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# Efficient palladium-catalyzed direct arylation of azines and diazines using ligand-free conditions

Luca Basolo [a], Egle M. Beccalli [a,*], Elena Borsini [b], Gianluigi Broggini [b]

[a] Istituto di Chimica Organica 'A. Marchesini', Facoltà di Farmacia, Università di Milano, via Venezian 21, 20133 Milano, Italy
[b] Dipartimento di Scienze Chimiche e Ambientali, Università dell'Insubria, via Valleggio 11, 22100 Como, Italy

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ABSTRACT

The use of the palladium-catalyzed direct arylation was successfully tested on different electron-deficient heterocycles. The results demonstrate the effectiveness of the method based on the intramolecular coupling reaction providing polyazacyclic systems. This new application was obtained by using ligand-free conditions with the mixture of $Pd(OAc)_2$ and TBAC as catalytic system. With suitable substrates different products arising from regioselective coupling were observed.



## 1. Introduction

Transition-metal mediated reactions are the most developed method for the construction of aryl–aryl bonds. Among these cross-coupling reactions are one of the most important tools. Recently palladium-catalyzed direct arylation reactions have emerged as attractive alternative to the mentioned methods,[1] meaning with this term the direct coupling of a non-activated aryl C–H bond with an activated arene. The advantages of these reactions are that simplified and readily available starting materials may be used through the substitution of one of the functionalized arenes, normally the organometallic coupling partner, with a simple arene, with an economical and practical advantage. Moreover the intramolecular version of the arylation reaction represents a very short synthetic sequence to generate heterocycles of significant molecular complexity as the poly(hetero)cyclic systems.

Besides the bi(hetero)aryl structural motif is a predominant feature in many pharmaceutically relevant and biologically active compounds. Some examples from recent literature are showed in Figure 1.[2]

Our previous contribution in this area concerned the intramolecular direct arylations of electron-rich heterocycles bearing both electron-withdrawing and electron-donor substituents in the presence of a Pd(0)-catalyst, under different conditions (ligand or ligand-free conditions).[3] This process provides a straightforward method to generate aza-substituted ring fused to (hetero)arenes.

In contrast to the numbers of papers reporting the utilization of electron-rich heterocycles in the direct arylation process,[4] both as intra- and intermolecular reactions, the direct arylation of simple aromatic rings remains a significant challenge[5] and even more the use of electron-poor heterocycles, such as azines and diazines is rare.[6,7] In these cases the few reported results gave five- or six-membered ring formation, in very low yields and following harsh reaction conditions.[6] Recently Fagnou and co-workers reported the intermolecular arylations of azines and diazines exploiting the transformation of these substrates on the more electron-rich azine- and diazine *N*-oxides.[7]

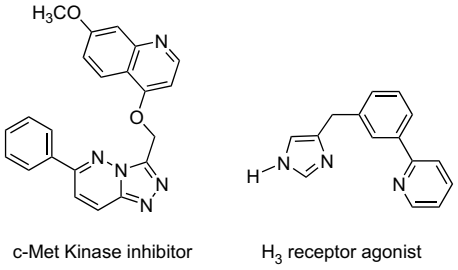


**Figure 1.**

In the present paper we report our studies on the direct arylation reactions of electron-poor heterocycles as azines and diazines. We feel that the results are noteworthy due to the literature data highlighting the poor reactivity of non-activated arenes.[8]

## 2. Results and discussion

Starting from nicotinic acids **1a**,**b** and 3-quinolinecarboxylic acid **1c**, the reaction with the 2-iodoaniline **2** followed by methylation on the amides **3a**–**c**, gave the corresponding tertiary amides **4a**–**c** as suitable substrates for the direct arylation reaction (Scheme 1). The

* Corresponding author. Tel.: +39 02 50314479; fax: +39 02 50314476.
*E-mail address:* egle.beccalli@unimi.it (E.M. Beccalli).

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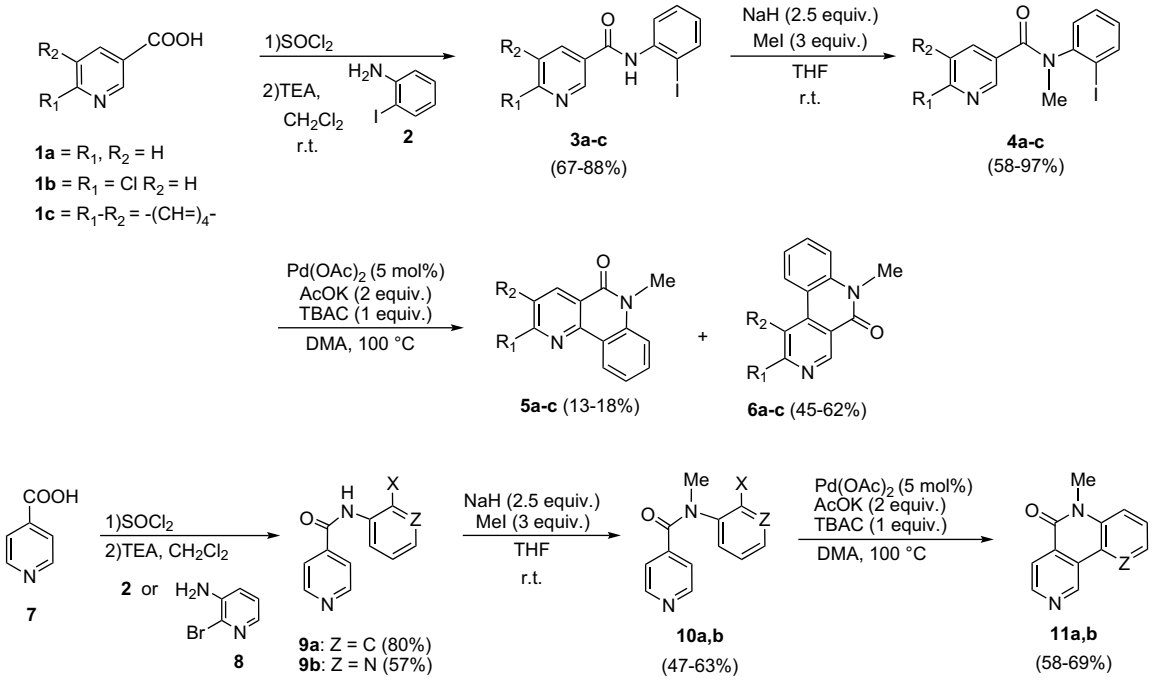



**Scheme 1.**

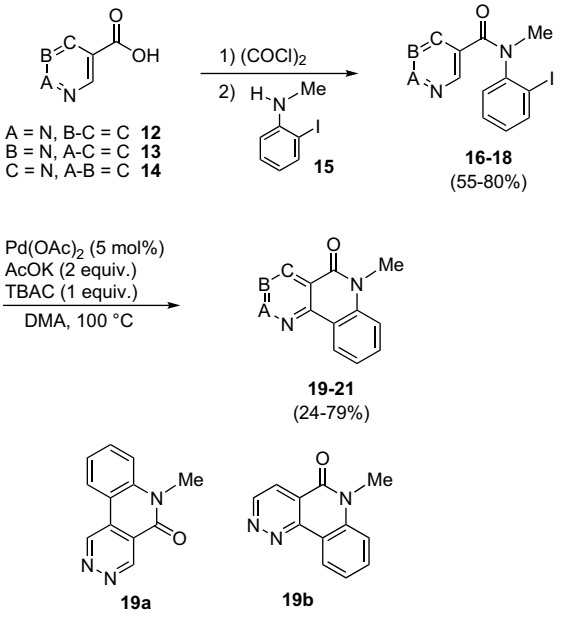
intramolecular process, obtained using $Pd(OAc)_2$ as precatalyst, AcOK as base, TBAC as additive and DMA as solvent, afforded two regioisomers **5a**–**c** and **6a**–**c** arising from the cyclization on position 2 or 4 of the pyridyl ring, in 1:3 ratio in favour of the *para* position.[9] Similarly the reaction of the isonicotinic acid **7** with 2-iodoaniline **2** or 2-bromo-3-aminopyridine **8** and subsequent methylation of **9a**,**b** afforded the amide **10a**,**b**, which cyclization gave the tricyclic systems **11a**,**b**. Usually direct arylation for rings of low reactivity necessitates the use of electron-rich and sterically hindered triethylphosphines,[10] however it should be noted that compared to the procedure exploited previously, ligand-free conditions (Jeffery's conditions) have been successfully used. On the contrary, optimizing the reaction conditions, we discovered that the presence of the base and polar solvent is required to obtain the products. In fact the absence of AcOK or solvent different than DMA or DMF, resulted in unreacted substrate. The addition of TBAC improves the yields. While temperatures higher than 100 °C are used for similar reactions and in most cases heating for several hours to days is necessary, the use of microwaves allowed considerably shortening of the reaction time (45 min).

To probe the feasibility of the arylation reactions on electron-poor heterocycles, we considered other substrates as the amides arising from the 1,2-, 1,3- and 1,4-diazines carboxylic acids **12**–**14**. In these cases, the amides **16**–**18** were obtained by reaction with 2-iodo-*N*-methylaniline **15** on the unisolated acyl chloride. In fact the methylation step carried out on the secondary amide must be avoided giving methylation also on the heterocyclic nitrogen atom. The cyclized products **19**–**21** were formed in one step from the corresponding amides. In the case of amide **16**, the cyclization reaction gave two regioisomers **19a**,**b** in 1:1 ratio, corresponding to the cyclization product, respectively, on position 3 and 5 of the pyridazyl ring, showing any selectivity in coupling reaction (Scheme 2).

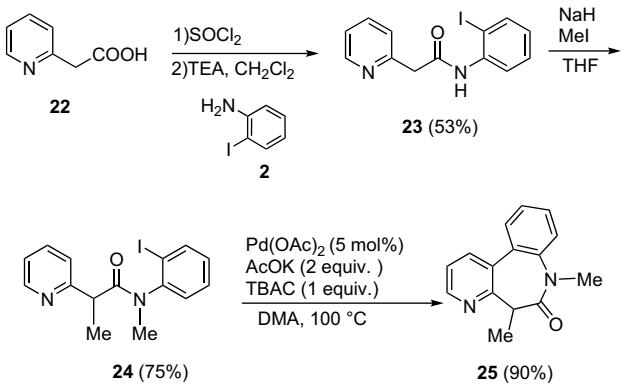
The choice to prepare specific polycyclic systems comes from the pharmacological properties recently reported for benzonaphthyridines **5**, **6** and **11** and pyrimidoquinolines **20**, ranging from antimalarial and antibacterial activities[11] to properties as topoisomerase inhibitor and antitumor agents.[12] To consider the possible influence of the ring size on the cyclization process and with the aim to obtain more challenging seven-membered rings, we focused our attention on the homologous of pyridine carboxylic acid, the pyridin-2-yl acetic acid **22** from which the corresponding amide was prepared via unisolable acyl chloride in the presence of triethylamine. The methylation step necessary to avoid the nitrogen coordination to palladium, gave in this case double methylation, involving benzylic carbon.

The tertiary amide **24** was then treated according to the reported conditions, to give the cyclized product **25** in good yield as shown in Scheme 3.

The results obtained in terms of satisfactory yields for all the cyclization processes allow us to comment on the mechanism involved into the coupling reaction.




**Scheme 2.**




**Scheme 3.**

Several pathways have been proposed for the palladium-catalyzed arylation of aromatic compounds, the process depending on the (hetero)aromatic substrate, base, ligand and solvent used. The involvement of an electrophilic aromatic substitution ($S_EAr$) was commonly accepted for π-electron-rich substrates,[1b,4e,h] while other mechanisms such as Heck-type process,[4k] or proton-abstraction[13] could be envisaged for different substrates. In all the proposed mechanisms, the first step generally occurs via oxidative addition of the aryl halide to the transition metal to give the intermediate **A**, followed by different possible carbon–carbon bond formation paths (Fig. 2). The electrophilic aromatic substitution ($S_EAr$) suggested for electron-rich heterocyclic substrates, through the intermediate **B** gave the palladacycle structure **D**, which in turn gives the cyclized product via reductive elimination with the contemporary Pd(0) catalyst regeneration. This hypothesis is not applicable in the case of electron-deficient heterocyclic nucleus. Recent work indicated that Heck-type process is rather unlikely,[14] and the literature data showed as a more probable mechanism the concerted proton-abstraction path (by the halogen anion or by an external base) operating via a four-membered transition state as showed for the intermediate **C**.[13] Support for the latter mechanism was proven through the comparison of two different arenes and the observation that the more electron-deficient substrate reacted preferentially.[15] This outcome is inconsistent with an $S_EAr$ mechanism.

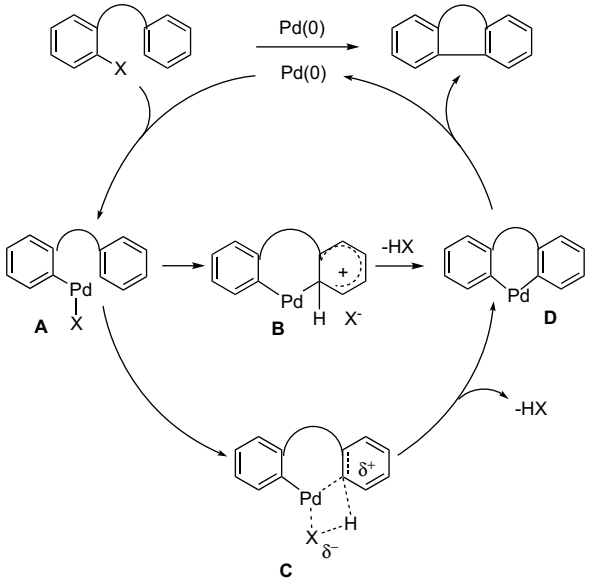



**Figure 2.**

## 3. Conclusion

The study has identified a practical and efficient direct arylation reaction of electron-poor heterocycles using ligand-free conditions, providing a straightforward synthesis of azapolycyclic systems. Compared to other metal-catalyzed reactions the method offers the advantage of simplified starting materials performing the synthesis in only two steps, using ligand-free conditions, with an economical benefit. Further research to extend these coupling reactions to intermolecular processes is currently underway.

## 4. Experimental

### 4.1. General

Melting points were determined on a Büchi B-540 heating apparatus and are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were obtained on an AVANCE Bruker 400 MHz in $CDCl_3$ as solvent. Chemical shifts are given in parts per million downfield from $SiMe_4$. $^{13}$C NMR spectra are $^1$H-decoupled and the determination of the multiplicities was achieved by the APT pulse sequence. IR spectra were recorded on a Jasco FT/IR 5300 spectrophotometer.

### 4.2. General procedure for the synthesis of the heteroamides 3a–c, 9a,b and 23

A mixture of acids **1a–c**, **7** or **22** (10 mmol) and $SOCl_2$ (10 mL, 137 mmol) was stirred at 100 °C for 2.5 h. After evaporation of the solvent, the residue was dissolved with $CH_2Cl_2$ (20 mL). A solution of **2** or **8** (15 mmol) and TEA (2.1 mL, 15 mmol) in $CH_2Cl_2$ (5 mL) was added dropwise at 0 °C. After stirring for 5 h at room temperature, the solution was washed with 5% HCl (2×20 mL) and then with 5% aqueous NaOH (2×20 mL). The organic layer was dried ($Na_2SO_4$) and the solvent evaporated under reduced pressure. The residue was chromatographed on a silica gel column, using $CH_2Cl_2$as eluent, to give compounds **3**, **9** and **23**.

#### *4.2.1. N-(2-Iodophenyl)-pyridine-3-carboxamide (**3a**)*

White solid, mp 134–136 °C; yield 67%. IR (Nujol): 3300, 1631 cm$^{-1}$. $^1$H NMR: δ 6.92 (1H, dd, *J*=5.0, 7.5 Hz), 7.41 (1H, dd, *J*=7.5, 7.8 Hz), 7.48 (1H, dd, *J*=5.0, 7.5 Hz), 7.83 (1H, d, *J*=7.8 Hz), 8.27–8.30 (1H, m), 8.32 (1H, br s, exch. $D_2O$), 8.33–8.39 (1H, m), 8.80 (1H, d, *J*=5.0 Hz), 9.22 (1H, s). $^{13}$C NMR: δ 91.1 (s), 122.6 (d), 124.1 (d), 127.0 (d), 129.8 (d), 130.6 (s), 135.6 (d), 138.1 (s), 139.3 (d), 148.5 (d), 153.2 (d), 163.8 (s). Anal. Calcd for $C_{12}H_9IN_2O$ (324.12): C, 44.47; H, 2.80; N, 8.64. Found: C, 44.34; H, 2.79; N, 8.80.

#### *4.2.2. N-(2-Iodophenyl)-6-chloro-pyridine-3-carboxamide (**3b**)*

White solid, mp 142–144 °C; yield 88%. IR (Nujol): 3280, 1638 cm$^{-1}$. $^1$H NMR: δ 6.88–6.96 (1H, m), 7.38–7.46 (1H, m), 7.49 (1H, dd, *J*=0.6, 8.4 Hz), 7.82 (1H, dd, *J*=1.3, 8.1 Hz), 8.20 (1H, br s, exch. $D_2O$), 8.22 (1H, dd, *J*=2.6, 8.4 Hz), 8.34 (1H, dd, *J*=1.3, 8.1 Hz), 8.98 (1H, dd, *J*=0.6, 2.6 Hz). $^{13}$C NMR: δ 90.9 (s), 122.3 (d), 124.9 (d), 127.0 (d), 129.4 (s), 129.8 (d), 137.7 (s), 138.2 (d), 139.2 (d), 148.6 (d), 155.2 (s), 162.6 (s). Anal. Calcd for $C_{12}H_8ClIN_2O$ (358,56): C, 40.20; H, 2.25; N, 7.81. Found: C, 40.06; H, 2.36; N, 7.94.

#### *4.2.3. N-(2-Iodophenyl)-quinoline-3-carboxamide (**3c**)*

Light brown solid, mp 221–222 °C dec; yield 76%. IR (Nujol): 3290, 1640 cm$^{-1}$. $^1$H NMR: δ 6.95–7.03 (1H, m), 7.39–7.47 (1H, m), 7.82–7.90 (2H, m), 8.00–8.09 (2H, m), 8.18 (1H, d, *J*=8.4 Hz), 8.64 (1H, d, *J*=8.4 Hz), 9.27–9.28 (1H, m), 9.71 (1H, br s), 10.05 (1H, s). $^{13}$C NMR: δ 91.5 (s), 123.0 (d), 127.1 (d), 127.3 (s), 127.5 (s), 128.5 (d), 128.6 (d), 129.3 (d), 129.7 (d), 132.7 (d), 137.9 (d), 138.1 (s), 139.2 (d), 147.5 (d), 148.1 (s), 163.3 (s). Anal. Calcd for $C_{16}H_{11}IN_2O$ (374.18): C, 51.36; H, 2.96; N, 7.49. Found: C, 51.30; H, 3.10; N, 7.56.

*4.2.4. N-(2-Iodophenyl)-pyridine-4-carboxamide[16] (**9a**)*

White solid, mp 122–124 °C (lit. mp 122–123 °C); yield 80%.

*4.2.5. N-(2-Bromopyridin-3-yl)-pyridine-4-carboxamide (**9b**)*

White solid, mp 139–141 °C; yield 57%. IR (Nujol): 3298, 1623 $cm^{-1}$. $^1H$ NMR: $\delta$ 7.35 (1H, dd, $J$=4.5, 8.1 Hz), 7.82–7.71 (2H, overlapping), 8.17 (1H, dd, $J$=1.5, 4.5 Hz), 8.54 (1H, br s, exch. $D_2O$), 8.81 (1H, dd, $J$=1.5, 8.1 Hz), 8.80–8.94 (2H, overlapping). $^{13}C$ NMR: $\delta$ 121.1 (d), 124.1 (d), 124.2 (d), 129.3 (d), 133.4 (s), 134.0 (s), 141.1 (s), 145.7 (d), 145.8 (d), 151.4 (d), 164.0 (s). Anal. Calcd for $C_{11}H_8BrN_3O$ (278.11): C, 47.51; H, 2.90; N, 15.11. Found: C, 47.63; H, 3.07; N, 15.22.

*4.2.6. N-(2-Iodophenyl)-2-pyridin-2-yl-acetamide (**23**)*

White solid, mp 110–112 °C; yield 53%. IR (Nujol): 3258, 1632 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.96 (2H, s), 6.82 (1H, dd, $J$=7.5, 7.6 Hz), 7.26–7.35 (3H, m) 7.73 (1H, dd, $J$=7.8, 8.2 Hz), 7.78 (1H, d, $J$=7.8 Hz), 8.24 (1H, d, $J$=8.2 Hz), 8.70 (1H, d, $J$=4.2 Hz), 9.88 (1H, s, exch. with $D_2O$). $^{13}C$ NMR: $\delta$ 46.4 (t), 89.7 (s), 122.7 (d), 122.8 (d), 124.5 (d), 126.2 (d), 129.3 (d), 137.9 (d), 138.4 (s), 139.5 (d), 149.7 (d), 155.2 (s), 167.9 (s). Anal. Calcd for $C_{13}H_{11}IN_2O$ (338.15): C, 46.18; H, 3.28; N, 8.28. Found: C, 46.30; H, 3.31; N, 8.20.

### 4.3. General procedure for the synthesis of the *N*-methyl-heteroamides 4a–c, 10a,b and 24

To a stirred solution of **3**, **9** or **23** (2 mmol) in dry THF (15 mL) cooled to 0 °C, 60% NaH (0.2 g, 5 mmol) was added under nitrogen atmosphere. The resulting mixture was allowed to warm to rt; then a solution of MeI (0.37 mL, 6 mmol) in dry THF (5 mL) was added dropwise. After 4 h the solvent was evaporated and the residue diluted with 1 M HCl (20 mL) and extracted with $Et_2O$ (2×20 mL). The organic layer was dried with $Na_2SO_4$ and solvent evaporated under reduced pressure. The residue was chromatographed on a silica gel column, eluent $CH_2Cl_2$/AcOEt 3:1.

*4.3.1. N-(2-Iodophenyl)-N-methyl-pyridine-3-carboxamide (**4a**)*

White solid, mp 117–118 °C; yield 58%. IR (Nujol): 1641 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.39 (3H, s), 6.92–6.96 (1H, m), 7.05–7.36 (3H, overlapping), 7.69–7.81 (2H, overlapping), 8.39–8.56 (2H, overlapping). $^{13}C$ NMR: $\delta$ 37.4 (q), 99.9 (s), 123.2 (d), 129.5 (d), 129.9 (d), 130.2 (d), 130.4 (d), 140.8 (d), 141.7 (d), 143.4 (s), 145.9 (s), 148.7 (d), 165.3 (s). Anal. Calcd for $C_{13}H_{11}IN_2O$ (338.15): C, 46.18; H, 3.28; N, 8.28. Found: C, 46.30; H, 3.10; N, 8.31.

*4.3.2. N-(2-Iodophenyl)-N-methyl-6-chloro-pyridine-3-carboxamide (**4b**)*

White solid, mp 114–115 °C; yield 95%. IR (Nujol): 1627 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.38 (3H, s), 6.94–7.02 (1H, m), 7.14–7.22 (2H, m), 7.27–7.36 (1H, m), 7.69 (1H, dd, $J$=2.4, 8.2 Hz), 7.81 (1H, dd, $J$=1.3, 8.0 Hz), 8.3 (1H, d, $J$=2.4 Hz). $^{13}C$ NMR: $\delta$ 37.8 (q), 99.3 (s), 123.7 (d), 130.0 (d), 130.1 (d), 130.2 (d), 130.7 (d), 139.0 (d), 140.8 (s), 146.1 (s), 149.6 (d), 152.6 (s), 167.3 (s). Anal. Calcd for $C_{13}H_{10}ClIN_2O$ (372.59): C, 41.91; H, 2.71; N, 7.52. Found: C, 42.06; H, 2.58; N, 7.61.

*4.3.3. N-(2-Iodophenyl)-N-methyl-quinoline-3-carboxamide (**4c**)*

Light orange solid, mp 163–161 °C; yield 97%. IR (Nujol): 1632 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.39 (3H, s), 6.79–6.88 (1H, m), 7.19–7.21 (2H, m), 7.39–7.47 (1H, m), 7.59–7.72 (3H, m), 7.93 (1H, d, $J$=8.6 Hz), 8.15 (1H, d, $J$=1.4 Hz), 8.82 (1H, s). $^{13}C$ NMR: $\delta$ 37.9 (q), 99.5 (s), 126.7 (s), 127.3 (d), 128.7 (d), 129.0 (s), 129.3 (d), 129.9 (d), 130.0 (d), 130.2 (d), 130.3 (d), 136.9 (d), 140.6 (d), 146.4 (s), 148.1 (s), 149.5 (d), 168.4 (s). Anal. Calcd for $C_{17}H_{13}IN_2O$ (388.20): C, 52.60; H, 3.38; N, 7.22. Found: C, 52.77; H, 3.29; N, 7.29.

*4.3.4. N-(2-Iodophenyl)-N-methyl-pyridine-4-carboxamide (**10a**)*

White solid, mp 80–82 °C (diisopropyl ether); yield 63%. IR (Nujol): 1623 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.38 (3H, s), 6.94 (1H, ddd, $J$=1.8, 7.6, 8.0 Hz), 7.12 (1H, dd, $J$=1.4, 7.8 Hz), 7.20–7.29 (3H, m), 7.79 (1H, dd, $J$=1.2, 8.0 Hz,), 8.39–8.46 (2H, m). $^{13}C$ NMR: $\delta$ 37.4 (q), 99.1 (s), 122.2 (d), 129.8 (d), 129.9 (d), 130.1 (d), 130.2 (d), 140.5 (d), 140.7 (d), 143.4 (s), 145.9 (s), 149.7 (d), 168.4 (s). Anal. Calcd for $C_{13}H_{11}IN_2O$ (338.15): C, 46.18; H, 3.28; N, 8.28. Found: C, 46.34; H, 3.11; N, 8.21.

*4.3.5. N-(2-Bromopyridin-3-yl)-N-methyl-pyridine-4-carboxamide (**10b**)*

White solid, mp 119–121 °C (diisopropyl ether); yield 47%. IR (Nujol): 1623 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.40 (3H, s), 7.18–7.35 (3H, m), 7.41 (1H, d, $J$=7.2 Hz), 8.25 (1H, br s), 8.42–8.55 (2H, m). $^{13}C$ NMR: $\delta$ 37.4 (q), 99.8 (s), 123.2 (d), 129.7 (d), 129.9 (d), 130.3 (d), 130.6 (d), 141.5 (d), 142.7 (d), 144.6 (s), 146.9 (s), 168.4 (s). Anal. Calcd for $C_{12}H_{10}BrN_3O$ (292.14): C, 49.34; H, 3.45; N, 14.38. Found: C, 49.49; H, 3.51; N, 14.22.

*4.3.6. N-(2-Iodophenyl)-N-methyl-2-pyridin-2-yl-propionamide (**24**)*

White solid, mp 82–84 °C; yield 75%. IR (Nujol): 1622 $cm^{-1}$. $^1H$ NMR: $\delta$ 1.50 (3H, d, $J$=6.8 Hz), 3.21 (3H, s), 3.65 (1H, q, $J$=6.8 Hz), 6.72 (1H, d, $J$=7.7 Hz), 7.01 (1H, dd, $J$=7.5, 7.7 Hz), 7.07–7.15 (3H, m), 7.56 (1H, dd, $J$=7.6, 7.7 Hz), 7.93 (1H, d, $J$=7.8 Hz), 8.41 (1H, br s). $^{13}C$ NMR: $\delta$ 19.6 (q), 36.9 (d), 47.3 (q), 100.3 (s), 122.0 (d), 129.5 (d), 129.7 (d), 130.1 (d), 130.2 (d), 137.0 (d), 140.3 (d), 145.8 (s), 149.3 (d), 161.5 (s), 173.0 (s). Anal. Calcd for $C_{15}H_{15}IN_2O$ (366.20): C, 49.20; H, 4.13; N, 7.65. Found: C, 49.34; H, 4.31; N, 7.60.

### 4.4. General procedure for the synthesis of amides 16–18

The acid **12**, **13** or **14** (0.124 g, 1 mmol) was suspended in DME (dimethoxyethane) (8 mL), cooled at 0 °C under nitrogen atmosphere. A solution of *N*-methyl-2-iodoaniline (**15**) (0.28 g, 1.2 mmol) in DME (4 mL) was dropped then a solution of DMC (2-chloro-1,3-dimethylimidazolium chloride) (0.169 g, 1 mmol) in $CH_2Cl_2$ (3 mL) and finally a solution of TEA (280 mL, 2 mmol) in $CH_2Cl_2$ (3 mL) was added. The reaction mixture was stirred for 1 h at 0 °C then allowed to warm to rt and left to react overnight. The mixture was then diluted with 300 mL of AcOEt and washed with 30 mL water, 30 mL of a saturated solution of $NaHCO_3$, 30 mL of water and 30 mL of brine. The organic layer was dried with $Na_2SO_4$ and the solvent evaporated under reduced pressure. The residue was chromatographed on a silica gel, eluent AcOEt, to give compounds **16**–**18**.

*4.4.1. N-(2-Iodophenyl)-N-methyl-pyridazine-4-carboxamide (**16**)*

Light amber-coloured solid, mp 166–168 °C; yield 70%. IR (Nujol): 1636 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.38 (3H, s), 6.96–7.04 (1H, m), 7.20–7.36 (3H, m), 7.75–7.79 (1H, m), 9.06 (1H, s), 9.05 (1H, s). $^{13}C$ NMR: $\delta$ 37.6 (q), 99.2 (s), 124.7 (d), 130.0 (d), 130.3 (d), 130.7 (d), 133.9 (s), 140.8 (d), 145.0 (s), 149.5 (d), 151.1 (d), 165.8 (s). Anal. Calcd for $C_{12}H_{10}IN_3O$ (339.13): C, 42.50; H, 2.97; N, 12.39. Found: C, 42.36; H, 3.09; N, 12.22.

*4.4.2. N-(2-Iodophenyl)-N-methyl-pyrimidine-5-carboxamide (**17**)*

White solid, mp 97–98 °C; yield 80%. IR (Nujol): 1630 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.36 (3H, s), 6.92–7.00 (1H, m), 7.21–7.36 (2H, m), 7.75–7.80 (1H, m), 8.64 (2H, s), 9.00 (1H, s). $^{13}C$ NMR: $\delta$ 37.7 (q), 99.4 (s), 129.9 (s), 130.0 (d), 130.2 (d), 130.5 (d), 140.8 (d), 145.5 (s), 156.4 (2d), 159.1 (d), 165.7 (s). Anal. Calcd for $C_{12}H_{10}IN_3O$ (339.13): C, 42.50; H, 2.97; N, 12.39. Found: C, 42.39; H, 3.08; N, 12.27.

*4.4.3. N-(2-Iodophenyl)-N-methyl-pyrazine-2-carboxamide (**18**)*

Pearl grey solid, mp 94–96 °C; yield 55%. IR (Nujol): 1640 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.42 (3H, s), 6.90–7.01 (1H, m), 7.26–7.36 (2H, m), 7.74–7.80 (1H, m), 8.16–8.19 (1H, m), 8.40 (1H, d, $J$=2.6 Hz), 8.97 (1H, s). $^{13}C$ NMR: $\delta$ 37.6 (q), 99.3 (s), 129.4 (d), 129.6 (d), 130.2 (d), 139.9 (d), 142.5 (d), 145.1 (d), 145.5 (d), 146.1 (s), 149.3 (s), 166.3 (s). Anal. Calcd for $C_{12}H_{10}IN_3O$ (339.13): C, 42.50; H, 2.97; N, 12.39. Found: C, 42.37; H, 3.09; N, 12.28.

## 4.5. General procedure for the cyclization of amides 4, 10, 16–18 and 24

A solution of **4a–c** or **10a,b** or **16–18** or **24** (1 mmol), $Pd(OAc)_2$ (0.011 g, 0.05 mmol), AcOK (0.196 g, 2 mmol) and $Bu_4NCl$ (0.278 g, 1 mmol) in DMA (8 mL) was stirred at 100 °C for 24 h. For compounds **4a–c** and **16–18** the cyclization was performed by microwaves irradiation for 45 min at 120 °C at 300 W. After cooling to room temperature, the mixture was diluted with brine (15 mL) and extracted with $Et_2O$ (3×30 mL). The organic layer was dried with $Na_2SO_4$ and solvent evaporated under reduced pressure. The residue was chromatographed on a silica gel column, eluent hexane/AcOEt 2:1, to give the cyclized product. In the case of amides **4a–c** the two regioisomers **5a–c** and **6a–c** were isolated, in ratio 1:3 nearly.

*4.5.1. 6-Methyl-benzo[h][1,6]naphthyridin-5-(6H)-one (**5a**)[17]*

White solid, mp 169–171 °C (lit. mp 173–175 °C); yield 18%. IR (Nujol): 1630 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.82 (3H, s), 7.36–7.46 (2H, m), 7.51 (1H, dd, $J$=4.6, 8.1 Hz), 7.60–7.69 (1H, m), 8.77 (1H, dd, $J$=1.8, 8.1 Hz), 8.90 (1H, dd, $J$=1.8, 7.9 Hz), 9.00 (1H, dd, $J$=1.8, 4.6 Hz). $^{13}C$ NMR: $\delta$ 30.1 (q), 114.8 (d), 120.9 (s), 123.1 (d), 123.2 (d), 125.5 (d), 129.2 (s), 131.6 (d), 137.0 (d), 139.4 (s), 150.5 (s), 153.9 (d), 161.9 (s). Anal. Calcd for $C_{13}H_{10}N_2O$ (210.23): C, 74.27; H, 4.79; N, 13.33. Found: C, 74.39; H, 4.86; N, 13.24.

*4.5.2. 6-Methyl-benzo[c][2,7]naphthyridin-5-(6H)-one (**6a**)[17]*

White solid, mp 188–191 °C (lit. mp 194–196 °C); yield 62%. IR (Nujol) 1662 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.80 (3H, s), 7.25–7.46 (2H, m), 7.67 (1H, dd, $J$=7.6, 7.8 Hz), 8.03 (1H, d, $J$=5.6 Hz), 8.27 (1H, d, $J$=7.6 Hz), 8.88 (1H, d, $J$=5.6 Hz), 9.72 (1H, s). $^{13}C$ NMR: $\delta$ 29.9 (q), 115.5 (d), 117.4 (s), 123.0 (d), 124.2 (d), 129.7 (d), 130.2 (s), 131.9 (d), 136.0 (d), 139.9 (s), 140.0 (s), 140.6 (d), 168.3 (s). Anal. Calcd for $C_{13}H_{10}N_2O$ (210.23): C, 74.27; H, 4.79; N, 13.32. Found: C, 74.43; H, 4.90; N, 13.22.

*4.5.3. 2-Chloro-6-methylbenzo[h][1,6]naphthyridin-5-(6H)-one (**5b**)*

White solid, mp 170–172 °C; yield 13%. IR (Nujol): 1625 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.80 (3H, s), 7.38–7.44 (2H, m), 7.48 (1H, d, $J$=8.2 Hz), 7.62–7.77 (1H, m), 8.68 (1H, d, $J$=8.2 Hz), 8.81 (1H, dd, $J$=1.3, 7.9 Hz). $^{13}C$ NMR: $\delta$ 30.0 (q), 114.8 (d), 115.7 (s), 119.9 (s), 123.3 (d), 124.0 (d), 125.9 (d), 132.3 (d), 139.9 (d), 151.1 (s), 153.0 (s), 155.9 (s), 161.1 (s). Anal. Calcd For $C_{13}H_9ClN_2O$ (244.68): C, 63.81; H, 3.71; N, 11.45. Found: C, 63.98; H, 3.89; N, 11.40.

*4.5.4. 2-Chloro-6-methylbenzo[c][2,7]naphthyridin-5-(6H)-one (**6b**)*

White solid, mp 212–214 °C; yield 48%. IR (Nujol): 1635 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.80 (3H, s), 7.34–7.47 (2H, m), 7.66–7.75 (1H, m), 8.07 (1H, s), 8.20 (1H, dd, $J$=1.3, 8.1 Hz), 9.50 (1H, s). $^{13}C$ NMR: $\delta$ 30.0 (q), 115.4 (d), 115.8 (d), 116.5 (s), 119.6 (s), 123.3 (d), 124.4 (d), 132.9 (d), 140.1 (s), 142.5 (s), 153.0 (d), 154.9 (s), 160.4 (s). Anal. Calcd for $C_{13}H_9ClN_2O$ (244.68): C, 63.81; H, 3.71; N, 11.45. Found: C, 63.92; H, 3.80; N, 11.38.

*4.5.5. 5-Methyl-dibenzo[b,h][1,6]naphthyridin-6-(5H)-one (**5c**)[18]*

Light yellow solid, mp 214–216 °C (lit. mp not reported); yield 16%. IR (Nujol): 1630 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.84 (3H, s), 7.39–7.47 (2H, m), 7.58–7.71 (2H, m), 7.84–7.93 (1H, m), 8.05–8.09 (1H, m), 8.25–8.29 (1H, m), 9.10–9.15 (1H, m), 9.35 (1H, s). $^{13}C$ NMR: $\delta$ 30.1 (q), 114.9 (d), 119.8 (s), 121.3 (s), 123.2 (d), 126.1 (d), 126.9 (d), 127.5 (s), 129.4 (d), 129.6 (d), 131.8 (d), 132.3 (d), 139.0 (d), 139.9 (s), 149.5 (s), 150.5 (s), 162.2 (s). Anal. Calcd for $C_{17}H_{12}N_2O$ (260.29): C, 78.44; H, 4.65; N, 10.76. Found: C, 78.55; H, 4.64; N, 10.68.

*4.5.6. 5-Methyl-dibenzo[c,f][2,7]naphthyridin-6-(5H)-one (**6c**)[19]*

Cream solid, mp 211–213 °C (lit. mp 217–218 °C); yield 45%. IR (Nujol): 1639 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.83 (3H, s), 7.36–7.45 (1H, m), 7.51–7.55 (1H, m), 7.66–7.75 (2H, m), 7.82–7.91 (1H, m), 8.26–8.31 (1H, m), 8.67 (1H, d, $J$=8.6 Hz), 8.79 (1H, d, $J$=8.6 Hz), 9.85 (1H, s). $^{13}C$ NMR: $\delta$ 30.4 (q), 115.5 (d), 118.1 (s), 118.3 (s), 122.6 (s), 122.7 (d), 127.2 (d), 127.6 (d), 129.7 (d), 130.8 (d), 130.9 (d), 131.6 (d), 138.9 (s), 140.3 (s), 150.1 (s), 150.3 (d), 161.2 (s). Anal. Calcd for $C_{17}H_{12}N_2O$ (260.29): C, 78.44; H, 4.65; N, 10.76. Found: C, 78.29; H, 4.79; N, 10.92.

*4.5.7. 6-Methyl-6H-benzo[c][2,6]naphthyridin-5-one (**11a**)[16]*

White solid, mp 192–194 °C (lit. mp 197–199 °C); yield 58%. IR (Nujol): 1659 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.74 (3H, s), 7.32 (1H, dd, $J$=7.5, 7.8 Hz), 7.37 (1H, d, $J$=7.8 Hz), 7.56 (1H, dd, $J$=7.5, 8.0 Hz), 8.19 (1H, d, $J$=5.1 Hz), 8.28 (1H, d, $J$=8.0 Hz), 8.75 (1H, d, $J$=5.1 Hz), 9.58 (1H, s). $^{13}C$ NMR: $\delta$ 30.5 (q), 115.6 (d), 117.4 (s), 117.5 (s), 121.0 (d), 123.0 (d), 123.5 (d), 128.0 (s), 130.8 (d), 138.5 (s), 145.8 (d), 148.3 (d), 160.5 (s). Anal. Calcd for $C_{13}H_{10}N_2O$ (210.24): C, 74.27; H, 4.79; N, 13.32. Found: C, 74.39; H, 4.87; N, 13.43.

*4.5.8. 6-Methyl-6H-pyrido[2,3-f][2,6]naphthyridin-5-one (**11b**)*

White solid, mp 215–218 °C (diisopropyl ether); yield 69%. IR (Nujol): 1630 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.81 (3H, s), 7.54 (1H, dd, $J$=4.4, 8.5 Hz), 7.74 (1H, d, $J$=8.5 Hz), 8.26 (1H, d, $J$=5.1 Hz), 8.66 (1H, d, $J$=4.4 Hz), 8.93 (1H, d, $J$=5.1 Hz), 10.18 (1H, s). $^{13}C$ NMR: $\delta$ 30.1 (q), 120.5 (d), 122.4 (d), 124.8 (d), 128.7 (s), 132.3 (s), 134.8 (s), 136.4 (s), 144.8 (d), 148.2 (d), 150.1 (d), 160.3 (s). Anal. Calcd for $C_{12}H_9N_3O$ (211.22): C, 68.24; H, 4.29; N, 19.89. Found: C, 68.39; H, 4.11; N, 19.96.

*4.5.9. 6-Methyl-pyridazino[4,5-c]quinolin-5-(6H)-one (**19a**)*

Cream solid, mp 250–252 °C; yield 28%. IR (Nujol): 1626 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.85 (3H, s), 7.44–7.55 (2H, m), 7.74–7.83 (1H, m), 8.39–8.44 (1H, m), 10.01 (1H, d, $J$=1.2 Hz), 10.10 (1H, d, $J$=1.2 Hz). $^{13}C$ NMR: $\delta$ 30.5 (q), 114.8 (s), 115.9 (d), 120.0 (s), 123.9 (d), 124.0 (d), 129.8 (s), 133.5 (d), 140.8 (s), 145.9 (d), 149.2 (d), 159.3 (s). Anal. Calcd for $C_{12}H_9N_3O$ (211.22): C, 68.24; H, 4.29; N, 19.89. Found: C, 68.37; H, 4.33; N, 19.75.

*4.5.10. 6-Methyl-pyridazino[4,3-c]quinolin-5-(6H)-one (**19b**)*

Light yellow solid, mp 200–202 °C; yield 24%. IR (Nujol): 1630 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.83 (3H, s), 7.45–7.53 (2H, m), 7.70–7.78 (1H, m), 8.39 (1H, d, $J$=5.3 Hz), 9.20–9.25 (1H, m), 9.55 (1H, d, $J$=5.3 Hz). $^{13}C$ NMR: $\delta$ 30.4 (q), 115.1 (d), 118.3 (s), 121.5 (s), 124.0 (d), 124.2 (d), 125.5 (d), 132.8 (d), 139.4 (s), 150.6 (d), 151.0 (s), 160.6 (s). Anal. Calcd for $C_{12}H_9N_3O$ (211.22): C, 68.24; H, 4.29; N, 19.89. Found: C, 68.33; H, 4.36; N, 19.80.

*4.5.11. 6-Methyl-pyrimido[5,4-c]quinolin-5-(6H)-one (**20**)*

White solid, mp 190–192 °C; yield 79%. IR (Nujol): 1628 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.36 (3H, s), 6.92–7.00 (1H, m), 7.21–7.36 (2H, m), 7.75–7.80 (1H, m), 8.64 (1H, s), 9.00 (1H, s). $^{13}C$ NMR: $\delta$ 29.9 (q), 115.0 (d), 117.9 (s), 118.8 (s), 123.4 (d), 125.9 (d), 133.9 (d), 141.1 (s), 155.9 (s), 159.4 (d), 160.4 (s), 160.9 (d). Anal. Calcd for $C_{12}H_9N_3O$ (211.22): C, 68.24; H, 4.29; N, 19.89. Found: C, 68.35; H, 4.35; N, 19.77.

*4.5.12. 6-Methyl-pyrazino[2,3-c]quinolin-5-(6H)-one (**21**)*

Ivory-coloured solid, mp 195–197 °C; yield 49%. IR (Nujol): 1633 $cm^{-1}$. $^1H$ NMR: $\delta$ 3.88 (3H, s), 7.39–7.49 (2H, m), 7.67–7.75 (1H, m), 8.84 (1H, dd, $J$=1.6, 7.9 Hz), 8.91–8.97 (2H, m,). $^{13}C$ NMR: $\delta$ 30.7 (q), 115.0 (d), 119.3 (s), 119.6 (s), 123.5 (d), 125.8 (d), 132.6 (d), 136.8 (s), 139.3 (s), 145.5 (d), 148.3 (d), 160.7 (s). Anal. Calcd for $C_{12}H_9N_3O$ (211.22): C, 68.24; H, 4.29; N, 19.89. Found: C, 68.40; H, 4.38; N, 19.83.

*4.5.13. 5,7-Dimethyl-5H,6H,7H-pyrido[2,3-d][1]benzazepin-6-one (**25**)*

White solid, mp 162–164 °C; yield 90%. IR (Nujol): 1632 $cm^{-1}$. $^1H$ NMR: $\delta$ 1.70 (3H, d, $J$=6.7 Hz), 3.37 (3H, s), 3.60 (1H, q, $J$=6.7 Hz), 7.33–7.37 (2H, m), 7.41 (1H, d, $J$=8.0 Hz), 7.49–7.56 (2H, m), 7.88 (1H, d, $J$=7.6 Hz), 8.68 (1H, d, $J$=4.7 Hz). $^{13}C$ NMR: $\delta$ 11.7 (q), 36.7 (d), 43.2 (q), 122.6 (d), 123.0 (d), 125.7 (d), 129.6 (d), 130.1 (d), 132.0 (s), 132.1 (s), 135.8 (d), 142.0 (s), 149.5 (d), 156.1 (s), 172.4 (s). Anal. Calcd for $C_{15}H_{14}N_2O$ (238.29): C, 75.61; H, 5.92; N, 11.76. Found: C, 75.54; H, 5.81; N, 11.60.

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