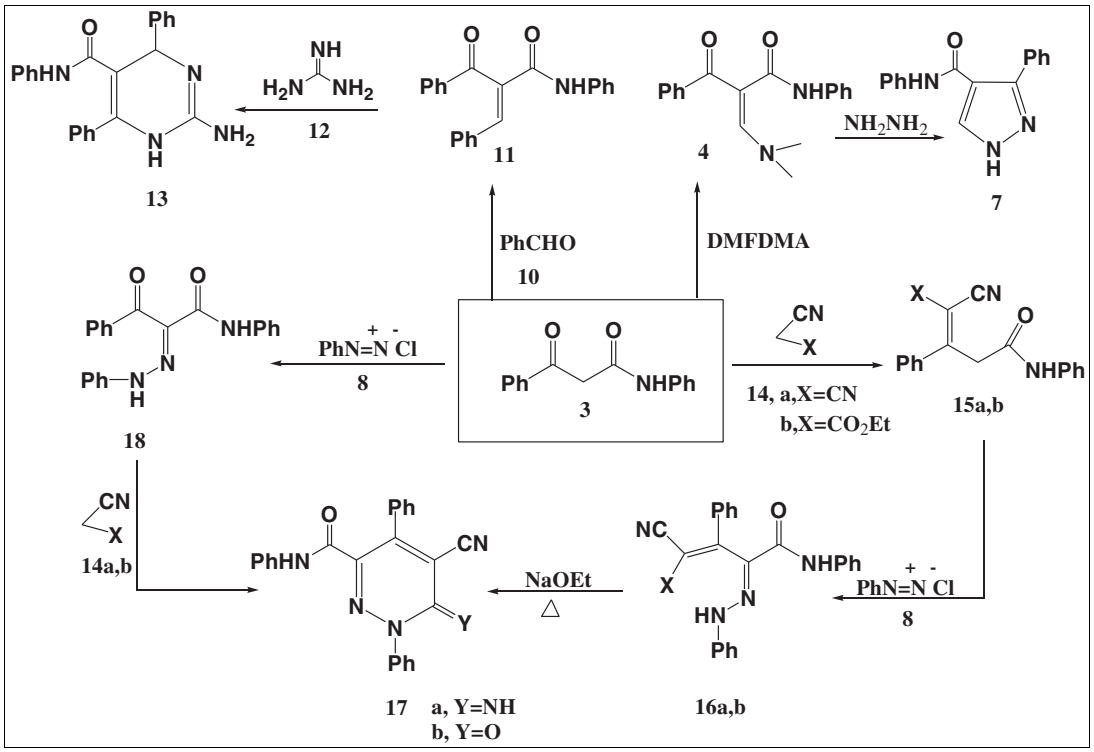
Fathy M. Abdelrazek,[a]* Yehia M. Elkholy,[b] Ali M. Salah,[b] Nagwa M. Abdelazeem,[b] and Peter Metz[c]

[a]Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt
[b]Chemistry Department, Faculty of Science, Helwan University, Helwan, Egypt
[c]Institute of Organic Chemistry, TU Dresden, Dresden 01062, Germany
*E-mail: prof.fmrazek@gmail.com

Received January 31, 2012
DOI 10.1002/jhet.1700
Published online 9 December 2013 in Wiley Online Library (wileyonlinelibrary.com).



The title compounds were obtained from the reactions of 3-oxo-3,N-diphenylpropionamide **3** with dimethylformamide dimethylacetal followed by hydrazine to afford the pyrazole **7**, condensation with benzaldehyde followed by cyclocondensation with guanidine to afford the pyrimidine derivative **13**, condensation with active methylenes followed by azo coupling of the products followed by cyclization to afford the pyridazines **17a,b**. The pyridazinone **17b** was explored for the synthesis of some novel pyridazine-fused heterocyclic compounds **19**, **21**, **24a–c**, and **26**. All structures were proved via their elemental analyses and spectral data.

J. Heterocyclic Chem., **51**, 824 (2014).

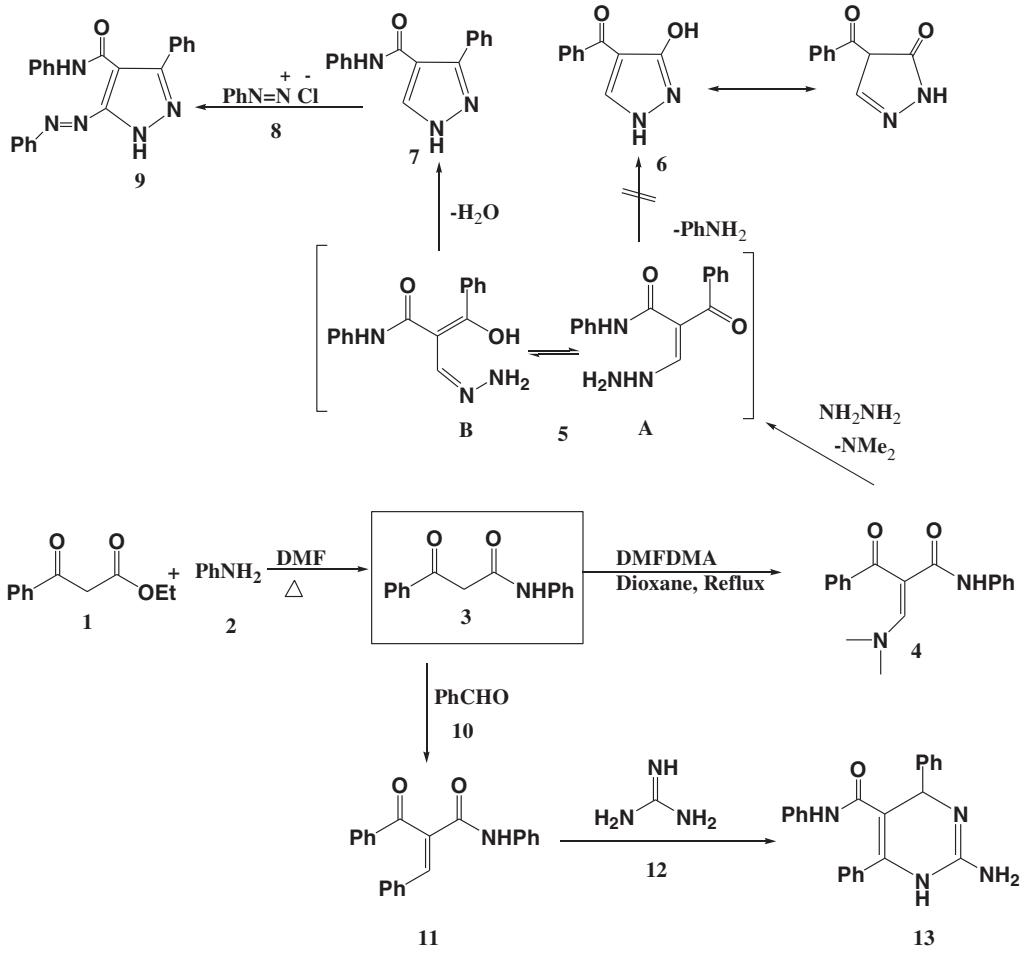
INTRODUCTION

Pyridazine derivatives have received considerable attention in the last two decades because of their diverse biological activities [1,2]. This class of compounds is reported to show aldose-reductase inhibitory effect [3]. They are also used as antihistaminic, analgesic, anti-inflammatory, [4] and cardiotonic agents with vasodilator activity [5]. In addition, these compounds were also reported to possess a good binding affinity toward α_1,α_2-adrenergic and 5-HT_{1A} serotoninergic receptors [6] and to show herbicidal and fungicidal [7,8] activities. In the last two decades, we have been involved in a program aiming at the synthesis of heterocyclic compounds of expected biological activity to be tested as biodegradable agrochemicals [9–12]. In the context of this program and because of the abovementioned stunning biological activities of pyridazine derivatives, we have reported several novel syntheses of some new pyridazine and fused-pyridazine derivatives [12–15]. Recently, some new substituted pyrazoles, pyrimidines, pyridazines, and their fused derivatives were required for biological activity studies. 3-Oxo-3,N-diphenylpropionamide **3** (Scheme 1) seemed a suitable candidate to fulfill this objective.

RESULTS AND DISCUSSION

3-Oxo-3,N-diphenylpropanamide **3** was obtained from the reaction of ethyl benzoylacetate **1** with aniline **2** in

Scheme 1. Synthesis of compounds 3,4,7,9,11 and 13.



refluxing DMF. The formation of compound **3** is assumed to proceed via the elimination of ethanol. Structure **3** was established based on elemental and spectral data. The IR spectrum of **3** revealed the presence of amide carbonyl at 1687 cm^{-1}, and the ^1H NMR revealed the presence of NH group at $\delta = 10.2$ ppm. (cf. Experimental).

Compound **3** was allowed to react with dimethylformamide dimethylacetal in refluxing dioxane to afford 2-benzoyl-3-(dimethylamino)-N-phenylacrylamide **4** in quantitative yield. Compound **4** reacts with hydrazine hydrate in refluxing ethanol to afford the intermediate **5A/5B** (Scheme 1). Cyclization of the intermediate **5** can take place via the elimination of aniline from **5A** to give the hydroxy-pyrazole/pyrazolone derivative **6** or via elimination of water from **5B** to give 3,N-diphenyl-1*H*-pyrazole-4-carboxamide **7**.

The IR spectrum of this reaction product revealed the presence of an amide carbonyl at 1652 cm^{-1}. The ^1H NMR seemed of no help in discriminating **6** and **7**; however, the elemental analysis showed a high carbon content and the mass spectrum showed $m/z = 263$ that is in favor of structure **7** who was established to this reaction product. Such selective cyclization to the carbonyl group leaving the amide or ester groups is well known in the literature [16].

Compound **7** was allowed to couple with the diazotized aniline **8** to afford 3-Phenyl-5-phenylazo-1*H*-pyrazole-4-carboxanilide **9** (Scheme 1).

The condensation of **3** with benzaldehyde **10** by using piperidine as the catalyst afforded the expected 2-benzoyl-3,N-diphenylacrylamide **11**. Compound **11** reacts with guanidine **12** in the presence of piperidine to afford the desired 2-amino-4,6-diphenyl-1,4-dihydro- pyrimidine-5-carboxanilide **13**. Compound **13** was established based on elemental and spectral data (Scheme 1; Experimental).

Compound **3** underwent condensation reaction with the active methylene compounds **14a**,**b** to afford the condensation products **15a**,**b**, respectively. These latter compounds couple with **8** to afford the hydrazo compounds **16a**,**b**. Analytical and spectral data are in complete agreement with structures **15a**,**b** and **16a**,**b** (cf. Experimental).

Compounds **16a,b** could be readily cyclized to the desired pyridazine derivatives **17a,b** upon reflux in ethanol containing sodium ethoxide as a basic catalyst. The cyclization presumably involves the addition of the hydrazone NH to

one of the CN groups to afford the imino pyridazine **17a** or elimination of ethanol to afford the pyridazinone **17b**, respectively. The structures of compounds **17a,b** were established based on analytical and spectral data (cf. Experimental; Scheme 2).

On the other hand, compound **3** was coupled smoothly with benzene diazonium salt **8** to afford the nicely colored hydrazo product **18**. This latter compound **18** was fused with malononitrile **14a** or ethyl cyanoacetate **14b** on an oil bath at 170 °C to afford directly the pyridazine derivatives **17a** and **17b**, respectively, presumably via the intermediacy of **16a**,**b** that underwent cyclization *in situ* without being isolated (Scheme 2).

The obtained pyridazinone derivative **17b** was explored to synthesize some other fused pyridazine derivatives. Thus, it was allowed to react with hydrazine hydrate, hydroxyl amine hydrochloride **20**, urea derivatives **12, 22**, and **23** and 1,2-phenylenediamine **25** to afford the pyrazolo pyridazine **19**, isoxazolo pyridazine **21**, pyrimido pyridazines **24a–c**, and pyridazino benzo[b]diazepine **26** derivatives, respectively. Analytical and spectral data are in complete agreement with these structures (cf. Experimental, Scheme 3).

EXPERIMENTAL

Melting points were determined on an electrothermal (9100) (Kleinfeld, Gehrden, Germany) apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer (Waltham, MA). The ^{1}H NMR and ^{13}C NMR spectra were taken on a Varian Gemini 300 MHz spectrometer (Varian, inc., Palo Alto, CA) 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) (Kyoto, Japan). Elemental analyses were carried out by the Microanalytical Center at Cairo University and a considerable part of the spectra were carried out in the Institute of Organic Chemistry, Technical University of Dresden, Germany.

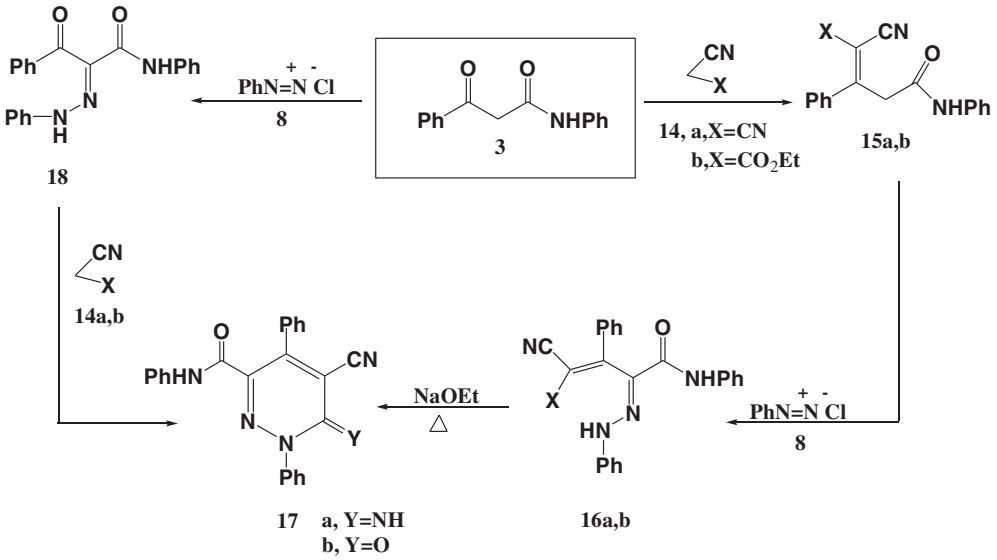
3-Oxo-3,N-diphenylpropanamide 3. A mixture of ethyl benzoyl acetate **1** (1.92 g; 0.01 mole) and aniline **2** (0.93 g; 0.01 mole) in dimethylformamide (25 mL) was refluxed for 3 h, whereby a homogeneous solution was obtained then left to cool to room temperature. The reaction mixture was then poured on ice-cold water. The solid precipitate that appeared was filtered off and recrystallized from ethanol to afford the pure product. Yellowish white crystals; yield 85%, mp: 111 °C (EtOH). υ_{max} = 3260 (NH), 1687 (CO), and 1663 (CO) cm^{-1}; MS: *m*/*z* = 239 [M$^+$]. δ_H = 4.14 (s, 2H, CH_2), 7.35−7.99 (m, 10H, 2Ph-H), 10.2 (s, 1H, NH). *Anal*. Calcd for $C_{15}H_{13}NO_2$ (239.26): C, 75.30; H, 5.48; N, 5.85. Found: C, 75.36; H, 5.54; N, 5.80.

2-Benzoyl-3-(dimethylamino)-N-phenylacrylamide 4. A mixture of **3** (2.39 g; 0.01 mole) and dimethylformamide dimethylacetal (1.19 g; 0.01 mole) in dioxane (25 mL) was refluxed for 3 h (TLC control), and then left to cool at room temperature. The contents of the flask were poured on ice-cold water. The precipitated solid was collected by filtration and recrystallized to give **4** as pale yellow crystals; yield 87%, mp. 86 °C (EtOH). υ_{max} = 3262 (NH), 1600 (CO), and 1660 (CO) cm^{-1}; MS: *m*/*z* = 294 [M$^+$]. δ_H = 3.33 (s, 6H, $2CH_3$), 7.18–7.99 (m, 10H, 2Ph-H), 7.75 (s, 1H, CH), 10.15 (s, 1H, NH). *Anal*. Calcd for $C_{18}H_{18}N_2O_2$ (294.35): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.48; H, 6.12; N, 9.58.

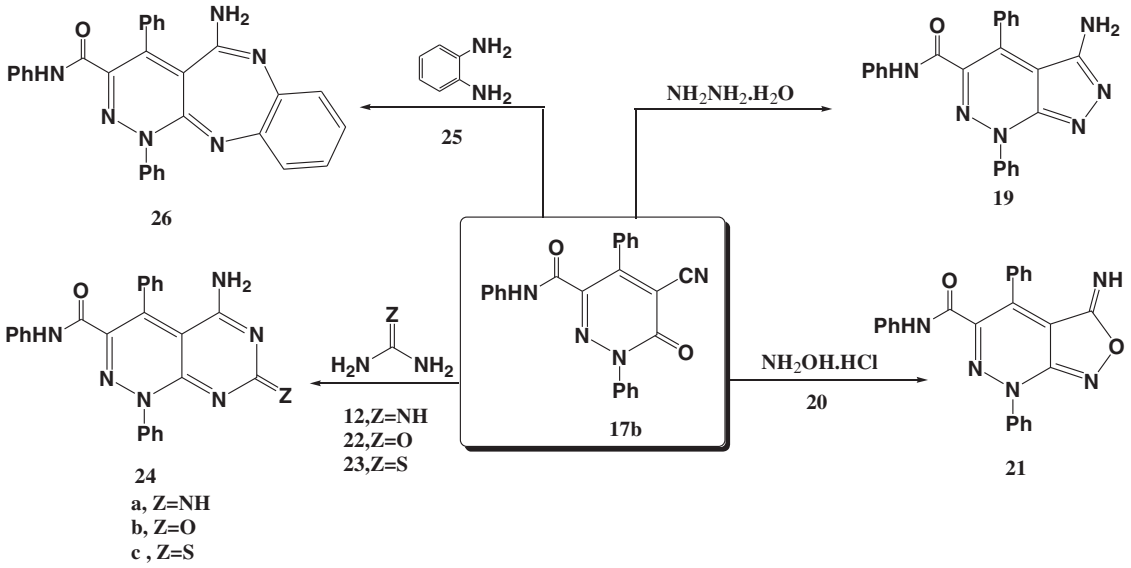
3-Phenyl-1*H*-pyrazole-4-carboxanilide 7. A mixture of **4** (2.94 g) and hydrazine hydrate (0.5 mmol) in ethanol (25 mL) was refluxed for 3 h (TLC control) and left to cool overnight. The reaction mixture was then poured on ice cold water. The precipitated solid was filtered off and recrystallized from ethanol. White crystals; yield 68%, mp: 185 °C (EtOH). υ_{max} = 3303, 3242 (NH), 1652 (CO) cm^{-1}. MS: *m*/*z* = 263 [M$^+$]. δ_H = 6.2 (s, 1H, CH), 7.17−7.76 (m, 10H, 2Ph-H), 10.1 (s, 1H, NH amide), 14.30 (s, 1H, NH ring). *Anal*. Calcd for $C_{16}H_{13}N_3O$ (263.29): C, 72.99; H, 4.98; N, 15.96. Found: C, 73.05; H, 5.10; N, 15.90.

3-Phenyl-5-phenylazo-1*H*-pyrazole-4-carboxanilide 9. Diazonium salt was freshly prepared by adding a solution of (0.7 g; 0.01 mole) of sodium nitrite in 5 mL of H_2O to a

Scheme 2. Synthesis of compounds 15,16,17 and 18.



Scheme 3. Synthesis of compounds 19,21,24 and 26.



cold solution of aniline hydrochloride (3 mL of conc. HCl + 1 mL of aniline) with stirring. The resulting solution of the diazonium salt was added to a cold solution of **7** (2.63 g; 0.01 mole), in ethanol (30 mL) containing sodium acetate (2 g). The reaction mixture was stirred at room temperature for 1 h and the solid products, so formed, was collected by filtration and recrystallized from ethanol. Brown crystals; yield 81%, mp195 °C (EtOH). υ_{max} = 3303, 3240 (2NH), 1652 (CO) cm^{-1}. MS: *m/z* = 367 [M^+]. δ_H = 6.75–7.76 (m, 15H, 3Ph-H), 10.15 (s, 1H, NH amide), 14.22 (s, 1H, NH ring). *Anal*. Calcd for $C_{22}H_{17}N_5O$ (367.40): C, 71.92; H, 4.66; N, 19.06. Found: C, 71.98; H, 4.56; N, 19.00.

2-Benzoyl-3,N-diphenylacrylamide 11. To a refluxing mixture of **3** (2.39 g; 0.01 mole) and benzaldehyde **10** (1.06 g; 0.01 mole) in ethanol (25 mL) was added piperidine (0.5 mL) with continuous reflux for 5 h (TLC control), then left to cool to room temperature. The reaction mixture was then poured on ice-cold water and neutralized by few drops of conc. HCl. The solid precipitate that appeared was filtered off and recrystallized from ethanol to afford **11**. Pale yellow powder; yield 62%, mp. 80 °C (EtOH). υ_{max} = 3475, 3343 (NH), 1689 (2CO) cm^{-1}. MS: *m/z* = 327 [M^+]. δ_H = 7.15–7.68 (m, 15H, 3Ph-H), 7.94 (s, 1H, CH), 10.25 (s, 1H, NH amide). *Anal*. Calcd for $C_{22}H_{17}NO_2$ (327.38): C, 80.71; H, 5.23; N, 4.28. Found: C, 80.65; H, 5.28; N, 4.42.

2-Amino-4,6-diphenyl-1,4-dihydropyrimidine-5-carboxanilide 13. To a refluxing mixture of **11** (3.27 g; 0.01 mole) and guanidine hydrochloride (0.96 g; 0.01 mole) in ethanol (25 mL) was added piperidine (0.5 mL) with continuous reflux for 4 h (TLC control), then left to cool to room temperature. The reaction mixture was then poured on ice-cold water and neutralized by few drops of conc. HCl. The solid precipitate that appeared was filtered off and recrystallized from ethanol to afford **13**. Yellow powder; yield 72%, mp.88 °C (EtOH). υ_{max} = 3261, 3198, and 3137 (NH and NH_2), 1687 (CO) cm^{-1}; MS, *m/z* = 366 [M^+-2]. δ_H = 3.85 (s, 1H, 4-H), 4.28 (s, 2H, NH_2), 7.05–7.58 (m, 15H, 3Ph-H), 7.84 (s, 1H, ring NH), 10.12 (s, 1H, NH amide). *Anal*. Calcd for $C_{23}H_{20}N_4O$ (368.43): C, 74.98; H, 5.47; N, 15.21. Found: C, 74.95; H, 5.54; N, 15.29.

Reaction of 3 with the active methylenes 14a,b: Preparation of 15a,**b**. To a mixture of **3** (2.39 g; 0.01 mole) and malononitrile **14a** (0.66 g; 0.01 mole) or ethyl cyanoacetate **14b** (1.13 g; 0.01 mole) in ethanol (25 mL), few drops of triethylamine were added as catalyst. The reaction mixture was refluxed for 3 h in each case then left to cool overnight. The reaction mixture was poured on ice cold water and neutralized with few drops of HCl. The precipitated solids were collected by filtration and recrystallized from ethanol.

4,4-Dicyano-3-phenylbut-3-enoic acid phenylamide 15a. Reddish brown powder; yield 85%, mp 90 °C (EtOH). IR: υ_{max} = 3473 (NH), 2206, 2363 (2CN), and 1662 (CO) cm^{-1}. MS: ***m/z*** = 287 [M^+]; δ_H = 2.78 (s, 2H, CH_2), 7.05–7.65 (m, 10H, 2Ph-H), 10.1 (s, 1H, NH). Anal**.** Calcd for $C_{18}H_{13}N_3O$ (287.32): C, 75.25; H, 4.56; N, 14.63. Found C, 75.28; H, 4.65; N, 14.50.

Ethyl 2-cyano-3-phenyl-4-phenylcarbamoyl-but-2-enoate 15b. White crystals; yield 76%, mp 105 °C (EtOH). IR: υ_{max} = 3262 (NH), 2236 (CN), and 1705, 1663 (2CO) cm^{-1}. MS: *m/z* = 334 [M^+]. δ_H = 1.18 (t, 3H, CH_3), 2.75 (s, 2H, CH_2), 3.81 (q, 2H, CH_2), 6.98–7.60 (m, 10H, 2Ph-H), 10.12 (s, 1H, NH). *Anal*. Calcd for $C_{20}H_{18}N_2O_3$ (334.37): C, 71.84; H, 5.43; N, 8.38. Found: C, 71.90; H, 5.48; N, 8.28.

Azo coupling of 15a,b: Preparation of 16a,**b**. Diazonium salt **8** was freshly prepared by adding a solution of (0.7 g; 0.01 mole) of sodium nitrite in 5 mL of H_2O to a cold solution of aniline hydrochloride (3 mL of conc. HCl + 1 mL of aniline) with stirring. The resulting solution of the diazonium salt was added to a cold solution of **15a** or **15b** (0.01 mole) in ethanol (25 mL) containing sodium acetate (2 g). The reaction mixture was stirred at room temperature for 1 h and the solid product, thus formed, was collected by filtration and recrystallized from ethanol to afford **16a** and **16b**, respectively.

4,4-Dicyano-3-phenyl-2-(phenyl-hydrazono)-but-3-enoic acid phenylamide 16a. Brown crystals; yield 96%, mp. 152 °C. υ_{max} = 3455, 3219 (2NH), 2231 (CN), 1654 cm^{-1} (CO); MS: *m/z* = 391 [M^+]. δ_H = 6.8–7.6 (m, 15H, 3Ph-H), 10.33 (s, 1H, NH amide), 12.53 (s, 1H, hydrazo NH). *Anal*. Calcd. for

$C_{24}H_{17}N_5O$ (391.42): C, 73.64; H, 4.38; N, 17.89. Found: C, 73.68; H, 4.45; N, 17.98.

Ethyl 2-cyano-3-phenyl-4-phenylcarbamoyl-4-(phenyl-hydrazono)-but-2-enoate 16b. Brown crystals; yield 96%, mp. 158 °C. υ_{max} = 3455, 3219 (2NH), 2231 (CN), 1654 cm^{-1} (CO); MS: *m/z* = 438 [M^+]. δ_H = 6.8–7.6 (m, 15H, 3Ph-H), 10.33 (s, 1H, NH amide), 12.53 (s, 1H, hydrazo NH). *Anal*. Calcd for $C_{26}H_{22}N_4O_3$ (438.48): C, 71.22; H, 5.06; N, 12.78. Found: C, 71.32; H, 4.96; N, 12.70.

Cyclization of 16a,b: Synthesis of the pyridazines 17a,b. To a solution of each of compounds **16a** and **16b** (0.01 mole) in ethanol (25 mL) was added 3 mL of freshly prepared sodium ethoxide (1.15 g, 0.05 mole of sodium metal dissolved in 10 mL of absolute ethanol). The reaction mixture was refluxed for 2 h and left overnight to cool, poured on ice-cold water and drops of conc. HCl were added till just neutral (pH 7). The precipitated solids were filtered off and recrystallized from ethanol to afford **17a** and **17b**.

5-Cyano-6-imino-1,4-diphenyl-1,6-dihydropyridazine-3-carboxanilide 17a. Brown crystals; yield 96%, mp. 152 °C (EtOH); IR: υ_{max} = 3455–3219 (2NH), 2231 (CN), and1654 (CO) cm^{-1}; MS: *m/z* = 391 [M^+]; δ_H = 6.65−7.62 (m, 15H, 3Ph-H), 10.33 (s, 1H, amide), 12.53 (s, 1H, imine). *Anal*. Calcd for $C_{24}H_{17}N_5O$ (391.42): C, 73.64; H, 4.38; N, 17.89. Found: C, 73.70; H, 4.15; N, 17.80.

5-Cyano-6-oxo-1,4-diphenyl-1,6-dihydropyridazine-3-carboxanilide 17b. Yellow crystals; yield 83%, mp. 158 °C (EtOH); IR: υ_{max} = 3315, 3226 (NH), 2235 (CN), 1727 (CO), 1654 (CO) cm^{-1}. MS: *m/z* = 392 [M^+]. δ_H = 6.90−7.62 (m, 15H, 3Ph-H), 10.20 (s, 1H, amide). *Anal*. Calcd for $C_{24}H_{16}N_4O_2$ (392.41): C, 73.46; H, 4.11; N, 14.28. Found: C, 73.55; H, 4.25; N, 14.15.

3-Oxo-3,N-diphenyl-2-(phenyl-hydrazono)-propionamide 18. Diazonium salt was freshly prepared by adding a solution of (0.7 g; 0.01 mole) of sodium nitrite in 5 mL of H_2O to a cold solution of aniline hydrochloride (3 mL of conc. HCl + 1 mL of aniline) with stirring. The resulting solution of the diazonium salt was added to a cold solution of **3** (2.39 g; 0.01 mole) in ethanol (25 mL) containing sodium acetate (2 g). The reaction mixture was stirred at room temperature for 1 h and the solid product, so formed, was collected by filtration and recrystallized from ethanol. Yellow crystalline product; yield 76%, mp: 140 °C (EtOH). υ_{max} = 3448, 3220 (2NH), 1731, and 1654 (2CO) cm^{-1}. MS: *m/z* = 343 [M^+]; δ_H = 7.0–7.89 (m, 15H, 3Ph-H), 11.08 (s, 1H, NH anilide), 13.56 (s, 1H, hydrazo NH). *Anal*. Calcd for $C_{21}H_{17}N_3O_2$ (343.38): C, 73.45; H, 4.99; N, 12.24. Found: C, 73.55; H, 5.09; N, 12.14.

The reaction of 18 with the active methylenes 14a,b: Alternative synthesis of 17a,b. To a mixture of **18** (3.43g; 0.01 mole) and malononitrile **14a** (0.66g; 0.01 mole) or ethyl cyanoacetate **14b** (1.13g; 0.01 mole) few drops of triethylamine were added as catalyst. The reaction mixture was fused together on an oil bath at 170 °C for 3 h then left overnight to cool. The solid product obtained in each case was triturated with ethanol and poured on ice cold water and neutralized with few drops of HCl. The precipitated solids were collected by filtration and recrystallized from ethanol to afford directly the pyridazine derivatives **17a,b** respectively.

3-Amino-4,7-diphenyl-7*H*-pyrazolo[3,4-*c*]pyridazine-5-carboxanilide 19. To compound **18b** (3.92 g; 0.01 mole) in ethanol (20 mL) hydrazine hydrate (0.5 mL) was added. The reaction mixture was refluxed for 3 h (TLC control) and left overnight. The reaction mixture was then poured on ice cold water. The precipitated solid was filtered off and recrystallized from ethanol to give **19**. Yellow crystalline product; yield 86%, mp. 161 °C. υ_{max} = 3439, 3220, 2298 (NH and NH_2), 1654 (CO) cm^{-1}. MS: *m/z* = 406 [M^+]. δ_H = 6.65–7.70 (m, 15H, 3Ph-H), 10.35 (s, 1H, NH amide), 11.1 (s, 2H, NH_2). δ_c = 115.15 (d), 115.66 (s), 118.55 (d), 120.33 (d), 124.46 (d), 127.66 (d), 128.19 (d), 128.97 (d), 129.49 (d), 130.01 (d), 131.6 (s), 137.46 (s), 138.51 (s), 142.04 (s), 153.25 (s), 161.99 (s), 162.88 (s). *Anal*. Calcd for $C_{24}H_{18}N_6O$ (406.44): C, 70.92; H, 4.46; N, 20.68. Found: C, 71.12; H, 4.50; N, 20.52.

3-Imino-4,7-diphenyl-3,7-dihydroisoxazolo[3,4-*c*]pyridazine-5-carboxanilide 21. To a refluxing mixture of **18b** (3.92 g; 0.01 mole) and hydroxylamine hydrochloride **20** (0.7 g; 0.01 mole) in ethanol (25 mL) piperidine (0.01 mole) was added. The reflux was continued for 4 h (TLC control) and then the reaction mixture was left to cool to room temperature. The reaction mixture was then poured on ice cold water and neutralized by few drops of conc. HCl. The solid precipitates that appeared were filtered off and recrystallized from ethanol to afford **21** as yellow crystalline product; yield 67%, mp. 161 °C. υ_{max} = 3451, 3378, 3295, 3232 (2NH), 1656 (CO) cm^{-1}. MS: MS: *m/z* = 407 [M^+]. δ_H = 6.60–7.72 (m, 15H, 3Ph-H), 10.35 (s, 1H, NH amide), 12.15 (s, 1H, imine NH). *Anal*. Calcd for $C_{24}H_{17}N_5O_2$ (407.42): C, 70.75; H, 4.21; N, 17.19. Found: C, 70.65; H, 4.25; N, 17.30.

Synthesis of the dihydropyrimido[4,5-*c*]pyridazine-3-carboxanilide derivatives 24a–c. To a mixture of **18b** (3.92 g; 0.01 mole) and guanidine hydrochloride **12** (0.96 g; 0.01 mole) or urea **22** (0.6 g; 0.01 mole) or thiourea **23** (0.76 g; 0.01 mole) in ethanol/dimethylformamide mixture 4:1 (25 mL) few drops of triethylamine were added as catalyst (molar amount in case of **12**). The reaction mixture was refluxed for 3 h, then left to cool to room temperature, diluted with cold water and acidified with few drops of HCl till just neutral. The precipitated solids were collected by filtration, washed thoroughly with cold water and recrystallized from DMF/ethanol to afford **24a–c**, respectively:

5-Amino-7-imino-1,4-diphenyl-1,7-dihydropyrimido[4,5-*c*] pyridazine-3-carboxanilide 24a. Dark yellow crystals; yield 85%, mp. 163 °C (EtOH). υ_{max} = 3440, 3220 (NH and NH_2), 1654 cm^{-1} (CO). MS: *m/z* = 433 [M^+]. δ_H = 6.52–7.38 (m, 17H, 3Ph-H + NH_2), 11.12 (s, 1H, amide NH), 12.05 (s, 1H, imine NH). δ_c =114.10 (s), 115.56 (d), 118.56 (d), 120.43 (d), 124.16 (d), 126.26 (d), 127.79 (d), 128.57 (d), 128.82 (d), 129.45 (d), 134.81 (s), 138.5 (s), 142.26 (s), 145.91 (s), 153.04 (s), 160.25 (s), 162.79 (s), 164.85 (s). *Anal*. Calcd for $C_{25}H_{19}N_7O$ (433.46): C, 69.27; H, 4.42; N, 22.62. Found: C, 69.35; H, 4.40; N, 22.68.

5-Amino-7-oxo-1,4-diphenyl-1,7-dihydropyrimido[4,5-*c*] pyridazine-3-carboxanilide 24b. Yellow crystalline product; yield 66%, mp. 164 °C. υ_{max} = 3437, 3129 (NH and NH_2), 1687 and 1654 cm^{-1} (2CO). MS: *m/z* = 434 [M^+]. δ_H = 6.75–7.82 (m, 17H, 3Ph-H + NH_2), 11.1 (s, 1H, NH). *Anal*. Calcd for $C_{25}H_{18}N_6O_2$ (434.45): C, 69.11; H, 4.18; N, 19.34. Found: C, 69.15; H, 4.28; N, 19.55.

5-Amino-1,4-diphenyl-7-thioxo-1,7-dihydropyrimido[4,5-*c*] pyridazine-3-carboxanilide 24c. Pale yellow crystalline product; yield 67%, mp. 167 °C. υ_{max} = 3443, 3220, 3129 (NH and NH_2), 1655 (CO) cm^{-1}. MS: *m/z* = 450 [M^+].

$\delta_H = 6.79–7.65$ (m, 17H, 3Ph-H + NH_2), 11.08 (s, 1H, NH). *Anal*. Calcd for $C_{25}H_{18}N_6OS$ (450.52): C, 66.65; H, 4.03; N, 18.65; S, 7.12. Found: C, 66.63; H, 4.13; N, 18.60; S, 7.17.

(5-Amino-1,4-diphenylhydrobenzo[b]pyridazino[3,4-*e*]-1,4-diazepin-3-yl)N-benzamide 26. To a refluxing mixture of **18b** (3.92 g; 0.01 mole) and 1,2-phenylenediamine **25** (1.08 g; 0.01 mole) in ethanol (25 mL) piperidine (0.5 mL) was added. The reflux was continued for 4 h (TLC control) and then the reaction mixture was left to cool to room temperature. The reaction mixture was then poured on ice cold water and neutralized by few drops of conc. HCl. The solid precipitates that appeared were filtered off and recrystallized from ethanol to afford **26** as pale yellow crystals; yield 62%, mp. 169 °C. $\upsilon_{max} = 3437$, 3357 (NH and NH_2), 1654 (CO) cm^{-1}. MS: $m/z = 482$ [M^+]. $\delta_H = 6.65–7.65$ (m, 21H, arom. + NH_2), 11.12 (s, 1H, amide NH) *Anal*. Calcd for $C_{30}H_{22}N_6O$ (482.54): C, 74.67; H, 4.60; N, 17.42. Found: C, 74.63; H, 4.65; N, 17.55.

Acknowledgments. We thank the Alexander von Humboldt Foundation (Germany) for granting a research fellowship (July 2011) to F. M. Abdelrazek; during this time, a considerable part of the spectra of this work was carried out. This work has been abstracted in part from the M. Sc. Thesis of Mrs. Nagwa M. Abdelazeem.

REFERENCES AND NOTES

[1] Tigler, M.; Stanovnik, B. Azolo- and azinopyridazines and some oxa and thia analogs. In Condensed Pyridazines Including Cinnolines and Phthalazines; Castle, R. N., Ed.; John Wiley & Sons, Inc.: New York, 1973; pp. 968–1012 and references within.

[2] a) Frank, H.; Heinisch, G. Pharmacologically active pyridazines Part I. In Progress in Medicinal Chemistry; Ellis, G.P., West, G. B., Eds.; Elsevier: Amsterdam, 1990; *Vol*. 27, 1.; b) Frank, H.; Heinisch, G. Pharmacologically active pyridazines Part II. In Progress in Medicinal Chemistry; Ellis, G.P., Luscombe, D.K., Eds.; Elsevier: Amsterdam, 1992; *Vol*. 29, 141.

[3] Mylari B. L., Zembrowski W. J. US Pat. 4 1990, 954, 629; *Chem Abstr* 1991, 114, 62105 u.

[4] Sahin M. F.; Badicoglu B.; Goekce M.; Kuepeli E. Arch Pharm Pharm Med Chem (Weinheim) 2004, 337, 445.

[5] Barrett J. A.; Woltmann R. F.; Swillo R. S.; Kasiewski C. J Cardiovascular Pharm 1990, 16, 537.

[6] Betti L.; Zanelli M.; Gannaccini G.; Manetti F.; Schenone S.; Strappaghetti G. Bioorg Med Chem 2006, 14, 2828.

[7] Hewett R.; Pettit S. N.; Smith P. Can Pat Appl CA 2 1993, 086, 898; *Chem Abstr* 1994, 121, 9415p.

[8] Stevenson T. M.; Crouse B. A.; Thieu T. V.; Gebreysus C.; Finkelstein B. L.; Sethuraman M. R.; Dubas-Cordery C. M.; Piotrowski D. L. J. Heterocyclic Chem. 2005, 42, 427.

[9] Abdelrazek F. M.; Fathy A. E. M. Arch. Pharm. Chem. Life Sciences (Weinheim) 2005, 338, 329.

[10] Abdelrazek F. M.; Metz P.; Metwally N. H.; El-Mahrouky S. F. Arch Pharm Chem life Sciences (Weinheim) 2006, 339*(8)*, 456.

[11] Abdelrazek F. M.; Metz P.; Kataeva O.; Jaeger A.; El-Mahrouky S. F. Arch Pharm Chem Life Sciences (Weinheim) 2007, 340*(10)*, 543.

[12] Abdelrazek, F. M.; Metwally, N. H. Synthetic Communications 2009, 39, 4088.

[13] Elkholy, Y. M. Heterocyclic Commun 2005, 11*(1)*, 89.

[14] Abdallah, T. A.; Metwally, N. H.; Abdelrazek, F. M. Afinidad 2008, 65*(537)*, 393.

[15] Abdelrazek F. M.; Fadda A. A.; Elsayed A. N. Synthetic Communications 2011, 41, 1119.

[16] Kappe, C. O. Tetrahedron 1993, 49, 6937.