Tetrahedron Letters 50 (2009) 4651–4653

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of tetraaryl-*p*-benzoquinones by Suzuki–Miyaura cross-coupling reactions of tetrabromo-*p*-benzoquinone

Ihsan Ullah[a], Rasheed Ahmad Khera[a], Munawar Hussain[a], Alexander Villinger[a], Peter Langer[a,b,*]

[a] *Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany*
[b] *Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany*

ARTICLE INFO

Article history:
Received 29 April 2009
Revised 27 May 2009
Accepted 29 May 2009
Available online 6 June 2009

Keywords:
Catalysis
Cross-coupling reactions
p-Benzoquinones
Palladium

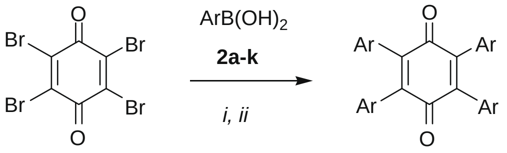
ABSTRACT

Suzuki–Miyaura cross-coupling reactions of tetrabromo-*p*-benzoquinone provide a convenient approach to tetraaryl-*p*-benzoquinones.

p-Dihydrobenzoquinones[1,2] and *p*-benzoquinones[1,3,4] play an important role in medicinal chemistry and occur in a number of pharmacologically relevant natural products, such as sorrentanone and α-tocopherolquinone. In addition, they have found many technical applications and also represent important synthetic building blocks. Tetrabromo- and tetrachlorobenzoquinone represent versatile synthetic building blocks. Known transformations include, for example, reactions with amines,[5] thiols,[6] Grignard reagents,[7] malodinitrile,[8] alkyne carbanions,[9] indole,[10] and cyclizations with *S,S*-, *N,S*-, and *N,O*-dinucleophiles,[11] and [4+2] cycloadditions.[12] Tetraaryl-*p*-benzoquinones are available by Meerwein-arylation of *p*-benzoquinone with diazonium salts[13] and by oxidation of 2,3,5,6-tetraarylphenols.[14]

Transition metal-catalyzed cross-coupling reactions of polyhalogenated molecules are of considerable current interest.[15] Recently, we have reported the synthesis of aryl-substituted thiophenes,[16] pyrroles,[17] and selenophenes[18] based on regioselective Suzuki–Miyaura reactions of tetrabromothiophene, tetrabromo-*N*-methylpyrrole, and tetrabromoselenophene, respectively. Transition metal-catalyzed cross-coupling reactions of tetrabromo- and tetrachloro-*p*-benzoquinone have, to the best of our knowledge, not been reported to date. Herein, we report the synthesis of tetraaryl-*p*-benzoquinones by Suzuki–Miyaura reactions of tetrabromo-*p*-benzoquinone with arylboronic acids.

Our starting point was to find suitable conditions for the synthesis of tetraphenyl-*p*-benzoquinone (**3a**) by Suzuki–Miyaura reaction of tetrabromo-*p*-benzoquinone (**1**) with phenylboronic acid (**2a**, 4.0 equiv) (Scheme 1, Table 1). The reaction of **1** with **2a** in the presence of $Pd(PPh_3)_4$ (5 mol %) and K_2CO_3 (THF/H_2O, 90 °C, 8–12 h) resulted in the formation of an inseparable 1:1 mixture of **3a** and of 2,3,5,6-tetraphenyl-*p*-dihydrobenzoquinone in high yield (method E, entry 5). Treatment of this mixture with DDQ resulted in the formation of pure **3a** in 70% overall yield (based on **1**).[19] The yield could be further increased (to 73%) when 10 mol % of the catalyst was employed (method F, entry 6). The increase of the amount of boronic acid (6.0 equiv) and an increase of the temperature did not result in an increase of the yield. The use of K_3PO_4 ($dioxane/H_2O$) also did not result in an increase of the yield. The use of 2.0 instead of 4.0 equiv of **2a** afforded **3a** in low



1

3a-k

Scheme 1. Synthesis of tetraaryl-*p*-benzoquinones **3a**–**k**. Reagents and conditions: (i) A: $Pd(OAc)_2$ (5 mol %), $N(CH_2CH_2OH)_3$, 90 °C, 36 h; B: $Pd(OAc)_2$ (5 mol %), **XPhos** (structure: see Scheme 2, 10 mol %), K_2CO_3 (8.0 equiv), K_2CO_3, THF, H_2O, 90 °C, 12 h; C: $Pd(OAc)_2$ (5 mol %), **SPhos** (structure: see Scheme 2, 10 mol %), K_2CO_3, THF, H_2O, 90 °C, 12 h; D: $Pd(OAc)_2$ (10 mol %), **SPhos** (20 mol %), K_2CO_3, THF, H_2O, 90 °C, 12 h; E: $Pd(PPh_3)_4$ (5 mol %), K_2CO_3, THF, H_2O, 90 °C, 8–12 h; F: $Pd(PPh_3)_4$ (10 mol %), K_2CO_3, THF, H_2O, 90 °C, 8–12 h; (ii) DDQ, benzene, 3 h, 20 °C.

---

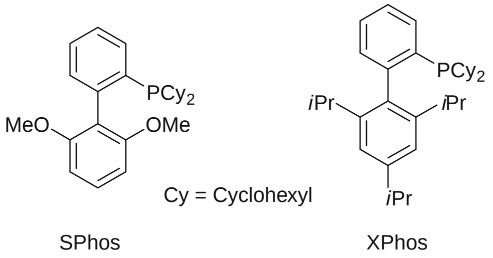
[*] Corresponding author. Tel.: +49 381 4986410; fax: +49 381 4986412.
E-mail address: peter.langer@uni-rostock.de (P. Langer).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.05.115

Table 1
Optimization of the synthesis of **3a** and **3b**

Entry	**3**	Ar	% (**3**)[a]	Method[b]
1	**a**	Ph	0	A
2	**a**	Ph	30	B
3	**a**	Ph	45	C
4	**a**	Ph	50	D
5	**a**	Ph	70	E
6	**a**	Ph	73	F
7	**b**	4-MeC$_6$H$_4$	0	A
8	**b**	4-MeC$_6$H$_4$	25	B
9	**b**	4-MeC$_6$H$_4$	50	C
10	**b**	4-MeC$_6$H$_4$	53	D
11	**b**	4-MeC$_6$H$_4$	75	E
12	**b**	4-MeC$_6$H$_4$	80	F

[a] Yield of isolated products.
[b] See legend of Scheme 1.



Scheme 2. Biaryl monophosphine ligands developed by Billingsley and Buchwald (Ref. 21).

yield. The formation of a diaryldibromo-*p*-benzoquinone was not observed. The use of tetrachloro- instead of tetrabromo-*p*-benzoquinone was not successful.

Recently, Li and Wang reported[20] that triethanolamine represents an efficient and reusable combined base, ligand, and solvent for Pd(OAc)$_2$-catalyzed reactions (method A, entry 1). However, its application to the reaction of **2a** with **1** proved to be unsuccessful. The use of Pd(OAc)$_2$ in the presence of **XPhos** (method B, entry 2) or **SPhos** (method C, entry 3), biaryl monophosphine ligands developed by Billingsley and Buchwald (Scheme 2),[21] and subsequent oxidation (DDQ) resulted in the formation of **3a** in 30% and 45% yield, respectively. In case of **SPhos**, the yield could be increased when the double amount of catalyst and ligand was used (method D, entry 4). The synthesis of tetra(4-tolyl)-*p*-benzoquinone (**3b**) was also optimized and a similar trend was observed (entries 7–12) (Table 1).

Tetraarylbenzoquinones **3a–k** were prepared, by application of method E, in 51–80% yields (Table 2). The best yields were obtained for (electron rich) 4-alkylarylboronic acids. The yields dropped for arylboronic acids which are sterically hindered or contain electron-withdrawing substituents. The structure of **3c** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[22]

Table 2
Synthesis of **3a**–**k** using procedure E

2,3	Ar	% (**3**)[a,b]
a	Ph	70
b	4-MeC$_6$H$_4$	75
c	4-EtC$_6$H$_4$	80
d	3,5-Me$_2$C$_6$H$_3$	73
e	4-*t*BuC$_6$H$_4$	78
f	2,3-Me$_2$C$_6$H$_3$	71
g	3-(H$_2$C=CH)C$_6$H$_4$	62
h	4-(H$_2$C=CH)C$_6$H$_4$	56
i	4-(F$_3$C)C$_6$H$_4$	51
j	3-PhC$_6$H$_4$	53
k	2-Naphthyl	63

[a] Yield of isolated products.
[b] Conditions: E: Pd(PPh$_3$)$_4$ (5 mol %), K$_2$CO$_3$, THF, H$_2$O, 90 °C, 8–12 h.

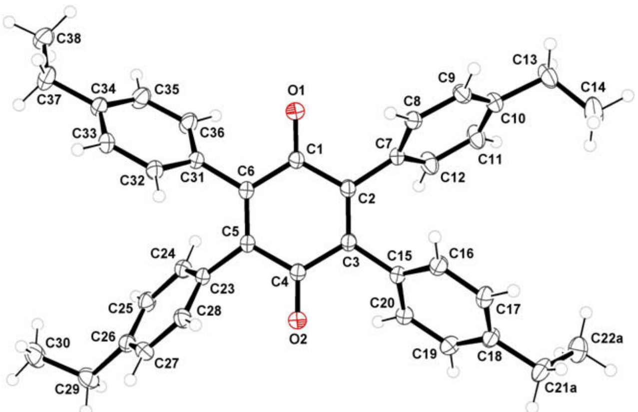


Figure 1. Crystal structure of **3c**.

In conclusion, we have reported the synthesis of tetraaryl-*p*-benzoquinones by Suzuki–Miyaura cross-coupling reactions of tetrabromo-*p*-benzoquinone. The preparative scope and applications are currently being studied.

Acknowledgments

Financial support by the State of Pakistan (HEC scholarships for I.U. and M.H.) and by the State of Mecklenburg-Vorpommern (scholarship for M.H.) is gratefully acknowledged.

References and notes

1. *Römpp Lexikon Naturstoffe*; Steglich, W., Fugmann, B., Lang-Fugmann, S., Eds.; Thieme: Stuttgart, 1997.
2. (a) Jinno, S.; Hata, K.; Shimidzu, N.; Okita, T. *J. Antibiot.* **1998**, *51*, 508; (b) Jinno, S.; Okita, T. *Chem. Pharm. Bull.* **1998**, *46*, 1688; (c) Papendorf, O.; Koenig, G. M.; Wright, A. D. *Phytochemistry* **1998**, *49*, 2383; Methoxymicareic acid: (d) Elix, J. A.; Jones, A. J.; Lajide, L.; Coppins, B. J.; James, P. W. *Aust. J. Chem.* **1984**, *37*, 2349.
3. Xanthanthusin E: (a) Mei, S.-X.; Jiang, B.; Niu, X.-M.; Li, M.-L.; Yang, H.; Na, Z.; Lin, Z.-W.; Li, C.-M.; Sun, H.-D. *J. Nat. Prod.* **2002**, *65*, 633; Blennione: (b) Spiteller, P.; Steglich, W. *J. Nat. Prod.* **2002**, *65*, 725; Lilacinone: (c) Spiteller, P.; Arnold, N.; Spiteller, M.; Steglich, W. *J. Nat. Prod.* **2003**, *66*, 1402; Sorrentanone: (d) Miller, R. F.; Huang, S. *J. Antibiot.* **1995**, *48*, 520; (e) Jakupovic, J.; Zdero, C.; Grenz, M.; Tsichritzis, F.; Lehmann, L. *Phytochemistry* **1989**, *28*, 1119; Helinudiquinone-6-*O*-methyl ether: (f) Jakupovic, J.; Kuhnke, J.; Schuster, A.; Metwally, M. A.; Bohlmann, F. *Phytochemistry* **1986**, *25*, 1133; Helinudiquinone: (g) Jakupovic, J.; Kuhnke, J.; Schuster, A.; Metwally, M. A.; Bohlmann, F. *Phytochemistry* **1986**, *25*, 1133.
4. α-Tocopherolquinone: (a) d'Ischia, M.; Costantini, C.; Prota, G. *J. Am. Chem. Soc.* **1991**, *113*, 8353; (b) Rosenau, T.; Habicher, W. D. *Tetrahedron Lett.* **1997**, *38*, 5959; Plastoquinone-8α-tocopherylquinone: (c) Lin, S.; Binder, B. F.; Hart, E. R. *J. Chem. Ecol.* **1998**, *24*, 1781; (d) Shanorellinacetat, C.-K. W.; Towers, G. H. N. *Phytochemistry* **1971**, *10*, 1355; Sargaquinol: (e) Segawa, M.; Shirahama, H. *Chem. Lett.* **1987**, 1365; 6-Methyl dihydrophytylplastoquinone: (f) Mahmood, U.; Shukla, Y. N.; Thakur, G. S. *Phytochemistry* **1984**, *23*, 1725; α-Tocopherolquinone methyl ether: (g) Rasool, N.; Khan, A. Q.; Ahmad, V. U.; Malik, A. *Phytochemistry* **1991**, *30*, 2800; helinudiquinone: (h) Jakupovic, J.; Kuhnke, J.; Schuster, A.; Metwally, M. A.; Bohlmann, F. *Phytochemistry* **1986**, *25*, 1133; Mochiquinone: (i) D'Armas, H. T.; Mootoo, B. S.; Reynolds, W. F. *J. Nat. Prod.* **2000**, *63*, 1593; Erectquinone A: (j) An, T.-Y.; Shan, M.-D.; Hu, L.-H.; Liu, S.-J.; Chen, Z.-L. *Phytochemistry* **2002**, *59*, 395; Lanciaquinone: (k) Manguro, L. O. A.; Midiwo, J. O.; Kraus, W.; Ugi, I. *Phytochemistry* **2003**, *64*, 855.
5. (a) Romanyuk, A. L.; Litvin, B. L.; Ganushchak, N. I.; Vishnevskii, R. M. *Russ. J. Gen. Chem.* **2006**, *76*, 1834; Romanyuk, A. L.; Litvin, B. L.; Ganushchak, N. I.; Vishnevskii, R. M. *Zh. Obshch. Khim.* **2006**, *76*, 1919; (b) Batra, M.; Kriplani, P.; Batra, C.; Ojha, K. G. *Bioorg. Med. Chem.* **2006**, *14*, 8519; (c) Kallmayer, H.-J.; Fritzen, W. *Arch. Pharm. (Weinheim Ger.)* **1988**, *321*, 293; (d) Soliman, A. M. *J. Heterocycl. Chem.* **2002**, *39*, 853; Review: (e) Petersen, S.; Gauss, W.; Urbschat, E. *Angew. Chem.* **1955**, *67*, 217.

6. Goeksel, F. S.; Ibis, C.; Bayrak, N. A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2005**, *180*, 1961.
7. Clar, E.; Engler, J. *Chem. Ber.* **1931**, *64*, 1597.
8. Gomaa, M. A.-M. *Tetrahedron Lett.* **2003**, *44*, 3493.
9. Bowles, D. M.; Palmer, G. J.; Landis, C. A.; Scott, J. L.; Anthony, J. E. *Tetrahedron* **2001**, *57*, 3753.
10. Harris, G. D.; Nguyen, A.; App, H.; Hirth, P.; McMahon, G.; Tang, C. *Org. Lett.* **1999**, *1*, 431.
11. Soliman, A. M.; Sultan, A. A.; El-Shafei, A. K. *Monatsh. Chem.* **1995**, *126*, 615.
12. (a) Mital, R. L.; Jain, S. K. *J. Chem. Soc. C* **1971**, 1875; (b) Aly, A. A.; Hassan, A. A.; El-Shaieb, K. M.; Shaker, R. M. *Z. Naturforsch. B* **2005**, *60*, 999; (c) Agarwal, N. L.; Jain, S. K. *Synthesis* **1978**, 437.
13. (a) LaBudde, R.; Heidelberger, W. *J. Am. Chem. Soc.* **1958**, *80*, 1225; (b) Takahashi, I.; Muramatsu, O.; Fukuhara, J.; Hosokawa, Y.; Takeyama, N. *Chem. Lett.* **1994**, *3*, 465; (c) Takahashi, I.; Nishimura, H.; Takeyama, N.; Muramatsu, O.; Fukuhara, J.; Kitajima, H. *Chem. Express* **1993**, *8*, 585.
14. (a) Eistert, B.; Langbein, A. *Justus Liebigs Ann. Chem.* **1964**, *678*, 78; (b) Dimroth, K. *Justus Liebigs Ann. Chem.* **1972**, *765*, 133.
15. Review: Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245.
16. Dang, T. T.; Rasool, N.; Dang, T. T.; Reinke, H.; Langer, P. *Tetrahedron Lett.* **2007**, *48*, 845.
17. Dang, T. T.; Dang, T. T.; Ahmad, R.; Reinke, H.; Langer, P. *Tetrahedron Lett.* **2008**, *49*, 1698.
18. Dang, T. T.; Villinger, A.; Langer, P. *Adv. Synth. Catal.* **2008**, *350*, 2109.
19. Typical procedure: To a mixture of **1** (0.21 g, 0.5 mmol), **2e** (0.33 g, 2.0 mmol), $Pd(PPh_3)_4$ (5 mol %) were added THF (5 mL) and aqueous K_2CO_3 (2 mL, 2 M) under argon atmosphere. The reaction mixture was refluxed for 12 h. The reaction mixture was allowed to cool to 20 °C and then ice-cooled water (8 mL) was added. After stirring for 15 min, the mixture was extracted with dichloromethane (3 × 20 mL). The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, heptanes/EtOAc = 7:3) to give a mixture of **3e** and of the corresponding *p*-dihydrobenzoquinone as an orange solid. A benzene solution (8.5 mL) of this mixture and of DDQ (0.192 g, 0.85 mmol) was stirred at 20 °C for 3 h. The reaction mixture was filtered, dried (Na_2SO_4), filtered and the filtrate was concentrated. The residue was purified by chromatography (silica gel, heptanes/EtOAc = 9:1) to give **3e** (0.248 g, 78% based on **1**) as a yellow solid, mp 273 °C. *2,3,5,6-Tetrakis(4-tert-butylphenyl)cyclohexa-2,5-diene-1,4-dione* (**4e**): ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (s, 36H, CH_3), 6.92–6.95 (d, $^3J = 8.6$ Hz, 8H, CH_{Ar}), 7.11–7.14 (d, $^3J = 8.6$ Hz, 8H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.1 (CH_3), 34.5 (C), 124.35 (CH_{Ar}), 130.1 (C_{Ar}), 130.6 (CH_{Ar}), 142.8 (C_{Ar}), 151.0 (C_{Ar}), 187.2 (CO). IR (neat, cm^{-1}): $\tilde{\nu} = 3085$, 3034 (w), 2958, 2865 (m), 1650 (s), 1582 (w), 1502 (m), 1434 (w), 1361 (m), 1304 (m), 1197 (m), 1100 (m), 1015 (m), 965 (w), 924 (w), 820 (s), 760 (m), 671 (w), 624 (m), 562 (s) cm^{-1}. Under the conditions of electronic ionization (EI) the compound was reduced to the dihydrobenzoquinone. GC–MS (EI, 70 eV): m/z (%) 640 (11), 639 (49), 638 (100), 636 (2), 304 (7), 129 (7), 125 (7), 123 (6), 111 (13), 98 (10), 97 (23), 85 (15), 83 (26), 71 (25), 69 (35), 57 (75), 55 (35), 43 (15). Electrospray ionization gave the correct molecular ion. HRMS (ESI-TOF): calcd for $C_{46}H_{53}O_2$ $[M+H]^+$: $m/z = 637.40401$; found: 637.40278.
20. Li, H. J.; Wang, L. *Eur. J. Org. Chem.* **2006**, 5099.
21. Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358. and references cited therein.
22. CCDC-734055 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; Fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk.