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Palladium-Catalysed Cross-Coupling Reactions of Arylboronic Acids with π-Deficient Heteroaryl Chlorides+1

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Abstract:The palladium-catalysed cross-coupling reactions of arylboronic acids with a variety of π-deficient heteroaryl chlorides proceed in high yield. [1,4-Bis(diphenylphosphino)butane]palladium(II) dichloride was found to be a very satisfactory catalyst for monocyclic heteroaryl chlorides, whereas tetrakis(triphenylphosphine)palladium(O) was found to be excellent for a range of chloroquinoline derivatives.

We have been involved for some time in the development of efficient new methods for the preparation of aryl substituted heterocycles of medicinal interest. There are very few useful general procedures for the introduction of aryl substituents into heteroaromatic compounds, while methods based on ring synthesis can be seriously limited with respect to availability of necessary starting materials. During the last few years palladium-catalysed coupling reactions have been found to be extremely efficient and flexible for the synthesis of biaryls, and hence we have investigated this approach for the preparation of heterobiaryls from π-deficient heterocycles. A variety of organometallic species have been employed successfully for the synthesis of biaryls;[2] we decided on boron as the metal of choice since arylboronic acids are stable, isolable compounds which can be prepared readily,[3] and there are now many examples of their successful application to biaryl synthesis.[4] It was also hoped that their non-basic nature would offer the possibility of carrying out reactions on substrates bearing labile protons.

It is widely accepted that palladium-catalysed cross-coupling reactions of arylboronic acids, and indeed of other organometallic species, proceed best with aryl or heteroaryl bromides or iodides, and either poorly, or more commonly, not at all with the corresponding chlorides.[3c,3d,3f,5] Both chlorobenzene[5a] and 3-chloropyridine,[5d] for example, have been reported to fail to react with phenylboronic acid when tetrakis(triphenylphosphine)palladium(O), $Pd(PPh_3)_4$, was used as catalyst, and at the start of our study the only successful examples of cross-coupling with heteroaryl chlorides were due to Gronowitz *et al.*,[6] who reported that 2-chloropyrimidine underwent coupling in satisfactory yield with thienyl- and selenophenylboronic acids, while 2,4-dichloropyrimidines could be selectively coupled in 59% yield at the 4-position with 2-thienylboronic acid. In a more recent study, Thompson *et al.*[7] have described the high yield coupling of two tetrasubstituted chloropyrazines with phenylboronic acid and 3-furanylboronic acid. Gronowitz's results were encouraging, as we were particularly interested in the introduction of aryl substituents into π-deficient azines, and for this class of compounds the chloro derivatives are cheaper and considerably more accessible than the bromides and iodides. We considered that the perceived unreactivity of

+ Dedicated to Professor Charles W. Rees on the occasion of his 65th birthday

the chloroheterocycles, Gronowitz's results notwithstanding, might not prove to be too serious a problem, especially if a catalyst more "active" than the commonly used $Pd(PPh_3)_4$ were to be employed.[3d,3f,5] A wide range of palladium catalysts has been employed for biaryl synthesis but as yet there is no reliable or meaningful "activity" scale. Purely in practical terms, therefore, we restricted our investigation to two catalysts: $Pd(PPh_3)_4$, and [1,4-bis(diphenylphosphino)butane]palladium(II) dichloride, $Ph(dppb)Cl_2$.[8] The current uncertainty in terms of catalyst selection for this type of reaction is well illustrated with respect to $Pd(dppb)Cl_2$: in couplings of organometallics with halo compounds using a palladium catalyst where direct comparisons are available, $Pd(dppb)Cl_2$ has been reported to be a superior[2a,2b,9] and an inferior[10,11] catalyst when compared with $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$.

Reaction of phenylboronic acid with either chlorobenzene or 3-chloropyridine in the presence of $Pd(PPh_3)_4$ failed to produce any coupled product, these results thus confirming previous literature reports.[5a,5d] When $Pd(dppb)Cl_2$ was used as catalyst, however, chlorobenzene reacted to give 28% of biphenyl, while 3-chloropyridine was smoothly converted into 3-phenylpyridine in 71% yield. These two results appeared to indicate the greater effectiveness of $Pd(dppb)Cl_2$ in this type of cross-coupling, and hence we examined the reactions of a range of monocyclic heteroaryl chorides with arylboronic acids in the presence of this catalyst. The results are summarised in Table I; all yields refer to isolated products. Disappointingly, although a low yield of the required product was obtained with 2-chloro-3-hydroxypyridine (entry 6), two other attempted cross-couplings using substrates containing labile hydrogens were completely unsuccessful (entries 2,7). Apart from these results, however, yields were good to excellent. 2,5-Dichloropyridine underwent smooth, selective cross-coupling at the 2-position (entry 3),[12] and access to bipyridyls is illustrated in the clean reaction of the π-deficient 4-pyridylboronic acid with 2-chloro-3-nitropyridine (entry 5). The couplings with the chloropyrimidines (entries 8-10) and 2-chloropyrazine (entry 11) were straightforward, and the presence of an electron donating group on either the pyrimidine or the boronic acid did not adversely affect the reaction.

The results summarised in Table I show that $Pd(dppb)Cl_2$ is an efficient catalyst for these monocyclic chloroazine coupling reactions. In connection with other studies, we needed to establish whether the same reactivity held true for benzo-fused heteroaryl chlorides, in particular with respect to choice of catalyst, and therefore extended our investigations to a range of chloroquinoline derivatives. The results of these studies are summarised in Table II; yields refer to isolated materials and, unless noted otherwise, reactions were carried out with 3 mole% of catalyst for 48 hours.

3-Chloro-4-methylquinoline (entry 3) reacted very slowly with phenylboronic acid in the presence of $Pd(PPh_3)_4$, and only 10% of 4-methyl-3-phenylquinoline was obtained after 48 hours. When $Pd(dppb)Cl_2$ was used as catalyst the yield increased to 32% with benzene as solvent, and could be improved to 45% in toluene. With the exception of 3-chloro-4-methylquinoline, however, and in contrast to the results obtained with monocyclic chloroazines, all of the 2- and 4-chloroquinolines studied underwent smooth coupling with the arylboronic acids when the simple $Pd(PPh_3)_4$ was used as catalyst, and yields were generally excellent. The low yields observed with 4-chloro-3-nitroquinoline (entry 5) were due to competitive hydrolysis to the quinolone under the reaction conditions, a problem which could almost certainly be avoided by using non-aqueous conditions.[7] Coupling of 4-chloro-8-methyl-5-nitroquinoline with 4-bromophenylboronic acid (entry 12) gave only 40-45% of the heterobiaryl due to self-coupling of the organometallic reagent and coupling of the initially formed 4-(4-bromophenyl)-8-methoxy-5-nitroquinoline with further phenylboronic acid. As expected, smooth selective cross-coupling in excellent yield was observed with 4,7- and 4,8-dichloroquinoline (entries 6 and 7). The majority of the transformations listed in Table II required approximately 48 hours for completion, but in two instances (entries 9,13) a significant rate increase was observed and the reactions were complete within 14 hours. In 4-chloro-8-methoxy-6-nitroquinoline (entry 13) there is mesomeric interaction between the nitro group and the 4-position of the quinoline ring which, in principle, could explain the increased lability of the 4-chloro substituent. No similar electronic interaction is possible with 4-chloro-8-methoxy-5-nitroquinoline (entry 9), which also reacts rapidly, even though there must be some steric hindrance to introduction of the 4-phenyl substituent. 4-Chloro-8-methoxy-7-nitroquinoline (entry 14), where there is neither a formal mesomeric interaction between the nitro group and the 4-position nor any great steric hindrance to phenylation, reacted considerably more slowly than the 5- or 6-nitro-

Table I. $Pd(dppb)Cl_2$ - Catalysed Coupling of Arylboronic Acids with Monocyclic Heteroaryl Chlorides

$ArB(OH)_2$ + Het Cl $\xrightarrow{Pd(dppb)Cl_2}$ ArHet

1 **2** **3**

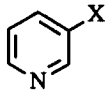
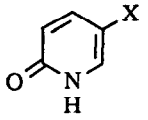
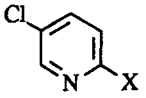
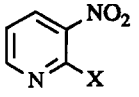
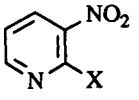
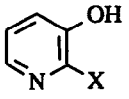
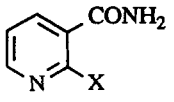
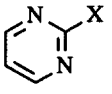
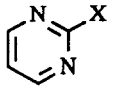
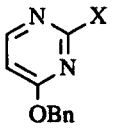
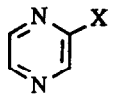
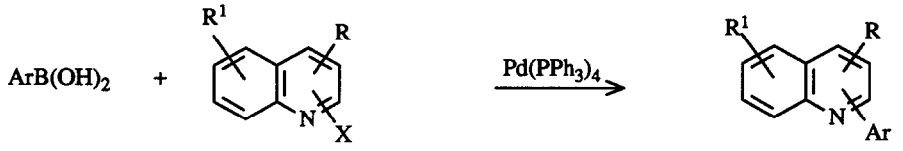
Entry	**1** and **3**, Ar=	**2**, X=Cl; **3**, X=Ar	Yield,%
1	C_6H_5		71
2	C_6H_5		0
3	C_6H_5		83
4	C_6H_5		73
5	4-Pyridyl		75
6	C_6H_5		15
7	C_6H_5		0
8	C_6H_5		65
9	2-$PrOC_6H_4$		98
10	2-$PrOC_6H_4$		66
11	C_6H_5		78

Table II. $Pd(PPh_3)_4$ - Catalysed Coupling of Arylboronic Acids with Chloroquinolines



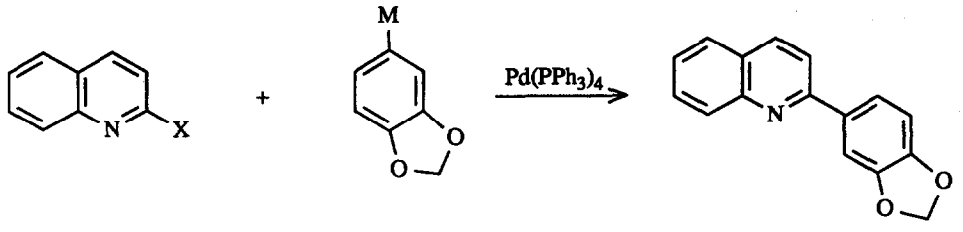
1 **4** **5**

Entry	**4**, X=Cl	**1** and **5**, Ar=	Yield, %
1	2-X; R=R'=H	C_6H_5	96
2	2-X; R=4-Me, R'=H	C_6H_5	92
3	3-X; R=4-Me, R'=H	C_6H_5	32,[a] 45[b]
4	4-X; R=R'=H	C_6H_5	92
5	4-X; R=3-NO_2, R'=H	C_6H_5	17, 35[c]
6	4-X; R=H, R'=7-Cl	C_6H_5	82
7	4-X; R=H; R'=8-Cl	C_6H_5	93
8	4-X; R=H, R'=OMe	C_6H_5	76
9	4-X; R=H, R'=5-NO_2, 8-OMe	C_6H_5	96[d]
10	4-X; R=H, R'=5-NO_2, 8-OMe	4-$MeOC_6H_4$	76
11	4-X; R=H, R'=5-NO_2, 8-OMe	3,4-$(MeO)_2C_6H_3$	95
12	4-X; R=H, R'=5-NO_2, 8-OMe	4-BrC_6H_4	40-45[e]
13	4-X; R=H, R'=6-NO_2, 8-OMe	C_6H_5	97[d]
14	4-X; R=H, R'=7-NO_2, 8-OMe	C_6H_5	84

[a] $Pd(dppb)Cl_2$ used as catalyst, benzene as solvent. [b] $Pd(dppb)Cl_2$ as catalyst, toluene as solvent. [c] Amount of catalyst increased from 3 to 5 mole% [d] 14 h reflux [e] Based on nmr.

isomers. These qualitative observations suggest that, like other palladium-catalysed reactions, the heterobiaryl couplings can be very sensitive to subtle electronic effects.

The above results clearly establish that the palladium-catalysed cross-coupling of arylboronic acids with a range of π-deficient heteroaryl chlorides is an excellent method for heterobiaryl synthesis, and there should be few, if any, instances where recourse to the less readily accessible bromides or iodides is necessary. The experimental procedure is simple, conditions are mild, isolation of pure products in high yield is straighforward, and it is not necessary to use a complex palladium catalyst. These features of the reaction are illustrated in the highly efficient synthesis of the simple alkaloid dubamine 8 by coupling of the commercially available 2-chloroquinoline 6a with 3,4-methylenedioxyphenylboronic acid 7a, which compares favourably with the recently described related synthesis using the triflate 6b and the arylstannane 7b.[13]



6 7 8

[a] X=Cl, M=$B(OH)_2$, 48h, 97%

[b] X=OTf, M=$SnMe_3$, 68h, 79%

Experimental

Starting materials:

(a) *Chlorazines*: Table I: All of the chloroazines in Table I were commercially available except 4-benzyloxy-2-chloropyrimidine, which was prepared in 53% yield by reaction of 2,4-dichloropyrimidine with benzyl alcohol and potassium hydroxide in the presence of 18-crown-6 at 20°C for 1 h. The pure product, m.p. 80-82°C, was obtained free of the isomeric 2-benzyloxy-4-chloropyrimidine by chromatography on silica using dichloromethane/petroleum ether (bp 60-80°C) as eluent.

(b) *Chloroquinolines*: Table II: 2-Chloroquinoline (entry 1), 2-chloro-4-methylquinoline (entry 2), 4-chloroquinoline (entry 4), and 4,7-dichloroquinoline (entry 6) were commercially available. 3-Chloro-4-methylquinoline[15] (entry 3) and 4-chloro-3-nitroquinoline[16] (entry 5) were prepared as described. 4,8-Dichloroquinoline[17] (entry 7), 4-chloro-8-methoxyquinoline[18] (entry 8) and 4-chloro-8-methoxy-6-nitroquinoline[19] (entry 13) have been prepared previously, but the literature syntheses were not used in the present study. Instead, 2-chloro-, 2-methoxy- and 2-methoxy-4-nitroaniline were smoothly converted into 8-chloro-, 8-methoxy- and 8-methoxy-6-nitro-4-quinolone respectively using the Meldrum's acid synthesis, [20] and the 4-quinolones then converted into the 4-chloroquinolines with phosphorus oxychloride.[21]

4-Chloro-8-methoxy-5-nitroquinoline (entries 9-12) and **4-chloro-8-methoxy-7-nitroquinoline** (entry 14): A solution of 4-chloro-8-methoxyquinoline (24.1 g, 0.125 mol; prepared as described above) in conc H_2SO_4 was cooled to 0°C and treated with 70% HNO_3 (13.5 g, 0.15 mol). The reaction mixture was stirred at room temperature for 4 h then poured on to ice (500-600 g) and the resulting mixture neutralised with 10% NaOH solution. The yellow solid which separated was collected by filtration, washed with water and dried to give 27.7 g of crude product. Crystallisation from ethyl acetate gave the pure 5-nitro isomer in 72-75% yield. Removal of the solvent from the filtrate from the crystallisation by evaporation under reduced pressure followed by column chromatography on silica gel (Merck 7734) using CH_2Cl_2/EtOAc (1:1) as eluent gave the pure 7-nitro isomer in 5% yield together with a further crop of 5-nitro isomer. The total yield of 5-nitro isomer was 82-86%.

4-Chloro-8-methoxy-5-nitroquinoline: mp 189-191 °C. ^{1}H nmr (60 MHz, $CDCl_3$): δ 8.81 (d, J = 4.8 Hz, 1H); 7.81 (d, J = 7.2 Hz, 1H); 7.61 (d, J = 4.8 Hz, 1H); 6.96 (d, J = 7.2 Hz, 1H); 4.1 (s, 3 H). ^{13}C nmr (22.5 MHz, $CDCl_3$): 152.28, 149.59, 140.96, 139.49, 125.64, 125.22, 119.70, 105.31, 78.31. m/z = 238, 192 (100). Anal C,H,N <0.06 for $C_{10}H_7ClN_2O_3$.

4-Chloro-8-methoxy-7-nitroquinoline: mp 142-144°C. ^{1}H nmr (90 MHz, $CDCl_3$): δ 8.91 (d, J = 4.64 Hz, 1H); 8.06 (d, J = 9.28 Hz, 1H); 7.90 (d, J = 9.28 Hz, 1H); 7.65 (d, J = 4.64 Hz, 1H); 4.36 (s, 3H). ^{13}C nmr (22.5 MHz, $CDCl_3$): 150.75, 150.54, 144.43, 143.26, 129.78, 123.60, 122.14, 119.72, 64.50. m/z 240, 238, 208 (100). Anal C,H,N < 0.33 for $C_{10}H_7Cl$, N_2O_3

(c) *Arylboronic acids*: Phenyl-, 4-bromophenyl- and 4-methoxyphenylboronic acid were commercially available. 3,4-Dimethoxyphenyl-[22,23] and 3,4-methylenedioxyphenylboronic acid,[22,23] and 4-pyridylboronic acid[24] were prepared as described.

2-n-Propoxyphenylboronic acid: An ether solution of the Grignard reagent derived from 2-bromo-n-propoxybenzene (0.175 mol) was added to a solution of tri-n-butylborate (40.5 g, 0.18 mol) in ether (150 ml), the temperature being kept below -70°C. On completion of the addition, the mixture was allowed to warm to 0°C, then left to stand at this temperature for 24 h. It was then added to cold (0°C) 10% aqueous sulphuric acid solution (120 ml). The layers were separated, the aqueous solution was extracted with ether (3 x 25 ml), and the combined organic fractions were evaporated under reduced pressure. Water was then added, the mixture was basified to pH 11 with dilute aqueous NaOH solution, and the resulting mixture was evaporated under reduced pressure to remove residual n-butanol. The residue was dissolved in water and the solution acidified with sulphuric acid to give the crude boronic acid. Crystallisation of the crude material from water gave 17.7 g (56%) of purified 2-n-propoxyphenylboronic acid. ^{1}H nmr (270 MHz d_6-DMSO): δ 7.62 (2H, s, $B(OH)_2$); 7.60 (1H, d, J = 7 Hz, arom H-6); 7.36 (1H, t, J = 7 Hz, arom H-4); 6.94 (2H, q, J = 7 Hz, arom H-3, H-5); 4.01 (2H, t, J = 6 Hz, OCH_2); 1.60 (2H, sextet, J = 6 Hz, CH_2CH_3); 1.00 (3H, t, J = 6 Hz, CH_3). m/z: 180 (M^+, 80%), 138 ($M^+ - C_3H_6$, 55%), 120 ($M^+ - C_3H_6$-H_2O, 100%).

(d) *Catalysts*: $Pd(PPh_3)_4$ was commercially available. $Pd(dppb)Cl_2$ was prepared as described.[8]

General procedure for coupling of monocyclic chloroazines (Table I, entries 1,3,4,6,8-11): A mixture of the chloroazine (2 mmol), the arylboronic acid (2.6 mmol) and $Pd(dppb)Cl_2$ (60 mg, 0.1 mmol) in toluene (4 ml), aqueous 1 m sodium carbonate solution (2 ml) and ethanol (1 ml) was heated under reflux for 24 h. The reaction mixture was then cooled, water (5 ml) was added, and the toluene layer was separated. The aqueous layer was extracted with ethyl acetate (2 x 10 ml) and the combined organic extracts were dried ($MgSO_4$), filtered, and the filtrate evaporated to dryness under reduced pressure. The crude product thus obtained was purified by column chromatography on silica gel using ethyl acetate/petroleum ether (bp 60-80°C) as eluent.

3-Nitro-2-(4-pyridyl)pyridine (Table I, entry 5): A mixture of 4-pyridylboronic acid (135 mg, 1.1 mol), 2-chloro-3-nitropyridine (160 mg, 1.0 mmol), $Pd(dppb)Cl_2$ (30 mg, 0.05 mmol) and sodium bicarbonate (240 mg, 3 mmol) in dimethoxyethane (3 ml) and water (1 ml) was heated under reflux for 4 h. The mixture was then cooled, diluted with ethyl acetate and water, and the organic layer separated. The aqueous layer was extracted with ethyl acetate (2 x 10 ml) and the combined organic layers were dried ($MgSO_4$), filtered, and the filtrate evaporated under reduced pressure. Column chromatography of the residue on silica gel using ethyl acetate as eluent gave 150 mg (75%) of pure product.

General procedure for coupling of chloroquinolines (Table II): A mixture of the chloroquinoline (1.7 mmol), the arylboronic acid (1.87 mmol) and $Pd(PPh_3)_4$ (0.058 g, 0.051 mmol) in benzene (4.2 ml), ethanol (0.57 ml) and 2 M aqueous sodium carbonate solution (1.89 ml) was stirred and heated under reflux under nitrogen for 48 h. It was then cooled, transferred to a separating funnel, and the reaction flask washed out with water (3 x 20 ml) and dichloromethane (3 x 50 ml), the washings being added to the separating funnel. The organic layer was separated and the aqueous phase extracted with dichloromethane (2 x 100 ml). The combined organic extracts were then washed with water (3 x 50 ml), dried ($MgSO_4$), filtered and the filtrate evaporated under reduced pressure. Column chromatography of the residue on silica gel using diethyl ether/petroleum ether (bp 40-60°C) as eluent gave the pure product.

In reactions with 3,4-dimethoxyphenyl- and 3,4-methylenedioxyphenylboronic acids a 30% excess of the boronic acid was used. For the synthesis of dubamine **8**, 5 mol % $Pd(PPh_3)_4$ was used. In all reactions with $Pd(dppb)Cl_2$ as catalyst, 5 mol% was used.

Products:

A. Monocyclic Arylazines (Table I)

3-Phenylpyridine (entry 1): Colourless oil. ^1H NMR: δ 8.87 (1 H, t, J = 1 Hz, py-H 2), 8.60 (1 H, dd, J = 1.3 Hz, py-H 6), 7.89 (1 H, dt, J = 6.1 Hz, py-H 4), 7.3-7.6 (6 H, m, py-H 5 and 5xPh). Accurate mass: found 155.0735, $C_{11}H_9N$ requires 155.0735.

5-Chloro-2-phenylpyridine (entry 3): mp 54-56°C. ^1H NMR: δ 8.66 (1 H, d, J = 1 Hz, py-H 6), 7.95 (2 H, m, py-H 3,4), 7.71 (2 H, m, Ph-H 2,6), 7.49 (3 H, m, Ph-H 3-5). Accurate mass: found 189.0366, $C_{11}H_8{}^{35}ClN$ requires 189.0345 m/z: 189 (M^+, 100), 154 (50). Anal C, H, N < 0.40 for $C_{11}H_8ClN$

3-Nitro-2-phenylpyridine (entry 4): Yellow oil. ^1H NMR: δ 8.87 (1 H, dd, J = 1.4 Hz, py-H 6), 8.17 (1 H, dd, J = 1.5 Hz, py-H 4), 7.4-7.6 (6 H, m, py-H 5 and 5xPh). Accurate mass: found 200.0591, $C_{11}H_8N_2O_2$ requires 200.0585. m/z: 200 (M^+, 50), 155 (100).

3-Nitro-2-(4-pyridyl)pyridine (entry 5): mp 115-116°C, ^1H NMR: δ 8.91 (1 H, d, J = 3 Hz, py_1-H 6), 8.75 (2 H, d, J = 4 Hz, py_2-H_2,6), 8.29 (1 H, d, J = 4 Hz, py_1-H 4), 7.58 (1 H, dd, J = 3.4 Hz, py_1-H 5), 7.46 (2 H, d, J = 4 Hz, py_2-H 3,5). m/z: 201 (M^+, 20), 173 (40), 171 (40), 155 (20), 128 (35). Anal C, H, N < 0.11 for $C_{10}H_7N_3O_2$.

3-Hydroxy-2-phenylpyridine (entry 6): Semi-solid. ^1H NMR: δ 8.20 (1 H, d, J = 3 Hz, py-H 6), 7.74 (2 H, d, J = 6 Hz, Ph-H 2,6), 7.45 (3 H, m, Ph-H 3-5), 7.15 (2 H, m, py-H 4,5).

2-Phenylpyrimidine (entry 8): mp 37-38°C, Lit[25] mp 39°C.

2-(2-Propoxyphenyl)pyrimidine (entry 9): Colourless oil. ^1H NMR: δ 8.82 (2 H, d, J = 4Hz, pm-H 4,6), 7.68 (1 H, dd, J = 1.6 Hz, Ph-H 6), 7.38 (1 H, dt, J = 1.6 Hz, Ph-H 4), 7.17 (1 H, t, J = 4 Hz, pm-H 5), 7.05 (2 H, m, Ph-H 3,5), 3.97 (2 H, t, J = 5 Hz, OCH_2), 1.72 (2 H, sextet, J = 5 Hz, CH_2CH_3), 0.92 (2 H, t, J = 5 Hz, CH_3). Accurate mass: found 214.1112, $C_{13}H_{14}N_2O$ requires 214.1106. m/z: 214 (M^+, 80), 199 (25), 185 (100), 172 (50), 156 (7).

4-Benzyloxy-2-(2-propoxyphenyl)pyrimidine (entry 10): Colourless oil ^1H NMR: δ 8.53 (1 H, d, J = 5 Hz, pm-H 6), 7.74 (1 H, dd, J = 4, 1 Hz, Ar-H 6), 7.3-7.5 (6 H, m, Ph-H 2-6 and Ar-H 4), 7.02 (2 H, m, Ar-H 3,5), 6.68 (1 H, d, J = 5 Hz, pm-H 4), 5.49 (2 H, s, CH_2Ph), 3.98 (2 H, t, J = 5 Hz, OCH_2) 1.74 (2 H, sextet, J = 5 Hz, CH_2CH_3), 0.96 (3 H, t, J = 5 Hz, CH_3). Accurate mass: found 320.1517, $C_{20}H_{20}N_2O_2$ requires 320.1525. m/z: 320 (M^+, 2), 291 (20), 261 (55), 91 (100).

2-(2-Propoxyphenyl)pyrazine (entry 11): mp 69-70°C, Lit[26] mp 70-70.5°C.

B. Arylquinolines (Table II)

2-Phenylquinoline (entry 1): mp 80-83°C, Lit[27] mp 86°C.

4-Methyl-2-phenylquinoline (entry 2): Colourless oil, Lit[28] bp 161-164°C/ 1.3 mm Hg. Anal C, H, N < 0.24 for $C_{16}H_{13}N$.

4-Methyl-3-phenylquinoline (entry 3): mp 58-61°C. ^{1}H NMR (400 MHz): δ 8.81 (1 H, s), 8.15 (1 H, d, J = 8.42 Hz), 8.06 (1 H, d, J, 8.42 Hz), 7.71 (1 H, t, J, 8.42, 6.96 Hz), 7.59 (1 H, t, J, = 8.06, 7.32 Hz), 7.48 (2 H, t, J, = 6.6, 7.69 Hz), 7.43 - 7.37 (3 H, m), 2.71 (3 H, s). m/z: 219 (M^+, 100). Anal C, H, N < 0.10 for $C_{16}H_{13}N$.

4-Phenylquinoline (entry 4): mp 60.5-61.6°C, Lit[29] mp 61-62°C.

3-Nitro-4-phenylquinoline (entry 5): mp 107.5-109.5°C, Lit[30] mp 109-110°C.

7-Chloro-4-phenylquinoline (entry 6): m.p. 73.3-74.5°C. ^{1}H NMR: δ 8.84 (1 H, d, J = 4.8 Hz), 8.12 (1 H, d, J = 2.4 Hz), 7.78 (1 H, d, J = 9.6 Hz), 7.40 (5 H, s), 7.30 (1 H, d, J = 9.6 Hz), 7.20 (1 H, d, J = 4.8 Hz), ^{13}C NMR: δ 150.87, 149.11, 148.36, 137.39, 135.12, 129.36, 128.73, 128.61, 127.45, 127.21, 125.09, 121.36. m/z: 238.8 (M^+, 100). Anal C, H, N < 0.23 for $C_{15}H_{10}ClN$.

8-Chloro-4-phenylquinoline (entry 7): mp 74-77°C. ^{1}H NMR: δ 9.06 (1 H, d, J = 4.8 Hz), 7.32 - 7.88 (9 H, m). Anal C, H N < 0.05 for $C_{15}H_{10}ClN$.

8-Methoxy-4-phenylquinoline (entry 8): mp 112-114°C. ^{1}H NMR: δ 8.94 (1 H, d, J = 4.8 Hz), 7.0-7.6 (9 H, m), 4.05 (3 H, s). ^{13}C NMR: δ 155.57, 148.65, 148.35, 140.60, 138.26, 129.45, 128.45, 128.28, 127.81, 126.51, 121.93, 117.59, 107.32, 56.06. m/z: 235 (M^+), 91 (100). Anal C, H, N < 0.37 for $C_{16}H_{13}NO$.

8-Methoxy-5-nitro-4-phenylquinoline (entry 9): mp 138-141°C, ^{1}H NMR: δ 8.97 (1 H, d, J = 4.8 Hz), 7.92 (1 H, d, J = 7.2 Hz), 7.56 (1 H, d, J = 4.8 Hz), 7.36 (5 H, s), 7.04 (1 H, d, J = 7.2 Hz), 4.2 (3 H, s). ^{13}C NMR δ 159.15, 149.65, 141.14, 140.72, 138.96, 126.98, 128.69, 125.99, 120.17, 105.09, 56.83. m/z: 280 (M^+), 55 (100). Anal C, H, N < 0.21 for $C_{16}H_{12}N_2O_3$.

8-Methoxy-4-(4-methoxyphenyl)-5-nitroquinoline (entry 10): mp 166-167°C. ^{1}H NMR (400 MHz): δ 9.01 (1 H, d, J = 4.4 Hz), 8.00 (1 H, d, J = 8.79 Hz), 7.52 (1 H, d, J = 4.39 Hz), 7.28 (2 H, d, J = 8.79 Hz), 7.04 (1 H, d, J = 8.43 Hz), 6.96 (2 H, d, J = 8.79 Hz), 4.20 (3 H, s), 3.84 (3 H, s). ^{13}C NMR: 160.09, 159.19, 149.68, 146.54, 141.44, 140.94, 131.66, 128.35, 125.84, 120.41, 114.23, 105.04, 56.83, 55.22. m/z: 310.1 (M^+, 68), 264.1(100). Anal C, H, N<0.14 for $C_{17}H_{14}N_2O_4$.

4-(3,4-Dimethoxyphenyl)-8-methoxy-5-nitroquinoline (entry 11): mp 235-238°C. ^{1}H NMR (400 M Hz): δ 9.02 (1 H, d, J = 4.39 Hz), 8.01 (1 H, d, J = 8.79 Hz), 7.56 (1 H, d, 4.4 Hz), 7.05 (1 H, d, J = 8.3 Hz), 6.93 (2 H, weakly resolved doublet), 6.85 (1 H, s), 4.21 (3 H, s), 3.93 (3 H, s), 3.89 (3 H, s). m/z: 340 (M^+, 11), 276.9 (100). Anal C, H, N < 0.28 for $C_{18}H_{16}N_2O_5$.

8-Methoxy-6-nitro-4-phenylquinoline (entry 13): mp 236-239°C. ^{1}H NMR: δ 9.14 (1 H, d, J = 4.8 Hz), 8.48 (1 H, d, J = 2.4 Hz), 7.86 (1 H, d, J = 2.4 Hz), 7.58 (6 H, s), 4.24 (3 H, s). ^{13}C NMR: δ 156.72, 151.86, 150.84, 145.98, 142.93, 136.73, 129.45, 129.27, 129.03, 126.47, 123.54, 114.62, 101.20, 56.80. m/z: 279.9 (M^+, 100). Anal C, H, N < 0.30 for $C_{16}H_{12}N_2O_3$.

8-Methoxy-7-nitro-4-phenylquinoline (entry 14): mp 149-151.5°C. ^{1}H NMR: δ 9.08 (1 H, d, J = 4.39 Hz), 7.79 (1 H, d, J = 9.16 Hz), 7.72 (1 H, d, J = 9.16 Hz), 7.46-7.56 (6 H, m), 4.39 (3 H, s). ^{13}C NMR: δ 150.72, 150.60, 149.11, 143.80, 142.33, 136.88, 130.16, 129.34, 128.97, 128.81, 123.53, 121.56, 120.80, 64.13. m/z: 280 (M^+, 5), 250 (100). Anal C, H, N < 0.26 for $C_{16}H_{12}N_2O_3$.

Dubamine: mp 95-96°C, Lit[31] mp 94-95°C. Anal C, H, N < 0.20 for $C_{16}H_{11}NO_2$.

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