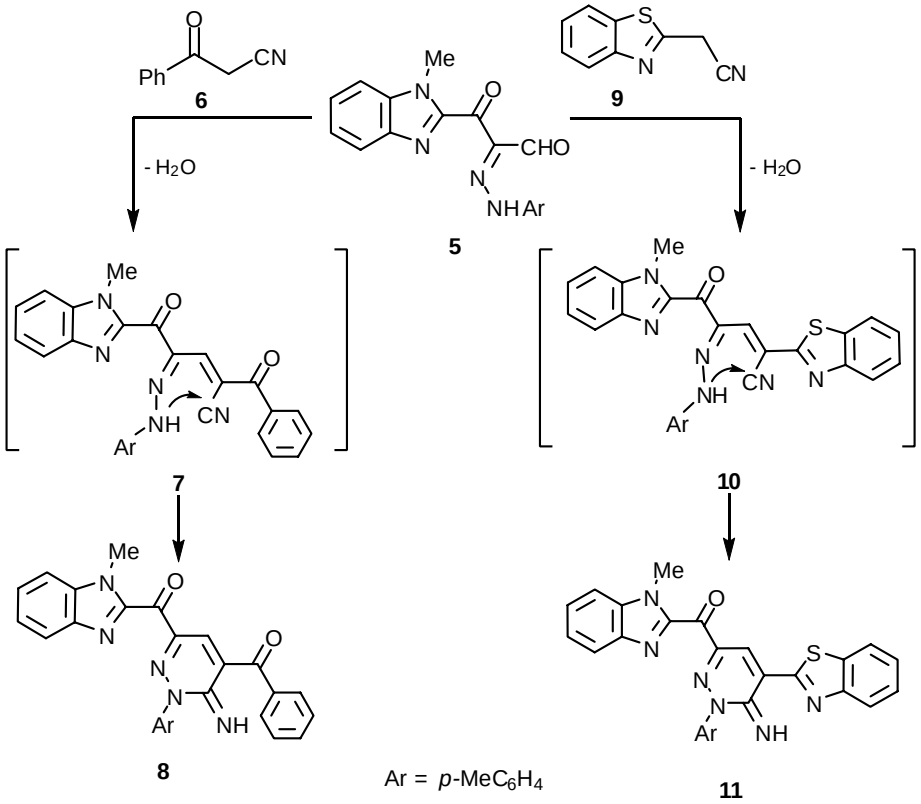
The formation of compound **5** is assumed to take place *via* coupling of the diazonium ion **2** at C-2 of the activated double bond in the enaminone **1**, followed by hydrolysis of the dimethylamino moiety at position 3 into the formyl group by the action of the aqueous base existing in the reaction medium as shown in Scheme 1.

The obtained hydrazone intermediate **5** has been utilized as a versatile building block for biologically interesting pyridazinone ring system. Thus, hydrazonopropanal **5** reacted readily and smoothly with benzoylacetonitrile **(6)** in the presence of a catalytic amount of piperidine to afford the corresponding 5-benzoyl-1,6-dihydro-6-imino-3-(1-methylbenzimidazol-2-yl)carbonyl-1-(4-methylphenyl)pyridazine **(8)** in a good yield *via* the non-isolable open structure intermediate **7** (Scheme 2).

The IR spectrum of the reaction product **8** revealed absorption bands at 1649 and 3332 cm^{-1} due to carbonyl and NH functions, respectively. Its ^{1}H NMR spectrum revealed the disappearance of the signal characteristic for the formyl proton.

Similarly, cyclocondensation of the hydrazone **5** with benzthiazol-2-ylacetonitrile **(9)** afforded the corresponding 5-(benzthiazol-2-yl)-6-iminopyridazine **11** *via* the non-isolable intermediate **10** (Scheme 2). The structure of the product **11** was established on the basis of its elemental analysis and spectral data. For example its ^{1}H NMR spectrum revealed a singlet signal at δ 2.61 due to methyl protons, a singlet

signal at δ 4.21 due to *N*-methyl protons, a singlet signal at δ 5.99 due to pyridazine-4-CH proton, a multiplet in the region of 6.37-8.03 due to aromatic protons, and a broad signal (D_2O-exchangable) at δ 11.78 due to NH function. Its IR spectrum revealed absorption bands at 1645 and 3332 cm^{-1} due to the carbonyl and NH functions, respectively.

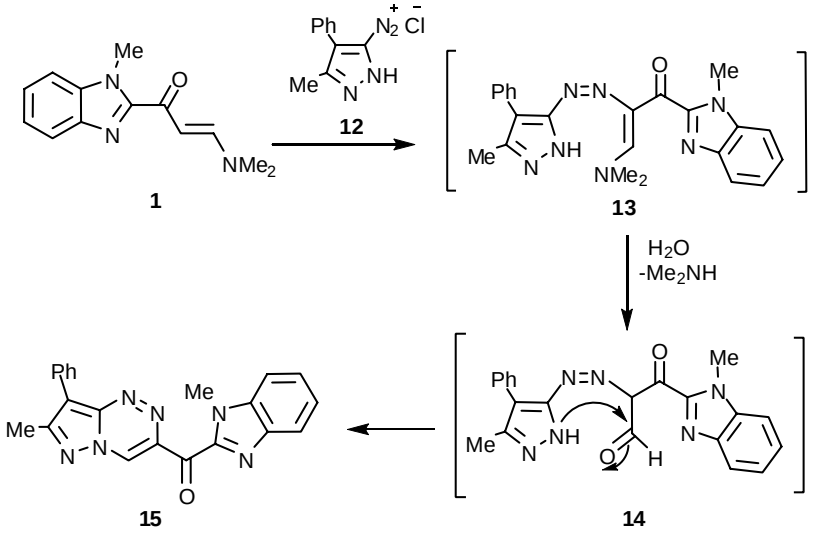


Scheme 2

The behavior of the enaminone **1** towards heterocyclic diazonium salts (*viz* pyrazole, triazole and benzimidazole-diazonium salts) as potential precursors for a single step synthesis of interesting biologically active bridgehead heterocyclic ring systems was also investigated. Thus, when the enaminone **1** was treated with 3-methyl-4-phenyl-1*H*-pyrazolediazonium chloride **(12)**, it afforded the corresponding pyrazolo[5,1-*c*]-[l,2,4]-triazine derivative **15** in single step *via* the non-isolable intermediates **13** and **14** which underwent intramolecular cyclization yielding the final bridgehead fused ring system **15** (Scheme 3). The IR spectrum of the product **15** revealed, no bands corresponding to the endocyclic NH of the pyrazole derivative **12** and showed a strong carbonyl absorption band at 1648 cm^{-1}. Its mass spectrum showed a peak corresponding to its molecular ion at *m/z* 368. The ^1H NMR spectrum of the same product revealed signals at δ 2.73, 4.21 and 10.08 due to CH_3, *N*-CH_3 and triazine proton, respectively, in addition to aromatic protons as a multiplet at δ 7.42-7.94.

A plausible mechanism for the formation of the pyrazolo[5,1-*c*]-1,2,4-triazine **15** is outlined in Scheme 3. Compound **15** is assumed to be formed *via* coupling at C-2 of the activated double bond in the

enaminone **1** with the diazonium ion **12** to afford the azo intermediate **13** followed by hydrolysis of dimethylamino moiety into formyl group (intermediate **14**) by action of the aqueous base present in the reaction medium. The intermediate **14** underwent intramolecular cyclization affording the final product pyrazolo[5,1-*c*]-[1,2,4]-triazine **15** (Scheme 3).



Scheme 3

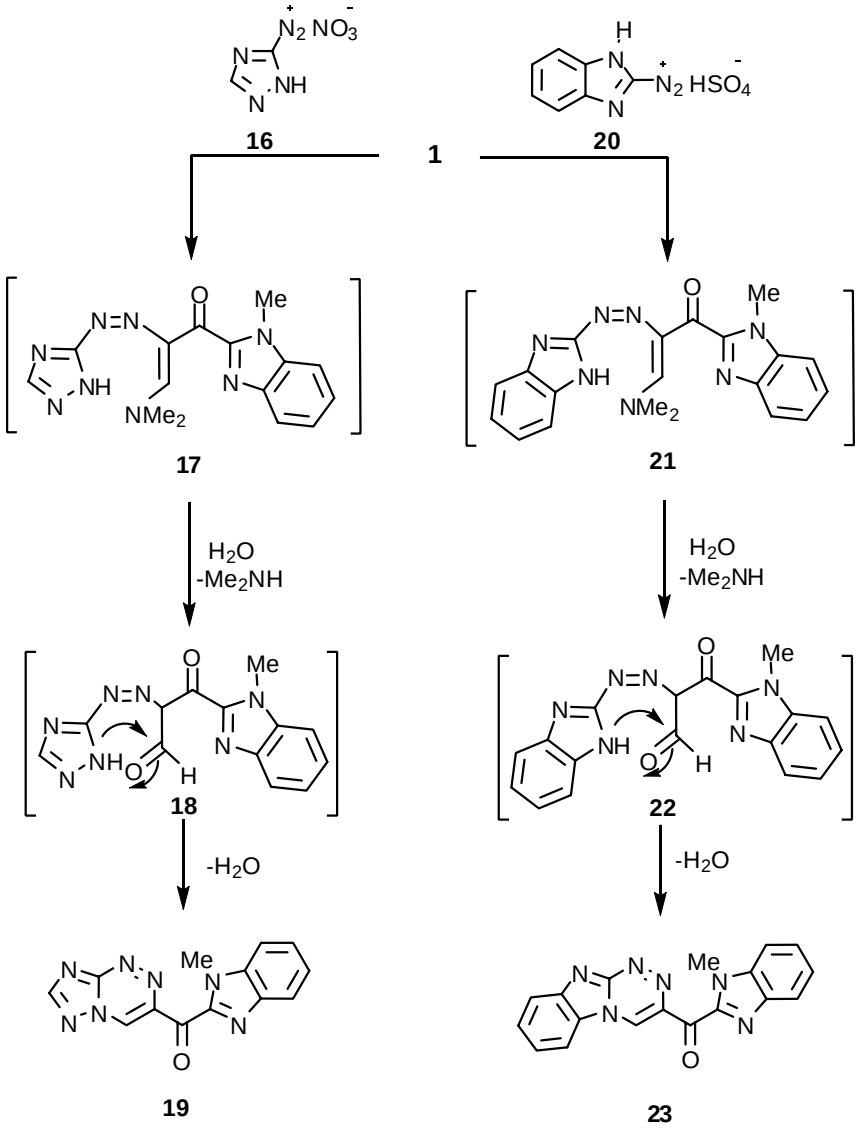
In a similar manner, the enaminone **1** reacted with l,2,4-triazole diazonium nitrate **(16)** to afford 1,2,4-triazolo[5,1-*c*]-[1,2,4]-triazine **19** (Scheme 4). The structure of the product **19** was established on the basis of its elemental analysis and spectral data (*cf.* Experimental Part).

The enaminone **1** reacted also with *1H*-benzimidazole diazonium sulfate **(20)** to afford 1,2,4-triazino[4,3-*a*]benzimidazole **23** (Scheme 4). The IR spectrum of the latter product revealed a band at 1656 cm^1 characteristic for carbonyl absorption. Its mass spectra showed a peak corresponding to its molecular ion at *m/z* 328. The ^{1}H NMR spectrum of compound **23** revealed characteristic signals at δ 4.11 and 10.01 due to *N*-CH_3 and triazine protons, respectively in addition a multiplet at δ 7.23-7.73 due to aromatic protons.

EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in deuterated chloroform ($CDCl_3$) or dimethyl sulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 e.V. Elemental analyses (C, H, N, S) were carried out at the Microanalytical Center of Cairo University, Giza, Egypt, the

results were found to be in good agreement (± 0.3%) with the calculated values.



Scheme 4

Benzoylacetonitrile **(6)**,[23] benzthiazol-2-ylacetonitrile **(9)**,[24] 3-methyl-4-phenyl-1*H*-pyrazole diazonium chloride **(12)**,[25] l,2,4-triazole diazonium nitrate **(16)**,[25] and *1H*-benzimidazole diazonium sulfate **(20)**[25] were prepared according to the reported literature.

(E)-3-(1-methyl-1H-benzimidazol-2-yl)-3-oxo-2-(2-p-tolylhydrazono)propanal (5).

To a stirred cold solution of the enaminone **1** (0.64 g, 20 mmol) in EtOH (50 mL) was added sodium acetate trihydrate (8 g). After stirring for 10 min. the mixture was cooled to 0 °C and treated with 4-methylbenzenediazonium salt solution [prepared by diazotizing *p*-toluidine (20 mmol) in HCl (6 M, 6 mL) with sodium nitrite solution (1.4 g, 20 mmol) in H_2O (15 mL)]. The addition of the diazonium salt was carried out with rapid stirring over a period of 30 min. The reaction mixture was stirred for further 2

h at 0 °C, and then left for 6 h at 4 °C in a refrigerator. The resulting solid was collected by filtration, washed thoroughly with water, then dried. The crude product was recrystallized from EtOH to give the hydrazone **5** in 85% yield. mp 197-199 ˚C. IR (KBr) ν_{max} /cm^{-1}**:** 3343 (NH), 2758 (CH formyl), 1675 (CO), 1648 (CO), 1611 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.88 (s, 3H, CH_3), 4.02 (s, 3H, *N*-CH_3), 7.01-8.03 (m, 8H, Ar-H's), 9.56, (s, 1H, CHO), 12.53, (s, 1H, D_2O-exchangeable, NH); ^{13}C NMR (DMSO-d_6): δ 21.99, 32.09, 110.92, 114.98, 124.65, 128.8, 129.68, 129.79, 137.58, 139.26, 140.56, 141.25, 142.50, 149.08, 189.89, 191.96; MS (*m/z*) 320 (M^+, 48%). Anal. Calcd for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.57; H, 5.01; N, 17.43.

Reaction of (E)-3-(1-methyl-1H-benzimidazol-2-yl)-3-oxo-2-(2-p-tolylhydrazono)propanal (5) with benzoylacetonitrile (6) and benzthiazol-2-ylacetonitrile (9).

General Procedure

To a solution of **5** (3.2 g, 10 mmol) was added benzoylacetonitrile **(6)** or benzthiazol-2-ylacetonitrile **(9)** (10 mmol), in EtOH (50 mL) and 3 drops of piperdine. The reaction mixture was refluxed for 3-4 h, then poured into ice cold H_2O, and neutralized with dil. HCl. The resulting solid product was collected by filtration, washed with EtOH and finally recrystalized from DMF, to afford the pyridazine derivative **8** and **11**, respectively.

(5-Benzoyl-6-imino-1-p-tolyl-1,6-dihydropyridazin-3-yl)(1-methyl-1H-benzoimidazol-2-yl)methanone (8).

Yield 69%. mp 250-252 ˚C. IR (KBr) υ_{max} /cm^{-1}: 3332 (NH), 1649 (CO), 1598 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.69 (s, 3H, CH_3), 4.18 (s, 3H, NCH_3), 6.01 (s, 1H, pyridazine-4-CH), 6.56-8.28 (m, 13H, Ar-H's), 11.19 (s, 1H, NH, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 22.38, 30.06, 110.92, 111.23, 114.24, 115.23, 123.86, 128.8, 129.68, 129.79, 133.65, 136.66, 138.25, 139.87, 140.56, 140.20, 142.26, 147.0, 152.98, 160.20, 185.29, 189.52; MS (*m/z*) 447 (M^+, 52%). Anal. Calcd for $C_{27}H_{21}N_5O_2$: C, 72.47; H, 4.73; N, 15.65. Found: C, 72.40; H, 4.86; N, 15.59.

(5-(Benzothiazol-2-yl)-6-imino-1-p-tolyl-1,6-dihydropyridazin-3-yl)(1-methyl-1H-benzoimidazol-2-yl)methanone (11).

Yield 75%. mp 278-280 ˚C. IR (KBr) υ_{max} /cm^{-1}: 3332 (NH), 1645 (CO); 1614 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.61 (s, 3H, CH_3), 4.21 (s, 3H, NCH_3), 5.99 (s, 1H, pyridazine-4-CH), 6.37-8.03 (m, 12H, Ar-H's), 11.78 (s, 1H, NH, D_2O-exchangeable); MS (*m/z*) 476 (M^+, 42%). Anal. Calcd for $C_{27}H_{20}N_6OS$: C, 68.05; H, 4.23; N, 17.64; S, 6.73 . Found: C, 68.21; H, 4.12; N, 17.61; S, 6.71.

Reaction of (E)-1-(1-methylbenzimidazol-2-yl)-3-(N,N-dimethylamino)prop-2-enone (2) with diazonium salt of heterocyclic amines 12, 16 and 19.

General Procedure

To a stirred cold solution of the enaminone **1** (2 mmol) in pyridine (30 mL) was added the appropriate diazonium salt prepared from 5-amino-3-methyl-4-phenylpyrazole **12**, 3-amino-l,2,4-triazole **16** or 2-aminobenzimidazole **(20)** (2 mmol) portionwise over a period of 30 min at 0-5 ºC. After complete addition, the reaction mixture was stirred for further 3 h at 0-5 ºC then left in a refrigerator for 6 h. The precipitated solid was collected by filtration, washed with water and dried. Recrystallization from DMF/H_2O afforded the corresponding fused ring systems **15, 19** and **23**, respectively.

(1-Methyl-1H-benzoimidazol-2-yl)(7-methyl-8-phenylpyrazolo[5,1-c]-1,2,4-triazin-3-yl)methanon (15).

Yield 80%. mp > 300 ˚C. IR (KBr) υ_{max} /cm^{-1}: 1648 (CO), 1597 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.73 (s, 3H, CH_3), 4.21 (s, 3H, *N*-CH_3), 7.42-7.94 (m, 9H, Ar-H's), 10.08 (s, 1H, triazine-4-CH); ^{13}C NMR (DMSO-d_6): δ 20.10, 31.66, 110.97, 111.22, 114.24, 115.23, 123.86, 124.89, 127.85, 128.28, 129.68, 133.65, 136.66, 138.25, 140.25, 145.60, 150.23, 183.22; MS (*m/z*) 368 (M^+, 42%). Anal. Calcd for $C_{21}H_{16}N_6O$: C, 68.47; H, 4.38; N, 22.81. Found: C, 68.59; H, 4.36; N, 22.71.

[1,2,4]Triazolo[5,1-c][1,2,4]triazin-3-yl(1-methyl-1H-benzoimidazol-2-yl)methanone (19).

Yield 72%. mp > 300 ˚C. IR (KBr) υ_{max} /cm^{-1}: 1656 (CO), 1607 (C=N); ^{1}H NMR (DMSO-d_6): δ 4.11 (s, 3H, NCH_3), 7.08-7.18 (m, 4H, Ar-H's), 7.27 (s, 1H, triazole-7-CH), 9.77 (s, 1H, triazine-4-CH); ^{13}C NMR (DMSO-d_6): δ 31.46, 111.22, 120.68, 123.15, 124.89, 128.42, 135.76, 138.32, 140.56, 146.23, 147.16, 150.23, 182.93 (CO); MS (*m/z*) 279 (M^+, 38%). Anal. Calcd for $C_{13}H_9N_7O$: C, 55.91; H, 3.25; N, 35.11. Found: C, 55.99; H, 3.21; N, 35.07.

3-(1-Methylbenzimidazol-2-oyl)-1,2,4-triazino[4,3-a]benzimidazole (23).

Yield 70%. mp > 300 ˚C. IR (KBr) υ_{max} /cm^{-1}: 1652 (CO), 1607 (C=N); ^{1}H NMR (DMSO-d_6): δ 4.11 (s, 3H, *N*-CH_3), 7.23-7.73 (m, 8H, ArH's), 10.01 (s, 1H, triazine-4-CH); ^{13}C NMR (DMSO-d_6): δ 31.84, 111.98, 121.69, 123.33 124.99, 128.55, 126.97, 128.45, 136.87, 138.32, 124.27, 141.61, 144.10, 156.33, 184.88; MS (*m/z*) 328 (M^+, 45%). Anal. Calcd for $C_{18}H_{12}N_6O$: C, 65.85; H, 3.68; N, 25.60. Found: C, 65.72; H, 3.79; N, 25.62.

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