Supporting information

Metal-Catalyzed Intramolecular Cyclization of Amido(hetero)arylboronic acid aldheydes to isoquinolinones and Derivatives

Carolina S. Marques*, Daniela Peixoto and Anthony J. Burke*

Department of Chemistry and Centro de Química de Évora, University of Évora, School of Science and Technology and Institute for Research and Advanced Training, Rua Romão Ramalho, 59, 7000 Évora, Portugal

ajb@uevora.pt
**General considerations:** All the reagents were obtained from Aldrich, Fluka, Acros and Alfa Aesar. The solvents used were dried using current laboratory techniques. All the reagents applied in this work were used as received. All reactions with transition metals were conducted under a nitrogen atmosphere. Column chromatography was carried out on silica gel (sds, 70-200μm). Thin layer chromatography (TLC) was carried out on aluminium backed Kiselgel 60 F254 plates (Merck). Plates were visualized either by UV light or with phosphomolybdic acid in ethanol. ¹H and ¹³C NMR spectra was recorded on a Bruker Avance III at 400 and 100 MHz, respectively, and the chemical shifts were quoted in parts per million (ppm) referenced to the appropriate non-deuterated solvent peak relative to 0.0 ppm for tetramethylsilane. Mass spectra (MS) using the ESI-TOF technique were obtained from the University of Vigo, C.A.C.T.I., Spain.

**General procedure for the synthesis of halogenated (hetero)arylamides acetals**

In a round bottom flash with THF, o-halo(hetero)aryl carboxylic acid and, 1,1'-carbonyldiimidazole (1 equiv.) were left stirring at room temperature for 30min and then the corresponding aminoacetals (1equiv.) were slowly added. The reaction was performed at room temperature overnight. The solvent was evaporated and after purification by column chromatography using 1:1 Hexane/ EtOAc, the pure compounds were obtained.

**N-(2,2-dimethoxyethyl)-2-iodobenzamide:** From 2-iodobenzoic acid (5.00 g, 0.02 mol) and 2,2-dimethoxyethanamine, according to the general procedure, the title compound was obtained as a white oil/solid (6.50 g, 0.0196 mol, 98%). ¹H NMR (400 MHz, CDCl₃): δ 3.41 (s, 6H, 2×OMe), 3.58 (d, J=5.2Hz, 2H, CH₂), 4.53 (t, J=5.2 Hz, 1H, CH), 6.02 (br s, 1H, NH), 7.06-7.10 (m, 1H, ArH), 7.34-7.36 (m, 2H, ArH), 7.83-7.86 (m, 1H, ArH) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 41.3 (CH₂), 53.3 (2×OMe), 92.2 (C), 102.0 (CH), 128.6 (2×CH), 131.0 (CH), 139.1 (CH), 143.2 (C), 169.6 (HNC=O) ppm.

---

N-(3,3-diethoxypropyl)-2-iodobenzamide: From 2-iodobenzoic acid (5.00 g, 0.0200 mol) and 3,3-diethoxypropan-1-amine, according to the general procedure, the title compound was obtained as a white oil/solid (7.40 g, 0.0196 mol, 98%). ¹H NMR (400 MHz, CDCl₃): δ 1.12-1.17 (m, 6H, 2×CH₃), 1.93-1.98 (m, 2H, CH₂), 3.50-3.59 (m, 4H, 2×CH₂), 3.64-3.70 (m, 2H, CH₂), 4.58-4.61 (m, 1H, CH), 6.59 (br s, 1H, NH), 7.06-7.09 (m, 1H, ArH), 7.33-7.36 (m, 2H, ArH), 7.83-7.86 (m, 1H, ArH) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 15.4 (2×CH₃), 32.8 (CH₂), 36.1 (CH₂), 62.1 (2×CH₂), 92.5 (C), 102.4 (CH), 128.0 (2×CH), 130.9 (CH), 139.8 (CH), 142.4 (C), 169.2 (HNC=O) ppm.

2-Bromo-N-(2,2-dimethoxyethyl)-5-methoxybenzamide: From 2-bromo-5-methoxybenzoic acid (10.00 g, 0.0430 mol) and 2,2-dimethoxyethanamine, according to the general procedure, the title compound was obtained as a white solid/oil (12.80 g, 0.04 mol, 93%). ¹H NMR (400 MHz, DMSO-d₆): δ 3.30 (s, 6H, 2×OMe), 3.35 (br s, 2H, CH₂), 3.77 (s, 3H, OMe), 4.49 (t, J = 5.2 Hz, 1H, CH), 6.90-6.95 (m, 2H, ArH), 7.51-7.53 (m, 1H, ArH), 8.50 (br s, 1H, NH) ppm. ¹³C NMR (100 MHz, DMSO-d₆): δ 41.5 (CH₂), 53.6 (2×OMe), 56.2 (OMe), 102.1 (CH), 109.5 (C), 114.7 (CH), 117.3 (CH), 134.0 (CH), 140.3 (C), 158.9 (C), 167.6 (HNC=O) ppm.

2-Bromo-N-(3,3-diethoxypropyl)-5-methoxybenzamide: From 2-bromo-5-methoxybenzoic acid (10 g, 0.0430 mol) and 3,3-diethoxypropan-1-amine, according to the general procedure, the title compound was obtained as a yellow solid/oil (14.66 g,
0.04 mol, 94%). ¹H NMR (400 MHz, CDCl₃): δ 1.16-1.25 (m, 6H, 2xCH₃), 1.91-1.95 (m, 2H, CH₂), 3.49-3.73 (m, 4H, 2xCH₂), 3.63-3.69 (m, 2H, CH₂), 3.78 (s, 3H, OMe), 4.62 (t, J=5.2Hz, 1H, CH), 6.60 (br s, 1H, NH), 6.77-6.80 (m, 1H, ArH), 7.06 (br s, 1H, ArH), 7.43-7.40 (m, 1H, ArH) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 15.4 (2xCH₃), 32.9 (CH₂), 36.2 (CH₂), 55.6 (OMe), 62.1 (2xCH₂), 102.4 (CH), 109.5 (C), 114.6 (CH), 117.7 (CH), 134.2 (CH), 138.9 (C), 158.9 (C), 167.3 (HNC=O) ppm.

2-Bromo-N-(2,2-dimethoxyethyl)-5-methylbenzamide: From 2-bromo-5-methylbenzoic acid (5.00 g, 0.023 mol) and 2,2-dimethoxyethanamine, according to the general procedure, the title compound was obtained as a white solid/oil (6.81 g, 0.022 mol, 97%). ¹H NMR (400 MHz, DMSO-d₆): δ 2.28 (s, 3H, CH₃), 3.30 (br s, 2H, CH₂), 3.35 (s, 6 H, 2xOMe), 4.48-4.51 (m, 1H, CH), 7.17-7.21 (m, 2H, ArH), 7.50 (d, J = 8.0 Hz, 1 H, ArH), 8.48 (br s, 1H, NH) ppm. ¹³C NMR (100 MHz, DMSO-d₆): δ 20.7 (CH₃), 41.3 (CH₂), 53.6 (2×OMe), 102.1 (CH), 116.0 (C), 129.7 (CH), 131.9 (CH), 132.9 (CH), 137.6 (C), 137.9 (C), 167.9 (HNC=O) ppm.

2-Bromo-N-(3,3-diethoxypropyl)-5-methylbenzamide: From 2-bromo-5-methylbenzoic acid (5 g, 0.023 mol) and 3,3-diethoxypropan-1-amine, according to the general procedure, the title compound was obtained as a white solid/oil (7.36 g, 0.0210 mol, 93%). ¹H NMR (400 MHz, CDCl₃): δ 1.16-1.19 (m, 6H, 2xCH₃), 1.91-1.95 (m, 2H, CH₂), 3.47-3.69 (m, 6H, 3xCH₂), 4.62 (t, J=5.2Hz, 1H, CH), 6.58 (br s, 1H, NH), 7.02-7.06 (m, 1H, ArH), 7.30 (br s, 1H, ArH), 7.40-7.42 (m, 1H, ArH) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 15.4 (2xCH₃), 20.8 (CH₃), 32.9 (CH₂), 36.2 (CH₂), 62.1 (2xCH₂), 102.5 (CH), 115.9 (C), 130.2 (CH), 132.0 (CH), 133.2 (CH), 137.7 (C), 137.9 (C), 167.7 (HNC=O) ppm.
2-bromo-N-(2,2-dimethoxyethyl)-4-methylbenzamide: From 2-bromo-4-methylbenzoic acid (5.00 g, 0.0230 mol) and 2,2-dimethoxyethanamine, according to the general procedure, the title compound was obtained as a white solid/oil (6.67 g, 0.022 mol, 96%). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.31 (s, 3H, CH$_3$), 3.30-3.35 (m, 8H, 2xOMe and CH$_2$), 4.49 (t, J=5.2Hz, 1H, CH), 7.21-7.25 (m, 2H, ArH), 7.48 (br s, 1H, ArH), 8.44 (br s, 1H, NH) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 20.8 (CH$_3$), 41.3 (CH$_2$), 53.6 (2xOMe), 102.2 (CH), 119.2 (C), 128.5 (CH), 129.1 (CH), 133.4 (CH), 136.5 (C), 141.4 (C), 167.9 (HNC=O) ppm.

2-bromo-N-(3,3-diethoxypropyl)-4-methylbenzamide: From 2-bromo-5-methylbenzoic acid (5 g, 0.023 mol) and 3,3-diethoxypropan-1-amine, according to the general procedure, the title compound was obtained as a yellow oil (7.52 g, 0.0218 mol, 95%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.16-1.19 (m, 6H, 2xCH$_3$), 1.91-1.95 (m, 2H, CH$_2$), 3.49-3.69 (m, 6H, 3xCH$_2$), 4.62 (t, J=5.2Hz, 1H, CH), 6.58 (br s, 1H, NH), 7.02-7.06 (m, 1H, ArH), 7.30 (br s, 1H, ArH), 7.40-7.42 (m, 1H, ArH) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 15.3 (2xCH$_3$), 21.0 (CH$_3$), 33.0 (CH$_2$), 36.1 (CH$_2$), 61.1 (2xCH$_2$), 102.4 (CH), 119.5 (C), 128.2 (CH), 129.4 (CH), 133.8 (CH), 135.2 (C), 141.7 (C), 167.5 (HNC=O) ppm.

4-Chloro-N-(2,2-dimethoxyethyl)-2-iodobenzamide: From 4-chloro-2-iodobenzoic acid (5.00 g, 0.0177 mol) and 2,2-dimethoxyethanamine, according to the general procedure, the title compound was obtained as a white oil (6.54 g, 0.018 mol, 78%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.43 (s, 6H, 2xOMe), 3.57-3.60 (m, 2H, CH$_2$), 4.53 (t,
J=5.2Hz, 1H, CH), 5.99 (br s, 1H, NH), 7.31-7.37 (m, 2H, ArH), 7.87 (br s, 1H, ArH) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): δ 41.6 (CH$_2$), 54.7 (2×OMe), 97.1 (C), 102.5 (CH), 128.6 (CH), 129.2 (CH), 136.4 (C), 139.5 (CH), 140.6 (C), 168.6 (HNC=O) ppm.

**4-Chloro-N-(3,3-diethoxypropyl)-2-iodobenzamide:** From 4-chloro-2-iodobenzoic acid (5 g, 0.0177 mol) and 3,3-diethoxypropan-1-amine, according to the general procedure, *title compound* was obtained as a colorless oil (6.05 g, 0.0147 mol, 83%). $^1$H NMR (400 MHz, CDCl$_3$): δ 1.16-1.25 (m, 6H, 2xCH$_3$), 1.92-1.96 (m, 2H, CH$_2$), 3.49-3.58 (m, 4H, 2xCH$_2$), 3.66-3.70 (m, 2H, CH$_2$), 4.63 (t, J=5.2Hz, 1H, CH), 6.50 (br s, 1H, NH), 7.28-7.35 (m, 2H, ArH), 7.85 (br s, 1H, ArH) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): δ 15.5 (2xCH$_3$), 33.8 (CH$_2$), 36.2 (CH$_2$), 62.3 (2xOMe), 92.8 (C), 102.7 (CH), 128.5 (CH), 129.0 (CH), 136.1 (C), 139.5 (CH), 141.0 (C), 168.2 (HNC=O) ppm.

**2-Chloro-N-(2,2-dimethoxyethyl)nicotinamide:** From 2-chloronicotinic acid (5.00 g, 0.032 mol) and 2,2-dimethoxyethanamine, according to the general procedure, *title compound* was obtained as a white solid/oil (7.22 g, 0.02950 mol, 93%). $^1$H NMR (400 MHz, CDCl$_3$): δ 3.42 (s, 6H, 2xOMe), 3.54-3.62 (m, 2H, CH$_2$), 4.51 (t, J=5.2Hz, 1H, CH), 6.73 (br s, 1H, NH), 7.30 (dd, J=4.8 and 7.6Hz, 1H, 5-H), 8.03 (dd, J=2.0 and 7.6Hz, 1H, 4-H), 8.43 (dd, J=2.0 and 4.8Hz, 1H, 6-H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): δ 41.8 (CH$_2$), 54.6 (2×OMe), 102.4 (CH), 122.8 (CH), 131.3 (C), 139.8 (CH), 147.3 (C), 151.1 (CH), 164.9 (HNC=O) ppm.
2-chloro-N-(3,3-diethoxypropyl)nicotinamide: From 2-chloronicotinic acid (5.00 g, 0.032 mol) and 3,3-diethoxypropan-1-amine, according to the general procedure, title compound was obtained as a yellow oil (8.44 g, 0.029 mol, 92%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.14-1.18 (m, 6H, 2xCH$_3$), 1.88-2.00 (m, 2H, CH$_2$), 3.47-3.68 (m, 6H, 3xCH$_2$), 4.60 (t, J=5.2Hz, 1H, CH), 7.14 (br s, 1H, NH), 7.32 (dd, J=4.8 and 7.6Hz, 1H, 5-H), 8.06 (dd, J=2.0 and 7.6Hz, 1H, 4-H), 8.44 (dd, J=2.0 and 4.8Hz, 1H, 6-H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 15.4 (2xCH$_3$), 32.8 (CH$_2$), 36.2 (CH$_2$), 62.3 (2×OMe), 102.5 (CH), 122.7 (CH), 131.7 (C), 139.5 (CH), 147.3 (C), 150.8 (CH), 164.7 (HNC=O) ppm.

3-Bromo-N-(2,2-dimethoxyethyl)thiophene-2-carboxamide: From 3-bromothiophene-2-carboxylic acid (5.00 g, 0.024 mol) and 2,2-dimethoxyethanamine, according to the general procedure, title compound was obtained as a white oil (6.75 g, 0.0230 mol, 95%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.42 (s, 6H, 2xOMe), 3.58-3.61 (m, 2H, CH$_2$), 4.49 (t, J=5.2Hz, 1H, CH), 7.01 (d, J=5.6Hz, 1H, HetArH), 7.23 (br s, 1H, NH), 7.42 (d, J=5.6Hz, 1H, HetArH) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 41.4 (CH$_2$), 54.6 (2×OMe), 102.6 (CH), 108.8 (C), 130.1 (CH), 132.1 (CH), 134.9 (C), 160.5 (HNC=O) ppm.

3-Bromo-N-(2,2-dimethoxyethyl)thiophene-2-carboxamide: From 3-bromothiophene-2-carboxylic acid (5.00 g, 0.024 mol) and 3,3-diethoxypropan-1-
amine, according to the general procedure, title compound was obtained as a white oil (7.59 g, 0.0220 mol, 94%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.22-1.69 (m, 6H, 2xCH$_3$), 1.89-1.94 (m, 2H, CH$_2$), 3.47-3.69 (m, 6H, 3xCH$_2$), 4.60 (t, $J$=5.2Hz, 1H, CH), 6.97 (d, $J$=5.6Hz, 1H, HetArH), 7.36 (br s, 1H, NH), 7.38 (d, $J$=5.6Hz, 1H, HetArH) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 15.4 (2xCH$_3$), 33.1 (CH$_2$), 36.0 (CH$_2$), 62.0 (2xCH$_2$), 102.1 (CH), 108.5 (C), 129.8 (CH), 132.0 (CH), 135.1 (C), 160.3 (HNC=O) ppm.

General procedure for the synthesis of borylated (hetero)arylamides acetals

The reactions were performed under a nitrogen atmosphere using a Radleys® 12 position carousel reactor. PdCl$_2$(dppf) (5.0 mol %), the halogenated arylamide acetals (1 equiv), NEt$_3$ (2 equiv.) and pinacolborane (1 equiv.) and 1,4-dioxane were added. The reaction was performed at 80ºC for 18h. The reactions were monitored by TLC, to follow the disappearance of the starting materials. After completion, the mixture was allowed to cool to room temperature. Then CH$_2$Cl$_2$ and water were added and the organic phase was separated, dried (MgSO$_4$) and filtered. Removal of the solvent under reduced pressure gave the crude products.

General procedure for the synthesis of Amido(hetero)arylboronic acid aldheydes

The borylated (hetero)arylamides acetals (unpurified) and HCl aq (1M) were added to a round bottom flask with THF. The reaction was performed at 80ºC for 12h. After completion, the mixture was allowed to cool to room temperature. Then NaHCO$_3$ (sat.) and CH$_2$Cl$_2$ were added and the organic phase was separated, washed with Brine, dried (MgSO$_4$) and filtered. Removal of the solvent under reduced pressure gave the corresponding product.

General procedure for the cyclization reaction

The reactions were performed under a nitrogen atmosphere using a Radleys® carousel reactor. The tubes were filled with [Rh(COD)Cl]$_2$ (1.0 mol %), amido(hetero)arylboronic acid aldehyde (unpurified), K$_2$CO$_3$ (3 equiv.) and dry toluene. The reaction was performed at 100ºC for 24h. After completion, the mixture was allowed to cool to room temperature. Then HCl (3N) and CH$_2$Cl$_2$ were added and the organic phase was separated, dried (MgSO$_4$) and filtered. Removal of the solvent under reduced pressure gave the crude product which was submitted to column chromatography using Et$_2$O as eluent.
4-Hydroxy-3,4-dihydroisoquinolin-1(2H)-one (4a):

$^1$H CDCl$_3$, 400MHz

$^{13}$C CDCl$_3$, 100MHz
DEPT 135, CDCl$_3$

5-Hydroxy-2,3,4,5-tetrahydro-1$H$-benzo[c]azepin-1-one (4b)

$^1$H CDCl$_3$, 400MHz
\(^{13}\)C CDCl\(_3\), 100MHz

DEPT 135, CDCl\(_3\)
4-Hydroxy-7-methoxy-3,4-dihydroisoquinolin-1(2H)-one (4c)

$^1$H CDCl$_3$, 400MHz

$^{13}$C CDCl$_3$, 100MHz
5-Hydroxy-8-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (4d)

$^1$H CDCl$_3$, 400MHz
$^{13}$C CDCl$_3$, 100MHz

HSQC CDCl$_3$ (Dept 135: $^1$H)
4-Hydroxy-7-methyl-3,4-dihydroisoquinolin-1(2H)-one (4e)

$^1$H CDCl$_3$, 400MHz

$^{13}$C CDCl$_3$, 100MHz
5-Hydroxy-8-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (4f)

$^1$H CDCl$_3$, 400MHz
$^{13}$C CDCl$_3$, 100MHz

DEPT 135, CDCl$_3$
4-Hydroxy-6-methyl-3,4-dihydroisoquinolin-1(2H)-one (4g)

$^1$H CDCl$_3$, 400MHz

$^{13}$C CDCl$_3$, 100MHz
5-Hydroxy-7-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (4h)

$^1$H CDCl$_3$, 400MHz
$^{13}$C CDCl$_3$, 100MHz

DEPT 135, CDCl$_3$
6-Chloro-4-hydroxy-3,4-dihydroisoquinolin-1(2H)-one (4i)

$^1$H CDCl$_3$, 400MHz

$^{13}$C CDCl$_3$, 100MHz
7-Chloro-5-hydroxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (4j)

$^1$H CDCl$_3$, 400MHz

$^{13}$C CDCl$_3$, 100MHz
8-Hydroxy-7,8-dihydro-1,6-naphthyridin-5(6H)-one (4k)

$^1$H CDCl$_3$, 400MHz
$^{13}$C CDCl$_3$, 100MHz

DEPT 135, CDCl$_3$
9-Hydroxy-6,7,8,9-tetrahydro-5H-pyrido[3,2-c]azepin-5-one (4l)

$^1$H CDCl$_3$, 400MHz

$^{13}$C CDCl$_3$, 100MHz
DEPT 135, CDCl$_3$

4-Hydroxy-5,6-dihydrothieno[2,3-c]pyridin-7(4H)-one (4m)

$^1$H CDCl$_3$, 400MHz
\[ ^{13}C \text{CDCl}_3, 100\text{MHz} \]

DEPT 135, CDCl\(_3\)
4-Hydroxy-6,7-dihydro-4H-thieno[2,3-c]azepin-8(5H)-one (4n)

$^1$H CDCl$_3$, 400MHz

$^{13}$C CDCl$_3$, 100MHz
DEPT 135, CDCl₃