Synthetic Studies with 3-Oxo-*N*-[4-(3-oxo-3-phenylpropionylamino)-phenyl]-3-phenylpropionamide

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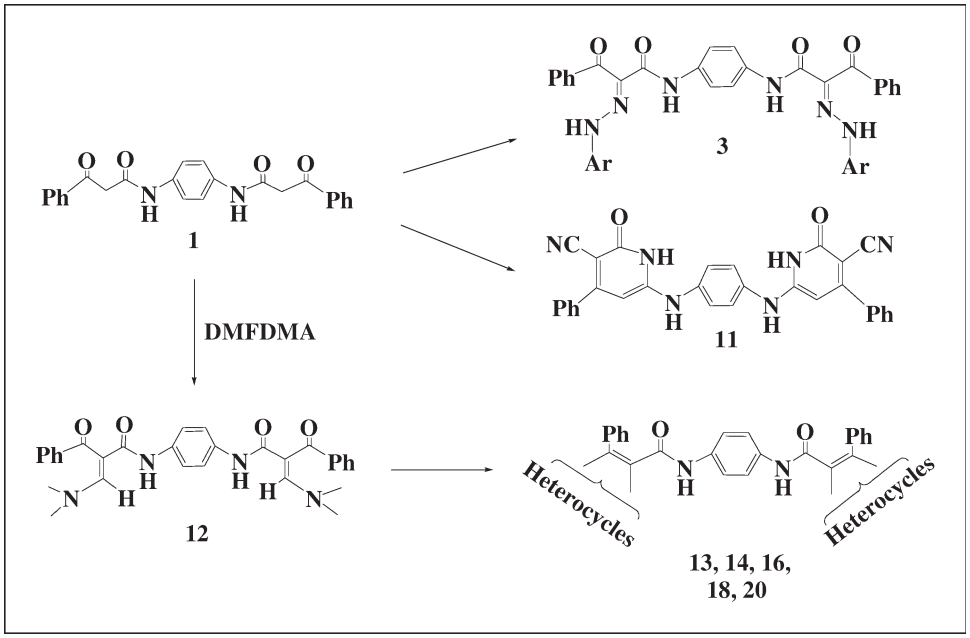

3-Oxo-*N*-[4-(3-oxo-3-phenylpropionylamino)-phenyl]-3-phenylpropionamide **1** and its derivative 2-benzoyl-*N*-[4-(2-benzoyl-3-(dimethylamino-acryloylamino)-phenyl]-3-dimethylaminoacrylamide **12** are used for the synthesis of the *hitherto* not known bis-heterocyclic amine and bis-heterocyclic carboxamide derivatives. Plausible mechanisms are discussed for the formation of the new compounds.

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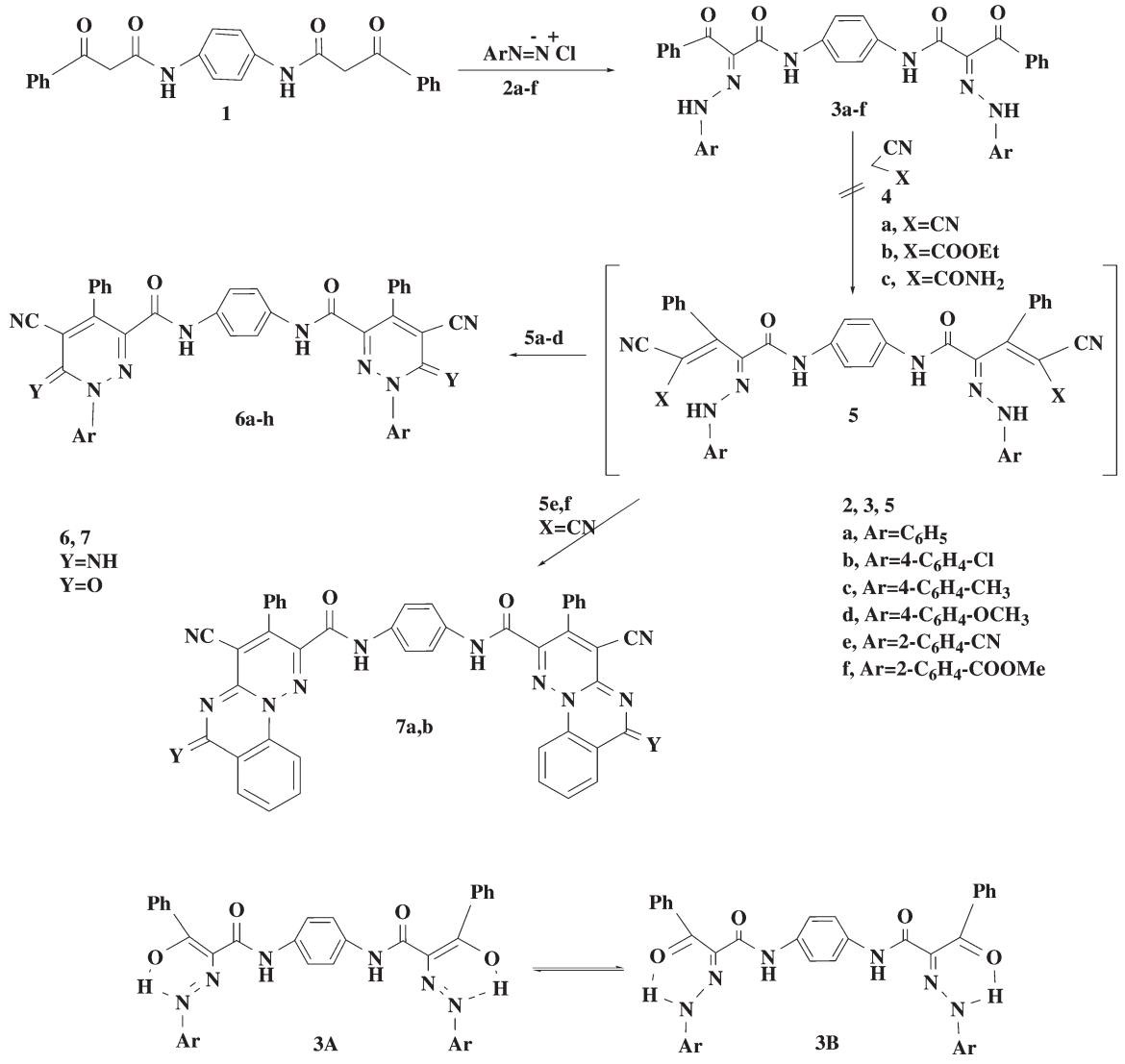
INTRODUCTION

Functionalized pyridines, pyrimidines, pyridazines, and pyrazoles and their fused derivatives have received much attention due to their diverse biological activities as immunosuppressant agents and antitumor active agents [1–9]. Azepines generally also represent an important class of heterocyclic compounds due to their psychopharmacological applications and general therapeutic activities [10]. The majority of attention has been so far paid to the development of syntheses of only one functionally substituted unit of these nuclei [11]. To our knowledge, there are only few reports describing the synthesis of bis-compounds containing two benzofuran units, two thiazepine, two chalcone [12], or two pyrimidine units [13], but those containing two pyridazine or two diazepine units are *hitherto* not investigated. The azo/hydrazo compounds are important precursors to pyridazines [14]. The reaction of enaminones with active methylene reagents [15], amines [16], or hydrazines [17] represents one of the strategies for the preparation of 2-1*H*-pyridones, pyrroles, and pyridazines, respectively. Over the last two decades, we have been involved in a program aiming at the synthesis of functionally substituted heterocyclic compounds from cheap laboratory available starting materials to be evaluated as biodegradable agrochemicals [18–22]. As a part of this program, some bis-pyridazine, bis-pyridine, and other bis-heterocyclic carboxamide derivatives were required for biological evaluation studies. 3-Oxo-*N*-[4-(3-oxo-3-phenylpropionylamino)-phenyl]-3-phenylpropionamide **1** and its derivative 2-benzoyl-*N*-[4-(2-benzoyl-3-(dimethylamino-acryloylamino)-phenyl]-3-dimethylaminoacrylamide **12** seemed to be good candidates to fulfill this objective.

Scheme 1. The azo coupling of compound **1** with aryl diazonium salts.



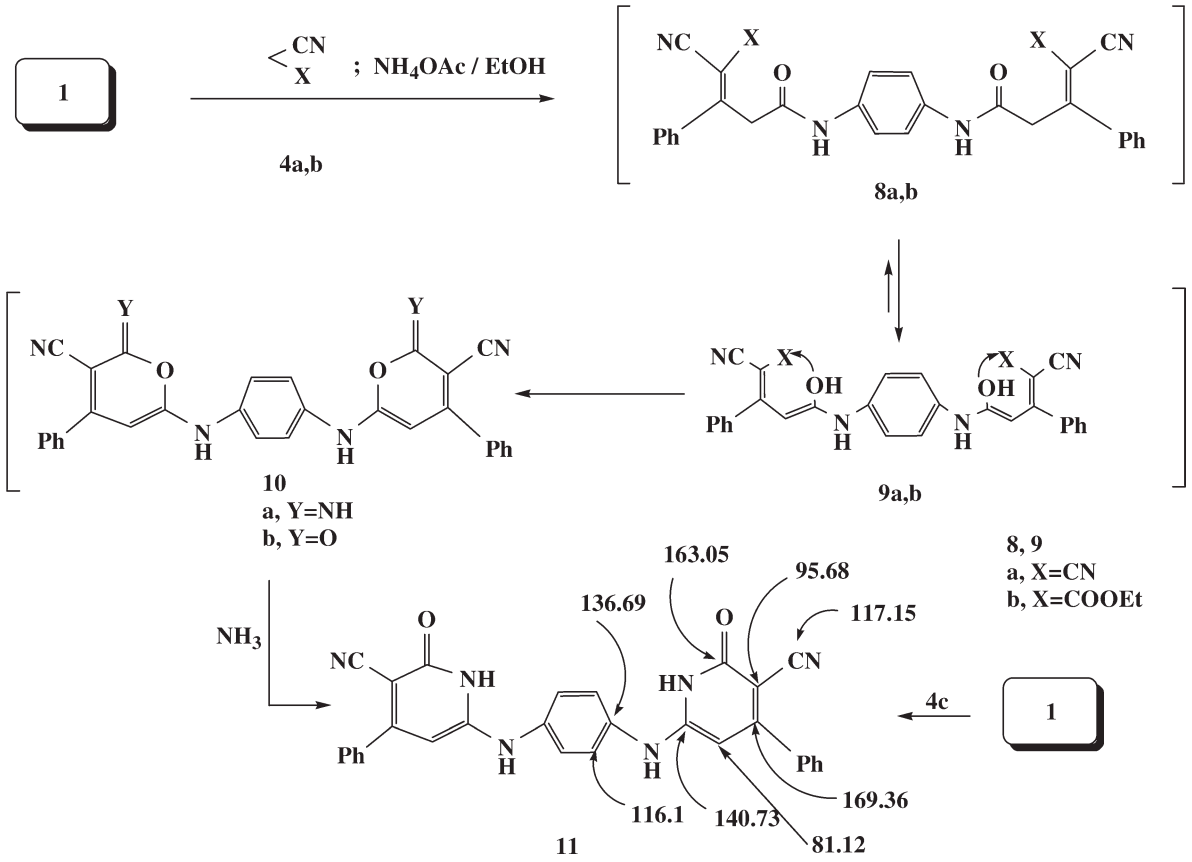
RESULTS AND DISCUSSION

It was planned to couple **1** with arene diazonium salts **2a–f** to obtain the bis-hydrazo derivatives **3a–f**. Condensation of these hydrazo derivatives with the active methylene reagents **4a–c** was thought to afford the intermediates **5**, which would cyclize to afford our target compounds **6a–d** (from **5a–d**) and **7a**,**b** (from **5e**,**f**; X = CN) as shown in (Scheme 1).

In our hands, compound **1** coupled smoothly with the diazonium salts **2a–f** to afford the nicely colored bis-hydrazo products **3a–f**; however, all trials to perform the condensation with either of **4a**, **4b**, or **4c** were unsuccessful under a variety of conditions even on fusion at above 350°C in the presence of ammonium acetate, triethylamine, or piperidine, and the hydrazo derivatives were recovered unchanged. It seemed to us that the coupling products **3** are present either in the azo enol forms **3A** or in the hydrazo keto forms **3B** (Scheme 1). In either case, the nucleophilic attack on the carbonyl groups with active methylenes is disfavored by being either enolized to OH (in **3A**) or blocked by the hydrogen bond (in **3B**). A similar behavior has been previously observed during the trials to condense the hyrazo derivatives of cyclic β-diketones with **4a** [20]. A detailed study of the azo coupling products confirms this behavior [23].

Therefore, an alternative route featuring a reversal of events was followed, that is, to perform the condensation reaction first and then to couple the resulting condensation product (compounds **8** in Scheme 2) with the diazonium salts **2a–d**. To this end, the bis-anilinde **1** was allowed to condense with malononitrile **4a** and ethyl cyanoacetate **4b** in refluxing acetic acid in

Scheme 2. The condensation of compound **1** with active methylene reagents.



presence of ammonium acetate. These two reactions were found to afford one and the same yellow crystalline product of m.p. >300°C (Scheme 2). The IR spectrum of this product shows only one amide carbonyl absorption band at $\upsilon_{max} = 1666$ cm^{-1}, a cyano absorption band at $\upsilon_{max} = 2215$ cm^{-1} beside absorption bands at $\upsilon_{max} = 3476$, 3314, 3189, and 3089 cm^{-1}, which are attributed to two NH groups. These IR spectral data are completely not applicable to **8** or the enol form **9**. The ^{1}H NMR spectra of this reaction product did not display the expected methylene protons signal in **8** δ at ≈ 3 ppm or any signals down 10 ppm that can be attributed to the OH protons in **9**. Based on these data structures, **8** and **9** were excluded.

A structure, such as the bis-iminopyrans **10a**, was also excluded on the basis of the presence of a carbonyl absorption band in the IR spectrum at $\upsilon_{max} = 1666$ cm^{-1}, and the bis-pyranone structure **10b** should have revealed the carbonyl absorption band at much higher value (>1700 cm^{-1}[24]). All the data of the IR and ^{1}H NMR spectra are completely applicable on the bis-2(1H)-pyridone structure **11**. It can be assumed that the condensation products **8a**,**b** are enolized under the reaction conditions to give **9a**,**b**, which are directly cyclized via addition of the OH to the cyano group to afford the bis-iminopyran **10a** or via elimination of ethanol to afford **10b**. These latter compounds **10a**,**b** undergo ring opening and recyclization in a Dimroth-type rearrangement under the effect of ammonia (from ammonium acetate) to afford the final isolable product **11**.

Rearrangement of iminopyrans or pyranones under the effect of ammonia or amines is well established in the literature as mentioned above [11,15,25]. It has also been found that compound **1** condenses with cyanoacetamide **4c** to afford **11**, which is apparently obtained via the condensation and elimination of water.

The identity of the products was inferred from the melting points and the spectral data. This last finding confirms the structure of **11** and approves the suggested mechanisms for its formation.

On the other hand, we have previously reported [13] on the reaction of **12** with malononitrile **4a** and cyanoacetamide **4c**; however, its reaction with ethyl cyanoacetate **4b** has not yet been investigated.

In our hands, this reaction of compound **12** with ethyl cyanoacetate **4b** in refluxing ethanol catalyzed by piperidine afforded a pale yellow crystalline product, which is formulated as the bis-pyranone-4-carboxamide derivative

13 on the basis of elemental analysis and spectral data (*cf*. Experimental). Fusion of this compound **13** with ammonium acetate above their melting points led to the formation of the bis-2(1H)-pyranone-4-carboxamide **14**. This last compound **14** was previously obtained from the reaction of **12** with cyanoacetamide **4c** [13]. The identity of the two products was inferred from their mixed melting point and identical analyses and spectra.

The formation of **13** is assumed to proceed through substitution of the dimethyl amine moiety on the attack of the active methylene anion of **4b** $(CNCHCOOEt)^-$, followed by elimination of ethanol. Compound **13** is easily attacked by ammonia (from heating ammonium acetate) to undergo ring opening and recyclization with loss of water to afford **14**. Ring opening of pyranones and iminopyrans under the effect of ammonia or amines is well established in the literature [11,15,25]. The structure of compound **14** was further elucidated by its alternative synthesis through the reaction of **12** with cyanoacetamide **4c** as previously reported [13].

Compound **12** reacts also with a twofold excess of the aminopyrazole **15** (Scheme 3) in refluxing ethanol to afford a yellow crystalline product for which the bis-pyrazolopyrimidine carboxamide **16** whose structure was assigned based on analytical and spectral data (*cf*. Experimental part). The reaction of **12** with 2-aminobenzimidazole **17** and with *o*-phenylenediamine **19** under the same reaction conditions followed the same route to afford the bis-benzimidazolopyrimidine carboxamide **18** and the bis-benzodiazepine **20**, respectively. In all these reactions, it is apparent that amino groups of **15**, **17**, or **19** readily substitute the dimethylamino groups in **12** followed by elimination of water.

CONCLUSIONS

We conclude that the 1,4-phenylene-bis-pyridazine-4-carboxamides such as **6** could not obtained either through azo coupling followed by condensation with active methylene reagents or via the reverse of events. We could also obtain some novel *p*-phenylene-*bis*-heterocyclic carboxamides from readily available cheap starting materials that could be useful for biological evaluation studies.

EXPERIMENTAL

Melting points were measured on an Electrothermal (9100) apparatus and 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 DMSO-d_6 using TMS as internal standard and chemical shifts are expressed in δ ppm values. Mass spectra were taken on a Shimadzu GCMS-GB 1000 PX (70 ev). Elemental analyses were carried out at the Microanalytical Center at Cairo University. A considerable part of the analyses and spectra has been carried out in the institute of organic chemistry, Technical University of Dresden, Germany; during an Alexander von Humboldt fellowship to F. M. Abdelrazek: July–August 2009.

The azo coupling of compound 1 with the aryl diazonium salts 2a–f. Aryl diazonium salts **2a–f** (20 mmol) were freshly prepared by adding a solution of 20 mmol of sodium nitrite in 5-mL H_2O to a cold solution of the respective arylamine hydrochloride (20 mmol) (aniline, *p*-chloroaniline, *p*-toluidine, *p*-anisidine, anthranilonitrile, or methyl anthranilate) respectively, in 7-mL conc. HCl with stirring. The resulting solutions of the aryl diazonium salts were added to a cold solution of **1** (4 g; 10 mmol), in pyridine (30 mL). The reaction mixture was stirred at room temperature for 2 h in each case, and the solid products, so formed, were collected by filtration and recrystallized from pyridine to afford the highly colored products **3a–f**, respectively.

***N,N′*-(1,4-Phenylene)bis(3-oxo-3-phenyl-2-(2-phenylhydrazono)-propanamide) 3a.** Yellow crystalline product: yield (5.29 g, 87%); m.p. 302–304°C; υ_{max} = 3209, 3140 (NH), 1640 (w), 1657 (CO) cm^{-1}; δ_H = 7.15–7.85 (m, 24H, Ar-H), 11.16 (s, 2H, 2CONH), 13.60 (s, 2H, 2 hydrazone H). Anal. Calcd. for $C_{36}H_{28}N_6O_4$ (608.65): C, 71.04; H, 4,64; N, 13.81. Found: C, 70.99; H, 5.11; N, 13.43.

***N,N′*-(1,4-Phenylene)bis(2-(2-(4-chlorophenyl)hydrazono)-3-oxo-3-phenylpropanamide) 3b.** Yellow flakes: yield (5.75 g, 85%); m.p. 318–320°C; υ_{max} = 3265, 3205, 3132 (NH), 1618 (w), 1657 (CO) cm^{-1}; δ_H = 7.25–7.90 (m, 22H, Ar-H), 11.05 (s, 2H, 2NH), 13.30 (s, 2H, 2NH). Anal. Calcd. for $C_{36}H_{26}Cl_2N_6O_4$ (677.54): C, 63.82; H, 3,87; N, 12.40. Found: C, 63.61; H, 4.07; N, 12.44.

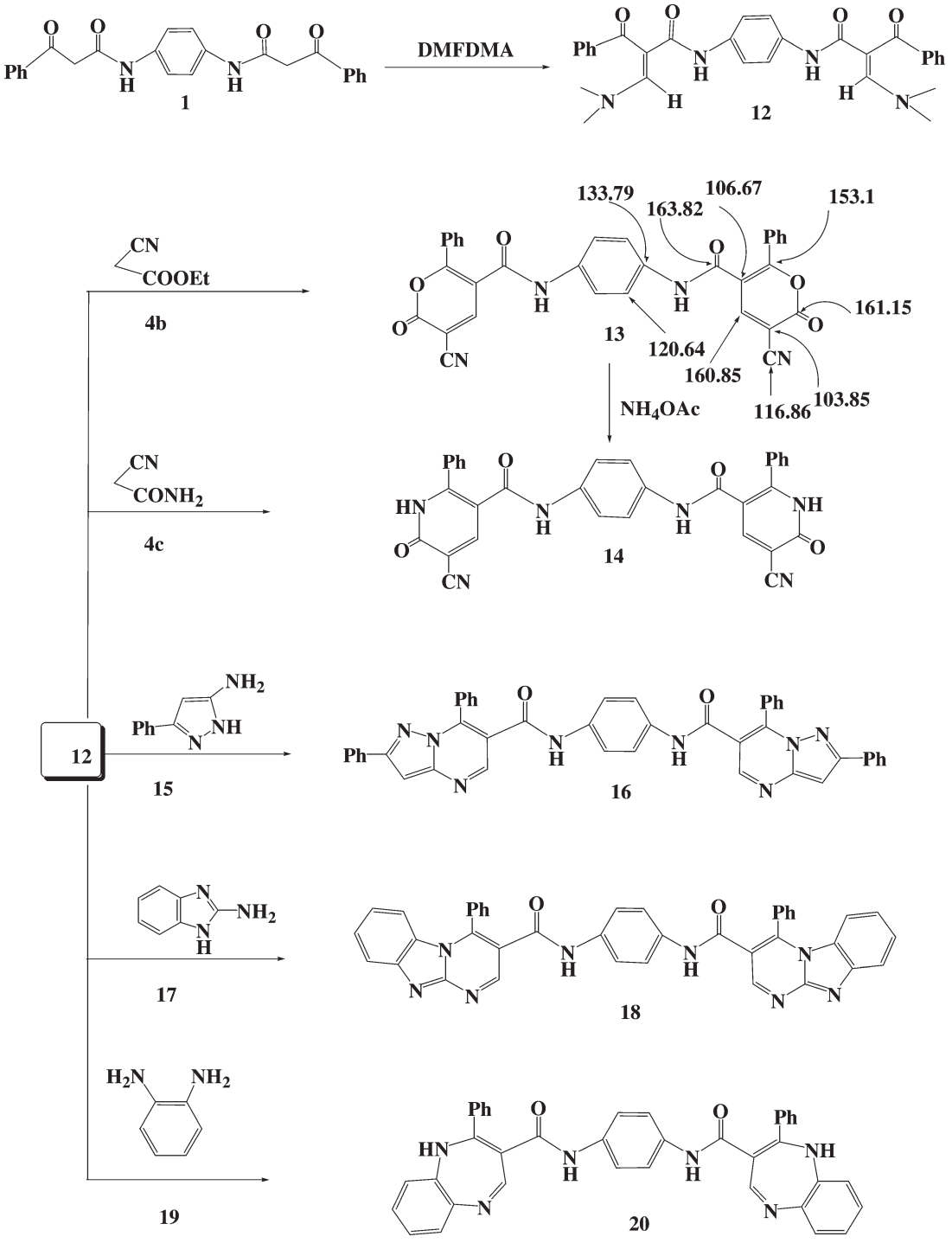
***N,N′*-(1,4-Phenylene)bis(3-oxo-3-phenyl-2-(2-(4-tolyl)hydrazono)-propanamide) 3c.** Dark yellow cotton like product: yield (4.77 g, 75%); m.p. 295–296°C; υ_{max} = 3205, 3144 (NH), 1632 (w), 1644 (CO) cm^{-1}; δ_H = 2.3 (s, 6H, $2CH_3$), 7.18–7.85 (m, 22H, Ar-H), 11.20 (s, 2H, 2NH), 13.80 (s, 2H, 2NH). Anal. Calcd. for $C_{38}H_{32}N_6O_4$ (636.70): C, 71.68; H, 5,07; N, 13.20. Found: C, 71.53; H, 5.04; N, 13.15.

***N,N′*-(1,4-Phenylene)bis(2-(2-(4-methoxyphenyl)hydrazono)-3-oxo-3-phenylpropanamide) 3d.** Canary yellow crystalline product: yield (5.20 g, 78%); m.p. 240–242°C; υ_{max} = 3218, 3144 (NH), 1643, 1697 (w) (CO) cm^{-1}; MS: *m*/*z* = 669 [M^++1, 8%]; δ_H = 3.75 (s, 6H, $2CH_3$), 6.95–8.00 (m, 22H, Ar-H), 11.35 (s, 2H, 2NH), 14.00 (s, 2H, 2NH). Anal. Calcd. for $C_{38}H_{32}N_6O_6$ (668.70): C, 68.25; H, 4,82; N, 12.57. Found: C, 68.23; H, 4.82; N, 12.43.

***N,N′*-(1,4-Phenylene)bis(2-(2-(2-cyanophenyl)hydrazono)-3-oxo-3-phenylpropa-namide) 3e.** Brick red crystalline product: yield (4.87 g, 74%); m.p. 305–307°C; υ_{max} = 3352, 3217 (NH), 2221 (CN), 1640 (w), 1658 (CO) cm^{-1}; MS: *m*/*z* = 658 [M^+, 11%]; δ_H = 7.25–8.10 (m, 22H, Ar-H), 11.00 (s, 2H, 2NH), 14.20 (s, 2H, 2NH). Anal. Calcd. for $C_{38}H_{26}N_8O_4$ (658.66): C, 69.29; H, 3.98; N, 17.01. Found: C, 69.32; H, 3.85; N, 17.21.

***N,N′*-(1,4-Phenylene)bis(2-(2-(2-methoxycarbonylphenyl)-hydrazono)-3-oxo-3-phenylpropa-namide) 3f.** Yellow powder product: yield (5.14 g, 71%); m.p. 321–323°C; υ_{max} = 3215, 3141 (NH); 1655, 1683 (w), 1713 (CO) cm^{-1}; δ_H = 3.98 (s, 6H, $2CH_3$), 7.18–8.05 (m, 22H, Ar-H), 11.00 (s, 2H,

Scheme 3. The reaction of the bis-enaminone **12** with ethyl cyanoacetate and binucleophiles.



2NH), 13.33 (s, 2H, 2NH). Anal. Calcd. for $C_{40}H_{32}N_6O_8$ (724.72): C, 66.29; H, 4.45; N, 11.60. Found: C, 66.35; H, 4.52; N, 11.67.

6-({4-[(5-Cyano-6-oxo-4-phenyl(2-hyropyridyl)-amino]-phenyl}-amino)-2-oxo-4-phenylhydro-pyridine-3-carbonitrile 11. A mixture of compound **1** (4 g; 10 mmol), malononitrile **4a** (1.32 g, 20 mmol) or ethyl cyanoacetate **4b** (2.26 g, 20 mmol) and ammonium acetate (2.31 g, 30 mmol) were fused together on an oil bath at 270°C for 3 h and then left to cool overnight. The solid mass, thus, obtained was dissolved in hot DMF and precipitated with cold acidified water (drops of HCl), and the solid precipitate was filtered off, washed with cold water, dried, and recrystallized from pyridine to afford compound **11** as pale olive green crystalline product; yield

(3.57 g, 72% from **4a** and 3.77 g, 76% from **4b**), m.p.>320°C. The same compound **11** was obtained from the reaction of **1** with cyanoacetamide **4c** under the same reaction conditions (3.70 g, 75%); υ_{max}= 3376, 3314, 3198 (NH), 2215 (CN), 1666 (CO) cm^{-1}; MS: m/z = 496 [M^+, 19%]; δ_H = 2.94 (s, 2H, 2NH), 5.78 (s, 2H, pyridone 5-H), 7.11–7.57 (m, 14H, Ar-H), 7.96 (s, 2H, 2NH). δ_C = 81.12 (d), 95.68 (s), 116.12 (d), 117.15 (s), 126.23 (d), 127.68 (d), 128.37 (d), 134.92 (s), 136.69 (s), 140.73 (s), 163.05 (s), 169.36 (s). Anal. Calcd. for $C_{30}H_{20}N_6O_2$ (496.52): C, 72.57; H, 4,06; N, 16.93. Found: C, 72.65; H, 4.22; N, 17.15.

***N,N′*-(1,4-Phenylene)bis(5-cyano-6-oxo-2-phenyl-6*H*-pyran-3-carboxamide) 13.** To a mixture of the enaminone **12** (5.1 g; 10 mmol) and ethyl cyanoacetate **4b** (2.26 g; 20 mmol) in dimethyl formamide (DMF; 25 mL) was added few drops of sodium ethoxide as catalyst. The reaction mixture was refluxed for 5 h and then left to cool to room temperature. The reaction mixture was poured on ice-cold water and neutralized with conc. HCl. The solid products thus, precipitated was collected by filtration and crystallized from acetic acid to afford compound **13** as yellow crystalline product: yield (4.21 g, 76%); m.p. 215–216°C (AcOH); υ_{max} = 3452, 3330, (NH), 2215 (CN), 1718 and 1686 (2CO) cm^{-1}; MS: m/z = 554 [M^+, 12%]; δ_H = 7.15–7.72 (m, 14H, Ar-Hs), 8.10 (s, 2H, pyran H), 10.05 (s, 2H, 2NH). δ_C = 103.85 (s), 106.67 (s), 116.86 (s), 120.64 (d), 126.24 (d), 127.68 (d), 128.43 (d), 134.93 (s), 133.79 (s), 153.1 (s), 160.85 (d), 161.15 (s), 163.82 (s). Anal. Calcd. for $C_{32}H_{18}N_4O_6$: (554.51): C, 69.31; H, 3.27; N, 10.10. Found: C, 69.35; H, 3.15; N, 10.38.

***N,N′*-(1,4-Phenylene)bis(5-cyano-6-oxo-2-phenyl-1,6-dihydropyridine-3-carboxamide) 14.** A mixture of the bis-pyranone **13** (5.54 g; 10 mmol) and ammonium acetate (3.85 g; 50 mmol) was fused on an oil bath adjusted at 300°C for 4 h and then left to cool overnight. The resulting mass was triturated with acetic acid, and the lumps were crushed; then the reaction mixture was boiled in acetic acid till complete dissolution and filtered while hot. On leaving to cool to room temperature, pale yellow crystals precipitated which were filtered off to give **14**; yield (3.97 g, 72%); m.p. 282–284°C (AcOH). Compound **14** was also prepared from **12** and cyanoacetamide **4c** in refluxing ethanol catalyzed by sodium ethoxide as described previously [13]; Yield (3.86 g, 70%) m.p. 284–285°C (AcOH); υ_{max}= 3451, 3333, 3141 (NH), 2213 (CN), 1687 (CO), and 1659 (CO) cm^{-1}; MS: m/z = 552 [M^+, 15%]; δ_H = 7.15–7.68 (m, 14H, Ar-Hs), 7.70 (s, 2H, 2NH), 7.99 (s, 2H, Pyridone 4-Hs), 10.07 (s, 2H, 2NH). Anal. Calcd for $C_{32}H_{20}N_6O_4$: (552.54): C, 69.56; H, 3.65; N, 15.21. Found: C, 69.55; H, 3.68; N, 15.28.

The reaction of 12 with the heteroaromatic amines 15, 17, 19. A mixture of each of the bis-enaminone **12** (5.1 g; 10 mmol) and the respective amine (aminopyrazole **15**, 2-aminobenzimidazole **17** or 1,2-phenylenediamine **19**) (20 mmol) in pyridine (25 mL) was refluxed for 5 h (TLC control). The reaction mixture was left to cool and then was poured onto ice-water. The solid precipitates, thus, formed were collected by filtration and recrystallized from pyridine to afford the products **16**, **18**, and **20**, respectively.

***N,N′*-(1,4-Phenylene)bis(2,7-diphenylpyrazolo[1,5-a]pyrimidine-6-carboxamide) 16.** Yellow crystalline product: yield (4.84 g, 69%); m.p. 293–295°C (pyridine); υ_{max} = 3332, 3140 (NH), 1656 (CO) cm^{-1}; MS: m/z = 703 [M^+ + 1, 7%]; δ_H = 6.73 (s, 2H, pyrazole H), 7.43–8.07 (m, 24H, Ar-H), 8.63 (s, 2H, Pyrimidine H), 10.22 (s, 2H, 2NH). δ_C = 103.92 (d), 120.72 (d), 126.65 (s), 127.12 (d), 127.28 (d), 128.55 (d), 128.59 (d), 129.25 (d), 129.32 (d), 134.15 (s), 134.63 (s), 136.57 (s), 137.15 (s), 150.48 (s), 159.82 (d), 165.55 (s), 166.09 (s). Anal. Calcd for $C_{44}H_{30}N_8O_2$: (702.76): C, 75.20; H, 4.30; N, 15.94. Found: C, 75.38; H, 4.50; N, 16.14.

***N,N′*-(1,4-Phenylene)bis(4-phenylbenzo[4,5]imidazo[1,2-a]-pyrimidine-3-carboxamide) 18.** Dark yellow crystalline product: yield (4.62 g, 71%); m.p. 313–315°C (pyridine); υ_{max}= 3335, 3142 (NH), 1662 (CO) cm^{-1}; MS: m/z = 650 [M^+, 11%]; δ_H = 7.25–8.62 (m, 22H, Ar-H), 8.64 (s, 2H, Pyrimidine H), 10.20 (s, 2H, 2NH). Anal. Calcd for $C_{40}H_{26}N_8O_2$: (650.69): C, 73.83; H, 4.03; N, 17.22. Found: C, 73.89; H, 4.22; N, 17.50.

(2-Phenyl (1*H*-benzo[*b*]-1,4-diazepin-3-yl))-*N*-{4-[(2-phenyl (1*H*-benzo[*b*]-1,4-diazepin-3-yl)-carbo-nylamino-]-phenyl}-carboxamide 20. Dirty brownish yellow crystals: yield (4.08 g, 68%); m.p. >350°C (pyridine); υ_{max}= 3315, 3248 (NH), 1656 (CO) cm^{-1}; MS: m/z = 600 [M^+, 15%]; δ_H = 5.2 (s, 2H, 2NH), 6.55–7.68 (m, 24H, Ar-H), 8.20 (s, 2H, 2NH). Anal. Calcd for $C_{38}H_{28}N_6O_2$: (600.67): C, 75.98; H, 4.70; N, 13.99. Found: C, 76.05; H, 4.78; N, 14.19.

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