Synthesis of pyrazole-4-carbohydrazide derivatives of pharmaceutical interest

Giuseppe Daidone*, Demetrio Raffa, Fabiana Plescia, Benedetta Maggio, and Angela Roccaro

Dipartimento di Chimica e Tecnologie Farmaceutiche
Via Archirafi, 3- I-90123 Palermo, Italy
E-mail: gdaidone@unipa.it

This paper is dedicated to Professor Domenico Spinelli on the occasion of his 70th birthday
(received 23 Oct 02; accepted 26 Dec 02; published on the web 03 Jan 03)

Abstract
New 1-phenyl- or 1-methyl-5-benzamidopyrazole-4-carbohydrazide derivatives were prepared in 70–90% yields from 1-methyl- or 1-phenyl-6-phenylpyrazolo[3,4-*d*]1,3-oxazin-4(1*H*)-one derivatives and hydrazine hydrate. Small quantities of the isomeric 5-aminopyrazole-4-(*N*-benzoyl)hydrazides were detected in some reaction mixtures, proving that intramolecular benzoyl migration can take place in the 5-benzamidopyrazole-4-carbohydrazide molecule. The direct formation of pyrazole-4-carbohydrazides from 5-benzamidopyrazole-4-carboxylic acid ethyl esters and hydrazine hydrate was unsuccessful.

Keywords: Pyrazole-4-carbohydrazides, pyrazole-4-(*N*-benzoyl)carbohydrazides, intramolecular benzoyl migration

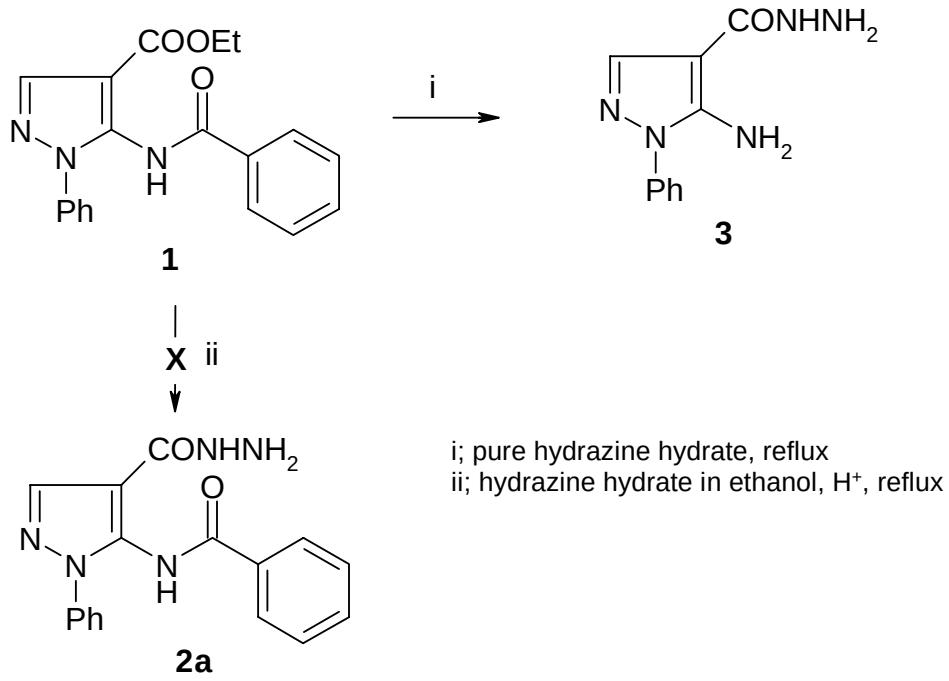
Introduction

In the course of our medicinal chemistry researches, we needed to prepare pyrazole-4-carbohydrazide derivatives **2a–h** (Schemes 1 and 2) in view of their potential pharmacological activities. In the literature it is reported that some benzohydrazides are used to inhibit fibrosis and to treat fibrosing disorder.[1] Several aryl- and heteroaryl- hydrazides produce inhibitory effects on glutamic acid decarboxylase (GAD), GABA-α-oxoglutarate amino transferase (GABA-T) and monoamine oxidase.[2,3] Moreover, Isoniazid®, namely pyridine-4-carbohydrazide, is the drug of choice in the treatment of tubercolosis.[4]

A review of the literature[5] revealed that 1-phenyl-5-benzamidopyrazole-4-carboxylic acid ethyl ester **1** (Scheme 1) when refluxed for 5 h in hydrazine hydrate afforded the 5-amino derivative **3**, by losing the benzoyl moiety, instead of the hydrazide derivative **2a**.

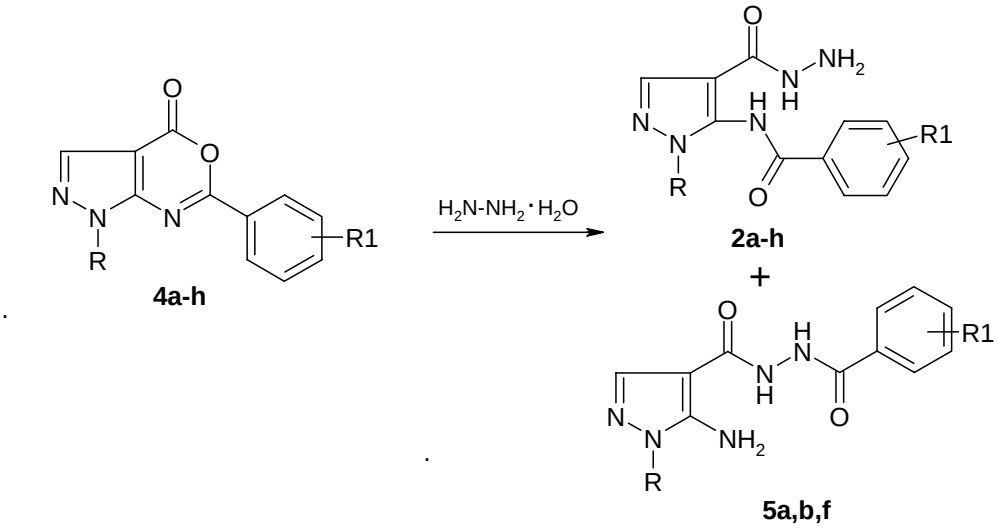
Results and Discussion

On the basis of the literature data, we heated the above mixture under reflux for 1h, obtaining the same result. At this point the formation of **2a** under other reaction conditions was attempted: an ethanolic solution of 1-phenyl-5-benzamidopyrazole-4-carboxylic acid ethyl ester and hydrazine hydrate in molar ratio 1:5 was heated under reflux for 15 hours, but TLC showed that the ester was not transformed. The experiment was repeated under acid catalysis, but the desired product **2a** was not obtained.



Scheme 1

Previously we have reported[6] that the reaction of pyrazole[3,4-*d*]-1,3-oxazin-4-one derivatives of type **4** with anilines afforded, in high yields, a number of phenylamides of 5-benzamidopyrazole-4-carboxylic acids. In analogy with this reaction we reacted the pyrazole[3,4-*d*]-1,3-oxazinones **4a–h** with hydrazine hydrate, hoping to obtain the pyrazole-4-carbohydrazides **2a–h**. When the pyrazolo-oxazinone **4a** was reacted with hydrazine hydrate, a product was obtained in 75% yield, together with a small amount of a second one. On the basis of elemental analysis and molecular weight (MS), they proved to be isomers. We assigned structure **2a** to the high-yield product and structure **5a** to the isomer (Scheme 2).



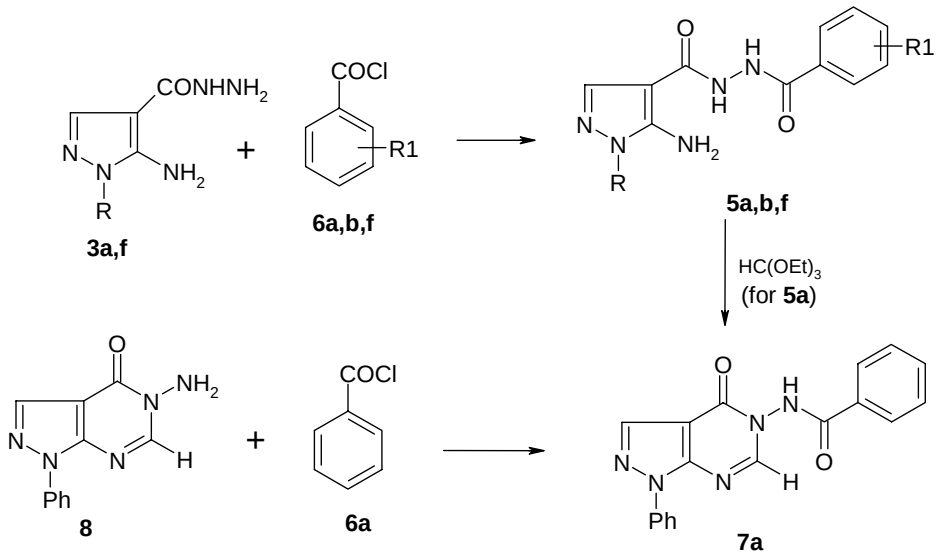
	a	**b**	**c**	**d**	**e**	**f**	**g**	**h**
R	Ph	Ph	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3
R1	H	p-Cl	H	p-Cl	o-NH_2	p-NO_2	o-NO_2	o-Cl

Scheme 2

The attribution of the structures was based on NMR data. The ^{1}H-NMR spectrum of the major product showed a signal for two hydrogens at δ4.39, exchangeable with D_2O, and the minor isomer produced the same signal at δ6.40; the low-field signal is attributable to the amino group bonded to the pyrazole nucleus, and the signal at δ4.39 to the more shielded hydrazide amino group. The latter value is in accordance with the signal reported in the literature for the hydrazide amino group of 2-pyridinecarbohydrazide.[7] The two NH signals of **5a** (9.96 and 10.36 δ) were closer than those of **2a** (9.43 and 10.40 δ) owing to a more similar environment of the NH groups in **5a**. In order to confirm the structure **5a**, the 1-phenyl-5-aminopyrazole-4-carbohydrazide **3a** and benzoyl chloride **6a** were reacted (Scheme 3), affording a compound identical in all respects to **5a**.

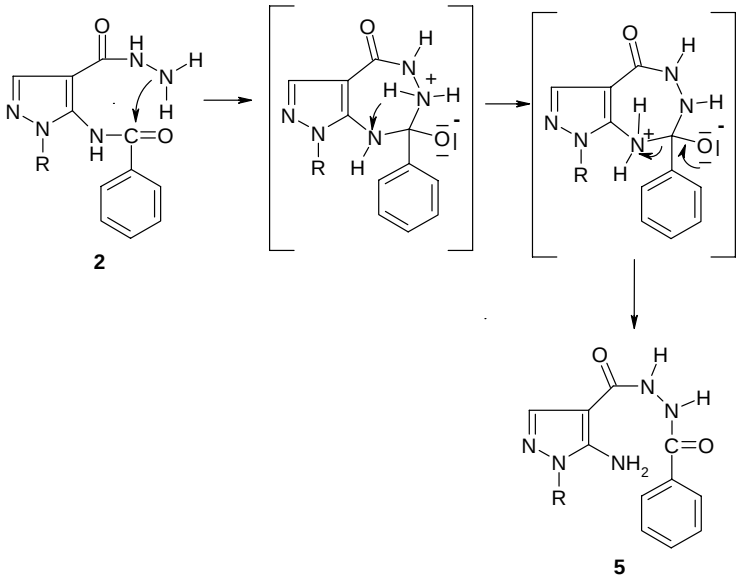
Moreover, reaction of this product **5a** with ethyl orthoformate gave the 1-phenyl-5-benzamido-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-one **7a** which was also obtained by benzoylation of the 5-amino-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-one **8**.[8] At this point, the other pyrazolo[3,4-*d*]oxazinones **4b–h** were reacted with hydrazine hydrate affording the related pyrazolo-4-carbohydrazides **2b–h** in 70–90% yields. The NMR spectra of these compounds showed the signal for the hydrazide amino group in the δ 4.32–4.39 range and those for the two NH groups at δ 9.20–10.79. The reaction mixtures of **2b–h** were monitored for the presence of **5b–h** by ^{1}H-NMR. On the basis of the 5-amino signal, the spectra revealed the presence of small amounts of **5b,f** (signals at 6.44 and 6.25 δ respectively). These results were confirmed by TLC using authentic specimens of **5b,f** as reference compounds. Compounds **5b,f** were synthesized as for **5a** (Scheme 3) and identified by elemental and spectroscopic data. The ^{1}H-NMR spectra of **5b,f**

showed the 5-amino signal at 6.45 and 6.22 δ, respectively. The formation of **2a–h** can easily be explained by a nucleophilic attack on the carbonyl group of the oxazinone ring of **4a–h**. It appears that this process can be followed by intramolecular migration of a benzoyl group in compounds **2a,b,f** to give the isomers **5a,b,f**, whose formation is rationalized in Scheme 4.



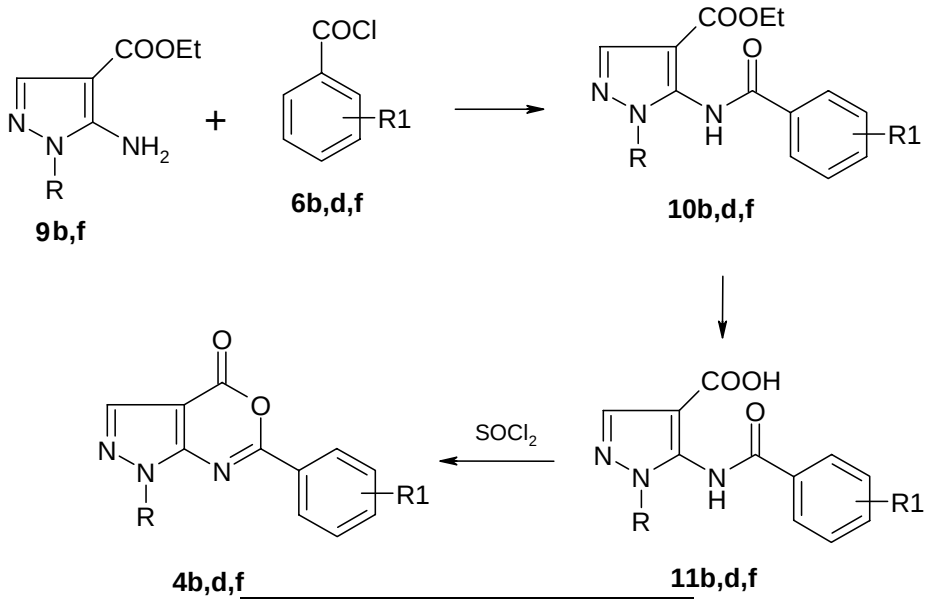
	a	b	f
R	Ph	Ph	CH_3
R1	H	p-Cl	p-NO_2

Scheme 3



Scheme 4

Lastly, the hitherto unknown pyrazolo-oxazinones **4b,d,f** were synthesized following Scheme 5. The structures of the above compounds, as well as those of the intermediate derivatives **10** and **11** were assigned on the basis of satisfactory elemental and spectroscopic data.



	b	d	f
R	Ph	CH_3	CH_3
R1	p-Cl	p-Cl	p-NO_2

Scheme 5

Experimental Section

General Procedures. Melting points were determined on a Büchi 530 capillary melting point apparatus and are uncorrected; IR spectra were recorded in Nujol mulls with a Jasco IR-810 spectrophotometer; ^{1}H-NMR spectra were obtained in DMSO-d_6 on a Bruker AC-E 250 MHz spectrometer (TMS as internal standard). Mass measurements at low resolution were obtained on an Autospect Ultima Orthogonal T.O.F.T. mass spectrometer operating at 75 eV. Elemental analyses (C, H, N), performed by Dipartimento di Scienze Farmaceutiche–Università di Catania, were within ±0.4% of theoretical values.

Reaction of 1-(*R*)-6-(substituted)phenyl-1*H*-pyrazolo[3,4-*d*]1,3-oxazin-4-one derivatives 4a–h with hydrazine hydrate. General procedure for 1-*R*-5-(substituted)benzamidopyrazole-4-carbohydrazides 2a–h. 4a,c,e,g,h [9] and **4b,d,f** (6 mmol) were reacted under reflux for 2h with 6 mmol of hydrazine hydrate (0.3 ml of 99% solution) in absolute ethanol (40 ml). The mixture, containing **2c–h**, was then allowed to cool at room temperature. The precipitate was filtered off,

and recrystallized from ethanol to give **2c–h**. In the case of **2b** the mixture was evaporated under vacuum and the solid recrystallized from ethyl acetate, whereas for **2a** the precipitate was obtained after scratching. Yields 70–90%. The mother liquors of **2a** were evaporated and the residue was chromatographed by flash chromatography:[10] silica gel (230–400 mesh), external column diameter 3.5 cm, ethyl acetate as eluent, fractions each 50 ml. The fractions 6–11 were collected and evaporated under reduced pressure to give 70 mg of pure 1-phenyl-5-amino-1*H*-pyrazole-4-(N-benzoyl)carbohydrazide **5a**. **2a** (75%); m.p. 183–185 °C; MS (*m/z*): 321 (M^+); IR (cm^{-1}): 3440–3115 (multiple bands, NH_2, and 2xNH), 1675–1625 (multiple bands, 2xCO); ^{1}H-NMR (δ): 4.39 (2H, s, exchangeable NH_2), 7.34–7.90 (10H, a set of signals, 2xC_6H_5), 8.17 (1H, s, pyrazole H-3), 9.43 (1H, s, exchangeable NH), 10.40 (1H, s, exchangeable NH). **5a** m.p. 255–258 °C; MS (*m/z*): 321 (M^+); IR (cm^{-1}): 3450–3100 (multiple bands, NH_2 and 2xNH), 1670, 1620 (br., 2xCO); ^{1}H-NMR (δ): 6.48 (2H, s, exchangeable NH_2), 7.39–7.98 (10H, a set of signals, 2xC_6H_5), 8.12 (1H, s, pyrazole H-3), 10.02 (1H, s, exchangeable NH), 10.42 (1H, s, exchangeable NH). **2b** (70%); m.p. 182–183 °C; MS (*m/z*): 355 (M^+); IR (cm^{-1}): 3400–3100 (multiple bands, NH_2, 2xNH), 1665, 1638 (2xCO); ^{1}H-NMR (δ): 4.41 (2H, s, exchangeable NH_2) 7.37–7.91 (9H, a set of signals, C_6H_5 and C_6H_4) 8.18 (1H, s, pyrazole H-3), 9.45 (1H, s, exchangeable NH), 10.49 (1H, s, exchangeable NH). **2c** (80%); m.p. 205–206 °C; MS (*m/z*): 259 (M^+); IR (cm^{-1}): 3450–3100 (multiple bands, NH_2, 2xNH), 1670–1630 (multiple bands, 2xCO); ^{1}H-NMR (δ): 3.67 (3H, s, CH_3), 4.32 (2H, s, exchangeable NH_2) 7.53–8.04 (6H, a set of signals, C_6H_5 and pyrazole H-3), 9.25 (1H, s, exchangeable NH), 10.34 (1H, s, exchangeable NH). **2d** (70%); m.p. 249–250 °C; MS (*m/z*): 293 (M^+); IR (cm^{-1}): 3400–3100 (NH2, 2xNH) 1705, 1635 (2xCO); ^{1}H-NMR (δ): 3.66 (3H, s, CH_3), 4.30 (2H, s, exchangeable NH_2), 7.62–8.05 (5H, a set of signals, C_6H_4 and pyrazole H-3), 9.24 (1H, s, exchangeable NH), 10.39 (1H, s, exchangeable NH). **2e** (78%); m.p. 208–209 °C; MS (*m/z*): 274 (M^+); IR (cm^{-1}): 3420, 3290 (br., 2xNH, 2xNH_2) 1690, 1680, 1630 (2xCO); ^{1}H-NMR (δ): 3.65 (3H, s, CH_3), 4.35 (2H, s, exchangeable NH_2) 6.25–8.00 (7H, a set of signals, C_6H_4, pyrazole H-3 and exchangeable NH_2), 9.22 (1H, s exchangeable NH), 10.00 (1H, s, exchangeable NH). **2f** (90%); m.p. 238–240 °C; MS (*m/z*): 304 (M^+); IR (cm^{-1}): 3400–3100 (multiple bands, 2xNH, NH_2), 1681, 1632 (2xCO); ^{1}H-NMR (δ): 3.68 (3H, s, CH_3), 4.36 (2H, br. s, exchangeable NH_2), 7.89 (1H, s, pyrazole H-3), 8.22–8.43 (4H, dd, C_6H_4), 9.29 (s, 1H, exchangeable NH), 10.67 (1H, br. s, exchangeable NH). **2g** (80%); m.p. 268–270 °C; MS (*m/z*): 304 (M^+); IR (cm^{-1}): 3360–3100 (multiple bands, 2xNH, NH_2) 1680, 1620 (br. bands, 2xCO); ^{1}H-NMR (δ): 3.75 (3H, s, CH_3), 4.36 (2H, s, exchangeable NH_2) 7.79–8.17 (5H, a set of signals, C_6H_4 and pyrazole H-3), 9.30 (s, 1H, exchangeable NH), 10.79 (1H, s, exchangeable NH). **2h** (85%); m.p. 244–245 °C; MS (*m/z*): 293 (M^+); IR (cm^{-1}): 3310, 3170 (br. NH and NH_2) 1700, 1650 (2xCO); ^{1}H-NMR (δ): 3.72 (3H, s, CH_3), 4.35 (2H, s, exchangeable NH_2) 7.52–7.89 (5H, a set of signals, C_6H_4 and pyrazole H-3), 9.20 (s, 1H, exchangeable NH), 10.49 (1H, s, exchangeable NH).

General procedure for 1-R-5-aminopyrazole-4-(N-benzoyl)carbohydrazides 5a,b,f

A solution of 0.01 moles of a pyrazole-4-carbohydrazide **3a–f** in acetonitrile (50 ml) was heated under reflux with 0.01 mole of the appropriate benzoyl chloride **6a,b,f** for 7h. The solid which separated was collected then recrystallized from ethanol to give pure **5**; yields 78–85%. **5a** (80%) identical in all respect to the low-yield product obtained by reacting **4a** with hydrazine hydrate. **5b** (78%); m.p. 263–265 °C; MS (*m/z*): 355 (M^+); IR (cm^{-1}): (Microanalysis Calc. for $C_{17}H_{14}N_5O_2Cl·H_2O$): 3500–3100 (multiple bands, NH_2 and NH-NH), 1660 (br., 2xCO); ^{1}H-NMR (δ): 6.45 (2H, br. s, exchangeable NH_2), 7.41–7.98 (9H, a set of signals, C_6H_5 and C_6H_4), 8.07 (1H, s, pyrazole H-3), 9.99 (1H, s, exchangeable NH), 10.47 (1H, s, exchangeable NH). **5f** (85%); m.p. 275–276 °C (ethanol); MS (*m/z*): 304 (M^+); IR (cm^{-1}) (Nujol): 3460–3100 (multiple bands, NH_2 and NH-NH), 1685, 1620 (br., 2xCO); ^{1}H–NMR (δ) (DMSO–d_6): 3.54 (3H, s, CH_3) 6.22 (2H, br. s, exchangeable NH_2), 7.42 (1H, s, pyrazole H–3), 7.74-8.34 (5H, dd, C_6H_5), 9.83 (1H, s, exchangeable NH), 10.59 (1H, s, exchangeable NH).

1-Phenyl-5-benzamido-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-one 7a. Method A. 1g (0.003 moles) of compound **5a** and 10 ml of triethyl orthoformate were heated at reflux for 4h. After cooling, the white solid product was collected and recrystallized from ethanol. **7a** (75%); m.p. 233–235 °C; MS (*m/z*): 331 (M^+); IR (cm^{-1}): 3256 (br., NH), 1685 (br., CO); ^{1}H-NMR (δ): 7.43–8.66 (12H, a set of signals, 2xC_6H_5, pyrazole H-3, quinazolinone H-2), 11.93 (1H, s, exchangeable NH).

Method B. Equimolar amounts (0.01 moles) of compound **8**[8] and the benzoyl chloride **6a** in pyridine/dioxane (1:1) mixture were heated under reflux for 1 h, then cooled and poured on cold diluted HCl. The solid which separated was collected, and recrystallized from ethanol to give pure **7a** which was identical to that synthesized by method A (Rf, mixed m.p., MS); yields 53%.

General procedure for ethyl 1-(*R*)-5-benzamido-1*H*-pyrazole-4-carboxylate 10b,d,f

Equimolar amounts (0.033 moles) of ethyl 1-R-5-aminopyrazole-4-carboxylate **9b,f** and the appropriate benzoyl chloride **6b,d,f** in anhydrous acetonitrile (150 ml) were heated at reflux for 5h. After the first hour, four portions of triethylamine, 2.2, 1.1, 0.6 and 0.6 ml each, were added at intervals of 1 h. The solution was evaporated in vacuum, the residue washed with water until it became solid, filtered off, and then recrystallized from ethanol to give compounds **10**; yields 65–80%. **10b** (78%); m.p. 126–127 °C; MS (*m/z*): 369 (M^+); IR (cm^{-1}): 3400–3200 (NH), 1700, 1685 (2xCO); ^{1}H-NMR (δ): 1.14 (3H, t, CH_3) 4.17 (2H, q, CH_2) 7.24–8.20 (10H, multiplet, C_6H_5 C_6H_4 and pyrazole H-3) 10.64 (1H, s, exchangeable NH). **10d** (65%); m.p. 148–150 °C; MS (*m/z*): 307 (M^+); IR (cm^{-1}): 3250 (NH) 1710–1665 (2xCO); ^{1}H-NMR (δ): 1.15 (3H, t, CH_3) 3.72 (3H, s, CH_3) 4.13 (2H, q, CH_2) 7.65–8.06 (5H, multiplet, C_6H_4 and pyrazole H-3) 10.56 (1H, s, exchangeable NH). **10f** (80%); m.p. 140–142 °C; MS (*m/z*): 318 (M^+); IR (cm^{-1}): 3330 (NH), 1690–1670 (2xCO); ^{1}H-NMR (δ): 1.14 (3H, t, CH_3) 3.32 (3H, s, CH_3) 4.13 (2H, q, CH_2) 7.98 (1H, s, pyrazole H-3) 8.20–8.44 (4H, dd, C_6H_4) 10.82 (1H, s, exchangeable NH).

General procedure for 1-(*R*)-5-benzamido-1*H*-pyrazole-4-carboxylic acids 11b,d,f

To a solution of ethyl 1-R-5-benzamido-1*H*-pyrazole-4-carboxylate **10b,d,f** (0.025 moles) in ethanol (100 ml) 120 ml of an aqueous sodium hydroxide solution (4%) was added. The mixture was heated at reflux for 15 min. then allowed to stand at room temperature for 12h. The solution was cooled (ice bath) and dilute hydrochloric acid was added to give complete precipitation (pH~2). The separated solid was filtered off and recrystallized from ethanol to give **11b,d,f**. Yields 80–85%. **11b** (80%); m.p. 233–235 °C; MS (*m/z*): 341 (M^+); IR (cm^{-1}): 3300–2500 (OH, NH), 1690, 1662 (2xCO); ^{1}H-NMR (δ): 7.36–8.13 (10H, C_6H_5, C_6H_4 and pyrazole H-3) 10.57 (1H, s, exchangeable NH) 12.57 (1H, br. s, exchangeable OH). **11d** (85%); m.p. 205–207 °C; MS (*m/z*): 279 (M^+); IR (cm^{-1}): 3590 (OH), 3320 (NH), 1700–1670 (2xCO); ^{1}H-NMR (δ): 3.69 (3H, s, CH_3) 7.65–8.06 (5H, multiplet, C_6H_4 and pyrazole H-3) NH and OH non-detectable signals. **11f** (80%); m.p. 227–230 °C; MS (*m/z*): 290 (M^+); IR (cm^{-1}): 3580–3320 (OH, NH), 1710–1680 (2xCO); ^{1}H-NMR (δ): 3.72 (3H, s, CH_3) 7.86 (1H, s, pyrazole H-3) 8.22–8.44 (4H, dd, C_6H_4), NH and OH non-detectable signals.

General procedure for 1-(*R*)-6-(4-R_1-phenyl)-pyrazolo[3,4-*d*]-1,3-oxazin-4-ones 4b,d,f

Thionyl chloride (10 ml) was added to a suspension of compound **11b,d,f** (0.025 moles) in anhydrous benzene (45 ml). The mixture was heated at reflux for 4 h, cooled, and the solid precipitate collected and recrystallized from ethanol; yields 68–75%. **4b** (70%); m.p. 210 °C; MS (*m/z*): 323 (M^+); IR (cm^{-1}): 1790–1780 (CO); ^{1}H-NMR (δ): 7.41–8.27 (10H, complex, C_6H_5 C_6H_4 and pyrazole H-3). **4d** (68%); m.p. 203–205 °C; MS (*m/z*): 261 (M^+); IR (cm^{-1}): 1795–1785 (CO); ^{1}H-NMR (δ): 3.99 (1H, s, CH_3), 7.67–8.27 (5H, complex, C_6H_4 and pyrazole H-3). **4f** (75%); m.p. 215–220 °C; MS (*m/z*): 272 (M^+); IR (cm^{-1}): 1780 (CO); ^{1}H-NMR (δ): 8.29–8.40 (5H, complex, C_6H_4 and pyrazole H-3).

Acknowledgments

Financial support from MIUR is gratefully acknowledged.

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