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Palladium-catalysed ortho arylation of acetanilides

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Abstract. The palladium-catalysed direct arylation of acetanilides by using C–H activation methodology has been demonstrated. Several acetanilides were coupled with aryl iodides in the presence of 10 mol% of $Pd(OAc)_2$, 1·0 equiv of $Cu(OTf)_2$, and 0·6 equiv of Ag_2O to afford the corresponding products in moderate to excellent yields. The results showed that the amount of Ag_2O was important for this protocol.

Keywords. Palladium; acetanilides; C–H activation; aryl iodides; 2-arylacetanilides; 2,6-diarylacetanilides.

1. Introduction

Aryl-aryl bond formation plays an important role in the area of modern organic synthesis. These bonds are common in natural products, pharmaceuticals, catalyst ligands, and materials.[1] Traditionally, transition metalcatalysed cross-coupling reactions of organometallic reagents and aryl halides or pseudohalides constitute one of the most useful methods for the synthesis of biaryl molecules. However, these strategies, requiring installation of functionality on both coupling components, are neither atom economic nor green.[2] C–H functionalization is the most sustainable and straight-forward method to construct complicated structures and has received significant attention in the past several decades.[3] Various functional groups containing heteroatoms such as acetoamino,[4] oxazolyl,[5] pyridyl,[6] or imino[7] groups act as directing groups, and influence the regioselectivity of the reaction. With the help of acetamido group, ortho C–H of acetanilide could be functionlized[8] regioselectively. Shi and coworkers have developed palladium-catalysed ortho-arylation of amides with aryl boronic acids[8f] and trialkoxysilanes,[8g] using $Cu(OTf)_2$ and Ag(I) as stoichiometric oxidants. Daugulis has reported coupling reactions of pivalanilides with aryl iodides using a catalytic amount of $Pd(OAc)_2$ and 1 equivalent of $Ag(OAc)_2$ as an additive.[8j] In this method, highly acidic CF_3COOH must be used as solvent, and only 2,6-diarylpivalanilides were obtained when pivalanilide and 4-substituted pivalanilides were used as substrates. Inspired by these results, we report here ortho arylation of acetanilide with aryl iodides in the presence of $Pd(OAc)_2$ (10 mol%), $Cu(OTf)_2$ (1·0 equiv), and Ag_2O (0·6 equiv).

2. Experimental

NMR spectra were recorded on a Mercury 4N-PEG-300 (^1H: 300 MHz; ^{13}C: 75 MHz) spectrometer, using $CDCl_3$ as a solvent and TMS as the internal standard. IR spectra were recorded on Nicolet Nexus 670 FT–TR spectrophotometer in KBr pellets or KBr film. Mass spectra were recorded by the EI method on a HP 5998 mass spectrometer.

2.1 *General experimental procedure*

A mixture of acetanilide **1** (0·2 mmol), aryl iodide **2** (1 mmol 5·0 equiv), $Pd(OAc)_2$ (0·02 mmol, 0·10 equiv), anhydrous $Cu(OTf)_2$ (0·2 mmol, 1·0 equiv), Ag_2O (0·12 mmol, 0·6 equiv.) and dried 1,2-dichloroethane (2 ml) was added to a 14 × 90 mm glass test tube. The tube was sealed with a rubber plug, and the reaction mixture was stirred and heated at 90°C in an oil bath. The progress of the reaction was monitored by thin-layer chromatography. After completion, the reaction mixture was poured into an excess of water and extracted with CH_2Cl_2 (3 × 1 ml). The organic phases were dried and the

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solvent was evaporated. The residue was purified by preparative TLC using petroleum ether-EtOAc (8 : 1) as the eluent to afford the desired coupled products.

2.1a *N-(4,5-Dimethyl-biphenyl-2-yl)-acetamide* (**3aa**): White solid; m.p.: 120–121°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7·95 (*s*, 1H, NH), 7·45–7.34 (*m*, 5H), 7·05 (*d*, *J* = 12·30 Hz, 2H), 2·30 (*s*, 3H), 2·26 (*s*, 3H), 2·00 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168·26, 138·31, 136·71, 132·93, 132·05, 131·01, 130·34, 129·17, 128·83, 127·53,123·47, 24·33, 19·69, 19·15; IR (KBr plate, $CDCl_3$, cm^{-1}) ν = 3276, 3025, 1667, 1521; MS (EI): *m*/*z* = 239, 197. Anal. Calcd. for $C_{16}H_{17}NO$: C, 80·30; H, 7·16; N, 5·85. Found: C, 80·48; H, 7·30; N, 5·92.

2.1b *N-(5-Chloro-biphenyl-2-yl)-acetamide* (**3ba**): White solid; m.p.: 115–116°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19 (*d*, *J* = 8·70 Hz, 1H, NH), 7·50–7·39 (*m*, 3H), 7·33–7·27 (*m*, 3H), 7·22–7·16 (*m*, 2H), 1·94 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168·17, 136·77, 133·72, 133·27, 129·71, 129·16, 128·93, 128·40, 128·13, 122·92, 24·41; IR (KBr plate, $CDCl_3$, cm^{-1}) ν = 3267, 2920, 1666, 1517; MS (EI): *m*/*z* = 247, 245, 203. Anal. Calcd. for $C_{14}H_{12}ClNO$: C, 68·44; H, 4·92; N, 5·70. Found: C, 68·61; H, 4·79; N, 5·54.

2.1c *N-Acetyl-4-chloro-2,6-diphenyl-aniline* (**4ba**): White solid; m.p.: 176–177°C ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7·43–7·35 (*m*, 12H), 6·51 (*s*, 1H, NH), 1·68 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 68·39, 142·50, 138·55, 133·16, 130·00, 129·65, 128·56, 128·33, 127·79, 22·69; IR (KBr plate, $CDCl_3$, cm^{-1}) ν = 3228, 2924, 1655, 1515; MS (EI): *m*/*z* = 323, 321, 279. Anal. Calcd. for $C_{20}H_{16}ClNO$: C, 74·65; H, 5·01; N, 4·35. Found: C, 74·71; H, 5·11; N, 4·28.

2.1d *N-(3-Methyl-biphenyl-2-yl)-acetamide* (**3ca**): White solid; m.p.: 106–108°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7·41–7·22 (*m*, 7H), 7·17–7·14 (*m*, 1H), 6·98 (*s*, 1H, NH), 2·27 (*s*, 3H), 1·93 (*s*, 3H);^{13}C NMR (75 MHz, $CDCl_3$): δ = 169·43, 139·57, 139·52, 136·70, 132·57, 129·95, 128·72, 128·15, 127·76, 127·27, 127·18, 22·77, 18·47; IR (KBr plate, $CDCl_3$, cm^{-1}) ν = 3257, 3027, 1660, 1524; MS (EI): *m*/*z* = 225, 183. Anal. Calcd. for $C_{15}H_{15}NO$: C, 79·97; H, 6·71; N, 6·22. Found: C, 80·15; H, 6·54; N, 6·39.

2.1e *N-(4-Chloro-biphenyl-2-yl)-acetamide* (**3ea**): White solid; m.p.: 108–109°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8·37 (*s*, 1H, NH), 7·51–7·42 (*m*, 3H), 7·34–7·30 (*m*, 2H), 7·24–7·14 (*m*, 1H), 7·11 (*s*, 2H), 2·00 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168·16, 137·00, 135·63, 133·94, 130·84, 130·16, 129·22, 129·06, 128·27, 124·20, 121·21 24·55· IR (KBr plate, $CDCl_3$, cm^{-1}) ν = 3278, 2919, 1673, 1516; MS (EI): *m*/*z* = 247, 245, 203. Anal. Calcd. for $C_{14}H_{12}ClNO$: C, 68·44; H, 4·92; N, 5·70. Found: C, 68·29; H, 4·99; N, 5·85.

2.1f *N-Biphenyl-2-yl-acetamide* (**3fa**): White solid; m.p.: 104–105°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (*d*, J = 8·10 Hz, 1H, NH), 7·51–7·34 (*m*, 6H), 7·25–7·13 (*m*, 3H), 2·02 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168·19, 138·07, 134·55, 132·34, 129·94, 129·06, 128·91, 128·22, 127·79, 124·32, 121·84, 24·33; IR (KBr plate, $CDCl_3$, cm^{-1}) ν = 3288, 3028, 1661, 1532; MS (EI): *m*/*z* = 211, 169. Anal. Calcd. for $C_{14}H_{13}NO$: C, 79·59; H, 6·20; N, 6·63. Found: C, 79·41; H, 6·38; N, 6·47.

2.1g *N-Acetyl-2,6-diphenyl-aniline* (**4fa**)*:* White solid; m.p.: 228–230°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7·45–7·33 (*m*, 13H), 6·73 (*s*, 1H, NH), 1·65 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169·36, 140·89, 139·76, 129·85, 129·11, 128·70, 128·10, 127·65, 127·21, 22·70; IR (KBr plate, $CDCl_3$, cm^{-1}) ν = 3232, 3025, 1653, 1522; MS (EI): *m*/*z* = 287, 245. Anal. Calcd. for $C_{20}H_{17}NO$: C, 83·59; H, 5·96; N, 4·87. Found: C, 83·44; H, 6·14; N, 5·01.

2.1h *N-(5-Methyl-biphenyl-2-yl)-acetamide* (**3ga**)*:* White solid; m.p.: 104–106°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8·06 (*d*, *J* = 8·40 Hz, 1H, NH), 7·48–7·33 (*m*, 5H), 7·16 (*d*, *J* = 8·40 Hz, 1H), 7·05 (*s*, 2H), 2·27 (*s*, 3H), 1·99 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168·19, 138·34, 134·06, 132·50, 132·05, 130·58, 129·13, 128·91, 128·87, 127·76, 122·06, 24·38, 20·80; IR (KBr plate, $CDCl_3$, cm^{-1}) ν = 3271, 3028, 1666, 1518; MS (EI): *m*/*z* = 225, 183. Anal. Calcd. for $C_{15}H_{15}NO$: C, 79·97; H, 6·71; N, 6·22. Found: C, 79·79; H, 6·89; N, 6·12.

2.1i *N-Acetyl-4-methyl-2,6-diphenyl-aniline* (**4ga**): White solid; mp: 206–208°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7·40–7·32 (*m*, 10H), 7·19 (*s*, 2H), 6·53 (*s*, 1H, NH), 2·42 (*s*, 3H), 1·63 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169·61, 140·81, 139·90, 137·52, 130·61, 129·11, 128·73, 128·60, 127·19,

22·79, 21·05; IR (KBr plate, $CDCl_3$, cm^{-1}) $\nu = 3275$, 3023, 1658, 1523; MS (EI): $m/z = 301$, 259. Anal. Calcd. for $C_{21}H_{19}NO$: C, 83·69; H, 6·35; N, 4·65. Found: C, 83·85 H, 6·19; N, 4·74.

2.1j *N-(3-Methoxy-4'-methyl-biphenyl-2-yl)-acetamide* (**3hb**)*:* White solid; m.p.: 124–125°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7·26–7·18$ (*m*, 5H), 6·93 (*d*, $J = 8·40$ Hz, 2H), 6·66 (*s*, 1H, NH), 3·87 (*s*, 3H), 2·40 (*s*, 3H), 2·00 (*s*, 2H), 1·68 (*s*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169·50$, 155·09, 140·91, 136·94, 136·45, 128·90, 128·44, 128·00, 122·83, 122·38, 110·29, 55·87, 23·14, 21·12; IR (KBr plate, $CDCl_3$, cm^{-1}) $\nu = 3254$, 2955, 1665, 1519; MS (EI): $m/z = 255$, 213. Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75·27; H, 6·71; N, 5·49. Found: C, 75·19; H, 6·88; N, 5·63.

2.1k *N-(4,4',5-Trimethyl-biphenyl-2-yl)-acetamide* (**3ab**): White solid; m.p.: 122–124°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7·95$ (*s*, 1H, NH), 7·24 (*t*, $J = 8·4$ Hz, 4H), 7·07 (*s*, 1H), 7·01 (*d*, $J = 14·4$ Hz, 1H), 2·40 (*s*, 3H), 2·29 (*s*, 3H), 2·24 (*s*, 3H), 2·00 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168·21$, 137·32, 136·50, 135·26, 132·78, 132·16, 131·03, 130·11, 129·57, 129·04, 123·22, 24·39, 21·11, 19·68, 19·16; IR (KBr plate, $CDCl_3$, cm^{-1}) $\nu = 3275$, 3022, 1668, 1522; MS (EI): $m/z = 253$, 211. Anal. Calcd. for $C_{17}H_{19}NO$: C, 80·60; H, 7·56; N, 5·53. Found: C, 80·72; H, 7·69; N, 5·59.

2.1l *N-(4-Chloro-4'methyl-biphenyl-2-yl)-acetamide* (**3eb**): White solid; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8·40$ (*s*, 1H, NH), 7·29 (*d*, $J = 8·40$ Hz, 2H), 7·21 (*d*, $J = 8·10$ Hz, 3H), 7·12 (*s*, 2H), 2·42 (*s*, 3H), 2·01 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168·14$, 138·23, 135·81, 134·04, 133·86, 131·86, 130·87, 129·98, 128·98, 124·16, 121·00, 24·61 21·18; IR (KBr plate, $CDCl_3$, cm^{-1}) $\nu = 3273$, 2920, 1668, 1517; MS (EI): $m/z = 261$, 259, 217. Anal. Calcd. for $C_{15}H_{14}ClNO$: C, 69·36; H, 5·43; N, 5·39. Found: C, 69·51; H, 4·60; N, 5·23.

2.1m *N-(3',4,5-Trimethyl-biphenyl-2-yl)-acetamide* (**3ac**): White solid; m.p.: 92–93°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7·98$ (*s*, 1H, NH), 7·34 (*t*, $J = 7·2$ Hz, 1H), 7·21–7·09 (*m*, 4H), 7·02 (*s*, 1H), 2·41 (*s*, 3H), 2·31 (*s*, 3H), 2·25 (*s*, 3H), 2·01 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168·15$, 138·64, 138·22, 136·59, 132·73, 132·12, 130·95, 130·23, 129·95,128·67, 128·28, 126·10, 123·18, 24·38, 21·40, 19·69, 19·14; IR (KBr plate, $CDCl_3$, cm^{-1}) $\nu = 3271$, 3022, 1665, 1522; MS (EI): $m/z = 253$, 211. Anal. Calcd. for $C_{17}H_{19}NO$: C, 80·60; H, 7·56; N, 5·53. Found: C, 68·49; H, 7·43; N, 5·62.

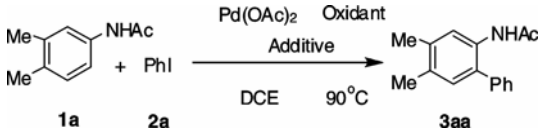
2.1n *N-(3'-Methyl-biphenyl-2-yl)-acetamide* (**3fc**): White solid; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8·27$ (*d*, $J = 7·20$ Hz, 1H, NH), 7·39–7·33 (*m*, 2H), 7·26–7·18 (*m*, 6H), 2·41 (*s*, 3H), 2·01 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168·19$, 138·89, 138·04, 134·68, 132,18 131·78, 129·97, 128·87, 128·66,128·27, 126·10, 124·21, 121·43, 24·59, 21·43; IR (KBr plate, $CDCl_3$, cm^{-1}) $\nu = 3291$, 3033, 1687, 1520; MS (EI): $m/z = 225$, 183. Anal. Calcd. for $C_{15}H_{15}NO$: C, 79·97; H, 6·71; N, 6·22. Found: C, 80·13; H, 6·58; N, 6·40.

2.1o *N-Acetyl-2,6-di-(3-chlorophenyl)-aniline* (**4fc**): White solid; m.p.: 110–112°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7·42–7·28$ (*m*, 4H), 7·21–7·14 (*m*, 7H), 6·55 (*s*, 1H, NH), 2·41 (*s*, 6H), 1·70 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 69·17$, 140·81, 139·76, 137·77, 131·18, 130·19, 129·80, 129·48, 127·98, 127·60, 125·72, 22·89, 21·46; IR (KBr plate, $CDCl_3$, cm^{-1}) $\nu = 3241$, 3027, 1657, 1526; MS (EI): $m/z =$ 315, 273. Anal. Calcd. for $C_{22}H_{21}NO$: C, 83·78; H, 6·71; N, 4·44. Found: C, 83·62; H, 6·86; N, 4·53.

2.1p *N-(4'-Methoxy-4,5-dimethyl-biphenyl-2-yl)-acetamide* (**3ad**): White solid; m.p.: 136–138°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7·95$ (*s*, 1H, NH), 7·27 (*d*, $J = 8·7$ Hz, 2H), 7·05–6·97 (*m*, 4H), 3·85 (*s*, 3H), 2·95 (*s*, 3H), 2·24 (*s*, 3H), 2·01 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168·16$, 159·05, 136·38, 132·78, 132·25, 131·07, 130·44, 130·31, 129·87, 123·21, 114·28, 55·26, 24·40, 19·66, 19·14; IR (KBr plate, $CDCl_3$, cm^{-1}) $\nu = 3289$, 1674, 1517; MS (EI): $m/z = 269$, 227. Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75·81; H, 7·11; N, 5·20. Found: C, 75·94; H, 7·01; N, 5·30.

2.1q *N-(4'-Ethoxy-4,5-dimethyl-biphenyl-2-yl)-acetamide* (**3ae**): White solid; m.p.: 102–103°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7·95$ (*s*, 1H, NH), 7·25 (*d*, $J = 8.4$ Hz, 2H), 7·07–6·95 (*m*, 4H), 4·08 (*dd*, $J = 6·9$, 6·9 Hz, 2H), 2·29 (*s*, 3H), 2·24 (*s*, 3H), 2·01 (*s*, 3H) 1·45 (*t*, $J = 6·9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168·16$, 158·42, 136·31, 132·74, 132·24, 131·06, 130·28, 129·92, 123·18, 114·78, 63·45, 24·39, 19·66, 19·14, 14·78; IR (KBr plate, $CDCl_3$, cm^{-1}) $\nu = 3286$, 1669, 1518; MS (EI): $m/z = 283$, 241. Anal. Calcd. for $C_{18}H_{21}NO_2$: C,

Table 1. Ortho arylation of acetanilide under different conditions[a]



1a 2a 3aa

Entry	Pd (mol %)	Oxidant (equiv)	Additive (equiv)	Solvent (ml)	**3aa**[b] %
1	$Pd(OAc)_2$ (10·0)	$Cu(OAc)_2$ (1·0)	–	DCE	16
2	$Pd(OAc)_2$ (10·0)	BQ (1·0)	–	DCE	0
3	$Pd(OAc)_2$ (10·0)	CuCl (1·0)	–	DCE	0
4	$Pd(OAc)_2$ (10·0)	$Cu(OTf)_2$ (1·0)	–	DCE	33
5	$Pd(OAc)_2$ (10·0)	$Cu(OTf)_2$ (1·0)	Ag_2O (1·0)	DCE	43
6	$Pd(OAc)_2$ (10·0)	$Cu(OTf)_2$ (2·0)	Ag_2O (1·0)	DCE	46
7	$Pd(OAc)_2$ (10·0)	$Cu(OTf)_2$ (1·0)	Ag_2O (0·6)	DCE	83
8	$Pd(OAc)_2$ (10·0)	$Cu(OTf)_2$ (1·0)	Ag_2O (0·5)	DCE	78
9	$Pd(OAc)_2$ (10·0)	$Cu(OTf)_2$ (1·0)	Ag_2O (0·6)	Toluene	80
10	$Pd(OAc)_2$ (10·0)	$Cu(OTf)_2$ (1·0)	Ag_2O (0·6)	Dioxane	78

[a]All the reactions were carried out in the presence of 0·1 mmol of **1a** and 0·5 mmol **2a** in the solvent mentioned in each entry (1·0 mL) at 90°C for14 h. [b]isolated yields

76·29; H, 7·47; N, 4·94. Found: C, 76·44; H, 7·61; N, 4·81.

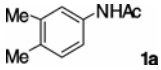
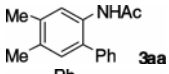
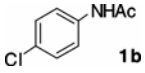
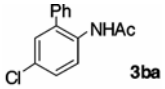
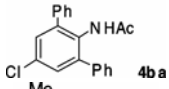
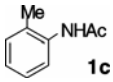
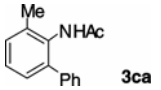
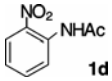
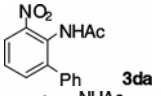
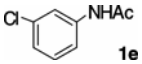
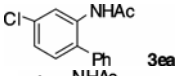
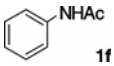
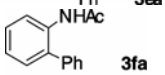
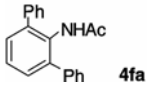
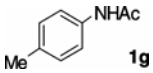
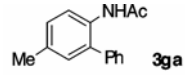
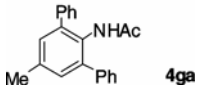
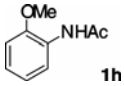
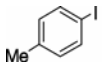
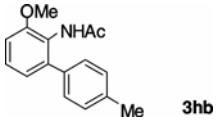
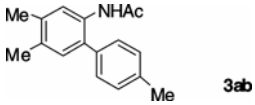
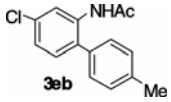
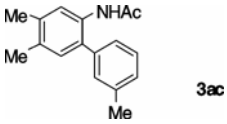
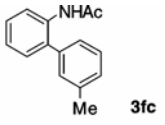
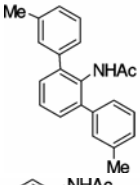
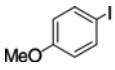
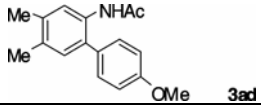
2.1r *N-(4-Chloro-4'-ethoxy-biphenyl-2-yl)-acetamide* (**3ee**): White solid; m.p.: 132–134°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8·38 (*s*, 1H, NH), 7·26–7·12 (*m*, 5H), 7·02 (*m*, 2H), 4·09 (*dd*, *J* = 7·20 Hz, 2H), 2·02 (*s*, 3H), 1·43 (*t*, *J* = 7·20 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168·11, 158·94, 135·85, 133·64, 130·91, 130·28, 129·79, 128·86, 124·08, 120·91, 115·15, 63·57, 24·65, 14·79; IR (KBr plate, $CDCl_3$, cm^{-1}) ν = 3301, 2920, 1666, 1517; MS (EI): *m*/*z* = 291, 289, 247. Anal. Calcd. for $C_{16}H_{16}ClNO_2$: C, 66·32; H, 5·57; N, 4·83. Found: C, 66·49; H, 5·41; N, 5·01.

2.1s *N-(3'-Chloro-4,5-dimethyl-biphenyl-2-yl)-acetamide* (**3af**)*:* White solid; m.p.: 106–108°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7·83 (*s*, 1H, NH), 7·37–7·34 (*m*, 3H), 7·26–7·22 (*m*, 1H), 7·00 (*s*, 2H), 2·29 (*s*, 3H), 2·25 (*s*, 3H), 2·01 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168·41, 140·27, 137·32, 133·41, 131·84, 130·86, 129·95, 129·43, 129·31, 127·63, 127·27, 124·25, 109·71, 24·23, 19·71, 19·17; IR (KBr plate, $CDCl_3$, cm^{-1}) ν = 3259, 3022, 1662, 1524; MS (EI): *m*/*z* = 275, 273, 231. Anal. Calcd. for $C_{16}H_{16}ClNO$: C, 70·20; H, 5·89; N, 5·12. Found: C, 70·36; H, 5·78; N, 5·16.

2.1t *N-(4'-Iodo-4,5-dimethyl-biphenyl-2-yl)-acetamide* (**3ag**)*:* White solid; m.p.: 176–178°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7·85 (*s*, 1H, NH), 7·77 (*d*, *J* = 8·40 Hz, 2H), 7·09 (*d*, *J* = 8·40 Hz, 2H), 6·96 (*d*, J = 10·80, 2H), 2·29 (*s*, 3H), 2·25 (*s*, 3H), 2·02 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168·39, 137·91, 137·21, 133·44, 131·79, 131·06, 130·81, 129·70, 124·24, 93·32, 24·28, 19·71, 19·18; IR (KBr plate, $CDCl_3$, cm^{-1}) ν = 3254, 3020, 1653, 1525; MS (EI): *m*/*z* = 365, 323. Anal. Calcd. for $C_{16}H_{16}INO$: C, 52·62; H, 4·42; N, 3·84. Found: C, 52·74; H, 4·33; N, 4·01.

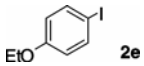
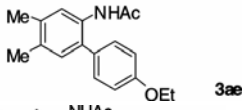
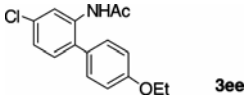
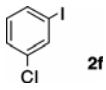
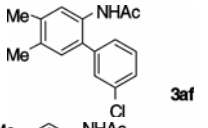
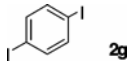
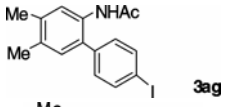
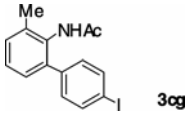
2.1u *N-(4'-Iodo-3-methyl-biphenyl-2-yl)-acetamide* (**3cg**)*:* White solid; m.p.: 148–150°C; ^{1}H NMR

Table 2. Arylation of acetanilides.[a]

Entry	Acetanilide	Aryl iodide	Arylation acetanilide	Time/h	Yield[b] %
1	 **1a**	 **2a**	 **3aa**	14	83
2	 **1b**	**2a**	 **3ba**  **4ba**	18	51 13
3	 **1c**	**2a**	 **3ca**	18	69
4	 **1d**	**2a**	 **3da**	24	0
5	 **1e**	**2a**	 **3ea**	16	65
6	 **1f**	**2a**	 **3fa**  **4fa**	18	60 21
7	 **1g**	**2a**	 **3ga**  **4ga**	18	53 24
8	 **1h**	 **2b**	 **3hb**	24	69
9	**1a**	**2b**	 **3ab**	14	79
10	**1e**	**2b**	 **3eb**	16	70
11	**1a**	 **2c**	 **3ac**  **3fc**	14	80 49
12	**1f**	**2c**	 **4fc**	18	18
13	**1a**	 **2d**	 **3ad**	15	82

(*Contd...*)

Table 2. (*Contd...*)

Entry	Acetanilide	Aryl iodide	Arylation acetanilide	Time/h	Yield[b] %
14	**1a**	 **2e**	 **3ae**	15	80
15	**1e**	**2e**	 **3ee**	16	73
16	**1a**	 **2f**	 **3af**	15	67
17	**1a**	 **2g**	 **3ag**	24	49
18	**1c**	**2g**	 **3cg**	24	40

[a]All the reactions were carried out with acetanilide **1** (0·2 mmol) and aryl iodide **2** (1·0 mmol) in the presence of Pd $(OAc)_2$ (10 mol%), $Cu(OTf)_2$ (1·0 equiv), and Ag_2O (0·6 equiv) in DCE (2 ml) at 90°C. [b]isolated yields

(300 MHz, $CDCl_3$): $\delta = 7{\cdot}72$ (*d*, $J = 8{\cdot}40$ Hz, 2H), 7·31–7·25 (*m*, 2H), 7·14–7·11 (*m*, 1H), 7·06 (*d*, $J = 8{\cdot}40$ Hz, 2H), 6·66 (*s*, 1H, NH), 2·29 (*s*, 3H), 2·01 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 69{\cdot}34$, 139·16, 138·67, 137·39, 137·03, 132·34, 130·72, 130·46, 128·46, 127·65, 94·25, 23·04, 18·54; IR (KBr plate, $CDCl_3$, cm^{-1}) $\nu = 3246$, 3022, 1646, 1524; MS (EI): $m/z = 351$, 309. Anal. Calcd. For $C_{15}H_{14}INO$: C, 51·30; H, 4·02; N, 3·99. Found: C, 51·46; H, 4·17; N, 3·84.

3. Results and discussion

In our initial screening experiments, acetanilide (**1a**) and iodobenzene (**2a**) were used as the prototype substrates for optimizing the reaction conditions. When **1a** and **2a** were catalysed with $Pd(OAc)_2$ in the presence of $Cu(OAc)_2$, **3aa** was isolated in low yield (table 1, entry 1). It was found that $Cu(OTf)_2$ was more effective than $Cu(OAc)_2$ as oxidant for this transformation (table 1, entry 4). We studied the effect of additive and solvent on this reaction. When **1a** was treated with **2a** under the conditions utilized by Shi group for the arylation of N-alkyl acetanilides, compound **3aa** was only isolated in 43% yield (table 1, entry 5). Further studies indicated that the amount of Ag_2O was very important for this reaction. A 83% yield of **3aa** was obtained when the amount of Ag_2O was decreased to 60 mol % (table 1, entry 7). Among the solvents tried, 1,2-dichloroethane (DCE) proved to be the most suitable (table 1, entry 7, 9 and 10).

The optimized reaction conditions were applied for the arylation of a number of differently substituted acetanilides with a variety of aryl iodides (table 2). Of the aromatic aryl iodides investigated, 1,4-diiodobenzene (**2g**) gave the lowest yield of arylated product (table 2, entry 17, 18). On the other hand, acetanilides substituted in 2-or 3-positions only afforded monoarylated products. Both monoarylation and diarylation products were attained, when acetanilide (**1f**) and 4-substituted acetanilides were used as substrates (table 2, entry 2, 6, 7, 12). We found that 2-nitroacetanilide did not undergo arylation under the standard reaction conditions (table 2, entry 4).

4. Conclusions

In conclusion, a direct and efficient method for the ortho arylation of acetanilides has been developed. A number of acetanilides were coupled with aryl iodides to afford the corresponding products in moderate to high yields. Further investigations on the scope and synthetic applications of this reaction are in progress.

Acknowledgement

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