An Improved Sonogashira Coupling Procedure for the Construction of Rigid Aromatic Multifunctional Monomers Bearing 1,3-Substituted Acetylenic Units

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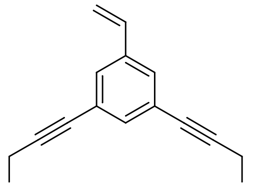
Abstract: The efficient synthesis of rigid multifunctional vinylic monomers **1** and **2** from 3,5-dibromobenzene derivatives and propargyl alcohol via the Sonogashira reaction is reported. For example, a series of 3,5-bis(3-hydroxyprop-1-ynl)benzoate ester derivatives have been prepared efficiently using an improved palladium catalyst system. Subsequent hydrolysis and reaction with 4-vinylaniline afforded a new monomer **2** for use in functional macroporous polymer systems. In addition, Sonogashira and Wittig methodologies have been optimised in order to construct successfully an alternative rigid monomer **1** from 3,5-dibromobenzaldehyde.

Key words: Sonogashira reaction, palladium, cross-coupling, organometallic reagents, tri-2-furylphosphine

The palladium(0)/copper(I) halide catalysed coupling of terminal alkynes with aryl or alkenyl halides, first reported[1] by Sonogashira and co-workers, is a widely used method for the synthesis of arylalkynes and conjugated enynes.[2] As part of our research towards the synthesis of novel rigid vinylic monomers **1** and **2** (Figure) for use in imprinted polymer systems,[3] an efficient and robust procedure for the coupling of propargyl alcohol to a range of 3,5-dibromobenzene derivatives was required. Consequently, use of Sonogashira coupling methodologies was investigated and the results of these studies are reported herein.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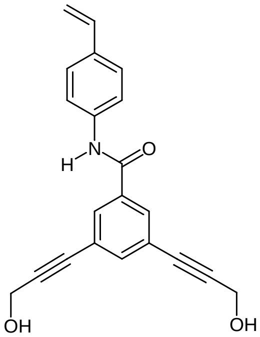
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Figure

The synthesis of monomer **1** employed the conditions reported[4] by Brown et al. for the synthesis of 3,5-dibromobenzaldehyde from 3,5-dibromobenzoic acid via a two step reduction/selective oxidation process (Scheme 1). Employing the original reaction conditions described[1] by Sonogashira and co-workers (0.4 mol% Pd $(PPh_3)_2Cl_2$, 0.8 mol% CuI, triethylamine, THF) in conjunction with 3,5-dibromobenzaldehyde and propargyl alcohol, the key intermediate 3,5-bis(3-hydroxyprop-1-yl)benzaldehyde **3** was constructed in good yield (Table, entry 1). The hydroxyl moieties of **3** were then protected in the form of their corresponding *tert*-butyldimethylsilyl (TBDMS) ethers. Subsequent conversion of the aldehyde group of the protected diol **4** to the corresponding olefin **5** employing standard Wittig conditions[5] followed by deprotection of the TBDMS groups afforded the desired monomer **1** in 96% yield.

In addition to monomer **1**, novel rigid monomers such as **2** (Figure), comprised of 3,5-bis-acetylenated aromatic units tethered to a polymerisable vinylic group, were also targeted to enable structure-property relationships of the resultant imprinted polymers to be studied. The approach used to obtain monomers such as **2** also involved use of the palladium mediated cross-couplings of propargyl alcohol to 3,5-dibromobenzoic acid ethyl ester (Scheme 2). However, in stark contrast to monomer **1**, the synthesis of monomer **2** required significant modification of the Sonogashira-based methodologies.

Under the original coupling conditions (Table, entry 2), the desired bis-acetylenic product **6a** was not isolated, only a moderate yield of mono-substituted product **7a** was obtained. This effect has also been observed[6] by Krause and co-workers in the coupling of trimethylsilylacetylene to methyl bromobenzoate derivatives and higher catalyst loadings were found to increase cross-coupling yields.[6] However, in the case of **6a**, this approach proved ineffective (Table, entry 3). In light of these initial disappointing results, a range of different palladium catalyst and ligand combinations were screened in order to optimise the coupling of propargyl alcohol to 3,5-dibromobenzoic acid ethyl ester (see Table). The catalytic system $PdCl_2/PPh_3$ reported by Philp et al.[7] (Table, entry 4) for the successful coupling of propargyl alcohol to 3,5-substituted halogenobenzenes unfortunately failed to yield the desired product **6a**. Several reports have detailed the use of

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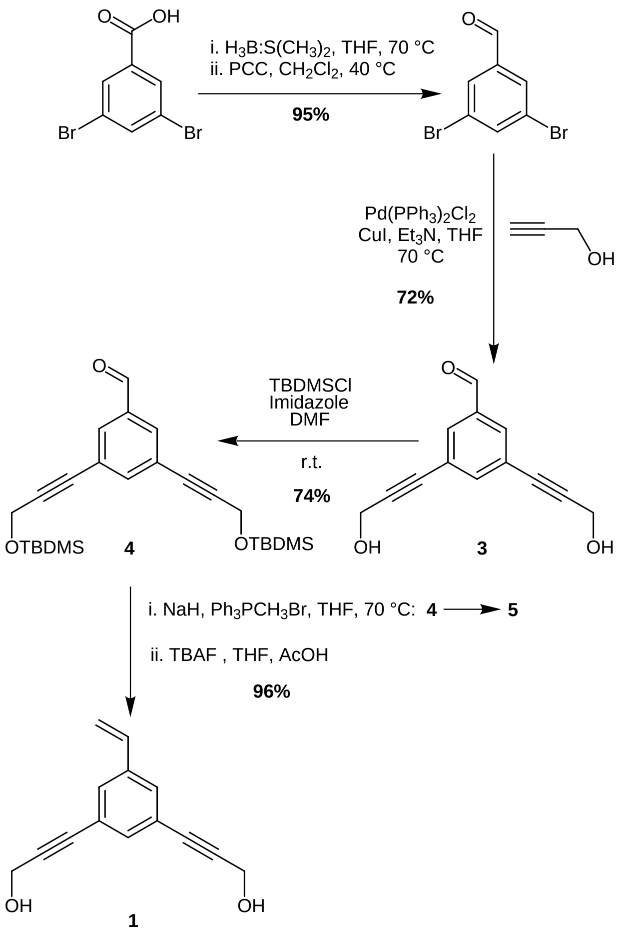
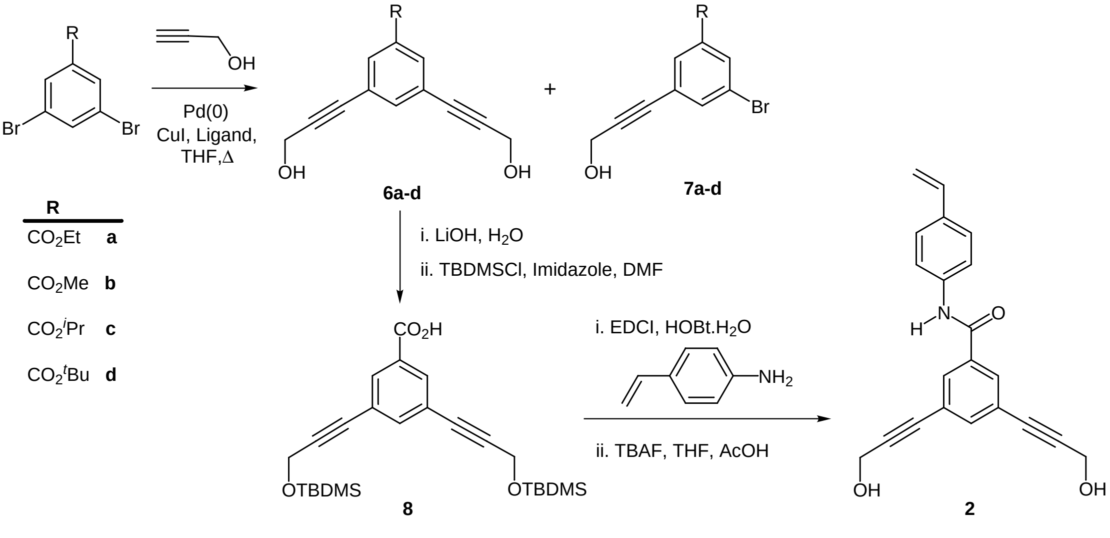


Scheme 1

$Pd_2(dba)_3$ or $Pd(dba)_2$ in the presence of phosphine ligands as effective catalysts in the Sonogashira reaction.[8–10] However, in the case of **6a,** this catalytic system required extensive heating in order to afford the desired product in moderate yield (Table, entry 5). Reetz et al.[11] have reported high catalytic activity from the use of palladium salts such as $Pd(OAc)_2$ in the presence of Ph_4PX (where X = Cl, Br, I) in Heck type arylations of unreactive aryl halides. This catalyst combination proved almost inactive for the Sonogashira coupling of propargyl alcohol to 3,5-dibromobenzoic acid ethyl ester, (Table, entry 6) with only a low yield of the mono-acetylenic ester **7a** obtained. Subsequent combination of the catalyst $Pd(dba)_2$ with Ph_4PCl also proved unsuccessful (Table, entry 7).

The prolonged reaction times of the procedures described above in conjunction with inefficient cross-couplings led to the consideration of the use of the tri-2-furylphosphine[12] (TFP) ligand. Farina and co-workers[13] first reported use of the TFP ligand in Stille cross-coupling reactions, demonstrating an increased rate of reaction that was attributed to the low electron donating ability of the TFP ligand. In addition, Vasella and co-workers have observed[14] that palladium catalysts incorporating the TFP ligand are the most effective systems for the cross-coupling of THP protected propargyl alcohol with iodoalkynes. Therefore, in light of these reports, the efficiency of the TFP ligand was tested in the Sonogashira coupling of propargyl alcohol to 3,5-dibromobenzoic acid ethyl ester. Initial use of the TFP ligand in combination with the $Pd_2(dba)_3$ catalyst (Table, entry 8) was disappointing and afforded poor results. None of the bis-acetylenic ethyl ester **6a** was isolated, and a high yield of a by-product incorporating the furyl unit was isolated. Buchwald et al. have reported[15] the successful use of the catalyst system $Pd(PhCN)_2Cl_2$ in the Sonogashira coupling of aryl bromides at room temperature. Consequently, the TFP ligand was utilised in combination with the $Pd(PhCN)_2Cl_2$ species (Table, entry 9) and delivered an acceptable yield[16] of the desired 3,5-bis(3-hydroxyprop-1-ynl)benzoic acid ethyl ester **6a** in a significantly shorter reaction time and a dramatic increase in the yield per coupling (up to 65%). Subsequent hydrolysis of the ethyl ester functionality to the corresponding carboxylic acid, followed by protection of the hydroxyl groups as their corresponding TBDMS



Scheme 2

Table Cross-coupling of Propargyl Alcohol to 3,5-Dibromo-benzene Derivatives

Entry[a]	R	Pd catalyst (mol%)	Ligand (mol%)	CuI (mol%)	Yield[b] (%)	
					6	**7**
1	CHO	$Pd(PPh_3)_2Cl_2$ (0.4)	n/a	0.8	72	21
2	CO_2Et	Pd $(PPh_3)_2Cl_2$ (0.4)	n/a	0.8	0	54
3	CO_2Et	Pd $(PPh_3)_2Cl_2$ (1.1)[c]	n/a	4.3	0	42
4	CO_2Et	$PdCl_2$ (0.5)	PPh_3 (1)	0.5	0	35
5	CO_2Et	$Pd(dba)_2$ (0.4)	PPh_3 (2)	0.4	34	62
6	CO_2Et	$Pd(OAc)_2$ (4)	Ph_4PCl (2.4)	8	0	10
7	CO_2Et	$Pd(dba)_2$ (0.05)	Ph_4PCl (1)	0.4	0	2
8	CO_2Et	$Pd_2(dba)_3$ (0.6)	TFP[d] (1.3)	0.4	0	33
9	CO_2Et	$Pd(PhCN)_2Cl_2$ (0.6)	TFP (1.3)	0.4	42	47
10	CO_2Et	$Pd(PhCN)_2Cl_2$ (0.6)	$AsPh_3$ (1.3)	0.4	0	61
11	CO_2Me	$Pd(PhCN)_2Cl_2$ (0.6)	TFP (1.3)	0.4	10	44
12	CO_2-*i*-Pr	$Pd(PhCN)_2Cl_2$ (0.6)	TFP (1.3)	0.4	22	61
13	CO_2-*t*-Bu	$Pd(PhCN)_2Cl_2$ (0.6)	TFP (1.3)	0.4	21	52

[a] In all cases, reactions were performed in refluxing THF with addition of 2.5 equiv triethylamine (distilled from calcium sulfate).

[b] Yields refer to compounds isolated by column chromatography on silica gel. All compounds were characterised completely, and were in full agreement with structures.

[c] With addition of 2.7 equiv DBU.

[d] TFP = tri-2-furylphosphine.

ethers afforded intermediate **8**. EDCI mediated amidation with 4-vinylaniline and subsequent deprotection of the TBDMS groups afforded the required vinylic monomer **2** in an acceptable yield of 72%.

In addition to the TFP ligand, Farina and co-workers have studied the use of other ligands of low donor ability in the Stille reaction, such as the triphenylarsine ligand.[17] Subsequent mixing of this ligand with sources of palladium(0) afforded catalysts that afforded fast coupling rates, but that were relatively unstable during the course of the reaction in comparison to the TFP derived systems. Comparable results were obtained in this study upon examination of the $Pd(PhCN)_2Cl_2$/triphenylarsine and $Pd(PhCN)_2Cl_2$/TFP systems. Therefore, although the triphenylarsine ligand did increase the rate of formation of the mono-acetylenic product **7a**, the catalyst appeared to decompose before the desired bis-acetylenic product **6a** could be formed, and thus only product **7a** was isolated (Table, entry 10).

Having uncovered that the enhanced reactivity of the $Pd(PhCN)_2Cl_2$/TFP catalyst allows formation of the bis-acetylenated derivative **6a**, presumably via the intermediacy of the bromide **7a**, we then examined the effect of variations of the ester functionality in the starting material upon the efficiency of this process (Scheme 2). This study proved surprisingly important with a noticeable change in the yield whichever ester was substituted for the original ethyl moiety. In the case of all the 3,5-dibrominated aromatic esters examined, moderate yields of the required bis-acetylenic esters **6b**–**d** were obtained (Table, entries 11–13). Only in the case of 3,5-dibromobenzoic acid methyl ester was a low yield of the bis-acetylenic product **6b** observed.

In summary, an improved method for the Sonogashira coupling of acetylenic systems to a range of 3,5-dibromobenzoate ester derivatives has been developed enabling the synthesis of several new rigid functional vinylic monomer systems. The catalyst $Pd(PhCN)_2Cl_2$ in conjunction with tri-2-furylphosphine afforded successfully the desired 3,5-bis(3-hydroxyprop-1-ynl)benzoic acid ethyl ester **6a** from the cross-coupling of propargyl alcohol to the 3,5-dibromobenzoic acid ethyl ester substrate in acceptable yields with concomitant short reaction times. This catalytic combination also proved to be active for the cross coupling of propargyl alcohol to other ester derivatives of 3,5-dibromobenzoic acid.

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References

(1) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Sonogashira, K. In *Comprehensive Organic Synthesis*, Vol. 3; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: New York, **1991**, 521.

(2) (a) Nicolaou, K. C.; Hwang, C.-K.; Smith, A. L.; Wendeborn, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 7416. (b) Nicolaou, K. C.; Smith, A. L.; Wenderborn, S. V.; Hwang, C.-K. *J. Am. Chem. Soc.* **1991**, *113*, 3106.

(3) For excellent reviews of molecular imprinted polymers, see: (a) Wulff, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1812. (b) Whitcombe, M. J.; Vulfson, E. N. *Adv. Mater.* **2001**, *13*, 467.

(4) Brown, H. C.; Gundu Rao, C.; Kulkarni, S. V. *Synthesis* **1979**, 704.

(5) Clark, R. D.; Jahinger, *J. Org. Chem.* **1989**, *54*, 1174.

(6) Thorand, S.; Krause, N. *J. Org. Chem.* **1998**, *63*, 8551.

(7) Robinson, J. M. A.; Kariuki, B. M.; Harris, D. M.; Philp, D. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2459.

(8) Böhm, V. P. W.; Hermann, W. A. *Eur. J. Org. Chem.* **2000**, 3679.

(9) Shen, W.; Thomas, S. A. *Org. Lett.* **2000**, *2*, 2857.

(10) Mori, A.; Kawashima, J.; Shimada, T.; Suguro, M.; Hirabayashi, K.; Nishihara, Y. *Org. Lett.* **2000**, *2*, 2935.

(11) (a) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem. Int. Ed.* **1998**, *37*, 481. (b) Reetz, M. T.; Wetsermann, E.; Lohmer, R.; Lohmer, G. *Tetrahedron Lett.* **1998**, *39*, 8449.

(12) For a comprehensive review of the use of 2-furylphosphines as ligands in palladium mediated reactions see: Andersen, N. G.; Keay, B. A. *Chem. Rev.* **2001**, *101*, 997.

(13) Farina, V.; Baker, S. R.; Benigni, D. A.; Sapino, C. *Tetrahedron Lett.* **1988**, *29*, 5739.

(14) Cai, C.; Vasella, A. *Helv. Chem. Acta* **1995**, *78*, 2053.

(15) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729.

(16) **Typical Procedure for the Preparation of 6a**: Bisbenzonitriledichloropalladium (75 mg, 0.20 mmol) and copper iodide (25 mg, 0.10 mmol) were added to a dry round bottomed flask which was purged with argon and filled with dry THF (10 mL). Tri-2-furylphoshine (94 mg, 0.40 mmol) and triethylamine (1.1 mL, 7.80 mmol) were added, followed by 3,5-dibromobenzoic acid ethyl ester (1.01 g, 3.30 mmol). The reaction was stirred at r.t. for 20 min. Propargyl alcohol (0.55 g, 9.80 mmol) was added gradually over 20 min, and the reaction was refluxed under argon for 10 h. The residue of palladium salts was filtered and washed with THF. The combined filtrate and washings were evaporated under reduced pressure. The residue was taken up in chloroform (50 mL) and washed with 1 M hydrochloric acid (20 mL) followed by brine (2×20 mL). The combined organic layers were dried over sodium sulfate, filtered at the pump and concentrated in vacuo to yield a brown oil. Subsequent purification using column chromatography (SiO_2, 6:4 CH_2Cl_2:EtOAc) afforded a white solid (mp 163–164 °C, 0.351 g, 42%).
^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.17$ (t, 3 H, $J = 7.1$ Hz, CH_3), 4.22 (q, 2 H, $J = 7.1$ Hz, CH_2), 4.42 (s, 4 H, $2 \times CH_2$), 7.43 (t, 1 H, $J = 1.6$ Hz, ArH), 7.86 (d, 2 H, $J = 1.6$ Hz, ArH). ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta = 13.2$ (CH_3), 50.2 (2 CH_2), 60.6 (CH_2), 82.5 ($2 \times C{\equiv}C$), 88.1 ($2 \times C{\equiv}C$), 122.3 ($2 \times$ ArCH), 129.7 (ArCH), 131.3 ($2 \times$ ArC-C), 137.3 (ArC-COOEt), 164.4 (C=O); IR: ν_{max} 666, 723, 1414, 1462, 1585, 1735, 2354, 2856, 2923 cm^{-1}; *m/z* (TOF MS ES+) mobile phase 70:30 CH_3CN:0.05 M NH_4OAc(aq), flow injection: calculated for $C_{15}H_{14}O_4$ 258.2732, found 792.3010 $[3 M + NH_4]^+$, 534.2120 $[2 M + NH_4]^+$, 517.1837 $[2 M + H]^+$, 481.1641 $[2 M + H - 2 H_2O]^+$, 300.1233 $[MH + CH_3CN]^+$, 259.0965 $[MH^+]$.

(17) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.