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Tetrahedron
Tetrahedron 62 (2006) 12281–12287

Nucleophilic aromatic substitutions on 4,5-dicyanopyridazine. Pyrrole and indole systems as carbon nucleophiles

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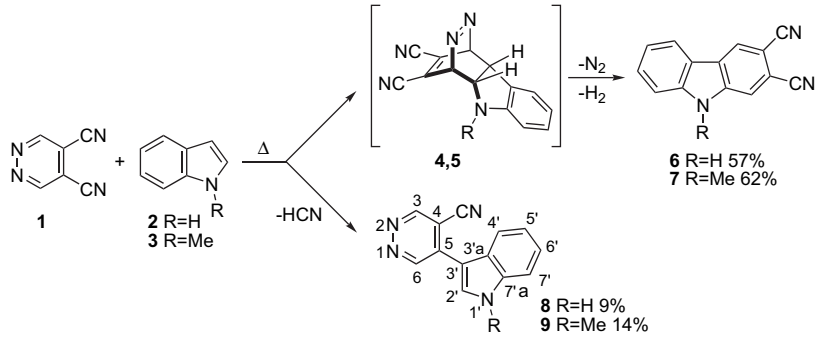
Received 20 July 2006; revised 20 September 2006; accepted 5 October 2006
Available online 31 October 2006

Abstract—4,5-Dicyanopyridazine was found to react with pyrrole and indole counterparts not only as heterocyclic azadiene in inverse electron-demand Hetero Diels–Alder reactions, as previously evidenced, but even as a very reactive heterocyclic electrophile at C-4 carbon, in formal S_NAr2 processes where a CN group acts as leaving group. In particular, operating in acetic acid as solvent, nucleophilic addition–elimination sequences allowed a facile access to pyrrolyl- and indolylpyridazines, through the corresponding 1,4-dihydropyridazine adducts.

1. Introduction

Electron-rich heterocycles with latent enamine functionalities, such as pyrrole and indole derivatives, have been widely exploited in the last 15 years as 2π electron components in inter- and intramolecular inverse electron-demand Hetero Diels–Alder (HDA) reactions with electron-deficient heteroaromatic azadienes and, in particular, the use of 1,2,4,5-tetrazines and 1,2,4-triazines as 4π electron counterparts allowed a facile access to complex indole alkaloids.[1] In this context, 1,2-diazines played a minor role, apart a few exceptions, such as tetramethyl pyridazine-3,4,5,6-tetracarboxylate,[2] polycondensed derivatives as 1,4-dicyanophthalazine[3] and 1,4-bis(trifluoromethyl)pyrido[3,4-*d*]-pyridazine,[4] and indolylalkylpyridazines,[5] which were able to react in intramolecular HDA processes.

Nevertheless, we recently demonstrated that even 4,5-dicyanopyridazine (DCP) (**1**) was able to react as heterocyclic azadiene in intermolecular inverse electron-demand HDA reactions with pyrrole and indole dienophiles.[6] For instance, when DCP was allowed to react with indole (**2**) and *N*-methylindole (**3**) in a sealed tube, respectively, in xylene at 150 °C and chloroform at 110 °C, we succeeded into the isolation in quite satisfactory yields of dicyanocarbazoles **6** and **7** from the primary adducts **4** and **5**, through nitrogen extrusion and aromatization. Anyway, the above HDA reactions had to reckon with competitive S_NAr2 pathways, responsible for the formation of minor amounts of indolylpyridazines **8** and **9** (Scheme 1). Moreover, with great astonishment, attempts to favour the final aromatization step leading to carbazole derivatives by operating in $CHCl_3$ at 110 °C, in the presence of catalytic amounts of palladium on carbon,[7]



Scheme 1.

Keywords: 4,5-Dicyanopyridazine; Pyrrole and indole nucleophiles; Pyrrolylpyridazines and indolylpyridazines; 1,4-Dihydropyridazine adducts; Nucleophilic aromatic substitutions; Addition–elimination processes.
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doi:10.1016/j.tet.2006.10.007

gave rise to the preferential formation of compounds **8** and **9** isolated in 35% and 70% yields, respectively, instead of **6** and **7**.[6]

The displacement of the cyano group in heterocyclic compounds by nucleophiles is rare and only a few cases have been reported concerning 1,2,4-triazinecarbonitriles,[8] 4-quinazolinecarbonitriles,[8b] 1-methyl-4(1*H*)-quinazolinone-2-carbonitrile[9] and 5-arylpyrazine-2,3-dicarbonitriles.[10] In the pyridazine series, to our knowledge, the formal replacement of the nitrile function by phenyl group has been just observed in the reactions of phenylmagnesium chloride with 4-cyano-3(2*H*)-pyridazinone and tetrazolo[1,5-*b*]pyridazine-8-carbonitrile.[11]

On this ground, and with the aim to gain better insight into the possibility to perform nucleophilic aromatic substitutions on the dinitrile **1**, exploiting the reactivity of the cyano group as leaving group, we decided to reinvestigate the behaviour of DCP towards pyrrole and indole systems through suitable modifications of the experimental conditions.

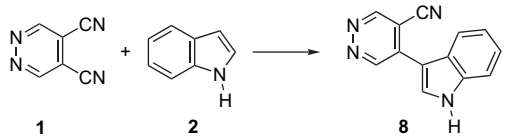
2. Results and discussion

First of all, to elucidate the role of palladium in the nucleophilic substitution pathway, we studied the reactivity of DCP with indole (**2**) (1–1.5 equiv) in the presence of different palladium catalysts, in different solvents and reaction conditions (Table 1). The observed results were quite unclear and the best one was that obtained employing 10% Pd/C in $CHCl_3$ at 50 °C, that afforded **8** in 90% yield (Table 1, entry 1).

At the same time, to investigate the solvent effect, we carried out the above reaction without palladium catalysts in different solvents. While DCP was absolutely inert towards indole in chloroform at 50 °C, operating in acetonitrile at the same temperature compound **8** was obtained as the predominant product (82% yield) after 17 days (Table 1, entries 7 and 8). Anyway, when dinitrile **1** was allowed to react with 1 equiv of **2** in glacial acetic acid for 9 days at room temperature, we succeeded into the isolation of **8** in 91% yield, as the sole reaction product (Table 1, entry 9).

These results clearly show the importance of the acidity in the nucleophilic substitution pathway, likely involving the LUMO of protonated DCP (E_{LUMO}=−5.883 eV) at lower energy with respect to the corresponding orbital of **1** (E_{LUMO}=0.067 eV).[12] Moreover, the acidic medium,

Table 1. Reactions of **1** with indole (**2**)

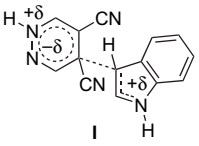


1 **2** **8**

Entry	Catalyst and co-reagents[a]	Solvent	Temp (°C)	Time (days)	**8** Yield[b] (%)
1	10% Pd/C	$CHCl_3$	50	11	90
2	10% Pd/C	MeCN	50	11	—
3	$Pd(PPh_3)_4$ (0.05)	MeCN	rt	11	—
4	$Pd(PPh_3)_2Cl_2$ (0.01), CuI (0.05), K_2CO_3 (1.5)	MeCN	rt	11	52
5	$Pd(OAc)_2$ (0.05), *p*-benzoquinone (1.5)	$CHCl_3$	rt	45	—
6	$Pd(OAc)_2$ (0.05), *p*-benzoquinone (1.5)	AcOH	rt	45	40
7	—	$CHCl_3$	50	12	—
8	—	MeCN	50	17	82
9	—	AcOH	rt	9	91

[a] Molar ratios with respect to **1** are reported in brackets.
[b] Isolated yields.

through protonation of the pyridazine nitrogen, seems to play a crucial role in the competition between HDA and S_NAr2 processes: the stabilization of transition state **I** can, in fact, justify the observed preference for the latter path (Fig. 1).

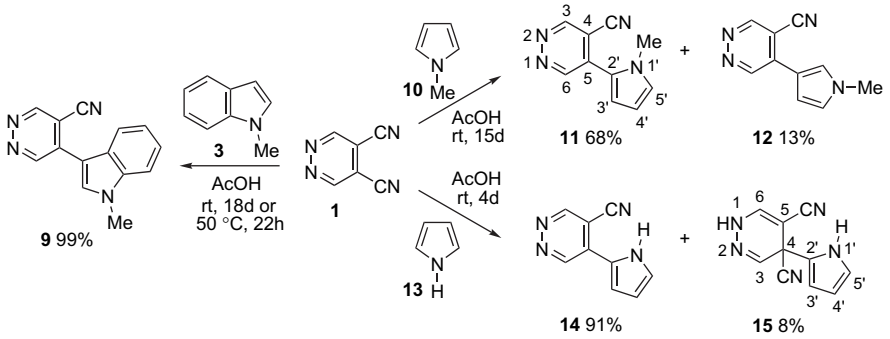


I

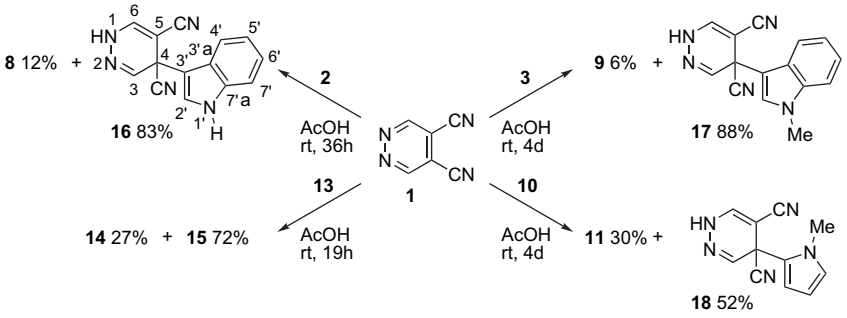
Figure 1.

This observation prompted us to study nucleophilic aromatic substitutions on DCP with indole and pyrrole systems as carbon nucleophiles, operating in glacial acetic acid as solvent.

When 4,5-dicyanopyridazine (**1**) was allowed to react with *N*-methylindole (**3**) (1–1.5 equiv) in AcOH at room temperature for 18 days, 4-cyano-5-(1-methyl-1*H*-indol-3-yl)pyridazine (**9**) was isolated in almost quantitative yield; the same result was achieved by heating at 50 °C for 22 h (Scheme 2). Treatment of **1** with 1.5 equiv of *N*-methylpyrrole (**10**) gave, after 15 days in acetic acid at room temperature, the regioisomeric pyrrolylpyridazines **11** and **12** in 68% and 13% yields,



Scheme 2.



Scheme 3.

respectively (Scheme 2).[13] Operating as above with the more reactive pyrrole (**13**), 4-cyano-5-(1*H*-pyrrol-2-yl)pyridazine (**14**) was isolated after 4 days in 91% yield, together with a minor amount (8%) of 4,5-dicyano-4-(1*H*-pyrrol-2-yl)-1,4-dihydropyridazine (**15**) (Scheme 2).

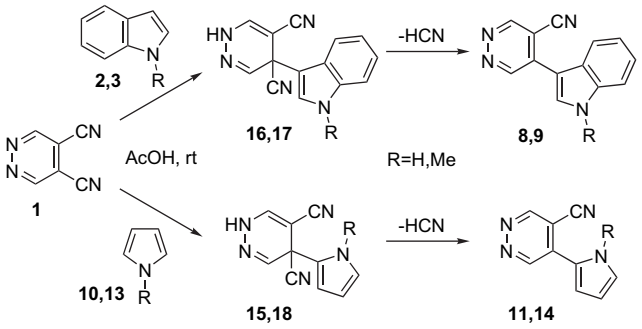
The formation of the 1,4-adduct **15** appeared really interesting to induce further investigations to elucidate the reaction mechanism.

Operating with 1 equiv of indole (**2**) for 36 h at room temperature, we succeeded in the isolation of compounds **8** and **16** in 12% and 83% yields, while *N*-methylindole (**3**) gave after 4 days in the same conditions **9** and **17** in 6% and 88% yields, respectively (Scheme 3).

Analogous results were obtained with stoichiometric amounts of pyrroles **10** and **13**: the former reacted with **1** to give, after 4 days at room temperature, derivatives **11** and **18** in 30% and 52% yields, while the latter afforded in 19 h compounds **14** and **15**, isolated in 27% and 72% yields, respectively (Scheme 3).

The 1,4-dihydropyridazine adducts **15–18** evolved slowly into pyridazine derivatives **8**, **9**, **11** and **14**, through HCN elimination, by simple stirring in AcOH at room temperature.[14]

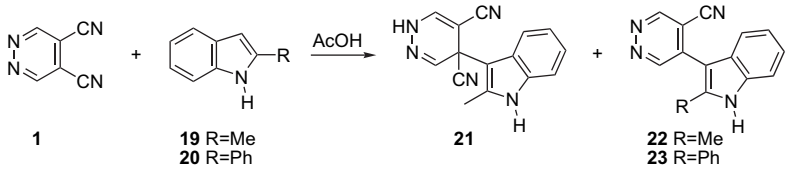
These data clearly show that the formal nucleophilic substitution products **8**, **9**, **11** and **14** are actually the fruit of a two-step process, involving nucleophilic addition and elimination reactions. Regioselective nucleophilic attacks of C-3 and C-2 carbons, respectively, of indole and pyrrole nucleophiles **2**, **3**, **10** and **13** on the strongly electrophilic C-4 carbon of DCP (or, more likely, protonated DCP) lead to intermediates **15–18** that, in turn, evolve into the aromatic species **8**, **9**, **11** and **14** through spontaneous HCN elimination (Scheme 4).



Scheme 4.

Then, to assess applications and limits of this new reactivity of DCP, we decided to study the behaviour of **1** towards different pyrrole and indole derivatives.

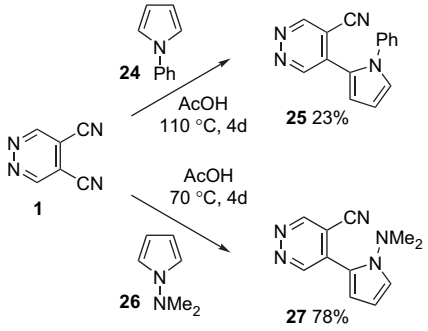
By treatment of **1** with 1 equiv of 2-methylindole (**19**) in acetic acid at room temperature for 16 h, we succeeded into the isolation of adduct **21** in 95% yield, together with a small amount of **22** (3%, Scheme 5, entry 1); on the other hand, operating at 50 °C with 1.5 equiv of **19** for 24 h, the only reaction product was the indolylpyridazine **22** (94%, Scheme 5, entry 2). The steric hindered 2-phenylindole (**20**) reacted with **1** more slowly and at higher temperature (72 h, 70 °C) to give the pyridazine derivative **23** in 88% yield (Scheme 5, entry 3).



entry	indole reagent (equiv)	temp (°C)	time	yield (%)
1	**19** (1)	rt	16 h	**21** 95, **22** 3
2	**19** (1.5)	50	24 h	**21** 0, **22** 94
3	**20** (1.5)	70	72 h	**23** 88

Scheme 5.

Reaction of the dinitrile **1** with the bulky *N*-phenylpyrrole (**24**) (1.5 equiv) was achieved in even more drastic conditions: after 4 days at 110 °C we succeeded into the isolation from a complex reaction mixture of the pyrrolylpyridazine **25** in 23% yield (Scheme 6).

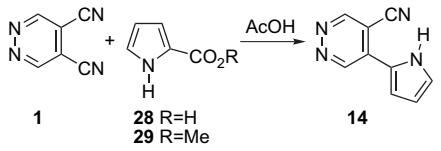


Scheme 6.

The electron-rich *N*-(dimethylamino)pyrrole (**26**) was absolutely inert towards DCP up to 70 °C in $CHCl_3$, in the presence of 10% Pd/C, or MeCN; when the above reaction was performed in AcOH at 70 °C for 4 days the 2-substituted pyrrole **27** was isolated in 78% yield (Scheme 6).

Treatment of DCP with an excess (3 equiv) of electron-deficient pyrrole or indole derivatives, such as *N*-(phenylsulfonyl)indole, *N*-acetylindole, indole-2-carboxylic acid, *N*-(phenylsulfonyl)pyrrole, methyl 1-pyrrolecarboxylate, in AcOH at 110 °C for several days, was absolutely unsuccessful leading to the recovery of unreacted starting materials.

Anyway, when compound **1** was allowed to react with pyrrole-2-carboxylic acid (**28**) (1.5 equiv) at 70 °C in acetic acid for 7 days, we isolated from a complex reaction mixture the (pyrrol-2-yl)pyridazine **14** in 42% yield, identical with the sample obtained from the reaction of **1** with pyrrole (**13**) (Scheme 7, entry 1). The formation of **14** was absolutely unexpected, and could not be ascribed to a decarboxylation process of the acid **28**, which itself proved to be perfectly stable under the reaction conditions. A possible mechanistic rationale could involve a first nucleophilic attack of the oxygen of the carboxylic group on the C-4 carbon of protonated DCP leading to the adduct **31**, through the intermediate **30**; at this level, the following aromatization of the pyridazine ring could be performed not only by HCN elimination but even through deprotonation and carbon–oxygen bond breaking with CO_2 extrusion. This latter possibility produces



entry	pyrrole reagent (equiv)	temp (°C)	time (days)	yield (%)
1	**28** (1.5)	70	7	**14** 42
2	**29** (1.5)	110	2	–

Scheme 7.

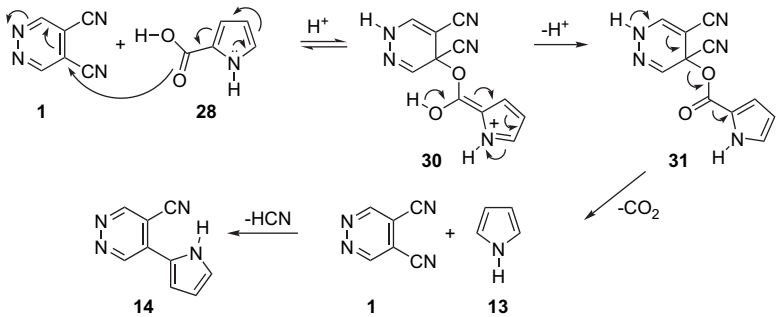
the dinitrile **1** and pyrrole **13**, able to react as previously observed to give **14** (Scheme 8).

This hypothesis could likely find support in the lack of reactivity observed for the corresponding methyl ester **29**, even in more drastic conditions (up to 110 °C, Scheme 7, entry 2). On the basis of the proposed mechanism, the first attack could yet be possible but the substitution of the OH with the OMe group certainly prevents the following evolution of intermediate **30** into **31**.

The structure of pyrrole derivatives **14**, **15**, **18**, **25** and **27**, as regioisomers substituted at position 2, was definitely assigned on the basis of the chemical shifts and multiplicities of the hydrogen atoms of the pyrrole moiety in the proton spectra, through comparison with the corresponding patterns of compounds **11** and **12**, previously characterized.[6]

3. Conclusions

These results clearly show a new facet of the reactivity of 4,5-dicyanopyridazine (**1**) towards pyrrole and indole systems, with interesting mechanistic and synthetic implications. In fact, DCP was not only able to react as heterocyclic azadiene in inverse electron-demand HDA reactions, but can also behave as a very reactive heterocyclic electrophile at C-4 carbon, in formal S_NAr2 processes where a CN group acts as leaving group. In particular, starting from the same reagents, it appears possible to modulate the reaction course by simple variation of the experimental settings. The same pyrrole and indole counterparts can indeed react with DCP as dienophiles at 110–150 °C in chloroform or xylene (sealed tube), leading to dicyano-indoles and –carbazoles, or as carbon nucleophiles, operating in acetic acid in milder



Scheme 8.

conditions (25–110 °C), to afford cyanopyrrolyl- and cyanoindolyl-pyridazines in satisfactory yields through addition–elimination processes.

The study of the general scope as well as synthetic applications of this new methodology is underway in our laboratory.

4. Experimental

4.1. General

Melting points were taken on a Büchi 510 apparatus and are uncorrected. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck, 230–400 mesh) were used for TLC and flash chromatographies (FC), respectively; petroleum ether (PE) employed for crystallizations and chromatographic workup refers to the fractions of bp 30–50 and 40–70 °C, respectively. IR spectra were recorded as KBr pellets with a Perkin–Elmer Spectrum BX FT-IR System spectrophotometer. Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded in acetone-d_6 solutions with a Varian Mercuryplus 400 instrument, operating at 400 and 100 MHz, respectively. Elemental analyses were performed with a Perkin–Elmer 2400 analyzer.

4.2. Reactions of DCP (1) with indole (2). General procedure

A mixture of **1** (0.065 g, 0.5 mmol), **2** (0.086 g, 0.75 mmol), Pd catalyst, and in some cases co-reagents, in the specified solvent (1.0 mL) was maintained at the reported temperature under magnetic stirring in a screw-capped tube (Pyrex N. 13). Unless otherwise stated, chromatographic purification (PE/EtOAc 1:1) of the crude product left by evaporation to dryness under reduced pressure afforded 4-cyano-5-(1*H*-indol-3-yl)pyridazine (**8**)[6] (R_f=0.32).

(A) Operating in chloroform at 50 °C in the presence of Pd/C (10%, 0.065 g), the indolylpyridazine **8** (0.099 g, 90%) was isolated as a yellow solid after 11 days.
(B) Performing the above reaction in the presence of $Pd(PPh_3)_2Cl_2$ (0.004 g, 0.006 mmol), CuI (0.005 g, 0.026 mmol) and K_2CO_3 (0.104 g, 0.75 mmol) in acetonitrile at room temperature for 11 days, compound **8** (0.057 g, 52%) was recovered through careful chromatographic resolution.
(C) The indolylpyridazine **8** (0.044 g, 40%) was isolated after 45 days at room temperature, working with $Pd(OAc)_2$ (0.006 g, 0.027 mmol) and *p*-benzoquinone (0.081 g, 0.75 mmol) in glacial acetic acid.
(D) When the above reaction was performed in MeCN at 50 °C for 17 days, without Pd catalysts, chromatographic purification afforded derivative **8** (0.090 g, 82%).
(E) Operating with a stoichiometric amount of **2** (0.059 g, 0.5 mmol) in glacial acetic acid at room temperature for 9 days, pyridazine **8** (0.100 g, 91%) was isolated by filtration from the reaction mixture and washing with dichloromethane.
(F) When the previous reaction was carried out in the same conditions for 36 h, chromatographic resolution (PE/EtOAc 2:1) afforded 4,5-dicyano-4-(1*H*-indol-3-yl)-1,4-dihydropyridazine (**16**) (0.103 g, 83%) as ivory prismatic crystals that yellows with gas evolution above 90 °C and melted at 285–286 °C (from ether) [Found: C, 67.78; H, 3.92; N, 28.62. $C_{14}H_9N_5$ requires C, 68.01; H, 3.67; N, 28.32]; R_f (PE/EtOAc 2:1) 0.30; ν_{max} 3323, 3065, 2247, 2209, 1636, 1612, 1453 cm^{-1}; δ_H 6.90 (s, 1H, H-3), 7.12 (ddd, *J*=8.0, 7.0, and 1.0 Hz, 1H, H-5′), 7.23 (ddd, *J*=8.1, 7.0, and 1.1 Hz, 1H, H-6′), 7.52–7.59 (m, 3H, H-2′, H-4′, H-7′), 7.62 (d, *J*=4.0 Hz, 1H, H-6), 10.46 (br s, 1H, 1-NH), 10.71 (br s, 1H, 1′-NH); δ_C 35.5, 77.8, 113.2, 113.4, 117.7, 118.3, 119.25, 120.8, 123.3, 124.4, 125.3, 132.8, 137.9, 138.6.

The following band gave compound **8** (R_f=0.19, 0.013 g, 12%).

4.3. Reactions of DCP (1) with indoles 3, 19, 20 and pyrroles 10, 13, 24, 26, 28 in glacial acetic acid. General procedure

A mixture of **1** (0.065 g, 0.5 mmol) and the indole or pyrrole derivative in glacial AcOH (0.5 mL) was maintained at the reported temperature under magnetic stirring in a screw-capped tube (Pyrex N. 13).

4.3.1. 4-Cyano-5-(1-methyl-1*H*-indol-3-yl)pyridazine (9) and 4,5-dicyano-4-(1-methyl-1*H*-indol-3-yl)-1,4-dihydropyridazine (17).

(A) Operating with *N*-methylindole (**3**) (0.098 g, 0.75 mmol) at 50 °C for 22 h, compound **9**[6] (R_f=0.33, 0.116 g, 99%) was isolated by chromatographic purification (PE/EtOAc 1:1).
(B) Evaporation to dryness of the mixture coming from reaction of DCP with a stoichiometric amount of *N*-methylindole (**3**) (0.066 g, 0.5 mmol) at room temperature for 18 days afforded exclusively indolylpyridazine **9** (0.116 g, 99%).
(C) Operating as above for 4 days, chromatographic resolution (PE/EtOAc 2:1) afforded the dihydropyridazine **17** (0.115 g, 88%) as yellow-orange needles: mp 211–212 °C (from ether) [Found: C, 68.59; H, 4.26; N, 26.70. $C_{15}H_{11}N_5$ requires C, 68.95; H, 4.24; N, 26.80]; R_f (PE/EtOAc 2:1) 0.26; ν_{max} 3333, 3051, 2934, 2241, 2206, 1628, 1608, 1475, 1445 cm^{-1}; δ_H 3.90 (s, 3H, NMe), 6.88 (s, 1H, H-3), 7.14 (t, *J*=7.9 Hz, 1H, H-5′), 7.28 (t, *J*=7.9 Hz, 1H, H-6′), 7.45 (s, 1H, H-2′), 7.49 (d, *J*=8.0 Hz, 1H, H-7′), 7.55 (d, *J*=8.0 Hz, 1H, H-4′), 7.62 (d, *J*=4.1 Hz, 1H, H-6), 10.49 (br s, 1H, NH); δ_C 33.0, 35.4, 77.7, 111.3, 112.4, 117.7, 118.2, 119.4, 120.8, 123.2, 125.6, 128.4, 132.7, 137.8, 139.1.

The slowest moving fractions yielded the pyridazine **9** (R_f=0.14, 0.007 g, 6%).

4.3.2. 4-Cyano-5-(1-methyl-1*H*-pyrrol-2-yl)pyridazine (11), 4-cyano-5-(1-methyl-1*H*-pyrrol-3-yl)pyridazine (12) and 4,5-dicyano-4-(1-methyl-1*H*-pyrrol-2-yl)-1,4-dihydropyridazine (18).

(A) Chromatographic purification (PE/EtOAc 1:1) of the residue coming from the reaction of **1** and *N*-methylpyrrole (**10**) (0.061 g, 0.056 mL, 0.75 mmol) at room temperature for 15 days allowed to isolate, respectively,

compounds **11**[6] (R_f=0.30, 0.063 g, 68%) and **12**[6] (R_f=0.20, 0.012 g, 13%).

(B) Operating with 1 equiv of **10** (0.041 g, 0.045 mL, 0.5 mmol) for 4 days, chromatographic purification (PE/EtOAc 1:1) gave the adduct **18** (0.055 g, 52%) that crystallized from ether in pale orange needles: mp 110–111 °C (dec) [Found: C, 62.40; H, 4.34; N, 32.87. $C_{11}H_9N_5$ requires C, 62.55; H, 4.29; N, 33.16]; R_f (PE/EtOAc 1:1) 0.42; ν_{max} 3368, 3136, 3105, 3085, 3046, 2977, 2948, 2242, 2210, 1636, 1611, 1465 cm^{-1}; δ_H 3.70 (s, 3H, NMe), 6.08 (dd, J=3.8 and 2.8 Hz, 1H, H-4′), 6.28 (dd, J=3.8 and 1.8 Hz, 1H, H-3′), 6.84 (dd, J=2.8 and 1.8 Hz, 1H, H-5′), 6.91 (s, 1H, H-3), 7.60 (s, 1H, H-6), 10.53 (br s, 1H, NH); δ_C 35.5, 36.7, 76.6, 107.9, 111.4, 117.3, 117.6, 127.0, 128.3, 131.3, 138.4.

The following band yielded compound **11** (R_f=0.30, 0.028 g, 30%).

4.3.3. 4-Cyano-5-(1*H*-pyrrol-2-yl)pyridazine (14) and 4,5-dicyano-4-(1*H*-pyrrol-2-yl)-1,4-dihydropyridazine (15).

(A) The crude product from the reaction of **1** and pyrrole (**13**) (0.050 g, 0.052 mL, 0.75 mmol) at room temperature for 4 days was resolved into two components by chromatographic purification (PE/EtOAc 1:1). The first band gave compound **15** (0.008 g, 8%) as pale yellow prismatic crystals: mp 209–210 °C (from ether) [Found: C, 60.64; H, 3.58; N, 35.37. $C_{10}H_7N_5$ requires C, 60.91; H, 3.58; N, 35.51]; R_f (PE/EtOAc 1:1) 0.31; ν_{max} 3307, 3136, 3099, 3042, 2248, 2217, 1636, 1616, 1499 cm^{-1}; δ_H 6.17 (m, 1H, H-4′), 6.27 (m, 1H, H-3′), 6.85 (s 1H, H-3), 6.94 (m, 1H, H-5′), 7.57 (s, 1H, H-6), 10.36 (br s, 1H, 1-NH), 10.45 (br s, 1H, 1′-NH); δ_C 36.4, 76.6, 108.8, 109.6, 117.5, 117.6, 122.2, 128.7, 131.6, 138.1.

The following one afforded derivative **14** (0.077 g, 91%) as pale yellow needles: mp 207–208 °C (from ether/acetone) [Found: C, 63.24; H, 3.66; N, 32.65. $C_9H_6N_4$ requires C, 63.52; H, 3.55; N, 32.92]; R_f (PE/EtOAc 1:1) 0.20; ν_{max} 3161, 3144, 3095, 2227, 1574, 1535, 1439, 1397 cm^{-1}; δ_H 6.47 (dd, J=4.0 and 2.5 Hz, 1H, H-4′), 7.35 (dd, J=2.5 and 1.4 Hz, 1H, H-5′), 7.48 (dd, J=4.0 and 1.4 Hz, 1H, H-3′), 9.24 (d, J=1.1 Hz, 1H, H-3), 9.69 (d, J=1.1 Hz, 1H, H-6), 11.32 (br s, 1H, NH); δ_C 103.8, 112.7, 116.8, 117.2, 123.9, 126.8, 131.3, 148.2, 152.2.

(B) Operating as above, chromatographic purification of the residue obtained by treatment of **1** with **13** (0.033 g, 0.034 mL, 0.5 mmol) at room temperature for 19 h led to derivatives **15** (R_f=0.31, 0.071 g, 72%) and **14** (R_f=0.20, 0.023 g, 27%), identical with the species previously isolated.

4.3.4. 4,5-Dicyano-4-(2-methyl-1*H*-indol-3-yl)-1,4-dihydropyridazine (21) and 4-cyano-5-(2-methyl-1*H*-indol-3-yl)pyridazine (22).

(A) When DCP was allowed to react with 2-methylindole (**19**) (0.098 g, 0.75 mmol) at 50 °C for 24 h, compound **22** (0.110 g, 94%) was isolated as deep yellow solid by filtration and washing with dichloromethane to remove unreacted **19**: mp 285–286 °C (from acetone) [Found: C, 71.57; H, 3.95; N, 24.21. $C_{14}H_{10}N_4$ requires C, 71.78; H, 4.30; N, 23.92]; ν_{max} 3146, 3050, 2993, 2227, 1564, 1538, 1461 cm^{-1}; δ_H (DMSO-d_6) 2.51 (s, 3H, Me), 7.12 (ddd, J=8.0, 7.0 and 1.0 Hz, 1H, H-5′), 7.19 (ddd, J=8.1, 7.1 and 1.0 Hz, 1H, H-6′), 7.45 (dt, J=8.0 and 1.0 Hz, 1H, H-7′), 7.53 (str d, J=7.9 Hz, 1H, H-4′), 9.57 (d, J=1.2 Hz, 1H, H-3), 9.61 (d, J=1.2 Hz, 1H, H-6), 11.96 (br s, 1H, NH); δ_C (DMSO-d_6) 13.15, 105.0, 110.3, 111.7, 116.1, 118.3, 120.7, 122.3, 126.0, 135.8, 136.8, 138.5, 151.7, 152.8.

(B) Chromatographic resolution (PE/EtOAc 2:1) of the crude coming from reaction of **1** and **19** (0.066 g, 0.5 mmol) at room temperature for 16 h afforded from the first band unreacted **1** (R_f=0.49, 0.003 g), and from the following one the adduct **21** (0.116 g, 89%) as pale yellow needles: mp 283–284 °C (from ether) [Found: C, 69.18; H, 4.56; N, 26.45. $C_{15}H_{11}N_5$ requires C, 68.95; H, 4.24; N, 26.80]; R_f (PE/EtOAc 2:1) 0.35; ν_{max} 3379, 3313, 3081, 2247, 2207, 1635, 1612, 1453 cm^{-1}; δ_H 2.62 (s, 3H, Me), 6.90 (s, 1H, H-3), 7.05 (ddd, J=8.1, 7.0 and 1.1 Hz, 1H, H-5′), 7.13 (ddd, J=8.1, 7.0 and 1.1 Hz, 1H, H-6′), 7.39 (dt, J=8.1 and 0.9 Hz, 1H, H-7′), 7.54 (d, J=4.1 Hz, 1H, H-6), 7.69 (str d, J=8.1 Hz, 1H, H-4′), 10.43 (br s, 1H, 1-NH), 10.52 (br s, 1H, 1′-NH); δ_C 12.75, 34.7, 78.4, 107.4, 111.9, 118.0, 118.7, 118.95, 120.5, 122.2, 127.1, 132.6, 134.7, 136.0, 137.1.

The slowest moving fractions gave pyridazine **22** (R_f=0.21, 0.004 g, 3%), identical with the sample previously isolated.

4.3.5. 4-Cyano-5-(2-phenyl-1*H*-indol-3-yl)pyridazine (23).

When DCP was allowed to react with 2-phenylindole (**20**) (0.145 g, 0.75 mmol) at 70 °C for 3 days, compound **23** (0.105 g, 71%) was isolated by filtration as yellow solid that, after crystallization from acetone, melted at 286–287 °C [Found: C, 76.75; H, 3.84; N, 19.25. $C_{19}H_{12}N_4$ requires C, 77.01; H, 4.08; N, 18.91]; ν_{max} 3102, 3023, 2232, 1558, 1491, 1451 cm^{-1}; δ_H (DMSO-d_6) 7.19 (ddd, J=8.1, 7.1 and 1.0 Hz, 1H, H-5′), 7.29 (ddd, J=8.2, 7.1 and 1.1 Hz, 1H, H-6′), 7.40–7.49 (m, 5H, Ph), 7.56–7.60 (m, 2H, H-4′ and H-7′), 9.35 (d, J=1.2 Hz, 1H, H-6), 9.54 (d, J=1.2 Hz, 1H, H-3), 12.36 (br s, 1H, NH); δ_C (DMSO-d_6) 104.4, 111.7, 112.5, 115.5, 118.9, 121.2, 123.4, 126.7, 128.75, 129.2, 129.4, 131.0, 136.6, 137.1, 139.6, 151.8, 153.4.

Chromatographic purification (PE/EtOAc 2:1) of the residue obtained by evaporation to dryness of the filtrate allowed to isolate a further amount of **23** (R_f=0.29, 0.025 g, 17%).

4.3.6. 4-Cyano-5-(1-phenyl-1*H*-pyrrol-2-yl)pyridazine (25).

Chromatographic workup (toluene/EtOAc 5:1) of the complex reaction mixture obtained by treatment of **1** with *N*-phenylpyrrole (**24**) (0.107 g, 0.75 mmol) at 110 °C for 4 days afforded compound **25** (0.028 g, 23%) as pale orange needles: mp 145–146 °C (from ether/PE) [Found: C, 73.45; H, 3.94; N, 22.45. $C_{15}H_{10}N_4$ requires C, 73.16; H, 4.09; N, 22.75]; R_f (toluene/EtOAc 5:1) 0.35; ν_{max} 3088, 2235, 1564, 1498, 1440 cm^{-1}; δ_H 6.57 (dd, J=3.9 and

2.8 Hz, 1H, H-4′), 7.19 (dd, J=3.9 and 1.6 Hz, 1H, H-3′), 7.34–7.37 (m, 2H, Ar-2H), 7.42 (dd, J=2.7 and 1.6 Hz, 1H, H-5′), 7.44–7.52 (m, 3H, Ar-3H), 8.71 (d, J=1.1 Hz, 1H, H-6), 9.35 (d, J=1.1 Hz, 1H, H-3); δ_C 109.3, 112.1, 116.1, 119.2, 124.5, 126.4, 128.8, 130.6, 130.8, 132.65, 140.0, 150.9, 152.1.

4.3.7. 4-Cyano-5-(1-dimethylamino-1*H*-pyrrol-2-yl)pyridazine (27). Chromatographic purification (PE/EtOAc 3:2) of the reaction crude obtained by treatment of **1** with 1-dimethylaminopyrrole (**26**) (0.083 g, 0.091 mL, 0.75 mmol) at 70 °C for 4 days afforded compound **27** (0.083 g, 78%) as pale yellow prismatic crystals: mp 95–96 °C (from ether) [Found: C, 61.63; H, 4.84; N, 33.15. $C_{11}H_{11}N_5$ requires C, 61.96; H, 5.20; N, 32.84]; R_f (PE/EtOAc 3:2) 0.28; ν_{max} 3109, 2959, 2864, 2829, 2227, 1553, 1450 cm^{-1}; δ_H 2.89 (s, 6H, NMe_2), 6.40 (dd, J=4.2 and 3.0 Hz, 1H, H-4′), 6.89 (dd, J=4.2 and 1.6 Hz, 1H, H-3′), 7.69 (dd, J=3.0 and 1.6 Hz, 1H, H-5′), 9.36 (d, J=1.2 Hz, 1H, H-3), 9.64 (d, J=1.2 Hz, 1H, H-6); δ_C 47.7, 108.8, 110.4, 113.65, 116.7, 121.5, 123.5, 131.6, 151.4, 152.1.

4.3.8. Reaction of 1 with pyrrol-2-carboxylic acid (28). When DCP was allowed to react with pyrrole derivative **28** (0.083 g, 0.75 mmol) at 70 °C for 7 days, compound **14** (R_f=0.20, 0.036 g, 42%) was isolated by chromatographic purification (PE/EtOAc 1:1).

Acknowledgements

Mrs. B. Innocenti and Mr. M. Passaponti are acknowledged for the analytical data. Authors thank the Ente Cassa di Risparmio di Firenze for the grant of the Varian Mercuryplus 400 instrument.

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14. The same conversion was also observed in the solid state, even if more slowly.