REDUCTIVE CLEAVAGE OF ISOXAZOLO[3,4-*d*]PYRIDAZINONES : A SYNTHETIC APPROACH TO VARIOUS 4,5-FUNCTIONALIZED 3(2*H*)-PYRIDAZINONES

Vittorio Dal Piaz*, Giovanna Ciciani, and Maria Paola Giovannoni
Dipartimento di Scienze Farmaceutiche dell'Università di Firenze, Via Gino Capponi 9, 50121 Firenze, Italy

Abstract- 4-Aminopyridazin-3(2*H*)-ones substituted at position 5 with a variety of oxygenated carbon chains were obtained in good yields by reductive opening of the pentatomic ring of isoxazolo[3,4-*d*]pyridazinones (1). Starting from ethyl 4-acylisoxazole-3-carboxylates , several 4,5-functionalized 3(2*H*)pyridazinones (3) are obtained in a one step by treatment with the appropriate hydrazine and Pd/C.

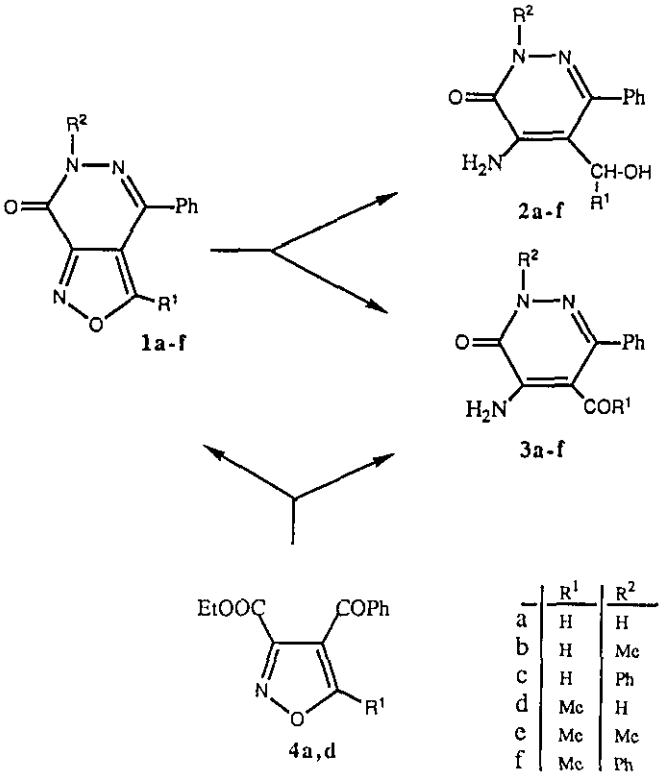
In the past decade our research group has focused its studies on the chemical behaviour of the isoxazolo[3,4-*d*]pyridazine derivatives . Thus we have shown that compounds of type (1) may be considered as versatile intermediates to various functionalized pyrazoles, [1,2] pyridazinones [3-5] and 1,2-diazepinones [6-7] through the opening of one or both of the heterocyclic rings. In the reaction products cyano, amino, nitro and ketonic carbonyl groups are present ; these originate from the isoxazolic C-3 and / or heteroatoms (*N,O*).
4,5-Functionalized-3(2*H*)pyridazinones are interesting as antinflammatory, antiaggregating and positive inotropic agents; [8] on the other hand the same compounds can be useful as building blocks for condensed nitrogen heterocycles. [9-12] Thus we report here a synthetic approach to 3(2*H*)pyridazinones substituted with an amino group at position 4 and a variety of oxygenated carbon chains at position 5, starting from isoxazolopyridazinones (1).[13] Primary or secondary amino alcohols (**2a-f**) are obtained after treatment of (1a-f) with sodium borohydride, while catalytic hydrogenation leads to amino aldehydes (**3a-c**) and amino ketones (3d-f) (see Table 2, method I). The latter compounds can also be obtained from (1) (R^1= Me) and hydrazines in the presence of Pd/C (method III). Treatment of compounds (1) (R^1 =H) with hydrazine (methylhydrazine) in the same conditions gives complex reaction mixtures, whereas using phenylhydrazine moderate yields (40-75%)

of required aldehydes (3a-c) are obtained (method IV). In these cases , however , the catalytic hydrogenation affords betters yields (80-90%) .

Ketones (3d , 3e) (yield 90 %) and the aldehydes (3a) and (3c) (yield 15 and 32% respectively) can be obtained in one step only by treatment of isoxazoles (4) with appropriate hydrazine and Pd/C (method II) . In this case the reagent thus gives rise to the closure of the pyridazinone and the reductive opening of the N-O linkage on the pentatomic ring. Since compounds (1f) and (1b) cannot be obtained directly from (4d) and (4a) with phenylhydrazine [13] or methylhydrazine [14] respectively, this one-step procedure is not however useful for the synthesis of the corresponding compounds (3f) and (3b).

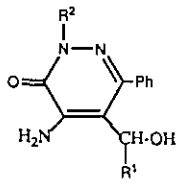
Synthetic and analytical data of the new compounds (2) and (3) are reported in Tables 1 and 2 ; ir and ^{1}H-nmr spectral data are reported in experimental section . The pattern of signals in ^{1}H-nmr spectra for compounds (3a-c) shows that these compounds in solution can be formulated as 5-formyl-1,2-dihydro-4-imino-6-phenylpyridazin-3-ones .

Scheme



	R^1	R^2
a	H	H
b	H	Me
c	H	Ph
d	Me	H
e	Me	Me
f	Me	Ph

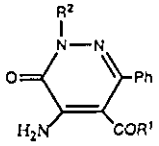
Table 1



2a-f

Compd	R^1	R^2	Formula	Yield (%)	mp °C	crystn solv.
2a	H	H	$C_{11}H_{11}N_3O_2$	47	275	EtOH
2b	H	Me	$C_{12}H_{13}N_3O_2$	67	155-157	EtOH
2c	H	Ph	$C_{17}H_{15}N_3O_2$	73	206-208	EtOH-H_2O
2d	Me	H	$C_{12}H_{13}N_3O_2$	57	277 decomp.	EtOH
2e	Me	Me	$C_{13}H_{15}N_3O_2$	78	241-242	EtOH
2f	Me	Ph	$C_{18}H_{17}N_3O_2$	61	178-180	EtOH-H_2O

Table 2



3a-f

Compd	R^1	R^2	Formula	Method Yields (%)				mp °C	crystn solv.
				I	II	III	IV		
3a	H	H	$C_{11}H_9N_3O_2$	90	15	-	40	251-253	EtOH
3b	H	Me	$C_{12}H_{11}N_3O_2$	98	-	-	71	149-150	EtOH
3c	H	Ph	$C_{17}H_{13}N_3O_2$	82	32	-	75	153-155	EtOH
3d°	Me	H		-	90	92	-	-	
3e°°	Me	Me		-	89	94	-	-	
3f	Me	Ph	$C_{18}H_{15}N_3O_2$	90	-	97	-	167-169	EtOH

° Literature 5; °° literature 3;
I : 1+ H_2, 10% Pd/C ; II: 4 + R^2-$NHNH_2$, 10% Pd/C ; III : 1 + N_2H_4 , 10% Pd/C ;
IV : 1 + $PhNHNH_2$

Starting from easily available intermediates the described methods , which are rapid and simple, appear attractive in view of the difficulty of obtaining compounds (2) and (3) by other synthetical approaches ; on the other hand (2) and (3) may be smoothly subjected to further chemical transformations .

The present approach confirm the great potentiality of the isoxazole ring as masked functionality. In particular the isoxazolic C-5 of compounds (1), depending on the reagents and the pattern of substitution , may be considered as synthetic equivalent of a hydroxyl or formyl group.

EXPERIMENTAL

Melting points were determined on a Buchi 510 melting points apparatus and are uncorrected. Ir spectra were measured for nujol mulls with a Perkin Elmer 681 spectrophotometer. ^{1}H-Nmr spectra were recorded with Varian Gemini 200 instrument ; chemical shifts are reported in ppm from internal tetramethylsilane. Extracts were dried over sodium sulphate and solvents were removed under reduced pressure. Silica gel plates (Merck F254) were used for analytical tlc and silica gel 60 (Merck 70-230 mesh) for column chromatography.

General procedure for Compounds **2a-f**

Sodium borohydride (265 mg, 7 mmol) was added portionwise to a stirred solution of (**1a-f**) (1.2 mmol) in DMSO (8-10 ml) and H_2O (0.2 ml) in 3-5 h at room temperature. The reaction mixture was diluted with H_2O (20 ml). Compounds (**2c**) and (**2f**) were collected by filtration; the others are obtained by extraction with ethyl acetate (3x 20 ml) and evaporation of the solvent.

4- amino- 5- hydroxymethyl - 6-phenylpyridazin-3(2H)-one **2a** :

Anal. calcd for $C_{11}H_{11}N_3O_2$: C 60.82 ; H 5.10 ; N 19.34 : Found : C 60.56; H 5.38; N 19.53 . Ir: 3500-3130 (NH_2, OH, NH) ; 1660 cm^{-1}(CO); ^{1}H-nmr (DMSO-d_6): 4.25 (d, J= 5 Hz, 2H, CH_2); 5.00 (exch. t, J=6 Hz, 1H, OH); 6.15 (exch. br s, 2H, NH_2); 7.40 (s, 5H, ArH_5); 12.70(exch. br s, 1H, NH).

4- amino- 5- hydroxymethyl - 2-methyl-6-phenylpyridazin-3(2H)-one **2b:**

Anal. calcd for $C_{12}H_{13}N_3O_2$: C 62.33; H 5.67; N18.17 : Found: C 61.97; H 5.37; N 18.04. Ir: 3400-3220 (NH_2,OH);1670 cm^{-1} (CO); ^{1}H-nmr ($CDCl_3$) : 2.30 (exch. t, J= 6 Hz, 1H, OH); 3.80 (s, 3H, NCH_3) ; 4.55 (d, J= 5 Hz, 2H, CH_2); 5.70 (exch. br s, 2H, NH_2); 7.45 (s, 5H, ArH_5).

4- amino- 5- hydroxymethyl - 2,6-diphenylpyridazin-3(2H)-one **2c** :

Anal. calcd for $C_{17}H_{15}N_3O_2$: C 69. 61 ; H 5.15 ; N 14.33 : Found: 69.73 ; H 5.28 ; N 14.03. Ir 3500-3200 (NH_2, OH); 1640 cm^{-1} (CO); ^{1}H-nmr (DMSO-d_6) : 4.20 (d, J= 5 Hz, 2H, CH_2) ; 5.00 (exch. t, J= 6 Hz, 1H, OH); 6.50 (exch. br s, 2H, NH_2); 7.35-7.55 (m, 10H, $2ArH_5$).

4- amino- 5-(1-hydroxyethyl)- 6-phenylpyridazin-3(2H)-one **2d:**

Anal. calcd for $C_{12}H_{13}N_3O_2$: C 62.33 ; H 5.67; N 18.17: Found : C 62.03 ; H 5.50; N 18.41. Ir: 3570 (OH); 3430-3320 (NH_2, NH); 1665 cm^{-1} (CO); ^{1}H-nmr (DMSO-d_6): 1.30 (d, J= 7 Hz, 3H, CCH_3); 4.50 (m,

1H, CH); 5.55 (exch. d, J= 4 Hz, 1H, OH); 6.15 (exch. br s, 2H, NH_2); 7.20-7.50 (m, 5H, ArH_5); 12.65 (exch. br s, 1H, NH).

4- amino- 5- (1-hydroxyethyl)- 2-methyl -6-phenylpyridazin-3(2H)-one **2e** :

Anal. calcd for $C_{13}H_{15}N_3O_2$:C 63.66 ; H 6.16; N 17.13: Found : C 63.67; H 6.43; N 17.31. Ir: 3430 (OH); 3400-3100 (NH_2) ; 1650 cm^{-1} (CO); ^{1}H-nmr (DMSO-d_6): 1.30 (d, J= 7 Hz, 3H, CCH_3); 3.70 (s, 3H, NCH_3); 4.55 (m, 1H, CH); 5.50 (d, J= 4 Hz, 1H, OH); 6.30 (exch.br s, 2H, NH_2) ; 7.40 (s, 5H, ArH_5).

4- amino- 5- (1-hydroxyethyl)- 2,6-diphenylpyridazin-3(2H)-one **2f:**

Anal.calcd for $C_{18}H_{17}N_3O_2$: C 70.34 ; H 5.58; N 13.67: Found: C 70.15; H 5.63; N 13.52. Ir: 3470 (OH) ; 3400-3120 (NH_2); 1640 cm^{-1}(CO); ^{1}H-nmr ($CDCl_3$): 1.50 (d, J= 7 Hz, 3H, CCH_3); 4.80 (m, 1H, CH) ; 6.00 (exch. br s, 2H, NH_2); 7.30-7.70 (m, 11H, $2ArH_5$ and OH).

General procedure for compounds **3**

Method I

- for compounds **3a-c** and **3f** :

A mixture of the appropriate compound (**1**) (1 mmol) , 10% palladium on charcoal (50 mg) and ethanol (50 ml) was shaken under hydrogen at room temperature and 2 bar for 10 min (3 h for **3f**). The catalyst was filtered off and the solvent was evaporated in vacuo.

Method II

- for compounds **3 a,d,e:**

To a mixture of **4a** or **4d** (1 mmol) and appropriate hydrazine (8 mmol) in EtOH (10 ml) , after refluxing for 2 min , 10% Pd /C (50 mg) was added . Then the suspension was refluxed again for 15-20 min . The catalyst was filtered off and the solvent was evaporated in vacuo.

- for compound **3c:**

A mixture of **4c** (1.2 mmol) and phenyhydrazine (3.5 mmol) was refluxed for 4 h; then 10% Pd/C (40 mg) was added and the suspension was refluxed again for 5 min.

-Compounds(**3e**) and(**3c**)were obtained by column chromatography (cyclohexane/ ethyl acetate 1/2 and 1/1 v/v respectively)

Method III

- for compounds **3 d,e,f:**

The appropriate compound (**1**) (1 mmol) , 100% hydrazine hydrate (4 mmol) and 10% Pd/C (30 mg) in EtOH (8 ml) was refluxed for 10-15 min; then the mixture was worked-up as above.

Method IV

- for compounds **3a,b,c:**

A mixture of the appropriate compound (1) (1 mmol) and phenylhydrazine (4 mmol) in EtOH (7 ml) and 10% Pd/C (50 mg) was refluxed for 10 min . The reaction mixture was worked up as above. Compound (3a) was obtained by column chromatography (cyclohexane/ ethyl acetate 1/2).

4-amino-5-formyl--6-phenylpyridazin3(2H)-one **3a** :

Anal. calcd for $C_{11}H_9N_3O_2$: C 61.39; H 4.22; N 19.52 : Found: C 61.51; H 4.42 ; N 19.61. Ir : 3490-3190 (NH_2, NH) ; 1680 and 1650 cm^{-1} (2xCO); ^{1}H-nmr (DMSOd_6) : 7.50 (s, 5H, ArH_5); 8.10 (exch. br s, 1H , NH) ; 9.05 (exch br s , 1H, NH) ; 9.60 (s, 1H , CHO) ; 12.40 (exch. br s , 1H, NH).

4-amino-5-formyl-2-methyl-6-phenylpyridazin3(2H)-one **3b:**

Anal. calcd for $C_{12}H_{11}N_3O_2$: C 62.87; H 4.84 ; N 18.33: Found: C 62.91; H 4.79; N 18.42. Ir : 3400-3260 (NH_2); 1670 and 1650 cm^{-1} (2xCO); ^{1}H-nmr ($CDCl_3$): 3.80 (s, 3H, NCH_3); 6.95 (exch. br s, 1H, NH), 7.45(s, 5H, ArH_5) ; 9.10 (exch. br s, 1H, NH) ; 9.70 (s, 1H, CHO).

4-amino-5-formyl-2,6-diphenylpyridazin3(2H)-one **3c:**

Anal. calcd for $C_{17}H_{13}N_3O_2$: C 70.09; H 4.50; N 14.42: Found C: 70.15; H 4.71; N 14.38. Ir 3400-3300 (NH_2), 1680 and 1650 cm^{-1} (2xCO); ^{1}H-nmr ($CDCl_3$) : 7.00 (exch. br s , 1H, NH) ; 7.30-7.70 (m, 10H, 2xArH_5) ; 9.25 (exch. br s, 1H, NH); 9.80 (s, 1H, CHO).

5-acetyl-4-amino-2,6-diphenylpyridazin3(2H)-one **3f:**

Anal. calcd for $C_{18}H_{15}N_3O_2$: C 70.81 ; H 4.95; N 13.76: Found: C 70.99; H 4.70 ; N 13.98. Ir: 3420-3300 (NH_2); 1640 cm^{-1} (CO); ^{1}H-nmr (DMSOd_6) : 1.75 (s, 3H, CH_3) ; 7.30-7.70 (m, 10H, 2ArH_5); 7.95 (exch. br s, 2H , NH_2).

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14. Since the chemical and spectroscopic properties of the reaction product between (**4a**) and methylhydrazine described in reference 13 did not agree with the structure (**1b**), we re-examined the reaction and estabilished that it is the regioisomeric 6-methyl-3-phenylisoxazolopyridazin-7(6*H*)-one . The authentic (**1b**) (mp=214 °C from EtOH) can be obtained from (**4a**) and methylhydrazine in the presence of polyphosphoric acid.

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