# Improved synthesis of 2-arylhydrazono-3-hydroxy-1-propanones and their utility in efficient synthesis of pyridazine derivatives

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**Abstract**

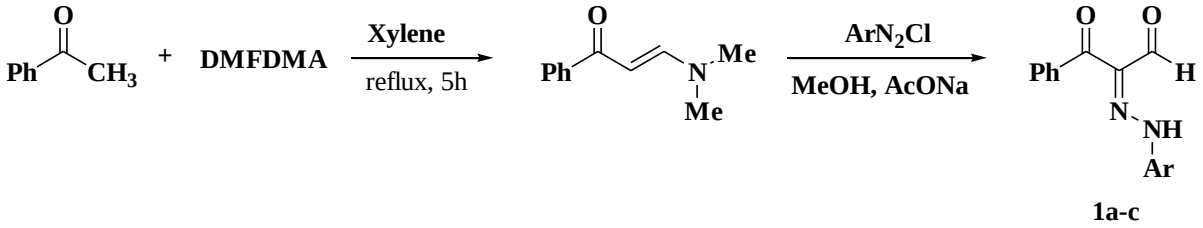
Reaction of 2-arylhydrazono-1-phenylethanones **2a-c** with formaldehyde either in presence of montmorillonite K10 or by simply stirring in methanol and TEA leads to selective synthesis of 2-arylhydrazono-3-hydroxy-1-phenylpropan-1-one derivatives **3a-c** in high yield. Heating **1a** with *N*-phenylmaleimide in DPE/DABCO using microwave irradiation for 5 minutes at 200 $^{o}$C results in a 73% yield of pyrrolo[3,4-*c*]pyridazine **8**. Compounds **2a-c** react with benzylidenemalononitriles **9a** or ethyl 2-cyanocinnamate **9b** in refluxing ethanol and piperidine or β-chitosan to yield new pyridazine derivatives **10a-f** which are converted into pyridazinones **11a-c** upon reflux in acetic/hydrochloric acids mixture.

**Keywords:** Arylhydrazonals, pyridazines, pyrrolopyridazine

## Introduction

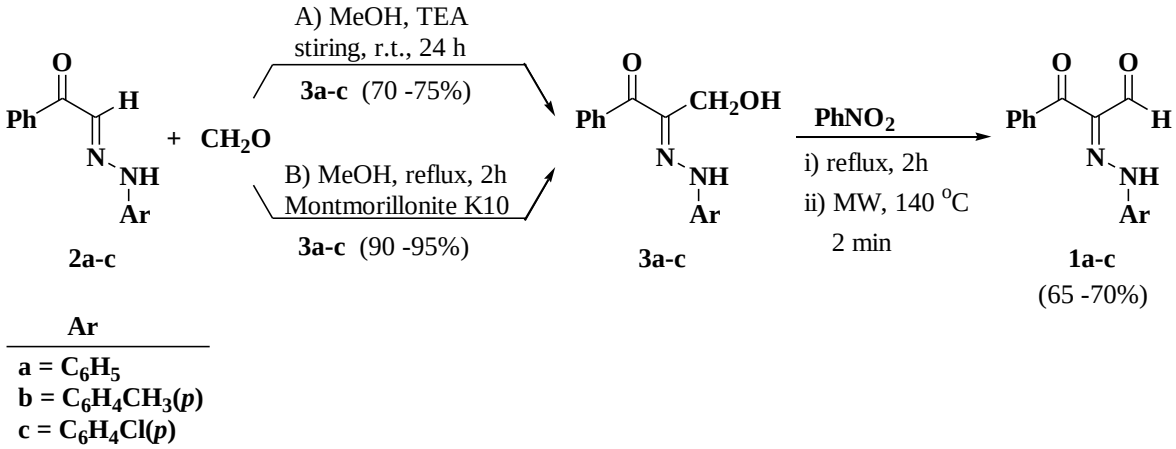
Pyridazines and their derivatives although known for more than a century[1] received little attention until the discovery of medicinally useful natural products.[2-4] Today, the pyridazine nucleus has been recognised as a versatile pharmacophore. This key structure is a constituent in many biologically active substances.[5-12] Recently we reviewed synthetic approaches to pyridazines and condensed pyridazines.[13] We have previously reported the synthesis of arylhydrazonals **1a-c** by heating of α-methyl-ketone with dimethylformamide dimethyl acetal (DMFDMA) for five hours in xylene and coupling the resulting enaminones with an aromatic diazonium chloride (Scheme 1).[14]




**Scheme 1**

In the present work we report an alternative approach for the synthesis of arylhydrazonals **1a-c** in good yield from 2-arylhydrazono-1-phenylethanone derivatives **2a-c** (Scheme 2). Arylhydrazonal **1a** was converted into a pyridazine via a Baylis-Hillman reaction with methyl vinyl ketone; we interpreted this[15] as involving the ready transformation of intermediate **4** into **5** which, on loss of water, yielded pyridazine **6**. In this work, the intermediate **5** has been isolated and fully characterized. Compound **2a** was heated with *N*-phenylmaleimide to form a new pyrrolo[3,4-*c*]pyridazine **8**. Compounds **2a-c** were reacted with **9a,b** to produce new pyridazine derivatives **10a-c**, **11a-**c.




**Scheme 2**

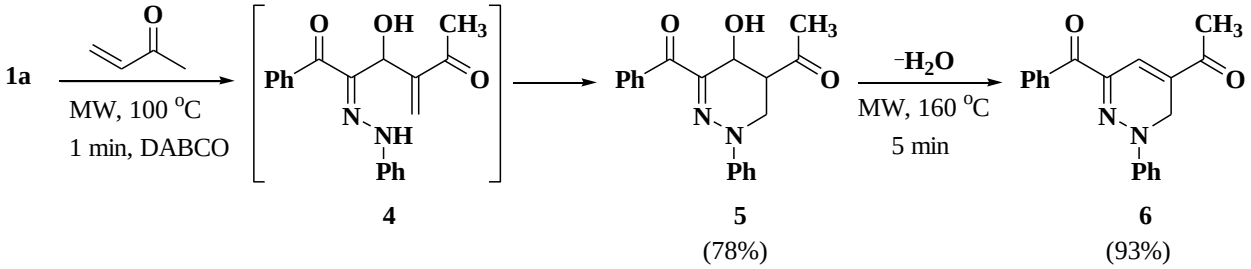
## Results and Discussion

Scheme 2 illustrates the selective synthesis of 2-arylhydrazono-3-hydroxy-1-phenylpropan-1-ones **3a-c** by reaction of arylhydrazono-1-phenylethanones **2a-c** with formaldehyde, using montmorillonite K10 as a shape selective catalyst that favours formation of slim molecules, by reflux in methanol or by simply stirring **2a-c** in methanol in presence of triethylamine with formaldehyde, yielding **3a-c** in 90-95% and 70-75% yields respectively. Refluxing **3a-c** with

nitrobenzene as solvent and oxidizing agent resulted in the formation of arylhydrazonals **1a-c** in 65-70% yields.

We have previously reported the reaction of **1a** with methyl vinyl ketone using microwave heating in the presence of DABCO to prepare 1-(6-benzoyl-2-phenyl-2,3-dihydropyridazine-4-yl)ethanone **6** in 92% yield.[15] This reaction was assumed to proceed via intermediates **4** and **5**. In the present work we have successfully isolated **5** in 78% yield and converted it into **6** via microwave heating for five minutes at 160 $^{o}$C in 93% yield (Scheme 3).




**Scheme 3**

The structure of compound **5** was confirmed by 2D NMR experiments. Figure 1 shows $^{1}$H and $^{13}$C NMR signal assignments and the H-C correlations in the HMBC 2-D experiment: H-6 at δ: 3.74, 4.23 correlates with C-5, C-12 at 46.8, 204.7; H-5 at δ: 2.88 correlates with C-6, C-12 at 39.6, 204.7; H-4 at δ: 5.36 correlates with C-3 at 139.5; H-9 at δ: 8.00 correlates with C-7, C-11 at 191.5, 131.9; H-10 at δ: 7.48 correlates with C-8 at 137.2; H-11 at δ: 7.56 correlates with C-9 at 130.5; H-13 at δ: 2.45 correlates with C-5, C-12 at 46.8, 204.7; H-15 at δ: 7.37 correlates with C-17 at 123.8; H-16 at δ: 7.37 correlates with C-14 at 145.6; H-17 at δ: 7.11 correlates with C-15 at 116.1.

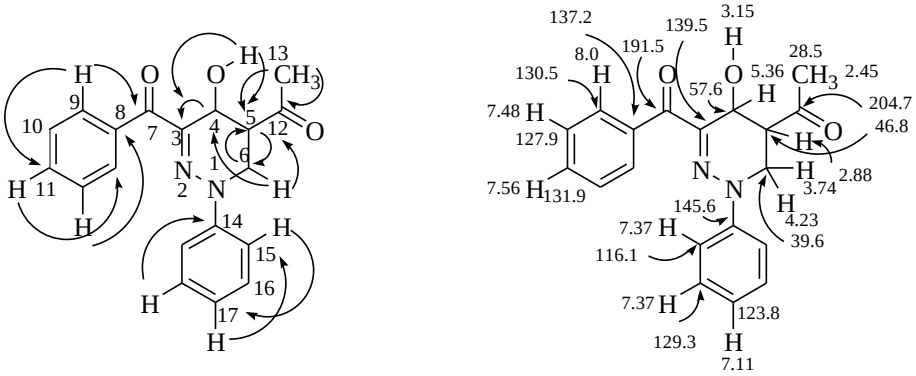


**Figure 1.** Important HMBC H-C correlation of compound **5.**

The X-ray structure of compound **6** confirms its structure as that shown in Figure 2.

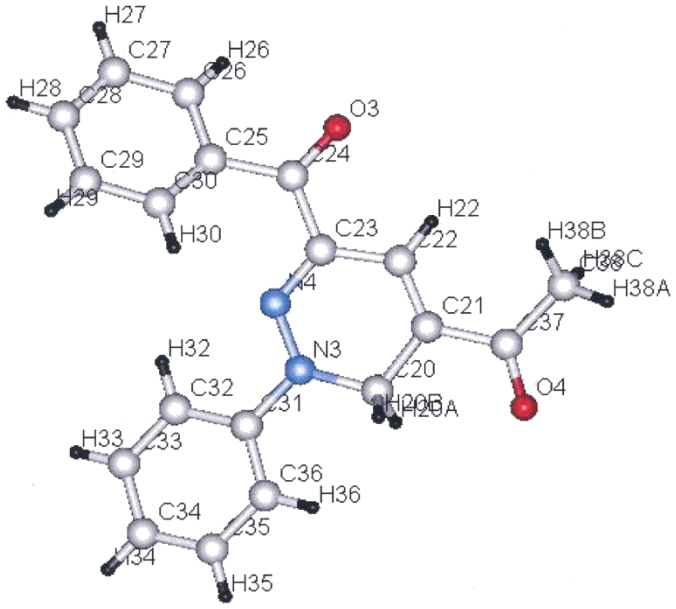
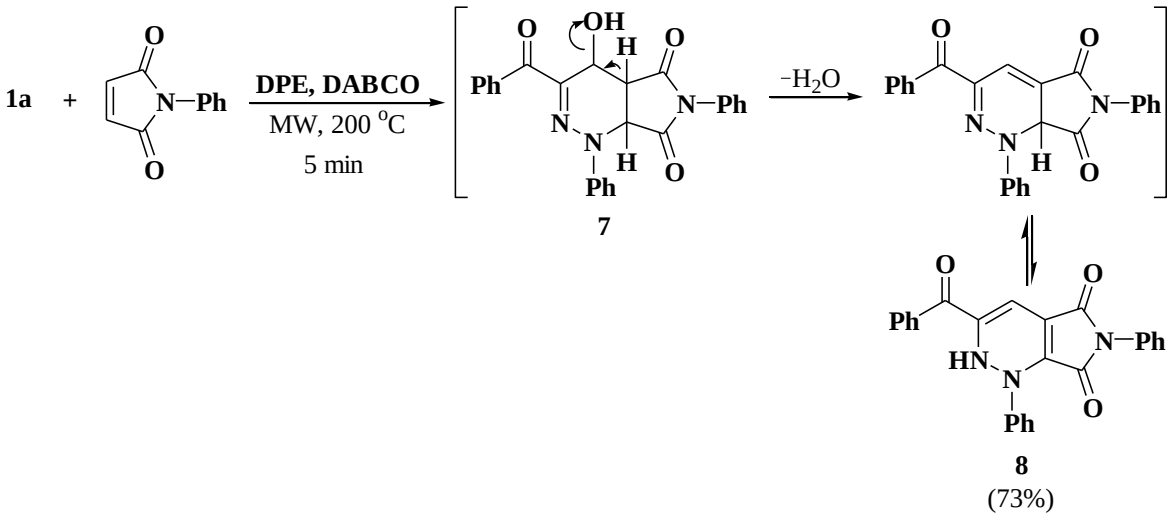



**Figure 2**. X-Ray crystallographic analysis of compound **6** (ball and stick representation)

Microwave heating of **1a** with *N*-phenylmaleimide at 200 °C for five minutes in diphenyl ether and DABCO gave 3-benzoyl-1,6–diphenyl-1,2-dihydropyrrolo[3,4-*c*]pyridazine-5,7-dione **8** in 73% yield via presumed intermediate **7** (Scheme 4).

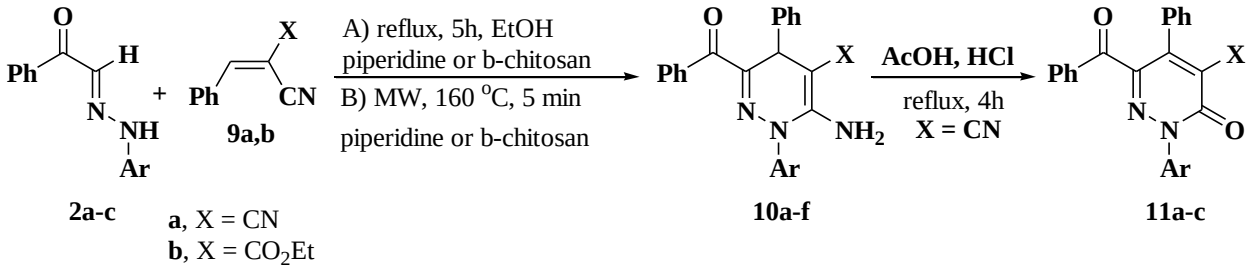



**Scheme 4**

Refluxing **2a-c** with benzylidenemalononitriles **9a** or ethyl 2-cyanocinnamate **9b** in ethanol in the presence of piperidine gave the corresponding 2,5-dihydropyridazine derivatives **10a-f** in

good yields. Compounds **10a-f** were also obtained when **2a-c** and **9a,b** were irradiated in the microwave oven at 160 $^{o}$C for five minutes. We have recently reported that β-chitosan is an efficient basic catalyst for a variety of Michael additions.[16a] Replacing piperidine with β-chitosan afforded **10a-f** in almost the same yields. Compounds **10a-c** were converted into the corresponding 2,3-dihydropyridazinones **11a-c** upon refluxing for four hours in acetic/hydrochloric acids mixture (Scheme 5). Hydrolysis of the amino function under these conditions is well established.[16b,c]




| Compd. | Ar | X | **10** (% yield) | **11** (% yield) |
|---|---|---|---|---|
| **10,11a** | $C_6H_5$ | CN | 79 | 56 |
| **10,11b** | $C_6H_4CH_3$(*p*) | CN | 76 | 58 |
| **10,11c** | $C_6H_4Cl$(*p*) | CN | 82 | 55 |
| **10d** | $C_6H_5$ | $CO_2Et$ | 86 | - |
| **10e** | $C_6H_4CH_3$(*p*) | $CO_2Et$ | 80 | - |
| **10f** | $C_6H_4Cl$(*p*) | $CO_2Et$ | 83 | - |

**Scheme 5**

## Conclusions

The synthetic approach to arylhydrazonals desribed here is more efficient and more atom economic than the original approach of coupling enaminones with arylhydrzonium salts. The recently reported synthesis of pyridazines via Baylis-Hillman reaction of arylhydrazonals with electron poor alkenes has been extended and the cyclic intermediate adduct suggested for this reaction was isolated and fully characterized; this led to the synthesis of two new structural types, **8** and **11a-c**.

## Experimental Section

**General.** Melting points were recorded on Gallenkamp apparatus. IR spectra were recorded in KBr disks on a Perkin Elmer System 2000 FT-IR spectrophotometer. $^{1}$H and $^{13}$C NMR spectra were recorded on a Bruker DPX 400 MHz super-conducting NMR spectrometer; proton spectra were measured at 400 MHz and carbon spectra at 100 MHz. IR data are in $cm^{-1}$. Mass spectra were measured on VG Auto-spec-Q (high resolution, high performance, tri-sector GC/MS/MS) and with LCMS using Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode. Microanalyses were performed on LECO CH NS-932 Elemental Analyzer. The microwave oven used was a single mode cavity Explorer Microwave (CEM Corporation, NC, USA) and irradiation was conducted in heavy-walled Pyrex tubes (capacity 10 mL) fitted with a PCS cap.

**2-Arylhydrazono-1-phenylethanones (2a-c)**. **General procedures**

The procedure described[17] for the synthesis of pyruvaldehyde-1-phenylhydrazone was adopted. Thus, to a solution of potassium hydroxide (3.5 g, 62 mmol) in water (100 mL) was added ethyl benzoylacetate (8.7 g, 10 mmol). The mixture was stirred at room temperature for 24 h, cooled to 0-5 ºC and aqueous HCl (20 mL, 2.5 M) was added slowly. The solution was made basic by adding sodium acetate (8.2 g, 100 mmol) in cooled water (30 mL), then gradually treated with stirring with the appropriate aromatic diazonium chlorides (10 mmol). After stirring for 2 h at 0-5 ºC the yellow precipitate was collected and recrystallized from ethanol to give **2a-c**.

**1-Phenyl-2-phenylhydrazonoethanone (2a)**. Yield 10.5 g (94%), yellow crystals from EtOH/$H_2O$ mp 146-148 ºC (lit.[18] mp 148-150 ºC). $^{1}$H NMR **(**$CDCl_3$): 14.52 (br, 1H, NH), 8.02 (d, 2H, *J* 7.6 Hz), 7.76 (s, 1H), 7.63 (t, 1H, *J* 7.7 Hz), 7.51 (t, 2H, *J* 7.8 Hz), 7.41-7.33 (m, 4H), 7.09 (t, 1H, *J* 7.6 Hz). $^{13}$C NMR ($CDCl_3$): 186.2, 140.7, 137.3, 132.9, 129.5, 128.9, 128.0, 123.9, 122.3, 114.9. *Anal. calcd.* for $C_{14}H_{12}N_2O$ (224.3): C 74.98; H 5.39; N 12.49. Found: C 74.89; H 5.31; N 12.40.

**1-Phenyl-2-*p*-tolylhydrazonoethanone (2b)**. Yield 11.0 g (92%), yellow crystals from EtOH, mp 114-115 ºC (lit.[19] mp 115-117 ºC). $^{1}$H NMR **(**$CDCl_3$): 14.58 (br, 1H, NH), 8.00 (dd, 2H, *J* 8.4, 1.6 Hz), 7.72 (s, 1H), 7.59 (t, 1H, *J* 7.4 Hz), 7.52 (t, 2H, *J* 7.5 Hz), 7.27 (d, 2H, *J* 8.4 Hz), 7.18 (d, 2H, *J* 8.4 Hz), 2.33 (s, 3H). $^{13}$C NMR ($CDCl_3$): 186.2, 140.3, 137.4, 133.7, 132.7, 130.0, 128.8, 128.0, 121.8, 114.9, 20.9. *Anal. calcd.* for $C_{15}H_{14}N_2O$ (238.3): C 75.61; H 5.92; N 11.76. Found: C 75.59; H 5.91; N 11.73.

**2-*p*-Chlorophenylhydrazono-1-phenylethanone (2c)**. Yield 11.0 g (88%), yellow crystals from EtOH, mp 148-150 ºC (lit.[20] mp 147-148 ºC). IR: 3224, 3055, 1631, 1595, 1502, 1475, 1240, 1089, 1045, 821. $^{1}$H NMR **(**DMSO-$d_6$): 11.59 (br, 1H, NH), 7.97 (d, 2H, *J* 7.4 Hz), 7.72 (s, 1H), 7.62 (t, 1H, *J* 7.6 Hz), 7.54 (t, 2H, *J* 7.8 Hz), 7.36 (d, 2H, *J* 8.8 Hz), 7.01 (d, 2H, *J* 8.8 Hz). $^{13}$C NMR ($CDCl_3$): 189.9, 142.9, 137.9, 135.0, 132.8, 130.1, 130.0, 128.9, 125.8, 115.8. MS: *m/z* (%) 260 (M + 2, 20), 258 ($M^+$, 25), 105 (100). *Anal. calcd.* for $C_{14}H_{11}ClN_2O$ (258.7): C 65.00; H 4.29; N 10.83. Found: C 64.79; H 4.21; N 10.73.

**2-Arylhydrazono-3-hydroxy-1-phenylpropan-1-ones (3a-c). General procedures**

**Method A**. A mixture of each of **2a-c** (10.0 mmol) and excess aqueous formaldehyde (3.2 g, 40.0 mmol, 37%) in methanol (20 mL), TEA (5 drops) was stirred at r.t. over night. After evaporation the solvent in vacuum, ice water (50 mL) was added and the yellow precipitate formed was collected by filtration and crystallized from the proper solvent to give **3a-c** in 70-75% yield

**Method B.** A mixture of each of **2a-c** (10.0 mmol) and aqueous formaldehyde (0.8 g, 10.0 mmol, 37%) was refluxed for 2 hours in methanol in presence of montmorilonite K10. After reflux, evaporation the solvent, ice water (50 mL) was added and the yellow precipitate formed was collected by filtration and crystallized to give **3a-c** in 90-95% yield.

**3-Hydroxy-1-phenyl-2-phenylhydrazonopropan-1-one (3a)**. Yield 1.8 g (70%), method A, 2.30 g (90%), method B, yellow crystals from benzene, mp 128-130 ºC (lit.[21] mp 126-127 ºC). IR: 3448, 3305, 3056, 2965, 1630, 1547, 1492, 1367, 1257, 986. $^1$H NMR **(**DMSO-$d_6$): 10.64 (s, 1H, NH), 7.81 (d, 2H, *J* 7.2 Hz), 7.58 (t, 1H, *J* 7.4 Hz), 7.50 (t, 2H, *J* 7.6 Hz), 7.27 (t, 2H, *J* 7.8 Hz), 7.16 (d, 2H, *J* 7.6 Hz), 6.93 (t, 1H, *J* 7.2 Hz), 5.20 (br, 1H, OH), 4.64 (s, 2H, $CH_2$). $^{13}$C NMR (DMSO-$d_6$): 190.9, 143.6, 141.1, 138.4, 131.2, 129.9, 129.3, 127.7, 121.8, 114.1, 53.5. LCMS *m/z* = 255 (M + 1). MS: *m/z* (%) 254 ($M^+$, 10), 229 (70), 182 (25), 91 (100). *Anal. calcd.* for $C_{15}H_{14}N_2O_2$ (254.3): C 70.85; H 5.55; N 11.02. Found: C 70.74; H 5.51; N 11.03.

**3-Hydroxy-1-phenyl-2-*p*-tolylhydrazonopropan-1-one (3b)**. Yield 2.0 g (75%), method A, 2.45 g (91%), method B, yellow crystals from EtOH/$H_2O$, mp 164-165 ºC. IR: 3438, 3184, 3056, 2961, 1638, 1566, 1515, 1449, 1240, 968, 728. $^1$H NMR **(**DMSO-$d_6$): 10.55 (br, 1H, NH), 7.79 (dd, 2H, *J* 8.4, 1.4 Hz), 7.52 (t, 1H, *J* 8.0 Hz), 7.49 (t, 2H, *J* 7.2 Hz), 7.08 (m, 4H), 5.30 (br, 1H, OH), 4.63 (s, 2H, $CH_2$), 2.51 (s, 3H, $CH_3$). $^{13}$C NMR **(**DMSO-$d_6$): 190.7, 141.3, 140.5, 138.5, 131.1, 130.7, 129.9, 129.7, 127.6, 114.1, 52.6, 20.3. LCMS *m/z* = 269 (M + 1). *Anal. calcd.* for $C_{16}H_{16}N_2O_2$ (268.3): C 71.62; H 6.01; N 10.44. Found: C 71.54; H 6.00; N 10.42.

**2-*p*-Chlorophenyhydrazono-3-hydroxy-1-phenylpropan-1-one (3c)**. Yield 2.1g (73%), method A, 2.7 g (94%), method B, yellow crystals from benzene, mp 166-168 ºC (lit.[22] mp 166-167 ºC). IR: 3379, 3307, 3056, 2969, 1633, 1551, 1486, 1362, 1251, 968, 728. $^1$H NMR (DMSO-$d_6$): 10.75 (br, 1H, NH), 7.80 (d, 2H, *J* 7.8 Hz), 7.56 (t, 1H, *J* 7.6 Hz), 7.50 (t, 2H, *J* 7.4 Hz), 7.32 (d, 2H, *J* 8.8 Hz), 7.16 (d, 2H, *J* 8.8 Hz), 5.33 (br, 1H, OH), 4.61 (s, 2H, $CH_2$). $^{13}$C NMR ($CDCl_3$): 191.2, 141.6, 139.6, 137.4, 131.8, 130.5, 129.4, 127.8, 127.5, 115.5, 57. MS: *m/z* (%) 288 ($M^+$, 20), 202 (50), 139 (85). Anal. calcd for $C_{15}H_{13}ClN_2O_2$ (288.7): C 62.40; H 4.54; N 9.70. Found: C 62.24; H 4.50; N 9.59.

**2-Arylhydrazono-3-oxo-3-phenylpropanals (1a-c). General procedure**

A mixture of each of **3a-c** (10.0 mmol) in nitrobenzene (10 mL) was refluxed for 2 h or irradiated in a microwave oven for 2 min at 140 ºC. After cooling, petroleum ether (50 mL) was added and the solid formed was collected by filtration and recrystallized from ethanol to yield **1a-c** in 65-70% yield.

**3-Oxo-3-phenyl-2-phenylhydrazonopropanal (1a).** Yield 1.64 g (65%), yellow crystals from EtOH, mp 82-83 ºC (lit.[15] mp. 82-84 ºC). LCMS: *m/z* = 253 (M + 1).

**3-Oxo-3-phenyl-2-*p*-tolylhydrazonopropanal (1b).** Yield 1.8 g (67%), red crystals from EtOH, mp 116-118 ºC (lit.[15] mp 115-17 ºC). LCMS: *m/z* = 267 (M + 1)

**2-*p*-Chlorophenylhydrazono-3-oxo-3-phenylpropanal (1c).** Yield 2.0 g (70%), red crystals from EtOH, mp 142-144 ºC (lit.[15] mp 143-45 ºC). LCMS: *m/z* = 286 (M + 1), 288 (M + 2)

**1-(6-Benzoyl-5-hydroxy-2-phenyl-2,3,4,5-tetrahydropyridazin-4-yl)ethanone (5).** A mixture of compound **1a** (0.50 g, 2.0 mmol), methyl vinyl ketone (0.3 g, 4.0 mmol,) and DABCO (0.224 g, 2.0 mmol) was mixed then placed in a microwave oven and irradiated at 100 ºC for 1 min. The mixture was then washed with hot petroleum ether (60-80) and crystallized from ethanol to give **5**. Yield 0.50 g (78%) yellow crystals from EtOH, mp 215-217 ºC. IR: 3359, 3063, 2906, 1704, 1627, 1549, 1493, 1334, 1271, 1222, 1175, 1065, 957, 876. $^1$H NMR ($CDCl_3$): 8.00 (dd, 2H, *J* 7.8, 1.6 Hz), 7.56 (t, 1H, *J* 7.6 Hz), 7.48 (t, 2H, *J* 7.4 Hz), 7.37 (m, 4H), 7.11 (m, 1H), 5.36 (m, 1H), 4.23 (dd, 1H, *J* 13.2 Hz), 3.74 (t, 1H, *J* 13.2 Hz), 3.13 (br, 1H, OH), 2.88 (dd, 1H, *J* 13.2 Hz), 2.45 (s, 3H). $^{13}$C NMR ($CDCl_3$): 204.7, 191.5, 145.6, 139.5, 137.2, 131.9, 130.5, 129.3, 127.9, 123.8, 116.1, 57.6, 46.8, 39.6, 28.5. MS: *m/z* (%) 322 ($M^+$, 60), 304 (20), 105 (85). *Anal. calcd.* for $C_{19}H_{18}N_2O_3$ (322.4): C 70.79; H 5.63; N 8.69. Found: C 70.52; H 5.63; N 8.66.

**1-(6-Benzoyl-2-phenyl-2,3-dihydropyridazine-4-yl)ethanone (6).** A mixture of **5** (0.32 g, 1.0 mmol), in acetic acid (5 mL), was placed in a microwave and irradiated at 160 ºC for 5 min. After cooling ice water (10 mL) was added and the yellow precipitate so formed was collected and crystallized from ethanol to give **6** in 0.28 g (93%), mp.160-162 ºC (lit.[15] mp160-162 ºC). $^1$H NMR ($CDCl_3$): 8.00 (d, 2H, *J* 8.0 Hz), 7.69 (s, 1H), 7.57 (t, 1H, *J* 7.8 Hz), 7.48 (t, 2H, *J* 7.6 Hz), 7.42 (m, 4H), 7.22 (m, 1H), 4.74 (s, 2H), 2.54 (s, 3H). $^{13}$C NMR ($CDCl_3$) 196.7, 189.0, 144.5, 137.1, 136.5, 132.0, 130.5, 129.3, 127.9, 127.5, 124.9, 123.3, 116.4, 43.7, 25.2. *Anal. calcd.* for $C_{19}H_{16}N_2O_2$ (304.4): C 74.93; H 5.30; N 9.20. Found: C 74.85; H 5.23; N 9.16. Crystal data: a = 9.7094(3), b = 10.0166(3), c = 16.0286(12) Å; α = 82.833(6), β = 86.536(6), γ = 84.749(6)°; space group P1; CCDC number 805703.

**3-Benzoyl-1,6-diphenyl-1,2-dihydropyrrolo[3,4-*c*]pyridazine-5,7-dione (8).** A mixture of compound **1a** (0.225 g, 1.0 mmol), *N*-phenylmaleimide (0.173 g, 1.0 mmol), DABCO (0.224 g, 2.0 mmol) and diphenyl ether (2.0 g) were microwave irradiated at 200 ºC for 5 min. The mixture was then washed with hot petroleum ether (60-80) and crystallized from DMF to give **8** as yellow crystals, yield 0.30 g (73%), mp 253-255 ºC. IR: 3359, 3063, 2906, 1704, 1627, 1549, 1493, 1334, 1271, 1222, 1175, 1065, 957, 876. $^1$H NMR ($CDCl_3$) 10.45 (br, 1H, NH), 9.70 (s, 1H), 7.90 (d, 2H, *J* 7.6 Hz), 7.80 (d, 2H, *J* 7.8 Hz), 7.61 (tt, 2H, *J* 7.8, 1.2 Hz), 7.56-7.48 (m, 6H), 7.39 (m, 2H), 7.31 (tt, 1H, *J* 7.8, 1.2 Hz). $^{13}$C NMR ($CDCl_3$): 195.6, 171.3, 168.4, 137.2, 131.9, 129.7, 129.1, 128.3, 127.7, 126.8, 126.3, 125.7, 125.5, 123.8, 121.9, 121.5, 119.4, 101.7, 96.9. LCMS: *m/z* = 408 (M + 1). MS: *m/z* (%) 407 ($M^+$, 100), 379 (20), 287 (25). *Anal. calcd.* for $C_{25}H_{17}N_3O_3$ (407.4): C 73.70; H 4.21; N 10.31. Found: C 73.59; H 4.13; N 10.26. HRMS = 407.1264 ($C_{25}H_{17}N_3O_3$ requires 407.1264)

**3-Amino-6-benzoyl-2,5-dihydropyridazine derivatives (10a-f)**. **General procedures**

**Method A.** A mixture of each of **2a-c** (2.0 mmol) and benzylidenemalononitrile and/or ethyl 2-cyanocinnamate (2.0 mmol) in ethanol (20 mL) and piperidine (5 drops) or β-chitosan (0.2 g, 13 mmol) was refluxed for 5 hours, the mixture was then poured into ice water (50 mL) and acidified with conc. HCl (2 mL). The yellow precipitate so formed was collected by filtration and crystallized from ethanol to yield compounds **10a-f**.

**Method B.** A mixture of each of **2a-c** (2.0 mmol), and benzylidenemalononitrile and/or ethyl 2-cyanocinnamate (2.0 mmol) in dioxane (5 mL) and piperidine (5 drops) or β-chitosan (0.2 g, 13 mmol) was mixed and placed in a microwave oven and irradiated at 160 ºC for 5 minutes. The mixture was then poured into ice water (50 mL) and acidified with conc. HCl (2 mL). The yellow precipitate was collected and crystallized from ethanol.

**3-Amino-6-benzoyl-2,5-diphenyl-2,5-dihydropyridazine-4-carbonitrile (10a).** Yield 0.56 g (74%) method A, 0.6 g (79%) method B, yellow crystals from EtOH, mp 163-164 ºC. IR: 3456, 3336, 3059, 2185, 1637, 1593, 1568, 1491, 1410, 1247, 1141. $^1$H NMR ($CDCl_3$): 7.92 (dd, 2H, *J* 7.6, 1.2 Hz), 7.53-7.34 (m, 13H), 5.27 (s, 1H), 4.37 (br, 2H, $NH_2$). $^{13}$C NMR ($CDCl_3$): 190.3, 149.4, 145.1, 141.0, 139.6, 136.2, 132.7, 130.5, 129.8, 129.2, 128.4, 128.0, 127.7, 127.4, 125.4, 119.8, 60.0, 37.0. LCMS: *m/z* = 379 (M + 1). MS: *m/z* (%) 378 ($M^+$, 10), 301 (25), 273 (100). *Anal. calcd.* for $C_{24}H_{18}N_4O$ (378.4): C 76.17; H 4.79; N 14.80. Found: C 76.12; H 4.79; N 14.65.

**3-Amino-6-benzoyl-5-phenyl-2-*p*-tolyl-2,5-dihydropyridazine-4-carbonitrile (10b).** Yield 0.57 g (73%) method A, 0.6 g (76%) method B, yellow crystals from EtOH, mp 198-200 ºC. IR: 3454, 3323, 3056, 2181, 1649, 1599, 1565, 1509, 1403, 1250, 1128, 872, 718, 698. $^1$H NMR ($CDCl_3$): 7.92 (dd, 2H, *J* 8.4, 1.2 Hz), 7.49 (tt, 1H, *J* 7.6, 1.2 Hz), 7.39-7.27 (m, 11H), 5.25 (s, 1H), 4.39 (br, 2H, $NH_2$), 2.42 (s, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$): 190.3, 149.6, 144.8, 141.2, 138.7, 137.1, 136.3, 132.5, 130.5, 130.4, 129.1, 127.9, 127.6, 127.2, 125.5, 119.9, 59.6, 37.0, 21.1. LCMS: *m/z* = 393 (M + 1). MS: *m/z* (%) 392 ($M^+$, 20), 315 (45), 287 (100), 105 (75). *Anal. calcd.* for $C_{25}H_{20}N_4O$ (392.5): C 76.51; H 5.14; N 14.28. Found: C 76.42; H 5.19; N 14.25.

**3-Amino-6-benzoyl-2-*p*-chlorophenyl-5-phenyl-2,5-dihydropyridazine-4-carbonitrile (10c).** Yield 0.60 g (73%) method A, 0.68 g (82%) method B, yellow crystals from EtOH, mp 203-204 ºC. IR: 3469, 3324, 3059, 2189, 1641, 1592, 1567, 1488, 1423, 1245, 1142, 873, 700. $^1$H NMR ($CDCl_3$): 7.90 (dd, 2H, *J* 8.4, 1.2 Hz), 7.53 (tt, 1H, *J* 7.6, 1.2 Hz), 7.48-7.29 (m, 11H), 5.26 (s, 1H), 4.42 (br, 2H, $NH_2$). $^{13}$C NMR ($CDCl_3$): 190.2, 149.3, 145.5, 140.7, 138.1, 136.1, 134.1, 132.7, 130.4, 129.9, 129.2, 128.0, 127.8, 127.1, 126.6, 119.6, 60.4, 37.2. LCMS: *m/z* = 413 (M + 1). MS: *m/z* (%) 414 (M + 2, 10), 412 ($M^+$ , 10), 335 (25), 307 (100), 105. *Anal. calcd.* for $C_{24}H_{17}ClN_4O$ (412.9): C 69.82; H 4.15; N 13.57. Found: C 69.72; H 4.19; N 13.45.

**3-Amino-6-benzoyl-2,5-diphenyl-2,5-dihydropyridazine-4-carboxylic acid ethyl ester (10d)**. Yield 0.66 g (77%), method A, 0.73 g (86%), method B, yellow crystals from EtOH, mp 168-170 ºC. IR: 3477, 3275, 3053, 1665, 1627, 1515, 1479, 1373, 1271, 1125, 1094. $^1$H NMR ($CDCl_3$): 7.93 (d, 2H, *J* 7.8 Hz), 7.49 (m, 5H), 7.39 (m, 5H), 7.29 (m, 2H), 7.21 (t, 1H, *J* 7.8 Hz), 6.28 (br, 2H, $NH_2$), 5.61 (s, 1H), 4.19 (q, 2H, *J* 7.0 Hz), 1.31 (t, 3H, *J* 7.0 Hz). $^{13}$C NMR ($CDCl_3$): 190.9, 169.2, 150.3, 147.9, 142.9, 139.8, 136.7, 132.3, 130.5, 129.6, 128.6, 127.9,

127.8, 127.6, 126.8, 125.5, 77.9, 59.6, 35.9, 14.5. LCMS: *m/z* = 426 (M + 1). MS: *m/z* (%) 425 ($M^+$, 15), 352 (100), 320 (70). *Anal. calcd.* for $C_{26}H_{23}N_3O_3$ (425.5): C 73.40; H 5.45; N 9.88. Found: C 73.42; H 5.39; N 9.85.

**3-Amino-6-benzoyl-5-phenyl-2-*p*-tolyl-2,5-dihydropyridazine-4-carboxylic acid ethyl ester (10e).** Yield 0.65 g (74%), method A, 0.70 g (80%), method B, yellow crystals from EtOH, mp 188-190 ºC. IR: 3482, 3302, 3058, 1656, 1626, 1507, 1453, 1371, 1243, 1126, 1094, 898. $^1$H NMR ($CDCl_3$): 7.92 (dd, 2H, *J* 8.4, 1.2 Hz), 7.49 (tt, 1H, *J* 7.6, 1.2 Hz), 7.39-7.34 (m, 5H), 7.31-7.27 (m, 5H), 7.21 (tt, 1H, *J* 7.8, 1.2 Hz), 6.27 (br, 2H, $NH_2$), 5.60 (s, 1H), 4.18 (q, 2H, *J* 7.0 Hz), 2.44, (s, 3H), 1.31 (t, 3H, *J* 7.0 Hz). $^{13}$C NMR ($CDCl_3$): 191.0, 169.3, 150.4, 147.6, 143.1, 138.1, 137.3, 136.8, 132.2, 130.5, 130.3, 128.6, 127.8, 127.6, 126.8, 125.6, 77.6, 59.6, 35.9, 21.1, 14.5. LCMS: *m/z* = 440 (M + 1). MS: *m/z* (%) 439 ($M^+$, 20), 366 (100), 334 (70), 105 (85). *Anal. calcd.* for $C_{27}H_{25}N_3O_3$ (439.5): C 73.79; H 5.73; N 9.56. Found: C 73.62; H 5.69; N 9.55.

**3-Amino-6-benzoyl-2-*p*-chlorophenyl-5-phenyl-2,5-dihydropyridazine-4-carboxylic acid ethyl ester (10f).** Yield 0.70 g (76%) method A, 0.76 g (83%) method B, yellow crystals from EtOH, mp 176-178 ºC. IR: 3483, 3285, 3059, 1658, 1618, 1493, 1370, 1242, 1125, 1083, 895, 704. $^1$H NMR ($CDCl_3$): 7.89 (dd, 2H, *J* 8.4, 1.2 Hz), 7.51 (t, 1H, *J* 7.4 Hz), 7.44 (m, 3H), 7.43-7.34 (m, 4H), 7.29 (m, 3H), 7.21 (t, 1H, *J* 7.2 Hz), 6.24 (br, 2H, $NH_2$), 5.62 (s, 1H), 4.18 (q, 2H, *J* 7.0 Hz), 1.31 (t, 3H, *J* 7.0 Hz). $^{13}$C NMR ($CDCl_3$): 190.9, 169.1, 150.0, 148.3, 142.6, 138.3, 136.6, 133.5, 132.4, 130.4, 129.8, 128.7, 127.9, 127.5, 126.9, 126.7, 78.4, 59.8, 36.0, 14.5. MS: *m/z* (%) 461 ($M^+$ + 2, 10), 460 (($M^+$ + 1, 30), 386 (30), 270 (100). *Anal. calcd.* for $C_{26}H_{22}ClN_3O_3$ (459.9): C 67.90; H 4.82; N 9.14. Found: C 67.88; H 4.79; N 9.15.

**6-Benzoyl-3-oxo-2,3-dihydopyridazine-4-carbonitrile (11a-c). General procedure**

A mixture of each of **10a-c** (2.0 mmol) in acetic acid (10 mL) and hydrochloric acid (5 mL) was refluxed for 4 h. The mixture was then poured into ice water (50 mL) and the yellow precipitate so formed was collected by filtration and recrystallized from ethanol to give **11a-c**.

**6-Benzoyl-3-oxo-2,5-diphenyl-2,3-dihydopyridazine-4-carbonitrile (11a).** Yield 0.42 g (56%) yellow crystals from EtOH, mp 258-260 ºC. IR: 3057, 3028, 2231, 1671, 1595, 1492, 1447, 1372, 1327, 1303, 1229, 1192, 1166, 1088, 990, 911, 869. $^1$H NMR ($CDCl_3$): 7.93 (dd, 2H, *J* 8.4, 1.4 Hz), 7.69 (dd, 2H, *J* 8.0, 1.2 Hz), 7.65 (t, 2H, *J* 7.8 Hz), 7.54-7.39 (m, 9H)). $^{13}$C NMR ($CDCl_3$): 188.5, 164.2, 156.1, 151.1, 143.6, 140.0, 135.0, 134.6, 131.2, 131.0, 130.4, 129.2, 129.1, 128.9, 128.8, 128.1, 124.9, 114.9. MS: *m/z* (%) 377 ($M^+$, 75), 348 (10), 105 (100). *Anal. calcd.* for $C_{24}H_{15}N_3O_2$ (377.4): C 76.38; H 4.01; N 11.13. Found: C 76.32; H 3.99; N 11.15.

**6-Benzoyl-3-oxo-5-phenyl-2-*p*-tolyl-2,3-dihydropyridazine-4-carbonitrile (11b).** Yield 0.46 g (59%) yellow crystals from EtOH, mp 228-230 ºC. IR: 3065, 3035, 2199, 1667, 1597, 1566, 1493, 1449, 1327, 1191, 1166, 870. $^1$H NMR ($CDCl_3$): 7.92 (dd, 2H, *J* 8.0, 1.4 Hz), 7.63 (t, 1H, *J* 7.8 Hz), 7.58-7.44 (m, 3H), 7.43-7.37 (m, 6H), 7.30 (d, 2H, *J* 8.0 Hz), 2.42 (s, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$): 188.5, 164.5, 156.1, 150.9, 143.4, 137.6, 135.7, 135.1, 134.1, 131.1, 130.4, 130.3, 129.6, 129.1, 128.8, 128.1, 124.6, 114.7, 21.2. MS: *m/z* (%) 391 ($M^+$, 30), 366 (25), 105

(100). *Anal. calcd.* for $C_{25}H_{17}N_3O_2$ (391.4): C 76.71; H 4.38; N 10.73. Found: C 76.62; H 4.29; N 10.65.

**6-Benzoyl-2-*p*-chlorophenyl-3-oxo-5-phenyl-2,3-dihydropyridazine-4-carbonitrile (11c).** Yield 0.45 g (55%), yellow crystals from EtOH, mp 236-238 $^{o}$C. IR: 3066, 3038, 2229, 1668, 1596, 1490, 1449, 1328, 1192, 1167, 1092, 834, 759, 688. $^{1}$H NMR ($CDCl_3$): 7.99 (dd, 2H, *J* 8.4, 1.4 Hz), 7.67 (m, 2H), 7.56-7.39 (m, 9H), 7.31 (t, 1H, *J* 7.8 Hz). $^{13}$C NMR ($CDCl_3$): 189.3, 165.9, 156.7, 151.3, 145.1, 144.0, 138.2, 137.1, 134.7, 133.9, 131.8, 130.7, 129.1, 128.8, 128.4, 128.0, 125.6, 115.2. MS: *m/z* (%) 413 (M + 2, 50), 412 ($M^+$ 1, 60), 386 (25), 105 (100). *Anal. calcd.* for $C_{24}H_{14}ClN_3O_2$ (411.8): C 69.99; H 3.43; N 10.20. Found: C 69.90; H 3.39; N 10.15.

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