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The chemistry of diaminomaleonitrile and its utility in heterocyclic synthesis

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1. Introduction

Over the last 30 years, the synthesis of organic compounds under prebiotic conditions has been studied. The search for reasonable routes to biochemicals, particularly polynucleotides, remains very active.[1] A wide range of biological compounds has been synthesised from HCN oligomers and other cyanide derivatives. Current theory supposes that the primitive earth contained limited amounts of reduced carbon.[2,3] As a result, HCN formation may have occurred from many diverse gases, such as $CO-N_2-H_2$ and $CO_2-N_2-H_2O$,[4] such formation depending mainly on the carbon and oxygen ratios. The formation of HCN by lightning discharges would be strongly based on the ratio of C and O and would be disfavoured in an atmosphere where C was mainly in the form of CO_2,[3] as recent calculations have suggested. Diaminomaleontrile (DAMN) **1**, one of the products formed from HCN polymerisation,[5,6] was considered as one of the versatile precursors to nucleotides and has been extensively utilised in the synthesis of various types of heterocyclic compounds. Ever since, there has been a great deal of interest in DAMN **1** and its derivatives as intermediates for heterocyclic synthesis.[1,7] In this review we report the chemistry and reactions of DAMN **1**.

Reviews on the utility of β-enaminonitriles and RNA have included some discussion about DAMN,[8,9] but recent developments in the field warrant a more detailed coverage.

2. Chemical structure and physical properties of DAMN

The structure of DAMN was in doubt until Webb et al.[10] and Bredreck et al.[11] showed that the DAMN exists as tetramer. Webb[10] reported the absence of a C–H bond in the crystalline tetramer by comparing its IR spectrum with that of the succinonitrile. He also examined the UV spectrum and found that the tetramer exists as **1** in solution. In addition, the dipole moment measurements supported a *cis*-configuration for DAMN **1**.

Keywords: diaminomaleonitrile; pyrazine; pyrimidine; purine; azepine; pyrrole; oxazole.

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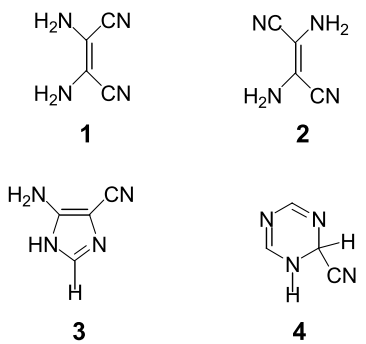
Further investigations by Bredreck[11,12] on the chemistry of DAMN **1** and its mono-, di- and tri-acetyl derivatives confirmed the structure **1**. A *cis* structure was assigned on the basis of the C=C stretching vibrational frequency in the IR spectrum. Such a structure was proposed by Grischkevitsch-Trochimovski,[13] based on the formation of derivatives like 2,3-dicyanopyrazine and 4,5-dicyano-1,2,3-triazole by condensation with glyoxal and nitrous acid, respectively.

Molecular orbital calculations and a single crystal X-ray diffraction analysis confirmed that the molecule has a *cis* configuration in the crystalline state,[14] and, in addition, molecular orbital calculations have demonstrated that for the isolated molecule, the completely planar *cis* configuration has the lowest energy.[15] The *trans* isomer, DAFN **2** which is an intermediate in the photochemical reactions of DAMN **1**, has also been isolated and characterised by spectroscopic methods and by X-ray diffraction.[16]

1 **2**

The *trans* isomer **2** has been prepared by irradiating a solution of DAMN **1** in acetonitrile at 25°C for 7.5 h in a Pyrex glass vessel, using wavelengths λ in the range 295–335 nm and a 100 W high pressure mercury lamp fitted with a filter containing aqueous potassium chromate solution (2 mM).[16] Evaporating the solvent under reduced pressure afforded a brown solid, which was recrystallised twice from *n*-butanol to give DAFN **2**. DAFN **2** has a mp of 169°C and is markedly labile in acidic or alkaline solutions reverting rapidly to DAMN **1**. The ^{1}H NMR spectrum of **2** in d_6-DMSO shows a single broad peak due to NH protons. The UV absorption maximum at λ 310 nm suggests the existence of a conjugate system in the molecule. The IR spectrum shows bands at 3394, 3350, 3254, and 3192 cm^{-1} for NH stretching vibrations and a band at 1618 cm^{-1} corresponding to C=C.[16]



1 **2** **3** **4**

Scheme 1.

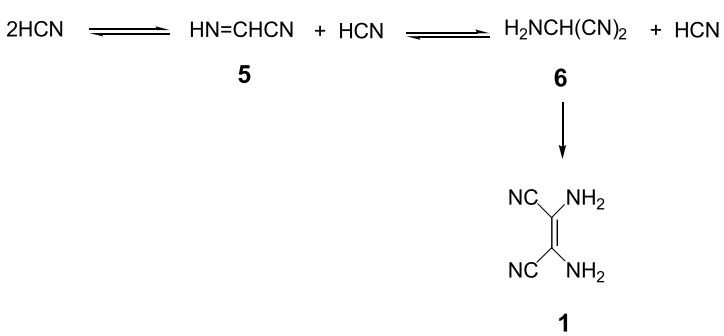
3. Synthetic approaches

An equilibrium mixture of different HCN oligomers can be formed by cyanide condensation reactions. These oligomers can be subdivided into: HCN dimers, HCN trimers, HCN tetramers, HCN pentamers and high oligomers $(HCN)_{n>5}$.[1] HCN has four known tetramers, DAMN **1**, DAFN **2**, 4-amino-5-cyanoimidazole **3** and 2-cyano-1,2-dihydro-*s*-triazine **4** (Scheme 1).

Many variations of the synthesis of DAMN from hydrogen cyanide have been developed. DAMN was readily formed in aqueous media containing 0.1–1.0 M HCN at room temperature.[17] and was also obtained in 78% yield upon polymerisation of hydrogen cyanide in different nitrile solvents containing a tertiary amine alone, with sodium cyanide or tetramethylammonium hydroxide.[5] Polymerisation of HCN in the presence of aluminium alkyls or their derivatives furnished DAMN in 98% yield.[6] Another method used organic solvents such as organic mercaptans or disulphides, in the presence of basic catalysts to give ~75% yield[18] or 51% yield by a catalysed tetramerisation of sodium cyanide in a polar solvent such as dimethylformamide.[19] On the other hand, DAMN purification can be achieved by extraction with a low molecular weight fatty acid ester, followed by washing with isopropyl acetate at 60°C, the extract is then washed twice with water at 40°C to furnish an excellent yield (94.5%) with 90.4% purity.[20]

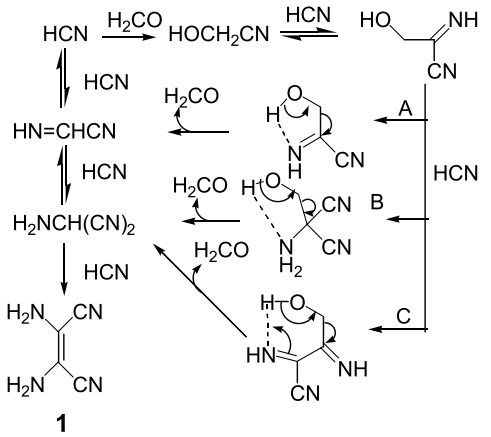
The initial product in all of these polymerisation reactions is the HCN dimer, iminoacetonitrile **5**. This reacts with another molecule of HCN to give aminomalonitrile **6**, which combines further with another molecule of HCN to furnish DAMN.[1] (Scheme 2).

Schwartz and Goverde[21] reported that DAMN formation could be accelerated by the addition of formaldehyde,

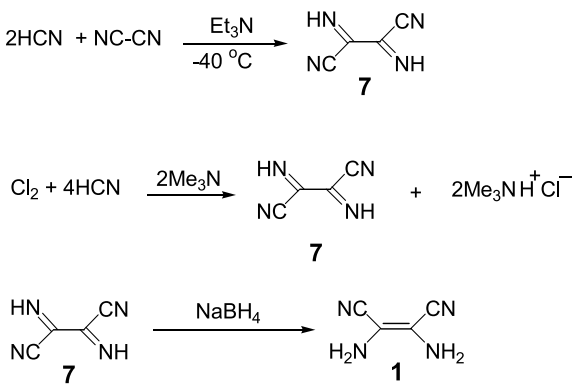


5 **6** **1**

Scheme 2.



Scheme 3. The pathway shown as A is probably the most likely.



Scheme 4.

Table 1. Different Schiff bases from DAMN

R	R	Time at rt	Yield (%)
Me	Ph	1 h	74
Me	4-$NO_2C_6H_4$	10 min	98
Ph	Ph	4 h	93
2-HOC_6H_4	2-HOC_6H_4	24 h	60
Me	β-Naphthyl	30 min	79
Me	2-Furyl	1 h	73
Me	CN	10 min	41
Et	CN	10 min	60
Ph	CN	15 min	52

acetaldehyde or acetone, but the mechanism is still unclear (Scheme 3).

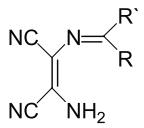
Oxidation of DAMN to diiminosuccinonitrile (DISN) **7** can be achieved by using MnO_2, PdO_2 or Fe^{3+} salts.[22,23] In addition, DISN **7** can be formed via a base-catalyst addition of HCN to cyanogen at −40°C or by passing chlorine gas into a toluene solution of HCN and trimethylamine at −15°C.[24] DISN **7** can be reduced using $NaBH_4$ to give DAMN **1** (Scheme 4).

4. Chemical reactivity

4.1. Synthesis of imine and imidazole derivatives

DAMN reacts with carbonyl compounds or orthoformates to give imine derivatives.[25–31] Under mild conditions, DAMN is condensed with electron-deficient aromatic ketones or acyl cyanides in the presence of ethanol and P_2O_5 to form Schiff bases **8** in 34–98% yield, respectively.[32] Similarly, condensation of DAMN with acyl cyanides using ethanol, P_2O_5 and 4-toluenesulphonic acid or even traces of hydrogen bromide gave **9** in 41–98% yield (Table 1, Scheme 5).

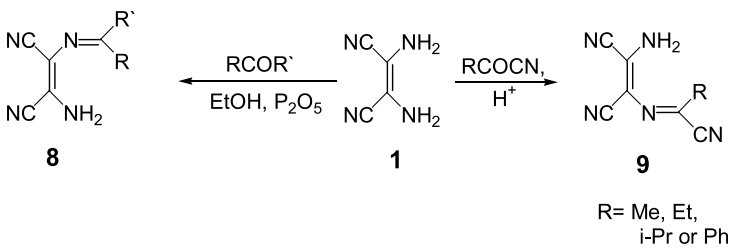
Reactions of DAMN with aromatic and aliphatic aldehydes without a catalyst in methanol,[33–35] or with an acid catalyst if the aldehyde is substituted by a strong electron withdrawing-group, affords the imines **8**.[33]



8

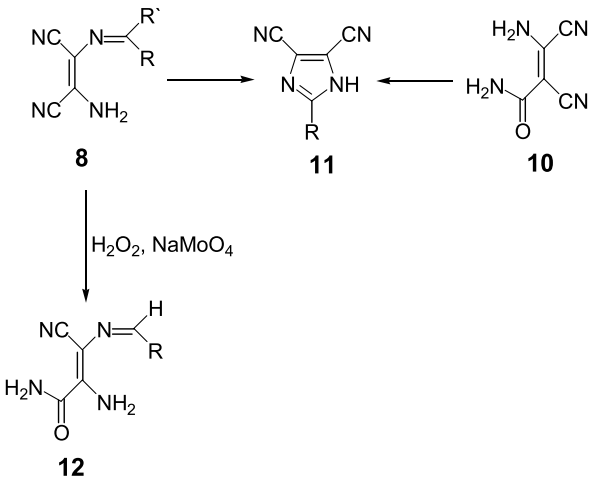
R = Alk or Ar ; R`= H

DAMN can also be condensed with acid anhydrides or acid chlorides to give **10**.[12,33] Dehydration of the latter derivative affords the 2-substituted-4,5-dicyanoimidazoles **11**. Transformation of the imine **8** (R=Ar) to the 2-substituted-4,5-dicyanoimidazoles **11** can also be accomplished in a shorter time (3 h) in yields of 64–78% using *N*-chlorosuccinamide and base in DMF at 40°C[36] Imidazoles were also prepared via the condensation of acrolein and DAMN.[37] On treatment of the Schiff bases **8** (R=Ar) with hydrogen peroxide and sodium molybdate in alcoholic solutions, the amides **12**

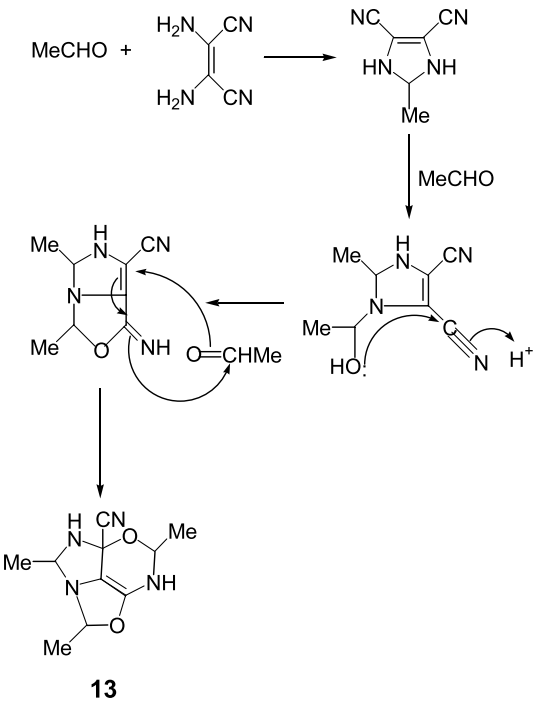


R= Me, Et, i-Pr or Ph

Scheme 5.



Scheme 6.

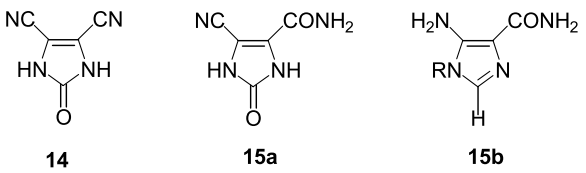


Scheme 7.

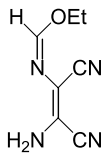
were obtained in 37% yield.[38] A catalytic amount of sodium molybdate has been found to improve the yield.[39] (Scheme 6).

DAMN reacts with acetaldehyde in a 1:3 molar ratio, using an aqueous buffer at pH 6.8 at 5°C to form **13** in 53% yield,[40] (Scheme 7).

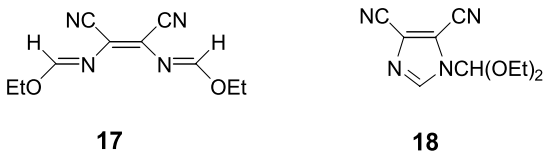
The action of phosgene[41] or chloroformates[42] on DAMN generated the imidazole **14**, while the amide derivatives **15a** and **15b** were obtained upon treating DAMN with either carbon dioxide under basic conditions or Schiff base (R=–NHR[1]) under basic conditions.[43,44]



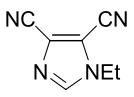
It has been reported in the patent literature[45] that DAMN reacts with triethyl orthoformate in refluxing dioxane to produce (*Z*)-ethyl-(*N*)-[2-amino-1,2-dicyanovinyl]formimidate **16** in high yield. This imidate has become a key intermediate for the preparation of nitrogen heterocyclic compounds such as imidazoles, novel 1,2-dihydropurines and purine derivatives, in which the latter compounds can be coupled to carbohydrate and pseudocarbohydrate systems through the N9 position.[45]



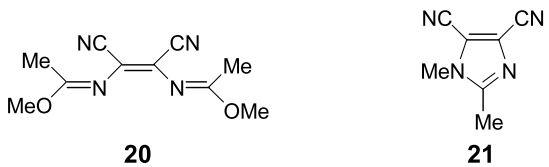
Reaction of triethyl orthoformate with DAMN at 140°C in the presence of Na_2CO_3 or K_2CO_3 has been reported to give the bisimidate **17** instead of 4,5-dicyano-1-(diethoxymethyl)imidazole **18** as originally claimed by Woodward.[45] Both the physical properties and elemental analyses for **17** and **18** are similar but the $^1H/^{13}C$ NMR and IR spectra are more consistent with structure **17**.



Johnson[46] has shown that 1-ethyl-4,5-dicyanoimidazole **19** is formed in 97% yield when 1 equiv. of DAMN reacts with 3 equiv. of triethyl orthoformate at 102°C for 4 h.

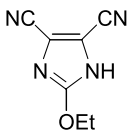


The reaction of DAMN with neat trimethyl orthoacetate affords **20** as a major product together with a small amount of 1,2-dimethylimidazole **21** in a 4:1 ratio. When a catalytic amount of 4-toluenesulphonic acid is used, **20** is the only product.[46]



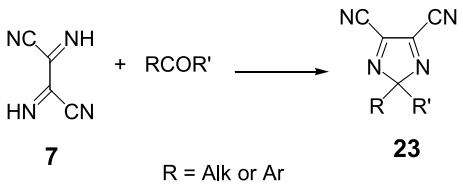
2-Ethoxy-4,5-dicyanoimidazole **22** can be synthesised

directly from the monoimidate **16** using dichlorodicyanoquinone (DDQ). The imidazole **22** has been prepared by refluxing the monoimidate **16** with DDQ in acetonitrile for 4 days to afford **22** as white crystals after purification by dry column flash chromatography (DCFC) using CH_2Cl_2/H_2O.[47]



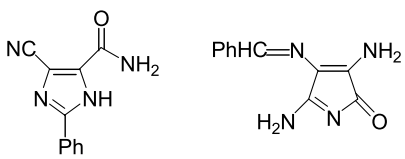
22

DISN **7** has been found to be a useful starting material for the preparation of 4,5-dicyanoimidazoles **23** by reaction with carbonyl compounds.[48] (Scheme 8).



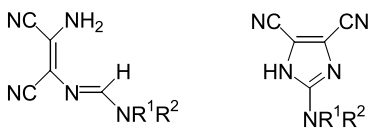
Scheme 8.

5-Cyano-2-phenylimidazole-4-carboxamide **24** was obtained when imine **12** (R=Ph) was heated with DDQ or sodium hypochlorite, while the pyrrole derivative **25** was produced when ammonia was added.[38]



24 **25**

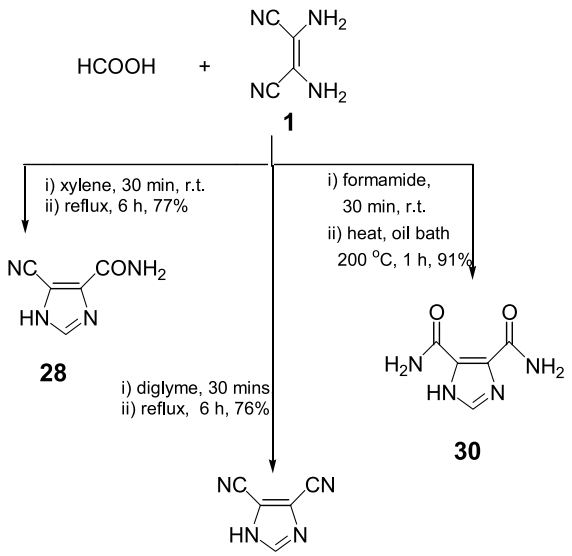
Condensation of DAMN with *o*-amides or *N*,*N*-dialkylformamide/$POCl_3$ leads to the amidines **26**, which on oxidation with DDQ furnish the 2-(dialkylamino)-4,5-dicyanoimidazoles **27**.[33]



26 **27**

R^1 = H
R^2 = Me

The reaction of DAMN and formic acid has been studied in several solvents and under specific conditions and found to give the imidazole derivatives **28**–**30** depending upon the reaction conditions used.[49] (Scheme 9).



Scheme 9.

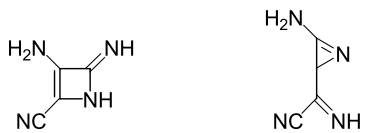
DAMN is a weak base and reacts with highly electrophilic nitrilium salts **31** to furnish the amidinium salts **32**.[50,51] These salts, on treatment with different bases under various conditions, afford the imidazoles **33** and **34a**–**c**. The salts also react with aldehydes and ketones at room temperature to give the 6-carbamoyl-1,2-dihydropurinium salts **35**. Similarly, 5-amino-4-(*C*-cyanoformimidoyl)imidazoles such as **33** react with ketones, 1,2- and 1,3-diketones, aldehydes and ketoesters to give the 6-carbamoyl-1,2-dihydropurines **36a**, which, in some cases are readily oxidised in air to the corresponding 6-carbamoylpurines **36b**[50,51] (Scheme 10).

4.2. Photosynthesis of 4-amino-5-cyanoimidazole

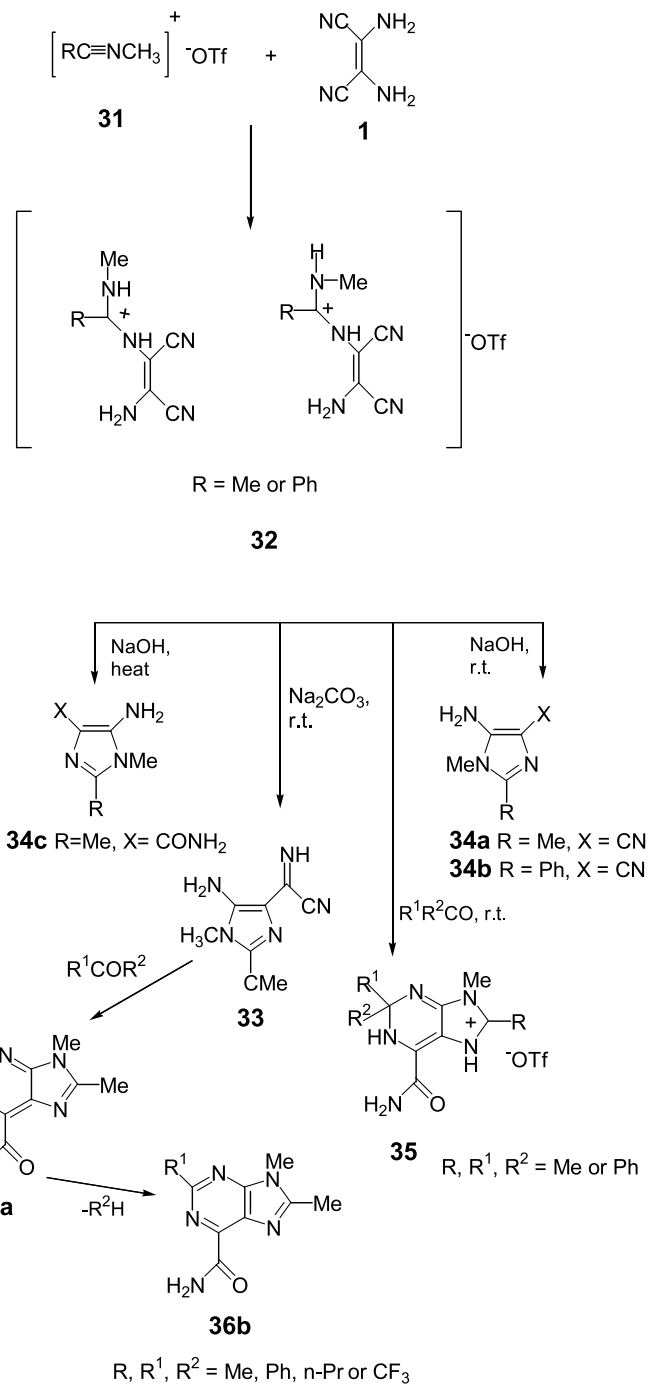
Ferris and Orgel[52] found that 4-amino-5-cyanoimidazole **3** could be obtained photochemically in 80% yield from DAMN, in aqueous solution at room temperature by irradiating it at 350 nm. Almost quantitative yields were achieved when the solution was carefully degassed to remove molecular oxygen.[53] The reaction involves two excited states:

1. Photoisomerisation of DAMN to diaminofumaronitrile DAFN **2**.[54] (Scheme 11).
2. Photochemical cyclisation of **2** to the imidazole **3**.[17,55]

The nature of the intermediate [X] **37** in the cyclisation of **2** remains uncertain.[54] Experimental studies indicate an azetine **38**,[55] while theoretical calculations support an azirine **39**.[56,57]



38 **39**



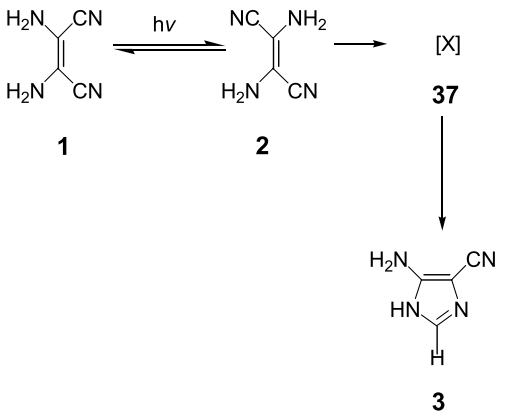
Scheme 10.

4.3. Synthesis of pyrazines

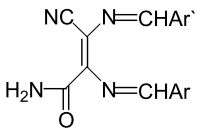
Schiff base derivatives of DAMN, such as **9**, afford aminopyrazines, e.g. **40** when they are refluxed in ethanol, while reduction of the phenyl and methyl derivatives of with $NaBH_4$ gives the corresponding aminonitriles **41**.[32] Cyclisation of these intermediates in refluxing ethanol forms tetrahydropyrazines **42**. The Schiff base **9** (R=Ph) can additionally be hydrated with $Na_2MoO_4-H_2O_2$ to furnish the pyrazine derivative **43**.[38] (Scheme 12).

Schiff base compounds of the type **8** (R=H, R=Ar) react with aldehydes in basic media at −5 to 20°C in either alcohol or acetonitrile as the solvent to give the corresponding 2,3-bis(arylideneamino)-3-cyanoacrylamides **44a–d**.[58] When **44a–d** are heated in DMSO for a shorter time followed by crystallisation from hot benzene a mixture of **45** and **46** is obtained.

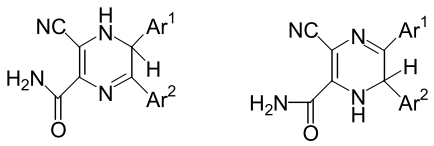
Condensation of DAMN with glyoxal to give 2,3-dicyanopyrazine **47** has been reported by several workers.[13,34,59] It



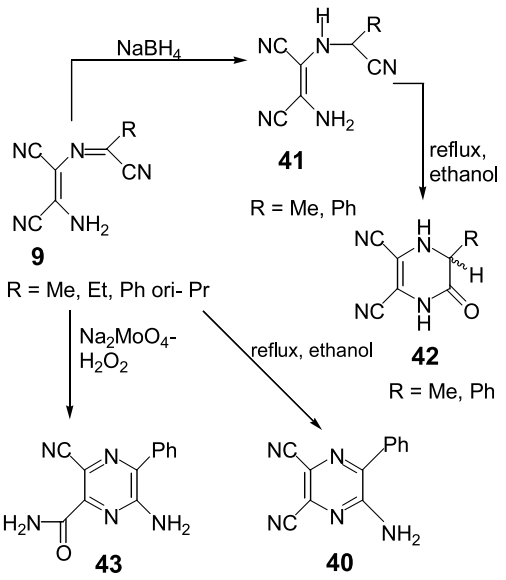
Scheme 11.



a) Ar' = Ph, Ar = Ph
b) Ar' = Ph, Ar = 4-MeC_6H_4
c) Ar' = 4-MeC_6H_4, Ar =Ph
d) Ar' = MeC_6H_4, Ar = MeC_6H_4

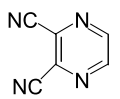


$Ar^1 = Ar^2$= Ph; $Ar^1 = Ar^2$= 4-MeC_6H_4
Ar^1 = Ph, Ar^2 = 4-i-PrC_6H_4 ; Ar^1 = Ph, Ar^2= 4-ClC_6H_4



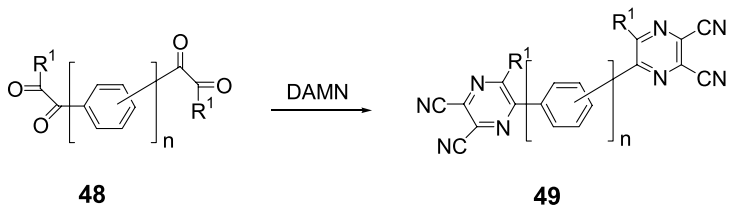
Scheme 12.

has been shown that the intermediate formed during condensation in water is the 2:1 adduct[60,61] and not the hydrated form of the product as described previously.[34] DAMN can also be condensed with α-keto aldehydes, α-keto oximes and diketones to furnish the mono- and di-substituted aryl- or alkyl-dicyanopyrazines in good yields.[62]



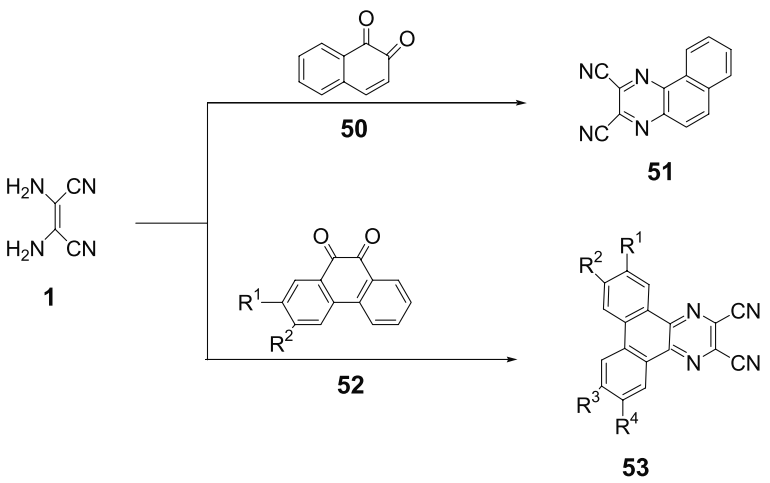
Bis(2,3-dicyanopyrazin-5-yl)benzene derivatives **49** are prepared by cyclocondensation of di(glyoxalyl)benzenes **48** with DAMN in high yields.[63] The use of DAMN in the synthesis of porphyrazine has also been reported.[64,65] (Scheme 13).

The fused dicyanopyrazines **51** and **53** were prepared via condensation of *o*-quinones **50** or the phenanthrenequinones **52** with DAMN in 10 and 80% yield, respectively.[66,67] (Scheme 14).

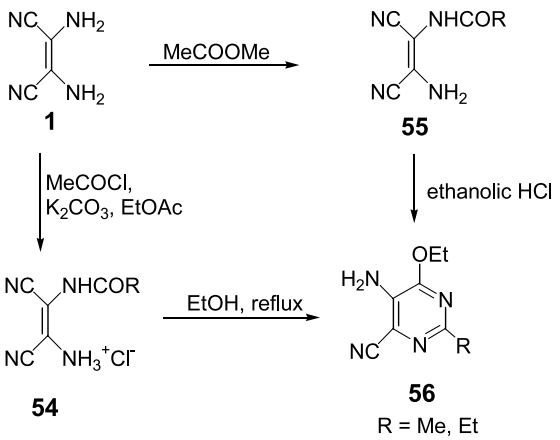


R^1 = H, (un)substituted lower Alk or Ar
n = 1 or 2

Scheme 13.



Scheme 14.



Scheme 15.

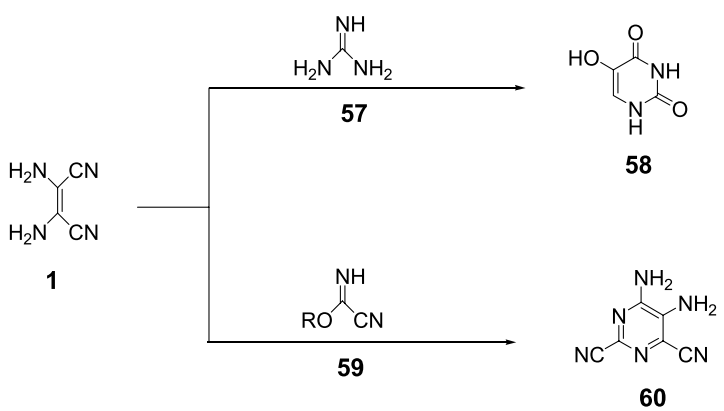
4.4. Synthesis of pyrimidines

The formation of highly functionalised 5-amino-6-ethoxy-2-alkylpyrimidine-4-carbonitriles **56** has been shown to take place by a simple reflux of *N*-(2-ammonio-1,2-dicyanovinyl)alkylamide chlorides **54** in ethanol or *N*-(2-amino-1,2-dicyanovinyl)acetamide derivatives **55** in ethanol, which are readily prepared from DAMN.[68] (Scheme 15).

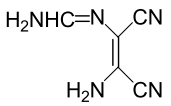
In addition, the pyrimidines **58** and **60** were obtained upon treating DAMN with guanidine **57** and cyanoformamidates **59**.[69–71] (Scheme 16).

4.5. Synthesis of purines

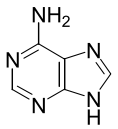
DAMN reacts with formamidine acetate to give *N*-(aminomethylidene)diaminomaleonitrile **61** and adenine **62** in 55% yield. Adenine can also be prepared in 24% yield by oligomerisation of HCN in liquid ammonia.[72–74]



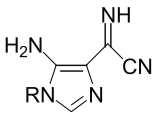
Scheme 16.



61



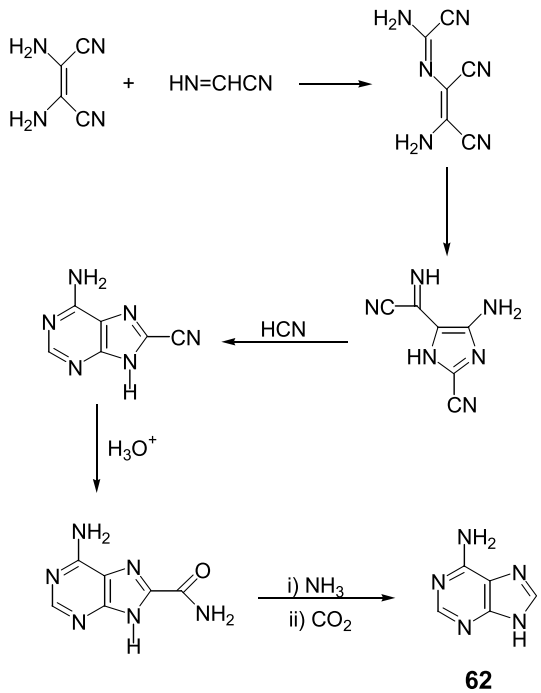
62



63

R = Alk, Ar

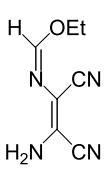
Schwartz et al.[75] have suggested a pathway for the synthesis of adenine in which the imidazole **3** is not involved (Scheme 17).



62

Scheme 17.

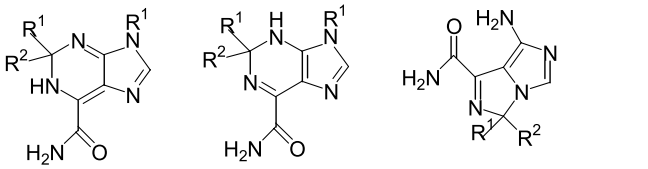
The nitrilium salt route to **63** was not possible since NH nitrilium salts are not stable. Formamidines **26** (R=H) are formed when amines react with the monoimidate **16** in solvents like ethanol or 1,4-dioxane with a catalytic amount of anilinium hydrochloride. The latter salt protonates the *N*-imine and prevents decomposition. These have been found to have a wide use as starting materials for heterocyclic compounds.[76a]



16

Base cyclisation[76,77] of the formamidines **26** with 1,8-diazobicyclo[5.4.0]undeca-7-ene (DBU) afforded imidazoles of the type **63** in good yield.

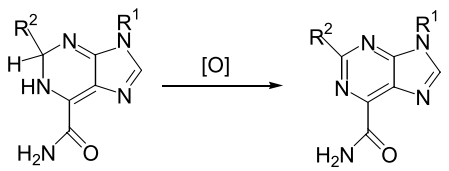
These imidazoles, when R=Ar, can react with ketones to give 2,2-disubstituted-6-carbamoyl-1,2-dihydropurines **64a** and **64b** as major products. The two tautomers were separated and identified by their X-ray structures.[76b] When R=H, however, purines **64** are formed with small amounts of the compounds **65**, which are believed to be the novel 7-amino-1-carbamoyl-3,3-disubstituted-3*H*-imidazo[1,5-*c*]imidazole derivatives.



64a **64b** **65**

R^1 = Ar $R^1 = R^2$ = Et, Bu, $PhCH_2$, Ph

On the other hand, the imidazo[1,5-*c*]imidazole **65** was the only product when benzophenone was used. Aldehydes also react with imidazoles **63** (R=alk or Ar) to give the 6-carbamoyl-1,2-dihydropurine derivatives **66** which can be oxidised to afford the 6-carbamoylpurines **67**.[76,77] (Scheme 18).

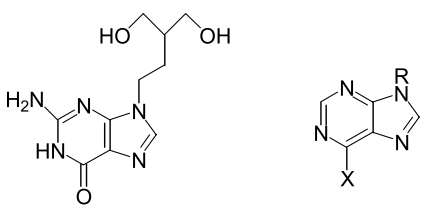


66 **67**

R `= Me or Et

Scheme 18.

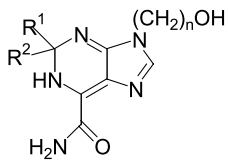
A great effort has been made to synthesise new cyclic nucleosides as anti-herpes simplex virus (HSV) and anti-human cytomegalovirus (HCMV) agents related to **68** and **69**.[78]



68 **69**

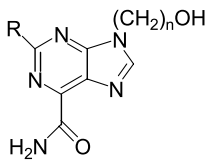
X = NH_2, HCl or OH
R = CH(CHMeOH)-$(CH_2)_5$Me

Starting from the amidines **26** (R^1=H, R^2=$(CH_2)_nOH$); n=2, 3 or 5, purines **70** and **71** have been prepared in 60–85% yield.[79]



70

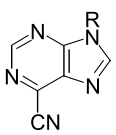
$R^1 = R^2$ = Me
$R^1 = R^2$ = Et



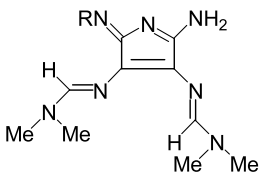
71

R = Me, CF_3, Ph or -CH=CHMe

The 6-cyanopurines **72**[80] have also been made starting from the formamidines **26** and 1–3 equiv. of DMFDEA in acetonitrile at room temperature, the novel pyrroles **73** being formed as minor products.



72



73

R = 4-ClC_6H_4, Ph,
4-MeC_6H_4 or 4-CNC_6H_4

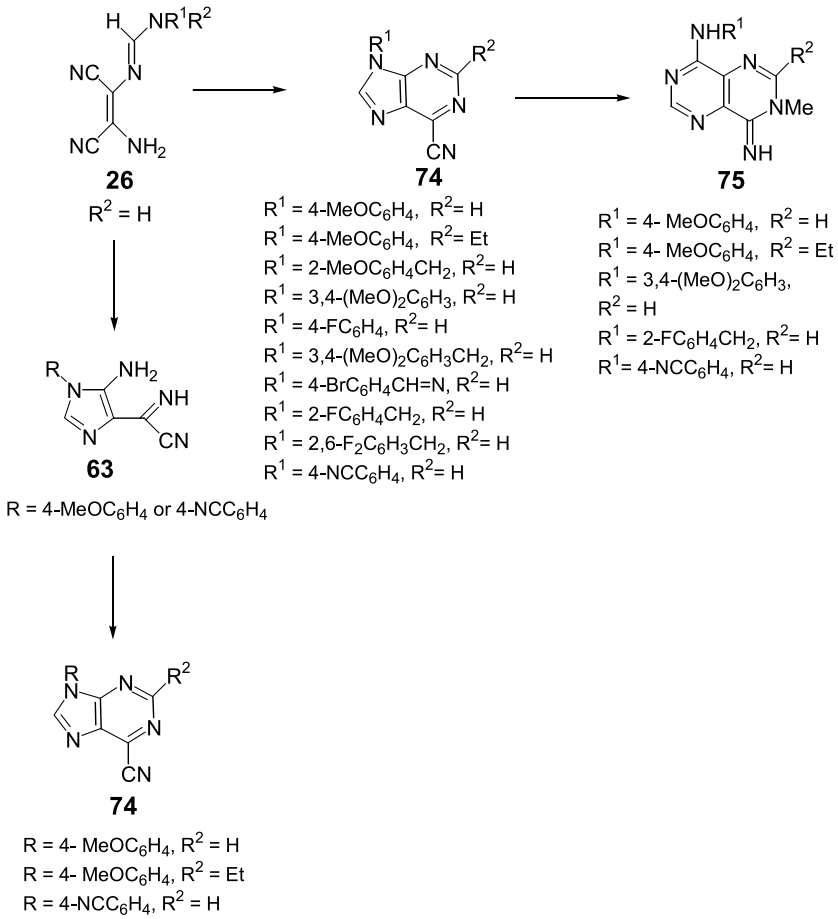
Another paper describing the preparation of the 6-cyano-9-substituted-9*H*-purines **74** in high yields has been published recently.[81] The one-step process involves refluxing triethyl orthoformate or orthopropionate with the corresponding (*Z*)-N^1-(aryl or benzyl)-N^2-(2-amino-1,2-dicyanovinyl) formamidines **26**. The reactions of the corresponding purines **74** with methylamine furnished the 8-(arylamino)-4-amino-3-methylpyrimidino[5,4-*d*]pyrimidines **75**. The imidasoles **63** also gave pyrimidinopyrimidines when reacted with methylamine (Scheme 19).

4.6. Synthesis of azepines

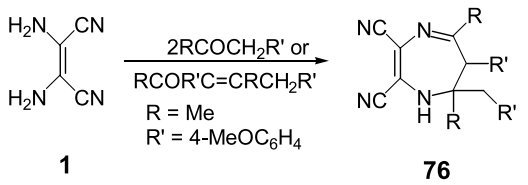
The reaction of DAMN with dialkyl ketones or α,β-unsaturated ketones under the same conditions used to prepare Schiff bases of the type **8** furnishes **76** as the major products.[32,33,82] (Scheme 20).

The compounds **77** were formed when formamidines derivatives **26** reacted with an excess of aldehydes or ketones in the presence of DBU.[83,84] (Scheme 21).

Novel 8-amino-3-substituted-5-oxo-7-tosylamino-imidazo[4,5-*d*]diazepines **78** were obtained in 33–99% yield instead of the expected 6-cyano-2-oxopurine derivatives **79** from the reaction of the imidazoles **63** with a slight excess of tosyl isocyanate in dry acetonitrile.[85]

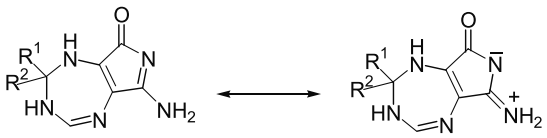


Scheme 19.



1 **76**

Scheme 20.

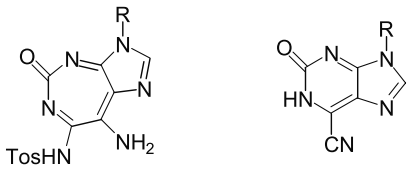


77

R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4 Me,Et or $(CH_2)_5$

R^2 = H, Me, Et or $_9(CH_2)_5$

Scheme 21.

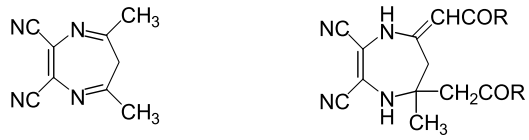


78 **79**

R = $-CH_2CH_2OH$, 4-MeC_6H_4, 4-CNC_6H_4 or 4-$MeOC_6H_4$

When ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formamidate **16** reacted with the carbonyl compounds **80** in the presence of triethylamine, the alkylideneamino derivatives **81** are formed. If the α-carbon of the ketone has at least one proton, however, prolonged contact of **82** with trimethylamine causes intramolecular cyclisation between its carbon and the imidate carbon, this being followed by cyclisation of the cyano and amino groups, causing the pyrrolo[4,3-*b*]-[1,4]diazepines **83** to form.[86] (Scheme 22).

The diazepine **84** is formed by the reaction of DAMN with acetylacetone. Benzoylacetophenone and β-ketoesters give the uncyclised products under mild conditions, but methyl acetoacetate and *N*,*N*-dimethylacetoacetamide furnished the tetrahydro-6*H*-diazepines **85** when $POCl_3$ is used as a catalyst.[32,33,87]



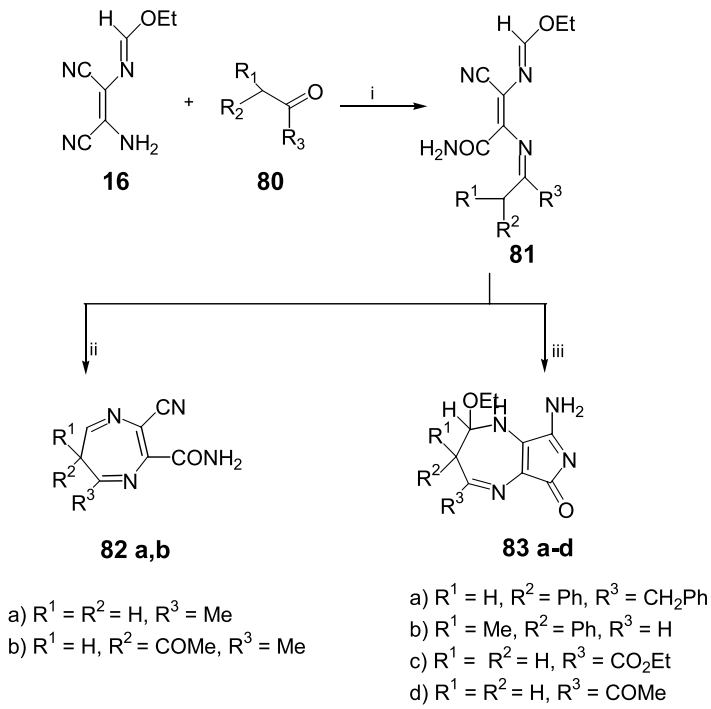
84 **85**

R = H, Alk, Ar

4.7. Synthesis of pyrroles

Compound **81** (R^1=R^2=H, R^3=Me) was used as the starting material to prepare the pyrrole derivatives **86** and **87**. The reaction product **86** was obtained upon treating **81** with methylamine in the presence of DBU and a mixture of (1:1) chloroform and ethanol, at 5°C, while the compound **87** was obtained in 76% yield via treating **81** in chloroform with methylamine at room temperature.[86,88–90] (Scheme 23).

The novel pyrroles **73** were formed as minor products from the reaction of the formamidines **26** and 1–3 equiv. of DMFDEA in acetonitrile at room temperature.[80]

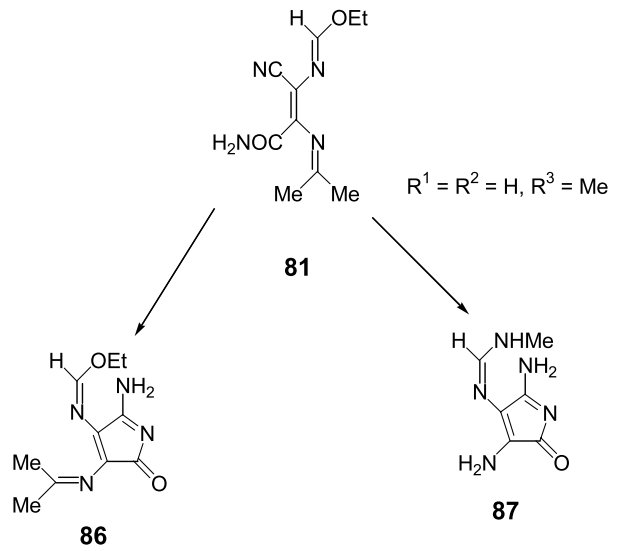


16 **80** **81** **82 a,b** **83 a-d**

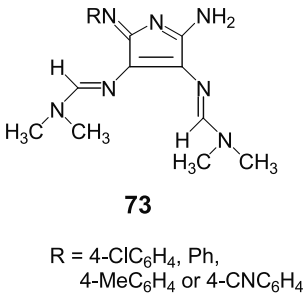
a) R^1 = R^2 = H, R^3 = Me
b) R^1 = H, R^2 = COMe, R^3 = Me

a) R^1 = H, R^2 = Ph, R^3 = CH_2Ph
b) R^1 = Me, R^2 = Ph, R^3 = H
c) R^1 = R^2 = H, R^3 = CO_2Et
d) R^1 = R^2 = H, R^3 = COMe

Scheme 22. (i) EtOH, NEt_3, 0°C–rt, 25 min–4 days; (ii) EtOH, NEt_3, rt, 4 h–2 days; (iii) EtOH, $PhCO_2H$, rt, 3 h–15 days.



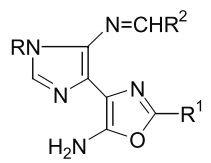
Scheme 23.



R = 4-ClC$_6$H$_4$, Ph, 4-MeC$_6$H$_4$ or 4-CNC$_6$H$_4$

4.8. Synthesis of oxazoles

The novel 5-amino-2-aryl-4-(1-aryl-5-alkylideneamino-imidazol-4-yl)-1,3-oxazoles **88** and **89** are produced when DBU is added to the (*Z*)-*N*^{1}-(aryl)-[2-amino-1,2-dicyano-vinyl]-*N*^{2}-formamidines **26** [R=CH$_3$] in benzaldehyde in low to medium yields.[83]

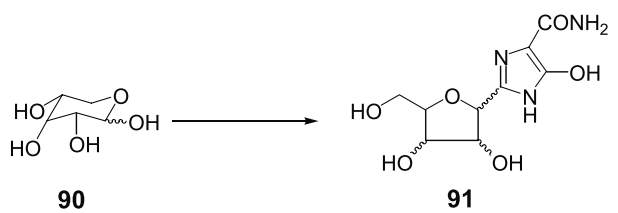


88 R = R^1= R^2= Ph

89 R = CH$_2$Ph, R^1 = 4-MeOC$_6$H$_4$, R^2 = 4-MeC$_6$H$_4$

4.9. Synthesis of nucleosides and their analogues

DAMN has been used in the thermal synthesis of several nucleoside analogues.[91] The C-nucleosides **91** can be obtained, for example, by the reaction of DAMN with D-ribose **90**, and both D-glucose or D-mannose can alternatively be used instead of D-ribose.[92] (Scheme 24).



Scheme 24.

5. Conclusions

DAMN has proved to be a rich source of various heterocyclic compounds, and the discovery of potential biologically active heterocyclic compounds has become increasingly probable. Starting from DAMN, our current work is focussed on synthesising novel heterocycles with or without sulphur that have biological activities against different diseases. The search for cheaper and simpler methods to synthesis such new compounds is continuing.

This review has summarised some of the achievements in the field of heterocyclic compounds derived from DAMN. Our knowledge of the chemistry and reactions of DAMN remains shallow, however, and this field needs to be explored in more detail. Further studies and investigations by us or other workers should continue to provide a strong background in the chemistry and reactions of DAMN.

Acknowledgements

The financial support of University of Kuwait received through Project SC04/01 is gratefully acknowledged.

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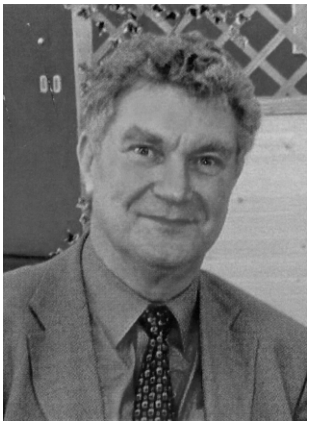

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