Nitrile Oxide [3 + 2] Cycloaddition: Application to the Synthesis of 6-Substituted 3(2*H*)-Pyridazinones and 6-Substituted 4,5-Dihydro-4-hydroxy-3(2*H*)-pyridazinones

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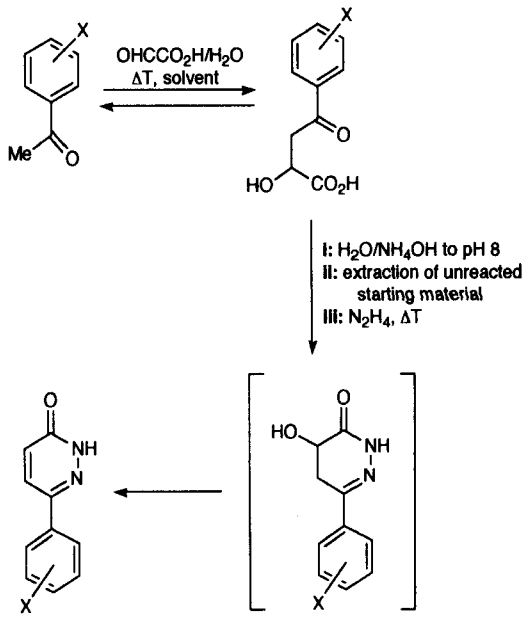
An efficient method for the preparation of 6-substituted 3(2*H*)-pyridazinones and 6-substituted 4,5-dihydro-4-hydroxy-3(2*H*)-pyridazinones starting from 3,5-disubstituted 4,5-dihydroisoxazoles is described. N–O bond cleavage of the isoxazoline ring promoted by molybdenum hexacarbonyl or by catalytic hydrogenation afforded the α-hydroxy γ-keto esters **4a–f** which were converted into 6-substituted 4,5-dihydro-4-hydroxy-3(2*H*)-pyridazinones **5a–f** or 6-substituted 3(2*H*)-pyridazinones **6a–f** on treatment with hydrazine hydrate at room temperature or reflux in high yield starting from **4a–f**. The flexibility of this protocol has been demonstrated by the synthesis of the *C*-nucleoside **7** starting from the known β-ribofuranosylnitromethane **8**. Moreover, an intramolecular version of this methodology has been developed to prepare the known antiulcer tricyclic 3(2*H*)-pyridazinone **12**.

The pyridazine nucleus is an interesting heterocyclic ring, which plays the role of pharmacophore in several classes of derivatives possessing a variety of pharmacological properties.[1] Recent reviews have focused on the importance of this moiety in designing new compounds of pharmacological interest.[2] In particular, great attention has been paid in the past to various 4,5-dihydro-3(2*H*)-pyridazinones and 3(2*H*)-pyridazinones having interesting positive inotropic and antihypertensive activities, such as imazodan,[3] and to antihypertensive pyridazines such as prizidilol.[4]

A recent paper by Coates and McKillop[5] on the one-pot preparation of 6-substituted 3(2*H*)-pyridazinones, performed during the development of the β-blocker and vasodilator antihypertensive agent prizidilol, prompts us to report our results on this topic. With regard to available synthetic methods for the preparation of 6-substituted 3(2*H*)-pyridazinones, one often employs a protocol that starts from 4-substituted 4-oxoalkanoic acids and uses the cyclization with hydrazine and subsequent oxidation of the dihydropyridazinone intermediate.[6] The synthetic method described by Coates and McKillop,[5] also called the "self-catalyzed glyoxylic acid process", involves the reaction of glyoxylic acid hydrate with a three-fold excess of a methyl ketone at 110 °C to give the aldol intermediate, which is dissolved in aqueous ammonia and heated with hydrazine to perform cyclization and dehydration. This method appears to be superior to other ones[7] because 6-substituted 3(2*H*)-pyridazinones are obtained in a one-pot procedure, without isolation of the intermediates (Scheme 1).

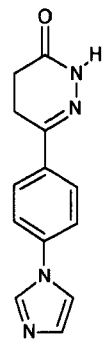


Scheme 1

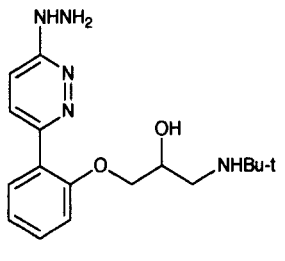
As a part of an ongoing project devoted to design and synthesize 3(2*H*)-pyridazinones endowed with biological activity,[8] we have continued to develop our synthetic strategy based on the [3 + 2] dipolar cycloaddition of readily available nitrile oxides with an alkyl acrylate, to produce 4,5-dihydroisoxazolines **3a–f**.[9] The latter in turn were converted into the final products in a two-step sequence involving: (i) molybdenum hexacarbonyl or catalytic hydrogenation promoted ring opening of 4,5-dihydroisoxazoles[10] to give α-hydroxy γ-keto esters **4a–f** in good yield; and (ii) ring closure with hydrazine hydrate at room or reflux temperature (Scheme 2).

Surprisingly, using the former experimental conditions ring closure to 3(2*H*)-pyridazinones occurs without elimination of the hydroxy group to furnish the 6-substituted 4,5-dihydro-4-hydroxy-3(2*H*)-pyridazinones **5a–f** in high yield (Scheme 2). Ring closure of **4a–f** with hydrazine hydrate in refluxing ethanol directly gave 6-substituted 3(2*H*)-pyridazinones **6a–f** in high yield, by intramolecular elimination of water, avoiding the need for an oxidation step.

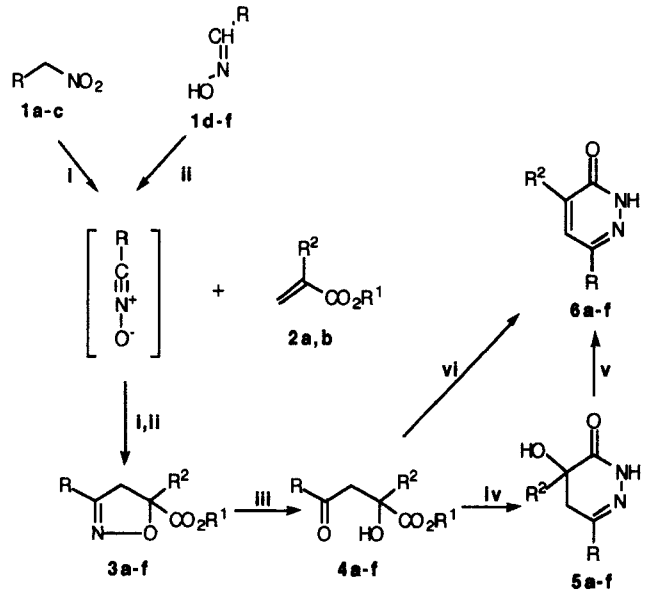
Thus, 3,5-disubstituted 4,5-dihydroisoxazoles **3a–f** were



imazodan



prizidilol



I: Ph-NCO, Ph-H, Et_3N; II: NCS, Py, Et_3N, 65-80%; III: $Mo(CO)_6$, MeCN/H_2O or H_2, Raney Ni,77-90%; IV: NH_2-NH_2,EtOH, r.t., 77-93%; V: EtOH, HCl 10%, 75-84%; VI: NH_2-NH_2, EtOH, reflux, 95%.

1–6	R	R^1	R^2
a	Me	Et	H
b	Bu	Et	H
c	Et	Me	Me
d	4-pyridyl	Et	H
e	4-HOC_6H_4	Et	H
f	2-pyridyl	Et	H

Scheme 2

obtained in high yield through a [3 + 2] cycloaddition of the nitrile oxides generated either from nitro derivatives **1a–c** (Mukaiyama conditions)[11] or oximes **1d–f** (Torsell conditions)[12] on acrylates **2a,b** (Table 1). N–O bond cleavage of the 3,5-disubstituted 4,5-dihydroisoxazoles **3a–f** in the presence of molybdenum hexacarbonyl or by catalytic hydrogenation furnished in good yield the corresponding α-hydroxy γ-keto esters **4a–f** (Table 1). Ring closure of the **4a–f** was readily accomplished in high yield with hydrazine in ethanol at room temperature. The mild conditions allowed isolation of the 4-hydroxypyridazinones **5a–f** (Table 2) which could easily be converted into aromatic derivatives **6a–f** by refluxing in ethanol in the presence of dilute hydrochloric acid. As further extension of the above reported synthetic methodology, we tested this general strategy to prepare 6-(1β-D-ribofuranosyl)pyridazin-3(2*H*)-one (**7**) as depicted in Scheme 3.

Treatment of the protected β-ribofuranosylnitromethane **8**[13] with ethyl acrylate in presence of phenyl isocyanate and triethylamine gave the isoxazoline **9** in 75% yield. Ring opening by molybdenum hexacarbonyl or catalytic hydrogenation delivered the α-hydroxy γ-keto ester **10** as a diastereomeric mixture.

Exposure of **10** to hydrazine in ethanol at reflux ensued cyclization to provide 6-(5′-*O*-benzoyl-β-D-ribofuranos-1′-yl)pyridazin-3(2*H*)-one (**11**) in quantitative yield, which after deprotection with methanolic ammonia gave the desired compound **7**.

Table 1. Compounds **3** and **4** Prepared

Product[a]	Yield[b] (%)	IR (neat) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
3a[c]	65	1735	1.3 (t, 3H, J = 7), 2.02 (s, 3H), 3.25 (dd, 2H, J = 8, 10), 4.23 (q, 2H, J = 7), 4.97 (dd, 1H, J = 8, 2)
3b[d]	70	1740	0.97 (t, 3H, J = 7), 1.3 (t, 3H, J = 7), 1.4 (m, 2H), 1.5 (m, 2H), 2.36 (t, 2H, J = 7), 3.2 (m, 2H), 4.2 (q, 2H, J = 7), 4.93 (dd, 1H, J = 8, 2)
3c	70	1740	1.1 (t, 3H, J = 7), 1.58 (s, 3H), 2.36 (q, 2H, J = 7), 2.91 (d, 1H, J = 18), 3.47 (d, 1H, J = 18), 3.77 (s, 3H)
3d	80	1735, 1600	1.3 (t, 3H, J = 7), 3.66 (d, 2H, J = 9), 4.25 (q, 2H, J = 7), 5.26 (pt, 1H), 7.53 (d, 2H, J = 6), 8.66 (d, 2H, J = 6)
3e	75	3300, 1740, 1610, 1420	1.3 (t, 3H, J = 7), 3.71 (d, 1H, J = 2.5), 3.76 (s, 1H), 4.27 (q, 2H, J = 7), 5.17 (dd, 1H, J = 11, 2.5), 6.9–7.5 (m, 4H), 9.56 (s, 1H)
3f	65	1750, 1590	1.25 (t, 3H, J = 7), 3.81 (d, 2H, J = 9), 4.25 (q, 2H, J = 7), 5.24 (pt, 1H), 7.38 (m, 1H), 7.72 (m, 1H), 7.95 (d, 1H, J = 5), 8.67 (d, 1H, J = 4)
4a	80 (78)	3500, 1740	1.3 (t, 3H, J = 7), 2.2 (s, 3H), 2.95 (m, 2H), 3.3 (d, 1H, J = 6), 4.22 (q, 2H, J = 7), 4.47 (q, 1H, J = 6).
4b	85 (80)	3450, 1750	0.95 (t, 3H, J = 7), 1.27 (t, 3H, J = 7), 1.3–1.6 (m, 4H), 2.48 (t, 2H, J = 7), 2.92 (m, 2H), 3.4 (d, 1H, J = 4), 4.2 (q, 2H, J = 7), 4.5 (m, 1H)
4c	77 (75)	3500, 1750	1.05 (t, 3H, J = 7), 1.4 (s, 3H), 2.45 (q, 2H, J = 7), 2.8 (d, 1H, J = 16), 3.1 (d, 1H, J = 16), 3.77 (s, 3H), 3.92 (s, 1H)
4d	90 (87)	3500–3350, 1740, 1600	1.2 (t, 3H, J = 7), 2.7 (m, 1H), 3.5 (m, 2H), 4.2 (q, 2H, J = 7), 4.7 (m, 1H), 7.72 (d, 2H, J = 6), 8.83 (d, 2H, J = 6)
4e	84 (88)	3450, 1735, 1610	1.3 (t, 3H, J = 7), 3.28 (d, 1H, J = 6), 3.54 (dd, 2H, 2H, J = 10, 6), 4.28 (q, 2H, J = 7), 4.64 (m, 1H), 6.9–7.01 (m, 2H), 7.5 (m, 2H), 7.5 (m, 1H), 7.72 (m, 1H), 11.94 (s, 1H)
4f	75 (86)	3450, 1740, 1620	1.2 (t, 3H, J = 7), 2.67 (d, 1H, J = 6), 3.57 (m, 2H), 4.25 (q, 2H, J = 7), 4.72 (s, 1H), 7.4 (m, 1H), 7.8 (m, 1H), 8.02 (d, 1H, J = 8), 8.7 (d, 1H, J = 4)

[a] Satisfactory microanalyses obtained: C ± 0.35, H ± 0.19, N ± 0.27%

[b] Isolated yield after flash column chromatography (EtOAc/light petroleum). Yields given in parentheses refer to yields obtained after ring opening by catalytic hydrogenation.

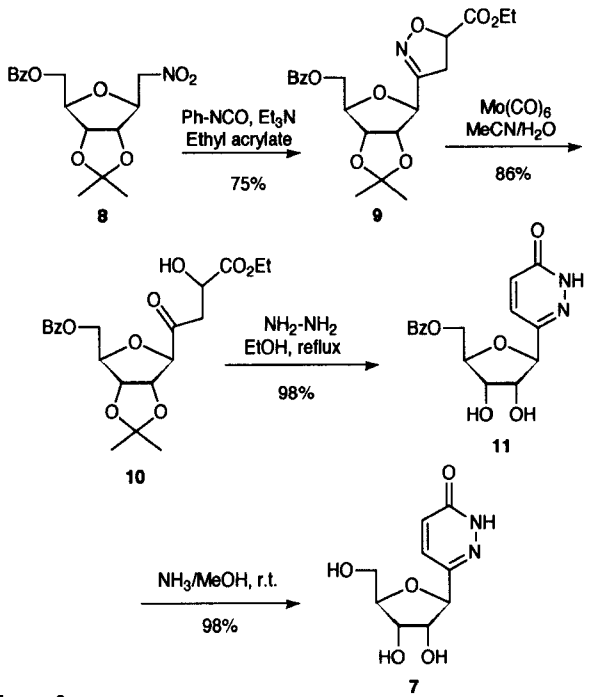
[c] **3a**, Lit.[9] IR and ^1H-NMR spectra are in full accord with the literature data.

[d] **3b**, Lit.[9] IR and ^1H-NMR spectra are in full accord with the literature data.

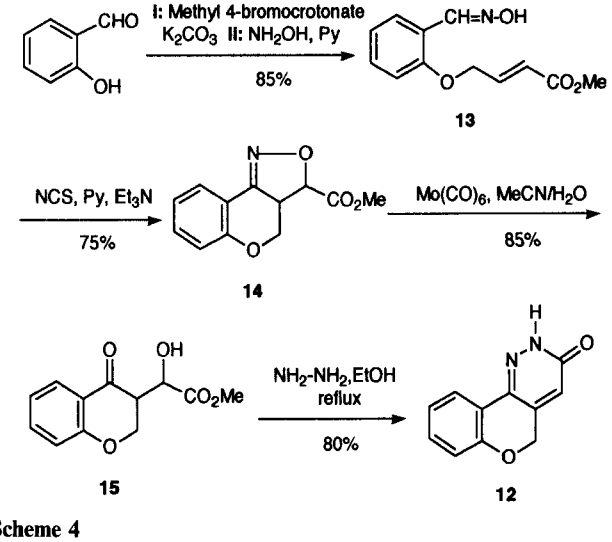
Table 2. Compounds **5** and **6** Prepared

Product[a]	mp(°C) (solvent)	Yield (%)	IR (Nujol) ν (cm^{-1})	^1H NMR (DMSO-d_6/TMS) δ, J (Hz)
5a	108 (Et_2O)	88	3500–3100, 1710, 1690	2.05 (s, 3H), 2.55 (dd, 1H, J = 12, 14), 2.75 (dd, 1H, J = 6, 14), 4.12 (dd, 1H, J = 6, 12), 5.12 (brs, 1H), 10.2 (brs, 1H)
5b	70 (Et_2O)	80	3450–3100, 1720–1690, 1510	0.9 (t, 3H, J = 7), 1.2–1.6 (m, 4H), 2.3 (t, 2H, J = 7), 2.6 (dd, 1H, J = 14, 16), 2.82 (dd, 1H, J = 8, 16), 4.23 (dd, 1H, J = 8, 14), 4.25 (brs, 1H), 9.29 (brs, 1H)
5c	65 (Et_2O)	93	3500–3100, 1710–1690	1.05 (t, 3H, J = 7), 1.2 (s, 3H), 2.2 (q, 2H, J = 7), 2.4 (s, 2H), 5.2 (brs, 1H), 10.42 (brs, 1H)
5d	218 (EtOAc)	85	3450–3100, 1710–1690, 1610	2.89 (dd, 1H, J = 10, 17), 3.22 (dd, 1H, J = 7, 17), 4.18 (m, 1H), 5.87 (d, 1H, J = 5), 7.63 (d, 2H, J = 6.5), 8.65 (d, 2H, J = 6.5), 10.42 (brs, 1H)
5e	250 (EtOAc)	77	3500–3100, 1710, 1690, 1600	3.04 (dd, 1H, J = 8, 14), 3.29 (dd, 1H, J = 6, 14), 4.17 (m, 1H), 5.92 (d, 1H, J = 4), 6.9 (m, 2H), 7.27 (m, 1H), 7.57 (m, 1H), 11.13 (s, 1H), 11.7 (s, 1H)
5f	202 (Et_2O)	82	3500–3100, 1715–1680, 1600	2.92 (dd, 1H, J = 11, 16), 3.17 (dd, 1H, J = 6, 16), 4.13 (m, 1H), 5.9 (brs, 1H), 7.44 (dd, 1H, J = 4, 8), 8.1 (d, 1H, J = 8), 8.58 (d, 1H, J = 4), 8.92 (d, 1H, J = 2), 11.12 (brs, 1H)
6a	115 (EtOAc)	75	3450–3350, 1660, 1610	2.34 (s, 3H), 6.95 (d, 1H, J = 9), 7.19 (d, 1H, J = 9), 12.8 (s, 1H)
6b	95 (EtOAc)	78	3400–3280, 1650, 1600, 1510	0.9 (t, 3H, J = 6), 1.3 (m, 2H), 1.6 (m, 2H), 2.49 (t, 2H, J = 16), 6.62 (d, 1H, J = 9), 7.33 (d, 1H, J = 9), 12.75 (s, 1H)
6c	83 (EtOAc)	84	3450–3300, 1660–1600	1.2 (t, 3H, J = 6), 2.01 (s, 3H), 2.45 (q, 2H, J = 6), 7.24 (s, 1H), 12.6 (s, 1H)

[a] Satisfactory microanalyses obtained: C ± 0.32, H ± 0.17, N ± 0.25. IR and ^{1}H-NMR spectra for compounds **6d–f** are in full accord with the literature data;[5] yield: **6d** (85%), **6e** (80%), **6f** (89%).



Scheme 3



Scheme 4

In order to extend the synthetic utility of this methodology we applied its intramolecular version[14] to the preparation of promising antiulcer and antisecretory tricyclic 3(2*H*)-pyridazinone **12**, recently reported by Cignarella et al.[15] (Scheme 4). Compound **12** was obtained through a five step sequence, involving an intramolecular nitrile oxide cyclization (INOC) of the precursor **13**. Compound **13** was obtained by alkylation of salicylaldehyde with methyl 4-bromocrotonate, and oximation with hydroxylamine. The cycloadduct **14**, obtained as a diastereomeric mixture (not separable in our hands), was heated with molybdenum hexacarbonyl in wet acetonitrile to furnish a diastereomeric mixture of γ-keto esters **15**. This was cyclized by refluxing with hydrazine hydrate in ethanol to give the tricyclic aromatic compound **12** in good yield.

The preparation of **12**[14] represents another example of the utility of intramolecular nitrile oxide cycloaddition (INOC) as a tool in organic synthesis. Pharmacological screening of the new series of 6-substituted 4,5-dihydro-4-hydroxy-3(2*H*)-pyridazinones described here is in progress, and their biological profiles will be described elsewhere.

Reaction courses and product mixtures were routinely monitored by TLC on silica gel (precoated F_{254} Merck plates) and visualized with I_2 or aqueous $KMnO_4$. IR spectra were measured on a Perkin-Elmer 257 instrument. ^{1}H NMR were obtained in $CDCl_3$ or DMSO-d_6 solutions with a Bruker AC 200 spectrometer, peak positions are given relative to TMS as internal standard, and J values are given in Hz. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Light petroleum refers to the fraction boiling at

40–60 °C. Melting points were determined on a Büchi-Tottoli instrument and are uncorrected. Chromatography was performed with Merck 60–200 mesh silica gel. All products reported showed IR and ^{1}H-NMR spectra in agreement with the assigned structures. Organic solutions were dried over anhydr. $MgSO_4$. Elemental analyses were performed by the microanalytical laboratory of Dipartimento di Chimica, University of Ferrara. Satisfactory microanalyses were obtained for the new compounds **7**, **11–15**: C ± 0.24, H ± 0.15, N ± 0.10.

4,5-Dihydroisoxazoles 3a–f; General Procedures:

Method A: Phenyl isocyanate (2.5 mL, 23 mmol) was slowly added (4 h) to a mixture of nitro derivatives **1a–c** (10 mmol) and the appropriate acrylate **2a–b** (20 mmol) in dry benzene (60 mL) containing Et_3N (20 μL). The mixture was stirred at r.t. for 2 d. The suspension was filtered to eliminate the precipitated diphenylurea and to the filtrate was added H_2O (100 mL). The resulting biphasic system was stirred for 2 h at r.t. After separation, the organic phase was separated, dried and concentrated in vacuo. The crude residue was purified by chromatography to give the 4,5-dihydroisoxazoles **3a–c** as colorless oils in a good yield (Table 1).

Method B: *N*-Chlorosuccinimide (NCS, 2.67 g, 20 mmol) was stirred in a flask containing anhydr. $CHCl_3$ (18 mL) and pyridine (0.1 mL). The oxime **1d–f** (20 mmol) was added at 25 °C in one portion, and then heated at 60 °C for 30 min. The chlorination of the oxime was usually complete in about 30 min as observed by the disappearance of the suspended NCS. The olefin (25 mmol) was added in one portion and the temperature raised to 40–50 °C. Et_3N (3 mL, 21 mmol) was added dropwise over 30 min. After a further 20 min at 40–50 °C, the solution was washed with H_2O, dried and evaporated in vacuo. The crude mixture was purified by chromatography to give **3d–f** as pale yellow oils in good yield (Table 1).

α-Hydroxy γ-Keto Esters 4a–f; General Procedures:

Method A: To a mixture of the 4,5-dihydroisoxazole **3a–f** (10 mmol) in MeCN (5 mL) containing H_2O (5 drops), $Mo(CO)_6$ (1.32 g, 5 mmol) was added and the well-stirred suspension heated to reflux. After 1 h, in order to complete the reaction, an additional amount of $Mo(CO)_6$ (0.26 g, 1 mmol) was added and the reflux continued until disappearance of starting material had disappeared (TLC). The mixture was cooled to r.t., silica gel (5 g) was added, the solvent evaporated in vacuo and the residue was chromatographed to furnish **4a–f** as yellow oils in good yield (Table 1).

Method B: A solution of **3a–f** (3 mmol) in MeOH/AcOH/H_2O (9 mL, 5:3:1) mixture was hydrogenated at 1 atmosphere in the presence of a catalytic amount of W-2 Raney nickel (0.25 g) for 5 h at r.t. After filtration through a Celite pad, the solvent was concentrated to dryness and the residue was purified as above to furnish **4a–f** (Table 1).

6-Substituted 4,5-Dihydro-4-hydroxy-3(2*H*)-pyridazinones 5a–f; General Procedure:

A mixture of **4a–f** (20 mmol) and 99% hydrazine hydrate (1.48 mL, 30 mmol) in 95% EtOH (10 mL) was stirred at r.t. for 2 h. The solvent was concentrated in vacuo, the residue diluted with H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried and concentrated in vacuo to give the products **5a–f** as solids which were recrystallized from an appropriate solvent (Table 2).

6-Substituted 3(2*H*)-Pyridazinones 6a–f; General Procedure:

A solution of **5a–f** (20 mmol) in 95% EtOH (10 mL) and 10% HCl (0.5 mL) was stirred at reflux for 2 h. The solvent was concentrated in vacuo and the residue diluted with a sat. solution of $NaHCO_3$ (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried and concentrated in vacuo to give the products **6a–f** as solids which were recrystallized from an appropriate solvent (Table 2).

3-(5′-*O*-Benzoyl-2′,3′-isopropylidene-β-D-ribofuranos-1′-yl)-5-ethoxycarbonyl-4,5-dihydroisoxazole (9):

Compound **9** was prepared by the same procedure used for compounds **3a–f** for the nitro derivative **8** (0.65 g, 1.92 mmol). After workup, the residue was purified by chromatography (Et_2O/light petroleum, 4:1) to furnish an approximately 1:1 diastereomeric mixture of **9** as a pale yellow oil; yield: 0.606 g (75%).

IR (neat) ν = 1730, 1450, 1380 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.21 (t, 3H, J = 7 Hz), 1.37 (s, 3H), 1.57 (s, 3H), 3.21–3.5 (m, 2H), 4.1–4.55 (m, 5H), 4.7–5.2 (m, 4H), 7.35–7.65 (m, 3H), 7.9–8.05 (m, 2H).

Ethyl 4-(5′-*O*-Benzoyl-2′,3′-isopropylidene-β-D-ribofuranos-1′-yl)-2-hydroxy-4-oxobutenoate (10):

The general procedure for the preparation of compounds **4a–f** was also applied to compound **10** starting from the 4,5-dihydroisoxazole **9** (1 g, 2.38 mmol). After workup, the residue was chromatographed with EtOAc/light petroleum (1:1) to give a diastereomeric mixture of **10** as a yellow oil; yield: 0.866 g (86%).

IR (neat): ν = 3500, 1730, 1460, 1375 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = diastereomeric mixture, 1.15 (t, 3H, J = 7 Hz), 1.31 (s, 3H), 1.48 (s, 3H), 2.8–2.9 (m, 2H), 4.0 (q, 2H, J = 7 Hz), 4.3–4.4 (m, 3H), 4.4–4.5 (m, 3H), 4.75–4.8 (m, 1H), 4.9–5.0 (m, 1H), 5.65 (m, 1H), 7.4–7.6 (m, 3H), 7.9–8.0 (m, 2H).

6-(5′-*O*-Benzoyl-β-D-ribofuranos-1′-yl)pyridazin-3(2*H*)-one (11):

A mixture of **10** (0.49 g, 1.15 mmol) and 99% hydrazine hydrate (0.10 mL, 1.30 mmol) was refluxed for 3 h. The solution was then cooled to r.t. and the solvent removed in vacuo. The residue was dissolved in EtOAc (30 mL) and washed with H_2O (2 × 15 mL). The organic layer was dried and concentrated in vacuo to afford the crude product which was recrystallized from MeOH to furnish as a white solid **11**; yield: 0.378 g (98%); mp 172°; $[\alpha]_D^{20}$ −60.5 (c = 1, $CHCl_3$).

IR (Nujol): ν = 3370, 3260, 1720, 1610, 1580 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.5–3.65 (m, 1H), 4.2–4.7 (m, 7H), 5.0 (d, 1H, J = 3 Hz), 6.81 (d, 1H, J = 9 Hz), 7.45–7.7 (m, 4H), 8.0–8.1 (m, 2H), 12.15 (br s, 1H).

6-β-D-Ribofuranosylpyridazin-3(2*H*)-one (7):

Compound **11** (0.2 g, 0.6 mmol) was dissolved in MeOH saturated with ammonia (20 mL). The solution was stirred overnight at r.t. until TLC analysis (EtOAc/MeOH, 8:2) showed the absence of starting material. The solution was concentrated in vacuo and the residue was purified by flash chromatography (EtOAc/MeOH, 8:2) to afford **7** as a white solid; yield: 0.13 g (98%); mp 177°C; $[\alpha]_D^{20}$ = −73 (c = 1, $CHCl_3$).

IR (Nujol): ν = 3500–3300, 1720, 1580 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.4–3.5 (m, 1H), 3.55–3.7 (m, 1H), 3.85–3.95 (m, 1H), 3.98–4.1 (m, 2H), 4.74 (m, 1H, exchang. with D_2O), 4.76 (d, 1H, J = 3 Hz), 4.97–4.99 (m, 1H, exchang. with D_2O), 5.04–5.05 (m, 1H, exchang. with D_2O), 6.81 (d, 1H, J = 9 Hz), 7.42 (d, 1H, J = 9 Hz), 12.87 (br s, 1H).

[*E*-(4-Carboxymethyl-3-propenyloxy)]benzaldehyde Oxime (13):

A mixture of salicylaldehyde (0.7 g, 5.73 mmol), K_2CO_3 (0.48 g, 3.43 mmol) and methyl 4-bromocrotonate (0.77 mL, 6.5 mmol) in anhydr. acetone (50 mL) was stirred at reflux for 3 h. When the TLC analysis (Et_2O) showed the disappearance of the starting material, the mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phase was dried and concentrated in vacuo. The resulting crude product was dissolved in absolute EtOH (30 mL) and to this solution pyridine (0.45 g, 5.73 mmol) and $NH_2OH \cdot HCl$ (0.40 g, 5.73 mmol) were added. After 2 h at r.t., the TLC analysis (Et_2O) showed the absence of starting material. The solvent was evaporated in vacuo and the residue was dissolved in H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The organic layer was dried and concentrated at reduced pressure and the residue was purified by chromatography (EtOAc) to give **13** as a yellow oil; yield: 1 g (75%).

IR (neat) ν = 3400–3150, 1720–1690, 1620 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.76 (s, 3H), 4.75 (m, 2H), 6.17 (d, 1H, J = 16 Hz), 6.8–7.5 (m, 5H), 8.54 (s, 1H), 9.07 (br s, 1H).

Methyl 3a,4-Dihydro-3*H*-[1]benzopyrano[4,3-*c*]isoxazole-3-carboxylate (14):
Compound **14** was prepared by Method B from the oxime **13** (1.06 g, 4.5 mmol). After workup, the residue was purified by chromatography (Et_2O/light petroleum, 2:1) to furnish a diastereomeric mixture of **14** (0.8 g, 75%) as a white solid; yield: 0.8 g (75%); mp 102–105 °C.

IR (Nujol): ν = 1730, 1610, 1470 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.88 (s, 3 H), 4–4.2 (m, 2 H), 4.72 (m, 2 H), 7.0 (m, 2 H), 7.31 (dd, 1 H, J = 9, 1 Hz), 7.77 (dd, 1 H, J = 9, 1 Hz).

Methyl 2-(2,3-Dihydro-4-oxobenzopyran-3-yl)-2-hydroxy Acetate (15):
The general procedure for the preparation of compounds **4a–f** (Method A) was also applied to compound **15** starting from the isoxazoline **14** (0.2 g, 0.8 mmol). After the usual workup, the residue was chromatographed on a silica gel column eluting with Et_2O to give a diastereomeric mixture of **15** as an oil; yield: 0.17 g (85%).

IR (neat): ν = 3400–3100, 1735, 1530 cm^{-1}.

^1H NMR ($CDCl_3$): δ = diastereomeric mixture, 3.1–3.5 (m, 2 H), 3.82 (s, 3 H), 4.31 (d, 1 H, J = 2 Hz), 4.62 (m, 2 H), 7.0 (m, 2 H), 7.48 (dd, 1 H, J = 9, 1 Hz), 7.81 (dd, 1 H, J = 9, 1 Hz).

5H-[1]-Benzopyrano[4,3-*c*]pyridazin-3(2*H*)-one (12):
A mixture of **15** (0.17 g, 0.72 mmol) and 99% hydrazine (0.032 mL, 0.72 mmol) was refluxed for 3 h. After this period the mixture was cooled and the solvent removed in vacuo. The residue was diluted with H_2O and extracted with EtOAc. Organic phase was dried and concentrated in vacuo. The residue was purified by chromatography (EtOAc) to furnish **12** as a white solid; yield: 0.11 g (80%); mp 250–251 °C (dec).

IR (Nujol): ν = 3270, 1710–1690, 1530 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.1 (s, 2 H), 6.84 (s, 1 H), 7.02 (d, 1 H, J = 9 Hz), 7.1 (m, 1 H), 7.38 (dd, 1 H, J = 9, 1 Hz), 7.87 (dd, 1 H, J = 9, 1 Hz), 13.15 (br s, 1 H).

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