HETEROCYCLES, Vol. 54, No. 2, pp.1011-1019, Received, 7th June, 2000

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

Franc Požgan, Slovenko Polanc, and Marijan Kočevar*

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, SI-1000 Ljubljana, Slovenia

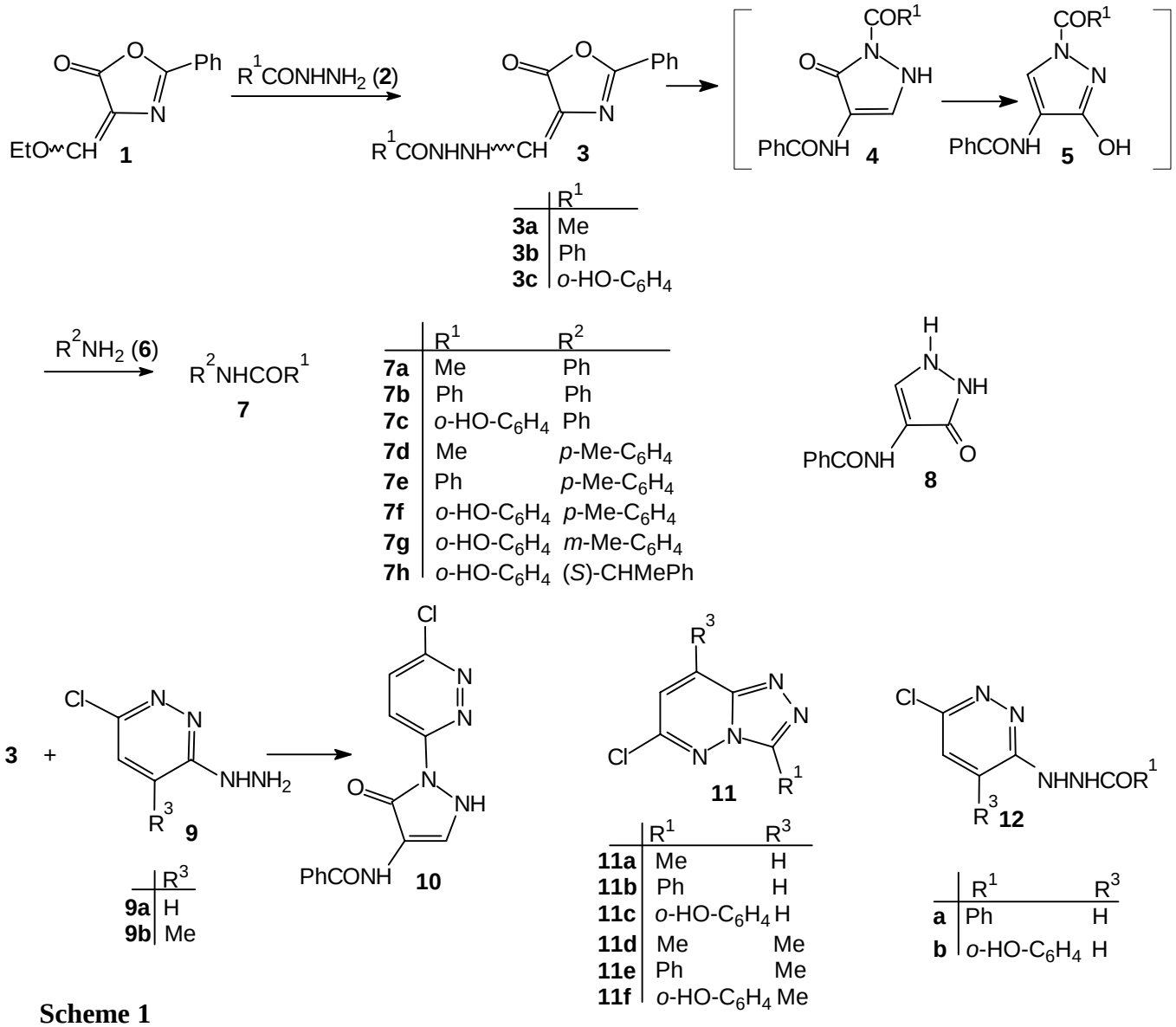
Abstract – A simple and general method for the acylation of an amino or hydrazino group by the application of hydrazides has been developed. It starts from hydrazides (**2**), which are converted with 4-ethoxymethylene-2-phenyl-oxazol-5(4*H*)-one (**1**) to the corresponding 4-acylhydrazinomethylene-2-phenyloxazol-5(4*H*)-ones (**3**). The latter react with nitrogen-containing nucleo-iles 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 biomolecules[3] 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-1*H*-pyrazoles as well as a method for the synthesis of various symmetrically *N*,*N*'-disubstituted hydrazines starting from 4-ethoxymethylene-2-phenyloxazol-5(4*H*)-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-1*H*-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



	R^1
3a	Me
3b	Ph
3c	*o*-HO-C_6H_4

	R^1	R^2
7a	Me	Ph
7b	Ph	Ph
7c	*o*-HO-C_6H_4	Ph
7d	Me	*p*-Me-C_6H_4
7e	Ph	*p*-Me-C_6H_4
7f	*o*-HO-C_6H_4	*p*-Me-C_6H_4
7g	*o*-HO-C_6H_4	*m*-Me-C_6H_4
7h	*o*-HO-C_6H_4	(*S*)-CHMePh

	R^3
9a	H
9b	Me

	R^1	R^3
11a	Me	H
11b	Ph	H
11c	*o*-HO-C_6H_4	H
11d	Me	Me
11e	Ph	Me
11f	*o*-HO-C_6H_4	Me

	R^1	R^3
a	Ph	H
b	*o*-HO-C_6H_4	H

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)	*p*-Me-C_6H_4 (1)	$ZrCl_4$ (0.15); 1	**7d**	(93)
8	**3b** (1)	*p*-Me-C_6H_4 (1)	$ZrCl_4$ (0.15); 1	**7e**	(72)
9	**3c** (1)	*p*-Me-C_6H_4 (1)	$ZrCl_4$ (0.15); 1	**7f**	(86)
10	**3c** (1)	*m*-Me-C_6H_4 (1)	$ZrCl_4$ (0.15); 1	**7g**	(72)
11	**3c** (1)	(*S*)-CHMePh (1)	$ZrCl_4$ (0.15); 0.5	**7h**	(67)

[a]Yields 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)

[a]Yields of TLC-pure products. [b]The 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 activity[11] 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. ^{1}H and ^{13}C 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(4*H*)-ones (3a–c):

A mixture of 4-ethoxymethylene-2-phenyloxazol-5(4*H*)-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(4*H*)-one (**3**) (1 mmol), aniline (0.1 mL, 1.1 mmol) and NEt_3 (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: $CHCl_3$/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 $CHCl_3$ (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 H_2O 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(4*H*)-one (**3**) (1 mmol), amine (**6**) (1 mmol; for R^2= Ph 1.1 mmol) and $ZrCl_4$ (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 CH_2Cl_2 and 25 mL of H_2O were added and the p*H* 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 CH_2Cl_2 (6x15 mL). Collected organic layers were washed with water (2x10 mL), dried over Na_2SO_4 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 $CHCl_3$/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); ^{1}H 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 $C_{14}H_{10}N_5O_2Cl$: 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 $ZrCl_4$ (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 $CHCl_3$/MeOH (10:1); the mixtures of **11b** and **12a** or **11c** and **12b** were separated first by the eluant $CHCl_3$/MeOH (25:1), then $CHCl_3$/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 $ZrCl_4$ (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 CH_2Cl_2 and 25 mL of H_2O were added and the p*H* 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 CH_2Cl_2 (6x15 mL). The collected organic layers were washed with water (2x10 mL), dried over Na_2SO_4 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(4*H*)-one (3a): mp 161.5–163 °C (MeOH/DMF) (lit.,[12] 165–167 °C); ^{1}H 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-Benzoylhydrazinomethylene-2-phenyloxazol-5(4*H*)-one (3b): mp 158–160 °C (MeOH/DMF); ^{1}H 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 $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67. Found: C, 66.64; H, 4.39; N, 13.68.

4-Salicyloylhydrazinomethylene-2-phenyloxazol-5(4*H*)-one (3c): mp 152–154 °C (1,4-dioxane); ^{1}H NMR δ 6.85–8.04 (m, 10H, Ph, C_6H_4, 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 $C_{17}H_{13}N_3O_4$: 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 (H_2O/EtOH) (lit.,[13a] 115 °C).

Benzanilide (7b): mp 160–161 °C (H_2O/EtOH) (lit.,[13b] 160 °C).

Salicylanilide (7c): mp 133.5–134.5 °C (H_2O/EtOH) (lit.[9] 135.8–136.2 °C; lit.,[13b] 135 °C).

***N*-(*p*-Methylphenyl)acetamide (7d):** mp 142–143 °C (H_2O/EtOH) (lit.,[13c] 145 °C).

***N*-(*p*-Methylphenyl)benzamide (7e):** mp 155–156 °C (H_2O/EtOH) (lit.,[13d] 155–156 °C).

***N*-(*p*-Methylphenyl)salicylamide (7f):** mp 153–154.5 °C (H_2O/EtOH) (lit.,[13e] 155–156 °C).

***N*-(*m*-Methylphenyl)salicylamide (7g):** mp 132.5–133.5 °C (H_2O/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); ^{1}H NMR δ 7.06 (m, 2H, C_6H_4), 7.46 (m, 1H, C_6H_4), 7.57 (d, *J* 9.6, 1H, 7-H), 7.93 (dd, J_1 7.7, J_2 1.5, 1H, C_6H_4), 8.56 (d, *J* 9.6, 1H, 8-H), 10.67 (s, 1H, OH); ^{13}C 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 $C_{11}H_7N_4OCl$: 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); ^{1}H 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 $C_{12}H_9N_4Cl$: 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); ^{1}H 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 $C_{12}H_9N_4OCl$: 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), ^{1}H 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 $C_{11}H_9N_4O_2Cl$: 264.0422. Found: 264.0414.

ACKNOWLEDGEMENTS

We thank the Ministry of Science and Technology of the Republic of Slovenia for financial support. Dr. B. Kralj and Dr. D. Žigon (Center for Mass Spectroscopy, "Jožef Stefan" Institute, Ljubljana, Slovenia) are gratefully acknowledged for the MS measurements.

REFERENCES

1. M. A. Ogliaruso and J. F. Wolfe, *The Chemistry of Acid Derivatives: Supplement B*, ed. by S. Patai, Interscience, Chichester, 1979; Part 1, pp. 267–490.
2. T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, J. Wiley & Sons, Inc., New York, 1991.
3. R. J. Simmonds, *Chemistry of Biomolecules: An Introduction*, The Royal Society of Chemistry, Cambridge, 1992.
4. M. Bodanszky, *Peptide Chemistry*, Springer, Berlin, 1993.
5. (*a*) H. Paulsen and D. Stoye, *The Chemistry of Amides*, ed. by J. Zabicky, Interscience, London, 1970, p. 515; (*b*) P. D. Bailey, I. D. Collier, and K. H. Morgan, *Comprehensive Organic Functional Group Transformations*, ed. by A. R. Katritzky, O. Meth-Cohn, and C. W. Rees, Pergamon, Oxford, 1995, Vol. 5, p. 257.

6. (a) M. A. E. Shaban and A. Z. Nasr, *Advances in Heterocyclic Chemistry: Synthesis of Condensed 1,2,4-Triazolo[3,4-z]Heterocycles*, ed. by A. R. Katritzky, Academic Press, Inc., San Diego, 1990, Vol. 49, p. 277; (b) P. Bourgeois, R. Cantegril, A. Chêne, J. Gelin, J. Mortier, and J. Moyroud, *Synth. Commun.*, 1993, **23**, 3195; (c) J. Košmrlj, M. Kočevar, and S. Polanc, *Synlett*, 1996, 652; (d) D. T. Hurst, *Progress in Heterocyclic Chemistry: Triazines, Tetrazines and Fused Polyaza Ring Systems*, ed. by G. W. Gribble and T. L. Gilchrist, Pergamon, Kidlington, 1998, Vol. 10, p. 275.
7. V. Kepe, F. Požgan, A. Golobič, S. Polanc, and M. Kočevar, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2813.
8. V. Kepe, S. Polanc, and M. Kočevar, *Acta Chim. Slov*., 1998, **45**, 455.
9. The Merck Index, 12th Ed., Merck & Co., Inc., Whitehouse Station, 1996, p. 1433.
10. (a) V. Kepe, V. Kozjan, S. Polanc, and M. Kočevar, *Heterocycles*, 1999, **50**, 315; (b) V. Kepe, V. Kozjan, S. Polanc, and M. Kočevar, *Heterocycles*, 2000, **52**, 443.
11. R. Lenaršič, M. Kočevar, and S. Polanc, *J. Org. Chem*., 1999, **64**, 2558.
12. J. W. Cornforth, *The Chemistry of Penicillin*, ed. by H. T. Clarke, J. R. Johnson, and R. Robinson, Princeton University Press, Princeton, 1949, p. 730.
13. (a) A. Kaufmann, *Ber*., 1909, **42**, 3480; (b) I. Goldberg, *Ber*., 1906, **39**, 1691; (c) G. G. Yakobson, *Zhur. Vsesoyuz. Khim. Obshchestva im. D. I. Mendelleev*, 1960, **5,** 708 (*Chem. Abstr*., 1961, **55**, 11344d); (d) C. L. Stevens and R. J. Gasser, *J. Am. Chem. Soc*., 1957, **79**, 6057; (e) H. W. Schultz, *J. Pharm. Sci*., 1963, **52**, 503 (*Chem. Abstr*., 1963, **59,** 5066e); (f) A. Mustafa and A. E. A. A. Hassan, *J. Am. Chem. Soc*., 1957, **79**, 3846; (g) L. D. Solov'eva, V. M Dem'yanovich, and V. M Potapov, *Zh. Org. Khim*., 1981, **17**, 1241 (*Chem. Abstr*., 1982, **96**, 68196f).
14. (a) N. Takahayashi, *J. Pharm. Soc. Japan*, 1955, **75**, 1242 (*Chem. Abstr*., 1956, **50**, 8655f); (b) S. Sunder and N. P. Peet, *J. Heterocycl. Chem*., 1980, **17**, 1527; (c) A. Pollak and M. Tišler, *Tetrahedron*, 1966, **22**, 2073; (d) M. Japelj, B. Stanovnik, and M. Tišler, *Monatsh. Chem*., 1969, **100**, 671; (e) R. Cantegril, A. Chene, J. Mortier, and R. Peignier, **Eur. Pat. Appl. EP 483,027** (1992) (*Chem. Abstr*. 1992, **117**, 131214e).