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A one-pot synthesis of unsymmetrical bis-styrylbenzenes

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ABSTRACT

An efficient and widely applicable one-pot synthesis of unsymmetrical (*E*,*E*)-bis-styrylbenzenes using successive Heck and Horner–Wadsworth–Emmons reactions is described.

Alzheimer's disease (AD)[1] is a common neurodegenerative disorder in the elderly.[2,3] Hallmarks of this disease are senile plaque deposition containing aggregated β-amyloid (Aβ) protein, neurofibrillary tangles (NFTs), reactive astrocytes and activated microglia in the brain parenchyma.[4,5] Based on the Aβ-binding dye Congo red,[6] bis-styrylbenzene derivatives such as (*E*,*E*)-1-fluoro-2,5-bis(3-carboxy-4-hydroxystyryl)benzene (FSB)[7] and (*E*,*E*)-1,4-bis(4-hydroxystyryl)benzene[8] have been identified as potent Aβ-binding ligands with potential for the early diagnosis of AD using positron emission tomography (PET) and magnetic resonance imaging (MRI). FSB has also been reported to inhibit Aβ fibril aggregation.[9]

One-step syntheses of symmetrical bis-styrylbenzenes using classic Wittig (Horner–Wadsworth–Emmons or HWE) couplings between benzaldehydes and ylides derived from tetraethyl *p*-xylylenediphosphonates have been described.[7,8] Other reports describe double HWE reaction sequences that could be applied to the synthesis of unsymmetrical bis-styrylbenzenes, but these require intervening adjustment of oxidation state,[10,11] adding extra steps to the synthesis. Other syntheses[12–14] employ alternating HWE and Heck reactions in a step-wise manner to form polymeric bis-styrylbenzenes known as oligo(phenylenevinylene)s; in these syntheses, unsymmetrical bis-styrylbenzene are often synthetic intermediates. Another report[15] describes a one-pot sequential Heck cross-coupling using aryl dihalides to form unsymmetrical bis-styrylbenzenes.

The structure–activity relationship (SAR) of this class of compounds for binding to Aβ fibrils and the inhibition of Aβ aggregation is based on data obtained only from symmetrical bis-styrylbenzenes. With this in mind, we identified the need for an efficient and widely applicable synthesis of unsymmetrical bis-styrylbenzenes. Herein, we report a one-pot[16] synthesis of unsymmetrical bis-styrylbenzenes **4a**–**4i** through successive Heck/HWE reactions in good yields (60–84%).

The first step in this procedure (Scheme 1) is a Heck coupling reaction between diethyl 4-iodobenzyl phosphonate (**1**) and a styrene (**2a**–**2c**) (2 mol equiv) to form the 4-substituted diethyl (*E*)-(4-'X'-styrylbenzyl) phosphonates in situ. This Heck reaction is based on an existing protocol[17] optimized for our purposes using $Pd(OAc)_2$ (3 mol %), phenylurea (6 mol %) and potassium carbonate (2 mol equiv) in DMF[16] with stirring at 110 °C. Attempted Heck reactions with the bromo analogue of **1** under these conditions were unsuccessful. The reaction is monitored by testing small aliquots with GC–MS until **1** is consumed, typically in 22 h. After verification of the disappearance of **1**, the reaction is cooled to 80 °C with continued stirring while benzaldehydes **3a**–**3e** (1.1 mol equiv) and sodium methoxide (30% w/v solution in methanol) (2 mol equiv) are added. After continued stirring for 1 h, the reaction is stopped by a water quench at which time products **4a**–**4i** precipitate and are filtered and rinsed with water and ether (Table 1).

In order to show applicability for styrenes containing electron-donating and electron-withdrawing groups, we tested the method with 4-methoxymethoxystyrene **2b** and 4-methoxycarbonylstyrene **2c** in the Heck coupling step and 4-methoxybenzaldehyde **3d** and 4-cyanobenzaldehyde **3a** in the HWE step. These reactions produced the desired products, **4f**–**4i** in slightly lower yields compared to those with styrene. The formation of **4h** required 2 mol equiv of **3d**.[18]

The one-pot method was compared to a sequential HWE/Heck two-step[19] pathway[12–14] to form bis-styrylbenzenes **4a**–**4d** from the isolated intermediate styrylbenzenes **5a**–**5d**[20] (Scheme 2). This

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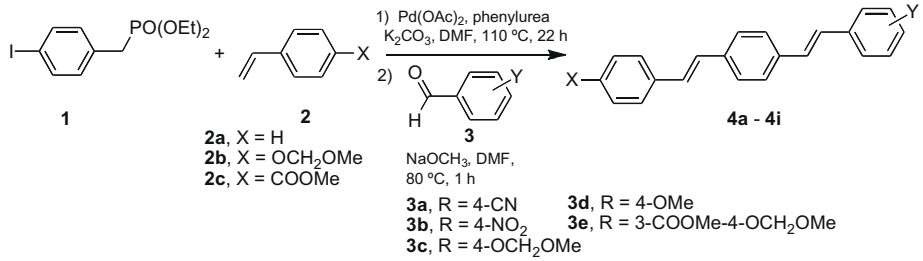
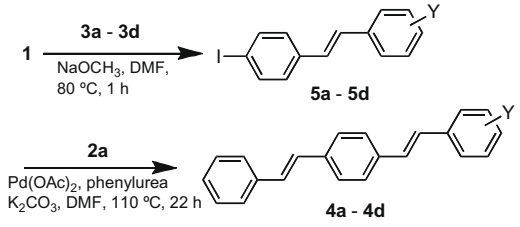


Scheme 1. Heck/HWE one-pot synthesis of unsymmetrical bis-styrylbenzenes **4a**–**4i**.

Table 1
Overall yields of bis-styrylbenzenes **4a**–**4i** from one-pot (Scheme 1) and two-pot (Scheme 2) syntheses

Compound	X	Y	Yield (one-pot)	Yield (two-pot)[a]
4a	4-H	4-Cyano	84	65
4b	4-H	4-Nitro	84	58
4c	4-H	4-Methoxymethoxy	79	50
4d	4-H	4-Methoxy	75	64
4e	4-H	3-Methoxycarbonyl 4-Methoxymethoxy	76	–
4f	4-Methoxymethoxy	4-Methoxy	60	–
4g	4-Methoxymethoxy	4-Cyano	64	–
4h	4-Methoxycarbonyl	4-Methoxy	62[b]	–
4i	4-Methoxycarbonyl	4-Cyano	76	–

[a] Yields based on the isolated products of sequential HWE and Heck reaction.
[b] 2 mol equiv of aldehyde utilized in second step.



Scheme 2. HWE/Heck two-pot synthesis of **4a**–**4e**.

process requires an extra isolation step between the HWE and Heck couplings leading to potentially lower yields from compound losses during work-up. Indeed, even using the previously described optimized Heck reaction conditions, the sequential HWE/Heck two-pot pathway gave lower overall yields than the one-pot method (Table 1).

Other reaction variants similarly gave lower yields or failed altogether. For example, **4f**–**4i** were synthesized in a reverse sequence HWE/Heck one-pot reaction, but yields were significantly lower in the range of 43–60%. Finally, attempts to perform a one-pot double Heck reaction with 1-bromo-4-iodobenzene failed, presumably due to the lack of reactivity of the bromo styrene intermediates.

In conclusion, this Letter describes the first one-pot synthesis of unsymmetrical bis-styrylbenzenes using a Heck/HWE sequence. The yields are shown to be comparable or higher than those reported from HWE/Heck two-pot reactions.[12–14] This method should be applicable to the synthesis of structurally diverse unsymmetrical bis-styrylbenzenes and could lead to advances in the SAR of this class of compounds in AD studies.

Acknowledgements

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Supplementary data

Experimental procedures for **2b, 2c, 3c** and **3e**. Experimental procedures and characterization of compounds **4a**–**4i** and **5a**–**5d**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.083.

References and notes

1. Goedert, M.; Spillantini, G. *Science* **2006**, *314*, 777.
2. Hebert, L. E.; Scherr, P. A.; Bienias, J. L.; Bennett, D. A.; Evans, D. A. *Arch. Neurol.* **2003**, *60*, 1119.
3. Brookmeyer, R.; Gray, S.; Kawas, C. *Am. J. Public Health* **1998**, *88*, 1337.
4. Alzheimer, A. *Allg. Z. Psychiatr.* **1907**, *64*, 146.
5. Selkoe, D. J. *Science* **1997**, *275*, 630.
6. Puchtler, H.; Sweat, F.; Levine, M. *J. Histochem. Cytochem.* **1962**, *10*, 355.
7. Sato, K.; Higuchi, M.; Iwata, N.; Saido, T. C.; Sasamoto, K. *Eur. J. Med. Chem.* **2004**, *39*, 573.
8. Flaherty, D. P.; Walsh, S. M.; Kiyota, T.; Dong, Y.; Ikezu, T.; Vennerstrom, J. L. *J. Med. Chem.* **2007**, *50*, 4986.
9. Masuda, M.; Suzuki, N.; Taniguchi, S.; Oikawa, T.; Nanoka, T.; Iwatsubo, T.; Hisanaga, S.-. I.; Goedert, M.; Hasegawa, M. *Biochemistry* **2006**, *45*, 6085.
10. Jung, M.; Lee, Y.; Moonsoo, P.; Kim, Ha.; Kim, He.; Lim, E.; Tak, J.; Sim, M.; Lee, D.; Park, N.; Oh, W. K.; Hur, K. Y.; Kang, E. S.; Lee, H.-C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4481.
11. Smith, T.; Modarelli, D. A. *Tetrahedron Lett.* **2008**, *49*, 526.
12. Hayek, A.; Nicoud, J. F.; Bolze, F.; Bourgogne, C.; Baldeck, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6466.
13. Jian, H.; Tour, J. *J. Org. Chem.* **2005**, *70*, 3396.
14. Viau, L.; Maury, O.; Le Bozec, H. *Tetrahedron Lett.* **2004**, *45*, 125.
15. Zhang, X.; Liu, A.; Chen, W. *Org. Lett.* **2008**, *10*, 3849.
16. *Representative one-pot procedure*: diethyl 4-iodobenzyl phosphonate (**1**) (0.23 g, 0.65 mmol) and vinylbenzene **2a** (0.14 g, 1.3 mmol) were mixed with palladium (II) acetate (0.004 g, 0.02 mmol), phenylurea (0.005 g, 0.04 mmol) and potassium carbonate (0.18 g, 1.3 mmol) in DMF (5 mL) and were stirred at 110 °C for 22 h. The reaction temperature was then lowered to 80 °C and to this mixture were added 4-cyanobenzaldehyde (**3a**) (0.094 g, 0.72 mmol) and 30% w/v sodium methoxide in MeOH (0.27 mL, 1.4 mmol). The reaction was stirred for 1 h at 80 °C and then cooled to rt and quenched with H_2O (15 mL). The solid was then filtered and rinsed with H_2O and ether to yield (*E,E*)-1-styryl-4-(4-cyanostyryl)benzene (**4a**) (0.17 g, 84%).

17. Cui, X.; Zhou, Y.; Wang, N.; Liu, L.; Guo, Q.-. X. *Tetrahedron Lett.* **2007**, *48*, 163.
18. Several attempts to synthesize **4h** with 1.1 mol equiv of **3d** using the one-pot procedure resulted in low yields of the desired product and recovery of the (*E*)-(4-methoxycarbonylstyrylbenzyl) phosphonate starting material. The lower reactivity of **3d** may be due to its less electrophilic carbonyl carbon.
19. *Representative two-pot procedure*: Step 1: diethyl 4-iodobenzyl phosphonate (**1**) (0.57 g, 1.6 mmol), 4-cyanobenzaldehyde **3a** (0.21 g, 1.6 mmol) and 30% w/v sodium methoxide in MeOH (0.62 mL, 3.3 mmol) were added to DMF (5 mL) and were stirred for 1 h at 80 °C. The reaction was quenched with water, filtered and rinsed with water to yield (*E*)-4-iodostyrylcyanobenzene (**5a**) (0.42 g, 79%). Step 2: Iodostyrene **5a** (0.13 g, 0.38 mmol) and **2a** (0.07 g, 0.68 mmol) were mixed with palladium (II) acetate (0.003 g, 0.010 mmol), phenylurea (0.003 g, 0.021 mmol) and potassium carbonate (0.094 g, 0.68 mmol) in DMF (5 mL) and stirred at 110 °C for 22 h. The reaction was then quenched with H_2O (15 mL) and filtered to yield (*E,E*)-1-styryl-4-(4-cyanostyryl)benzene (**4a**) (0.086 g, 82%).
20. Using a HWE reaction, we were able to isolate **5c** in 90% yield using sodium methoxide at 80 °C compared to a previously reported (Kung, H. F.; Lee, C.-W.; Zhuang, Z.-P.; Kung, M.-P.; Hou, C.; Plssl, K. *J. Amer. Chem. Soc.* **2001**, *123*, 12740.) 30% yield using sodium hydride at room temperature.