SHORT PAPER

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Synthesis of *N*-substituted derivatives of *tert*-butyl 4-aminobenzoate via a palladium-catalysed reaction

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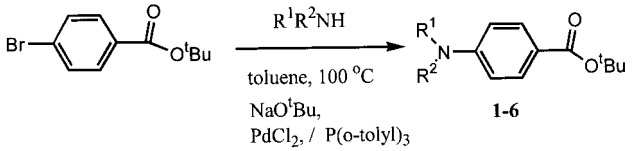
Amination of *tert*-butyl 4-bromobenzoate using $PdCl_2$ (7% mol) and P(*o*-tolyl)$_3$ provides a convenient route to *N*-substituted derivatives of *tert*-butyl 4-aminobenzoate.

In connection with ongoing work aimed at the synthesis of anticancer agents we were interested in the preparation of *N*-substituted derivatives of *tert*-butyl 4-aminobenzoate.

It was thought that this class of compounds could be prepared via a palladium-catalysed amination of *tert*-butyl 4-bromobenzoate with the appropriate free amine. The catalytic amination of aryl bromides with free amines was first reported by Buchwald[1] and Hartwig[2] and constitutes one of the most exciting developments in the carbon–nitrogen bond formation.[3,4]

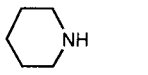
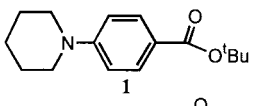
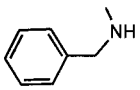
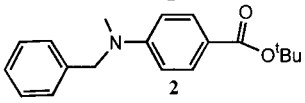
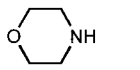
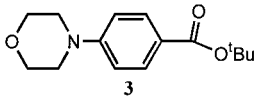
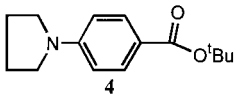
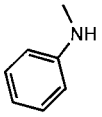
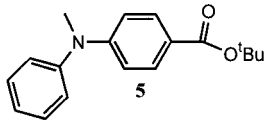
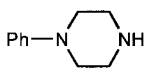
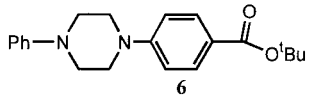


Scheme 1

In our initial attempts to synthesise **1** (Table 1) a variety of conditions, based on Buchwald's protocol,[1] were employed including $Pd_2(dba)_3$ / P(o-tolyl)$_3$, NaO^{t}Bu that afforded the desired compound in 63% yield. Interestingly, we found that compound **1** could also be obtained in 80% yield utilising $PdCl_2$ (7% mol) and P(o-tolyl)$_3$ (Scheme 1). Subsequently, the scope of this catalyst system ($PdCl_2$ / P(o-tolyl)$_3$) for the amination of *tert*-butyl 4-bromobenzoate was further explored, and compounds **1–6** were prepared in yields higher than 60% (Table 1). It should be noted that 7% mol $PdCl_2$ catalyst was required for the reaction to work satisfactorily. In addition, we found that more consistent results were obtained using toluene that was dried by distillation over P_2O_5 than the commercially available anhydrous solvent. All compounds prepared in this study are new with the exception of compound **1** that has been recently synthesised by a different methodology.[5]

In conclusion, amination of *tert*-butyl 4-bromobenzoate using $PdCl_2$ / P(o-tolyl)$_3$ as the catalyst system provides a convenient route to *N*-substituted derivatives of *tert*-butyl 4-aminobenzoate. These compounds could be useful intermediates for the synthesis of chemotherapeutic agents.

Table 1 *N*-Substituted Derivatives of *tert*-butyl 4-aminobenzoate

Amine	Product	Yield
	 **1**	80%
	 **2**	62%
	 **3**	61%
	 **4**	64%
	 **5**	60%
	 **6**	72%

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Experimental

General: Proton NMR spectra were recorded using a Bruker AC250 spectrometer, and field strengths are expressed in units of δ relative to tetramethylsilane. Fast atom bombardment (FAB) mass spectra were determined with a VG ZAB-SE spectrometer. Electrospray ionisation (ESI) mass spectra were recorded using a TSQ 700 triple quadrupole mass spectrometer. Thin layer chromatography (TLC) was performed on precoated sheets of silica $60F_{254}$ (Merck Art 5735), and visualisation was achieved under UV. Merck silica 60 (Art 15111) was used in low pressure column chromatography. Melting points were determined on a Kofler block and are uncorrected. Elemental analysis were determined by C.H.N. Analysis Limited, Leicester, UK. Commercially available chemicals were purchased from Aldrich Chemical Co, Gillingham, Dorset, UK or Lancaster Synthesis Ltd, Lancashire UK. Petrol refers to light petroleum (b.p. 60-80 °C). Toluene was dried by distillation over P_2O_5. *Tert*-Butyl 4-bromobenzoate was prepared according to the literature methodology.[6]

Tert-butyl 4-piperidin-1-yl-benzoate **(1)**: To a stirred solution of *tert*-butyl 4-bromobenzoate (0.180 g, 0.70 mmol) in anhydrous toluene (5 ml) under argon was added piperidine (0.071 g, 0.84 mmol) followed by NaO^{t}Bu (0.094 g, 0.98 mmol) $PdCl_2$ (8.7 mg, 0.05 mmol), and P(o-tolyl)$_3$ (0.059 g, 0.20 mmol). The reaction mixture was stirred at room temperature for 4 min, then it was placed in an oil bath preheated to 100 °C and was stirred at this temperature for 2 h under argon. The reaction mixture was allowed to cool to room temperature and then partitioned between ethyl acetate (40 ml) and brine (30 ml). The aqueous layer was extracted with more ethyl acetate (30 ml). The combined ethyl acetate extracts were dried (Na_2SO_4), and concentrated *in vuo*. Purification by column chromatography, on elution with 10% ethyl acetate in hexanes, afforded the title compound **1** as a white solid (0.145 g, 80%), m.p. 99–102 °C; ^{1}H-NMR ($CDCl_3$) δ 1.57 (s, 9H, ^{t}Bu), 1.60–1.75 (m, 6H, piperidine $CH_2CH_2CH_2$), 3.28-3.34 (m, 4H, piperidine CH_2NCH_2), 6.85 (d, *J* = 8.9 Hz, 2H, 3,5-ArH), 7.86 (d, *J* = 8.8 Hz, 2H, 2,6-ArH); MS (ESI, *m/z*) 262 $(M+H)^+$; Found C, 73.6; H, 8.8; N, 5.1; $C_{16}H_{23}NO_2$ requires C, 73.5; H, 8.9; N, 5.4%.

Tert-Butyl 4-(N-benzyl-N-methyl)aminobenzoate **(2)**: The method followed that used to prepare **1**, but using *tert*-butyl 4-bromobenzoate (0.180 g, 0.70 mmol) in anhydrous toluene (5 ml),

N-methylbenzylamine (0.101 g, 0.84 mmol), NaO^{t}Bu (0.094 g, 0.98 mmol), $PdCl_2$ (8.7 mg, 0.05 mmol), and P(o-tolyl)$_3$ (0.059 g, 0.20 mmol). The reaction mixture was stirred at 100 °C for 5 h. Work-up and purification as described for **1** afforded the title compound **2** as a solid (0.128 g, 62%), m.p. 78 °C; ^{1}H-NMR ($CDCl_3$) δ 1.56 (s, 9H, ^{t}Bu), 3.11 (s, 3H, N-Me), 4.62 (s, 2H, PhC*H*$_2$), 6.68 (d, *J* = 9.0 Hz, 2H, 3,5-ArH), 7.20-7.65 (m, 5H, Ph), 7.84 (d, *J* = 8.0 Hz, 2H, 2,6-ArH); MS (ESI, *m/z*) 298 (M+H)$^+$; Found C, 76.6; H, 7.8; N, 4.6; $C_{19}H_{23}NO_2$ requires C, 76.7; H, 7.8; N, 4.7%.

Tert-Butyl 4-morpholin-4-yl-benzoate **(3)**. The method followed that used to prepare **1**, but using *tert*-butyl 4-bromobenzoate (0.180 g, 0.70 mmol) in anhydrous toluene (5 ml), morpholine (0.073 g, 0.84 mmol), NaO^{t}Bu (0.094 g, 0.98 mmol), $PdCl_2$ (8.7 mg, 0.05 mmol), and P(o-tolyl)$_3$ (0.059 g, 0.20 mmol). The reaction mixture was stirred at room temperature for 4 min, then at 100°C for 4.5 h. Work-up and purification as described for **1** afforded the title compound **3** as a white solid (0.112 g, 61%), m.p. 121–122°C; ^{1}H-NMR ($CDCl_3$) δ 1.58 (s, 9H, ^{t}Bu), 3.27 (t, *J* = 4.8 Hz, 4H, CH_2NCH_2), 3.87 (t, *J* = 4.8 Hz, 4H, CH_2OCH_2), 6.86 (d, *J* = 8.9 Hz, 2H, 3,5-ArH), 7.90 (d, *J* = 8.9 Hz, 2H, 2,6-ArH); MS (ESI, *m/z*) 264 (M+H)$^+$; Found C, 68.3; H, 8.1; N, 5.3; $C_{15}H_{21}NO_3$ requires C, 68.4; H, 8.0; N, 5.3%.

Tert-Butyl 4-pyrrolidin-1-yl-benzoate **(4)**. The method followed that used to prepare **1**, but using *tert*-butyl 4-bromobenzoate (0.180 g, 0.70 mmol) in anhydrous toluene (5 ml), pyrrolidine (0.059 g, 0.84 mmol), NaO^{t}Bu (0.094 g, 0.98 mmol), $PdCl_2$ (8.7 mg, 0.05 mmol), and P(o-tolyl)$_3$ (0.059 g, 0.20 mmol). The reaction mixture was stirred at room temperature for 4 min, then at 100 °C for 4.5 h. Work-up and purification as described for **1** afforded the title compound **4** as a white solid (0.110 g, 64%), m.p. 132-134 °C; ^{1}H-NMR ($CDCl_3$) δ 1.57 (s, 9H, ^{t}Bu), 2.00-2.06 (m, 4H, pyrrolidine CH_2CH_2), 3.30–3.37 (m, 4H, CH_2NCH_2), 6.49 (d, *J* = 8.9 Hz, 2H, 3,5-ArH), 7.86 (d, *J* = 9.2 Hz, 2H, 2,6-ArH); MS (ESI, *m/z*) 248 (M+H)$^+$; Found C, 72.8; H, 8.6; N, 5.7; $C_{15}H_{21}NO_2$ requires C, 72.8; H, 8.6; N, 5.6%.

Tert-Butyl 4-(N-methyl-N-phenyl)aminobenzoate **(5)**. The method followed that used to prepare **1**, but using *tert*-butyl 4-bromobenzoate (0.129 g, 0.5 mmol) in anhydrous toluene (3.5 ml), *N*-methylaniline (0.064 g, 0.60 mmol), NaO^{t}Bu (0.067 g, 0.70 mmol) $PdCl_2$ (6.2 mg, 0.035 mmol), and P(o-tolyl)$_3$ (0.042 g, 0.14 mmol). The reaction mixture was stirred at room temperature for 4 min, then at 100 °C for 18 h. More catalyst (0.003 g), and tri(o-tolyl)phosphine (0.010 g) were added and stirring was continued for 2 h. Work-up and purification as described for **1** afforded the title compound **5** as a pale yellow gum (0.084 g, 60%), ^{1}H-NMR ($CDCl_3$) δ 1.57 (s, 9H, ^{t}Bu), 3.36 (s, 3H, NCH_3), 6.77 (d, *J* = 7.5 Hz, 2H, 3,5-ArH), 7.14–7.21 (m, 3H) and 7.35 (t, *J* = 5.2 Hz, 2H) (5H, N-Ph), 7.83 (d, *J* = 8.5 Hz, 2H, 2,6-ArH); MS (FAB, *m/z*) 283 (M)$^+$; Found C, 76.2; H, 7.5; N, 4.7; $C_{18}H_{21}NO_2$ requires C, 76.3; H, 7.5; N, 4.9%.

Tert-Butyl 4-(4-phenylpiperazin-1-yl)benzoate **(6)**. The method followed that used to prepare **1**, but using *tert*-butyl 4-bromobenzoate (0.180 g, 0.7 mmol) in anhydrous toluene (5 ml), 1-phenylpiperazine (0.139 g, 0.84 mmol), NaO^{t}Bu (0.094 g, 0.98 mmol), $PdCl_2$ (8.7 mg, 0.05 mmol), and P(o-tolyl)$_3$ (0.059 g, 0.2 mmol). The reaction mixture was stirred at room temperature for 4 min, then at 100 °C for 12 h. Work-up and purification as described for **1** afforded the title compound **6** as a white solid (0.170 g, 72%), m.p. 160–161 °C, ^{1}H-NMR (DMSO-d_6) δ 1.52 (s, 9H, ^{t}Bu), 3.24–3.32 (m, 4H), 3.42–3.47 (m, 4H), ($N(CH_2CH_2)_2N$), 6.81 (t, *J* = 6.8 Hz, 1H), 7.24 (t, *J* = 8.3 Hz, 2H), N-Ph *m*- and *p*-H), 7.00 (t (two overlapping doublets), *J* = 7.4 Hz, 4H, 3,5-ArH and N-Ph *o*-H), 7.74 (d, *J* = 8.4 Hz, 2,6-ArH); MS (ESI, *m/z*) 339 (M+H)$^+$; Found C, 74.6; H, 7.8; N, 8.3; $C_{21}H_{26}N_2O_2$ requires C, 74.5; H, 7.7; N, 8.3%.

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