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(54) Title: PYRAZINES

(57) Abstract

There are provided novel pyrazines and a method of making them by reacting 5-halo substituted pyrazines with an arylboronic acid, the novel pyrazines can be used in the synthesis of coelenterazine.

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Pyrazines

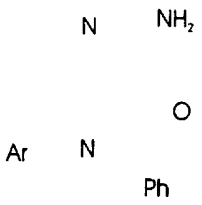
The present invention relates to novel pyrazines and to methods of their use in preparing further imidazopyrazine compounds.

It is known that the luminescent chromophores, such as Coelenterazine which can be isolated from Aequora Victoria, as described in the Article by Shimomura O, Johnson Fitt. and Morisett in Biochemistry 1974, 13,3278-3286, contain the imidazopyrazine ring system.

Coelenterazine has been extensively studied because of the bioluminescent process which is triggered by calcium ions and has proved to be a sensitive method for the detection and quantification of calcium ions. Coelenterazine and analogues have been prepared by the "Kishi route", as described in the Article by Shimomura O, Musieki B. Kishi Y, Biochem J., 1989, 261,913-920.

We have prepared novel pyrazine compounds which can be used as intermediates in the preparation of imidazopyrazine compounds such as coelenterazine.

According to the invention there is provided a pyrazine of formula

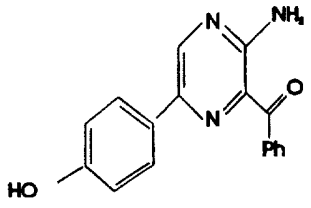


(I)

where Ar is an aromatic or substituted aromatic group.

The aromatic groups Ar, which can be used include groups such as phenyl, naphthyl and thiophenyl. The substituted aromatic groups include alkyl, aryl and substituted aryl, alkaryl, halides, halide substituted aryl groups and groups such as trifluoromethyl, fluoro and alkoxy groups. The Ph group can be substituted by any of the substituents listed above.

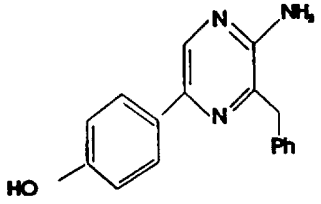
The invention also provides pyrazines of the formula



(II)

where Ph is an aromatic or substituted aromatic group e.g.as Ar in (I).

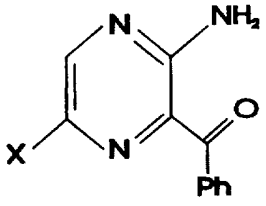
The invention further provides pyrazines of formula



(III)

where Ph is as defined above.

The compounds (I) of the present invention can be prepared by the reaction of the 5-halo substituted pyrazine:-



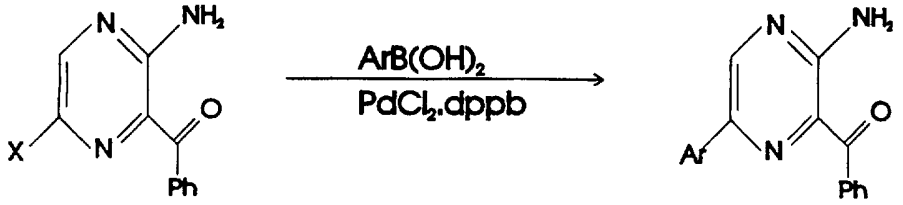
(B)

where X is a halide group, preferably bromide, with an arylboronic acid of formula $ArB(OH)_2$ in the presence of a catalyst, where Ar is as above.

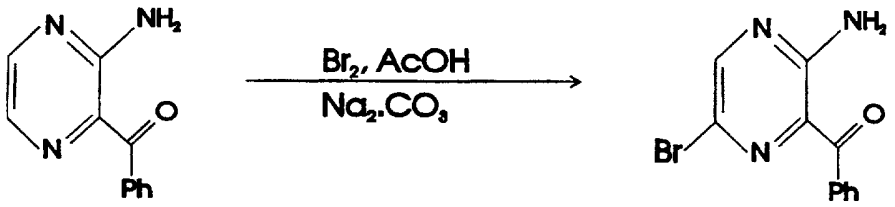
The catalysts which can be used in the process of the present invention include, but are not limited to, platinum groups catalysts, particularly palladium compounds. The preferred palladium catalysts are Pd(II) complexes, particularly organic palladium compounds such as diphenyl phosphino complexes of Pd(II) e.g. [1,4-bis(diphenylphosphino)butane]palladium(II) chloride and [1,1 - bis(diphenylphosphino)ferrocene]palladium(II) acetate.

The reaction of compound B with the arylboronic acid preferably takes place in a solvent which will depend on the nature of the catalyst used. Particular solvents which can be used are toluene, tetrahydrofuran, dimethyl formamide, optionally in the presence of co-solvents such as water or an amine such as triethylamine.

The reaction can be illustrated as follows:



Preferred Ar groups are 4-$MeOC_6H_4$, C_6H_5, naphthyl, 4-FC_6H_4, 4-$CF_3C_6H_4$ and 2-thienyl. Compound B can be prepared by bromination of the corresponding pyrazine:-

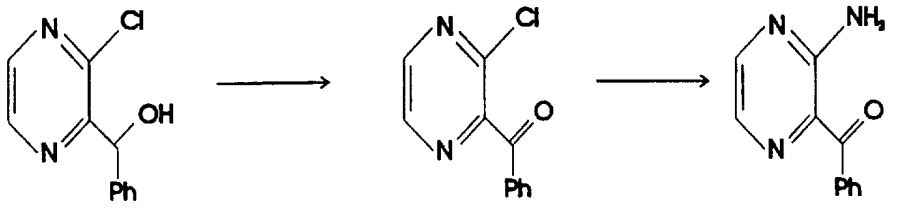


(C) (B)

The bromination can be carried out using known methods; however, we have found that a preferred bromination system used bromine in acetic acid in the presence of sodium carbonate.

The pyrazine C can be prepared by known methods, for example, as described in the Article by Turek A, Mojovie L, Queguiner G, Synthesis 1988, 881-884. In this 2-chloropyrazine was metallated using lithium tetramethylpiperidide and reacted with benzaldehyde to afford the alcohol (3) in 88% yield. Oxidation of (3) using freshly-prepared MnO_2 gave the ketone (4) in 93% yield. Introduction of the amino group was achieved by heating ketone (4) with a solution of ammonia in ethanol at 120°C overnight leading to aminopyrazine (5) in 63% yield.

This is shown by the reaction scheme.



(3) (4) (5)

The aminopyrazine was reacted with bromine in acetic acid, containing solid sodium carbonate and the desired bromopyrazine was isolated in 88% yield in 20 minutes.

Compounds of formula (II) above can be prepared by cleavage of the methyl aryl ether of formula (I) according to the reaction.



(II)

The preferred method for cleaving the methyl aryl ether is by reaction with ethanethiolate. The phenol (II) obtained can be converted to the phenol (III) by reduction.

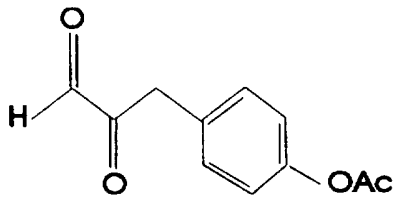
Any reduction which reduces the ketone group can be used such as using a metallic catalyst such as platinum or palladium or carbon, treatment with zinc and hydrochloric acid under usual Clemenson conditions (M Lucas and F Solano, Anal. Biochem, 1992 206,273). Reduction of the ketone to alcohol, e.g. using $NaBH_4$ in methanol followed by treatment of the alcohol with Et_3SiH and trifluoracetic acid.

A preferred method is a Wolff-Kishner reduction by reaction with hydrazine hydrate and potassium hydroxide in ethylene glycol.

The above compounds of the present invention can be used as intermediates to prepare compounds containing the imidazopyrazine ring system such as

coelenterazine by reduction of the benzoyl substituent to benzyl, condensation with 4-methoxybenzylglyoxal and cleavage of the methyl ethers using pyridinium bromide or by reaction with a ketoaldehyde.

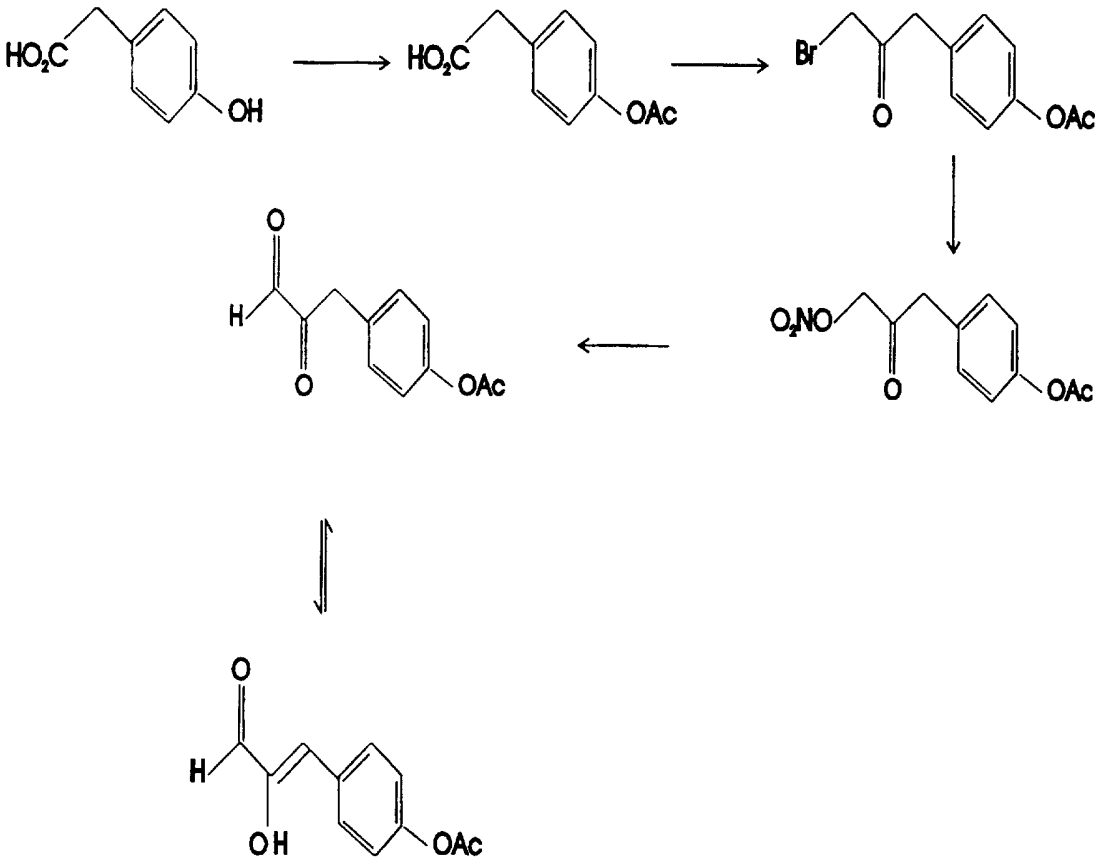
In order to prepare coelenterazine, the compound (III) is reacted with an α-ketoaldehyde of formula.



(V)

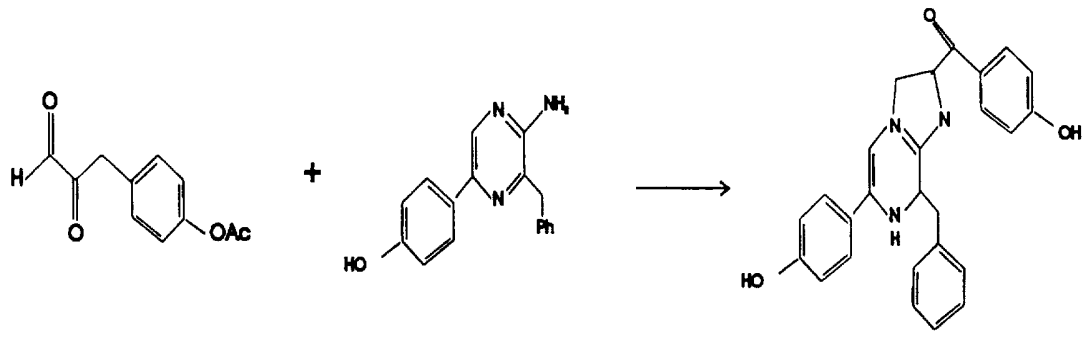
The α-ketoaldehyde can be prepared by known methods, for example by the route described by S Inove, S Sugiura, H Kakoi and K Hasizume, Chem. Letters 1975, 141. In this route the phenol group in 4-hydroxy phenyl acetic acid is acylated, converted to the acid chloride (with $SOCl_2$) and reacted with diazomethane to give the α-diazoketone. The α-diazoketone was reacted with dry HBr to give the bromomethyl ketone which is reacted with silver nitrate in acetonitrile to give the nitrate ester which is reacted with sodium acetate to give the α-ketoaldehyde.

This route is shown in the reaction scheme.


HO2C
OH
HO2C
OAc
Br
O
OAc
O2NO
O
OAc
O
H
O
OAc
O
H
OH
OAc

The compound (V) is found to exist mainly in the enol form in solution in many solutions.

To form coelenterazine compound (V) is reacted with compound (III) according to the reaction scheme



(V) (III) coelenterazine

The invention is further described in the following Examples in which Examples 1 to 7 describe the preparation of the novel pyrazines of the invention and Example 8 illustrates the production of coelenterazine with the preparation of the 2-amino-3-benzoyl-5-(4'-methoxyphenyl)pyrazine used in Example 8 prepared as in Example 1.

Example 1

Coupling Procedure; Method A

A mixture of bis(benzonitrile) palladium (II) chloride (7 mg) and 1.4-bis(diphenylphosphino) butane (9 mg) in dry toluene (0.7 ml) was stirred at room temperature under an atmosphere of argon for 30 minutes until a creamy orange slurry of [1.4-bis(diphenylphosphino)butane] - palladium (II) chloride has formed. 2-Amino-3-benzoyl-5-bromopyrazine (100mg, 0.36mmol.), 4-methoxyphenylboronic acid (71 mg, 0.47 mmol.) ethanol (0.15 ml), aqueous sodium carbonate solution (0.36 ml. 1M) and dry toluene were added to the preformed catalyst and the mixture heated under reflux for 7 hours. After cooling to room temperature, water (2 ml) was added and the mixture diluted with ethyl acetate. The aqueous phase was separated and extracted with ethyl acetate. The combined organic phases were dried and evaporated. The crude product was purified by flash chromatography (40% ethyl acetate in hexane) to give 2-amino-3-benzoyl-5-(4'-methoxyphenyl)pyrazine (101 mg 92%) as a bright yellow solid, mp. 159-160°C.

Coupling Procedure; Method B

A stirred mixture of palladium (II) acetate (3mg.) and [1,1-bis(diphenylphosphino)ferrocene] (6mg.) in dry dimethyl formamide (0.5ml) was warmed to 50^0C for 15 mins. After cooling to room temperature, 2-amino-3-benzoyl-5-bromopyrazine (50mg.), 4-methoxyphenylboronic acid (36mg.) and dry triethylamine (0.04ml) were added and the mixture heated with stirring at 90^0C for four hours. After cooling to room temperature, the reaction mixture was concentrated on a rotary evaporator and dissolved in chloroform. The solution was washed with aqueous ammonia solution, dried and evaporated to dryness. The crude product was purified by flash chromatography (40% ethyl acetate in hexane) to give 2-amino-3-benzoyl-5-(4-methoxyphenyl)pyrazine (35mg, 70%) as a bright yellow solid, mp. 158-160^0C.

Examples 2-7

The process of Example was repeated using different arylboronic acids and the results are shown in the Table below:-

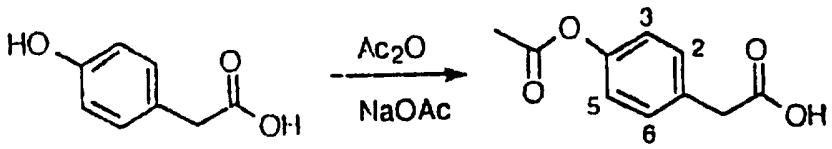
Table: Coupling of 6 with arylboronic acids

1	4-Methoxyphenyl-boronic acid	A	7 h	7a	92%
2	4-Methoxyphenyl-boronic acid	B	4 h	7a	70%
3	Phenylboronic acid	A	3 h	7b	92%
4	Naphthalene-2-boronic acid	A	4 h	7c	96%
5	4-Fluorohenyl-boronic acid	A	3 h	7d	92%
6	4-Trifluoromethyl-phenylboronic acid	A	6 h	7e	82%
7	Thiophene-2-boronic acid	A	48 h	7f	96%

Phenyl and naphthylboronic acids reacted cleanly with (6) and gave the heterobiaryl products 7b and 7c in very high yields (entries 3 and 4). The introduction of electron-withdrawing substituents on the boronic acid moiety presented no problems and both the 4-fluoro and the 4-trifluoromethyl-substituted boronic acids reacted within a reasonable timescale to give the respective coupled products 7d and 7e in high yields.

However, the thiophene-2-boronic acid reacted only slowly with bromopyrazine (6) under these conditions and after 48 hours the reaction had only proceeded to 60% conversion, as judged by recovered starting material. The reaction is still clean and gave only 7f as can be seen from the yield based on recovered starting material.

p-Acetoxyphenylacetic acid

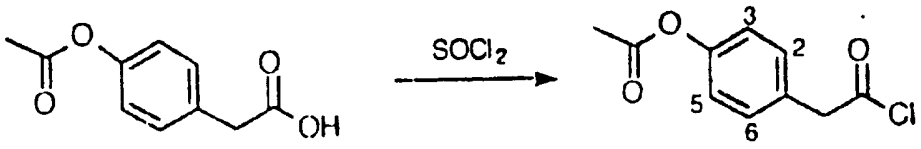


$C_8H_8O_3$
Mol. Wt.: 152.1494

$C_{10}H_{10}O_4$
Mol.Wt.: 194.1866

A slurry of *p-hydroxyphenylacetic acid* (2 g, 13 mmol) and sodium acetate 2.16 g, 26 mmol) in acetic anhydride (12 ml) were heated under reflux for two hours. On cooling, crushed ice was added and the organic layer separated, diluted with ethyl acetate and dried. The solvents were removed under reduced pressure to give *p-acetoxyphenylacetic acid* (2.1 g, 84%) as a colourless solid, m.p. 106-108°C. Lit [Beames, 1974 #22]. 108°C; ν_{max}/cm^{-1} (Nujol mull) 3100 (broad, OH), 1747, 1699 (C=O) and 1596, 1509 (C=C); δ_H(360 MHz; $CDCl_3$) 7.21 (2H, d, *J* 8.5, H2, H6), 7.05 (2H, d, *J* 8.5, H3, H5), 3.71 (2H, s, CH_2Ar) and 2.29 (3H, s, OCH_3); δ_c($CDCl_3$) 169.2 ($\underline{C}O_2CH_3$), 166.5 ($\underline{C}O_2H$), 150.0 (C4), 130.4 (C2, C6) 129.4 (C1), 121.9 (C3, C5), 41.2 ($\underline{C}H_2Ar$) and 21.0 ($\underline{C}H_3$).

p-Acetoxyphenylacetylchloride

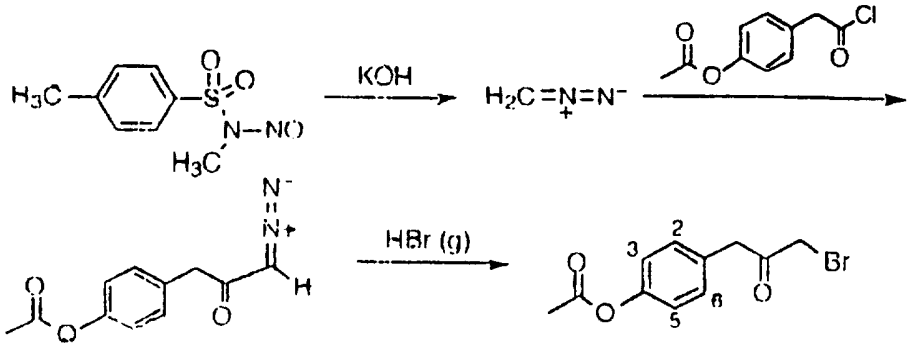


$C_{10}H_{10}O_4$
Mol.Wt.: 194.1866

$C_{10}H_{10}O_4$
Mol.Wt.: 194.1866

A solution of 4-acetoxyphenylacetic acid (2.1 g, 10 mmol) in thionyl chloride (4 ml) was stirred overnight at room temperature. Excess thionyl chloride was removed under reduced pressure to yield *p-acetoxyphenylacetylchloride* (2.3 g, quant.) as a viscous yellow oil which was used without further purification; ν_{max}/cm^{-1} ($CDCl_3$) 2907 (C-H), 1797 (C=O, acid chloride) and 1783 (C=O, ester); δ_H(360 MHz; $CDCl_3$) 7.28 (2H, d, *J* 8.5, H2, H6), 7.10 (2H, d, *J* 8.5, H3, H5), 4.13 (2H, s, CH_2Ar) and 2.30 (3H, s, OCH_3); δ_c($CDCl_3$) 171.7 ($\underline{C}OCl$), 169.3 ($\underline{C}O_2CH_3$), 150.5 (C4), 130.6 (C2, C6), 128.7 (C1), 122.1 (C3, C5), 52.3 ($\underline{C}H_2Ar$) and 21.0 ($\underline{C}H_3$).

1-Bromo-3(p-acetoxyphenyl)propan-2-one



$C_{11}H_{11}BrO_3$
Mol. Wt.:271.1101

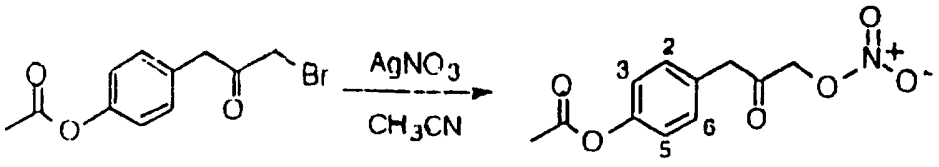
Preparation of diazomethane

A solution of Diazald (7.4 g, 0.02 mol) in dry diethyl ether (82 ml) was added dropwise to a warm solution of aqueous potassium hydroxide (7.4 g, in 12 ml of H_2O) and di(ethyleneglycol)ethyl ether (17 ml). Diazomethane was collected as a co-distillate with diethyl ether.

p-Acetoxyphenylacetylchloride (2.3 g, 0.01 mol) in dry ether (20 ml) was added dropwise to an excess of freshly prepared diazomethane in diethyl ether (80 ml) at 0°C. The reaction was maintained at this temperature for 90 mins, then the solvent evaporated. An infrared spectrum of the solution was run at this point to confirm that the diazoketone had been generated (sharp peak at ca. 2100cm^{-1}) and was used without purification.

A steady stream of dried hydrogen bromide gas was passed over the diazoketone in diethyl ether (30 ml) at 0°C for 30 mins with stirring. Water was carefully added to the resulting mixture which was subsequently washed with aqueous $NaHCO_3$ and water. The organic phase was separated and the solvent removed to yield an orange oil. Purification via a silica gel plug (eluent 3:1Et_2O:hexane) gave *1-bromo-3-(p-acetoxyphenyl)propan-2-one* (2.61 g, 73% from protected acid) as an unstable, light sensitive powdery colourless solid, m.p. 82-84°C Lit.[Inoue, 1975 #23] 84°C; R_f(3:1, Et_2O:hexane) 0.45; ν_{max}/cm^{-1} Diazoketone (neat) 2104 (R=N=N); Bromoketone ($CDCl_3$) 1759 (C=O, ester) and 1722 (C=O); δ_H(360 MHz; $CDCl_3$) 7.25 (2H, d, *J* 8.5, H2, H6), 7.08 (2H, d, *J* 8.5, H3, H5), 3.95 (2H, s, $\underline{C}H_2Ar$), 3.92 (2H, s, $\underline{C}H_2Br$) and 2.30 (3H, s, $\underline{C}H_3$); δ_C($CDCl_3$) 150.0 (C4), 130.6 (C1), 130.5 (C2, C6), 122.0 (C3, C5), 45.9 ($\underline{C}H_2Ar$), 33.5 ($\underline{C}H_2Br$) and 21.1 ($\underline{C}H_3$); (*$\underline{C}O_2CH_3$ and $\underline{C}O$ not observed.*

2-Oxo-3-(p-acetoxyphenyl)propylnitrate

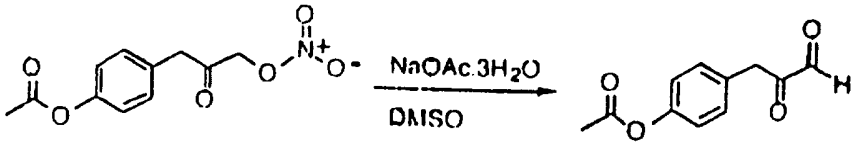


$C_{11}H_{11}BrO_3$
Mol. Wt.:271.1101

$C_{11}H_{11}NO_6$
Mol. Wt.:253.2110

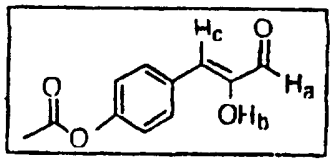
A solution of silver nitrate (1.09 g, 6.4 mmol) in acetonitrile (6 ml) was added to a solution of 1-bromo-3-(*p*-acetoxyphenyl)propan-2-one (750 mg, 2.8 mmol) in acetonitrile (3 ml). The mixture was stirred at room temperature overnight and then filtered through celite. Water and diethyl ether were added to the solution. After separation, the organic phase was dried and the solvent removed under reduced pressure. Purification via column chromatography (eluent 3:1 Et_2O:hexane) gave *2-oxo-3-(p-acetoxyphenyl)propyl nitrate* (684 mg, 98%) as a colourless powdery solid, m.p 81-85°C:Lit. xx:R_f(3:1, Et_2O:hexane) 0.6: ν_{max}/cm^{-1} ($CHCl_3$) 3021, 2941 (C-H), 1757 (C=O, ester), 1739 (C=O) and 1653, 1284 (ONO_2); δ_H(360 MHz; $CDCl_3$) 7.22 (2H, d, *J* 8.5, H2, H6), 7.08 (2H, d, *J* 8.6, H3, H5), 4.96 (2H, s, CH_2ONO_2), 3.76 (2H, s, CH_2Ar) and 2.30 (3H, s, CH_3); δ_C($CDCl_3$) 198.6 (C=O), 169.3 ($COCH_3$), 150.1 (C4), 130.4 (C2, C6), 129.3 (C1), 122.2 (C3, C5), 73.3 CH_2ONO_2), 45.5 (CH_2Ar) and 21.0 (CH_3); m/z 253 (4%, M^+), 184 (30%), 164 (34%) and 107 (100%); (Found: M^+, 253.0586. $C_{11}H_{11}NO_6$ requires *M*. 253.0586).

2-Oxo-3-(p-acetoxyphenyl)propanal



$C_{11}H_{11}NO_6$
Mol. Wt.:253.2110

exists as the enol tautomer

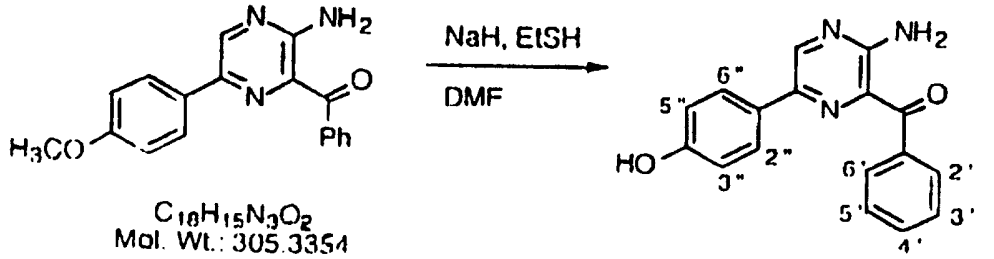


$C_{11}H_{10}O_4$
Mol. Wt.:206.1976

A solution of 2 oxo-3-(*p*-acetoxyphenyl)propyl nitrate (400 mg, 1.58 mmol) in DMSO (14 ml) was treated slowly with sodium acetate trihydrate (202 mg). The resulting

solution was stirred at room temperature for 20-25 mins, then poured into ice-water. The resulting mixture was saturated with NaCl and then extracted into diethyl ether. The organic phase was washed with saturated $NaHCO_3$ solution and brine and dried. The solvent was removed under reduced pressure to yield *2-oxo-3-(p-acetoxyphenyl)propanal* (285 mg, 88%) as a powdery colourless solid, m.p. 189-191°C (acetone/hexane). Lit. xx °C; R_f(1:1, Et_2O:hexane) 0.25: ν_{max}/cm^{-1} ($CDCl_3$) 3230, (broad OH), 3019 (CHO), 1755 (C=O) and 1646 (C=COH); δ_H(360 MHz; $CDCl_3$) 9.24 (1H, d, *J* 1.3, H_a), 7.86 (2H, d, *J* 8.6, H2, H6), 7.15 (2H, d, *J* 8.6, H3, H5), 6.65 (1H, t, *J* 1.3, H_c) and 6.15 (1H, d, *J* 1.2, H_b); δ_c($CDCl_3$) 188.1 (CH_a), 169.2 ($COCH_3$), 151.1 (C4), 148.6 (COH_b), 131.6 (C2, C6), 131.3 C1), 121.9 (C3, C5), 121.6 (CH_c) and 21.1 (CH_3): m/z 206 (77%, M^+), 184 (59%), 164 (97%) and 107 (100%); (Found: M^+, 206.0521. $C_{11}H_{10}O_4$ requires *M*. 206.0579).

2-Amino-3-benzoyl-5-(p-hydroxyphenyl)pyrazine



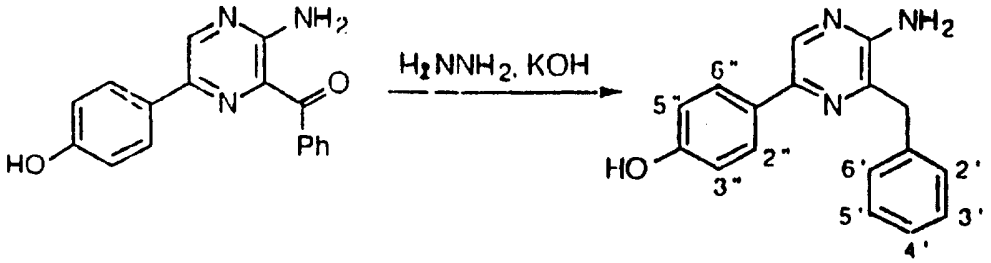
$C_{18}H_{15}N_3O_2$
Mol. Wt.: 305.3354

$C_{17}H_{13}N_3O_2$
Mol. Wt.: 291.3806

Ethanethiol (0.6 ml. 8 mmol), dissolved in dry DMF (3 ml) was added to a suspension of sodium hydride (5.5 equiv) in dry DMF (2 ml) under an atmosphere or argon. The mixture was stirred for 5 mins before a solution of 2-amino-3-benzoyl -5-(p-methoxyhenyl)pyrazine (520 mg, 1.7 mmol) in DMF (4 ml) was added. The solution was heated at 100°C for 8 hours. On cooling, the mixture was acidified with 10% aqueous HCl and washed with EtOAc. The aqueous phase was made alkaline (10% aqueous NaOH) and extracted with EtOAc. The organic phase was concentrated under reduced pressure and washed with 10% aqueous NaOH. The alkaline phase was back-extracted with EtOAc several times. All organic phases were combined, dried and the solvent removed under reduced pressure. Purification via column chromatography (eluent 3:2 EtOAe:hexane) gave *2-amino-3-benzoyl-5-(p-hydroxyphenyl)pyrazine* as an orange-brown solid (400 mg,

81%), m.p. 177°C; R_f(3:2, EtOAc:hexane) 0.46: ν_{max}/cm^{-1} 3538, (broad O-H), 1631 (broad, C=O and C=C); δ_H(360 MHz; CD_3OD) 8.69 (H1, s, H6), 7.97 (2H, d, *J* 7, H2', H6'). 7.72 (.....H, d, *J* 8.7, H2", H6"), 7.59 (1H, t, *J* 7.4, H4'), 7.49 (2H, t, *J* 7.5 H3', H5') and 6.81 (2H, d, *J* 8.8, H3", H5"); δ_c(CD_3OD) 197 (CO), 159.4, 156.0 (C2, C4"), 145.0 (C6), 142.1 (C3 or C5), 139.8 (C1"), 133.0 (C4'), 131.9 (C2', C6'), 129.4, 129.2 (C1', C3 or C5), 128.8, 128.0 (C3', C5', C2", C6") and 116.7 (C3", c5"); m/z 291 (M^+, 100%), 290 (54%), 281 (27%), 162 (36%) and 151 (40%): (Found: M^+, 291.0945, $C_{17}H_{13}N_43O_2$ requires *M*.291.1008).

2-Amino-3-benzoyl-5-(p-hydroxyphenyl)pyrazine

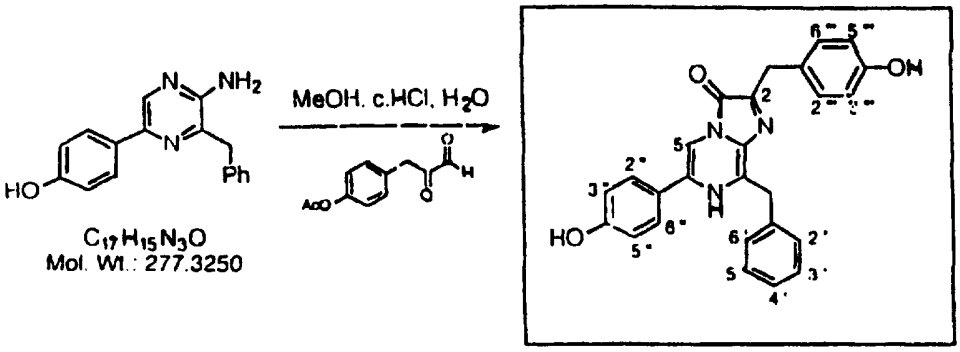


$C_{17}H_{13}N_3O_2$
Mol. Wt.: 291.3086

$C_{17}H_{15}N_3O$
Mol. Wt. :277.3250

2-Amino-3-benzoyl-5-(*p*-hydroxyphenyl)pyrazine (200 mg, 0.69 mmol), 80% hydrazine hydrate (0.57 ml) and potassium hydroxide (1.3 g, 32.5 mmol) in ethylene glycol (3.71 ml) were heated under reflux for 3 hours. On cooling, the solution was acidified with 2M HCl and extracted several times with EtOAc. The combined organic extracts were washed with brine, dried and the solvent removed under reduced pressure. Purification via column chromotography (eluent 1:1 EtOAc:hexane) gave *2-amino-3-benzyl-5-(p-hydroxyphenyl)pyrazine (x x)* as a pale yellow solid (159 mg, 84%), m.p. 220-222°C, Lit. [Kishi, 1972 #45] 217-219°C; R_f(1:1, EtOAc:hexane) 0.18: ν_{max}/cm^{-1} (Nujol) 3479 (N-H), 3348 (sharp, O-H) and 1637, 1607, 1514 (C=C); δ_H(360 MHz; DMSO-d_6) 9.51 (1H, s, OH), 8.30 (1H, s, H6), 7.73 (2H, d, *J* 8.7, H2", H6"), 7.34 (2H, d, *J* 7, H2' H6'), 7.28 (2H, t, *J* 7.4 H3', H5'), 7.19 (1H, t, *J* 7.2, H4'), 6.80 (2H, d, *J* 8.7, H3", H5"); 6.21 (2H, s, NH_2) and 4.07 (2H, s, CH_2Ph); δ_c(DMSO-d_6) 157 (C4"), 151.9 (C2), 139.6, 139.4, 138.2 (C1', C1", C3 or C5), 135.8 (c6), 128.8, 128.2, 126.1 (Aryl-CH), 115.4 (C3", C5") and 38.6 (CH_2Ph): *C3 or C5 and aryl-CH not observed*: m/z XX; (Found: M^+, x x. $C_{17}H_{15}N_3O$ requires *M*.x x).

2-(*p-Hydroxybenzyl*)-6-(*p-hydroxyphenyl*)-8-*Benzyl*-3,7-*dihydroimidazo*[1,2-a]*pyrazine*-3-*one* (Coelenterazine)



$C_{17}H_{15}N_3O$
Mol. Wt.: 277.3250

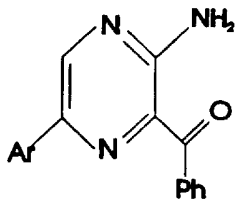
Coelenterazine
$C_{26}H_{21}N_3O_3$
Mol. Wt.: 423.4702

Under an inert argon atmosphere and in the absence of strong light, 2-amino-3-benzyl-5-(*p*-hydroxyphenyl)pyrazine (68 mg, 0.25 mmol) and 2-oxo-3-(*p*-acetoxyphenyl)propanal (45 mg, 0.22 mmol) were dissolved in ethanol (3.7 ml) and water (0.37 ml) and 3% (by volume) ethanoic HCl (0.8 ml) were added.

The mixture was heated at 80°C for 4.5 hours, then evaporated to dryness. Purification via column chromatography using compressed nitrogen and in the absence of strong light (eluent 4:96 MeOH:CH_2Cl_2) gave 2-(*p-hydroxybenzyl*)-6-(*p-hydroxyphenyl*)-8-*benzyl*-3,7-*dihydroimidazo*[1, 2-a]*pyrazine*-3-*one* (Coelenterazine) (57 mg, 62%) as a tan solid, m.p. dec. 177°C, Lit. [Inoue, 1972 #44] 175-178°C; R_f(4:96 MeOH:CH_2Cl_2)).1; ν_{max} (Nujol mull)/cm^{-1} x x; δ_H(360 MHz; CD_3OD) 7.55 (1H, br, s, NH), 7.40 (2H, d, *J* 8.1, H2", H6"), 7.35 (2H, d, *J* 7.2 H2' H6'), 7.28-7.24 (3H, m, H5 and H3', H5') 7.20 (1H, d, *J* 7.1, H4'), 7.13 (2H, d, *J* 8.5, H2"', H6"'), 6.83 (2H, d, *J* 8.5, H3", H5"), 6.68 (2H, d, *J* 8.5, H3"', H5"'), 4.37 (2H, s, CH_2Ar) and 4.04 (2H, s, CH_2Ar); δ_C($CDCl_3$) 160.2 (CO), 156.7 (C4" or C4"'), 137.9 (C_q), 130.8 (CH), 130.6, 130.0 (C_q), 129.8, 129.75 (CH), 129.7, 129.6 (C_q), 129.4, 128.2 (CH), 128.19, 127.6 (C_q), 116.8 (CH), 116.5 (C_q), 116.2 (CH), 107.8 (C5) and 64.3 (CH_2); *one* CH_2*Ar not observed*; m/z XX;

Claims.

1. A Pyrazine of formula



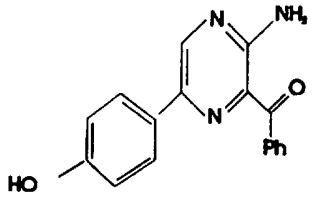
(I)

where Ar is an aromatic or substituted aromatic group.

2. A pyrazine as claimed in claim 1 in which the aromatic group Ar is a phenyl, naphthyl, thiophenyl group, or an aromatic group substituted by alkyl, aryl, alkaryl, halide, trifluoromethyl, fluoro or alkoxy groups and the Ph group is an unsubstituted phenyl group or a phenyl group substituted by an alkyl, aryl, alkaryl, halide, trifluoromethyl, fluoro or alkoxy group.

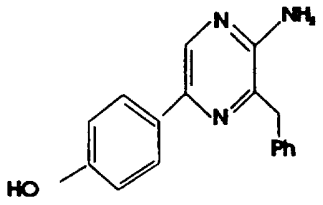
3. A pyrazine as claimed in claim 1 in which Ar is 4-$MeOC_6H_4$, C_6H_5, naphthyl, 4-FC_6H_4, 4-$CF_3C_6H_4$ or 2-thienyl.

4. A pyrazine of formula



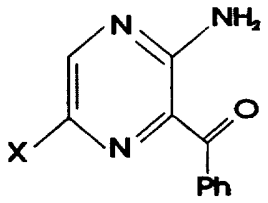
(II)

5. A pyrazine of formula



(III)

6. A process of preparing a compound of formula (I) herein which comprises reacting a 5-halo substituted pyrazine of formula.



(B)

where X is a halide group, preferably bromide, with an arylboronic acid of formula $ArB(OH)_2$ in the presence of a catalyst, where Ar is as specified in claim 1, 2 or 3.

7. A process as claimed in claim 7 in which the catalyst is a platinum group catalyst.

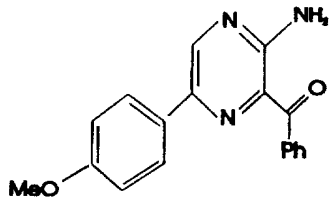
8. A process as claimed in claim 8 in which the catalyst is a Pd(II) organic complex.

9. A process as claimed in claim 8 in which the catalyst is a diphenyl phosphino complex of Pd(II), [1,4-bis(diphenylphosphino)butane] palladium(II) chloride, [1,1 - bis(diphenylphosphino)ferrocene] palladium(II) acetate.

10. A process as claimed in claim in any one of claims 6 to in which the reaction takes place in a solvent selected from toluene, tetrahydrofuran, dimethyl formamide, optionally in the presence of co-solvents such as water or an amine such as triethylamine.

11. A process as claimed in any one of claims 6 to 10 in which the Ar group is 4-$MeOC_6H_4$, C_6H_5, naphthyl, 4-FC_6H_4, 4-$CF_3C_6H_4$ or 2-thienyl.

12. A method of forming a compound of formula (II) which comprises reacting a methyl aryl ether of formula



with an ether cleaving agent .

13. A process as claimed in claim 12 in which the ether cleaving agent is ethanethiolate.

14. A process as claimed in claim 12 or 13 in which the methyl aryl ether is formed by the process of any one of claims to 11.

15. A process for forming a compound of formula (III) which comprises reducing the compound of formula (II) by reaction with a reducing agent.

16. A process as claimed in claim 14 in which the reducing agent is a metallic catalyst such as platinum or palladium or carbon.

17. A process as claimed in claim 15 in which the reduction is carried out by treatment with zinc and hydrochloric acid.

18. A process as claimed in claim 15 which comprises reducing the compound of formula (II) by reaction with hydrazine hydrate and potassium hydroxide in ethylene glycol.

19. A method of forming an imidazopyrazine which comprises reacting an α-ketoacetaldehyde with a compound of formula (III).

20. A process as claimed in claim 19 in which Ph is an unsubstituted phenyl group and the imidazopyrazine is coelenterazine.

21. Compounds of formula (I) made by the process of any one of claims 6 to 11.

22. Compounds of formula (II) herein made by the process of any one of claims 12 to 14.

23. A compound of formula (III) herein when made by the process of any one of claims 15 to 18.

24. Coelenterazine when made by the process of claim 20.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/01227

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D241/20 C07D409/04 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, vol. 63, no. 11, 1990, TOKYO JP, pages 3132-3140, XP002037163 K.TERANISHI,T.GOTO: "SYNTHESIS AND CHEMILUMINESCENCE OF COELENTERAZINE." see page 3132 - page 3138 -----	1,5

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 August 1997	26. 08. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Francois, J

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