Synthesis of new derivatives of 2,3-dicyano-imidazo [1,2-*a*]pyrimidine from 4-hydroxy-6-methylpyran-2-ones

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Abstract
The reactions of 2-amino-4,5-dicyanoimidazole **1** with lactone **2** in refluxing alcohol has been carried out for the first time and afforded imidazo[1,2-*a*]pyrimidines **4** and **5a-d**. Condensation of compound **1** with 3-acetyl-4-hydroxy-6-methylpyran-2-one in refluxing n-butanol afforded bis(imidazopyrimidine) derivative **6**. Reaction of hydrazine hydrate with ester **5** yielded the corresponding hydrazides **8**. Condensation of o-phenylenediamines **9** with compound **5** in refluxing xylene or with hydrazides by melting reagents afforded 2,3-dicyano-5-[benzimidazol-2-yl]methyl-7-methylimidazo[1,2-*a*] pyrimidines **10a-d**.

Keywords: 2-Amino-4,5-dicyanoimidazole, 4-hydroxy-6-methylpyran-2-one, 3-acetyl-4-hydroxy-6-methylpyran-2-one, imidazo[1,2-*a*]pyrimidines, o-phenylenediamines, benzimidazoles

Introduction

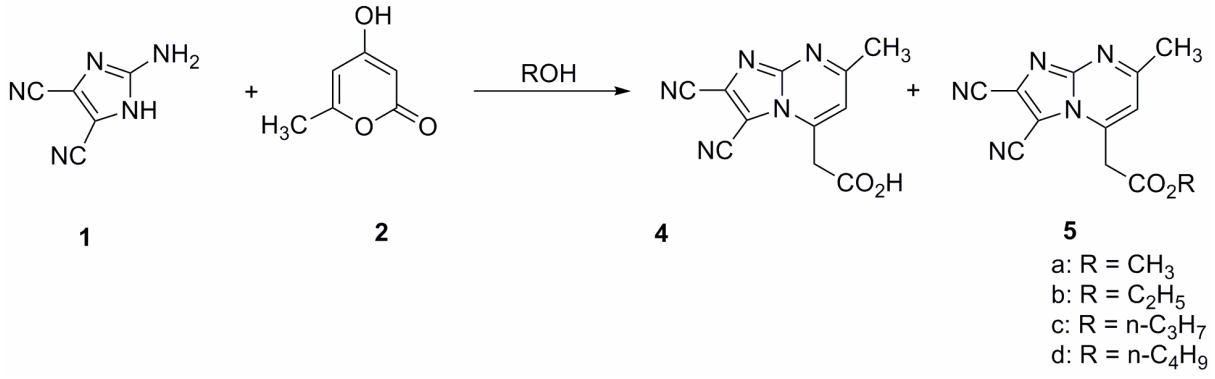
In the past few years there has been a growing interest in the chemistry of imidazo[1,2-a] pyrimidines, which is due to the extent of their applications in pharmacological science. Indeed they are known for their anxiolytic,[1] cardiovascular,[2] analgesic,[3,4] antihypertensive[4] and neuroleptic[5,6] properties.

A general method for the preparation of imidazo[1,2-*a*]pyrimidines consists of the formation of the pyrimidine cycle by condensation reaction between 2-aminoimidazoles and aliphatic 1,3-difunctional compounds.[7-12]

In order to prepare new imidazo[1,2-*a*]pyrimidines with possible pharmacological or biological properties, we have examined for the first time the action of 2-amino-4,5-dicyanoimidazole **1** on the oxygenated heterocycles: 4-hydroxy-6-methylpyran-2-one **2** and its acetylated derivative 3-acetyl-4-hydroxy-6-methylpyran-2-one **3**.[13-20]

Results and Discussion

The reaction of imidazole **1** with pyran-2-one **2** was carried out at reflux temperature in linear aliphatic alcohols for different time periods (24-48 hours). This allowed us to obtain two imidazopyrimidines (Scheme 1) namely the substituted acetic acid **4** and the corresponding esters **5a-d**.



Scheme 1. Reaction of imidazole **1** and pyran **2** in aliphatic alcohols.

The structures of the compounds **4** and **5a-d** were obtained from their ^{1}H NMR, ^{13}C NMR and mass spectra, and X-ray crystallography. In the ^{1}H NMR spectra, besides the signals due to the ester groups, two singlets appear at δ 7.01-7.12 and δ 3.93-3.95 which could be attributed respectively to the pyrimidine protons and to the methylene groups α to the ester groups. The ^{13}C NMR spectra of **5a-d** showed, in particular, a signal at δ (167.3 – 168.6) which corresponds to the carbonyls of esters groups, as well as two signals at δ 43.7-43.8 and δ 114.3-114.4 due respectively to the methylene groups α to the ester groups and to C-6 of the bicyclic system. The results and yields are summarised in Table 1.

Table 1. Yields of the compounds **4** and **5a-d** in different alcohol solvents

Product/ROH	MeOH	EtOH	n-PrOH	n-BuOH
4	17	23	32	36
5	75	70	64	57

A crystallographic study was also carried out on the compound **5a** which provided further evidence for the proposed structures (Figure 1).

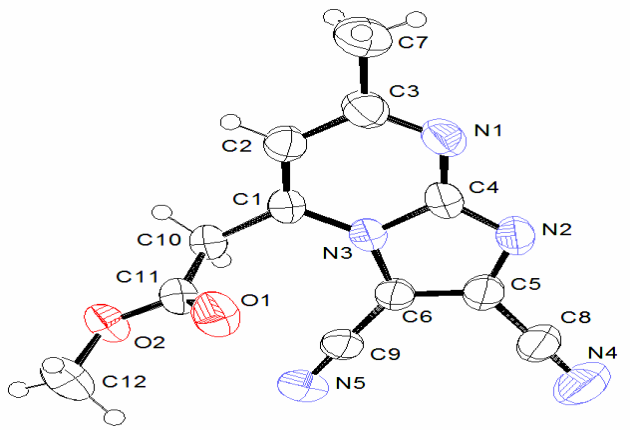


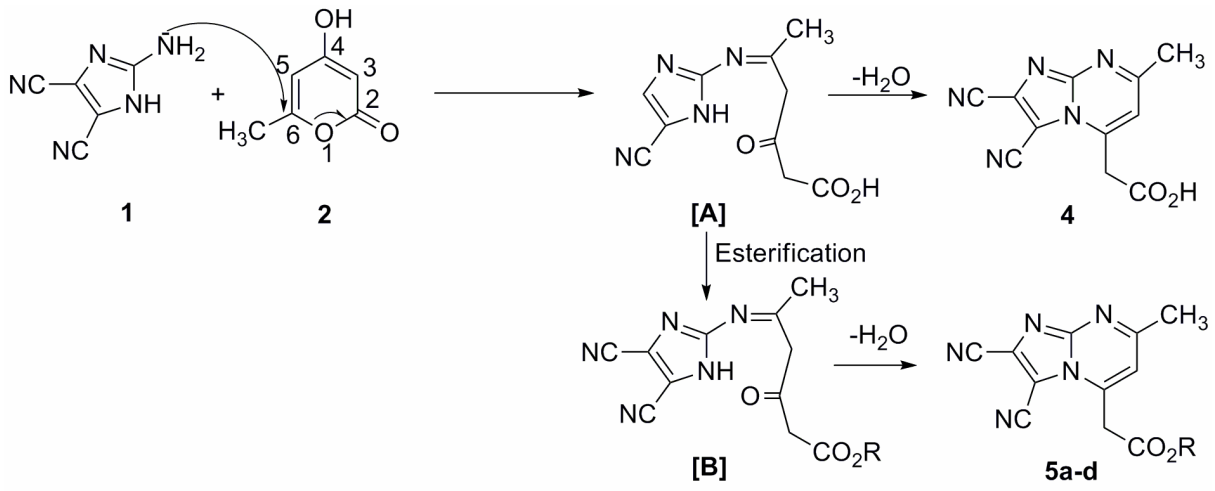
Figure 1. Molecular structure (ORTEP) of the compound **5a**.

As shown in Figure 1, the molecule of the product **5a** is built up of two plane cycles. The cohesion of the molecules in crystal **5a** is assured by their interpenetration.

It should be mentioned that the yields of the products **4** and **5** vary according to the nature of solvent employed in the reaction. The more sterically hindered alcohols give less of the ester.

The results obtained from the condensation of **1** and **2** allow us to propose a mechanism explaining the formation of the compounds **4** and **5a-d** (Scheme 2). In fact, the attack of the amino group of aminoimidazole **1** on the C-6 of pyrone **2** leads to the intermediate [**A**], which acts according to two competitive reactions. An esterification leads to the intermediate [**B**], which cyclises towards compounds **5a-d** and an intramolecular cyclisation of [A] leads to the compound **4**.

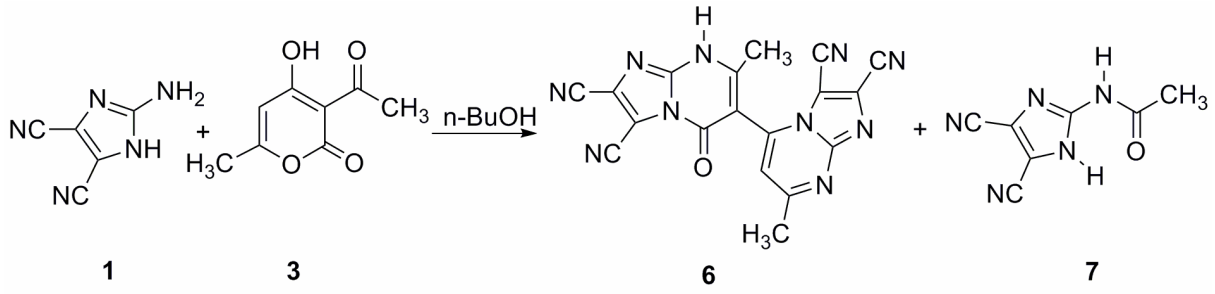
We have also examined the condensation of 2-amino-4,5-dicyanoimidazole **1** with 4-hydroxy-6-methylpyran-2-one 2 in *t*-butanol. Thus it was shown, after 24 h of reflux that the reaction is complete and leads exclusively to the formation of the compound **4** with a yield of 90 % .



Scheme 2. The proposed mechanism for the formation of the compounds **4** and **5**.

The esterification reaction of compound **4** was carried out at reflux temperature for 48 hours in a mixture of ethanol/sulfuric acid (82/18) leading to the ester **5a**.

The condensation of the 3-acetyl-4-hydroxy-6-methylpyran-2-one **3** with two equivalents of 2-amino-4,5-dicyano imidazole **1** at reflux in *n*-butanol for 48 hours afforded two products (Scheme 3) the bis(imidazopyrimidine) derivative **6** and 2-acetamido-4,5-dicyanoimidazole **7**.



Scheme 3. Condensation of dehydroacetic acid **3** and 2-amino-4,5-dicyano imidazole **1**.

The structures of the compounds **6** and **7** were identified by NMR analysis, mass spectra and X-ray structure. The ^{1}H NMR spectrum of compound **6** shows a singlet at δ7.72 due to the pyrimidine proton and two singlets at δ 2.38 and δ 2.74 which could be attributed to the protons of the methyl groups. Further evidence was obtained from mass spectrum (FAB, MNBA) showing that two molecules of 2-aminoimidazole were involved during this reaction. The structure of the compound 6 was proven by X-ray diffraction study (Figure 2).

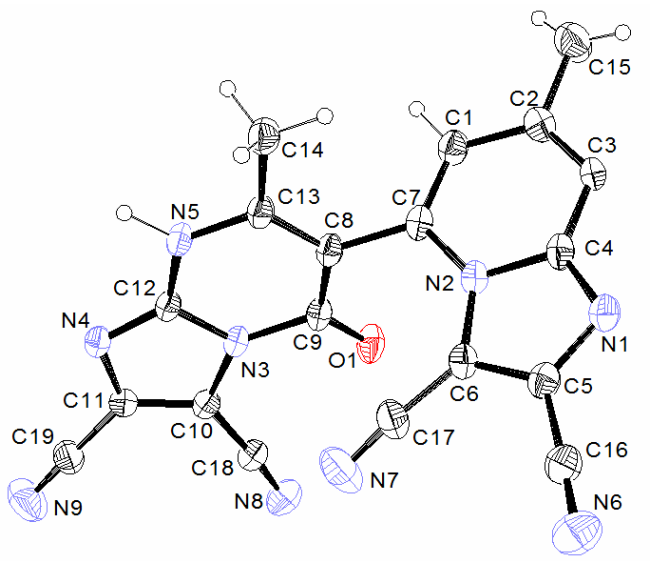
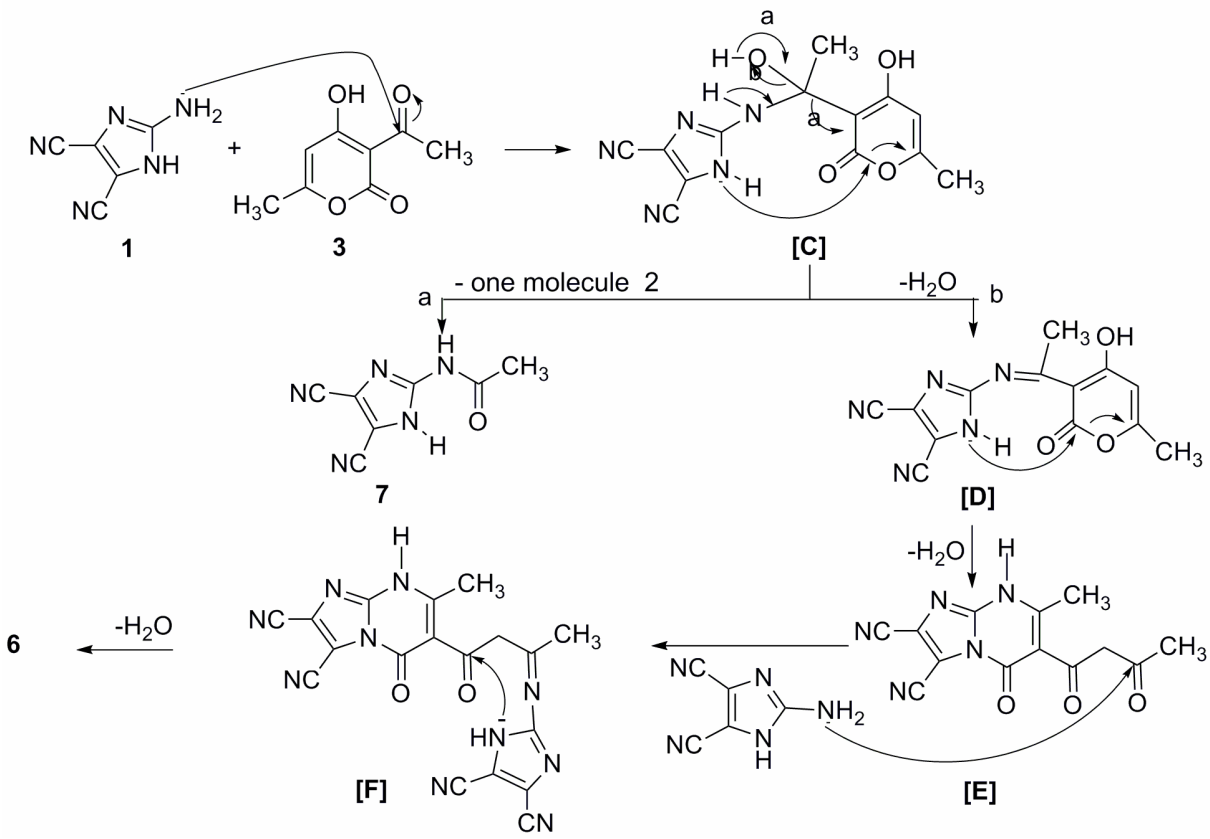


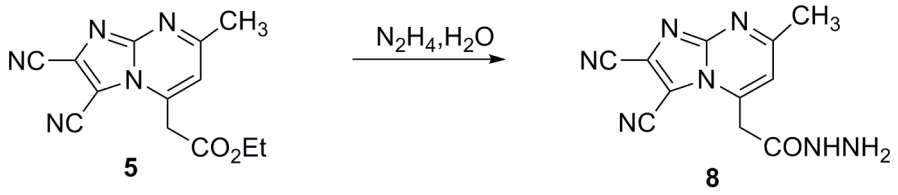
Figure 2. Molecular structure (ORTEP) of compound **6**.

In the ^{1}H NMR spectrum of the compound **7**, a singlet appearing at δ 2.13 could be assigned to the protons of the methyl group of the acetamide. Analogously, these results allowed us to propose a plausible mechanism for the formation of the compounds **6** and **7**. In fact, the amino group of the aminoimidazole **1** attacks the carbon of the acetyl group of the 3-acetyl-4-hydroxy-6-methylpyran-2-one **3,** leading to the intermediate [**C**], which acts according to two competitive reactions. First, loss of one molecule of pyran-2-one **2** gives 2-acetamido-4,5-dicyanoimidazole **7.** Secondly, the loss of one molecule of water gives the intermediate [**D**], which cyclises to afford the intermediate [**E**]. The latter undergoes attack of the amino group of the second molecule of aminoimidazole **1** giving the intermediate [**F**], which leads to the compound **6** by intramolecular cyclisation (Scheme 4).



Scheme 4

The action of hydrazine hydrate on the esters **5a-d** at reflux temperature in methanol gives the corresponding hydrazide **8** (Scheme 5).



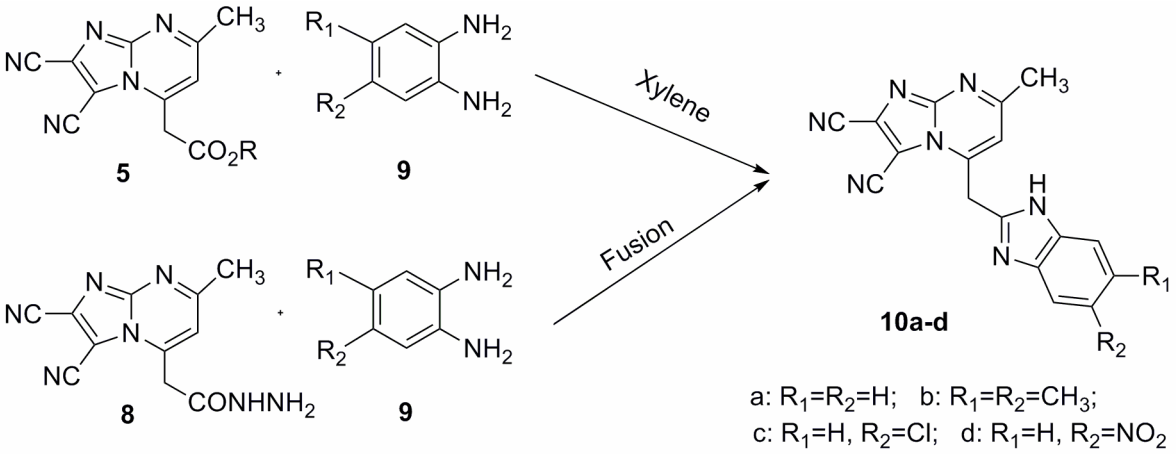
Scheme 5. Synthesis of hydrazide **8**.

The structure of compound **8** was established on the basis of ^{1}H NMR, mass and IR spectral data. The ^{1}H NMR spectrum shows in particular two signals at δ 9.47 and 4.01 which correspond respectively to the protons of the NH and NH_2 groups of the hydrazide.

The IR spectrum revealed the presence of two characteristic bands around 3260 cm^{-1} and 3100 cm^{-1} which correspond respectively to the stretching ν_{NH} and ν_{NH2} and a band between 1655 - 1660 cm^{-1} attributed to the carbonyl group of hydrazide.

At these stage, we wanted to prepare new systems associating benzimidazole and imidazopyrimidine rings. To this end, we have examined the condensation of o-phenylenediamines **9** with esters **5a** at reflux temperature of xylene or with hydrazide **7** by fusion of the reagents.

This reaction allowed us to obtain [benzimidazol-2-yl]methylimidazo[1,2-*a*]pyrimidines **10a-d** (Scheme 6).



Scheme 6

The ^{1}H NMR spectra of compound **10** shows the disappearance of the signals of the protons of the esters groups and reveal the presence of signals at δ 3.98-4.13 and 7.46-7.50 corresponding respectively to the protons of methylenes groups and to the aromatic protons of the benzimidazole ring.

Conclusions

We report in this work a novel method for the synthesis of new imidazopyrimidine derivatives, starting from 4-hydroxy-6-methylpyran-2-one and 3-acetyl-4-hydroxy-6-methylpyran-2-one. The synthesized compounds were characterized with elementary analysis, NMR, and mass spectrometry.

Experimental Section

General Procedures. All solvents for the spectroscopic measurements were of spectroscopic grade and were used without further purification. The chemicals for the synthesis were of reagent grade quality, procured from commercial sources, and used as received. ^{1}H and ^{13}C NMR spectra

were recorded at room temperature on a Bruker Avance 300 instrument operating at a frequency of 300 MHz for ^{1}H and 75 MHz for ^{13}C. ^{1}H NMR spectra were referenced to tetramethylsilane (0.00 ppm) as an internal standard. Chemical shift multiplicities are reported as s = singlet, d = doublet, q = quartet and m = multiplet. ^{13}C NMR spectra were referenced to the $CDCl_3$ (77.67 ppm) signal. Mass spectra were detected in mass spectrometer using Fast-atom bombardment (FAB-MS) or Electrospray mass spectrometry (ES-MS) in positive mode. Infrared (IR) spectra were measured with a Perkin Elmer 1760x spectrometer.

Action of 2-amino-4,5-dicyano imidazole (1) on 4-hydroxy-6-methylpyran-2-one (2). 2-amino-4,5-dicyanoimidazole **1** (1.33 g, 10^{-2} mol) and 4-hydroxy-6-methylpyran-2-one **2** (1.26 g, 2.10^{-2} mol)[21] were refluxed in different alcohols during 24 to 48 hours. The solvent was removed under reduced pressure and the residue dissolved in methanol. The resulting product **5** precipitated out and dried under vacuum. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate (7:3, v/v) as eluent.

2,3-Dicyano-5-methoxycarbonylmethyl-7-methylimidazo[1,2-*a*]pyrimidines (5a). White crystals, yield = 75%; mp: 228-229 °C (methanol) ; ^{1}H NMR (CDCl3) δ 7.09(s, 1H, H-6), 3.94(s, 2H, CH_2), 2.97(s, 3H, CH_3), 3.38 (s, 3H, CH_3) ; ^{13}C NMR ($CDCl_3$) δ 168.2, 162.5, 149.7, 147.1, 128.4, 114.3(2), 111.4, 109.6, 51.5, 43.7, 19.2 ; ES-MS : m/z 256[M+H]+; Anal. Calcd for $C_{12}H_9N_5O_2$: C, 56.47; H, 3.55; N, 27.44. Found: C, 56.59; H, 3.49; N, 27.25.

Crystallographic data for 5a (CCDC No. : 663299). (C_{24} H_{18} N_{10} O_4, M = 510.47); Triclinic, P-1; Z = 2; a = 10.9166(2) Å; b = 11.4539(2) Å; c = 11.4969(2) Å; α = 60.30; β = 78.99; γ = 86.41°; V = 1224.85(4) $Å^3$; ρ_{calcd} =1.384 Mg/m^3; F(000) = 528; λ = 0.71073 Å; T = 293(2) K; Absorption coefficient: 0.100 mm^{-1}, Reflections : 4498 / 4498 [R(int) = 0.0000]; the structure was refined on F to $R_1 = 0.0601$, $wR_2 = 0.1484$.

2,3-Dicyano-5-ethoxycarbonylmethyl-7-methylimidazo[1,2-*a*]pyrimidine (5b). White crystals, yield = 70 %; mp: 215-214 °C (methanol) ; ^{1}H NMR ($CDCl_3$) δ 7.01(s, 1H, H-6), 4.23(q, 2H, CH_2), 3.94(s, 2H, CH_2), 2.97 (s, 3H, CH_3), 1.10 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 167.3, 162.6, 149.9, 147.1, 128.1, 114.4(2), 111.5, 109.7, 63.1, 43.8, 19.8, 12.7; ES-MS : *m/z* 270$[M+H]^+$; Anal. Calcd for $C_{13}H_{11}N_5O_2$: C, 57.99; H, 4.12; N, 26.01. Found : C, 58.07; H, 4.18; N, 25.92.

2,3-Dicyano-7-methyl-5-propoxycarbonylmethylimidazo[1,2-*a*]pyrimidine (5c). White crystals, yield = 64 %; mp 202-201 °C (methanol) ; ^{1}H NMR ($CDCl_3$) δ 7.13(s, 1H, H-6), 4.12(t, 2H, CH_2), 3.95(s, 2H, CH_2), 3.03 (s, 3H, CH_3), 1.47(m, 2H, CH_2), 0.92(m, 3H, CH_3) ; ^{13}C NMR ($CDCl_3$) δ 168.5, 162.5, 149.5, 147.0, 129.0, 114.7(2); 111.4, 109.6, 67.5, 43.7, 21.8, 19.3, 10.3 ; ES-MS : m/z 284[M+H]+; Anal. Calcd for $C_{14}H_{13}N_5O_2$: C, 59.36; H, 4.63; N, 24.72. Found : C, 59.10; H, 4.80; N, 24.90.

5-Butoxycarbonylmethyl-2,3-dicyano-7-methylimidazo[1,2-*a*]pyrimidine (5d). White crystals, yield = 57 %; mp 189-188 °C (methanol) ; ^{1}H NMR ($CDCl_3$) δ 7.12(s, 1H, H-6); 4.13(t, 2H, CH_2); 3.93(s, 2H, CH_2); 3.02 (s, 3H, CH_3), 1.4(m, 4H, $2CH_2$), 0.87(m, 3H, CH_3) ; ^{13}C NMR ($CDCl_3$) δ 168.6, 162.5, 149.4, 147.0, 128.9, 114.3(2), 111.4, 109.6, 65.8, 43.7, 30.4, 19.2, 19.0,

13.6 ; ES-MS : *m/z* 298[M+H]$^+$; Anal. Calcd for $C_{15}H_{15}N_5O_2$: C, 60.60; H, 5.09; N, 23.56. Found: C, 60.23; H, 5.31; N, 23.37.

5-Carbonylmethyl-2,3-dicyano-7-methylimidazo[1,2-*a*] pyrimidine (4). White crystals, **y**ield = 17-36%; mp = 236-235 °C (methanol) ; ^{1}H NMR ($CDCl_3$) δ 7.45(s,1H,H-6), 4.10(s, 2H, CH_2), 2.94(s, 3H, CH_3) ; ^{13}C NMR ($CDCl_3$) δ 170.1, 161.7, 148.3, 146.7, 127.2, 114.9, 111.6, 108.8, 32.6, 22.6 ; ES-MS : *m/z* 242[M+H]$^+$.

Esterification of compound 4

The acid **4** (1.44g, 610^{-3} mol) was dissolved in ethanol (23 mL) and concentrated sulphuric acid (1mL) was refluxed for 48 hours. The solution was cooled down and then ice (5g) was added to this solution under stirring. The solution was neutralised with ammoniac in order to make it strongly alkaline. The product **5b** extracted with chloroform and recrystallised from ethanol to afford **5b** in 80 % yield.

Action of 2-amino-4,5-dicyanoimidazole (1) on dehydroacetic acid (3). General Procedure.

2-Amino-4,5-dicyanoimidazole 1 (2.66 g, 2.10-2 mole) and dehydroacetic acid **3** (1.68g, 10^{-2} mole) were refluxed in n-butanol for 48 hours. The volume of the solvent was concentrated under reduced pressure and the product **7** precipitated, filtered out and recrystallised from ethanol. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate (7:3, v/v) as eluent.

2,3-Dicyano-6-[2,3-dicyano-7-methylimidazo[1,2-*a*]pyrimidin]-6-yl-7-methylimidazo [1,2-*a*]pyrimidin-5-one (6). This compound was obtained as brown crystals, yield = 70 % ; mp °C 259-257 (n-butanol) ; ^{1}H NMR (DMSO-d_6) δ 7.72(s, 1H, H-6); 2.74(s, 3H, CH_3), 2.38(s, 3H, CH_3) ; ^{13}C NMR (DMSO-d_6) δ 165.2, 162.6, 160.1, 154.3, 149.7, 142.6, 126.4, 118.9, 117.3, 116.6, 116.2, 114.2, 109.3, 109.1, 21.2, 15.3 ; MS: FAB; MNBA; *m/z* = 380 [M+H]$^+$. Anal. Calcd for $C_{18}H_8N_{10}O$: C, 56.84; H, 2.12; N, 36.83. Found : C, 56.67; H, 2.31; N, 36.92.

Crystallographic data for 6 (CCDC No. : 663300). (C_{57} H_{21} N_{27} O_3, M = 1132.01); Triclinic, P-1; Z = 2; a = 10.0650(1) Å; b = 18.4670(2) Å; c = 18.4660(3) ;α = 116.77;β = 100.47; γ = 100.47°; V = 2874.26(6) Å^3; ρ_{calcd} =1.308 Mg/m^3; F(000) = 1152; λ = 0.71073 Å; T = 293(2) K; Absorption coefficient: 0.090 mm^{-1}, Reflections : 10744 / 10744 [R(int) = 0.0000]; the structure was refined on F to R_1 = 0.0943, wR_2 = 0.2446.

2-Acetamido-4,5-dicyanoimidazole (7). This compound was obtained as white crystals, **y**ield = 10 % ; mp 107-106 °C (diethyl ether) ; ^{1}H NMR ($CDCl_3$) δ 2.13(s, 3H, CH_3) ; MS: EI; M$^+$ (*m/z)*= 175.

Synthesis of 2,3-dicyano-7-hydrazidocarbonylmethyl-5-methylimidazo[l,5-a] pyrimidine (8). To a solution of esters **4** (5 10^{-3} mol) in ethanol (25 mL) were added 2,5 equivalents of hydrazine hydrate. The mixture was refluxed for 4 hours. After removal of the solvent under reduced pressure. The product **8** was recrystallised from ethanol to give brown crystals, yield =

91 %; mp 221-222 °C (ethanol) ; ^{1}H NMR (DMSO-d_6) δ 9.44(s, 1H, NH), 7.01(s, 1H, H-6), 3.97(s, 2H, CH_2-5), 4.01 (s, 2H, NH_2), 2.92 (s, 3H, CH_3-7).

Synthesis of 2,3-dicyano-5-[benzimidazol-2-yl]methyl-7-methyl-imidazo[1,2-*a*] pyrimidine (10a-d)

Procedure A. A mixture of esters **5b** (5.10^{-3} mol) and o-phenylenediamines **9a(9b, 9c or 9d)** (6.10^{-3} mol) were refluxed in xylene for 2-4 days. The resulting product **10a-d** was isolated directly by filtration of the reaction mixture and purified by recrystallisation from mixture of methanol and water.

Procedure B. o-Phenylenediamines **9a(9b, 9c or 9d)** (28.10^{-3} mol) and hydrazide **8** (7.10^{-3} mol) were fused at 240°C, until the release of gas stops and the mixture solidifies. The products **10a-d** obtained were washed with diethylether and chloroform, and then recrystallised from a mixture of methanol and water.

2,3-Dicyano-5-[benzimidazol-2-yl]methyl-7-methylimidazo[1,2-*a*]pyrimidine (10a). Brown crystals, yield = 80 % (procedure A); =70 % (procedure B); mp > 268 °C (methanol-water) ; ^{1}H NMR (DMSO-d_6) δ 9.71(s, 1H, NH), 7.19(s, 1H, H-6), 7.50(m, 4H, H-ar), 4.13 (s, 2H, CH_2), 2.99 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 163.2, 148.2, 146.7, 142.4, 135.9, 134.1, 128.8, 122.6, 122.2, 119.4, 118.2, 114.6, 110.9, 108.7, 31.2; MS-ES: *m/z*= 314$[M+H]^+$; Anal. Calcd for $C_{17}H_{11}N_7$: C, 65.17; H, 3.54; N, 31.29. Found : C, 65.35; H, 3.67; N, 30.98.

2,3-Dicyano-5-[5,6-dimethylbenzimidazol-2-yl]methyl-7-methyl-imidazo[1,2-*a*]pyrimidine (10b). Brown crystals, yield = 80 % ; mp = 259-261 °C (methanol-water) ; ^{1}H NMR (DMSO-d_6) δ 7.18(s, 1H, H-6), 7.48 (m, 2H, H-ar), 4.02(s, 2H, CH_2), 2.90 (s, 3H, CH_3), 2.31 (s, 6H, CH_3-ar) ; MS-ES: *m/z* = 342$[M+H]^+$; Anal. Calcd for $C_{19}H_{15}N_7$: C, 66.85; H, 4.43; N, 28.72. Found : C, 66.71; H, 4.63; N, 28.66.

2,3-Dicyano-5-[5(6)-chlorobenzimidazol-2-yl]methyl-7-methyl-imidazo[1,2-*a*]pyrimidine (10c). Brown crystals, yield = 60 %; mp > 270 °C (methanol-water) ; ^{1}H NMR (DMSO-d_6) δ 7.19(s,1H,H-6); 7.49 (m, 3H, H-ar); 3.97(s, 2H, CH_2); 3.00 (s, 2H, CH_3) ; MS-ES: *m/z* = 348 $[M+H]^+$; Anal. Calcd for $C_{17}H_{10}ClN_7$: C, 58.71; H, 2.90; Cl, 10.19; N, 28.19. Found : C, 58.54; H, 3.07; Cl, 10.38; N, 28.01.

2,3-Dicyano-5-[5(6)-nitrobenzimidazol-2-yl]methyl-7-methyl-1,2,4-imidazo[1,2-*a*]pyrimidine (10d). Brown crystals, yield = 61% ; mp = 270-271°C (methanol-water) ; ^{1}H NMR (DMSO-d_6) δ 7.19(s, 1H, H-6), 7.46(m, 4H, H-ar), 3.98 (s, 2H, CH_2) 2.98 (s, 3H, CH_3); MS-ES: *m/z* = 359 $[M+H]^+$; Anal. Calcd for $C_{17}H_{10}N_8O_2$: C, 56.98; H, 2.81; N, 31.27. Found : C, 57.10; H, 2.68; N, 31.02.

Supporting Information Available

X-ray crystallographic files in CIF format. These crystallographic data can be obtained free of charge on application to the Cambridge Crystallographic Data Centre {12 Union Road, Cambridge, CB2 1EZ, U.K. [fax (internat.) + 44(0)1223/336033; E-mail: deposit@ccdc.cam.ac.uk}.

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