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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 6529–6532

Efficient, protection-free Suzuki–Miyaura synthesis of *ortho*-biphenyltetrazoles

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Received 14 April 2005; revised 12 July 2005; accepted 19 July 2005

Abstract—We describe an efficient protocol for the Suzuki–Miyaura synthesis of *ortho*-biphenyltetrazoles from non-protected 2-bromophenyltetrazole and arylboronic acids. The optimised conditions were achieved using [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) as catalyst and Na_2CO_3 as base. A panel of structurally diverse arylboronic acids was used to demonstrate the scope of the coupling procedure.

The palladium-catalysed Suzuki–Miyaura cross-coupling reaction of aryl halides with arylboronic acids and esters has become a common and convenient synthetic method for the production of biaryl compounds.[1] This method has been introduced with success for the preparation of *ortho*-biphenyltetrazoles[2] and applied for the industrial-scale synthesis of a non-peptide angiotensin II receptor antagonist.[3]

In addition to their pivotal pharmacophoric role in the binding to the angiotensin II receptors, biphenyltetrazoles provide unique pharmacokinetics properties.[4] Biphenyltetrazoles have thus been introduced in the design of non-peptidic ligands for GHS receptor.[5]

More recently, this privileged structure has been used for the design of biphenyltetrazole derivatives showing competitive inhibition potency for the Carbapenem- and Cephamycin-resistant dinuclear zinc metallo-β-lactamase from *Bacteroides fragilis*.[6]

Xu et al. have also published potent 3-biphenyltetrazole containing inhibitors of DPP-IV, a novel therapeutic approach to the treatment of type 2 diabetes.[7]

All reported syntheses to date make use of a two steps protection–deprotection sequence. The classical protecting group employed for tetrazole is the trityl group.[8] In this paper, we describe an optimised Suzuki–Miyaura cross-coupling of non-protected and commercial 2-bromophenyltetrazole with arylboronic acids.

The first part of the study aims at the optimisation of reaction conditions for the Suzuki–Miyaura microwave synthesis using the coupling reaction of 2-bromophenyltetrazole (**1a**) and 3-methoxyphenylboronic acid (**2a**) as a model.

Three parameters have been investigated: (1) nature of the palladium catalyst, (2) palladium catalyst concentration and (3) nature of the base.

Firstly, based on known conditions, we examined different catalysts ($Pd(PPh_3)_2Cl_2$,[9a] $Pd(PPh_3)_4$,[9b] $Pd(OAc)_2$,[9c] Pd/C,[9d] $PdCl_2(dppf)$[9e]) using Na_2CO_3 as base and a mixture of DME/H_2O as solvent, at 115 °C. Microwave irradiation conditions were used to speed up the synthesis. The results are presented in Table 1.

The highest conversion to **3a** (83%) was observed in the presence of 10% $PdCl_2(dppf)$ as catalyst together with the lowest occurrence of the debrominated side product **4a** (16%) (entry 5).

Next, we examined the effect of base in the cross-coupling of 2-bromophenyltetrazole (**1a**) and 3-meth-

Keywords: *ortho*-Biphenyltetrazole; Suzuki–Miyaura cross-coupling; Microwave synthesis.
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URL: http://www.magicbullet.org.

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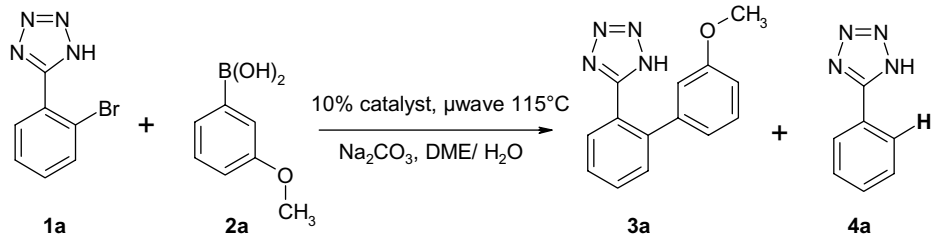
doi:10.1016/j.tetlet.2005.07.082

Table 1. Effects of palladium catalyst nature on the Suzuki–Miyaura cross-coupling of **1a** and **2a**[a]

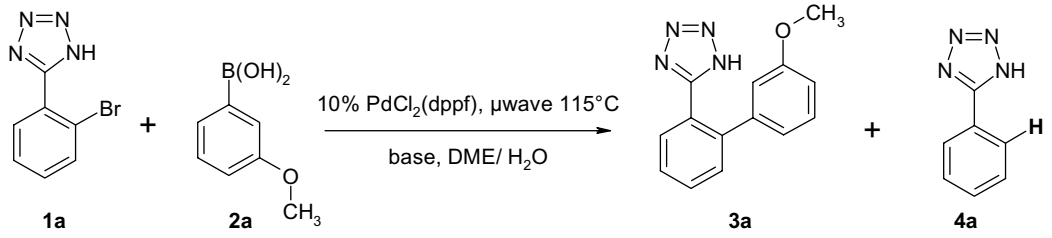


1a **2a** **3a** **4a**

Entry	Catalyst	**3a** formation (%)[b]	**4a** formation (%)[b]	Conversion (%)[b]
1	$Pd(PPh_3)_2Cl_2$	53	40	93
2	$Pd(PPh_3)_4$	53	25	78
3	$Pd(OAc)_2$	17	39	56
4	Pd/C	31	31	62
5	**$PdCl_2$(dppf)**	**83**	**16**	**99**

[a] All couplings were carried out with 0.3 mmol of 2-bromophenyltetrazole, 0.6 mmol of 3-methoxyphenylboronic acid, 0.45 mmol of Na_2CO_3 and 0.03 mmol of Pd catalyst in a mixture of 1.5 mL of DME and 0.6 mL of H_2O under Argon at 115 °C in microwave for 30 min.
[b] Formation is controlled with HPLC at 215 nm.

Table 2. Effect of base on the Suzuki–Miyaura cross-coupling of **1a** and **2a** with 10% $PdCl_2$(dppf)[a]



1a **2a** **3a** **4a**

Entry	Base	**3a** formation (%)[b]	**4a** formation (%)[b]	Conversion (%)[b]
1	**Na_2CO_3**	**83**	**16**	**99**
2	CsF	4	48	52
3	NaOH	8	45	53
4	$NaHCO_3$	38	34	72

[a] All couplings were carried out with 0.3 mmol of 2-bromophenyltetrazole, 0.6 mmol of 3-methoxyphenylboronic acid, 0.45 mmol of base and 0.03 mmol of $PdCl_2$(dppf) in a mixture of 1.5 mL of DME and 0.6 mL of H_2O under Argon at 115 °C in microwave for 30 min.
[b] Formation is controlled with HPLC at 215 nm.

oxyphenylboronic acid (**2a**) in the presence of 10% $PdCl_2$(dppf). The results are shown in Table 2.

The results show a dramatic effect of the nature of the base by the conversion to the desired biphenyltetrazole **3a** and on the formation of the undesired debrominated phenyltetrazole **4a**. The formation of this side product is increased when using non-carbonate bases such as CsF or NaOH. The best results were obtained using Na_2CO_3.

Finally, we investigated the minimum quantity of catalyst required to achieve a fast and complete conversion. We compared four conditions with decreasing amount of $PdCl_2$(dppf) using Na_2CO_3 as base. The results are shown in Table 3. The best results were obtained in the presence of a 10% catalyst concentration.

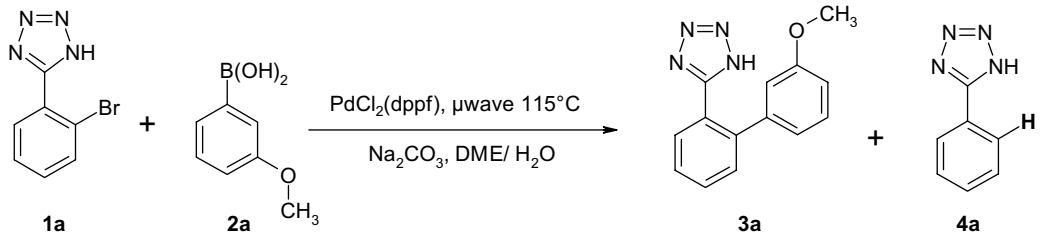
The formation of **4a** could be explained by a failure in the transmetallation step of the catalytic cycle. This bimolecular step could be compromised by a low concentration or reactivity of one of the two implied partners: (a) Ar–Pd(II)L_2–X and (b) Ar–$B(OH)_3^-$. Without transmetallation the Ar–Pd(II)L_2–X complex evolves to give Ar–H (**4a**).

Moreover the reaction was carried out with a classic heating mode (oil bath) as shown in Table 4. The formation of **3a** in such conditions is much slower than with the microwave one and the presence of by-product **4a** is also less significant.

To evaluate the scope and limitations of this procedure we examined the reaction of a variety of arylboronic acids using the following optimised conditions: 10% $PdCl_2$(dppf) catalyst, Na_2CO_3 as base in DME/H_2O, 30 min at 115 °C under microwaves. The results are presented in Table 5.

4-Pyridineboronic acid did not react quantitatively. By contrary, arylboronic acids with electron-withdrawing

Table 3. Effects of $PdCl_2$(dppf) concentrations on the Suzuki–Miyaura cross-coupling of **1a** and **2a**[a]



1a **2a** **3a** **4a**

Entry	$PdCl_2$(dppf) (equiv)	**3a** formation (%)[b]	**4a** formation (%)[b]	Conversion (%)[b]
1	**0.1**	**83**	**16**	**99**
2	0.033	55	31	86
3	0.01	30	33	63
4	0.0025	20	35	55

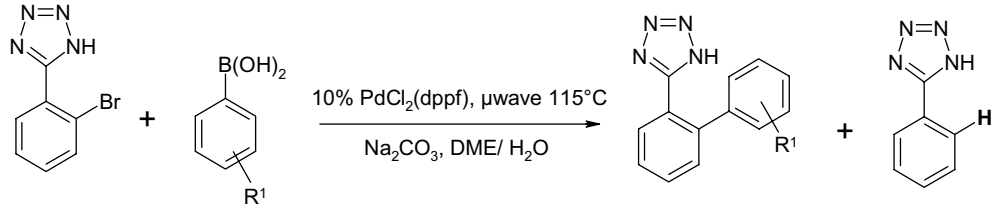
[a] All couplings were carried out with 0.3 mmol of 2-bromophenyltetrazole, 0.6 mmol of 3-methoxyphenylboronic acid, 0.45 mmol of Na_2CO_3 and *x* equiv of $PdCl_2$(dppf) in a mixture of 1.5 mL of DME and 0.6 mL of H_2O under Argon at 115 °C in microwave for 30 min.
[b] Formation is controlled with HPLC at 215 nm.

Table 4. Effects of the microwave on the kinetic of the Suzuki–Miyaura cross-coupling of **1a** and **2a**[a]

Heating mode	Reaction time	**3a** formation (%)[b]	**4a** formation (%)[b]	Conversion (%)[b]
Oil bath[c]	96 h	47	0.6	48
Microwave[d]	**0.5 h**	**83**	**16**	**99**

[a] All couplings were carried out with 0.3 mmol of 2-bromophenyltetrazole, 0.6 mmol of 3-methoxyphenylboronic acid, 0.45 mmol of Na_2CO_3 and 0.03 mmol of Pd catalyst in a mixture of 1.5 mL of DME and 0.6 mL of H_2O under Argon.
[b] Formation is controlled with HPLC at 215 nm.
[c] Temperature: 90 °C.
[d] Temperature 115 °C, pressure between 8 and 12 bar.

Table 5. $PdCl_2$(dppf) catalysed Suzuki–Miyaura cross-coupling of 2-bromophenyltetrazole **1a** and arylboronic acids[a]



1a **2** **3** **4a**

Entry	Product	R^1	**3** formation (%)[b]	**4a** formation (%)[b]	Yield (%)
1	**3a**	3-OCH_3	83	16	58
2	**3b**	4-CH_2OH	82	17	55
3	**3c**	4-CF_3	73 (23[c])	4	55
4	**3d**	4-$C(CH_3)_3$	73	5	57
5	**3e**	4-CHO	88	7	55
6	**3f**	3-F	91	6	58
7	**3g**	3-NH_2	93	5	60
8	**3h**	4-pyridine	40	10	30

[a] All couplings were carried out with 0.3 mmol of 2-bromophenyltetrazole, 0.6 mmol of 3-methoxyphenylboronic acid, 0.45 mmol of Na_2CO_3 and 0.03 mmol of $PdCl_2$(dppf) in a mixture of 1.5 mL of DME and 0.6 mL of H_2O under Argon at 115 °C in microwave for 30 min.
[b] Formation is controlled with HPLC at 215 nm.
[c] Formation of hydrolysed by-product.

substituents such as CF_3, CHO, F or electron-donating substituents such as NH_2, OCH_3 coupled readily with non-protected 2-bromophenyltetrazole with excellent yields (73–93%). Compound **3b**, with a free alcohol

group, was obtained with high yield, indicating that this group does not require a specific protection under the coupling conditions.[10]

In summary, this study shows that non-protected 2-bromophenyltetrazole can be efficiently coupled with a wide variety of arylboronic acids under $PdCl_2$(dppf) catalysed Suzuki–Miyaura cross-coupling procedure. This procedure is efficient, rapid and the compounds are recovered after a simple liquid/liquid extraction. This methodology is an efficient tool for the introduction of the 5-biphenyl-2-yl-1*H*-tetrazole core and the synthesis of biphenyltetrazoles, which are gaining increasing interest in medicinal chemistry.

Acknowledgements

The authors would like to thank Professors Jean-Claude Gesquière and André Tartar for helpful discussions, Gerard Montagne and Nathalie Azaroual from Lille 2 Biophysics laboratories for NMR experiments.

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10. Suzuki–Miyaura cross-coupling reaction: General procedure A glass tube was loaded with 2-bromophenyltetrazole (68 mg, 0.3 mmol), the appropriate arylboronic acid (0.6 mmol), Na_2CO_3 (48 mg, 0.45 mmol), $PdCl_2$(dppf) (24.5 mg, 0.03 mmol), DME (1.5 mL) and H_2O (0.6 mL). After one vacuum/Argon cycle to remove oxygen, the reaction tube was sealed; the mixture was stirred and heated at 115 °C in microwave oven for 30 min. The mixture was diluted with $NaHCO_3$ (5%) and ethyl acetate (10 ml). The organic layer was extracted with $NaHCO_3$ (5%) (4×20 mL) and aqueous layers were combined, washed with ethyl acetate (5 mL), acidified (pH = 1) and extracted with ethyl acetate (5×30 mL). The combined organic layers were dried ($MgSO_4$). The solvent was removed in vacuo.
5-(3′-Methoxy-biphenyl-2-yl)-1H-tetrazole (**3a**): Yield: 58%, pale yellow oil, ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 7.60$ (m, 3H, Harom); 7.43 (d, 1H, $J_{HH} = 7.5$ Hz, Harom); 7.30 (t, 1H, $J_{HH} = 7.5$ Hz, Harom); 7.18 (d, 1H, $J_{HH} = 6.3$ Hz, Harom); 6.99 (t, 1H, $J_{HH} = 7.2$ Hz, Harom); 6.86 (d, 1H, $J_{HH} = 8.4$ Hz, Harom); 3.30 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 132.1$ (*C*Harom); 131.4 (1*C*Harom); 131.3 (1*C*Harom); 130.1 (1*C*Harom); 128.2 (1*C*Harom); 121.2 (1*C*Harom); 111.5 (1*C*Harom); 55.31 (O–*C*H$_3$), LCMS (EI): $m/z = 253$ (base peak).
[2′-(1H-Tetrazol-5-yl)-biphenyl-4-yl]-methanol (**3b**): Yield: 55%, colourless oil, ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 7.69$ (m, 2H, Harom); 7.58 (m, 2H, Harom); 7.20 (t, 1H, $J_{CH} = 7.8$ Hz, Harom); 6.87 (dd, 1H, $J_{CH} = 8.1$ Hz, $J_{HH} = 1.8$ Hz, Harom); 6.63 (m, 2H, Harom); 3.67 (s, 2H, CH_2OH), ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 131.7$ (1*C*Harom); 131.2 (1*C*Harom); 130.0 (1*C*Harom); 127.6 (1*C*Harom); 121.7 (1*C*Harom); 115.0 (1*C*Harom); 113.7 (1*C*Harom); 55.6 (1*C*H$_2$OH), LCMS (EI): $m/z = 253$ (base peak), 235.
5-(4′-Trifluoromethyl-biphenyl-2-yl)-1H-tetrazole (**3c**): Yield: 55%, pale yellow oil, ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 7.67$ (m, 6H, Harom); 7.33 (d, 2H, $J_{CH} = 7.8$ Hz, Harom); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 131.7$ (1*C*Harom); 131.4 (1*C*Harom); 130.4 (2*C*Harom); 129.2 (1*C*Harom); 125.6 (2*C*Harom); 113.5 (1*C*Harom); LCMS (EI): $m/z = 291$ (base peak).
5-(4′-tert-Butyl-biphenyl-2-yl)-1H-tetrazole (**3d**): Yield: 57%, yellow oil, ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 7.62$ (m, 4H, Harom); 7.33 (d 2H, $J_{HH} = 8.4$ Hz, Harom); 7.02 (d, 2H, $J_{HH} = 8.4$ Hz, Harom); 1.26 (s, 9H, C(CH_3)$_3$), ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 131.7$ (1*C*Harom); 131.3 (2*C*Harom); 129.1 (2*C*Harom); 128.1 (1*C*Harom); 125.7 (2*C*Harom); 31.6 (C(*C*H$_3$)$_3$), LCMS (EI): $m/z = 279$ (base peak).
2′-(1H-Tetrazol-5-yl)-biphenyl-4-carbaldehyde (**3e**): Yield: 55%, pale yellow solid mp: 162–164 °C, ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 10.05$ (s, 1H, C*H*O); 7.85 (d, 2H, $J_{CH} = 7.5$ Hz, Harom); 7.62 (m, 4H, Harom); 7.33 (m, 2H, $J_{CH} = 7.5$ Hz, Harom), ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 193.4$ (1*C*HO); 135.4 (1*C*Harom); 131.8 (1*C*Harom); 131.3 (1*C*Harom); 130.3 (1*C*Harom); 130.0 (1*C*Harom); 129.25 (1*C*Harom); 128.9 (1*C*Harom); 127.6 (1*C*Harom), LCMS (EI): $m/z = 251$ (base peak).
5-(3′-Fluoro-biphenyl-2-yl)-1H-tetrazole (**3f**): Yield: 58%, pale yellow solid; mp 128–129 °C, ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 7.7$ (m, 2H, Harom); 7.58 (m, 2H, Harom); 7.34 (q, 1H, $J_{CH} = 6.3$ Hz, Harom); 7.15 (td, 1H, $J_{CH} = 8.7$ Hz, $J_{HH} = 2.4$ Hz, Harom); 6.99 (dt, 1H, $J_{CH} = 10.2$ Hz, $J_{HH} = 2.4$ Hz, Harom); 6.86 (d, 1H, $J_{CH} = 7.5$ Hz, Harom), ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 131.8$ (1*C*Harom); 131.3 (1*C*Harom); 131.2 (1*C*Harom); 130.8 (d, 1*C*harom-F); 128.9 (1*C*Harom); 125.6 (1*C*harom-F); 116.3 (d, 1*C*harom-F); 115.0 (d, 1*C*harom-F), LCMS (EI): $m/z = 241$ (base peak).
2′-(1H-Tetrazol-5-yl)-biphenyl-3-ylamine (**3g**): Yield: 60%, white solid recovered as hydrochloride salt; mp $\geqslant$300 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 8.22$ (sb, 2H, NH$_2$); 7.80 (t, 1H, $J_{HH} = 4.2$ Hz, Harom); 7.70 (m, 2H, Harom); 7.60 (t, 1H, $J_{HH} = 6.3$ Hz, Harom); 7.50 (d, 1H, $J_{HH} = 7.5$ Hz, Harom); 7.43 (d, 2H, $J_{HH} = 4.8$ Hz, Harom); 7.30 (t, 1H, $J_{HH} = 7.8$ Hz, Harom); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 131.9$ (1*C*Harom); 131.7 (1*C*q); 131.3 (1*C*Harom); 131.2 (1*C*Harom); 129.3 (1*C*Harom); 129.0 (1*C*Harom); 128.8 (1*C*Harom); 125.3 (1*C*Harom); LCMS (EI): $m/z = 238$ (base peak).
4-[2-1H-Tetrazol-5-yl)-phenyl]-pyridine (**3h**): Yield: 30%, white solid recovered as hydrochloride salt; mp $\geqslant$300 °C, ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 8.84$ (m, 2H, Harom); 8.32 (m, 2H, Harom), 7.84 (m, 4H, Harom); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 142.3$ (1*C*Harom); 140.6 (1*C*Harom); 132.1 (1*C*Harom); 131.6 (1*C*Harom); 131.3 (1*C*Harom); 131.2 (1*C*Harom); 127.9 (1*C*Harom); 125.3 (1*C*Harom); LCMS (EI): $m/z = 224$ (base peak).