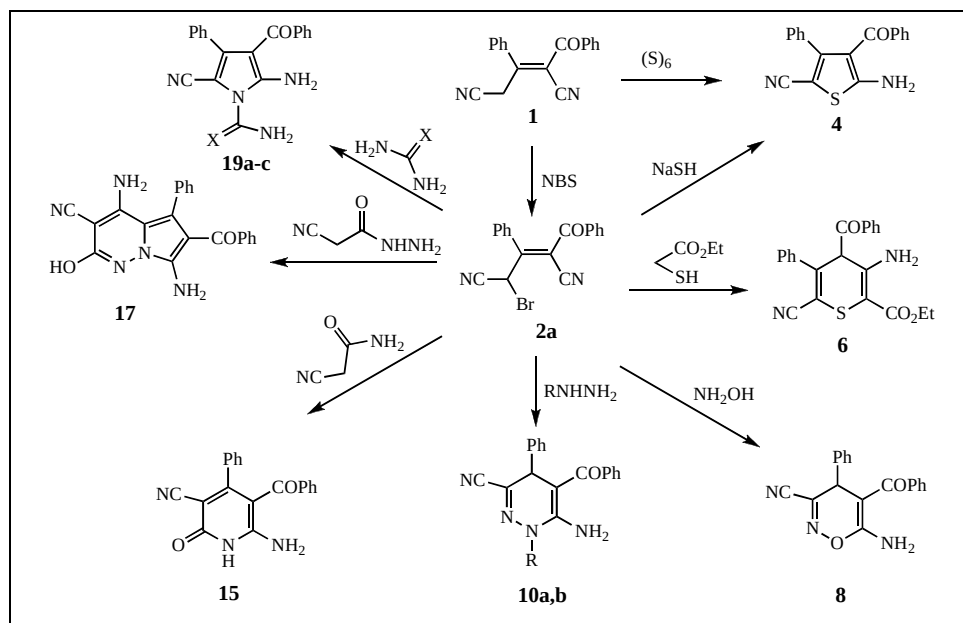


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2-Benzoyl-3-phenylpent-2-ene-1,5-dinitrile **1** undergoes bromination with *N*-bromosuccinimide (NBS) to afford the bromo derivative **2a**. This bromo derivative undergoes reactions with sodium hydrogen sulfide, ethyl thioglycollate, hydroxylamine hydrochloride, hydrazines, cyanoacetamide, cyanacetohydrazide and urea derivatives to afford the thiophene **4**, 4*H*-thiopyran **6**, 4*H*-1,2-oxazine **8**, 4*H*-pyridazines **10a,b**, the pyridine **15**, pyrrolo[1,2-*b*]pyridazine **17** and the *N*-substituted-pyrrole derivatives **19a-c** respectively.

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INTRODUCTION

In the last few years we have been involved in a program aiming to develop new simple procedures for the synthesis of functionally substituted heterocycles of anticipated biological activity that can be used as biodegradable agrochemicals, from laboratory available starting materials [1-3]. In the context of this program some new functionally substituted pyridazine, pyrrole and pyrrolo-fused derivatives were required. 2-Benzoyl-3-phenylpent-2-ene-1,5-dinitrile **1** (Scheme 1) seemed to be a good candidate to fulfill our objective *via* its bromination and then reacting the bromo derivative with the suitable reagents.

RESULTS AND DISCUSSION

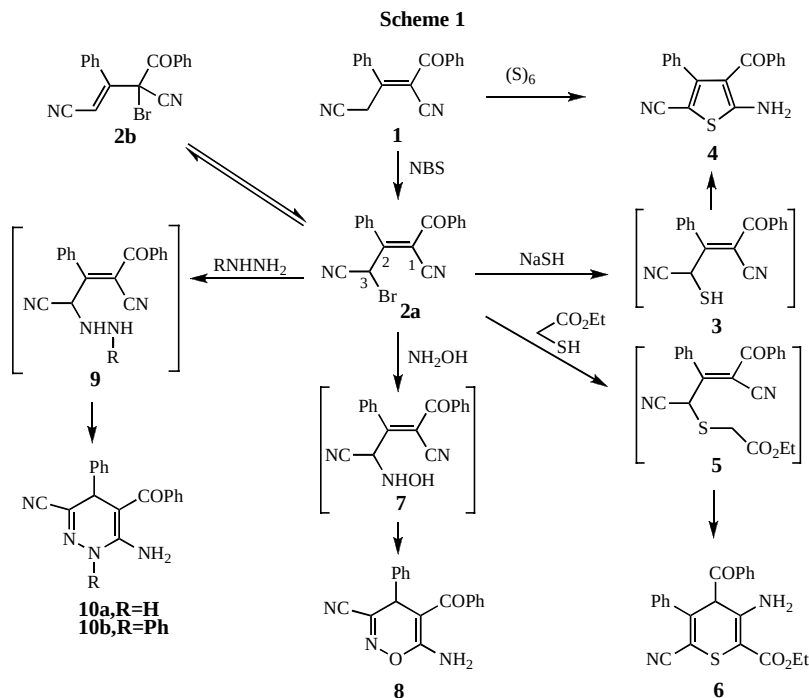
Thus compound **1**, obtained recently by us [4], was allowed to react with *N*-bromosuccinimide (NBS) in dimethylformamide (DMF) at room temperature to afford

the bromo derivative **2a** (Scheme 1) in 75% yield. The IR spectrum of **2a** showed absorption bands at ν_{max} 2207, 2198 and 1689 cm⁻¹ corresponding to two CN and one CO groups, respectively. The ¹H NMR spectrum of this bromo derivative revealed an aromatic multiplet (10 H) at δ =7.20-7.85 and a singlet at δ = 5.10 ppm integrated for (1H). It is assumed that the bromination took place on the methylene group of **1** to afford **2a**. In spite of the fact that compound **1** can in principle tautomerize to 4-benzoyl-3-phenylpent-2-ene-1,5-dinitrile, however the bromo isomer **2b** was not observed presumably due to steric factors, which favour the attack on the less hindered methylene group in **1**. Mass spectral measurements, analytical and ¹³C NMR data are in complete agreement with structure **2a** (*cf.* experimental part).

Compound **2a** reacts with sodium hydrogen sulfide [5] in refluxing ethanol to afford a dark yellowish brown solid product. The IR spectrum of this product showed absorption bands at ν 3430-3320 (NH₂), 2212 (CN) and

1680 (CO) cm^{-1} respectively. Elemental analysis of this product showed the disappearance of the bromine atom and was in good agreement with structure **4** (Scheme 1). It is assumed that the bromine atom in compound **2a** is substituted by SH to afford the intermediate **3**, which

synthetic and pharmaceutical importance and different approaches for their synthesis have been developed [10,11]. In the last few years we have reported several syntheses of pyrrole derivatives [12,13]. In the present work we explore the synthetic potentialities of **2a** to



brings about cyclization by addition to the CN groups under these basic conditions to afford the thiophene derivative **4**. Mass spectral measurements and the ^1H NMR spectrum are consistent with structure **4**.

Compound **4** could also be obtained by reacting **1** with elemental sulphur in presence of a basic catalyst according to the literature methods [6]. The identity of the two products was inferred from mp, TLC analysis and analytical data.

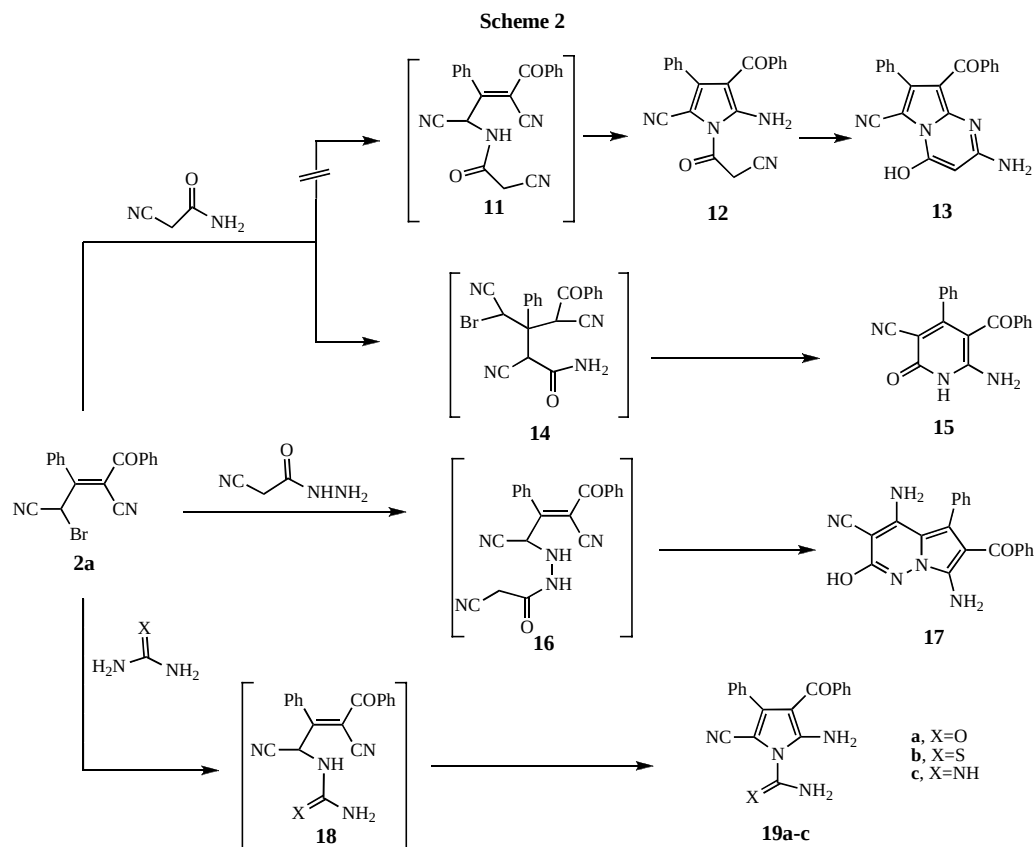
Compound **2a** reacts with ethyl thioglycollate, hydroxylamine hydrochloride, hydrazine hydrate and phenyl hydrazine in the presence of sodium acetate to afford dark colored solid products. Structures **6**, **8** and **10a,b** (Scheme 1) were assigned to these products respectively on the basis of their analytical and spectral data (*cf.* Experimental part). The formation of these products is assumed to proceed *via* the initial elimination of HBr to afford the acyclic intermediates **5**, **7** and **9** respectively, followed by cyclization [5,7] to afford the final isolable products. This behaviour is similar to a previously reported work on related systems [8,9].

Pyrroles and fused pyrrole derivatives represent an interesting class of heterocyclic compounds due to their

obtain some novel N-substituted pyrroles and pyrrolo-fused pyridazine.

Thus compound **2a** was allowed to react with cyanoacetamide aiming to obtain the pyrrole derivative **12** or its cyclized pyrrolo[1,2-*a*]pyrimidine derivative **13** through a normal sequence *via* the intermediate **11**. However the IR spectrum of the obtained product showed two carbonyl absorption bands at $\nu_{\text{max}} = 1665$ and 1682 cm^{-1} and only one cyano absorption band at $\nu_{\text{max}} = 2218 \text{ cm}^{-1}$. The ^1H NMR spectrum of this product showed no signals that can be attributed to methylene group (in **12**), or the pyrimidine 5-H (in **13**).

Furthermore, the ^{13}C NMR spectrum of the product showed only 15 signals (*cf.* experimental), while a structure like **12** or **13** would reveal 17 signals. Based on these data as well as the elemental analysis the pyridine structure **15** was assigned to this product (Scheme 2). It seems that the NH_2 in cyanoacetamide is less reactive than the methylene group which undergoes a Michael addition to the activated double bond in **2a** to afford the acyclic intermediate **14**, which in turn undergoes cyclization with loss of bromoacetonitrile (BrCH_2CN). A similar behaviour has been observed previously [13].



Compound **2a** reacts with cyanoacetohydrazide through the terminal hydrazine moiety with elimination of HBr to afford the nonisolable acyclic intermediate **16** which undergoes two cyclizations *via* the addition of NH to the 1-CN, and of the active methylene to the other CN group in the assumed formed pyrrole to afford the pyrrolo[1,2-*b*]pyridazine derivative **17**. A similar behavior of cyanoacetohydrazide has been previously reported with related systems [13]. In analogous manner compound **2a** reacted with urea, thiourea or guanidine to afford pyrrole N-amide, N-thioamide or N-amidine derivatives **19a-c** respectively, presumably *via* the acyclic intermediates **18**. Elemental analyses and spectral data are in complete agreement with the proposed structures **17** and **19a-c** (*cf.* experimental part).

EXPERIMENTAL

Melting points were determined on an electrothermal (9100) apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer. The ^1H -NMR and ^{13}C -NMR spectra were taken on a Varian Gemini 300 MHz spectrometer in $\text{DMSO}-d_6$ using TMS as internal standard and chemical shifts are expressed in δ (ppm) values. Assignments were made by correlation of the off-resonance decoupled ^{13}C -NMR spectra and determination of the ^1H chemical shifts. Mass spectra were taken on a Shimadzu GCMS-GB 1000 PX (70 eV).

Elemental analyses were carried out by the Microanalytical Center at Cairo University.

Bromination of 1: Preparation of 1-Benzoyl-3-bromo-2-phenylpropenedinitrile (2a). To a solution of 2.7 g (0.01 mole) of **1** in 25 mL of dry DMF was added 1.78 g (0.01 mole) of NBS. The reaction mixture was stirred for 4 hours at room temperature and then left overnight. The mixture was then poured on ice-cold water and neutralized with drops of HCl. The solid precipitate that appeared was collected by filtration and recrystallized from ethanol to afford (2.6 g, ~75%) of **2a** as brownish violet crystalline solid, mp 205-207 °C; ir: ν_{max} = 2207, 2198 (2CN), 1689 (C=O) cm^{-1} , (m/e 350,352). ^1H nmr (300 MHz, $\text{DMSO}-d_6$): δ_{H} 5.10 (s, 1H, CH); 7.20-7.85 (m, 10H, Ar. H); ^{13}C nmr: δ_{C} 32.55 (d)(C3), 101.4(s)(C1), 114.50(s)(CN), 116.90(s)(CN), 126.25(d), 127.52(d), 128.5(d), 129.15(d), 129.7(d), 134.20(d), 135.1 (s), 136.8(s), 168.15(s)(C2), 187.38 (s)(C=O).

Anal. Calcd for $(\text{C}_{18}\text{H}_{11}\text{BrN}_2\text{O})$: C, 61.56; H, 3.16; Br, 22.75; N, 7.98. Found: C, 61.5; H, 3.2; Br, 23.1; N, 8.3.

5-Amino-4-benzoyl-3-phenylthiophene-2-carbonitrile (4). To a solution of 3.5 g (0.01 mole) of **2a** in 25 mL of ethanol was added 0.56 g (0.01 mole) of sodium hydrogen sulfide and the reaction mixture was heated on a water bath for 1 hour. The mixture was allowed to cool down, then poured on ice-cold water and acidified with HCl till just neutral. The brown precipitate that appeared was collected by filtration and recrystallized from ethanol to afford (2 g, 68%) of **4**, mp 232-233 °C; ir: ν_{max} (KBr) 3430-3320 (NH_2), 2212 (CN), 1680 (C=O) cm^{-1} , (m/e=304); ^1H nmr (300 MHz, $\text{DMSO}-d_6$): δ_{H} 6.55 (s, 2H, NH_2 , exch.), 7.20-7.80 (m, 10H, Ar. H). This compound

was found to be identical with an authentic sample obtained from the reaction of **1** with elemental sulfur as described in the literature for similar systems [5].

Anal. Calcd for ($C_{18}H_{12}N_2OS$): C, 71.03; H, 3.97; N, 9.20; S, 10.54. Found: C, 70.80; H, 4.20; N, 9.50; S, 10.80.

Ethyl 3-Amino-4-benzoyl-6-cyano-5-phenyl-4H-thiopyran-2-carboxylate (6). To a mixture of 3.5 g (0.01 mole) of **2a** and 1.20 g (0.01 mole) of ethyl thioglycollate in 30 mL of ethanol was added 1.64 g (0.02 mole) of sodium acetate. The mixture was stirred at room temperature for 4 hours, then poured on ice-cold water and neutralized with HCl. The formed dark-colored precipitate was collected by filtration and recrystallized to afford (2 g, 65%) of **6**, brown crystalline solid, mp 175-176 °C (EtOH); *ir*: $\nu_{\max}$ (KBr) 3435-3235 (NH_2), 2215 (CN), 1687 & 1708 ($2C=O$) cm^{-1} , ($m/e=390$). 1H nmr (300 MHz, DMSO- d_6): δ_H 1.35 (t, $J=7Hz$, 3H, CH_3), 4.15 (q, $J=7Hz$, 2H, CH_2), 4.30 (s, 1H, 4-H), 7.15-7.90 (m, 10H, Ar. H), 8.25 (s, 2H, NH_2 exch.); ^{13}C nmr: δ_C 14.0(q), 55.5(d), 60.9(t), 99.8(s), 105.1(s), 116.2(s), 126.4(d), 127.8(d), 128.3(d), 128.5(d), 128.7(d), 133.2(d), 135.1(s), 137.6(s), 151.1(s), 152.4(s), 164.9(s), 195.4(s).

Anal. Calcd for ($C_{22}H_{18}N_2O_3S$): C, 67.67; H, 4.65; N, 7.17; S, 8.21. Found: C, 67.50; H, 4.90; N, 7.40; S, 8.45.

6-Amino-5-benzoyl-4-phenyl-4H-[1,2]-oxazine-3-carbonitrile (8). To a mixture of 3.5 g (0.01 mole) of **2a** and 0.7 g (0.01 mole) of hydroxylamine hydrochloride in 30 ml of ethanol was added a solution of potassium carbonate (2.76 g; 0.02 mole in the minimum amount of water). The reaction mixture was refluxed for 2 hours then left to cool to room temperature, diluted with ice-cold water and neutralized with HCl. The yellow precipitate that formed was collected by filtration and recrystallized from ethanol to give (2.2 g, 72%) of **8**, mp 155-156 °C (EtOH); *ir*: $\nu_{\max}$ (KBr) 3445-3260 (NH_2), 2219 (CN), 1682 ($C=O$) cm^{-1} , ($m/e=303$); 1H nmr (300 MHz, DMSO- d_6): δ_H 4.1 (s, 1H, 4-H), 7.1-7.8 (m, 10H, Ar. H), 8.1 (s, 2H, NH_2 exch.). *Anal.* Calcd for ($C_{18}H_{13}N_3O_2$): C, 71.28; H, 4.32; N, 13.85. Found: C, 71.50; H, 4.50; N, 14.10.

The Reaction of 2a with Hydrazine Hydrate and Phenyl Hydrazine (General Procedure). To a solution of 3.5 g (0.01 mole) of **2a** in 25 ml of ethanol was added an excess of hydrazine hydrate (~2 ml) or 1.08 g (0.01 mole) of phenyl hydrazine, and the reaction mixture was refluxed for 2 hours in each case, after which it was left to cool to room temperature. The formed solid precipitates were collected by filtration and recrystallized from EtOH/DMF (1:1) to afford **10a** and **10b** respectively:

6-Amino-5-benzoyl-4-phenyl-1,4-dihydropyridazine-3-carbonitrile (10a). Dark yellow crystalline solid, mp 207-209 °C (EtOH/DMF) (2 g, 73%); *ir*: $\nu_{\max}$ (KBr) 3455-3255 (NH_2 & NH), 2220 (CN), 1683 ($C=O$) cm^{-1} , ($m/e=302$); 1H nmr (300 MHz, DMSO- d_6): δ_H 3.95 (s, 1H, 4-H), 4.65 (s, 2H, NH_2 , D_2O exch.), 7.05-7.80 (m, 10H, Ar. H), 8.3 (br. s, 1H, NH , exch.).

Anal. Calcd for ($C_{18}H_{14}N_4O$): C, 71.51; H, 4.67; N, 18.53. Found: C, 71.70; H, 4.80; N, 18.20.

6-Amino-5-benzoyl-1,4-diphenyl-1,4-dihydro pyridazine-3-carbonitrile (10b). Brownish yellow crystalline solid, mp 239-241 °C (EtOH/DMF) (2.4 g, 63%); *ir*: $\nu_{\max}$ (KBr) 3390-3220 (NH_2), 2215 (CN), 1683 ($C=O$) cm^{-1} , ($m/e=378$); 1H nmr (300 MHz, DMSO- d_6): δ_H 4.05 (s, 1H, 4-H), 6.50-7.80 (m, 15H, Ar. H), 7.85 (br. s, 2H, NH_2 exch.).

Anal. Calcd for ($C_{24}H_{18}N_4O$): C, 76.17; H, 4.79; N, 14.81. Found: C, 76.30; H, 4.50; N, 14.60.

The Reaction of 2a with Cyanoacetamide, Cyanoaceto-hydrazide and Urea Derivatives (General Procedure). To a

solution of **2a** (3.5 g; 0.01 mole) in 30 ml of ethanol was added 0.01 mole of cyanoacetamide, cyanoaceto-hydrazide, urea, thiourea or guanidine nitrate followed by a conc. solution of potassium carbonate (1.38 g, 0.01 mole, in the least amount of water). The respective reaction mixtures were refluxed for 3 h, left to cool, poured on cold water and neutralized with HCl. The appearing precipitates were collected by filtration and recrystallized to afford products.

6-Amino-5-benzoyl-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (15). Dark yellow crystalline solid, mp 245-246 °C (EtOH/DMF) (2.4 g, 78%); *ir*: $\nu_{\max}$ (KBr) 3420-3220 (NH_2 & NH), 2213 (CN), 1678 & 1687 ($2C=O$) cm^{-1} , ($m/e=315$); 1H nmr (300 MHz, DMSO- d_6): δ_H 7.10-7.80 (m, 10H, Ar. H), 8.2 (br. s, 2H, NH_2 exch.), 10.25 (s, 1H, NH exch.); ^{13}C nmr: δ_C 94(s), 95.5(s), 116.1(s), 124.9(s), 126.3(d), 127.5(d), 128.6(d), 129.1(d), 129.6(d), 134.2(d), 136.9(s), 152.0(s), 162.5(s), 169.1(s), 185.4(s).

Anal. Calcd for ($C_{19}H_{13}N_3O_2$): C, 72.37; H, 4.16; N, 13.3. Found: C, 72.30; H, 4.50; N, 13.60.

4,7-Diamino-6-benzoyl-2-hydroxy-5-phenylpyrrolo[1,2-b]-pyridazine-3-carbonitrile (17). Brownish crystalline solid, mp 285-286 °C (EtOH/DMF) (2.6 g, ~70%); *ir*: $\nu_{\max}$ (KBr) 3450-3230 (NH_2 & OH), 2218 (CN), 1682 ($C=O$) cm^{-1} , ($m/e=369$); 1H nmr (300 MHz, DMSO- d_6): δ_H 4.85 (s, 2H, NH_2 exch.), 6.8 (s, 1H, OH exch.), 7.2-7.8 (m, 10H, Ar. H), 8.3 (s, 2H, NH_2 exch.).

Anal. Calcd for ($C_{21}H_{15}N_5O_2$): C, 68.28; H, 4.09; N, 18.96. Found: C, 68.20; H, 4.20; N, 19.30.

2-Amino-3-benzoyl-5-cyano-4-phenylpyrrole-1-carboxamide (19a). Yellow crystalline solid, mp 195-197 °C (EtOH/DMF) (2.4 g, ~73%); *ir*: $\nu_{\max}$ (KBr) 3425-3215 (NH_2), 2215 (CN), 1660 & 1687 ($2C=O$) cm^{-1} , ($m/e=330$); 1H nmr (300 MHz, DMSO- d_6): δ_H 5.2 (s, 2H, NH_2 exch.), 7.25-7.85 (m, 10H, Ar. H), 8.32 (s, 2H, NH_2 exch.).

Anal. Calcd for ($C_{19}H_{14}N_4O_2$): C, 69.08; H, 4.27; N, 16.96. Found: C, 69.20; H, 4.50; N, 17.10.

2-Amino-3-benzoyl-5-cyano-4-phenylpyrrole-1-thiocarboxamide (19b). Reddish brown crystalline solid, mp 172-173 °C (EtOH/DMF) (2.5 g, 72%); *ir*: $\nu_{\max}$ (KBr) 3395-3225 (NH_2), 2217 (CN), 1684 (CO) cm^{-1} , ($m/e=346$); 1H nmr (300 MHz, DMSO- d_6): δ_H 5.25 (s, 2H, NH_2), 7.20-7.80 (m, 10H, Ar. H), 8.35 (s, 2H, NH_2 exch.).

Anal. Calcd for ($C_{19}H_{14}N_4OS$): C, 65.88; H, 4.07; N, 16.17; S, 9.26. Found: C, 65.50; H, 4.10; N, 16.30; S, 9.40.

2-Amino-3-benzoyl-5-cyano-4-phenylpyrrole-1-carboxamide (19c). Yellowish brown crystalline solid, mp 257-259 °C (EtOH/DMF) (2.4 g, 73%); *ir*: $\nu_{\max}$ (KBr) 3385-3165 (NH_2 & NH), 2215 (CN), 1680 (CO) cm^{-1} , ($m/e=329$); 1H nmr (300 MHz, DMSO- d_6): δ_H 4.95 (s, 2H, NH_2), 7.1-7.8 (m, 10H, Ar. H), 8.28 (s, 2H, NH_2), 8.72 (s, 1H, NH).

Anal. Calcd for ($C_{19}H_{15}N_5O$): C, 69.29; H, 4.59; N, 21.26. Found: C, 69.00; H, 4.80; N, 21.60.

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