Synthesis of New Imidazo[4,5-*d*][1,3]diazepine Derivatives from 5-Amino-4-(cyanoformimidoyl)imidazoles

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Dedicated to the memory of Professor Nicholas Alexandrou

N^1-[(*Z*)-2-Amino-1,2-dicyanovinyl]formamidines **1a-d** react readily with tosyl isocyanate to form novel 8-amino-3-substituted-5-oxo-7-tosylaminoimidazo[4,5-*d*][1,3]diazepines **6a-d** rather than the 6-cyano-2-oxopurine derivatives **5a-d** expected. Compound **5a** has been synthesized from **1a** by reaction with ethyl chloroformate and base-catalyzed cyclization of the resultant 5-ethoxycarbonylamino-4-(cyanoformimidoyl)imidazole. Treatment of the 5-amino-4-cyanoimidazoles **7a** and **b** with tosyl isocyanate under similar conditions gives the 4-cyano-5-(3'-tosylureido)imidazoles **8a** and **b**, which on treatment with ethanolic ammonia cyclizes to the corresponding isoguanines **10a** and **b**.

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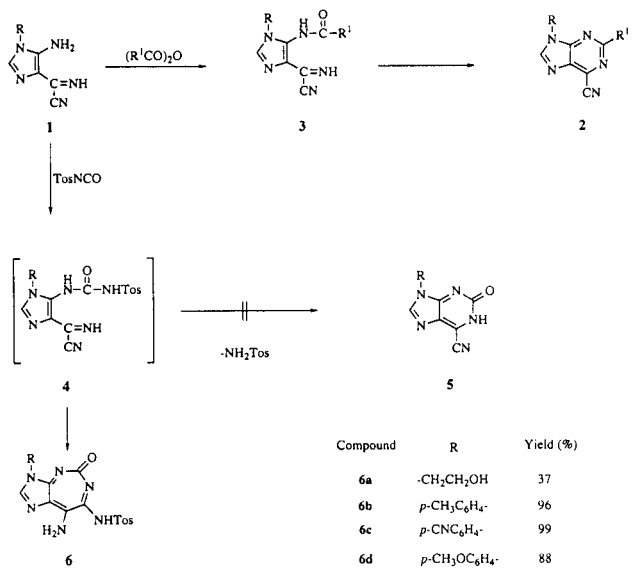
Previous work in our group has shown that 5-amino-4-(cyanoformimidoyl)imidazoles **1** are readily prepared from the corresponding N^1-[(*Z*)-2-amino-1,2-dicyanovinyl]formamidines upon treatment with a suitable base [1,2], and can easily be converted to a variety of 1,2-dihydropurine derivatives on reaction with ketones [1,2], 6-carboxamidopurines with aldehydes [1,2], or 6-cyanopurines **2** (R = alkyl or trifluoromethyl) [3,4] on treatment with carboxylic acid anhydrides. In these last reactions it has been shown that initial acylation occurs at the 5-amino group of **1** to give the intermediate **3**, which then cyclizes. In an effort to extend the utility of the compounds **1** we have investigated their reactions with tosyl isocyanate in the expectation that initial attack would occur at the 5-amino position leading to intermediate **4**, followed by a 6-*exo-trig* ring closure to the 2-oxo-6-cyanopurine with elimination of tosylamide.

When a slight excess of tosyl isocyanate was added to a suspension of **1a** (R = CH_2CH_2OH) in acetonitrile, at -15°C, a deep orange colour developed immediately with the gradual formation of a greenish-yellow solid. When the solution was then allowed to warm to 15-20°C the orange color disappeared leaving an insoluble greenish solid, which was shown by tlc to be a mixture of two compounds. When a solution of this solid in pyridine was warmed at 60-70°C for 7 hours a single product was obtained. Comparison of its ir and nmr spectra with those of an authentic sample of 6-cyano-9-(2'-hydroxyethyl)-2-oxopurine (*vide infra*) showed significant differences and elemental analysis and mass spectrometry showed that the product had a molecular formula of $C_{15}H_{16}N_6O_4S$ indicating that no fragments were lost during the reaction and one equivalent of tosyl isocyanate had been incorporated.

Scheme 1

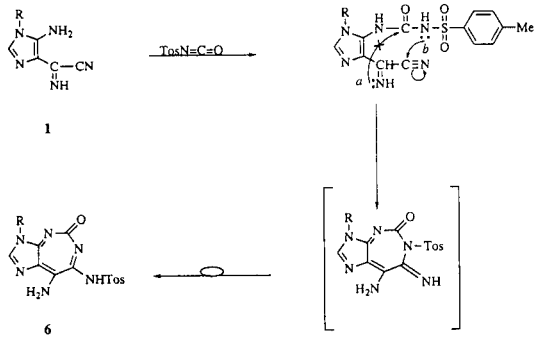


Compound	R	Yield (%)
6a	-CH_2CH_2OH	37
6b	*p*-$CH_3C_6H_4$-	96
6c	*p*-CNC_6H_4-	99
6d	*p*-$CH_3OC_6H_4$-	88

The ir spectrum indicated that the compound contained an NH_2 group and a strong band at 1653 cm^{-1} suggested a C=O group. The ^1H nmr spectroscopy confirmed the presence of a tosyl moiety and a one proton singlet at δ 8.4 ppm suggested that the compound was not a purine, but contained an imidazole ring conjugated to another unsaturated heterocyclic ring. The ^{13}C nmr spectrum confirmed

the presence of the tosyl and hydroxyethyl groups accounting for 9 C atoms and it showed the 6 additional bands predicted from the molecular formula. One of these C atoms at 151.5 ppm was bonded to a hydrogen atom, but the other five carbons were unsaturated and had no substituents. On the basis of the elemental and spectroscopic information, structure **6** is the only possibility. All attempts to obtain crystals suitable for X-ray crystallography proved unsuccessful and gave only very thin needles. This compound may arise by a 7-*exo-dig* cyclization of the nitrogen atom adjacent to the carbonyl and sulfonyl groups on the cyano group of the formimidoyl moiety (path *b*, Scheme 2), followed by a Dimroth rearrangement to give the thermodynamic product. The nitrogen linked to the tosyl group is only weakly nucleophilic, and it seems probable that the reaction is base catalyzed.

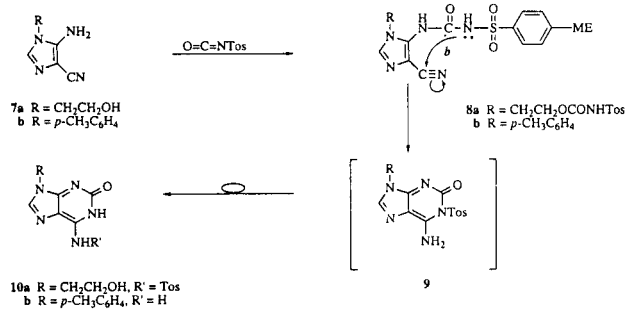
Scheme 2



This reaction appears to be a general one and similar products **6b-d** have been isolated in excellent yields as yellow solids from the reaction of tosyl isocyanate with the 5-amino-4-(cyanoformimidoyl)imidazoles **1b-d**. The analytical and spectroscopic data for these compounds are reported in Tables 1-3.

These results suggested the possibility that by starting from a 5-amino-4-cyanoimidazole it should be possible to prepare an isoguanine derivative by reaction with tosyl isocyanate under comparable conditions by the route shown in Scheme 3. When tosyl isocyanate was added to a solution of imidazole **7a** in acetonitrile at -15°C and the

Scheme 3



temperature was then allowed to reach 20°C a white precipitate formed. The ir spectrum showed a band of medium intensity at 2235 cm^{-1} for a cyano group and two strong carbonyl stretching vibrations at 1741 and 1706 cm^{-1}. The ^1H and ^{13}C nmr spectra indicated the presence of two tosyl residues and the one proton singlet at δ 7.8 ppm indicated that the compound was an imidazole derivative. On the basis of spectroscopic and elemental analysis the compound has been assigned the structure **8a** in which both the 5-amino group and the hydroxyl group on the alkyl side chain have reacted with the tosyl isocyanate to form the tosylureido and tosylcarbamate groups respectively. A similar reaction occurs with **7b** to form **8b** in 77% isolated yield, although in this case, of course, the 1-substituent is unaffected. This type of reaction is not without precedent. Grözinger [5] has described the reactions of several 5-amino-4-cyanoimidazoles with methyl isocyanate in DMF at room temperature and reports the isolation of 5-ureido intermediates, which cyclise on hydrol-

Table 1

Physical and Analytical Data

Compound	Yield (%)	mp (°C)	Molecular Formula	Found: C, H, N (%)	Requires: C, H, N (%)	ms (70ev) m/z (%)
5	74	210-214 dec	$C_8H_7N_5O_2$	46.8, 3.4, 33.8	46.8, 3.4, 34.1	206 [$(M+1)^+$, 100]
6a	37	243-244 dec	$C_{15}H_{16}N_6O_4S$	47.7, 4.2, 22.4	47.9, 4.3, 22.3	377 [$(M+1)^+$, 100]
6b	96	>250 dec	$C_{20}H_{18}N_6O_3S$	56.6, 4.1, 19.6	56.9, 4.3, 19.9	423 [$(M+1)^+$, 100]
6c	99	180-190 dec	$C_{20}H_{15}N_7O_3S$	55.1, 3.8, 22.3	55.4, 3.5, 22.6	434 [$(M+1)^+$, 100]
6d	88	190-200 dec	$C_{20}H_{18}N_6O_4S$	54.5, 4.2, 18.9	54.8, 4.1, 19.2	439 [$(M+1)^+$, 100]
8a	62	139-140	$C_{22}H_{22}N_6O_7S_2$	48.3, 3.7, 15.1	48.3, 4.0, 15.4	547 [$(M+1)^+$, 100]
8b	77	169-171	$C_{19}H_{17}N_5O_3S$	58.0, 4.0, 17.6	57.7, 4.3, 17.7	396 [$(M+1)^+$, 100]
10b	53	>300 dec	$C_{12}H_{11}N_5O$	hrms 242.1052	hrms 242.1042	242 [$(M+1)^+$, 100]
11	50	138-141 dec	$C_{10}H_{13}N_5O_3$	47.7, 5.0, 27.6	47.8, 5.2, 27.9	252 [$(M+1)^+$, 53.9]
12	54	186-187 dec	$C_{13}H_{17}N_5O_5$	48.5, 5.5, 21.6	48.3, 5.3, 21.7	324 [$(M+1)^+$, 100]
13	55	191-192 dec	$C_{17}H_{23}N_7O_2$	57.4, 6.5, 27.3	57.1, 6.5, 27.4	205 [$(M)^+$, 26.1]

Table 2

^{1}H NMR and IR Data

Compound	IR (Nujol), ν (cm^{-1})	^{1}H NMR, δ, J (Hz)	Solvent
5	3470 m, 3391 m, 3213 s, 3143 s, (3300-2400) s, br, 1795 s, 1782 s,	3.8 (2H, t, J 6, OCH_2), 4.3 (2H, t, NCH_2), 8.6 (1H, s, CH)	$(CD_3)_2SO$
6a	3383 m, 3316 m, 3204 m, 1653 s, 1623 s, 1596 s, 1567 s, 1522 m	2.4 (3H, s, $ArCH_3$), 3.9 (2H, t, OCH_2), 4.2 (2H, t, NCH_2), 5.0 (<1H, br s, OH), 7.4 (2H, d, ArH), 7.9 (2H, d, ArH), 8.4 (1H, s, CH), 8.7 (<1H, br s, NH), 9.2 (<1H, br s, NH)	$(CD_3)_2SO$
6b	3365 m, 3298 w, 3233 w, 3126 w, 1830 w, 1737 w, 1658 s, 1636 s, 1580 s, 1519 s	2.4 (6H, s, 2ArCH3), 7.4 (4H, d, ArH), 7.7 (2H, d, ArH), 7.9 (2H, d, ArH), 8.7 (<1H, br s, NH), 8.8 (1H, s, CH), 9.2 (<1H, br s, NH), 12.2 (<1H, br s, NH)	$(CD_3)_2SO$
6c	3347 m, 3262 w, 3141 w, 3115 w, 2234 w, 1830 w, 1708 w, 1640 s, 1584 s, 1521 s	2.4 (3H, s, $ArCH_3$), 7.4 (2H, d, ArH), 7.8 (2H, d, ArH), 7.9 (2H, d, ArH), 8.7 (<1H, br s, NH), 9.0 (1H, s, CH), 9.2 (<1H, br s, NH)	$(CD_3)_2SO$
6d	3366 m, 3239 w, 3116 w, 1828 w, 1740 w, 1659 s, 1642 s, 1584 s, 1518 s	2.4 (3H, s, ArCH3), 3.8 (3H, s, OCH_3), 7.2 (2H, d, ArH), 7.4 (2H, d, ArH), 7.7 (2H, d, ArH), 7.9 (2H, d, ArH), 8.7 (<1H, br s, NH), 8.8 (1H, s, CH), 9.2 (<1H, br s, NH), 12.2 (<1H, br s, NH)	$(CD_3)_2SO$
8a	3318 s, 3234 m, 2235 m, 1741 s, 1706 s, 1598 w, 1527 m	2.4 (6H, s, $2ArCH_3$), 3.8 (3H, t, J 5, NCH_2), 4.05 (3H, t, J 5, OCH_2), 7.1-7.4 (<1H, br s, NH), 7.4 (4H, d, 2ArH), 7.7 (2H, d, ArH), 7.8 (2H, d, ArH), 7.8 (1H, s, CH), 9.9 (<1H, br s, NH)	$(CD_3)_2SO$
8b	3261 m, 3200 m, 3124 w, 2236 m, 1670 s, 1594 m, 1578 w, 1517 w	2.4 (6H, s, $2ArCH_3$), 7.2 (4H, q, ArH), 7.4 (2H, d, ArH), 7.7 (2H, d, ArH), 8.1 (1H, s, CH), 8.9 (<1H, br s, NH), 11.5 (<1H, br s, NH)	$(CD_3)_2SO$
10a	3497 w, 3273 m, 2637 w, 1705 s, 1621 s, 1574 m	[a]	
10b	3403 m, 3304 m, 3099 s, 2360 w, 1814 w, 1660 s, 1643 s, 1622 s, 1606 s, 1516 s	2.4 (3H, s, $ArCH_3$), 7.3 (2H, d, ArH), 7.2-7.8 (<2H, br s, NH), 7.7 (2H, d, ArH), 8.1 (1H, s, CH), 8.9 (<1H, br s, NH), 10.5 (<1H, br s, NH)	$(CD_3)_2SO$
11	3332 m, 3225 m, 3163 m, 3068 s, 1665 m, 1648 m, 1641 w, 1577 w, 1514 w	1.4 (3H, t, J 7, CH_3), 3.8 (2H, q, J 5, OCH2), 4.0 (2H, t, J 5, OCH_2), 4.3 (2H, t, J 5, NCH_2), 8.2 (<2H, br s, NH)	$(CD3)_2SO$
12	3269 m, 3217 m, 3094 m, 1739 w, 1685 w, 1641 w, 1579 w, 1550 w, 1505 m	1.3 (3H, t, J 7, CH_3), 4.25 (2H, q, OCH_2), 4.3 (2H, t, J 5, OCH_2), 4.4 (2H, t, NCH_2), 8.3 (<2H, br s, NH)	$(CD_3)_2SO$
13	3126 s, 3073 s, 3019 s, 2230 s, 1643 w, 1606 w, 1582 s, 1556 m, 1542 s, 1518 w	3.8 (2H, t, J 5, OCH_2), 4.1 (2H, t, J 5, NCH_2), 5.3 (1H, br s, OH), 7.9 (1H, s, CH), [3.6 (2H, m), 3.6 (2H, t, J 6), 3.4 (2H, m), 2.0 (2H, t), 1.75 (6H, m) for DBU]	$(CD_3)_2SO$

[a] The ^{1}H nmr spectrum was not determined.

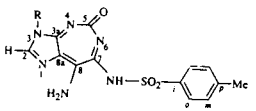
ysis with an aqueous solution of sodium hydrogenphosphate to yield *N*-methylisoguanines. Similar reactions have also been reported by Cooke [6,7], although in these cases the intermediate 5-ureido derivative was not isolated, but was hydrolysed to the corresponding *N*-methylisoguanine derivatives in moderate to poor yields by treatment with aqueous ammonia in ethanol.

Both compounds **8a** and **b** proved to be sensitive to hydrolysis to the 5-amino-4-cyanoimidazole. This reaction is very slow upon standing at room temperature in wet DMSO-d_6 solution, but hydrolysis appears to compete with cyclization upon heating in aqueous ammonia and ethanol. So, for example, compound **8a** gave a complex mixture under these conditions, and attempts to cyclize this compound by warming a dry pyridine solution at 60-70°C for *ca.* 5 hours, gave only a 23% yield of the isoguanine **10a** (identified only on the basis of its ^{13}C nmr spectrum) after dry flash chromatography. The major product of this last reaction was **7a** (47% isolated yield) presumably formed by hydrolysis of the starting material on the silica column. A moderate yield of isoguanine **10b** (53%) was obtained upon refluxing a solution of **8b** in aqueous ethanolic ammonia over 3 hours with continuous passage of ammonia through the solution.

The unsuccessful efforts to prepare 6-cyano-2-oxopurines prompted us to investigate the synthesis of carbamate derivatives of **1** in the expectation that these would cyclize upon treatment with a base. Dropwise addition of

Table 3

^{13}C NMR Chemical Shifts [δC $(CD_3)_2SO$] for



Compound	R	C-5	C-7	C-8	C-3a	C-8a	C-2	C-*i*	C-*o*	C-*m*	C-*p*	Me	R
6 a	CH_2CH_2OH	164.2	161.8	150.4	160.5	129.8	151.5	143.1	133.3	130.3	146.6	24.9	62.7 (OCH_2) 49.7 (NCH_2)
6 b	*p*-MeC_6H_4	164.7	161.9	151.8	159.8	134.0	149.5	143.1	133.3	130.3	146.6	24.9	141.6 (C-*i*) 127.3 (C-*o*) 133.8 (C-*m*) 135 (C-*p*) 24.5 (Me)
6 c	*p*-CNC_6H_4	164.6	161.6	152.3	159.5	134.0	149.0	143.1	133.3	130.3	146.7	24.9	141.6 (C-*i*) 131.5 (C-*o*) 133.5 (C-*m*) 135 (C-*p*) 122.2 (CN)
6 d	*p*-$MeOC_6H_4$	164.8	162.1	150.1	163.0	[a]	151.6	143.3	133.3	130.4	146.8	25.1	[a] (C-*i*) 129.7 (C-*o*) 118.7 (C-*m*) 135 (C-*p*) 59.6 (OMe)

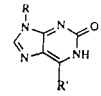
[a] These bands were not detected due to low solubility of the sample in $(CD_3)_2SO$.

Table 4
^{13}C NMR Chemical Shifts [δC $(CD_3)_2SO$] for

Compound	R	R'	R"	C-2	C-4	C-5	R	R'	R"
8a	$(CH_2)_2OR'$	CONHTos	CN	142.3	112.1	137.9	25.1 (Me), 131.4, 131.5, 133.6, 133.7, 140.0, 140.2, 148.5, 148.9, 154.5 (C=O), 154.7 (C=O)		118.8
8b	*p*-$CH_3C_6H_4$	CONHTos	CN	141.9	113.6	134.9	24.5 (Me), 128.6 (C-*o*) 133.8 (C-*m*) 137.8 (C-*p*) 140.5 (C-*i*)	25.0 (Me), 131.1 (C-m), 133.4 (C-*o*), 142.8 (C-*i*), 147.9 (C-*p*), 154.1 (C=O)	118.2
11	CH_2CH_2OH	COOEt	C=NH(CN)	143.0	115.9	141.5	49.8 (NCH_2), 62.7 (OCH_2)	18.0 (CH_3), 65.6 (CH_2), 165.2 (C=O)	125.4 (C≡N), 154.8 (C=N)
12	$(CH_2)_2OR'$	COOEt	C=NH(CN)	142.3	115.8	141.6	18.0 (CH_3), 18.3 (CH_3), 46.2 (NCH_2), 65.6 (CH_2), 67.9 (OCH_2), 68.6 (CH_2), 158.1 (C=O), 165.2 (C=O)		124.9 (C≡N), 154.8 (C=N)

Table 5

^{13}C NMR Chemical Shifts [δC $(CD_3)_2SO$] for

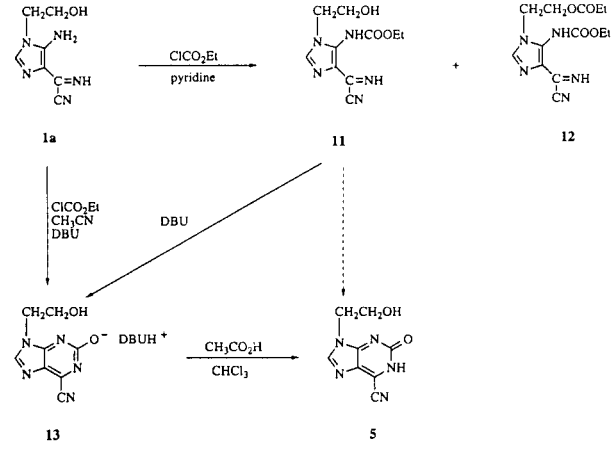


Compound	R	R'	C-2	C-4	C-5	C-6	C-8	R	R'
5	$(CH_2)_2OH$	CN	165.7	160.1	133.01	134.6	153.1	50.1 (NCH_2), 62.8 (OCH_2)	118.3
13 (DBU salt of **5**)	$(CH_2)_2OH$	CN	169.4	160.4	129.4	134.2	149.2	49.1 (NCH_2), 62.9 (OCH_2)	118.6
10a	$(CH_2)_2OH$	NHTos	154.3	146.8	117.7	152.5	143.6	50.8 (NCH_2) 63.3 (OCH_2)	25.0 (Me) 130.1, 133.5, 144.1, 146.5
10b	*p*-$CH_3C_6H_4$	NH_2	[a]	[a]	[a]	[a]	142.1	[a]	24.6 (Me), 126.6, 133.7, 136.6, 140.5

[a] This band was not detected due to the low concentration of the sample.

ethyl chloroformate to a suspension of **1a** in acetonitrile at -15°C in the presence of pyridine gave a mixture containing mainly the desired carbamate **11**, together with a minor amount of **12** (see Scheme 4) which were separated by chromatography. Compound **12** could be isolated in 54% yield by use of a 2 mole excess of ethyl chloroformate and pyridine under similar conditions. When the reaction of **1a** and ethyl chloroformate (1:1 mole ratio) was repeated without pyridine and the reaction mixture was allowed to warm to room temperature before addition of 1 mole equivalent of DBU, the major product (isolated in 50% yield after 3 days) was the DBU salt of the 6-cyano-2-oxopurine **13**, which was easily converted to **5** (74% yield) upon treatment with glacial acetic acid in chloroform solution. Addition of DBU to a solution of **11** in acetonitrile at 4°C also gave the salt **13b** in 55% yield over a period of 3 days. Addition of DBU to a solution of **12** in ethyl acetate followed, after 1 day at room temperature, by addition of acetic acid gave **5** in 60% isolated yield.

Scheme 4



EXPERIMENTAL

The ^{1}H nmr spectra were recorded on Bruker XL300 (300 MHz) instrument (with *J*-values given in Hz), ^{13}C nmr spectra (with DEPT 135) either on a Bruker WP80 or XL300 instrument, and ir spectra on a Shimadzu IR-435. Mass spectra were recorded on a Kratos Concept instrument, and uv spectra on a Perkin-Elmer Lamda 15 uv/vis spectrometer. The melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected. Physical and spectroscopic data for compounds **6-10** are given in Tables 1-5.

8-Amino-3-(2'-hydroxyethyl)-5-oxo-7-tosylaminoimidazo[4,5-*d*][1,3]diazepine (**6a**).

A suspension of imidazole **1a** (0.32 g, 1.8 mmoles) in dry acetonitrile (15 ml) was kept at -15°C under a nitrogen atmosphere with magnetic stirring. A solution of tosyl isocyanate (0.54 g, 2.9 mmoles) in dry acetonitrile (*ca.* 2 ml) was added dropwise through the serum cap over a period of 20 minutes. A deep orange color developed upon the addition of the first drop of isocyanate solution and after 20 minutes all the starting material had been consumed (as evidenced by tlc). The greenish-yellow suspension in an orange solution was stirred at room temperature for an additional 25 minutes, when the solution became colorless. The solid was filtered and washed with chloroform leading to a greenish solid (0.67 g) showing two fluorescent spots on

tlc. The solid was solubilized in dry pyridine (20 ml), silica gel 60 was added (*ca.* 0.5 g) and the mixture was warmed in a water bath (60-70°C) for 7 hours, when tlc showed that a single product was present. Dry flash chromatography using acetone as the solvent led to a pale yellow solid identified as compound **6a** (0.25 g, 0.67 mmole, 37%).

8-Amino-3-(4'-methylphenyl)-5-oxo-7- tosylaminoimidazo[4,5-*d*][1,3]diazepine (**6b**).

A suspension of imidazole **1b** (0.43 g, 1.91 mmoles) in dry acetonitrile (15 ml) was kept at 0°C under a nitrogen atmosphere with magnetic stirring. A solution of tosyl isocyanate (0.76 g, 3.78 mmoles) in dry acetonitrile (*ca.* 2.5 ml) was added dropwise through the serum cap over a period of 30 minutes. The resulting orange suspension was stirred at room temperature for 4 hours, when the starting material was no longer present (as evidenced by tlc). The yellow solid was filtered and washed with diethyl ether to give compound **6b** (0.77 g, 1.82 mmoles, 96%).

8-Amino-3-(4'-cyanophenyl)-5-oxo-7- tosylaminoimidazo[4,5-*d*][1,3]diazepine (**6c**).

A suspension of imidazole **1c** (0.12 g, 0.51 mmole) in dry acetonitrile (15 ml) was kept at 0°C under a nitrogen atmosphere with magnetic stirring. A solution of tosyl isocyanate (0.2 g, 1.02 mmoles) in dry acetonitrile (*ca.* 1 ml) was added dropwise through the serum cap over a period of 15 minutes. An orange suspension was formed and this evolved to a homogeneous orange solution while still in the ice bath. Immediately after the removal of the ice bath, a pale yellow solid started to precipitate out of solution, and the mixture was stirred at room temperature for 18 hours. The yellow solid was filtered and washed with diethyl ether to give compound **6c** (0.22 g, 0.51 mmole, 99%).

8 -Amino- 3- (4'-methoxyphenyl) -5-oxo-7- tosylaminoimidazo-[4,5-*d*][1,3]diazepine (**6d**).

A suspension of imidazole **1d** (0.29 g, 1.20 mmoles) in dry acetonitrile (10 ml) was kept at 0°C under a nitrogen atmosphere with magnetic stirring. A solution of tosyl isocyanate (0.47 g, 2.40 mmoles) in dry acetonitrile (*ca.* 3 ml) was added dropwise through the serum cap over a period of 30 minutes. An orange suspension was obtained which was stirred at room temperature, while the orange solid gradually turned into a yellow solid. The mixture was stirred at room temperature for 18 hours, when the solid was filtered and washed with diethyl ether to give compound **6d** (0.47 g, 1.06 mmoles, 88%).

4-Cyano-1-(2'-tosylaminocarbonyloxyethyl)-5-(3'-tosylureido)-imidazole (**8a**).

A suspension of imidazole **1a** (0.48 g, 3.1 mmoles) in dry acetonitrile (16 ml) was kept at -15°C under a nitrogen atmosphere and with magnetic stirring. A solution of tosyl isocyanate (1.3 g, 6.6 mmoles) in dry acetonitrile (*ca.* 4 ml) was added dropwise through the serum cap. The temperature was allowed to rise to room temperature and 20 minutes later a white solid started to precipitate out of solution. The solid was filtered and washed with acetonitrile and chloroform. The product was identified as imidazole **8a** (1.06 g, 1.94 mmoles, 62%).

4-Cyano-1-(3'-tosylureido)-1-(*p*-tolyl)imidazole (**8b**).

A suspension of imidazole **1b** (0.58 g, 2.9 mmoles) in dry acetonitrile (15 ml) was kept at -4°C under a nitrogen atmosphere and with magnetic stirring. A solution of tosyl isocyanate (1.3 g, 6.6 mmoles) in dry acetonitrile (*ca.* 4 ml) was added dropwise through the serum cap. The solution immediately became deep orange and a white solid precipitated out. After 1 hour at -4°C, the solid was filtered and washed with acetonitrile. The product was identified as imidazole **8b** (0.89 g, 2.2 mmoles, 77%).

9-(2'-Hydroxyethyl)-6-tosylisoguanine (**10a**).

A solution of imidazole **8a** (0.23 g, 0.42 mmoles) in dry pyridine (5 ml) was kept at 70-80°C and after 5 hours all the starting material had been consumed. Dry flash chromatography using acetonitrile as solvent enabled the isolation of two different products, which crystallized selectively from acetonitrile: 5-amino-4-cy-ano-(2'-hydroxyethyl)imidazole (0.03 g, 0.1 mmole, 47%) and isoguanine **10a** (0.03 g, 0.1 mmole, 24%).

9-(*p*-Tolyl)isoguanine (**10b**).

A solution of imidazole **8b** (0.3 g, 0.76 mmole) in ethanol (10 ml) and 25% ammonia (10 ml) was kept in a two-neck, round-bottom flask equipped with a reflux condenser and a long needle to enable continuous bubbling of ammonia in the reaction mixture. The reaction mixture was refluxed for 3 hours and a white solid precipitated out on cooling. The solid was filtered and washed with ethanol. The product was identified as isoguanine **10b** (0.1 g, 0.4 mmole, 53%).

5-Amino-4-(cyanoformimidoyl)-1-(2'-hydroxyethyl)imidazole **1a** with Ethyl Chloroformate.

Method A.

A suspension of imidazole **1a** (0.45 g, 2.5 mmoles) in dry acetonitrile (30 ml) was kept at -15°C under a nitrogen atmosphere with magnetic stirring. Dry pyridine (0.3 ml, 3.7 mmoles) was added through the serum cap followed by ethyl chloroformate (0.28 g, 2.6 mmoles), which was added dropwise over a period of 30 minutes. As the temperature was allowed to rise slowly to room temperature a dark brown suspension developed in a clear yellow solution. The suspension was removed by filtration through glass fibre paper and the solution was concentrated to a small volume in the rotary evaporator. Chloroform (30 ml) was added and a yellow solid precipitated after 19 hours at -10°C and was filtered and washed with chloroform. This product was identified as imidazole **11** (0.20 g). Dry flash chromatography on the mother liquid enabled the separation of two different compounds: imidazole **12** which was isolated when chloroform and ethyl acetate were used as eluant (0.12 g, 0.36 mmole, 14%) and imidazole **11** (0.12 g) isolated from acetone. The total isolated yield of imidazole **11** was (0.32 g, 1.25 mmoles, 50%).

Method B.

A suspension of imidazole **1a** (0.63 g, 3.5 mmoles) in dry acetonitrile (30 ml) was kept at -4°C under a nitrogen atmosphere with magnetic stirring. Dry pyridine (0.85 ml, 10 mmoles) was added through the serum cap followed by ethyl chloroformate (0.85 g, 8 mmoles), which was added dropwise over a period of 15 minutes. After this time, all the starting material had been consumed and the mixture was stirred at room temperature for 1 hour. Dry flash chromatography using chloroform and ethyl acetate as eluants led to a yellow solid identified as imidazole **12** (0.61 g, 1.9 mmoles, 54%).

6-Cyano-9-(2'-hydroxyethyl)-2-oxopurine (**5**).

Method A.

A solution of imidazole **11** (0.15 g, 0.6 mmole) in dry acetonitrile (50 ml) was stirred at room temperature. Addition of DBU (0.11 g, 0.72 mmole) led to a brownish-yellow solution which was stirred at 4°C. A white solid started to precipitate out after 6 hours and the reaction was complete after 3 days, as evidenced by tlc. The off-white solid was filtered as the DBU salt of 6-cyano-2-oxopurine, **13** (0.12 g, 0.32 mmole, 55%).

A suspension of **13** (0.27 g, 0.77 mmole) in chloroform (30 ml) was neutralized by addition of glacial acetic acid (0.55 g, 0.92 mmole). A colorless homogeous solution was obtained immediately and shortly after a white solid precipitated. The solid which was filtered and washed with chloroform and diethyl ether was identified as purine **5** (0.12 g, 0.57 mmole, 74%).

Method B.

A suspension of imidazole **1a** (1.12 g, 6.25 mmoles) in dry acetonitrile was kept at -15°C under a nitrogen atmosphere and with magnetic stirring. Dry pyridine (1.18 ml, 14.8 mmoles) was added through the serum cap followed by ethyl chloroformate (0.79 g, 7.3 mmoles). A deep yellow color developed immediately and after 15 minutes tlc indicated that the imidazole **11** was the major product in solution. The temperature was slowly allowed to rise to room temperature and DBU (2.26 g, 14.88 mmoles) was added. After 5 days the white solid suspension was filtered and washed with diethyl ether. The solid was identified as the DBU salt of 6-cyano-2-oxopurine **13** (1.1 g, 3.1 mmoles, 50%).

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