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SYNTHESIS OF METHYL 2-[(BENZYLOXYCARBONYL)AMINO]-3-CYANOPROPENOATE AND ITS TRANSFORMATIONS INTO DERIVATIVES OF PYRROLE, 2,5-DIOXOIMIDAZOLIDINE, 1*H*-PYRAZOLE, AND 4,6-DIAMINOPYRIDAZINE.

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Abstract – Methyl (*E*)-2-[(benzyloxycarbonyl)amino]-3-cyanopropenoate (**4**) was, as a versatile multifunctional reagent, transformed with hydrazine and monosubstituted aromatic and heteroaromatic hydrazines under various conditions into derivatives of pyridazine (**6**), pyrrole (**7**), imidazole-2,4-dione (**9**), and pyrazole (**13**).

INTRODUCTION

Amino acid derivatives are important building blocks for many heterocyclic systems, among others for pyrazoles,[1] imidazoles,[2] and 1,2,4-triazines.[3] There are only a few synthetic approaches to 1,2,4-triazin-6-ones. They have been prepared either by cyclization of α-(acylamino)carbohydrazides,[4-8] obtained as minor products by alkaline hydrolysis of 1-methyl-1,2,4-triazinium iodides,[9] and by oxidation of 6-methyl-1,2,4-triazines and related compounds.[10,11] The amidines, derived from esters of α-amino acids have been converted into 1,2,4-triazin-6(1*H*)-one derivatives, while amidines of α,β-unsaturated-α-amino acids (propenoates) have been cyclized into 1-substituted imidazol-5-one derivatives.[12] The use of phosgenated γ-nitrophenyl(polystyrene)ketoxime (Phoxime resin) in combinatorial synthesis of α-ureidoacetamides, 3-amino hydantoines and 1,2,4-triazine-3,6-diones has been recently described.[13] 1,2,4-Triazine-3,6-dione derivatives have been obtained also in reactions of amino acid hydrazides with α-isocyanatocarboxylic acid derivatives.[14] Reactions of *N*-benzyloxycarbonyl-(*Z*)-dehydrophenylalanine and other derivatives with phenylhydrazine in the presence of sodium hydroxide have been reported to produce isomeric (*Z*)-5-benzylidene-2-phenyl-1,2,4-triazine-3,6-diones and/or (*Z*)-1-anilino-4-benzylideneimidazolidine-2,5-diones.[15] There are many methods for the preparation of hydantoins and

thiohydantoins described in the literature.[16] 3-Anilinohydantoin is formed in the base-catalyzed cyclization of benzylthiocarboxyglycine, phenylhydrazine, ethoxycarbonylphenylhydrazide, and *N*-carboxyphenylhydrazidoglycine ethyl ester.[17]

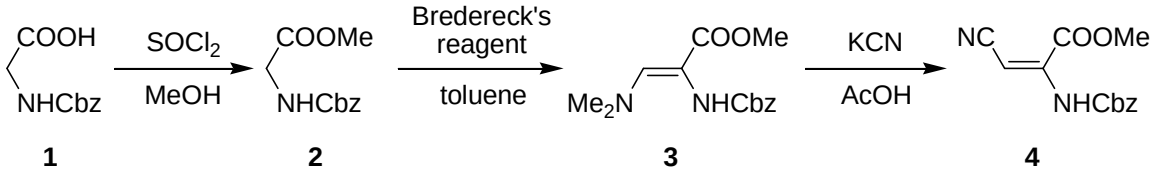
Recently, a series of alkyl 2-substituted 3-(dimethylamino)propenoates and related enaminones have been prepared as versatile reagents for the preparation of various dehydroalanine derivatives, heterocyclic systems, and natural product analogues. In extension, chiral cyclic enamino lactams and lactones, derived from α-amino acids and (+)-camphor have been used in the synthesis of functionalized heterocycles, such as heteroarylalanines, heteroarylalaninols, heteroarylpropanediols, 3-heteroaryl-(+)-camphors, and heterocyclic compounds with an α-amino acid or a dipeptide structural element incorporated into the ring system.[18,19] Recently, alkyl 2-substituted 3-(dimethylamino)propenoates and related enaminones have been employed in combinatorial synthesis of heterocycles and *N*-acyldehydroalanines esters[20] and in the synthesis of natural product analogues, such as aplysinopsins,[21] meridianins,[22] and dipodazines.[23]

Methyl (*E*)-2-(acetylamino)-3-cyanopropenoate and its 2-benzoyl analogue have been prepared from the corresponding methyl (*Z*)-2-(acylamino)-3-(dimethylamino)propenoates. These multifunctional compounds are versatile synthons for preparation of polysubstituted heterocyclic systems, such as pyrroles, pyrimidines and pyridazines. In all these cases cyclization occurs between cyano group and ester or acetylamino group.[24]

In this report we present the transformations of methyl (*E*)-2-[(benzyloxycarbonyl)amino]-3-cyano-propenoate (**4**), as another multifunctional reagent, into polysubstituted pyridazines (**6**), pyrroles (**7**), imidazoles (**9**), and pyrazoles (**13**).

DISCUSSION

Methyl (*E*)-2-[(benzyloxycarbonyl)amino]-3-cyanopropenoate (**4**) was prepared from *N*-(benzyloxy-carbonyl)glycine (**1**) in three steps according to procedures described in literature[25] (Scheme 1).



Scheme 1

Due to the multifunctionality of methyl (*E*)-2-[(benzyloxycarbonyl)amino]-3-cyanopropenoate (**4**), this reagent offers the possibility for the synthesis of a wide range of heterocyclic systems, such as pyridazines, pyrroles, pyrazoles, imidazole-2,4-diones, and 1,2,4-triazine-3,6-diones (Figure 1).

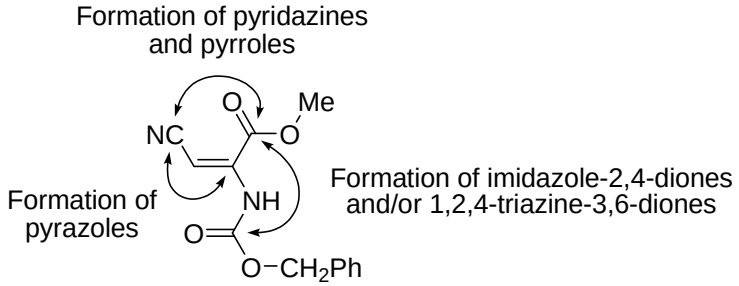
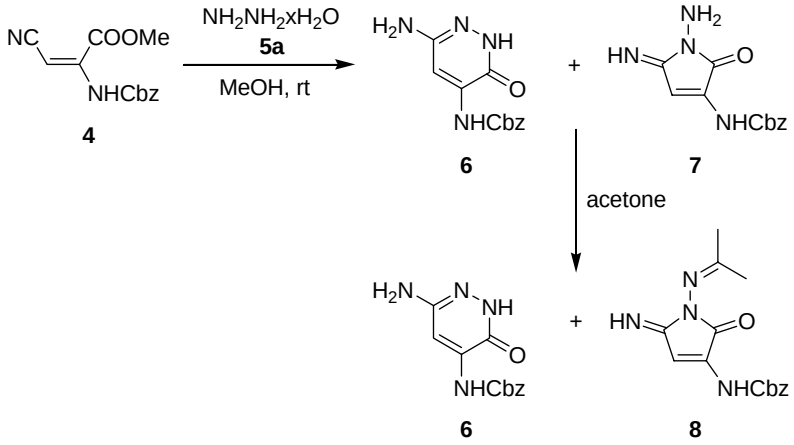


Figure 1. Expected transformations of compound (**4**) with hydrazines into various heterocyclic systems

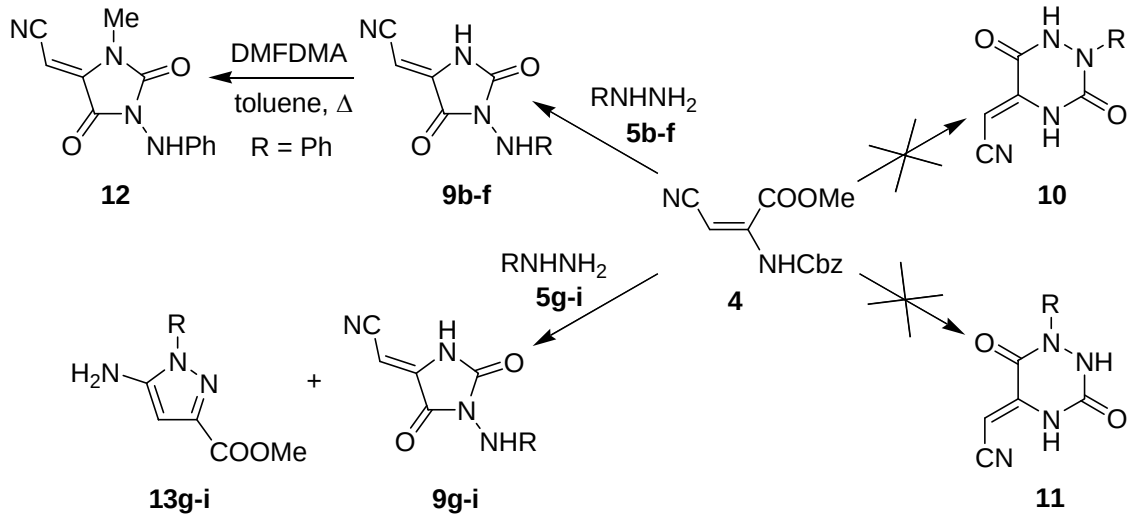
When compound (**4**) reacted with hydrazine monohydrate (**5a**) in methanol at room temperature a mixture of two products, benzyl (6-amino-3-oxo-2,3-dihydropyridazin-4-yl)carbamate (**6**) and benzyl (1-amino-5-imino-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)carbamate (**7**), were formed. The satisfactory separation of both products was not successful by employing various methods of chromatography. In order to separate both compounds the mixture was treated with acetone at room temperature. In this procedure compound (**7**) was transformed into the corresponding hydrazone (**8**), while compound (**6**) remained unchanged. Compounds (**6** and **8**) were separated by column chromatography (Scheme 2).



Scheme 2. Synthesis of derivatives of pyridazine (**6**) and *N*-aminopyrrole (**7**)

On the other hand, when compound (**4**) reacted with monosubstituted aromatic and heteroaromatic hydrazines (**5b-i**) in DMF under reflux, in most cases one product was formed. In some instances, this major product was accompanied with another product. From the analytical and spectral data for the major

product three possible structures are feasible, 3-[(hetero)arylamino]imidazolidine-2,4-dione (**9**), or isomeric 1,2,4-triazine-3,6-diones (**10** and **11**) (Scheme 3). Since we were unable to determine the structure on the basis of analytical and spectral data, we transformed the product obtained from **4** and phenylhydrazine with *N*,*N*-dimethylformamide dimethyl acetal into the corresponding *N*-methyl derivative. The X-Ray analysis confirmed the structure to be (*Z*)-2-[3-methyl-2,5-dioxo-1-(phenylamino)imidazolidin- 4-ylidene]acetonitrile (**12**) (Figure 3), derived from **9b**.



Compound	**R**	Reflux (min)	Yield of **9** (%)	Yield of **13** (%)
9b	phenyl	30	55	
9c	4-nitrophenyl	90	58	
9d	4-carboxyphenyl	40	51	
9e	pyrimidin-2-yl	70	50	
9f	imidazo[1,2-b]pyridazin-6-yl	45	28	
9g, **13g**	pyridin-2-yl	65	26	19
9h, **13h**	3-chloropyridazin-6-yl	95	22	11
9i, **13i**	6-phenylpyridazin-3-yl	45	19	26

Scheme 3. Synthesis of 2,5-dioxoimidazolidines (**9**) and 5-amino-1*H*-pyrazol-3-carboxylates (**13**)

With heteroaromatic hydrazines (**5g-i**), also compounds (**13g-i**) were formed as minor products besides the major products (**9g-i**). The X-Ray analysis of the minor product, obtained in the reaction between **4** and 2-hydrazinopyridine (**5g**), showed it to be methyl 5-amino-1-(pyridin-2-yl)-1*H*-pyrazole-3-carboxylate (**13g**) (Figure 4).

Structural determination

The structures of all compounds were established on the basis of elemental analyses, IR, MS, and ^{1}H and ^{13}C NMR spectra. The orientation around the double bond in compounds (**4** and **9b**) was established on the basis of 2D-HMBC NMR spectral techniques. The magnitude of heteronuclear coupling constants, $^{3}J_{C\text{-}H}$, for the nuclei ***H***–C=C–***C***=O with *cis* configuration around the C=C double bond are smaller (2–6 Hz) than those for the *trans*-orientated ones (8–12 Hz).[26] Accordingly, the heteronuclear coupling constants in compound (**4**), $^{3}J_{C\text{-}H}$ = 11 Hz, indicates the (*E*)-orientation, while in **9b**, $^{3}J_{C\text{-}H}$ = 5 Hz, indicates the (*Z*)-orientation (Figure 2).

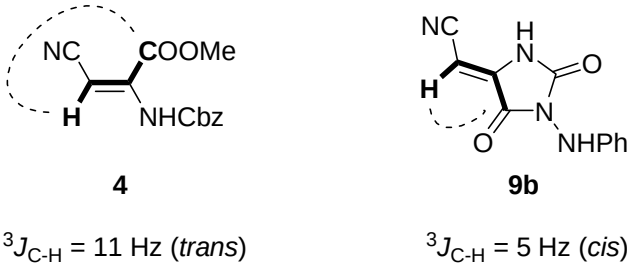


Figure 2. Determination of configuration around the C=C double bonds in compounds (**4** and **9b**) by NMR techniques

X-Ray structure analysis

Single crystal X-Ray diffraction data of compounds (**12** and **13g**) were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[27] DENZO and SCALEPACK[28] were used for indexing and scaling of the data and the structures were solved by means of SIR97.[29] Refinement was done using Xtal3.4[30] program package. Crystal structures were refined on *F* values using the full-matrix least-squares procedure. The non-hydrogen atoms were refined anisotropically in all cases, while the positions of hydrogen atoms were geometrically calculated and their positional and isotropic atomic displacement parameters were not refined. Absorption correction was not necessary. Regina[31] weighting scheme was used in all cases. The resulting crystal data and details concerning data collection and refinement for the two compounds are quoted in Table 1. Final atomic coordinates and equivalent isotropic displacement parameters with their e.s.d.'s are reported in Tables 2 and 4. Bond lengths and bond angles for nonhydrogen atoms are listed in Tables 5 and 7 for **12** and **13g**, respectively. ORTEP III[32] drawings of the content of asymmetric units of the two compounds showing the atom-labeling scheme are presented in Figures 2 and 3.

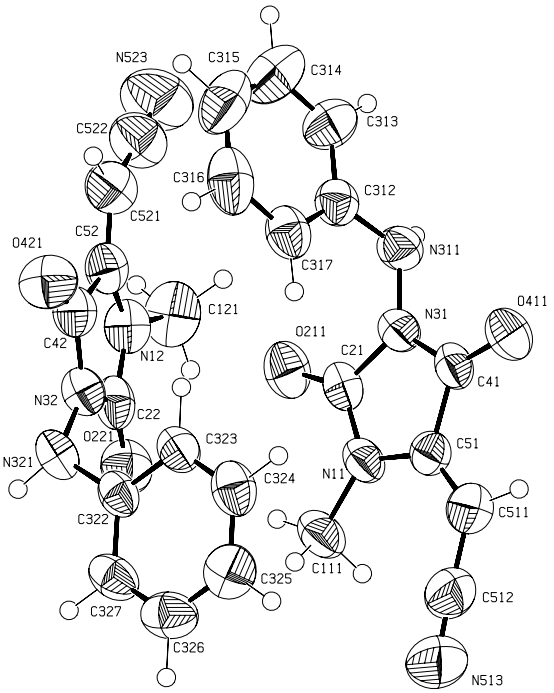


Figure 3. Ortep view of compound (**12**) at the 50% probability level. H atoms are drawn as ellipsoids of arbitrary radii

Table 1. Crystal data, data collection and structure refinement for compounds (**12** and **13g**)

	compound (**12**)	compound (**13g**)
Formula	$C_{12}H_{10}N_4O_2$	$C_{10}H_{10}N_4O_2$
Rel. formula weight	242.2	218.2
Crystal System	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$
a (Å)	7.4286(1)	12.0933(3)
b (Å)	22.1649(4)	12.3188(3)
c (Å)	14.6162(3)	14.2561(5)
α (˚)	90.0000	90.0000
β (˚)	93.1143(6)	97.9487(10)
γ (˚)	90.0000	90.0000
V ($Å^3$)	2403.06(7)	2103.40(10)
Z	4	4
ρ (Mg m^{-3})	1.339	1.403
μ (mm^{-1})	0.096	0.104
Color of crystal	yellowish	colourless
Shape of crystal	plate	plate
Dimensions (mm)	0.25×0.20×0.1	0.25×0.25×0.1

Temperature (K)	293(1)	293(1)
Wavelength (Å)	0.71073	0.71073
θ_{max} (°)	25.01	27.49
No. of integr. refl.	22780	23987
No. of indep. refl.	4357	5036
R_{int}	0.034	0.053
No. of observed refl.	325	289
Threshold criterion	$I > 2.0\sigma(I)$	$I > 2.0\sigma(I)$
Final R and R_w	0.056, 0.052	0.059, 0.047
$(\Delta/\sigma)_{max}$	0.0001	0.0002
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	-0.27, 0.40	-0.33, 0.41

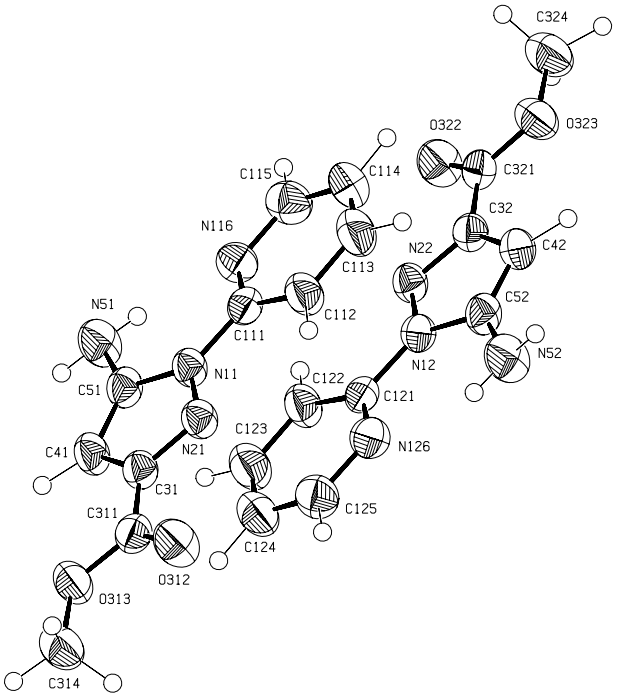


Figure 4. Ortep view of compound (**13g**) at the 50% probability level. H atoms are drawn as ellipsoids of arbitrary radii

Table 2. Fractional Coordinates and Equivalent Temperature Factors (Å2) for compound (**12**). U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor

	x/a	y/b	z/c	U_{eq}
O(211)	0.3120(3)	0.30067(11)	0.08980(14)	0.0762(13)
O(221)	0.0429(3)	0.31190(12)	-0.08812(14)	0.0815(14)
O(411)	0.5478(3)	0.20004(11)	0.34058(13)	0.0765(13)
O(421)	-0.2462(3)	0.39045(11)	0.15307(16)	0.0810(14)

N(11)	0.3332(3)	0.19866(11)	0.12431(14)	0.0573(13)
N(12)	0.1002(3)	0.39640(12)	0.00293(16)	0.0648(14)
N(31)	0.4475(3)	0.26486(10)	0.22495(14)	0.0552(12)
N(32)	-0.1334(3)	0.33749(11)	0.03235(15)	0.0591(13)
N(311)	0.5012(3)	0.31940(11)	0.26402(16)	0.0608(13)
N(321)	-0.2639(3)	0.29247(12)	0.02143(16)	0.0667(14)
N(513)	0.2731(5)	0.02264(16)	0.1071(3)	0.117(3)
N(523)	0.3222(6)	0.5445(2)	0.1058(3)	0.125(3)
C(21)	0.3578(3)	0.25909(14)	0.13881(17)	0.0552(15)
C(22)	0.0108(4)	0.34458(15)	-0.02567(18)	0.0623(16)
C(41)	0.4774(3)	0.21037(13)	0.26581(17)	0.0549(15)
C(42)	-0.1383(4)	0.38290(14)	0.09474(19)	0.0612(16)
C(51)	0.4007(3)	0.16574(13)	0.19854(18)	0.0548(15)
C(52)	0.0212(4)	0.42103(13)	0.07673(18)	0.0597(15)
C(111)	0.2564(4)	0.17610(17)	0.0366(2)	0.0727(18)
C(121)	0.2749(5)	0.41235(19)	-0.0318(3)	0.088(2)
C(312)	0.3615(4)	0.35636(13)	0.29600(17)	0.0586(16)
C(313)	0.4104(5)	0.41411(15)	0.3217(2)	0.079(2)
C(314)	0.2868(7)	0.45119(18)	0.3590(3)	0.101(3)
C(315)	0.1152(7)	0.4320(2)	0.3694(3)	0.100(3)
C(316)	0.0636(4)	0.3744(2)	0.3429(2)	0.088(2)
C(317)	0.1887(4)	0.33525(16)	0.30639(19)	0.0678(17)
C(322)	-0.2178(3)	0.23531(13)	0.05822(17)	0.0542(14)
C(323)	-0.1357(3)	0.23016(14)	0.14566(18)	0.0598(15)
C(324)	-0.1048(4)	0.17386(16)	0.1835(2)	0.0692(18)
C(325)	-0.1552(4)	0.12234(16)	0.1358(2)	0.077(2)
C(326)	-0.2386(4)	0.12773(16)	0.0497(2)	0.076(2)
C(327)	-0.2702(3)	0.18377(15)	0.01048(19)	0.0645(17)
C(511)	0.4032(4)	0.10673(16)	0.2143(2)	0.073(2)
C(512)	0.3300(5)	0.06112(17)	0.1538(3)	0.086(2)
C(521)	0.0643(5)	0.46910(16)	0.1287(2)	0.076(2)
C(522)	0.2111(6)	0.50979(19)	0.1150(3)	0.090(2)

Table 3. Fractional Coordinates and Equivalent Temperature Factors ($Å^2$) for compound (**13g**). U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor

	x/a	y/b	z/c	U_{eq}
O(312)	0.68996(16)	-0.07937(18)	0.35576(16)	0.0647(13)
O(313)	0.87080(16)	-0.10151(17)	0.40749(15)	0.0575(11)
O(322)	0.80648(17)	0.82880(18)	0.15035(16)	0.0616(12)
O(323)	0.62667(17)	0.8419(2)	0.08994(16)	0.0652(12)
N(11)	0.80250(16)	0.18367(17)	0.21802(15)	0.0408(10)
N(12)	0.69757(15)	0.55706(18)	0.27891(14)	0.0403(10)
N(21)	0.74367(16)	0.10446(17)	0.25651(16)	0.0432(11)
N(22)	0.75530(17)	0.63790(18)	0.24213(16)	0.0419(10)
N(51)	0.99304(17)	0.2376(2)	0.2123(2)	0.0614(14)
N(52)	0.50829(17)	0.5016(2)	0.2850(2)	0.0635(14)

N(116)	0.80370(18)	0.34393(18)	0.13311(16)	0.0486(12)
N(126)	0.69779(17)	0.3961(2)	0.36298(16)	0.0493(12)
C(31)	0.8212(2)	0.0444(2)	0.30636(17)	0.0428(12)
C(32)	0.6770(2)	0.6989(2)	0.19285(17)	0.0434(13)
C(41)	0.92969(19)	0.0823(2)	0.3027(2)	0.0480(13)
C(42)	0.5690(2)	0.6588(2)	0.1969(2)	0.0491(14)
C(51)	0.9162(2)	0.1723(2)	0.24505(18)	0.0445(13)
C(52)	0.58370(19)	0.5680(2)	0.25260(18)	0.0454(13)
C(111)	0.7433(2)	0.2637(2)	0.16121(18)	0.0413(13)
C(112)	0.6275(2)	0.2559(2)	0.1385(2)	0.0546(15)
C(113)	0.5752(2)	0.3373(3)	0.0826(3)	0.0683(19)
C(114)	0.6360(3)	0.4214(3)	0.0507(2)	0.0662(18)
C(115)	0.7486(3)	0.4210(2)	0.0779(2)	0.0595(16)
C(121)	0.75814(19)	0.4761(2)	0.33521(17)	0.0385(12)
C(122)	0.8731(2)	0.4849(2)	0.3571(2)	0.0519(15)
C(123)	0.9267(2)	0.4033(3)	0.4122(2)	0.0643(18)
C(124)	0.8653(3)	0.3187(3)	0.4438(2)	0.0644(18)
C(125)	0.7532(2)	0.3182(2)	0.4168(2)	0.0580(16)
C(311)	0.7842(2)	-0.0505(2)	0.35667(18)	0.0459(15)
C(314)	0.8438(3)	-0.1944(3)	0.4603(3)	0.072(2)
C(321)	0.7129(2)	0.7957(2)	0.14430(19)	0.0460(15)
C(324)	0.6528(3)	0.9361(3)	0.0384(3)	0.077(2)

Table 4. Bond Distances (Å) and Bond Angles (°) with e.s.d.'s in parentheses for compound (**12**)

O(211)-C(21)	1.205(4)	O(221)-C(22)	1.199(4)
O(411)-C(41)	1.208(3)	O(421)-C(42)	1.213(4)
N(11)-C(21)	1.367(4)	N(12)-C(22)	1.380(4)
N(11)-C(51)	1.379(3)	N(12)-C(52)	1.369(4)
N(11)-C(111)	1.463(4)	N(12)-C(121)	1.463(4)
N(31)-N(311)	1.386(3)	N(32)-N(321)	1.395(3)
N(31)-C(21)	1.398(3)	N(32)-C(22)	1.410(4)
N(31)-C(41)	1.360(3)	N(32)-C(42)	1.360(4)
N(311)-C(312)	1.421(4)	N(321)-C(322)	1.412(4)
N(513)-C(512)	1.157(6)	N(523)-C(522)	1.142(6)
C(41)-C(51)	1.486(4)	C(42)-C(52)	1.490(4)
C(51)-C(511)	1.328(4)	C(52)-C(521)	1.338(4)
C(312)-C(313)	1.377(4)	C(322)-C(323)	1.391(4)
C(312)-C(317)	1.382(4)	C(322)-C(327)	1.384(4)
C(313)-C(314)	1.368(6)	C(323)-C(324)	1.379(5)
C(314)-C(315)	1.360(7)	C(324)-C(325)	1.379(5)
C(315)-C(316)	1.382(7)	C(325)-C(326)	1.378(5)
C(316)-C(317)	1.398(5)	C(326)-C(327)	1.382(5)
C(511)-C(512)	1.431(5)	C(521)-C(522)	1.438(5)

C(21)-N(11)-C(51)	110.9(2)	C(22)-N(12)-C(52)	110.5(2)
C(21)-N(11)-C111)	120.9(2)	C(22)-N(12)-C(121)	121.2(3)
C(51)-N(11)-C(111)	128.1(3)	C(52)-N(12)-C(121)	127.1(3)

N(311)-N(31)-C(21)	124.3(2)	N(321)-N(32)-C(22)	123.8(2)
N(311)-N(31)-C(41)	123.8(2)	N(321)-N(32)-C(42)	124.2(2)
C(21)-N(31)-C(41)	111.9(2)	C(22)-N(32)-C(42)	111.7(2)
N(31)-N(311)-C(312)	116.1(2)	N(32)-N(321)-C(322)	116.5(2)
O(211)-C(21)-N(11)	128.8(2)	O(221)-C(22)-N(12)	128.4(3)
O(211)-C(21)-N(31)	124.8(3)	O(221)-C(22)-N(32)	125.4(3)
N(11)-C(21)-N(31)	106.4(2)	N(12)-C(22)-N(32)	106.2(2)
O(411)-C(41)-N(31)	128.2(3)	O(421)-C(42)-N(32)	128.0(3)
O(411)-C(41)-C(51)	127.2(3)	O(421)-C(42)-C(52)	127.4(3)
N(31)-C(41)-C(51)	104.7(2)	N(32)-C(42)-C(52)	104.5(2)
N(11)-C(51)-C(41)	106.2(2)	N(12)-C(52)-C(42)	107.0(2)
N(11)-C(51)-C(511)	131.2(3)	N(12)-C(52)-C(521)	131.7(3)
C(41)-C(51)-C(511)	122.7(3)	C(42)-C(52)-C(521)	121.3(3)
N(311)-C(312)-C(313)	116.0(3)	N(321)-C(322)-C(323)	120.6(3)
N(311)-C(312)-C(317)	122.7(3)	N(321)-C(322)-C(327)	119.5(2)
C(313)-C(312)-C(317)	121.2(3)	C(323)-C(322)-C(327)	119.6(3)
C(312)-C(313)-C(314)	119.6(3)	C(322)-C(323)-C(324)	119.9(3)
C(313)-C(314)-C(315)	120.7(4)	C(323)-C(324)-C(325)	120.8(3)
C(314)-C(315)-C(316)	120.3(4)	C(324)-C(325)-C(326)	119.1(3)
C(315)-C(316)-C(317)	120.1(3)	C(325)-C(326)-C(327)	120.9(3)
C(312)-C(317)-C(316)	118.1(3)	C(322)-C(327)-C(326)	119.7(3)
C(51)-C(511)-C(512)	126.0(3)	C(52)-C(521)-C(522)	125.5(3)
N(513)-C(512)-C(511)	177.5(4)	N(523)-C(522)-C(521)	176.4(5)

Table 5. Bond Distances (Å) and Bond Angles (°) with e.s.d.'s in parentheses for compound (**13g**)

O(322)-C(321)	1.195(3)	O(312)-C(311)	1.192(3)
O(323)-C(321)	1.337(3)	O(313)-C(311)	1.345(3)
O(323)-C(324)	1.432(5)	O(313)-C(314)	1.432(4)
N(12)-N(22)	1.362(3)	N(11)-N(21)	1.366(3)
N(12)-C(52)	1.383(3)	N(11)-C(51)	1.383(3)
N(12)-C(121)	1.419(3)	N(11)-C(111)	1.407(3)
N(22)-C(32)	1.331(3)	N(21)-C(31)	1.322(3)
N(52)-C(52)	1.353(4)	N(51)-C(51)	1.360(4)
N(126)-C(121)	1.319(3)	N(116)-C(111)	1.324(3)
N(126)-C(125)	1.348(4)	N(116)-C(115)	1.349(4)
C(32)-C(42)	1.404(3)	C(31)-C(41)	1.401(3)
C(32)-C(321)	1.474(4)	C(31)-C(311)	1.473(4)
C(42)-C(52)	1.369(4)	C(41)-C(51)	1.376(4)
C(121)-C(122)	1.387(3)	C(111)-C(112)	1.397(3)
C(122)-C(123)	1.380(4)	C(112)-C(113)	1.378(5)
C(123)-C(124)	1.390(5)	C(113)-C(114)	1.383(5)
C(124)-C(125)	1.357(4)	C(114)-C(115)	1.364(5)

C(321)-O(323)-C(324)	115.6(2)	C(311)-O(313)-C(314)	116.1(2)
N(22)-N(12)-C(52)	111.6(2)	N(21)-N(11)-C(51)	111.6(2)
N(22)-N(12)-C(121)	118.68(18)	N(21)-N(11)-C(111)	118.65(19)
C(52)-N(12)-C(121)	129.7(2)	C(51)-N(11)-C(111)	129.7(2)

N(12)-N(22)-C(32)	104.5(2)	N(11)-N(21)-C(31)	104.2(2)
C(121)-N(126)-C(125)	116.8(2)	C(111)-N(116)-C(115)	117.0(2)
N(22)-C(32)-C(42)	112.2(2)	N(21)-C(31)-C(41)	113.0(2)
N(22)-C(32)-C(321)	118.0(2)	N(21)-C(31)-C(311)	117.7(2)
C(42)-C(32)-C(321)	129.7(2)	C(41)-C(31)-C(311)	129.2(2)
C(32)-C(42)-C(852)	105.3(2)	C(31)-C(41)-C(51)	104.9(2)
N(12)-C(52)-N(52)	122.8(2)	N(11)-C(51)-N(51)	123.0(2)
N(12)-C(52)-C(42)	106.3(2)	N(11)-C(51)-C(41)	106.2(2)
N(52)-C(52)-C(42)	130.7(2)	N(51)-C(51)-C(41)	130.7(2)
N(12)-C(121)-N(126)	115.5(2)	N(11)-C(111)-N(116)	116.0(2)
N(12)-C(121)-C(122)	119.7(2)	N(11)-C(111)-C(112)	120.0(2)
N(126)-C(121)-C(122)	124.8(2)	N(116)-C(111)-C(112)	124.0(2)
C(121)-C(122)-C(123)	116.6(3)	C(111)-C(112)-C(113)	116.7(3)
C(122)-C(123)-C(124)	120.0(3)	C(112)-C(113)-C(114)	120.8(3)
C(123)-C(124)-C(125)	118.0(3)	C(113)-C(114)-C(115)	117.4(3)
N126)-C(125)-C(124)	123.8(3)	N(116)-C(115)-C(114)	124.1(3)
O(322)-C(321)-O(323)	123.5(3)	O(312)-C(311)-O(313)	122.6(3)
O(322)-C(321)-C(32)	125.4(2)	O(312)-C(311)-C(31)	125.9(2)
O(323)-C(321)-C(32)	111.1(2)	O(313)-C(311)-C(31)	111.5(2)

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H NMR, ^{13}C NMR and 2D NMR HMBC were obtained on a Bruker Advance DPX 300 (300 MHz) spectrometer with DMSO-d_6 or $CDCl_3$ as solvent and TMS as internal standard (δ in ppm, *J* in Hz). IR spectra were recorded with Perkin-Elmer Spectrum BX FTIP and BIO RAD Excalibur Series FTS 3000 MX FTIR spectrophotometers (KBr discs, ν in cm^{-1}). MS spectra were obtained on an Autospeck Q spectrometer. The microanalyses for C, H, and N were obtained on a Perkin Elmer Series II CHN *Analyser* 2400.

Methyl 2-[(benzyloxycarbonyl)amino]-3-cyanopropenoate (4).

Potassium cyanide (0.358 g, 5.5 mmol) was added into a solution of methyl 2-[(benzyloxycarbonyl)-amino]-3-dimethylaminopropenoate (**3**) (1.390 g, 5 mmol) in acetic acid (20 mL) and kept at rt for two days. When the reaction was completed volatile components were evaporated *in vacuo*. The residue was crystallized from water and methanol (1 : 1). Yield: 61 % (0.793 g); mp 103–105°C. *Anal*. Calcd for $C_{13}H_{12}N_2O_4$: C 60.00; H 4.65; N 10.76. Found, C 59.77; H 4.55; N 11.09. ^{1}H NMR ($CDCl_3$): δ 3.99 (s, 3H, CH_3), 5.20 (s, 2H, CH_2), 5.20 (s, 1H, CH), 7.34–7.42 (m, 5H, Ph), 7.64 (br s, 1H, NH). ^{1}H NMR (DMSO-d_6): δ 3.80 (s, 3H, CH_3), 5.16 (s, 2H, CH_2), 5.94 (s, 1H, CH), 7.36–7.40 (m, 5H, Ph), 10.49 (br s, 1H, NH).

Reaction of compound (4) with hydrazine monohydrate (5a).

A mixture of methyl 2-[(benzyloxycarbonyl)amino]-3-cyanopropenoate (**4**) (0.260 g, 1 mmol) and hydrazine hydrate (**5a**) (0.049 mL, 1.0 mmol) in methanol (3 mL) was stirred at rt. After 30 min another equivalent of hydrazine hydrate (0.049 mL, 1.0 mmol) was added and the reaction mixture was stirred for additional 2 h. When the reaction was completed methanol (6 mL) was added and the mixture heated to boiling point. Hot solution was filtered and the filtrate evaporated *in vacuo*. The nonvolatile residue was desolved in acetone and left standing at room temperature. After 15 min the acetone was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel (ethyl acetate : petroleum ether = 2 : 3 and 1 : 1). Fractions containing the products were combined and evaporated *in vacuo*.

Benzyl (6-amino-3-oxo-2,3-dihydropyridazin-4-yl)carbamate (6).

Yield: 21 % (0.055 g); mp decomposition above 190°C (ethyl acetate–petroleum ether). *Anal*. Calcd for $C_{12}H_{12}N_4O_3$: C 55.38; H 4.65; N 21.53. Found, C 55.50; H 4.86; N 21.00. MS: *m*/*z* (M^+, 260). HRMS: *m*/*z* (calcd, 206.090940, found, 260.091350). IR (cm^{-1}): 3421, 3372, 3275, 3204, 3035, 2963, 2899, 1734, 1694, 1628, 1560, 1520, 1467, 1367, 1280, 1238, 1204, 1059, 743, 697. ^{1}H NMR (DMSO-d_6): δ 5.20 (s, 2H, CH_2); 5.58 (s, 2H, NH_2); 7.33–7.47 (m, 6H, Ph and 5-H); 8.73 (br s, 1H, NH); 11.92 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 67.4; 106.1; 128.7; 128.9; 129.3; 126.9; 136.9; 150.6; 153.6.

Benzyl [5-imino-2-oxo-1-(propan-2-ylideneamino)- 2,5-dihydro-1*H*-pyrrol-3-yl]carbamate (8).

Yield: 36 % (0.108 g); mp 138–141°C. *Anal*. Calcd for $C_{15}H_{16}N_4O_3$: C 59.99; H 5.37; N 18.66. Found, C 60.00; H 5.41; N 18.57. MS: *m*/*z* (M^+, 300). HRMS: *m*/*z* (calcd, 300.122241; found, 300.123150) IR (cm^{-1}): 3462, 3294, 3274, 3061, 1727, 1649, 1627, 1543, 1365, 1315, 1215, 1058, 821, 767, 731. ^{1}H NMR ($CDCl_3$): δ 2.08 (s, 3H, CH_3); 2.11 (s, 3H, CH_3); 5.25 (s, 2H, CH_2); 6.76 (br s, 1H, NH); 7.24 (br s, 1H, CH); 7.35–7.41 (m, 5H, Ph); 8.16 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 18.9; 25.8; 68.5; 108.3; 128.7; 129.0; 129.1; 134.8; 135.5; 152.9; 153.0; 165.6; 169.3.

General Procedure for the Preparation of Imidazolidindiones (9b-i) and Pyrazoles (13g-i):

A mixture of methyl 2-[(benzyloxycarbonyl)amino]-3-cyanopropenoate (**4**) (0.260 g, 1 mmol) and hydrazine (**5**) (1.0 or 1.1 mmol) in DMF (4 mL) was refluxed. Volatile components were evaporated *in vacuo* and the residue was purified by column chromatography on silica gel. Fractions containing the product were combined and evaporated *in vacuo*.

Reaction of compound (4) with phenylhydrazine (5b). Procedure: phenylhydrazine (0.114 mL, 1.1 mmol), 30 min reflux, chromatography (ethyl acetate : petroleum ether = 2 : 3).

(*Z*)-2-[2,5-Dioxo-1-(phenylamino)imidazolidin-4-ylidene]acetonitrile (9b).

Yield: 55 % (0.158 g); mp 201–204°C (toluene–DMF). *Anal*. Calcd for $C_{11}H_8N_4O_2$: C 57.89; H 3.53; N 24.55. Found, C 58.19; H 3.64; N 24.25. MS: *m*/*z* (M^+, 228). IR (cm^{-1}): 3353, 3251, 2221, 1792, 1733,

1668, 1605, 1499, 1450, 1417, 1242, 1190, 751. ^{1}H NMR (DMSO-d_6): δ 5.73 (s, 1H, CH); 6.72–6.86 (m, 3H, Ph); 7.12–7.22 (m, 2H, Ph); 8.50 (s, 1H, NH); 12.18 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 75.0; 112.3; 115.3; 120.0; 128.9; 142.3; 146.0; 152.4; 160.6.

Reaction of compound (4) with 4-nitrophenylhydrazine (5c). Procedure: 4-nitrophenylhydrazine (0.172 g, 1.1 mmol), 90 min reflux, chromatography (ethyl acetate : petroleum ether = 1 : 1).

(*Z*)-2-[1-(4-Nitrophenylamino)-2,5-dioxoimidazolidin-4-ylidene]acetonitrile (9c).

Yield: 58 % (0.158 g); mp 211–215°C (toluene–DMF). *Anal*. Calcd for $C_{11}H_7N_5O_4$: C 48.36; H 2.58; H 25.63. Found, C 48.42; H 2.75; N 25.41. IR (cm^{-1}): 3478, 3339, 3280, 3046, 2232, 1795, 1754, 1673, 1600, 1505, 1440, 1348, 1269, 1194, 748. ^{1}H NMR (DMSO-d_6): δ 5.78 (s, 1H, CH); 6.99–7.05 (m, 2H, Ar); 8.05–8.11 (m, 2H, Ar); 9.53 (s, 1H, NH); 12.29 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 75.3; 111.7; 115.3; 125.5; 139.8; 142.5; 151.8; 152.1; 160.1.

Reaction of compound (4) with 4-hydrazinobenzoic acid (5d). Procedure: 4-hydrazinobenzoic acid (0.156 g, 1.0 mmol), 40 min reflux, chromatography (ethyl acetate : petroleum ether = 1 : 1).

(*Z*)-4-[4-(Cyanomethylene)-2,5-dioxoimidazolidin-1-ylamino]benzoic acid (9d).

Yield: 51 % (0.139 g); mp 258–261°C (toluene–DMF). *Anal*. Calcd for $C_{12}H_8N_4O_4$: C 52.95; H 2.96; N 20.58. Found, C 53.18; H 3.28; N 20.32. IR (cm^{-1}): 3345, 3208, 2225, 1811, 1747, 1676, 1608, 1431, 1402, 1326, 1296, 1246, 1180, 769. ^{1}H NMR (DMSO-d_6): δ 5.74 (s, 1H, CH); 6.83–6.88 (m, 2H, Ar); 7.74–7.80 (m, 2H, Ar); 9.03 (s, 1H, NH); 12.24 (br s, 1H, NH or COOH); 12.43 (br s, 1H, NH or COOH). ^{13}C NMR (DMSO-d_6): δ 76.0, 112.5, 116.3, 122.9, 131.8, 143.6, 151.0, 153.2, 161.4, 167.9.

Reaction of compound (4) with 2-hydrazinopyrimidine (5e). Procedure: 2-hydrazinopyrimidine (0.110 g, 1.0 mmol), 70 min reflux, chromatography (ethyl acetate : petroleum ether = 1 : 1).

(*Z*)-2-[2,5-Dioxo-1-(pyrimidin-2-ylamino)imidazolidin-4-ylidene]acetonitrile (9e).

Yield: 50 % (0.115 g); mp 260–262°C (toluene–DMF). *Anal*. Calcd for $C_9H_6N_6O_2$: C 46.96; H 2.63; N 36.51. Found, C 46.97; H 2.83; N 35.93. MS: *m*/*z* (M$^+$, 230). HRMS: *m*/*z* (calcd, 230.055224; found, 230.055850). IR (cm^{-1}): 3215, 3175, 2990, 2224, 1804, 1764, 1679, 1603, 1580, 1444, 1416, 1194, 767. ^{1}H NMR (DMSO-d_6): δ 5.79 (s, 1H, CH); 6.96 (t, 1H, *J* = 4.9, 4'-H); 8.46 (d, 2H, *J* = 4.5, 3'-H and 5'-H); 10.02 (s, 1H, NH); 12.34 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 75.9; 114.3; 115.0; 141.8; 152.1; 158.5; 160.2; 160.5.

Reaction of compound (4) with 6-hydrazinoimidazo[1,2-*b*]pyridazine (5f). Procedure: 6-hydrazinoimidazo[1,2-*b*]pyridazine (0.150 g, 1.0 mmol), 45 min reflux, chromatography (ethyl acetate).

(*Z*)-2-[1-(Imidazo[1,2-b]pyridazin-6-ylamino)-2,5-dioxoimidazolidin-4-ylidene]acetonitrile (9f).
Yield: 28 % (0.75 g); mp 262–265°C (toluene–DMF). *Anal*. Calcd for $C_{11}H_7N_7O_2$: C 49.07; H 2.62; N 36.42. Found, C 49.06; H 2.90; N 34.40. MS: *m*/*z* (M^+, 269). HRMS: *m*/*z* (calcd, 269.066123; found, 269.066850). IR (cm^{-1}): 3446, 3291, 3150, 3090, 2221, 1802, 1752, 1671, 1630, 1559, 1490, 1437, 1338, 1280, 1208, 1187, 1148, 754. ^{1}H NMR (DMSO-d_6): δ 5.81 (s, 1H, CH); 6.91 (d, 1H, *J* = 9.8, Het); 7.52 (s, 1H, Het); 7.96 (s, 1H, Het); 7.98 (d, 1H, *J* = 9.8, Het); 9.84 (s, 1H, NH); 12.36 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 76.8; 110.1; 116.1; 117.8; 128.0; 132.8; 137.4; 143.0; 152.5; 152.8; 160.9.

Reaction of compound (4) with 2-hydrazinopyridine (5g). Procedure: 2-hydrazinopyridine (0.120 g, 1.1 mmol), 65 min reflux, chromatography (ethyl acetate : petroleum ether = 1 : 2 and 1 : 1).

(*Z*)-2-[2,5-Dioxo-1-(pyridin-2-ylamino)imidazolidin-4-ylidene]acetonitrile (9g).
Yield: 26 % (0.060 g); mp 158–160°C (toluene–DMF). *Anal*. Calcd for $C_{10}H_7N_5O_2$: C 52.40; H 3.08; N 30.56. Found, C 53.07; H 3.28; N 29.61. MS: *m*/*z* (M^+, 229). HRMS: *m*/*z* (calcd, 229.059975; found, 229.060520). IR (cm^{-1}): 3267, 3030, 2222, 1796, 1755, 1669, 1607, 1582, 1439, 1283, 1197, 772, 753, 735. ^{1}H NMR (DMSO-d_6): δ 5.75 (s, 1H, CH); 6.79–6.86 (m, 2H, Py); 7.62 (ddd, 1H, *J* = 1.8, 7.2, 8.5, Py); 8.04 (ddd, 1H, *J* = 0.9, 1.7, 5.0, Py); 9.34 (s, 1H, NH); 12.23 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 76.2; 108.7; 116.1; 117.1; 138.8; 143.1; 148.4; 153.5; 156.9; 161.6.

Methyl 5-amino-1-(pyridin-2-yl)-1*H*-pyrazole-3-carboxylate (13g).
Yield: 19 % (0.041 g); sublimation 143°C (toluene). *Anal*. Calcd for $C_{10}H_{10}N_4O_2$: C 55.04; H 4.62; N 25.68. Found, C 54.99; H 4.75; N 25.61. IR (cm^{-1}): 3410, 3312, 2954, 1729, 1613, 1592, 1484, 1466, 1441, 1394, 1245, 1169, 1154, 1088, 819, 777, 752, 696. ^{1}H NMR (DMSO-d_6): δ 3.81 (s, 3H, CH_3); 5.83 (s, 1H, 4-H); 6.94 (s, 2H, NH_2); 7.32–7.38 (m, 1H, Py); 7.88-7.92 (deg dd, 1H, *J* = 8.4, Py); 8.01 (ddd, 1H, *J* = 1.9, 7.3, 8.4, Py); 8.46 (ddd, 1H, *J* = 0.8, 1.9, 5.0, Py).

Reaction of compound (4) with 3-chloro-6-hydrazinopyridazine (5h). Procedure: 3-chloro-6-hydrazinopyridazine (0.144 g, 1.0 mmol), 95 min reflux, chromatography (ethyl acetate : petroleum ether = 2 : 3 and ethyl acetate).

(*Z*)-2-[1-(6-Chloropyridazin-3-ylamino)-2,5-dioxoimidazolidin-4-ylidene]acetonitrile (9h).
Yield: 22 % (0.058 g); mp 202–206°C (toluene–DMF). *Anal*. Calcd for $C_9H_5ClN_6O_2$: C 40.85; H 1.90; H 31.76. Calcd for $C_9H_5ClN_6O_2$ x $2/3C_7H_8$ (toluene), C 50.14; H 3.38; N 25.52. Found, C 50.34; H 3.19; N 25.78. Percentage of toluene confermed with ^{1}H NMR spectra. IR (cm^{-1}): 3316, 3087, 2228, 1811, 1760, 1676, 1595, 1424, 1298, 1190, 1155, 837. ^{1}H NMR (DMSO-d_6): δ 5.80 (s, 1H, CH); 7.34 (d, 1H, *J* = 9.3, pyridazine); 7.70 (d, 1H, *J* = 9.3, pyridazine); 9.99 (s, 1H, NH); 12.35 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 75.8; 115.1; 117.4; 130.2; 142.0; 149.5; 151.7; 156.9; 160.0.

Methyl 5-amino-1-(6-chloropyridazin-3-yl)-1*H*-pyrazole-3-carboxylate (13h).

Yield: 11 % (0.028 g); sublimation 145°C (toluene). *Anal*. Calcd for $C_9H_8ClN_5O_2$: C 42.62; H 3.18; N 27.61. Found, C 42.86; H 3.15; N 27.50. MS: *m*/*z* (M^+, 253). IR (cm^{-1}): 3432, 3321, 2956, 1728, 1692, 1611, 1481, 1429, 1354, 1345, 1253, 1153, 1072, 772. ^{1}H NMR (DMSO-d_6): δ 3.82 (s, 3H, CH_3); 5.88 (s, 1H, 4-H); 6.98 (s, 2H, NH_2); 8.08 (d, 1H, *J* = 9.3, pyridazine); 8.24 (d, 1H, *J* = 9.3, pyridazine).

Reaction of compound (4) with 3-hydrazino-6-phenylpyridazine (5i). Procedure: 3-hydrazino-6-phenylpyridazine (0.186 g, 1.0 mmol), 45 min reflux, chromatography (ethyl acetate : petroleum ether = 2 : 3 and 1 : 1).

(*Z*)-2-[2,5-Dioxo-1-(6-phenylpyridazin-3-ylamino)imidazolidin-4-ylidene]acetonitrile (9i).

Yield: 19 % (0.058 g); mp 241–243°C. *Anal*. Calcd for $C_{15}H_{10}N_6O_2$: C 58.82; H 3.29; N 27.44. Found, C 58.54; H 3.48; N 27.15. IR (cm^{-1}): 3298, 3074, 2226, 1797, 1744, 1672, 1599, 1453, 1439, 1306, 1194, 781, 745, 731. ^{1}H NMR (DMSO-d_6): δ 5.81 (s, 1H, CH); 7.32 (d, 1H, *J* = 9.3, pyridazine); 7.43–7.55 (m, 3H, Ph); 8.01 (dd, 2H, *J* = 1.4, 8.0, Ph); 8.08 (d, 1H, *J* = 9.3, pyridazine); 9.86 (s, 1H, NH); 12.35 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 76.6; 115.5; 116.1; 126.9; 127.3; 129.8; 130.1; 137.0; 143.1; 153.1; 154.7; 157.25; 161.3.

Methyl 5-amino-1-(6-phenylpyridazin-3-yl)-1*H*-pyrazole-3-carboxylate (13i).

Yield: 26 % (0.077 g); sublimation 168°C. *Anal*. Calcd for $C_{15}H_{13}N_5O_2$: C 61.01; H 4.44; N 23.72. Found, C 61.28; H 4.56; N 23.61. MS: *m*/*z* (M^+, 295). HRMS: *m*/*z* (calcd, 295.106925; found, 295.107850). IR (cm^{-1}): 3423, 3317, 2924, 1722, 1610, 1589, 1552, 1479, 1450, 1429, 1399, 1262, 1158, 782. ^{1}H NMR (DMSO-d_6): δ 3.83 (s, 3H, CH_3); 5.91 (s, 1H, 4-H); 7.09 (s, 2H, NH_2); 7.55–7.63 (m, 3H, Ph); 8.16–8.21 (m, 2H, Ph); 8.25 (d, 1H, *J* = 9.3, pyridazine); 8.47 (d, 1H, *J* = 9.4 Hz, pyridazine).

(*Z*)-2-[3-Methyl-2,5-dioxo-1-(phenylamino)imidazolidin-4-ylidene]acetonitrile (12).

A solution of DMFDMA (0.113 mL, 0.75 mmol) in toluene (4 mL) was added dropwise into a suspension of (*Z*)-2-[2,5-dioxo-1-(phenylamino)imidazolidin-4-ylidene]acetonitrile (**9b**) (0.114 g, 0.5 mmol) in toluene (5 mL). The reaction mixture was refluxed for 45 min. Volatile components were evaporated *in vacuo* and the residue was purified by colomn chromatography on silica gel (ethyl acetate : petroleum ether = 1 : 3). Fractions containing the product were combined and evaporated *in vacuo*. Yield: 61 % (0.148 g); mp 166–167°C (toluene-hexane). *Anal*. Calcd for $C_{12}H_{10}N_4O_2$: C 59.50; H 4.16; N 23.13. Found, C 59.35; H 4.19; N 23.23. MS: *m*/*z* (M^+, 242). IR (cm^{-1}): 3290, 3037, 2924, 2216, 1799, 1752, 1659, 1636, 1604, 1498, 1456, 1399, 1307, 1242, 1137, 747. ^{1}H NMR ($CDCl_3$): δ 3.63 (s, 3H, CH_3); 5.59 (s, 1H, CH); 6.06 (br s, 1H, NH); 6.80–6.85 (m, 2H, Ph); 7.02–7.08 (m, 1H, Ph); 7.26–7.33 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$): δ 28.8; 76.9; 114.9; 115.0; 123.7; 129.9; 141.1; 144.8; 152.6; 159.7.

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