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Palladium-catalysed synthesis of imidates, thioimidates and amidines from aryl halides

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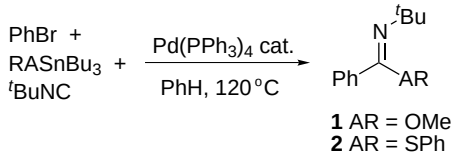
Abstract—Palladium-catalysed coupling between aryl- or heteroaryl-bromides, alkoxides, aryloxides or thioalkoxides, and isocyanides gives aryl-imidates and -thioimidates in high yield. Amidines can be synthesised in a one-pot procedure via imidates.

Imidates and thioimidates are important building blocks in organic synthesis, especially for heterocyclic compounds.[1] They also undergo displacement reactions with amines to give amidines,[2] which are important constituents of many biologically active compounds.[3] The most important methods for their preparation include reaction between imidoyl halides and *O*- or *S*-nucleophiles[4] and conversion of amides and thioamides to imidates and thioimidates, respectively.[5] A more recent method is based on the use of imidoyl-benzotriazoles as synthetic equivalents of the very hydrolysis sensitive imidoyl chlorides.[6] All these routes require several steps, and a one-pot method would be of great use, especially for applications in parallel synthesis.

Palladium-catalysed coupling reactions have found widespread application as tools for parallel synthesis. Important examples are elaborations of aryl halides, for example by Suzuki couplings with arylboronates,[7] or Buchwald/Hartwig coupling with amines.[8] We recently described a palladium-catalysed three-component coupling between aryl bromides, *tert*-butyl isocyanide and amines to give amidines.[9] We now report the analogous synthesis of imidates and thioimidates in which a variety of isocyanides may be used, and the in situ conversion of the former into amidines.

Kosugi[10] described a palladium-catalysed coupling reaction between bromobenzene, *tert*-butyl isocyanide and tributylstannyl methoxide (10% $[Pd(PPh_3)_4]$, benzene, 120°C, 20 h) to afford the imidate **1** ($AR^1 = OMe$) in 63% yield by gas chromatography (GC), whereas use of tributylstannyl thiophenoxide gave the thioimidate **2** ($AR^1 = SPh$) in a GC yield of 10% (Eq. (1)). The palladium-catalysed synthesis of esters from aryl halides, carbon monoxide and alcohols is a well-known reaction.[11]



(1)

Initial studies used bromobenzene, *tert*-butyl isocyanide, palladium dichloride (5 mol%), 1,1′-bis(-diphenylphosphino)ferrocene (dppf, 10 mol%) and ethanol in toluene at 110°C. With caesium carbonate as a base, as used in our synthesis of amidines,[9] conversion into the imidate **3a** was 50% after 2 h, and complete after 19 h. Using sodium ethoxide, conversion into **3a** was quantitative after 2 h, so these conditions were selected for preparative reactions. Thus, the imidate **3a** could be formed in 92% isolated yield from bromobenzene (1 mmol), sodium ethoxide (5 mmol in 1 mL ethanol), *tert*-butyl isocyanide (1.5 mmol), $PdCl_2$ (0.05 mmol), dppf (0.10 mmol) in toluene (5 mL) at 109°C for 2 h (Eq. (2), Table 1, entry 1). Ethyl *N*-*tert*-butyl imidates could be formed from electron-rich, electron-poor, and heteroaromatic precursors (Table 1, entries 2–4). We were delighted to find that reaction of cyclohexyl- and *n*-butyl-isocyanides with bromobenzene and sodium ethoxide gave the imidates **3e** and **3f** in

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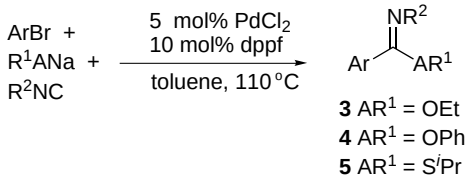


(2)

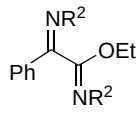
Table 1. Palladium-catalysed synthesis of imidates and thioimidates

Entry	ArX	R^1ANa	R^2NC	Product (**3**–**5**)	Yield of **3**–**5** (%)[a]
1	C_6H_5Br	EtONa	^{t}BuNC	**3a**	92
2	*p*-$MeOC_6H_4$	EtONa	^{t}BuNC	**3b**	82
3	*p*-NCC_6H_4	EtONa	^{t}BuNC	**3c**	89
4	3-Bromopyridine	EtONa	^{t}BuNC	**3d**	70
5	C_6H_5Br	EtONa	CyNC	**3e**	39/84[b]
6	C_6H_5Br	EtONa	BuNC	**3f**	30/70[b]
7	C_6H_5Br	EtONa	BnNC	**3g**	52[b]
8	*p*-NCC_6H_4	EtONa	CyNC	**3h**	72
9	3-Bromopyridine	EtONa	CyNC	**3i**	69
10	C_6H_5Br	PhONa	^{t}BuNC	**4a**	86
11	C_6H_5Br	PhONa	CyNC	**4b**	69
12	C_6H_5Br	PhONa	BuNC	**4c**	68
13	*p*-NCC_6H_4	PhONa	CyNC	**4d**	83
14	C_6H_5Br	^{i}PrSNa	^{t}BuNC	**5a**	74
15	C_6H_5Br	^{i}PrSNa	CyNC	**5b**	64
16	C_6H_5Br	^{i}PrSNa	BuNC	**5c**	62
17	C_6H_5Br	^{i}PrSNa	BnNC	**5d**	40

[a] Isolated yield. Conditions: 1.0 equiv. aryl bromide, 1.5 equiv. R^2NC, 5 mol% $PdCl_2$, 10 mol% dppf, 5.0 equiv. $NaOR^1$ or $NaSR^1$, toluene, 109°C, 2–5 h.

[b] As footnote a but using dioxane as the solvent, $[Pd_2dba_3{\cdot}CHCl_3]$ 2.5 mol%, 98°C, isocyanide added over 2 h.

moderate yields. The main side reaction was formation of the double insertion product **6**.[12] Changing the catalyst to (dibenzylideneacetone)dipalladium(0)–chloroform adduct $[Pd_2dba_3{\cdot}CHCl_3]$ and the solvent to dioxane improved the ratio of **3e**:**6** from 1:2 to 1:1.2. The formation of **6** could be completely suppressed by slow addition of the isocyanide affording **3e** and **3f** in excellent yields (Table 1, entries 5 and 6, conditions b). Under these conditions a moderate yield of **3g** was obtained using benzyl isocyanide. It is interesting that the electron-poor aromatic halides 4-bromobenzonitrile and 3-bromopyridine gave good yields of the imidates **3h** and **3i** from cyclohexyl isocyanide without resort to slow addition (Table 1, entries 8 and 9).



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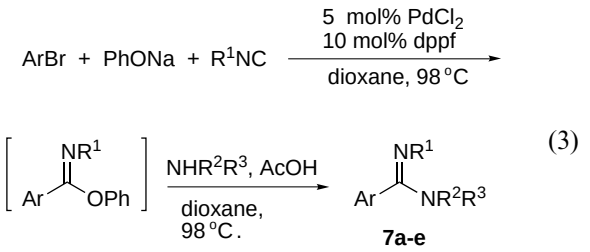
Next, we tried the reaction with the less basic sodium phenoxide, which gave rise to the expected mono-insertion products **4a**–**d** in very good yields for *tert*-butyl as well as other isocyanides without the need of slow addition (Table 1, entries 10–13). Although phenol is much more acidic than ethanol, phenoxide has comparable nucleophilicity to ethoxide.[13] Finally, use of the sodium salt of isopropane thiol allowed for the synthesis of thioimidates **5a**–**d** (Table 1, entries 14–17), whereas the sodium salt of thiophenol did not work.

A drawback of our previously reported amidine synthesis is that it only worked well with *tert*-butyl isocyanide.[9] Since the imidate/thioimidate synthesis reported above works with a range of isocyanides we looked to apply the conversion of imidates to amidines[2] to overcome the limitation. Reaction of the phenoxyimidate **4b** with 5 equiv. of pyrrolidine and 2 equiv. of HCl in dioxane at reflux for 24 h gave the amidine **7a** in reasonable yield. The weaker acid catalysts acetic acid and trifluoroacetic acid gave much faster conversions. Dioxane proved a suitable solvent for both the palladium-catalysed imidate formation, and subsequent conversion to amidines; thus, a one-pot procedure was possible. Thus palladium-catalysed reaction of an aryl bromide with sodium phenoxide and cyclohexyl- or *n*-butyl-isocyanide in dioxane at 98°C for 4 h followed by addition of an amine (5 equiv.) and acetic acid (3 equiv.) and heating for a further 3 h gave the amidines **7** in excellent overall yields (Eq. (3), Table 2).

Overall, we have demonstrated that a representative range of imidates and thioimidates may be formed in good yield from aryl halides, isocyanides, and alkanols, phenols, or alkanethiols. A one-pot procedure for the synthesis of amidines via the corresponding imidates, which overcomes the isocyanide component limitations of the direct amidine synthesis, has also been established. The developed methodologies should find application in the synthesis of valuable intermediates as well as in pharmaceutical discovery.



(3)

Table 2. Synthesis of amidines via imidates

ArX	Amine R^2, R^3	R^1NC	**7**	Yield of **7** (%)[a]
C_6H_5Br	-$(CH_2)_4$-	CyNC	**a**	60
p-$MeCOC_6H_4Br$	Ph, H	CyNC	**b**	84[b]
C_6H_5Br	-$(CH_2)_2O(CH_2)_2$-	BuNC	**c**	56
C_6H_5Br	-$(CH_2)_2O(CH_2)_2$-	CyNC	**d**	64
3-Bromopyridine	-$(CH_2)_4$-	CyNC	**e**	83
C_6H_5Br	$PhCH_2$, H	BuNC	**f**	49

[a] Isolated yield. Conditions: 1.0 equiv. aryl bromide, 1.5 equiv. R^2NC, 5 mol% $PdCl_2$, 10 mol% dppf, 5.0 equiv. NaOPh, dioxane, 98°C, 4 h. Addition of 5.0 equiv. amine and 3.0 equiv. of AcOH. Heating at 98°C for 2 h.

[b] Aniline required heating for 74 h in the amidine formation step.

Experimental

Compound **7d**: To a 50 mL Schlenk flask with a reflux condenser under argon at room temperature was added dppf (0.12 g, 0.22 mmol), sodium phenoxide (6 mL of a 1.7 M soln. in THF, 10 mmol), bromobenzene (0.324 g, 2.1 mmol) in dioxane (2 mL), and cyclohexyl isocyanide (380 μL, 3.0 mmol). Palladium(II) chloride (19.1 mg, 0.11 mmol) was then added against a counterflow of argon; then dry and deoxygenated dioxane (13 mL) was used to wash all solids from the sides of the flask. The flask was then heated at 98°C (oil bath temp, the internal temp was 92°C) for 3 h, when GC indicated complete loss of bromobenzene. The reaction mixture was allowed to cool to room temperature before morpholine (0.88 g, 10 mmol) and glacial acetic acid (0.24 g, 4.0 mmol) in dioxane (2×1 mL) were added. After heating for 8 h at 98°C, GC indicated complete loss of the intermediate imidate. After cooling to room temperature diethyl ether (20 mL) was added and the resulting slurry extracted with aqueous hydrochloric acid (6×10 mL, 0.2 M). The combined aqueous layers were washed with ether (6×15 mL) then made strongly basic by addition of KOH pellets. The aqueous layer was then extracted with diethyl ether (6×30 mL), the ethereal layer dried over $MgSO_4$ filtered and evaporated to give brown–greyish crystals which were Kugelrohr distilled (oven temp. 120–130°C/1 mmHg) to give white crystals of the amidine **7d** (0.348 g, 64%); mp 74–76°C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.42 (3H, m), 7.149 (2H, dd, $J=7.8$, 2 Hz), 3.640 (4H, t, $J=4.8$ Hz), 3.148 (4H, t, $J=4.8$ Hz), 2.752 (1H, tt, $J=10.2$, 4.1 Hz), 1.646 (2H, d pentet, $J=13$, 3.7 Hz), 1.46–1.50 (3H, m), 1.343 (2H, qd, $J=11.7$, 3.3 Hz), 1.147 (1H, qt, $J=12.0$, 3.5 Hz), 1.038 (2H, qt, $J=12.2$, 3.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.41 (C), 135.07 (C), 128.91 (CH), 128.76 (CH), 128.15 (CH), 67.33 (CH_2), 58.71 (CH), 46.87 (CH_2), 35.76 (CH_2), 26.15 (CH_2), 25.23 (CH_2); MS (electrospray): m/z 273.1 ($(M+H)^+$, 100%); IR (neat): ν 2955 (m), 2930 (m), 2879 (m), 1608 (s), 1586 (m), 1407 (m), 1337 (m), 719 (m). Elemental analysis (%) calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28. Found: C, 74.89; H, 8.96; N, 10.11%.

Acknowledgements

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