

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

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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 antiinflammatory, 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) ($R^1 = \text{Me}$) and hydrazines in the presence of Pd/C (method III). Treatment of compounds (1) ($R^1 = \text{H}$) with hydrazine (methylhydrazine) in the same conditions gives complex reaction mixtures, whereas using phenylhydrazine moderate yields (40-75%)

of required aldehydes (3a-e) are obtained (method IV). In these cases, however, the catalytic hydrogenation affords better 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 phenylhydrazine¹³ or methylhydrazine¹⁴ 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 ¹H-NMR spectral data are reported in experimental section. The pattern of signals in ¹H-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

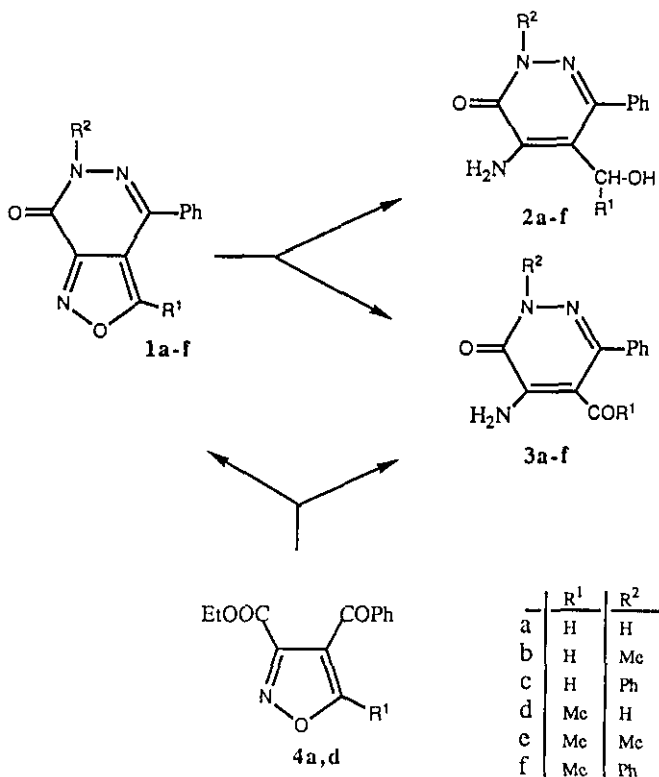
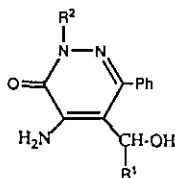


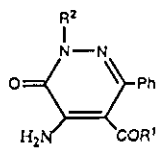
Table 1



2a-f

Compd	R ¹	R ²	Formula	Yield (%)	mp °C	crystn solv.
2a	H	H	C ₁₁ H ₁₁ N ₃ O ₂	47	275	EtOH
2b	H	Me	C ₁₂ H ₁₃ N ₃ O ₂	67	155-157	EtOH
2c	H	Ph	C ₁₇ H ₁₅ N ₃ O ₂	73	206-208	EtOH-H ₂ O
2d	Me	H	C ₁₂ H ₁₃ N ₃ O ₂	57	277 decomp.	EtOH
2e	Me	Me	C ₁₃ H ₁₅ N ₃ O ₂	78	241-242	EtOH
2f	Me	Ph	C ₁₈ H ₁₇ N ₃ O ₂	61	178-180	EtOH-H ₂ O

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 ₉ N ₃ O ₂	90	15	-	40	251-253	EtOH
3b	H	Me	C ₁₂ H ₁₁ N ₃ O ₂	98	-	-	71	149-150	EtOH
3c	H	Ph	C ₁₇ H ₁₃ N ₃ O ₂	82	32	-	75	153-155	EtOH
3d ^o	Me	H		-	90	92	-	-	
3e ^{oo}	Me	Me		-	89	94	-	-	
3f	Me	Ph	C ₁₈ H ₁₅ N ₃ O ₂	90	-	97	-	167-169	EtOH

^o Literature 5; ^{oo} literature 3;

I: 1 + H₂, 10% Pd/C; II: 4 + R²-NHNH₂, 10% Pd/C; III: 1 + N₂H₄, 10% Pd/C;

IV: 1 + PhNHNH₂

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 synthetic approaches; on the other hand (2) and (3) may be smoothly subjected to further chemical transformations.

The present approach confirms 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. $^1\text{H-Nmr}$ 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 $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_2$: 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); $^1\text{H-nmr}$ (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 $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_2$: C 62.33; H 5.67; N 18.17 : Found: C 61.97; H 5.37; N 18.04. Ir: 3400-3220 (NH_2 ,OH); 1670 cm^{-1} (CO); $^1\text{H-nmr}$ (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 $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_2$: 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); $^1\text{H-nmr}$ (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 $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_2$: 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); $^1\text{H-nmr}$ (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, NH₂); 7.20-7.50 (m, 5H, ArH₅); 12.65 (exch. br s, 1H, NH).

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

Anal. calcd for C₁₃H₁₅N₃O₂: C 63.66 ; H 6.16; N 17.13: Found : C 63.67; H 6.43; N 17.31. Ir: 3430 (OH); 3400-3100 (NH₂) ; 1650 cm⁻¹ (CO); ¹H-nmr (DMSO-d₆): 1.30 (d, J= 7 Hz, 3H, CCH₃); 3.70 (s, 3H, NCH₃); 4.55 (m, 1H, CH); 5.50 (d, J= 4 Hz, 1H, OH); 6.30 (exch. br s, 2H, NH₂) ; 7.40 (s, 5H, ArH₅).

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

Anal. calcd for C₁₈H₁₇N₃O₂: C 70.34 ; H 5.58; N 13.67: Found: C 70.15; H 5.63; N 13.52. Ir: 3470 (OH) ; 3400-3120 (NH₂); 1640 cm⁻¹(CO); ¹H-nmr (CDCl₃): 1.50 (d, J= 7 Hz, 3H, CCH₃); 4.80 (m, 1H, CH) ; 6.00 (exch. br s, 2H, NH₂); 7.30-7.70 (m, 11H, 2ArH₅ 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 phenylhydrazine (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} ($2\times CO$); 1H -nmr (DMSO- d_6) : 7.50 (s, 5H, ArH₅); 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} ($2\times CO$); 1H -nmr ($CDCl_3$): 3.80 (s, 3H, NCH₃); 6.95 (exch. br s, 1H, NH), 7.45 (s, 5H, ArH₅) ; 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} ($2\times CO$); 1H -nmr ($CDCl_3$) : 7.00 (exch. br s, 1H, NH) ; 7.30-7.70 (m, 10H, $2\times ArH_5$); 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); 1H -nmr (DMSO- d_6) : 1.75 (s, 3H, CH₃) ; 7.30-7.70 (m, 10H, $2ArH_5$); 7.95 (exch. br s, 2H, NH_2).

ACKNOWLEDGEMENT

This work was supported by a grant from the MURST (ROMA).

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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 established that it is the regioisomeric 6-methyl-3-phenylisoxazopyridazin-7(6H)-one. The authentic (1b) (mp=214 °C from EtOH) can be obtained from (4a) and methylhydrazine in the presence of polyphosphoric acid.

Received, 25th March, 1991