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Synthesis of 5-methylfuro[3,2-*c*]quinolin-4(5*H*)-one via palladium-catalysed cyclisation of *N*-(2-iodophenyl)-*N*-methyl-3-furamide

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Abstract—A new synthesis of the furo[3,2-*c*]quinolin-4(5*H*)-one heterocycle has been developed using a palladium-catalysed cyclisation of *N*-(2-iodophenyl)-*N*-methyl-3-furamide. By varying the catalyst, base and solvent, the yield of the cyclisation was optimised. It was found that the use of palladium oxide with potassium acetate in *N*,*N*-dimethylacetamide (DMA) with a small amount of tetrabutylammonium chloride gave the highest yield of 5-methylfuro[3,2-*c*]quinolin-4(5*H*)-one (**9**).

Alkaloids containing the furoquinolinone core constitute a significant group of the quinoline alkaloids and this class of compounds have been shown to exhibit a range of biological activities including, antifungal, antibacterial, antiviral, antimicrobial, antimalarial, insecticidal, antineoplastic, antidiuretic, antiarrhythmic and sedative properties.[1–4] Some examples of natural products containing the furoquinolinone core structure include (+)-araliopsine, isolated from *Ariliopsis soyauxii*,[5] and almeine (the absolute configuration of which remains unknown), isolated from *Almeida guyanensis*[6] (Fig. 1). Both of these plants belong to the family Rutaceae.

Several syntheses of natural and synthetic compounds containing the furoquinolinone core structural unit **1** (Fig. 2) have been published.[2–4,7,8] However, the majority of these syntheses use commercially available 4-hydroxy-1-methyl-2(1*H*)quinolone (**2**) or derivatives thereof, as the starting material. When **2** is used as the starting material an alkylation/cyclisation step using various methods is required to build on the furan ring.[2–4] Alternatively, syntheses have been developed using a palladium-catalysed arylation, to link the benzene and the furan rings. Functional group manipulation to allow the amide bond to form between the benzene and furan rings generates the complete tricycle.[7,8] We wished to investigate an alternative strategy, which has been used previously in the synthesis of other similar tricyclic compounds.[9,10] An example of this is the synthesis of 1*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one (**3**), an analogous structure to that of the furoquinolinone core (**1**), developed by Kuroda and Suzuki.[10]

The alternative strategy, which was used in the synthesis of **3**,[10] when applied to the synthesis of the furoquinolinone core **1**, involves first forming an amide bond between the benzene and furan rings followed by an

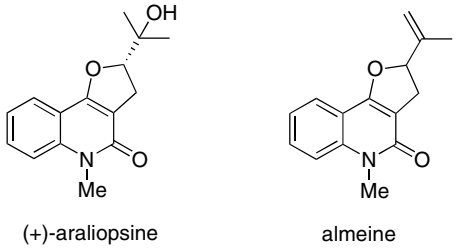
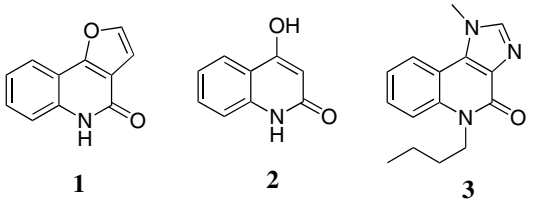


Figure 1.



1 **2** **3**

Figure 2.

Keywords: Furoquinolinones; Palladium catalyst; Palladium oxide.
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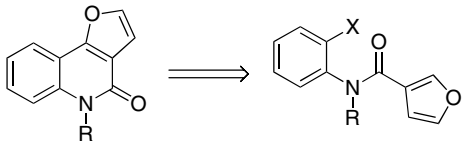


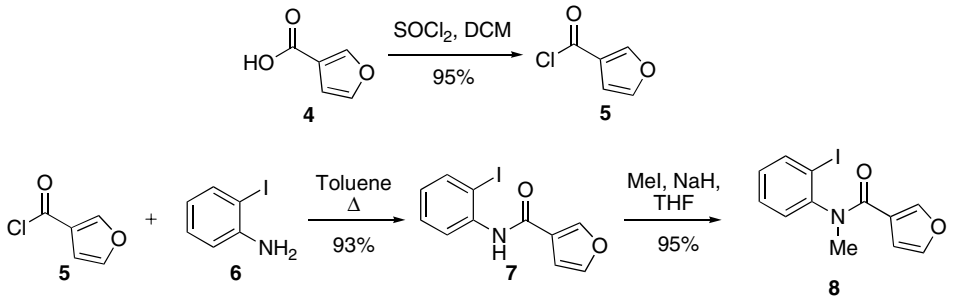
A **B**

Scheme 1.

intramolecular palladium-catalysed cyclisation. This can be illustrated retrosynthetically where disconnection of a C–C bond in **A** gives an *N*-phenyl-3-furamide derivative **B**, as the precursor (Scheme 1). The key step in this approach would then be an intramolecular phenyl-furan coupling reaction.

The synthesis of the amide precursor **B**, to be used in the investigation of the palladium-catalysed cyclisation, is shown in Scheme 2. The reaction of acid chloride **5** (generated from furoic acid **4** and thionyl chloride) with 2-iodoaniline **6** gave *N*-(2-iodophenyl)-3-furamide **7**,[11] which upon methylation, using methyl iodide and sodium hydride in THF, gave tertiary amide **8**.[12] It had been reported previously,[9,10] that the palladium cyclisation had failed where a secondary amide was used as the starting material. Therefore, the amide was protected with an *N*-methyl group to aid the cyclisation reaction. Indeed, it was found that all attempts to perform the palladium-catalysed cyclisation reaction using **7** as the starting material gave no indication of the cyclised product.

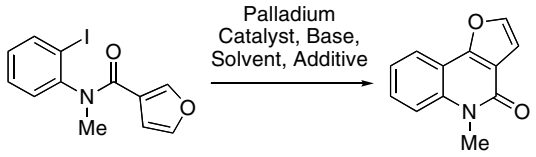
The optimum conditions for the palladium-catalysed cyclisation were found through a series of experiments where sequential changes were made to the catalyst, base and the solvent used (Table 1). Kuroda and Suzuki[10] had found that the use of palladium acetate and sodium hydrogen carbonate, with the addition of tetrabutylammonium chloride as additive, gave the best result for cyclisation to give stricycle **3**. The use of these conditions in our system gave the cyclised product **9**,[13] in 83% yield (entry 1), however, if the catalyst was exchanged for palladium tetrakis or palladium oxide, the yield was dramatically reduced. It was also noted that there was a poor recovery of starting material in these cases (entries 2 and 3). Performing the same reactions in a non-polar solvent such as toluene gave only trace amounts of the cyclisation product and an almost complete recovery of the starting material when all three types of catalysts were used (entries 4–6). Changing the base to potassium acetate gave good yields for the cyclisation product **9**, and complete consumption of the starting material, with all of the catalysts when the



4 **5** **6** **7** **8**

Scheme 2.

Table 1. Palladium-catalysed cyclisation of **8**



8 **9**

Entry[a]	Solvent	Catalyst (0.1 equiv)	Base (1.4 equiv)	Temp (°C)	Yield **9** (%)	Recovered **8** (%)
1	DMA	$Pd(OAc)_2$	$NaHCO_3$	150	83	0
2	DMA	$Pd(PPh)_4$	$NaHCO_3$	150	9	0
3	DMA	PdO	$NaHCO_3$	150	10	0
4	Toluene	$Pd(OAc)_2$	$NaHCO_3$	100	<5	90
5	Toluene	$Pd(PPh)_4$	$NaHCO_3$	100	<5	90
6	Toluene	PdO	$NaHCO_3$	100	<5	90
7	DMA	$Pd(OAc)_2$	KOAc	150	76	0
8	DMA	$Pd(PPh)_4$	KOAc	150	64	0
9	DMA	PdO	KOAc	150	89	0
10	Toluene	$Pd(OAc)_2$	KOAc	100	14	30
11	Toluene	$Pd(PPh)_4$	KOAc	100	12	55
12	Toluene	PdO	KOAc	100	26	27

[a] All reactions were performed in the presence of tetrabutylammonium chloride (0.25 equiv) as additive and heated for 18 h under nitrogen.

reaction was run in DMA (entries 7–9). The best catalyst was interestingly found to be palladium oxide under these conditions, giving the cyclised product **9** in 89% yield (entry 9). Repeating the reactions using potassium acetate in toluene gave only slightly better yields of **9** (entries 10–12) compared with the reactions using sodium hydrogen carbonate (entries 4–6), while the amount of starting material recovered was significantly lower.

In conclusion, a convenient and high yielding route to 5-methylfuro[3,2-*c*]quinolin-4(5*H*)-one has been developed using palladium-catalysed cyclisation as a key step. It has been found that one of the simplest palladium catalysts available, palladium oxide, in combination with potassium acetate as base and tetrabutylammonium chloride in DMA, gave the best yield for the intramolecular cyclisation.

Acknowledgements

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11. *Data for* **7**: mp 95–97 °C. IR (KBr) ν_{max}: 3369, 3264, 3124, 3054, 2337, 1654, 1561, 1502, 1426, 1310, 1158, 1065, 1018, 866, 744 cm^{-1}. UV λ_{max} (MeOH): 205.8 nm (21460), 225.0 nm (19732). ^1H NMR ($CDCl_3$, 500 MHz): δ 6.82 (s, 1H), 6.90 (dd, $J = 8$, 8 Hz, 1H), 7.41 (dd, $J = 8$, 8 Hz, 1H), 7.54 (s, 1H), 7.83 (d, $J = 8$ Hz, 1H), 7.90 (s, 1H, N*H*), 8.12 (s, 1H), 8.41 (d, $J = 8$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 90.2, 108.5, 121.9, 123.5, 126.2, 129.7, 138.1, 139.0, 144.5, 145.6, 160.6. MS (ESI): *m*/*z* 314 $[M+H]^+$, 187 $[M+H-I^{\cdot}]^+$. Anal. Calcd for $C_{11}H_8INO_2$: C, 42.20; H, 2.58; N, 4.47. Found: C, 42.03; H, 2.51; N, 4.35.
12. *Data for* **8**: mp 80–82 °C. IR (KBr) ν_{max}: 3440, 3135, 2917, 1631 cm^{-1}. UV λ_{max} (MeOH) 204.6 nm (13460), 226.2 nm (10716). ^1H NMR ($CDCl_3$, 500 MHz): δ 3.35 (s, 3H), 6.22 (s, 1H), 6.82 (s, 1H), 7.14 (ddd, $J = 7.5$, 7.5, 1.5 Hz, 1H), 7.19 (s, 1H), 7.32 (dd, $J = 7.5$, 1.5 Hz, 1H), 7.44 (ddd, $J = 7.5$, 7.5, 1.5 Hz, 1H), 7.95 (dd, $J = 7.5$, 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 37.23, 100.2, 111.2, 122.1, 130.0, 130.1, 130.4, 140.6, 142.4, 145.5, 146.5, 163.2. MS (ESI): *m*/*z* 328 $[M+H]^+$, 350 $[M+Na]^+$. Anal. Calcd for $C_{12}H_{10}INO_2$: C, 44.06; H, 3.08; N, 4.28. Found: C, 43.88; H, 3.04; N, 4.14.
13. *Data for* **9**: mp 126–128 °C. IR (KBr) ν_{max}: 3579, 1660, 1257, 738 cm^{-1}. UV λ_{max} (MeOH): 228.8 nm (82846), 285.2 nm (15376), 319.2 nm (19621), 332.2 nm (18589). ^1H NMR ($CDCl_3$, 500 MHz): δ 3.81 (s, 3H), 7.10 (d, $J =$ 2 Hz, 1H), 7.33 (dd, $J = 7.5$, 7.5 Hz, 1H), 7.48 (d, $J = 7.5$ Hz, 1H), 7.58 (dd, $J = 7.5$, 7.5 Hz, 1H), 7.64 (d, $J = 2$ Hz, 1H), 8.04 (d, $J = 7.5$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 29.7, 108.6, 113.5, 115.3, 115.6, 121.5, 122.5, 129.8, 138.4, 144.2, 155.4, 159.7. MS (ESI): *m*/*z* 200 $[M+H]^+$. Anal. Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.14; H, 4.53; N, 6.86.