

**4-ACYLHYDRAZINOMETHYLENE-2-PHENYLOXAZOL-5(4H)-ONES
AS ACYLATING AGENTS: SYNTHESIS OF SALICYLANILIDES AND
1,2,4-TRIAZOLO[4,3-*b*]PYRIDAZINES[#]**

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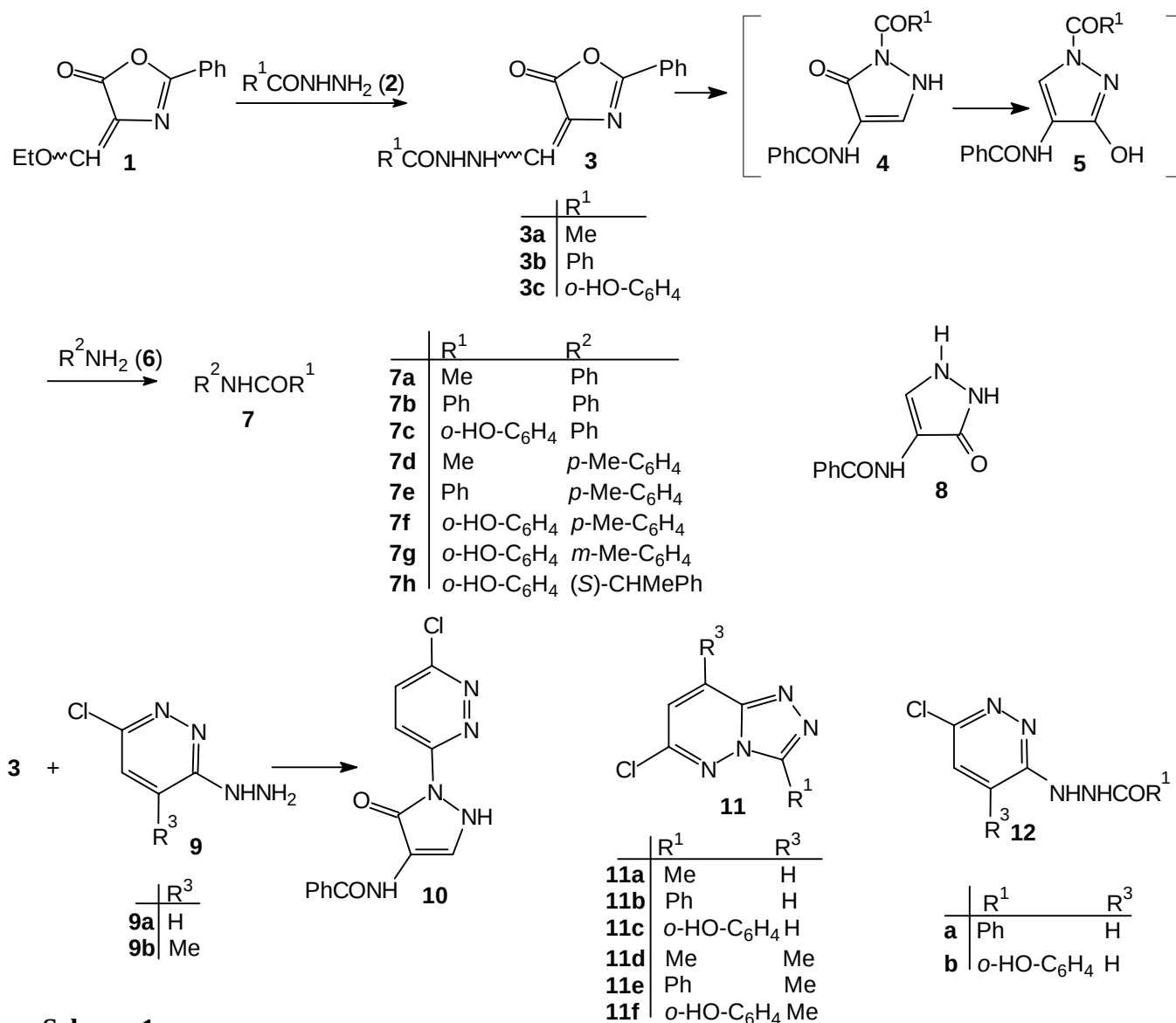
Abstract – A simple and general method for the acylation of an amino or hydrazino group by the application of hydrazides has been developed. It starts from hydrazides (**2**), which are converted with 4-ethoxymethylene-2-phenyloxazol-5(4H)-one (**1**) to the corresponding 4-acylhydrazinomethylene-2-phenyloxazol-5(4H)-ones (**3**). The latter react with nitrogen-containing nucleophiles in 1,4-dioxane in the presence of triethylamine or zirconium(IV) chloride to give the corresponding amides (**7**) or mixtures of hydrazides (**12**) and 1,2,4-triazolo[4,3-*b*]pyridazines (**11**). Upon prolonged heating, compounds (**11**) are the main products.

Acylation is a very important reaction in organic chemistry.¹ Acyl groups serve as protecting groups,² they are fragments in biomolecules³ and other important natural products like peptides,^{4,5} etc. 1,2,4-Triazolo[4,3-*b*]pyridazines can be prepared from different starting compounds.⁶ Recently, we have described a very convenient synthesis of various 1-acyl-3-hydroxy-1H-pyrazoles as well as a method for the synthesis of various symmetrically *N,N'*-disubstituted hydrazines starting from 4-ethoxymethylene-2-phenyloxazol-5(4H)-one and hydrazides, 4-phenylsemicarbazide, 4-phenylthiosemicarbazide and benzyl carbazate in boiling dioxane.⁷ The method represents a possible way for the activation of hydrazides, which are not known as useful donors of acyl units due to their high resonance stability. We also described a general application of 1-acyl-3-hydroxy-1H-pyrazoles as convenient acylating agents for alcohols or phenols, amines and hydrazines; an application of a hydrazide for a direct acylation of an alcohol in the presence of

[#] Dedicated to Professor Sho Ito, Professor of Bunri University of Tokushima, on the occasion of his 77th birthday.

4-ethoxymethylene-2-phenyloxazol-5(4*H*)-one was also briefly discussed.⁸

As a continuation of our research in this field we report here a novel employment of our acylating system for the preparation of different amides as well as 1,2,4-triazolo[4,3-*b*]pyridazines *via* the corresponding



Scheme 1

hydrazides (Scheme 1). Our idea was to trap an acyl group while it was migrating from one ring nitrogen to the other, *i.e.* during the transformation of the intermediate (**4**) to **5**. In the first step we transformed hydrazides (**2**) into acylhydrazinomethylene derivatives (**3**) by the application of the oxazolone derivative (**1**) at room temperature or by heating at 60 °C in a methanolic solution. The derivatives (**3**) are stable compounds and can be stored at room temperature for a longer period of time. In the second step, derivatives (**3**) reacted with various amines (**6**) to give products (**7**) in 29–93% yields (Table 1). The reactions were carried out in boiling 1,4-dioxane and in the presence of triethylamine or zirconium(IV) chloride as a catalyst. The side-product in this reaction was the pyrazolone derivative (**8**), which was separated from

products (**7**) by column chromatography, by an extraction or by a filtration. The method represents an alternative for the synthesis of the antifungal agent salicylanilide (**7c**)⁹ and related compounds.

Table 1. Reaction conditions and yields of products (**7a–h**):

Run	Substrate 3 (mmol)	6 (R ² =, mmol)	Catalyst (mmol); (h)	Product (yield, %) ^a
1	3a (1)	Ph (1.1)	NEt ₃ (1.07); 1	7a (41)
2	3b (1)	Ph (1.1)	NEt ₃ (1.07); 5	7b (29)
3	3c (1)	Ph (1.1)	NEt ₃ (1.2); 4	7c (67)
4	3a (1)	Ph (1.1)	ZrCl ₄ (0.15); 0.5	7a (84)
5	3b (1)	Ph (1.1)	ZrCl ₄ (0.15); 1	7b (67)
6	3c (1)	Ph (1.1)	ZrCl ₄ (0.15); 1	7c (73)
7	3a (1)	<i>p</i> -Me-C ₆ H ₄ (1)	ZrCl ₄ (0.15); 1	7d (93)
8	3b (1)	<i>p</i> -Me-C ₆ H ₄ (1)	ZrCl ₄ (0.15); 1	7e (72)
9	3c (1)	<i>p</i> -Me-C ₆ H ₄ (1)	ZrCl ₄ (0.15); 1	7f (86)
10	3c (1)	<i>m</i> -Me-C ₆ H ₄ (1)	ZrCl ₄ (0.15); 1	7g (72)
11	3c (1)	(<i>S</i>)-CHMePh (1)	ZrCl ₄ (0.15); 0.5	7h (67)

^aYields of TLC-pure products.

We wanted to apply the same methodology for the preparation of fused 1,2,4-triazolo[4,3-*b*]pyridazines (**11**) starting from oxazolone derivatives (**3**) and hydrazinopyridazines (**9**). Our first attempts to prepare products (**11a,b**) from oxazolones (**3a,b**) and 3-chloro-6-hydrazinopyridazine (**9a**) in 1,4-dioxane in the absence of a catalyst failed; the pyrazolone derivative (**10**) was isolated in a 45-54% yield instead (Table 2, runs 1, 2). In a mixture of 1,4-dioxane and pyridine, product (**11a**) was isolated in a 79% yield after 4 h of heating (run 3). The reaction was strongly accelerated in the presence of a catalytic amount of zirconium(IV) chloride and product (**11a**) was isolated in a 85% yield after 15 min of heating (run 4). The same methodology was also used for the synthesis of other representatives of 1,2,4-triazolo[4,3-*b*]pyridazines. In the case of starting **3b** and **3c** we isolated, after a short heating period (15 min to 1 h), intermediates (**12a**) and (**12b**) in addition to products (**11b**) and (**11c**). A prolonged heating period improved the yields of products of type (**11**).

The reaction towards the formation of the pyrazolone derivative (**10**) can be explained by the substitution of the acylhydrazino moiety in compounds (**3**) with the nucleophilic nitrogen of the 3-chloro-6-hydrazinopyridazine (**9a**) followed by the nucleophilic attack of the second nitrogen of the hydrazino group at position 5 of the oxazolone ring yielding product (**10**). A similar preparation of pyrazolone derivatives from 4-dimethylaminomethylene-2-pyrazinyloxazol-5(4*H*)-one and related methyl 3-dimethylamino-2-

(pyrazinylcarbonylamino)propenoate has been recently described.¹⁰ On the other side, in the presence of either pyridine or zirconium(IV) chloride the acyl group of a derivative (**3**), which is (most probably) first transformed into the intermediate (**4**) (or possibly also **5**) is migrating onto the hydrazino group in the pyridazine derivative (**9**), thus yielding first products (**12**) and, after their cyclisation, the corresponding 1,2,4- triazolo[4,3-*b*]pyridazines (**11a–f**). It is also clearly evident that acidic zirconium(IV) chloride is much more efficient than basic triethylamine.

Table 2. Reaction conditions and yields of the products (**10–12**):

Run	Substrate 3 (mmol)	Compd 9 (mmol)	Catalyst (mmol); Δ (h)	Product (yield, %) ^a
1	3a (0.4)	9a (0.4)	-; 2	10 (54)
2	3b (0.4)	9a (0.4)	-; 2	10 (45)
3	3a (0.4)	9a (0.4)	-; 4	11a (79) ^b
4	3a (1)	9a (1)	ZrCl ₄ (0.15); 0.25	11a (85)
5	3b (1)	9a (1)	ZrCl ₄ (0.15); 0.25	11b (26)+ 12a (66)
6	3b (1)	9a (1)	ZrCl ₄ (0.15); 23	11b (73)
7	3c (1)	9a (1)	ZrCl ₄ (0.15); 1	11c (26)+ 12b (71)
8	3c (1)	9a (1)	ZrCl ₄ (0.15); 23	11c (67)+ 12b (29)
9	3a (1)	9b (1)	ZrCl ₄ (0.15); 1	11d (78)
10	3b (1)	9b (1)	ZrCl ₄ (0.15); 1	11e (78)
11	3c (1)	9b (1)	ZrCl ₄ (0.15); 1	11f (70)

^aYields of TLC-pure products. ^bThe reaction was carried out in a mixture of 1,4-dioxane and pyridine.

In conclusion, we have described 4-acylhydrazinomethylene-2-phenyloxazol-5(4*H*)-ones as sources of acyl units and developed novel methodologies for the synthesis of different amides and 1,2,4-triazolo[4,3-*b*]pyridazines. The main advantages of this method are easily available, cheap and stable chemicals and relatively mild reaction conditions. Zirconium(IV) chloride has proven once again its interesting catalytic activity¹¹ by changing the selectivity of reactions between oxazolones (**3**) and hydrazines or amines. It was obviously much more efficient as a catalyst than triethylamine or pyridine.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage, and are uncorrected. ¹H and ¹³C NMR spectra were recorded in DMSO-*d*₆ with the Bruker Avance DPX 300 spectrometer, using TMS as an internal standard. The coupling constants (*J*) are given in Hz. IR spectra were obtained with a Perkin

Elmer FT-IR spectrophotometer Spectrum 1000. MS spectra were recorded with a VG-Analytical AutoSpec Q instrument. Elemental analyses (C, H, N) were performed with a Perkin Elmer 2400 CHN Analyzer. Thin-layer chromatography was carried out on Fluka silica gel TLC-cards. Fluka Silica gel 60 (220–440 mesh) was used for the column chromatography.

General procedure for the preparation of 4-acylhydrazinomethylene-2-phenyloxazol-5(4H)-ones (3a–c):

A mixture of 4-ethoxymethylene-2-phenyloxazol-5(4H)-one (**1**) (434 mg, 2 mmol) and a hydrazide (**2a–c**) (2 mmol) in 7 mL of methanol was stirred at rt (for **3b**) or at 60 °C (for **3a** and **3c**) for 1 h. Upon cooling, the separated product was filtered off and washed with a small amount of methanol. Yields: **3a** (82%), **3b** (89%), **3c** (92%).

General procedure for the preparation of anilides (7a–c) in the presence of triethylamine:

A mixture of 4-acylhydrazinomethylene-2-phenyloxazol-5(4H)-one (**3**) (1 mmol), aniline (0.1 mL, 1.1 mmol) and NEt₃ (108–121 mg, 1.07–1.2 mmol) in 4 mL of 1,4-dioxane was refluxed for 1–5 h. Products (**7a–b**) were isolated by column chromatography (eluant: CHCl₃/MeOH 50:1). For the isolation of product (**7c**), the reaction mixture was evaporated to dryness, followed by the addition of benzene (3 mL) and CHCl₃ (1 mL). Upon cooling, the separated product was filtered off (140 mg, 69%) and identified as pyrazolone (**8**) (mp 201–203 °C; lit.,¹² 204–205 °C). The filtrate was evaporated to dryness, then 2 mL of H₂O and 1 mL of EtOH were added. Upon cooling, the separated product (**5c**) was filtered off. For yields see Table 1.

General procedure for the preparation of products (7a–h) in the presence of zirconium(IV) chloride:

A mixture of 4-acylhydrazinomethylene-2-phenyloxazol-5(4H)-one (**3**) (1 mmol), amine (**6**) (1 mmol; for R²= Ph 1.1 mmol) and ZrCl₄ (35 mg, 0.15 mmol) in 8 mL of 1,4-dioxane was refluxed for 0.5–1 h, it was then evaporated to dryness. For the isolation of the products (**7a–c**), 30 mL of CH₂Cl₂ and 25 mL of H₂O were added and the pH value was adjusted to 8–9 with solid sodium hydrogen carbonate in order to dissolve the pyrazolone (**8**). The layers were separated and the water layer was extracted with CH₂Cl₂ (6x15 mL). Collected organic layers were washed with water (2x10 mL), dried over Na₂SO₄ and concentrated *in vacuo* to give (**7a–c**); the product (**7b**) was further purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluant. For the isolation of the products (**7d–h**), the reaction mixture was purified by column chromatography and the products (**7d–h**) were obtained: the eluant for

7d, **7e** and **7g** was CHCl₃/MeOH (25:1), for **7f** and **7h** hexane/EtOAc (5:1). Yields are given in Table 1.

***N*-[1-(6-Chloropyridazin-3-yl)-1,2-dihydro-5-oxo-5*H*-pyrazol-4-yl]benzamide (**10**):**

A mixture of **3a,b** (0.4 mmol) and 3-chloro-6-hydrazinopyridazine (**9a**) (58 mg, 0.4 mmol) in 4 mL of 1,4-dioxane was refluxed for 2 h. The reaction mixture was evaporated to dryness. After the addition of MeOH (2 mL), the separated product was filtered off and identified as the pyrazolone derivative (**10**). mp 263–264 °C (AcOH); ¹H NMR δ 7.53 (m, 3H, Ph), 7.98 (m, 2H, Ph), 8.06 (d, *J* 9.4, 1H, 5'-H), 8.19 (s, 1H, NH), 8.67 (d, *J* 9.4, 1H, 4'-H), 9.82 (s, 1H, NH), 11.65 (br s, 1H, NH); MS (*m/z*, %) 315 (*M*⁺, 49), 105 (100); IR (KBr) 3267 br, 3076, 1652, 1634, 1598, 1580, 1539. HRMS Calcd for C₁₄H₁₀N₅O₂Cl: 315.0530. Found: 315.0523.

General procedure for the preparation of 1,2,4-triazolo[4,3-*b*]pyridazines (11a–c**) and products (**12a,b**):**

Method A. A mixture of 4-acylhydrazinomethylene-2-phenyloxazol-5(4*H*)-one (**3**) (1 mmol), pyridazine derivative (**9a**) (145 mg, 1 mmol) and ZrCl₄ (35 mg, 0.15 mmol) in 8 mL of 1,4-dioxane was refluxed for 0. 25–23 h. The products (**11a–c**) and (**12a,b**) were isolated by column chromatography: the eluant for **11a** was CHCl₃/MeOH (10:1); the mixtures of **11b** and **12a** or **11c** and **12b** were separated first by the eluant CHCl₃/MeOH (25:1), then CHCl₃/MeOH (10:1). Yields are given in Table 2.

Method B. The product (**11a**) was also prepared by refluxing (4 h) **3a** (98 mg, 0.4 mmol) and **9a** (58 mg, 0.4 mmol) in a mixture of 1 mL of 1,4-dioxane and 1 mL of pyridine. Purification as above. The yield is given in Table 2.

General procedure for the preparation of 1,2,4-triazolo[4,3-*b*]pyridazines (11d–f**):**

A mixture of 4-acylhydrazinomethylene-2-phenyloxazol-5(4*H*)-one (**3**) (1 mmol), the pyridazine derivate **9b** (159 mg, 1 mmol) and ZrCl₄ (35 mg, 0.15 mmol) in 8 mL of 1,4-dioxane was refluxed for 1 h. The reaction mixture was evaporated to dryness, then 30 mL of CH₂Cl₂ and 25 mL of H₂O were added and the pH value was adjusted to 8–9 with solid sodium hydrogen carbonate in order to dissolve the pyrazolone (**8**). The layers were separated and the water layer was extracted with CH₂Cl₂ (6x15 mL). The collected organic layers were washed with water (2x10 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Products (**11d**) and (**11e**) were isolated by column chromatography with petroleum ether/EtOAc (1:5) as the eluant. For the isolation of **11f**, the solid residue was suspended in 2 mL of ethanol and filtered off. Yields are given in Table 2.

Analytical and spectroscopic data of products:

4-Acetylhydrazinomethylene-2-phenyloxazol-5(4H)-one (3a): mp 161.5–163 °C (MeOH/DMF) (lit.,¹² 165–167 °C); ¹H NMR (60 °C) δ 1.93 (br s, 3H, Me), 7.27 (br s, 1H, CH), 7.51 (m, 3H, Ph), 7.87 (m, 2H, Ph), 10.15 (br s, 1H, NH), 10.39 (br s, 1H, NH); MS (m/z, %) 245 (M⁺, 33), 105 (100); IR (KBr) 1805, 1753, 1734, 1696, 1640 br, 1557 br.

4-Benzoylhiazinomethylene-2-phenyloxazol-5(4H)-one (3b): mp 158–160 °C (MeOH/DMF); ¹H NMR δ 7.35–7.70 (m, 8H) and 7.87–8.02 (m, 3H) (two Ph, CH), 10.57 (br s), 11.16 (br s) and 11.23 (br s) (two NH); MS (m/z, %) 307 (M⁺, 16), 105 (100); IR (KBr) 1805, 1769, 1736, 1673, 1630 br, 1569, 1551 br. Anal. Calcd for C₁₇H₁₃N₃O₃: C, 66.44; H, 4.26; N, 13.67. Found: C, 66.64; H, 4.39; N, 13.68.

4-Salicyloylhiazinomethylene-2-phenyloxazol-5(4H)-one (3c): mp 152–154 °C (1,4-dioxane); ¹H NMR δ 6.85–8.04 (m, 10H, Ph, C₆H₄, CH), 9.69, 10.01 (br s), 11.50 (br s) and 12.15 (br s) (OH, two NH); MS (m/z, %) 323 (M⁺, 8), 121 (100); IR (KBr) 1732, 1720, 1668, 1635, 1604, 1573, 1559 br. Anal. Calcd for C₁₇H₁₃N₃O₄: C, 63.16; H, 4.05; N, 13.00. Found: C, 62.92; H, 4.12; N, 12.84.

Acetanilide (7a): mp 113–114 °C (H₂O/EtOH) (lit.,^{13a} 115 °C).

Benzanilide (7b): mp 160–161 °C (H₂O/EtOH) (lit.,^{13b} 160 °C).

Salicylanilide (7c): mp 133.5–134.5 °C (H₂O/EtOH) (lit.⁹ 135.8–136.2 °C; lit.,^{13b} 135 °C).

N-(p-Methylphenyl)acetamide (7d): mp 142–143 °C (H₂O/EtOH) (lit.,^{13c} 145 °C).

N-(p-Methylphenyl)benzamide (7e): mp 155–156 °C (H₂O/EtOH) (lit.,^{13d} 155–156 °C).

N-(p-Methylphenyl)salicylamide (7f): mp 153–154.5 °C (H₂O/EtOH) (lit.,^{13e} 155–156 °C).

N-(m-Methylphenyl)salicylamide (7g): mp 132.5–133.5 °C (H₂O/EtOH) (lit.,^{13e} 135–136 °C).

(S)-N-(1-Phenylethyl)salicylamide (7h): mp 102.5–103.5 °C (EtOAc/petroleum ether) (lit.,^{13f} 103 °C; lit.,^{13g} 111–112 °C).

6-Chloro-3-methyl-1,2,4-triazolo[4,3-b]pyridazine (11a): mp 109–110 °C (petroleum ether/EtOAc) (lit.,^{14a} 103.5 °C; lit.,^{14b} 106–107 °C).

6-Chloro-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine (11b): mp 199.5–201 °C (lit.,^{14c} 200–201 °C).

6-Chloro-3-(o-hydroxyphenyl)-1,2,4-triazolo[4,3-b]pyridazine (11c): mp 247–249 °C (petroleum ether/EtOAc); ¹H NMR δ 7.06 (m, 2H, C₆H₄), 7.46 (m, 1H, C₆H₄), 7.57 (d, *J* 9.6, 1H, 7-H), 7.93 (dd, *J*₁ 7.7, *J*₂ 1.5, 1H, C₆H₄), 8.56 (d, *J* 9.6, 1H, 8-H), 10.67 (s, 1H, OH); ¹³C NMR δ 111.65, 116.48, 119.10, 123.03, 127.19, 129.47, 132.01, 142.99, 146.72, 148.98, 156.51; MS (m/z, %) 246 (M⁺, 100). IR (KBr) 3094, 3030, 1622, 1589, 1577, 1528, 1480, 1466. Anal. Calcd for C₁₁H₇N₄OCl: C, 53.56; H, 2.86; N, 22.71. Found: C, 53.59; H, 2.69; N, 23.03.

6-Chloro-3,8-dimethyl-1,2,4-triazolo[4,3-b]pyridazine (11d): mp 169–170 °C (petroleum ether/EtOAc) (lit.,^{14d} 170–171 °C).

6-Chloro-8-methyl-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine (11e):^{14e} mp 182–183 °C (petroleum ether/

EtOAc); ^1H NMR 2.68 (d, J 1.3, 3H, Me), 7.46 (q, J 1.3, 1H, 7-H), 7.61 (m, 3H, Ph), 8.30 (m, 2H, Ph); MS (m/z , %) 244 (M^+ , 100); IR (KBr) 3034, 1599, 1555, 1463. Anal. Calcd for $\text{C}_{12}\text{H}_9\text{N}_4\text{Cl}$: C, 58.91; H, 3.71; N, 22.90. Found: C, 59.17; H, 3.79; N, 22.76.

6-Chloro-3-(*o*-hydroxyphenyl)-8-methyl-1,2,4-triazolo[4,3-*b*]pyridazine (11f): mp 254–255 °C (EtOH/DMF); ^1H NMR δ 2.68 (d, J 1.2, 3H, Me), 7.06 (m, 2H, C_6H_4), 7.44 (m, 1H, C_6H_4), 7.48 (pseudo q, J ca. 1.2, 1H, 7-H), 7.94 (dd, J_1 7.8, J_2 1.6, 1H, C_6H_4), 10.69 (s, 1H, OH); ^{13}C NMR (60 °C) δ 15.44, 111.40, 116.39, 118.87, 120.70, 128.65, 131.64, 139.06, 144.08, 146.80, 148.62, 156.37; MS (m/z , %) 260 (M^+ , 100); IR (KBr) 1621, 1579, 1561, 1479, 1464. Anal. Calcd for $\text{C}_{12}\text{H}_9\text{N}_4\text{OCl}$: C, 55.29; H, 3.48; N, 21.49. Found: C, 55.19; H, 3.51; N, 21.63.

3-Benzoylhydrazino-6-chloropyridazine (12a): mp 151–152 °C (EtOH) (lit.,^{14c} 83–84 °C; from EtOAc).

3-Salicyloylhydrazino-6-chloropyridazine (12b): mp 92–95 °C (from EtOAc precipitated by petroleum ether), ^1H NMR δ 6.96 (m, 2H, C_6H_4), 7.13 (d, J 9.2, 1H, 5'-H or 4'-H), 7.45 (m, 1H, C_6H_4), 7.57 (d, J 9.2, 1H, 4'-H or 5'-H), 7.90 (dd, J_1 7.8, J_2 1.6, 1H, C_6H_4), 9.43 (s, 1H), 10.75 (br s, 1H), 11.72 (br s, 1H) (OH, two NH); MS (m/z , %) 264 (M^+ , 26), 121 (100); IR (KBr) 3456, 3238, 3061, 1642, 1603, 1558. HRMS Calcd for $\text{C}_{11}\text{H}_9\text{N}_4\text{O}_2\text{Cl}$: 264.0422. Found: 264.0414.

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