Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 9255–9258

TETRAHEDRON
LETTERS

Selective double Suzuki cross-coupling reactions. Synthesis of unsymmetrical diaryl (or heteroaryl) methanes

Sandrine Langle, Mohamed Abarbri and Alain Duchêne*

Laboratoire de Physicochimie des Interfaces et des Milieux Réactionnels, Faculté des Sciences de Tours, Parc de Grandmont, F-37200 Tours, France

Received 12 August 2003; revised 15 September 2003; accepted 23 September 2003

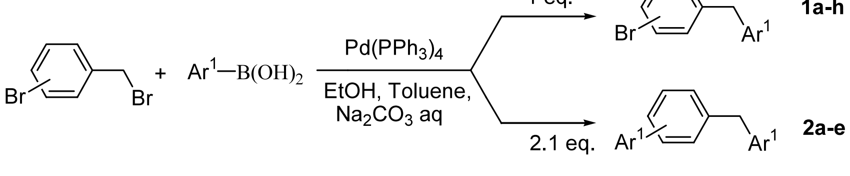
Abstract—Using a double Suzuki cross-coupling reaction *ortho*- or *para*-bromobenzyl bromides are easily transformed into unsymmetrical diaryl (or heteroaryl) methanes

The Suzuki reaction is one of the most versatile and often used reactions for the selective construction of carbon–carbon bonds, in particular for the preparation of biaryl-containing molecules.[1] Diarylmethanes are frequently used as subunits in the design of supramolecular structures such as macrocycles, catenanes and rotaxanes.[2] In addition, some diarylmethane derivatives have been shown to possess interesting biological and medicinal properties.[3] Morever biaryl units constitute important building blocks in natural products and advanced materials.[4] One of the best procedures for the synthesis of the title compounds is transition metal catalysed cross-couplings between either aryl nucleophiles and benzyl halides or aryl halides and benzylic nucleophiles. However the nucleophiles required are organomagnesium or organozinc halides which are incompatible with a variety of functional groups.[5]

Although the Suzuki coupling reaction is known with electrophiles that contain C(sp^2)–X bonds (e.g. aryl and vinyl halides or sulfonates),[6] there are few general methods to cross-couple electrophiles that contain C(sp^3)–X bonds. However, several reports on this subject have recently appeared in the literature, for example coupling of naphthylboronic acids with benzyl bromide,[7] 2-bromo-*N*,*N*-dimethylacetamide,[8] or ethyl bromoacetate,[9] alkyl bromides[10] and alkyl tosylates.[11] In view of the surprising lack of literature on the reactivity of the two bromine atoms of *p*-bromobenzyl bromide we wondered if a chemoselective reaction could be achieved.

In order to expand the scope of the Suzuki-type coupling reaction and to develop a convenient and practical method for the synthesis of new unsymmetrical diaryl (or heteroaryl) methanes, we decided to look more closely at the substitution reaction during the Suzuki cross-coupling reaction in the presence of palladium complexes.

We were able to substitute selectively only the bromine atom [C(sp^3)–Br] at the benzylic position of the starting *ortho*- or *para*-bromobenzyl bromides if we used 1 equiv. of aryl- or heteroarylboronic acid, toluene or



Scheme 1.

Keywords: boronic acids; palladium catalyst; Suzuki cross-coupling reactions.

* Corresponding author. Fax: +33-(0)2-4736-6960; e-mail: duchene@delphi.phys.univ-tours.fr

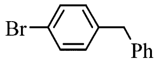
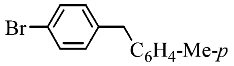
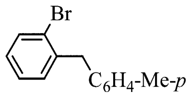
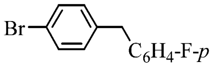
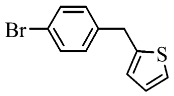
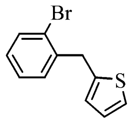
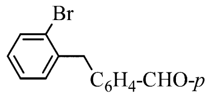
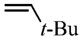
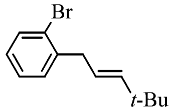
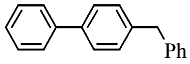
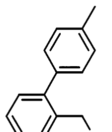
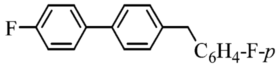
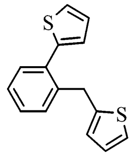
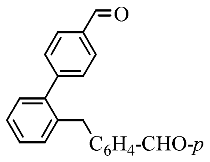
0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.10.080

benzene as solvent and 3 mol% of tetra-kis(triphenylphosphine)palladium(0) as catalyst (Scheme 1).[12]

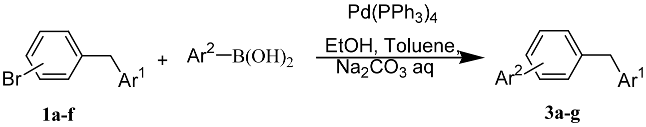
The results are reported in Table 1.

As can be seen in the results reported in Table 1, neither *para*-bromobenzyl bromide nor *ortho*-bromobenzyl bromide yielded a mixture of mono and bis-coupling products. As already reported,[7] clean double

Table 1.

Entry	Ar^1	Equiv.	Time/temp	Product	Yield[a] %	N°
1	Ph	1	15 h/80 °C		84	**1a**
2	p-Me-C_6H_4	1	15 h/80 °C		83	**1b**
3	p-Me-C_6H_4	1	15 h/80 °C		85	**1c**
4	p-F-C_6H_4	1	24 h/rt		71	**1d**
5	2-Thienyl	1	24 h/rt		59	**1e**
6	2-Thienyl	1	24 h/rt		61	**1f**
7	p-CHO-C_6H_4	1	36 h/rt		72	**1g**
8		1	24 h/50 °C		61	**1h**
9	Ph	2.1	15 h/80 °C		86	**2a**
10	p-Me-C_6H_4	2.1	15 h/80 °C		87	**2b**
11	p-F-C_6H_4	2.1	24 h/rt		79	**2c**
12	2-Thienyl	2.1	24 h/rt		59	**2d**
13	p-CHO-C_6H_4	2.1	18 h/80 °C		84	**2e**

[a] isolated yield



Scheme 2.

cross-coupling occurred using 2.1 equiv. of boronic acid (entries 9–13, Table 1).

As shown in Scheme 2 a clean second substitution is also possible under Suzuki conditions providing acceptable but not optimized yields of the new unsymmetric diaryl (or heteroaryl) methanes **3a**–**g**.[13] The results are presented in Table 2.

In conclusion we have described the synthesis of new *ortho*- and *para*-unsymmetric diarylmethanes, in good yields and under mild experimental conditions, from commercially available *o*- or *p*-bromobenzyl bromides through a double cross-coupling reaction.

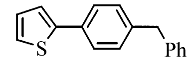
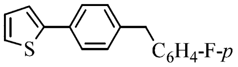
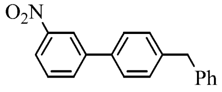
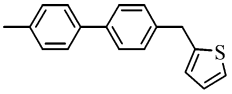
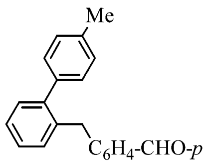
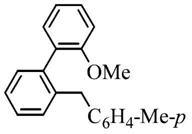
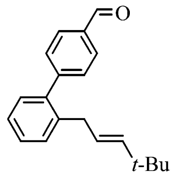
Acknowledgements

We thank the CNRS and MRT for providing financial support, and the 'Service d'analyse chimique du Vivant de Tours' for recording NMR and mass spectra.

References

1. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168; (c) Klingensmith, L.; Leadbeater, N. *Tetrahedron Lett.* **2003**, *44*, 765–768; (d) Leadbeater, N.; Marco, M. *J. Org. Chem.* **2003**, *68*, 888–892.
2. (a) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303–1324; (b) Jäfer, R.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 630.
3. (a) Rische, T.; Eilbracht, P. *Tetrahedron* **1999**, *55*, 1915–1920; (b) Prat, L.; Mojovic, L.; Levacher, V.; Dupas, G.; Quéquiner, G.; Bourguignon, J. *Tetrahedron: Asymmetry* **1998**, *9*, 2509–2516; (c) Ku, Y.-Y.; Patel, R. P.; Savick, D. P. *Tetrahedron Lett.* **1996**, *37*, 1949–1952; (d) de Lang, R.-J.; van Hooijdonk, M. J.; Brandsma, L.; Kramer, H.; Seinen, W. *Tetrahedron* **1998**, *54*, 2953–2956.

Table 2.

Entry	Ar^1	Ar^2	Time/temp	Product	Yield[a] %	N°
1	Ph	2-Thienyl	24 h/rt		60	**3a**
2	*p*-F-C_6H_4	2-Thienyl	24 h/rt		58	**3b**
3	Ph	*m*-NO_2-C_6H_4	15 h/80 °C		75	**3c**
4	2-Thienyl	*p*-Me-C_6H_4	15 h/80°C		77	**3d**
5	*p*-CHO-C_6H_4	*p*-Me-C_6H_4	15 h/80 °C		85	**3e**
6	*p*-Me-Ph	*o*-MeO-C_6H_4	15 h/80 °C		86	**3f**
7	=*t*-Bu	*p*-CHO-C_6H_4	18 h/80 °C		75	**3g**

[a] isolated yield

4. (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schultz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469; (b) Stanforth, S. *Tetrahedron* **1998**, *54*, 263–303.
5. Rottländer, M.; Knochel, P. *Tetrahedron Lett.* **1997**, *38*, 1749–1752 and references cited therein.
6. *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. S., Eds.; Wiley-VCH: New York, 1998.
7. (a) Chowdhury, S.; Georghiou, P. *Tetrahedron Lett.* **1999**, *40*, 7599–7603; (b) Oh, C. H.; Lim, Y. M. *Bull. Korean Chem. Soc.* **2002**, *23*, 663–664.
8. (a) Lu, T.-Y.; Xue, C.; Luo, F.-T. *Tetrahedron Lett.* **2003**, *44*, 1587–1590; (b) Liu, X.; Deng, M. *Chem. Commun.* **2002**, 622–623.
9. Gooßen, L. *Chem. Commun.* **2001**, 669–670.
10. Netherton, M.; Dai, C.; Neuschütz, F. G. *J. Am. Chem. Soc.* **2001**, *123*, 10099–10100.
11. Netherton, M.; Fu, G. *Angew. Chem., Int. Ed.* **2002**, *20*, 3910–3912.

12. **Typical experiment**: An oven-dried Schlenk flask was evacuated and back-filled with argon and charged with ethanol (33 mL), toluene (40 mL), bromobenzyl bromide (5 g, 20 mmol) and arylboronic acid (19 mmol). The flask was evacuated and back-filled with argon and then 2.3 mL of a 1 M solution of Na_2CO_3 and tetrakis(triphenylphosphine)palladium(0) (0.7 g, 0.6 mmol) were added. The reaction mixture was stirred at the desired temperature until completion of reaction at the benzylic position. The solution was then filtered through a Celite pad and the solvents were evaporated. The residue was extracted with diethyl ether, and dried over $MgSO_4$. After purification by flash chromatography the products were characterized by IR, ^{1}H, ^{13}C NMR and GC–MS. **1b**: Mp: 32–34°C; IR: 3033, 2921, 2857, 1632, 1514, 1487, 1435, 1404, 1265; ^{1}H NMR δ ppm ($CDCl_3$, 200 MHz): 2.35 (s, 3H), 3.92 (s, 2H), 7.06–7.12 (m, 6H), 7.42 (dt, $J=8.3$, 1.9 Hz, 2H); ^{13}C NMR δ ppm ($CDCl_3$, 50 MHz): 21.7, 41.5, 120.5, 129.4 (2C), 129.9 (2C), 131.2 (2C), 132.1 (2C), 136.4, 138.0, 141.0. MS (70 eV) m/z: 262 ($M^{+\bullet}$, 38), 260 ($M^{+\bullet}$, 39), 247 (20), 245 (20), 181 (100), 165 (97), 166 (97), 105 (15), 104 (11), 103 (11), 91 (13), 90 (29), 89 (75), 77 (37), 76 (44), 75 (18), 65 (23), 63 (47), 51 (39), 50 (34), 39 (54). **1c**: IR: 3051, 3021, 2920, 1566, 1513, 1438, 1025; ^{1}H NMR δ ppm ($CDCl_3$, 200 MHz): 2.43 (s, 3H), 4.19 (s, 2H), 7.16–7.31 (m, 7H), 7.66 (d, $J=7.9$ Hz, 1H); ^{13}C NMR δ ppm ($CDCl_3$, 50 MHz): 21.6, 41.9, 125.4, 128.0, 128.3, 129.4 (2C), 129.7 (2C), 131.6, 133.3, 136.3, 136.9, 141.2; MS (70 eV): $m/z=262$ ($M^{+\bullet}$, 47), 260 ($M^{+\bullet}$, 48), 247 (9), 245 (10), 181 (100), 178 (15), 166 (71), 165 (62), 89 (27), 76 (17), 63 (11), 39 (10). **1d**: IR: 3040, 2916, 1898, 1604, 1508, 1488, 1435, 1404, 1223; ^{1}H NMR δ ppm ($CDCl_3$, 200 MHz): 3.91 (s, 2H), 6.94–7.24 (m, 6H), 7.42 (d, $J=8.4$ Hz, 2H); ^{13}C NMR δ ppm ($CDCl_3$, 50 MHz): 40.9, 115.8 ($J_{C-F}=21.1$ Hz, 2C), 120.6, 130.7 ($J_{C-F}=7.5$ Hz, 2C), 131.0 (2C), 132.1 (2C), 136.6, 140.4, 162.0 ($J_{C-F}=244$ Hz); MS (70 eV) m/z: 266 ($M^{+\bullet}$, 30), 264 ($M^{+\bullet}$, 30), 185 (100), 183 (58), 165 (67), 109 (21), 92 (16), 90 (12), 89 (22), 83 (24), 76 (11), 75 (25), 73 (16), 63 (32), 62 (14), 57 (17), 51 (21), 50 (40), 39 (29); ^{19}F NMR δ ppm: −117.3.

13. Compounds **3** were obtained using the same methodology described in Ref. 12. **3b**: Mp: 45–47°C; IR: 3084, 3061, 3027, 2920, 1602, 1531, 1515, 1453, 1349; ^{1}H NMR δ ppm ($CDCl_3$, 200 MHz): 4.09 (s, 2H), 7.24–7.38 (m, 7H), 7.57–7.65 (m, 3H), 7.89–7.95 (m, 1H), 8.18–8.23 (m, 1H), 8.45–8.47 (m, 1H); ^{13}C NMR δ ppm ($CDCl_3$, 50 MHz): 42.1, 122.2, 122.3, 126.8, 127.7 (2C), 129.1 (2C), 129.4 (2C), 130.2 (3C), 133.3, 136.9, 141.1, 142.3, 143.1, 149.2; MS (70 eV): $m/z=289$ ($M^{+\bullet}$, 100), 254 (14), 242 (38), 241 (21), 167 (19), 165 (34), 152 (16), 120 (13), 91 (78), 65 (18). **3c**: Mp: 57–59°C; IR: 3043, 2918, 1600, 1507, 1431, 1413, 1350, 1264, 1222; ^{1}H NMR δ ppm ($CDCl_3$, 200 MHz): 4.00 (s, 2H), 6.98–7.33 (m, 9H), 7.59 (d, $J=8.3$ Hz, 2H); ^{13}C NMR δ ppm ($CDCl_3$, 50 MHz): 41.2, 115.7 ($J=21.1$ Hz, 2C), 123.3, 125.0, 126.6 (2C), 128.4, 129.8 (2C), 130.7 ($J=7.6$ Hz, 2C), 132.9, 137.0, 140.7, 144.7, 161.9 ($J=244$ Hz); MS (70 eV): $m/z=268$ ($M^{+\bullet}$, 100), 267 (22), 233 (21), 183 (24), 173 (29), 171 (21), 134 (12), 128 (13), 115 (28), 109 (39), 97 (15), 89 (17), 83 (27), 75 (19), 69 (14), 63 (26), 58 (15), 57 (17), 51 (16), 50 (12), 45 (46), 39 (29); ^{19}F NMR δ ppm ($CDCl_3$, 188 MHz): −117.7.