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Palladium catalysed synthesis of cyclic amidines and imidates

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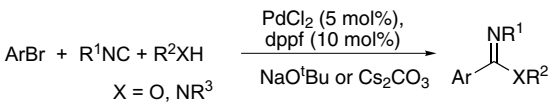
Abstract—The palladium catalysed insertion of isonitriles into aryl bromides carrying pendant amine or alcohol groups on the *ortho* position affords cyclic amidines or imidates in good yield.

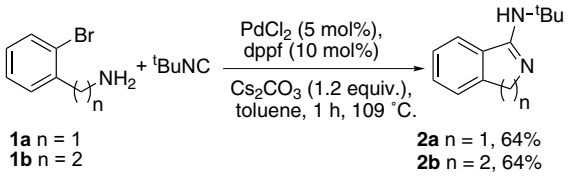
We recently reported the palladium catalysed three component synthesis of aryl-amidines or -imidates from aryl bromides, isonitriles, and amines or alcohols respectively (Scheme 1).[1] We now report that the reactions work well in an intramolecular fashion to afford cyclic amidines and imidates.

The formation of cyclic lactones and lactams by intramolecular cyclisation of aryl halides on to alcohols or amines with incorporation of carbon monoxide is known.[2] The stoichiometric insertion of isonitriles into 1-palladaisoindolines to afford isoindolinium salts has also been reported.[3]

Treatment of 2-bromobenzylamine **1a** and 2-(2-bromophenyl)ethanamine **1b** with *tert*-butylisonitrile (1.5 equiv), dry Cs_2CO_3 (1.2 equiv), 5 mol% $PdCl_2$ and 10 mol% 1,1′-diphenylphosphinoferrocene (dppf) in toluene at 109 °C for 1 h gave quantitative (by GC) conversion into the cyclic amidines **2** (Scheme 2). Work-up by extraction into 2.5% acetic acid in water, basification, extraction into ether and Kugelrohr distillation afforded **2a** and **2b** as white crystalline solids, each in 64% yield. Only the endocyclic imine tautomers were observed, as



Scheme 1.



Scheme 2.

judged from the proton chemical shift of the *tert*-butyl groups of 1.54 and 1.49 ppm, respectively. In a variety of amidines ArC(=N^{t}Bu)NR$_2$ and ArC(=NR)NH^{t}Bu the proton shift of the *tert*-butyl group was 1.0 in the former, 1.41–1.45 in the latter.[4]

Unfortunately, the cyclisation has the same limitation to *tert*-alkylisonitriles that we observed for the analogous intermolecular process—both cyclohexyl- and *n*-butylisonitriles gave low yields. Surprisingly, the reaction also failed when cyclisation of secondary amines was tried.

We then turned our attention to the formation of cyclic imidates, and found a much more versatile process (Scheme 3, Table 1). Treatment of the appropriate bromoalcohol **3** or **4** with an isonitrile (1.5 equiv), sodium *tert*-butoxide (1.3 equiv), $PdCl_2$ (5 mol%) and dppf (10 mol%) in toluene at 109 °C for 4–16 h gave clean conversion into the desired imidates **5** and **6**. The best work-up method was found to be to dilute the cold reaction mixture with diethyl ether and filter through a pad of silica eluting with 5% triethylamine in diethylether. After removal of solvent the crude product was chromatographed on silica eluting with 5%

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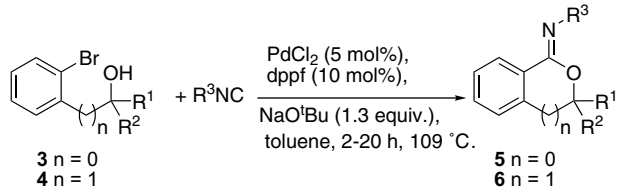

Scheme 3.

Table 1. Palladium catalysed synthesis of imidates **5** and **6**

R^1	R^2	R^3	Product	Yield %[a]
H	H	^{t}Bu	**5a**	76
H	H	^{n}Bu	**5b**	61
H	H	*c*-C_6H_{11}	**5c**	75
H	H	CH_2Ph	**5d**	44
H	Me	^{t}Bu	**5e**	82
Me	Me	^{t}Bu	**5f**	63
H	H	^{t}Bu	**6a**	60
H	H	^{n}Bu	**6b**	38
H	H	*c*-C_6H_{11}	**5c**	50
Me	Me	^{t}Bu	**6d**	84

[a] Isolated yield.

triethylamine in petrol to afford the pure cyclic imidates. Aqueous work-up, or chromatography without the presence of base gave partial hydrolysis to the corresponding lactones.

It is notable that both 5- and 6-membered ring imidates could be formed, the isonitrile could be primary, secondary or tertiary, and the alcohol could be primary, secondary or tertiary. The conversions to **5a**, **5f** and **6a** after 1 h were 37%, 51% and 21%, respectively, indicating that neither the size of ring formed, nor steric hindrance of the alcohol has a big effect on the rates of reaction and suggesting that the rate of attack of the alcohol on the supposed iminoacylpalladium intermediate is not rate limiting.

Although we have not proven the shown (*Z*)-stereochemistry of the imidates **5** and **6** formed, calculations indicate it to be substantially more stable than the (*E*)-form.[5] Exposure of the imidates to acid—conditions expected to equilibriate the geometric isomers—caused only slow hydrolysis to afford the expected lactones.

In conclusion we have shown that benzo-fused cyclic amidines and imidates are readily obtained by a palladium catalysed coupling, and the latter, in particular is a versatile process.[6]

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5. The (*E*)-isomer of **5/6** was more stable than the (*Z*)- by between 24 (**5b**) and 72 (**6d**) kJ/mol according DFT (B3YLP/6-31G*) calculations. Calculations were carried out using Spartan04, Wavefuntion Inc. In the case of *N*-*tert*-butyl-substituted imidates *E*/*Z* isomerisation would be expected to be fast at room temperature: Gallis, D. E.; Crist, D. R. *Magn. Reson. Chem.* **1987**, *25*, 480–483.
6. (*Z*)-*N*-(Isobenzofuran-1(3*H*)-ylidene)-2-methylpropan-2-amine **5a**. Dry sodium *tert*-butoxide (0.25 g, 2.6 mmol), dppf (0.111 g, 0.20 mmol) and 2-bromobenzyl alcohol (0.374 g, 2 mmol) were added to a 20 mL tube equipped with a reflux condenser and the vessel flushed with argon. Dry degassed toluene (10 mL), *tert*-butylisonitrile (0.25 g, 3.0 mmol in 1 mL toluene) were added by syringe before solid palladium dichloride (17.4 mg, 0.1 mmol) was added against a flow of argon. The tube was then heated at 109 °C with stirring in a thermostatically controlled block under an argon atmosphere for 8 h. After cooling to room temperature the reaction mixture was filtered through a 1–2 cm bed of silica on a sinter funnel washing through with a solution of 5% triethylamine in diethyl ether. After removal of solvent the residue was chromatographed on silica eluting with 3% triethylamine in petrol (bp 40–60 °C) to afford the title compound **5a** as a pale yellow oil, which solidified on storage. Recrystallisation from hexane gave very pale yellow crystals of the *title imidate* mp 61–63 °C. Anal. $C_{12}H_{15}NO$ requires: C, 76.16; H, 7.99; N, 7.40%. Found: C, 75.80; H, 8.02; N, 7.33%. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.81 (1H, br d, J = 7.4 Hz), 7.46 (1H, br t, J = 7.4 Hz), 7.39 (1H, br t, J = 7.5 Hz), 7.32 (1H, br d, J = 7.6 Hz), 5.30 (2H, s), 1.40 (9H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 157.0 (C), 142.6 (C), 132.2 (C), 131.0 (CH), 128.4 (CH), 123.9 (CH), 121.3 (CH), 72.2 (CH_2), 53.7 (C), 30.3 (CH_3) ppm. MS (ES^+) *m*/*z* 204 ($M+H^+$, 100%). IR (neat) 1691 (br s), 1467 (m), 1352 (s), 1215 (s), 1035 (s), 994 (s), 723 (s) cm^{-1}.