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 °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 century1 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-phenylethanol derivatives 2a-c (Scheme 2). Arylhydrazonal 1a was converted into a pyridazine via a Baylis-Hillman reaction with methyl vinyl ketone; we interpreted this 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. 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 °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-dihydropyrrololo[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 °C for five minutes. We have recently reported that β-chitosan is an efficient basic catalyst for a variety of Michael additions.\textsuperscript{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.\textsuperscript{16b,c}

![Chemical structure]

\[
\begin{align*}
\text{Compd.} & \quad \text{Ar} & \quad X & \quad 10 \ (\% \ yield) & \quad 11 \ (\% \ yield) \\
10,11a & \quad C_6H_5 & \quad \text{CN} & \quad 79 & \quad 56 \\
10,11b & \quad C_6H_4CH_3(p) & \quad \text{CN} & \quad 76 & \quad 58 \\
10,11c & \quad C_6H_4Cl(p) & \quad \text{CN} & \quad 82 & \quad 55 \\
10d & \quad C_6H_5 & \quad \text{CO}_2\text{Et} & \quad 86 & \quad - \\
10e & \quad C_6H_4CH_3(p) & \quad \text{CO}_2\text{Et} & \quad 80 & \quad - \\
10f & \quad C_6H_4Cl(p) & \quad \text{CO}_2\text{Et} & \quad 83 & \quad - \\
\end{align*}
\]

\textbf{Scheme 5}

\textbf{Conclusions}

The synthetic approach to arylhydrazonals described here is more efficient and more atom economic than the original approach of coupling enaminoles with arylhydrazonium 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 $^\circ$C 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 $^\circ$C 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$_2$O mp 146-148 $^\circ$C (lit.$^{18}$ mp 148-150 $^\circ$C). $^1$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$_2$O (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 $^\circ$C (lit.$^{19}$ mp 115-117 $^\circ$C). $^1$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$_2$O (238.3): C 74.74; H 5.39; N 11.76. Found: C 74.68; H 5.31; N 11.73.

**2-p-Chlorophenylhydrazono-1-phenylethanone (2c).** Yield 11.0 g (88%), yellow crystals from EtOH, mp 148-150 $^\circ$C (lit.$^{20}$ mp 147-148 $^\circ$C). 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$_2$O (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 montmorillonite 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 °C (lit.21 mp 126-127 °C).

General procedures

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/H2O, mp 164-165 °C. IR: 3438, 3184, 3056, 2961, 1638, 1566, 1449, 1240, 968, 728. 1H NMR (DMSO-d6): 10.55 (s, 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, CH2), 2.51 (s, 3H, CH3). 13C NMR (DMSO-d6): 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 C15H14N2O2 (254.3): C 70.85; H 5.55; N 11.02. Found: C 70.74; H 5.51; N 11.03.

2-p-Chlorophenylhydrazono-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 °C (lit.22 mp 166-167 °C). IR: 3379, 3307, 3056, 2969, 1633, 1551, 1486, 1362, 1251, 968, 728. 1H NMR (DMSO-d6): 10.75 (s, 1H, NH), 7.80 (d, 2H, J 8.2 Hz), 7.56 (b, 1H, J 7.6 Hz), 7.50 (t, 2H, J 8.4 Hz), 7.32 (d, 2H, J 8.8 Hz), 7.16 (d, 2H, J 8.8 Hz), 3.53 (br, 1H, OH), 4.61 (s, 2H, CH2). 13C NMR (CDCl3): 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 C15H13ClN2O2 (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 °C. 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 °C (lit. mp 82-84 °C). 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 °C (lit. mp 115-17 °C). 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 °C (lit. mp 143-45 °C). LCMS: m/z = 286 (M + 1), 288 (M + 2)

1-(6-Benzoyl-5-hydroxy-2-phenyl-2,3,4,5-tetrahydropyridazin-4-yl)ethane (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 °C 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 °C. IR: 3359, 3063, 2960, 1704, 1627, 1549, 1493, 1334, 1271, 1222, 1175, 1065, 957, 876. 1H NMR (CDCl3): 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). 13C NMR (CDCl3): 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 C19H18N2O3 (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)ethane (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 °C 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 °C (lit. mp160-162 °C). 1H NMR (CDCl3): 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). 13C NMR (CDCl3): 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 C19H16N2O3 (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 °C for 1 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 °C. IR: 3359, 3063, 2906, 1704, 1627, 1549, 1493, 1334, 1271, 1222, 1175, 1065, 957, 876. 1H NMR (CDCl3) 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). 13C NMR (CDCl3): 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 C25H17N3O3 (407.4): C 73.70; H 4.21; N 10.31. Found: C 73.59; H 4.13; N 10.26. HRMS = 407.1264 (C25H17N3O3 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 benzylidemalononitrile 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 benzylidemalononitrile 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 °C 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 °C. IR: 3456, 3336, 3059, 2185, 1637, 1593, 1568, 1491, 1410, 1247, 1141. 1H NMR (CDCl3): 7.92 (dd, 2H, J 7.6, 1.2 Hz), 7.53-7.34 (m, 13H), 5.27 (s, 1H), 4.37 (br, 2H, NH2). 13C NMR (CDCl3): 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 C25H18N4O (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 °C. IR: 3454, 3323, 3056, 2181, 1649, 1599, 1565, 1509, 1403, 1250, 1128, 872, 718, 698. 1H NMR (CDCl3): 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, NH2), 2.42 (s, 3H, CH3). 13C NMR (CDCl3): 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 C25H20N4O (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 °C. IR: 3469, 3324, 3059, 2189, 1641, 1592, 1567, 1488, 1423, 1245, 1142, 873, 700. 1H NMR (CDCl3): 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, NH2). 13C NMR (CDCl3): 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 (%) 412 (M+, 10), 412 (M+, 10), 335 (25), 307 (100), 105. Anal. calcd. for C24H17ClN4O (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 °C. IR: 3477, 3275, 3053, 1665, 1627, 1515, 1479, 1373, 1271, 1125, 1094. 1H NMR (CDCl3): 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, NH2), 5.61 (s, 1H), 4.19 (q, 2H, J 7.0 Hz), 1.31 (t, 3H, J 7.0 Hz). 13C NMR (CDCl3): 190.9, 169.2, 150.3, 147.9, 142.9, 139.8, 136.7, 132.3, 130.5, 129.6, 128.6, 127.9,
26.8, 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 C₂₆H₂₃N₃O₃ (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 °C. IR: 3482, 3302, 3058, 1656, 1626, 1507, 1453, 1371, 1243, 1126, 1094, 898. ¹H NMR (CDCl₃): 7.92 (dd, 2H, J 8.4, 12.2 Hz), 7.49 (tt, 1H, J 7.6, 12.2 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, NH₂), 5.60 (s, 1H), 4.18 (q, 2H, J 7.0 Hz), 2.44 (s, 3H), 1.31 (t, 3H, J 7.0 Hz). ¹³C NMR (CDCl₃): 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 C₂₇H₂₅N₃O₃ (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-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 °C. IR: 3483, 3285, 3059, 1658, 1618, 1493, 1370, 1242, 1125, 1083, 895, 704. ¹H NMR (CDCl₃): 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, NH₂), 5.62 (s, 1H), 4.18 (q, 2H, J 7.0 Hz), 1.31 (t, 3H, J 7.0 Hz). ¹³C NMR (CDCl₃): 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 C₂₇H₂₅ClN₃O₃ (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-dihydropyridazine-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-dihydropyridazine-4-carbonitrile (11a). Yield 0.42 g (56%) yellow crystals from EtOH, mp 258-260 °C. IR: 3057, 3028, 2231, 1671, 1595, 1492, 1447, 1372, 1327, 1303, 1229, 1192, 1166, 1088, 990, 911, 869. ¹H NMR (CDCl₃): 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)). ¹³C NMR (CDCl₃): 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 C₂₄H₁₅N₃O₂ (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 °C. IR: 3065, 3035, 2199, 1667, 1597, 1566, 1493, 1449, 1327, 1191, 1166, 870. ¹H NMR (CDCl₃): 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, CH₃). ¹³C NMR (CDCl₃): 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$_3$O$_2$ (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-dihydropyrazidine-4-carbonitrile** (11c). Yield 0.45 g (55%), yellow crystals from EtOH, mp 236–238 °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$_3$O$_2$ (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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**References**

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