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ETHYL CARBOETHOXYFORMIMIDATE IN HETEROCYCLIC CHEMISTRY

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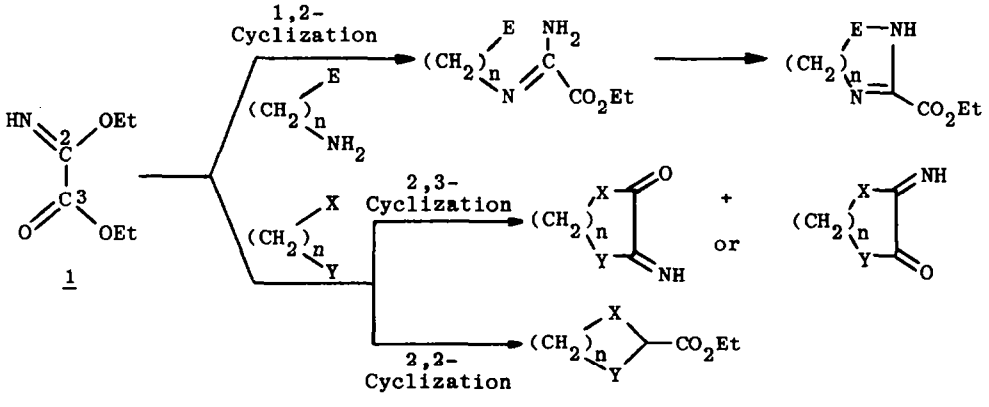
Abstract The reactions of ethyl carboethoxyformimidate with various bidentate reagents illustrate its usefulness as a reagent in heterocyclic chemistry.

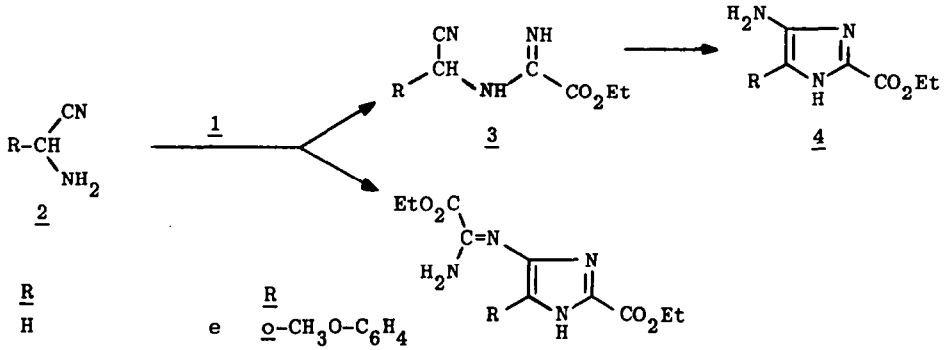
Ethyl carboethoxyformimidate 1, which is readily available from ethyl cyanoformate,[1,2] has been little used in synthesis, in contrast to many structurally simpler imidates and in spite of its analogy with ethyl oxalate, widely used as a reagent in organic synthesis. In a preliminary communication[3] we have reported some of its applications to the synthesis of several mono- and bicyclic heterocyclic systems. Now we show how its two electrophilic carbon atoms (named arbitrarily 2 and 3) can react with nucleophiles via three different ways of cyclization (Scheme 1).



Scheme 1

1. Reactions with aminonitriles

The reaction of 1 with α-aminonitriles 2a-2h gives 1,2-cyclizations. Thus, from an ethereal solution of aminoacetonitrile (2a) and 1 at room temperature a crystalline product precipitated after about 24 hours. It was identified as N-cyanomethyl carboethoxyformamidine (3a), which gave the final cyclization product, ethyl 4(5)-aminoimidazole-2-carboxylate (4a), after 2 hours at reflux in absolute ethanol. We were interested in extending this reaction to other α-substituted-α-aminonitriles (2b-2f), obtained from the corresponding aldehydes by the Strecker procedure[4] (Scheme 2).



	R		R
a	H	e	o-CH_3O-C_6H_4
b	CH_3	f	p-Cl-C_6H_5
c	C_6H_5	g	CO_2Et
d	p-CH_3O-C_6H_4	h	$CONH_2$

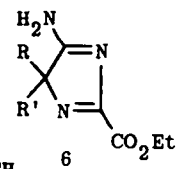
Scheme 2

Conversely, these aminonitriles (except 2e) gave ethyl 4(5)-carboethoxyformamidino-imidazole-2-carboxylates (5) instead of intermediates of the type 3 or imidazoles of the type 4. Compound 2e did not react under these reaction conditions and starting materials were recovered. Condensation products similar to those of type 5 have been described from other α-aminonitriles and thioimidate hydrochlorides.[5]

Although the above results suggested a simple method for the preparation of purine derivatives by condensation of 1 with appropriate α-substituted-α-aminonitriles such as ethyl aminocyanoacetate (2g),[6-8] the main condensation product was 4g instead of the expected 5g, and attempts to condense 4g with 1 or 1.HCl to give the purine derivative through the possible 5g were fruitless. Diethyl 5-aminoimidazole-2,4-dicarboxylate (4g) has been described[9] as a dimerization product of 2g (18.5% yield), but the yield found in our case (94%) implies the condensation of the aminonitrile with the imidate 1. Some literature references to ethyl aminocyanoacetate (2g) support the suggestion that the C-5(4) carboethoxy group of 4g must prevent condensation to 5g. Thus, while benzyl thiobenzimidate reacts with α-aminopropionitrile to give compounds of the type 5, the same thioimidate reacts with 2g to give compounds of the type 4.[5] The aminonitrile 2h[10] reacted under the same conditions with 1 to give a 50% yield of 4h and a small amount of 5h. The latter compound was obtained in good yield by reaction of 4h with excess of 1. Attempts at further condensation to give the purine were unsuccessful.

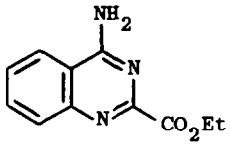
α,α-Disubstituted-α-aminonitriles[4] condense with 1 to give ethyl 4,4-disubstituted-4H-imidazole-2-carboxylates (6). A study on the scope of this reaction has shown its limitations.[11]

o-Aminobenzonitrile gave, under acid catalysis, ethyl 4-aminoquinazoline-2-carboxylate (7) via a 1,2-cyclization reaction.



a; R = R' = CH_3 6

b; R,R' = $(CH_2)_5$ c; R,R' = $(CH_2)_4$



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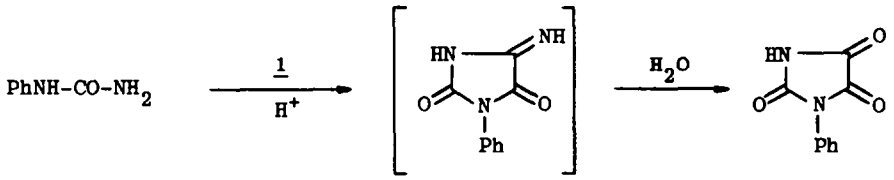
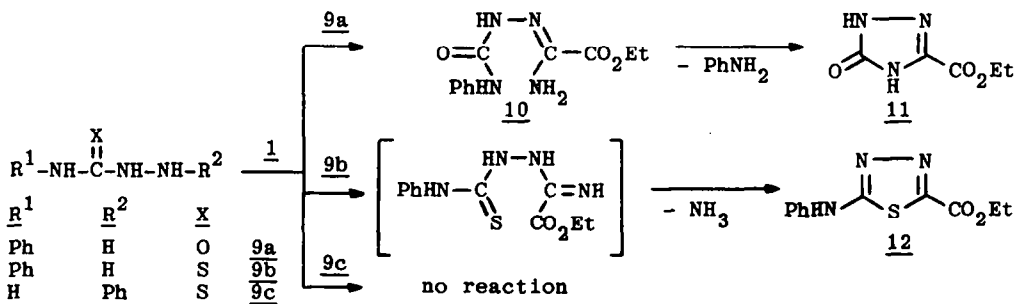
Although 1.HCl is more reactive than the imidate base, its reactions gave moderate yields because of decomposition to ammonium chloride, diethyl oxalate and ethyl oxamate.

2. Reactions with ureas and related compounds

Acid catalysis was also necessary to cyclize N-phenylurea and, under such conditions, the known N-phenylparabanic acid (8) was isolated as a hydrolytic product. Negative results were obtained for urea, thiourea and N-phenylthiourea; all gave products which could not be identified.



Semicarbazide derivatives 9a-9c reacted via two different pathways (Scheme 3). With 9a, the substituted amidine 10 could be isolated together with 11, which is a 1,2-cyclization product formed from 10 by loss of aniline. Although with 9b the open amidine intermediate was not isolated; it is presumably formed to give 12 through a 1,2-cyclization by loss of ammonia. In the case of 9c, the intermediate amidine could not cyclize and the reaction did not take place. Compound 11 has apparently been obtained among other products in the ammonolysis of diethyl 5-oxo-1,2,4-oxadiazol-2-ine-3,4-dicarboxylate.[12]

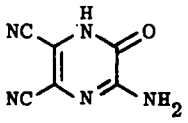


R^1	R^2	X	
Ph	H	O	9a
Ph	H	S	9b
H	Ph	S	9c

Scheme 3

3. Reactions with o-phenylenediamines, o-aminophenols and o-aminothiophenol

o-Phenylenediamines yielded 2,3-cyclizations with 1 giving quinoxaline derivatives in almost quantitative yields.[3,13] Similarly 2,3-diaminomaleonitrile gave 13 and o-aminophenols gave 3-amino-1,4-benzoxazin-2-ones (14) in high yields.[13]



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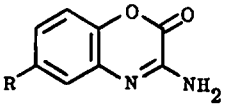

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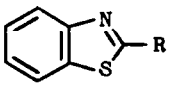
14a R = NO_2

14b R = CH_3

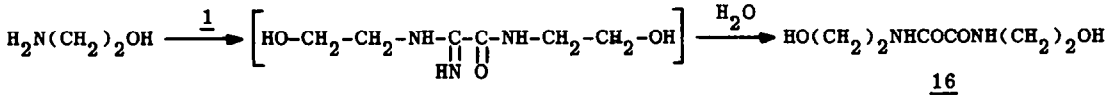
By contrast, o-aminothiophenol follows a 2,2-cyclization pathway to give the known benzothiazole derivatives 15. The small amount of carboxamide 15b, which was previously described as a benzothiazinone,[3] must be formed from partial ammonolysis of 15a since the reaction of 15a with ammonia gave 15b.



15a R = CO_2Et

15b R = $CONH_2$

With 2-aminoalcohols, such as 2-aminoethanol, oxamide derivatives (e.g. 16) were isolated. These results can be explained on the basis of the greater nucleophilicity of the aliphatic amino groups which do not differentiate between the two electrophilic carbon centres of the imidate 1, giving open chain products which readily hydrolyze. 1,2-Aliphatic diamines gave polymeric products which can be similarly explained.



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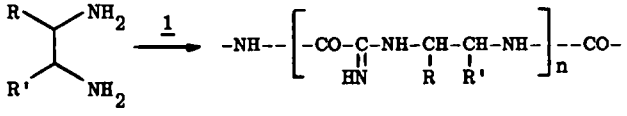
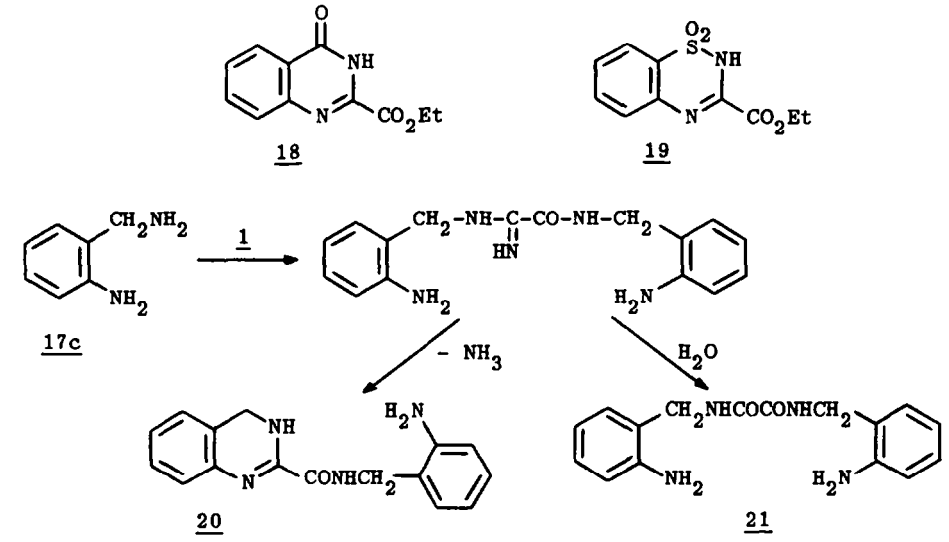


4. Reactions with o-aminobenzamide (17a), o-aminobenzenesulphonamide (17b) and o-aminobenzylamine (17c)

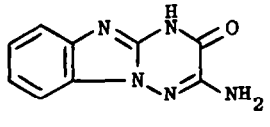
1,3-Dinucleophiles 17a-17c underwent 2,2- or 1,2-cyclizations with 1 in moderate yields. Compounds 17a and 17b yielded 18 and 19, which could be formed from 1,2- or 2,2-cyclizations. In the case of 17c, the aliphatic and more nucleophilic amino group reacted indiscriminately with the two electrophilic centres of 1 and the intermediate amidine cyclized in anhydrous medium to give quinazoline derivatives (20). In the presence of water, the oxamide 21 was obtained as a hydrolysis product (Scheme 4). Compound 18 is a known product of condensation of 17a with oxalic acid derivatives, and compound 19 has been obtained previously by a more complex method.[14]



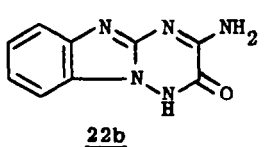
Scheme 4

5. Reactions with N-aminoderivatives

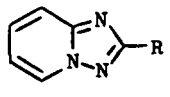
1,2-Diaminobenzimidazole gave 22a and/or 22b in 80% yield by a 2,3-cyclization pathway, but 1,2-diaminopyridinium iodide reacted with 1 and bases to give products of 2,2- or 3,3-cyclizations. Thus, in ethanol at room temperature, with KOH or Et_3N, a mixture of 23a and 23b was obtained. When the free base of 1,2-diaminopyridinium iodide was generated by passing a methanolic solution of its salt through a column of Amberlite IRA-400 ion exchange resin, pure 23c was obtained in excellent yield, as a transesterification product. The preparation of compound 23a has been described previously from ethyl s-triazolo[1,5-a]pyridine-2-carboxylate 3-oxide[15] and has been studied by X-ray crystallography.[16]



22a



22b



23a R = CO_2Et

23b R = C(NH)OEt

23c R = C(NH)OMe

Conclusions

From all of the above results it may be concluded that 2,3-cyclization reactions with 1 can be achieved with soft dinucleophiles such as o-phenylenediamines or o-aminophenols and constitute excellent synthetic procedures. The behaviour of o-aminothiophenol with 1 is unusual in this context, as condensation gives the 2,2-cyclization product. 2,2-Cyclizations seem to be limited to cases in which competitive 2,3-cyclization is less probable.

1,2-Cyclizations incorporate the azomethine group in the product heterocycle and take place with reagents which contain both nucleophilic and electrophilic centres such as aminonitriles.

With highly nucleophilic reagents, such as aliphatic amines, the simultaneous attack on both electrophilic centres gives open chain products.

Finally, 3,3-cyclizations are rare.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 457 spectrophotometer. ^{1}H nmr spectra were recorded on a Perkin-Elmer (60 MHz) spectrometer at room temperature; data are given in ppm downfield from TMS. Mass spectra were recorded on a Hitachi Perkin-Elmer RMV-6M.

Ethyl carboethoxyformimidate 1 was obtained according to references 1,2. Aminonitriles 2b-2h were obtained by standard procedures;[4,7,8,10] in some cases the crude products were used for further condensations. 2-Aminobenzylamine (17c) was obtained by reduction of 2-aminobenzonitrile with $LiAlH_4$. 2-Aminobenzenesulphonamide (17b), 1,2-diaminobenzimidazole and 1,2-diaminopyridinium iodide were prepared following references 17-19 respectively.

N-Cyanomethyl-carboethoxyformamidine (3a)

A solution of 1 (2 mmol) and 2a (3 mmol) in dry ether (6 ml) was kept at r.t. for 24 hr. The solid which precipitated was filtered and washed with dry ether to give 3a (92%). Mp 101-3°C. Anal calcd for $C_6H_9N_3O_2$: C, 46.44; H, 9.07; N, 27.08. Found: C, 46.12; H, 9.01; N, 26.88%. ^{1}H nmr ($CDCl_3$): δ 4.35 (q,2H); 4.22 (s,2H); 1.38 (t,3H). IR (KBr): 3430 (N-H); 2270 (C≡N); 1755 (C=O); 1650 cm^{-1} (C=N and NH). m/e 155 (M^+).

Ethyl 4(5)-aminoimidazole-2-carboxylate hydrobromide (4a.HBr)

A solution of 3a in ethanol was refluxed for 2 hr and the solvent was removed under vacuum. The resulting oil was treated with 48% HBr to give 4a.HBr. Mp 181-183°C (from ethanol/ether). Anal calcd for $C_6H_{10}BrN_3O_2$: C, 30.51; H, 4.27; N, 17.79. Found: C, 30.93; H, 4.26; N, 18.30. ^{1}H nmr (D_2O): δ 7.05 (s,1H); 4.44 (q,2H); 1.42 (t,3H). IR (KBr): 2860 and 2050 (NH), 1730 cm^{-1} (C=O).

Ethyl 5-aminoimidazole-2,4-dicarboxylate (4g)

a) A solution of 1 (15 mmol) and 2g (15 mmol) in ether was kept at r.t. for 24 hr and then stirred at r.t. for 72 hr. The solid which had separated (4g) was collected by filtration (51.4%).

b) An ethereal solution of 2g (17 mmol) and 1 (34 mmol) was refluxed with 35 ml of ethanol for 24 hr and was then kept for several days at r.t. Compound 4g was collected from the reaction mixture (92%). Mp 202-3°C (from acetone). Anal calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.76; N, 18.49. Found: C, 47.67; H, 5.97; N, 18.33. ^{1}H nmr (DMSO-d_6): δ 12.4 (s,1H); 5.95 (s,2H); 4.25 (q,q, 4H); 1.3 (t,6H). IR (KBr): 3495, 3220 and 3060 (N-H); 1735 (C=O); 1680 cm^{-1} (C=N). m/e 227 (M^+).

Ethyl 4(5)amino-5(4)carbamoyl-imidazole-2-carboxylate (4h)

A solution of 2h (10 mmol) and 1 (10 mmol) in dry ethanol was refluxed for 45 min and then was kept at r.t. for 24 hr. Compound 4h was collected by filtration (50.5%). Mp 236-8°C (from ethanol). Anal calcd for $C_7H_{10}N_4O_3.1H_2O$: C, 38.89; H, 5.59; N, 25.91. Found: C, 38.80; H, 5.77; N, 25.89. ^{1}H nmr (DMSO-d_6): δ 6.95 (s,2H); 5.90 (s,2H); 4.3 (q,2H); 1.3 (t,3H). IR (KBr): 3460-3250 (NH); 1705 (C=O, CO_2Et); 1650 (C=O, $CONH_2$); 1615 cm^{-1} (C=N).

Ethyl 4(5)carboethoxyformamidino-5(4)-carbamoyl-imidazole-2-carboxylate (5h)

a) This compound was isolated from the mother liquors of the above reaction in 6.7% yield.

b) When 1 mmol of 4h and 2 mmol of 1 were refluxed in dry ethanol and the solvent removed under vacuum, compound 5h was isolated in 50.5% yield. Mp 211°C (dec.) (from ethanol). Anal calcd for $C_{11}H_{15}N_5O_5$: C, 44.44; H, 5.09; N, 23.56. Found: C, 44.79; H, 5.34; N, 23.95. ^{1}H nmr (DMSO-d_6): δ 4.3 (q,4H); 1.3 (t,6H). IR (KBr): 3450, 3360 and 3220 (NH); 1735 and 1715 (C=O, CO_2Et); 1670 cm^{-1} (C=O, $CONH_2$).

General procedure for the preparation of compounds 5b-5d, 5f, and 6a-6c

A solution of the imidate 1 and the α-aminonitrile 2 (molar ratio 2:1)[20] in dry ether was kept for 10-20 days at room temperature in a sealed flask. Any solid which had precipitated was filtered and the ether removed under vacuum to give an oil which was treated with petroleum ether/acetone or ethanol to yield the product.

Ethyl 5-methyl-4-carboethoxyformamidino-imidazole-2-carboxylate (5b)

Mp 145-7°C (from acetone/petroleum ether) (26% yield). Anal calcd for $C_{11}H_{16}N_4O_4$: C, 49.25; H, 6.01; N, 20.88. Found: C, 49.37; H, 6.27; N, 20.77. ^1H nmr ($CDCl_3$): δ 4.75 (q,q,4H); 2.75 (s,3H); 1.8 (t,6H); 11.9 (s,1H). IR (KBr): 3420 and 3225 (NH); 1730 and 1710 (C=O); 1680 and 1630 cm^{-1} (C=N).

Ethyl 5-phenyl-4-carboethoxyformamidino-imidazole-2-carboxylate (5c)

Mp 199-200°C (from benzene/petroleum ether) (26% yield). Anal calcd for $C_{16}H_{18}N_4O_4$: C, 56.17; H, 5.49; N, 16.96. Found: C, 57.98; H, 5.86; N, 17.00. ^1H nmr ($CDCl_3$): δ 10.9 (s,1H); 8.15 and 7.4 (m,5H); 4.45 (q,q,4H); 1.45 (t,6H). IR (KBr): 3440 and 3290 (NH); 1730 and 1700 (C=O); 1650 cm^{-1} (C=N).

Ethyl 5-p-chlorophenyl-4-carboethoxyformamidino-imidazole-2-carboxylate (5f)

Mp 258-260°C (from chloroform/petroleum ether) (19.4% yield). Anal calcd for $C_{16}H_{17}ClN_4O_4.1/2H_2O$: C, 51.40; H, 4.85; N, 14.99. Found: C, 51.15; H, 4.75; N, 14.84. ^1H nmr (DMSO-d_6): δ 8.4 (d,2H); 7.4 (d,2H); 4.2 (q,q,4H); 1.3 (t,6H). IR (KBr): 3450 and 3300 (NH); 1735 and 1700 (C=O); 1650 cm^{-1} (C=N).

Ethyl 5-amino-4,4-dimethyl-4H-isoimidazole-2-carboxylate (6a)

Mp 137-140°C (from acetone) (28% yield). Anal calcd for $C_8H_{13}N_3O_2.1H_2O$: C, 50.00; H, 7.29; N, 21.87. Found: C, 49.80; H, 7.48; N, 21.94. ^1H nmr ($CDCl_3$): δ 4.4 (q,2H); 1.4 (t,9H). IR (KBr): 3400-3000 (N-H); 1745 (C=O); 1660 cm^{-1} (C=N).

Ethyl 5-amino-4,4-pentamethylene-4H-isoimidazole-2-carboxylate (6b)

Mp 202-3°C (from benzene/petroleum ether) (44.4% yield). Anal calcd for $C_{11}H_{17}N_3O_2.1H_2O$: C, 54.75; H, 7.93; N, 17.41. Found: C, 54.84; H, 8.09; N, 17.48. ^1H nmr ($CDCl_3$): δ 4.45 (q,2H); 2-1.45 (m,13H). IR (KBr): 3400-3000 (N-H); 1740 (C=O); 1670 cm^{-1} (C=N). m/e 223 (M^+).

Ethyl 5-amino-4,4-tetramethylene-4H-isoimidazole-2-carboxylate (6c)

Mp 198-200°C (from acetone/ether) (23.9% yield). Anal calcd for $C_{10}H_{15}N_3O_2.1/2H_2O$: C, 55.03; H, 7.39; N, 19.25. Found: C, 54.81; H, 7.15; N, 18.92. ^1H nmr ($CDCl_3$): δ 4.45 (q,2H); 2.3-1.7 (m,8H); 1.4 (t,3H). IR (KBr): 3400-3000 (N-H); 1745 (C=O); 1660 cm^{-1} (C=N).

Ethyl 4-aminoquinazoline-2-carboxylate (7)

A suspension of o-aminobenzonitrile (10 mmol) and 1.HCl (10 mmol) in dry ethanol (25 ml) was refluxed for 1 hr. The precipitated ammonium chloride was filtered off and the solvent removed under vacuum. The solid which had precipitated was filtered and neutralised with aqueous potassium carbonate. Mp 223-5°C (from acetone) (25% yield). Anal calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.35. Found: C, 60.44; H, 5.06; N, 19.01. IR (KBr): 3380, 3300 and 3180 (N-H); 1747 cm^{-1} (C=O). m/e 217 (M^+).

N-Phenylparabanic acid (3-phenyl-1-imidazolidine-2,4,5-trione) (8)

To a solution of 10 mmol of 1 and 10 mmol of phenylurea in anhydrous tetrahydrofuran (THF) at r.t. was added, with stirring, THF saturated with HCl. The resulting suspension was refluxed overnight, and the solid which had precipitated was filtered and recrystallized. Mp 202-3°C (from water) (56% yield). Anal calcd for $C_9H_6N_2O_3$: C, 56.84; H, 3.18; N, 14.73. Found: C, 56.49; H, 3.05; N, 14.70. ^1H nmr (DMSO-d_6): δ 7.45 (m). IR (KBr): 3240 (N-H); 1805, 1790 and 1735 cm^{-1} (C=O).

N-Phenyl-N-carboethoxyformamidino-urea (10)

A solution of 10 mmol of 1 and 10 mmol of 9a in 35 ml of dry ethanol was refluxed overnight. A part of the solvent was removed under vacuum and the solid which precipitated (10) was collected by filtration. Mp 158-160°C (from ethanol) (22% yield). Anal calcd for $C_{11}H_{14}N_4O_3$: C, 52.79; H, 5.64; N, 22.39. Found: C, 53.12; H, 5.32; N, 22.14. ^1H nmr ($CDCl_3$): δ 10.4 (s,1H); 8.3 (s,1H); 7.2 (m,5H); 5.8 (s,2H); 4.35 (q,2H); 1.35 (t,3H). IR (KBr): 3470, 3370, 3230 and 3100 (N-H); 1720 (C=O, COOEt); 1680 (C=O, CONH); 1655 cm^{-1} (C=N).

Ethyl 5-oxo-1,2,4-triazol-2-ine-3-carboxylate (11)

Compound 11 was obtained from the above reaction after removing the solvent under vacuum and treating the resulting oil with diethyl ether. Mp 198-200°C (from acetone) (45% yield). Anal calcd for $C_5H_7N_3O_3$: C, 38.22; H, 4.49; N, 26.74. Found: C, 37.96; H, 4.52; N, 26.90. ^1H nmr (DMSO-d_6): δ 12.2 (s,1H); 4.35 (q,2H); 1.3 (t,3H). IR (KBr): 3160-3000 (N-H); 1730 (C=O, COOEt); 1710 (C=O, CONH); 1680 cm^{-1} (C=N).

Ethyl 5-phenylamino-1,3,4-thiadiazole-2-carboxylate (12)
A solution of 10 mmol of 1 and 10 mmol of 9b in 35 ml of dry ethanol was refluxed for two days. Any solid which precipitated was filtered off and the solvent removed under vacuum. The resulting oil was treated with diethyl ether to give compound 12. Mp 174-5°C (from benzene)[21] (40% yield). Anal calcd for $C_{11}H_{11}N_3O_2S$: C, 53.01; H, 4.44; N, 16.86. Found: C, 53.02; H, 4.52; N, 17.25. ^1H nmr (DMSO-d_6): δ 7.5 (m,5H); 4.15 (q,2H); 1.1 (t,3H). IR (KBr): 3150 (N-H); 1735 cm^{-1} (C=O). m/e 249 (M^+).

3-Amino-5,6-dicyano-2-pyrazinone (13)
A solution of 10 mmol of 1 and 11 mmol of 2,3-diaminomaleonitrile in 25 ml of absolute ethanol was refluxed for 1 hr and then stirred for 3 hr. The solid which precipitated was collected by filtration. Mp 290°C (from ethanol or water) (72% yield). Anal calcd for $C_6H_3N_5O$: C, 44.72; H, 1.88; N, 43.47. Found: C, 44.75; H, 2.12; N, 43.80. IR (KBr): 3500-3200 (N-H); 2245 (C≡N); 1685 cm^{-1} (C=O). m/e 161 (M^+).

6-Nitro-3-amino-1,4-benzoxazin-2-one (14a)
To a solution of 10 mmol of 2-amino-4-nitrophenol in 25 ml of dry ethanol was added 10 mmol of 1. The reaction mixture was kept at r.t. for two days. The solid which precipitated, (14a), was collected by filtration. Mp 257°C (dec) (from methanol) (92% yield). Anal calcd for $C_8H_5N_3O_4$: C, 46.38; H, 2.43; N, 20.28. Found: C, 46.61; H, 2.11; N, 19.94. ^1H nmr (DMSO-d_6): δ 8.1-7.35 (m). IR (KBr): 3410 and 3100 (N-H); 1750 (C=O); 1680 cm^{-1} (C=N).

6-Methyl-3-amino-1,4-benzoxazin-2-one (14b)
A solution of 10 mmol of 1 and 10 mmol of 4-methyl-2-aminophenol in 25 ml of dry ethanol was refluxed overnight. The solid which precipitated was filtered. Mp 284-6°C (from ethanol) (79.5% yield). Anal calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.01; H, 4.34; N, 15.96. ^1H nmr (CF_3COOD): δ 7.3 (m,3H); 2.4 (s,3H). IR (KBr): 3420 and 3100 (N-H); 1730 (C=O); 1650 cm^{-1} (C=N).

Ethyl benzothiazole-2-carboxylate (15a)
A solution of 10 mmol of 1 and 10 mmol of 2-aminothiophenol in 25 ml of dry ethanol was refluxed under N_2 for 2.5 hr and then stirred for 1 hr. The solid which precipitated (15b) was collected by filtration and the solvent removed under vacuum to give an oil which soon crystallized. Mp 60-3°C (from petroleum ether) (87% yield). Anal calcd for $C_{10}H_9NO_2S$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.87; H, 4.13; N, 7.10. ^1H nmr ($CDCl_3$): δ 8.3-7.4 (m,4H); 4.5 (q,2H); 1.45 (t,3H). IR (KBr): 1750 cm^{-1} (C=O). m/e 207 (M^+).

Benzothiazole-2-carboxamide (15b)
This was isolated from the above reaction mixture: Mp 230-2°C (from ethanol) (8.4% yield). Anal calcd for $C_8H_6N_2OS$: C, 53.93; H, 3.39; N, 15.72. Found: C, 53.58; H, 3.56; N, 15.52. ^1H nmr (DMSO-d_6): δ 8.5-7.5 (m,4H); 8.3 (s,2H). IR (KBr): 3320 and 3220 (N-H); 1700 (C=O); 1665 cm^{-1} (C=N). m/e 178 (M^+).

N,N-Bis-2-hydroxyethyloxamide (16)
A solution of 10 mmol of 1 and 10 mmol of 2-aminoethanol in ethanol was stirred at r.t. overnight and the solid which precipitated was collected by filtration. Mp 143-5°C (from ethanol) (57% yield). Anal calcd for $C_6H_{12}N_2O_4$: C, 40.90; H, 6.87; N, 15.90. Found: C, 40.70; H, 6.48; N, 16.27. ^1H nmr (CF_3COOD): δ 8.7 (s,2H); 4.65 (t,2H); 4.1-3.6 (m,8H). IR (KBr): 3390, 3300 (N-H and OH); 1665 cm^{-1} (C=O). m/e 176 (M^+).

Ethyl 3,4-dihydro-4-oxoquinazoline-2-carboxylate (18)
This was isolated by the same procedure used for compound 14b. Mp 193-4°C (from ethanol) (42% yield). Anal calcd for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.32; H, 4.54; N, 12.79. ^1H nmr (DMSO-d_6): δ 7.9 (m,4H); 4.45 (q,2H); 1.4 (t,3H); 10.9 (s,1H). IR (KBr): 3180-3000 (N-H); 1740 and 1730 (C=O, COOEt); 1680 cm^{-1} (C=O, CONH).

2H-3-Carboethoxy-benzo[e]-1,2,4-thiadiazine-1,1-dioxide (19)
This was obtained by the same procedure used for compound 14b. Mp 178-9°C (from ethanol) (44% yield). Anal calcd for $C_{10}H_{10}N_2O_4S$: C, 47.25; H, 3.96; N, 11.02. Found: C, 47.23; H, 3.70; N, 10.98. ^1H nmr (DMSO-d_6): δ 7.7 (m,5H); 4.45 (q,2H); 1.35 (t,3H). IR (KBr): 3300 (N-H); 1735 (C=O); 1630 and 1600 cm^{-1} (C=N and δ NH).

3,4-Dihydro-N-o-aminobenzylquinazoline-2-carboxamide (20)
This was obtained from freshly distilled 2-aminobenzylamine by the same procedure used for compound 16. Mp 180-3°C (from ethanol) (35% yield). Anal calcd for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.39; N, 19.98. Found: C, 68.46; H, 5.72; N, 19.63. ^1H nmr (DMSO-d_6): δ 8.9 (t,1H); 7.7 (m,1H); 7.1-6.5 (m,8H); 5.1 (s,2H); 4.6 (m,2H); 4.2 (m,2H). IR (KBr): 3340 and 3220 (N-H); 1675 (C=O); 1620 cm^{-1} (C=N).

N,N-Bis-o-aminobenzyloxamide (21)

This was obtained from crude 2-aminobenzylamine by the same procedure used for compound 16. Mp 208-10°C (from ethanol) (54% yield). Anal calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.40; H, 5.83; N, 19.03. ^1H nmr (DMSO-d_6): δ 9.1 (t,2H); 7-6.3 (m,8H); 5 (s,2H); 4.2 (m,4H); 3.3 (s,2H). IR (KBr): 3420, 3390, 3340, 3290 and 3160 (N-H); 1675 and 1650 (C=O); 1630 cm^{-1} (δ NH).

1,3-Dihydro-3-amino-1,2,4-triazino[2,3-a]benzimidazole-2-one (22a) and/or 3,4-dihydro-2-amino-1,2,4-triazino[2,3-a]benzimidazole-3-one (22b)

This was obtained by the same procedure used for compound 14b. Mp > 300°C (purified by dissolving in aqueous potassium carbonate and acidification of the filtrated solution to pH-4) (80% yield). Anal calcd for $C_9H_7N_5O$: C, 53.73; H, 3.50; N, 34.81. Found: C, 53.38; H, 3.16; N, 34.43. ^1H nmr (CF_3COOD): δ 7.85 (m). IR (KBr): 3380-2400 (N-H); 1690 and 1680 cm^{-1} (C=O).

Ethyl s-triazolo[1,5-a]pyridine-2-carboxylate (23a)

To a solution of 2.5 mmol of KOH and 2.5 mmol of 1,2-diaminopyridinium iodide in 17 ml of ethanol was added, with stirring, 2.5 mmol of 1 and the mixture was stirred overnight at r.t. The filtered solution was evaporated under vacuum and the residue was dissolved in water and extracted with ether. The dried layers gave 23a. Mp 135-6 °C (from benzene/petroleum ether). Anal calcd for $C_9H_9N_3O_2$: C, 56.53; H, 4.74; N, 21.98. Found: C, 56.64; H, 4.97; N, 22.09. ^1H nmr ($CDCl_3$): δ 8.7 (d,1H); 8-7 (m,3H), 4.6 (q,2H); 1.5 (t,3H). IR (KBr): 1730 (C=O); 1640 cm^{-1} (C=N). m/e 191 (M^+).

Ethyl s-triazolo[1,5-a]pyridine-2-formimidate (23b)

This was collected together with 23a from the above reaction mixture. Mp 135°C (from ethanol/petroleum ether). Anal calcd for $C_9H_{10}N_4O$: C, 56.83;H, 5.29; N, 29.46. Found: C, 56.50; H, 5.42; N, 29.85. ^1H nmr (DMSO-d_6): 9.05 (m,2H); 7.8-7 (m,3H); 4.35 (q,2H); 1.35 (t,3H). IR (KBr): 3230 (N-H); 1650 cm^{-1} (C=N). m/e 190 (M^+).

Methyl s-triazolo[1,5-a]pyridine-2-formimidate (23c)

A solution of 6.7 mmol of 1,2-diaminopyridinium iodide in 27 ml of methanol was passed through a column (1x20 cm) of Amberlite IRA-400 ion exchange resin regenerated by passing through 1N NaOH. The eluate was added to 6.1 mmol of 1 and the resulting solution was kept overnight at r.t. and then refluxed for 1 hr. The solvent was removed under vacuum to give 0.8 g (81.6%) of 23c. Mp 143-5°C (from ethanol/petroleum ether). Anal calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.75; H, 4.32; N, 31.50. ^1H nmr (DMSO-d_6): δ 9 (m,2H); 7.8-7.1 (m,3H); 3.9 (s,3H). IR (KBr): 3230 (N-H); 1665 cm^{-1} (C=N). m/e 176 (M^+).

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13. Full details of the scope and limitations of the condensation of 1 with 1,2-diamino and 1-hydroxy-2-amino aromatic and heteroaromatic substrates will be the subject of a forthcoming publication.

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