Studies With 1-Functionally Substituted Alkylbenzotriazoles: An Efficient Route for the Synthesis of 1-Azolylbenzotriazoles, Benzotriazolylazines and Benzotriazolylazoloazines

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A new approach to the synthesis of pyrazole, isoxazole, pyridine and pyrazolo[1,5-*a*]pyrimidine derivatives is reported. The structure of the newly synthesized compounds was elucidated by elemental analyses, ir and ^{1}H nmr spectra, and in some cases by ^{13}C nmr investigation.

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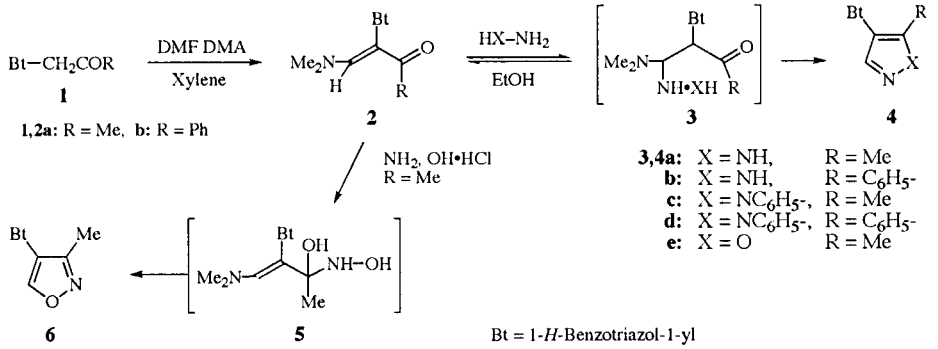
In conjunction with previous interest in developing efficient syntheses of azoles, azines and azoloazines, as potential biodegradable agrochemicals, [1,4] from readily obtainable inexpensive starting material [5-9], I report here on the utility of 1-substituted alkylbenzotriazole [10,11] **1a,b** for the synthesis of pyrazolylbenzotriazoles, isoxazolylbenzotriazole, pyridylbenzotriazole and benzotriazolylpyrazolo-[1,5-*a*]pyrimidine. These compounds were required as part of an agrochemical program for testing as potential biodegradable agrochemicals.

Thus, treatment of benzotriazol-1-ylacetone **1a** and benzotriazol-1-ylacetophenone **1b** with dimethylformamide dimethylacetal (DMF DMA) in dry xylene at reflux temperature afforded the enaminones **2a,b** in good yields. The structure of the isolated products were confirmed on the basis of elemental analysis and spectral data. The reactivity of the enaminones **2a,b** towards certain nitrogen nucleophiles was also investigated. Thus, treatment of compounds **2a,b** with hydrazine hydrate and with phenylhydrazine in refluxing ethanol, the novel pyrazolbenzotriazoles **4a-d** were produced (Scheme 1). The structure of **4** was established on the basis of its elemental analysis and spectral data. For example, the ^{1}H nmr showed a resonance at approximately 8.10 ppm corresponding to H-3' of the pyrazole ring. Moreover, the ^{13}C nmr spectrum of the reaction product showed pyrazole carbons resonating at δ_C 145 and δ 136 ppm. The higher field carbon is coupled with hydrogen and thus assigned for C-3' pyrazole in **4c** [12]. It is believed that both hydrazine hydrate and phenylhydrazine adds reversibly across the α,β-unsaturated moiety in **2a,b** to form the nonisoluble acyclic intermediate **3,** which readily undergoes intramolecular cyclization into pyrazole derivatives **4a-d** *via* loss of dimethylamine and water molecule (Scheme 1).

Compound **2a** also reacted with hydroxylamine to yield an isoxazole derivative that was assigned structure **6** rather than **4e** based on both ^{1}H and ^{13}C nmr. The ^{1}H nmr spectrum showed a resonance at δ_H = 9.7 corresponding to H-5' of isoxazole. If the reaction products is **4e** then the H-3' proton should resonate at higher field δ_H 8.2 ppm [13,14]. Moreover, the ^{13}C nmr of the reaction product revealed two low field signals at δ_C 155 and δ_C 148 ppm. The signal at δ_C 148 corresponds to the tertiary carbon while that at δ_C 155 coresponds to the carbon coupled with a proton. As in the isoxazole system, the carbon resonating at lowest field corresponds to C-5' [13-15]. The observations described above are consistent with structure **6** (Scheme 1).

Scheme 1



1 2 3 4 5 6

1,2a: R = Me, b: R = Ph

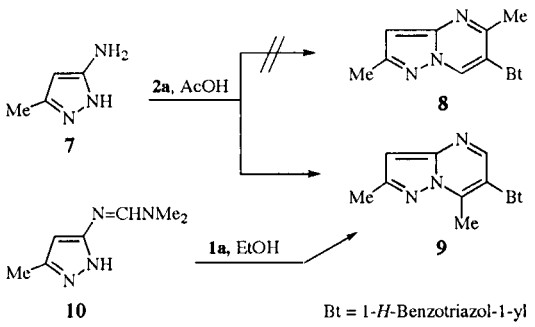
3,4a: X = NH, R = Me
b: X = NH, R = C_6H_5-
c: X = NC_6H_5-, R = Me
d: X = NC_6H_5-, R = C_6H_5-
e: X = O R = Me

Bt = 1-*H*-Benzotriazol-1-yl

The formation of **6** is assumed to proceed *via* 1,2-addition at the carbonyl group in **2** to form the non-isoluble intermediate **5** that readily undergoes intramolecular cyclization into isoxazole derivatives **6** *via* loss of dimethylamine and a

water molecule (Scheme 1). Prompted by the aforementioned results, I have also investigated the reactivity of **2a** toward certain heterocyclic amines. Thus when compound **2** was treated with 3-methyl-1*H*-pyrazol-5-amine (**7**) in refluxing acetic acid, it afforded an excellent yield of single product identified as a pyrazolo[1,5-*a*]pyrimidine derivative, which may react to form **8** or its isomer **9**. Spectral data seemed to be of little help in discriminating **8** and **9**. The compound **9** was obtained by an independent synthetic route where treatment of 5-*N*-(*N*,*N*'-dimethylaminomethyleneimino)-3-methyl-1*H*-pyrazol (**10**) with benzotriazol-1-yl-acetone (**1a**) in refluxing ethanol. This procedure afforded a yellow product identified as 6-benzotriazol-1-yl-2,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**9**) identical in all respects (mp and spectral data) with that obtained previously from reaction **2** with **7**.

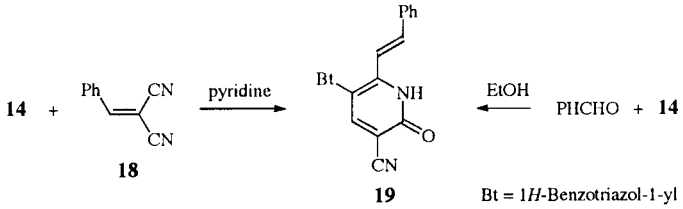
Scheme 2



The enaminone **2a** upon reaction with malononitrile in refluxing ethanol in the presence of a catalytic amount of piperidine yielded a product that could be formulated as **14** or isomer **17**. Similarly condensation of **2a** with cyanoacetamide in refulxing ethanolic sodium ethoxide afford a product identical in all respects (mp, tlc and spectra) with that obtained previously from the reaction of **2a** with malononitrile. The formation of **14** is assumed to proceed *via* initial addition of active methylene reagent across double bond in **2a** yielding the intermediate Michael adduct **11** that then cyclise into **12** which undergoes Dimroth type rearrangement and aromatises *via* loss of a hydrogen molecule and dimethylamine to yield final isolated product **14**. Alternately, initial condensation of **2a** with malononitrile could yield the initial condensation product **15** that is then hydrolyzes into **16** and subsequently cyclises to **17**.

Because the product failed to react with sulphur to yield a condensed thiphene, as is characteristic of azines with vicinal methyl and carbonitrile substituents [6], structure **17** was ruled out and the product assigned to **14**. Moreover, treatment of **14** with benzylidenemalononitrile **18** resulted in the formation of the benzylidene derivative **19** which was also obtained form reaction of **14** with benzaldehydes (Scheme 4).

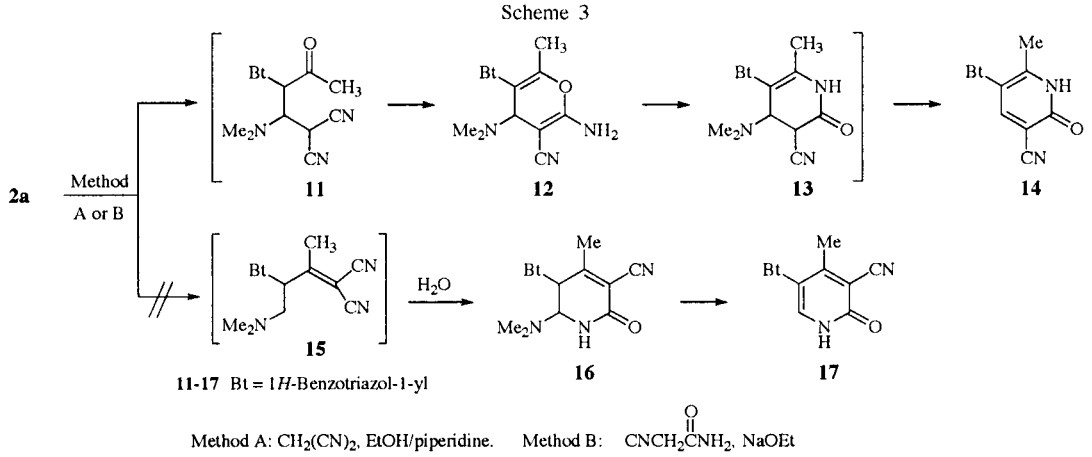
Scheme 4



Compound **19** was assigned the *E* conformation on the basis of ^{1}H nmr which revealed the ethylene protons as two doublets at δ 6.25 and 7.00 with J = 15Hz, as required for such E-coupled protons. Its mass spectrum revealed a molecular ion peak at m/z 339(M^+).

In a similar manner, compound **2a** reacted also with cyanothioacetamide in refluxing ethanolic sodium ethoxide to give a high yield of a crystalline product for which structure **20** was assigned on the basis of its spectral data (ir and ^{1}H nmr spectra). Thus, the ir spectrum of the reaction product, showed NH and nitrile absorptions at 3437 and 2226 cm^{-1} respectively (Scheme 5). Compound **20** was treated with

Scheme 3

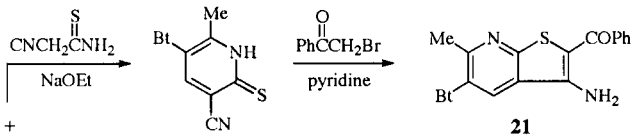


Method A: $CH_2(CN)_2$, EtOH/piperidine. Method B: $CNCH_2\overset{O}{\overset{\|}{C}}NH_2$, NaOEt

α-bromoacetophenone in the presence of pyridine to afford **21**. The structure of **21** was established on the basis of elemental analysis and spectral data (See Experimental).

It is thus evident that **2a,b** are versatile starting materials for the synthesis of hitherto unreported azolylbenzotriazoles, benzotriazolylazoloazines and benzotriazolylazines.

Scheme 5



2a **20** **21**

Bt = 1*H*-Benzotriazol-1-yl

EXPERIMENTAL

All melting points are uncorrected. ir spectra were recorded on a Perkin-Elmer 2000 FT-IR spectrometer. ^1H and ^{13}C nmr spectra were recorded on a Bruker 80 MHz spectrometer with DMSO-d_6 or $CDCl_3$ as solvent and tetramethylsilane (TMS) as an internal standard; chemical shifts are reported as δ units (ppm). Mass spectra were measured on GS/MS INCOL XL Finnigan MAT. Microanalysis were performed on a Leco-CHNS 932 analyzer. Compounds **1a,b** were prepared following literature procedure [10,11].

3-Benzotriazol-1-yl-4-(*N,N*-dimethylamino)-3-buten-2-one (**2a**).

To a suspension of **1a** (1.75 g, 10 mmol) in xylene (30 mL) was treated with dimethylformamide dimethylacetal (1.33 g, 10 mmol). The reaction mixture was refluxed for 3 hours, then allowed to cool at room temperature. The solid product, so formed was collected by filtration and crystallized from a mixture of ethanol/dimethylformamide (2:1) to give **2a** (73%); mp: 140-142°; ir: ν 1655.30 (CO); ^1H nmr: δ1.99 (s, 3H, Me), 2.31 (s, 6H, NMe_2), 6.00 (s, 1H, H-4), 7.33-8.15 (m, 4H, Ar-H). ^{13}C nmr (DMSO-d_6): δ189.93 (CO), 149.60, 149.0 (C-3 and C-4), 145.10, 136.75, 128.44, 124.34, 119.67, 111.14 (aromatic carbons), 46.06 (NMe_2), 24.85 (Me).

Anal. Calcd. for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.64; H, 6.11; N, 23.98.

2-Benzotriazol-1-yl-3-(*N,N*-dimethylamino)-1-phenyl-2-propenone (**2b**).

A suspension of **1b** (4.98 g, 20 mmol) in xylene (50 mL) was treated with dimethylformamide dimethylacetal (2.51 g, 20 mmol). The reaction mixture was refluxed for 16 hours. The solvent was evaporated under reduced pressure and allowed to cool in the refrigerator. The solid product, so formed was collected by filtration and crystallized from a mixture of cyclohexane and benzene (1:1). This compound was obtained as yellow orange crystal in 65% yield; mp: 156-157°; ir: ν 1643.74 (CO); ^1H nmr: δ 2.32 (s, 6H, NMe_2), 7.16-8.11 (m, 10H, Ar-H & H-3); ^{13}C nmr (DMSO-d_6): δ188.82 (CO), 152.30, 151.99 (C-2 and C-3), 145.12, 140.04, 136.64, 130.51, 128.45, 128.05, 124.35, 119.64, 111.18, 105.64 (aromatic carbons), 48.02 (NMe_2); ms: (CI), *m/z* = 293 (M^+).

Anal. Calcd. for $C_{17}H_{16}N_4O$: C, 69.84; H, 5.51; N, 19.16. Found: C, 69.96; H, 5.42; N, 19.36.

General Procedure for the synthesis of 1-(5'-Substituted-(1H')-pyrazol-4'-yl)benzotriazol (**4a-d**).

To a solution of **2a,b** (10 mmol) in ethanol was added (20 mL) hydrazine hydrated (10 mmol) or phenyl hydrazine (10 mmol). The reaction mixture was refluxed for 12 hours, left to cool at room temperature. The product, so formed was collected by filtration and crystallized from the proper solvent.

1-(5'-methyl-(1*H'*)-pyrazol-4'-yl)benzotriazole (**4a**).

This compound was obtained in 73% yield; mp: 96-98° (ethanol); ir: ν 3176 (NH); ^1H nmr: δ 2.22 (s, 3H, Me), 7.47-8.22 (m, 5H, Ar-H & H-3'), 13.20 (br, 1H, NH).

Anal. Calcd. for $C_{10}H_9N_5$: C, 60.29; H, 4.55; N, 35.16. Found: C, 60.18; H, 4.35; N, 35.40.

1-(5'-phenyl-(1*H'*)-pyrazol-4'-yl)benzotriazole (**4b**).

This compound was crystallized from cyclohexane and benzene (1:1) as yellow crystals in 60% yield; mp: 78-80°; ir: ν 3405 (NH); ^1H nmr: 7.22-8.14 (m, 9H, Ar-H), 8.33 (s, 1H, H-3'), 13.80 (br, 1H, NH); ms: (CI) *m/z* = 261 (M^+).

Anal. Calcd. for $C_{15}H_{11}N_5$: C, 68.95; H, 4.24; N, 26.81. Found: C, 68.61 ; H, 4.28; N, 27.14.

1-(5'-methyl-1'-phenylpyrazol-4'-yl)benzotriazole (**4c**).

This compound was obtained in 92% yield; mp: 146-148° (ethanol); ^1H nmr: 2.30 (s, 3H, Me), 7.55-7.75 (m, 9H, Ar-H), 8.22 (s, 1H, H-3'); ^{13}C NMR (DMSO-d_6): 145.32 (C-3'), 139.48 (C-4'), 136.15 (C-5'), 135.58, 134.00, 129.81, 128.93, 128.83, 125.24, 124.95, 119.96, 118.71, 111.02 (aromatic carbons), 10.86 (Me).

Anal. Calcd. for $C_{16}H_{13}N_5$: C, 69.80; H, 4.76; N, 25.49. Found: C, 70.28; H, 4.68; N, 25.48.

1-(1',5'-Diphenylpyrazol-4'-yl)benzotriazole (**4d**).

This compound was crystallized from a mixture of cyclohexane and benzene (1:1) in 70% yield; mp: 177-178°C; ^1H nmr: 7.13-7.35 (m, 14H, Ar-H) , 8.04 (s, 1H, H-3'); ms: (CI), *m/z* = 337 (M^+).

Anal. Calcd. for $C_{21}H_{15}N_5$: C, 74.76; H, 4.48; N, 20.76. Found: C, 74.72; H, 4.69; N, 20.87.

1-(3'-methyl-isoxazol-4'-yl)benzotriazole (**6**).

A mixture of **2a** (2.30g, 10 mmol) and hydroxylamine hydrochloride (0.69g, 10 mmol) in ethanol (30 mL) was refluxed for 7 hours and left to cool at room temperature. The solid product, so formed, was collected by filtration and crystallized from ethanol as rose colored crystals in 69% yield; mp: 118-120°; ^1H nmr: 2.35 (s, 3H, Me), 7.50-8.26 (m, 4H, Ar-H) 9.74 (s, 1H, H-5'); ^{13}C nmr: 155.07 (C-5'), 148.32 (C-3'),142.20, 138.21, 133.54, 129.37, 125.35, 120.05, 111.04 (aromatic carbons), 9.88 (Me).

Anal. Calcd. for $C_{10}H_8N_4O$: C, 59.99; H, 4.03; N, 27.99. Found: C, 59.84; H, 3.96; N, 28.43.

6-Benzotriozol-1-yl-2,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**9**).

Method A:

A solution of compound **2a** (2.35g, 10 mmol) in acetic acid (30 mL) was treated with 5-amino-3-methyl-1*H*-pyrazole (0.97 g, 10 mmol). The reaction mixture was refluxed for 2 hours, and left to cool at room temperature. The solid product, so formed, was collected by filtration and crystallized from acetic acid as pale yellow crystals in 81% yield.

Method B:

To a suspension of **1a** (1.75 g, 10 mmol) in ethanol (30 mL) was treated with compound **10** (1.52 g, 16 mmol). The mixture was stirred for 48 hours, and the solvent was evaporated under reduced pressure. The solid product, so formed, was collected by filtration and crystallized from ethanol as yellow crystal in 72% yield; mp: 180-182°; ^{1}H nmr: 2.56 (s, 6H, Me), 6.80 (s, 1H, H-3), 7.66-8.04 (m, 4H, Ar-H), 8.92, (s, 1H, H-5); ms: (CI), *m/z* = 264 (M^+).

Anal. Calcd. for $C_{14}H_{12}N_6$: C, 63.62; H, 4.58; N, 31.80. Found: C, 63.76; H, 4.58; N, 31.84.

5-*N*-(*N,N'*-Dimethylaminomethylenimino)-3-methyl(1*H*)-pyrazole (**10**).

A mixture of 5-amino-3-methyl-1*H*-pyrazol (**7**) (0.97g, 10 mmol) and dimethylformamide dimethylacetal(1.33 g, 10 mmol) in xylene (30 mL) was refluxed for 10 minutes. The solvent was evaporated under pressure and the residue crystallized from ethanol as yellow crystal in 81% yield; mp: 120-122°; ir: ν 3450 (NH) cm^{-1}; ^{1}H nmr: δ 2.08 (s, 3H, Me), 2.84 (s, 6H, NMe_2), 5.56 (s, 1H, methylenic CH), 7.88 (s, 1H, H-4).

Anal. Calcd. for $C_7H_{12}N_4$: C, 55.24; H, 7.95; N, 36.82. Found: C, 54.87; H, 8.17; N, 36.81.

5-Benzotriozol-1-yl-1,2,dihydro-6-methyl-2-oxopyridine-3-carbonitrile (**14**).

Method A:

A mixture of compound **2a** (2.30 g, 10 mmol) and malononitrile in absolute ethanol (50 mL) and a few drops of piperidine was stirred for 8 hours. The solvent was evaporated under reduced pressure. The solid product, so formed, was collected by filtration and crystallized from dimethylformamide/ethanol (1:2).

Method B:

A mixture of compound **2a** (2.30 g, 10 mmol) and cyanoacetamide (0.84 g, 10mmol) was refluxed in 30 mL sodium ethoxide solution (prepared from 0.6 g in 30 mL absolute ethanol). The mixture was stirred for 3-4 hours, then poured into ice cold water and neutralized with HCl (10%). The solid product, so formed, was collected by filtration and crystallized from dimethylformamide/ethanol (3:1) as brown crystal in 75% yield; mp: > 300°; ir: ν: 3442 (NH), 2223 (CN), 1658 cm^{-1} (CO); ^{1}H nmr: δ 1.99 (s, 3H, Me), 7.58-8.10 (m, 4H, Ar-H), 8.43 (s, 1H, H-4), 13.20 (br, 1H, NH); ^{13}C nmr (DMSO-d_6): 160.47 (C-2), 153.10, 147.77, 145.25, 134.37, 129.12, 125.06, 119.97, 116.02, 111.05, 101.13 (aromatic carbons), 114.59 (CN), 16.31 (Me).

Anal. Calcd. for $C_{13}H_9N_5O$: C, 62.14; H, 3.61; N, 27.88. Found: C, 62.05; H, 3.64; N, 27.41.

5-Benzotriazol-1-yl-1,2-dihydro-6-styryl-2-oxo-pyridine-3-carbonitrile (**19**).

To a suspension of compound **14** (3.30 g, 10 mmol) in pyridine (30 mL), was added benzylidinemalononitrile (1.54 g, 10 mmol). The mixture was stirred for 4 hours, neutralized with HCl (10%) then poured into ice-cold water. The solid product, so formed, was collected by filtration and crystallized from dimethylformamide/ethanol (3:1) as orange crystals in 73% yield; mp: 328-330°; ir: ν 3437 (NH), 2225 (CN), 1656 cm^{-1} (ring CO); ^{1}H nmr: δ 6.25 (d, 1H, J=15 Hz, vinylic-H), 7.00(d, 1H, J=15 Hz, H, vinylic-H) 7.31-8.47 (m, 9H, ArH) 8.61 (s, 1H, H-4), 13.0 (br, 1H, NH); ms: (CI), *m/z* = 339 (M^+).

Anal. Calcd. for $C_{20}H_{13}N_5O$: C, 70.78; H, 3.86; N, 20.64. Found: C, 70.51; H, 3.94; N, 20.20.

5-Benzotriazol-1-yl-1,2-dihydro-6-methyl-2-thioxopyridine-3-carbonitrile (**20**).

To a suspension of compound **2a** (2.3 g, 10 mmol) and cyanothioacetamide (12g, 10 mmol) was refluxed in sodium ethoxide (prepared from 0.6 g sodium metal and 60 mL ethanol) for 8 hours, then poured into ice-cold water and neutralized with HCl (10%). The solid product, so formed, was collected by filtration and crystallized from dimethylformamide/ethanol (3:1) as orange crystals in 79% yield; mp: 212-214°C; ir: ν 3437 (NH), 2226 cm^{-1} (CN); ^{1}H nmr: δ 2.18 (s, 3H, Me), 7.52-8.42 (m, 4H, Ar-H)), 8.57 (s, 1H, H-4), 14.40 (br, 1H, NH).

Anal. Calcd. for $C_{13}H_9N_5S$: C, 58.41; H, 3.39; N, 26.19. Found : C, 58.29; H, 3.68; N, 26.08.

3-Amino-5-benzotriazol-1-yl-2-benzoyl-6-methyl-thieno[2,3-*b*]-pyridine (**21**).

To a suspension of **20** (2.67 g, 10 mmol) in pyridine (20 mL), was added phenacylbromide (1.99 g, 10 mmol). The mixture was stirred for 3 hours, then allowed to cool and neutralized with HCl (10%). The solid product, so formed, was collected by filtration and crystallized from dimethylformamide/ethanol (3:1) as green crystal in 69% yield; mp: 190-192°; ir: ν 3404 and 3292 (NH_2), 1663 cm^{-1} (CO); ^{1}H nmr: 2.38 (s, 3H, Me), 7.44-8.65 (m, 11H, Ar-H, NH_2), 8.92 (s, 1H, H-4); ^{13}C nmr (DMSO-d_6): 189.01 (CO), 161.42 (C-3), 157.44, 150.25, 145.32, 140.79, 133.86, 132.01, 130.8, 128.61, 128.21, 127.4, 124.34, 124.02, 119.85, 115.45, 109.23, 104.12, (aromatic carbons), 21.37 (Me); ms: (CI), *m/z* = 385 (M^+).

Anal. Calcd. for $C_{21}H_{15}N_5OS$: C, 65.54; H, 3.92; N, 18.17. Found: C, 65.92; H, 4.22; N, 17.91.

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