

A Domino Approach (Hydrolysis/Dehydrohalogenation/Heck Coupling) for the Synthesis of Styrene Sulfonate Salts

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S Supporting Information

ABSTRACT: A domino approach of hydrolysis/dehydrohalogenation/Heck coupling was used to synthesize styrene sulfonate salts from iodoarenes and chloroethanesulfonyl chloride in good to excellent yields. Methodology was applicable for heterocyclic as well as disubstituted iodoarenes. Some of the key features of this synthetic methodology include the use of phosphine free catalytic system, water as an environmentally friendly solvent, short reaction times, and absence of additives.

Domino reactions are one of the most elegant approaches in modern synthetic organic chemistry in which multiple bond formation reactions take place under identical reaction conditions where one of the reaction components formed in the first reaction reacts in the subsequent reaction and so on.^{1–4} The 2010 Nobel Prize winning palladium catalyzed cross-coupling Heck reaction is ideal as one of the steps in domino reactions. As a part of our continuing interest in developing proton exchange membranes for fuel cell and material chemistry applications, we were interested in synthesizing styrene sulfonic acid salts in water. Our initial idea was to synthesize styrene sulfonate salts^{5–18} via traditional Heck coupling of iodoarene and commercially available sodium vinyl sulfonate in water. While we were able to synthesize the corresponding styrene sulfonate salt from a reaction between iodobenzene and sodium vinyl sulfonate, purification of the product became daunting because of the impurity present in the commercial sodium vinyl sulfonate. This impurity appears to be ethane sulfonate salt (saturated form of vinyl sulfonate, based on its ¹H NMR).

This impurity issue forced us to rethink our strategy of using Heck coupling to synthesize styrene sulfonate salts. Conventional Heck coupling, which is usually carried out in strongly basic medium, can also be used to generate *in situ* alkenes (or olefins) via dehydrohalogenation of a suitably substituted alkyl halide. On the basis of this, we envisioned an initial dehydrohalogenation of a suitably substituted haloalkanesulfonyl halide to generate the olefin/alkene *in situ* followed by a Pd-catalyzed Heck coupling under the identical basic reaction conditions. Many other combinations of domino processes involving Heck coupling as one of the step have been reported earlier;^{19–33} however, examples of a domino process in which an olefin is made *in situ* prior to Heck coupling are scarce.³⁴ Herein, we

report the synthesis of potassium styrene sulfonate salts from easily accessible iodoarenes (and bromobenzene) and chloroethanesulfonyl chloride via a novel domino, hydrolysis/dehydrohalogenation/Heck coupling pathway using phosphine free palladium catalyst in *only* water with no additives.

To test our hypothesis, we chose iodobenzene as the substrate and reacted this with 2-chloroethanesulfonyl chloride in water (solvent) using palladium(II) acetate (2 mol %)³⁵ as the pre-catalyst and potassium carbonate (2 equiv) as a base. To avoid longer reaction times at high temperatures, microwave heating (180 °C) was employed (Scheme 1).^{36–44}

Initial reaction under these conditions showed promising results with the desired product being observed in the NMR of the crude reaction mixture. While decreasing the equivalents of base had a detrimental effect on the formation of the Heck-coupled product, an increase in base equivalents from 2 to 3 equiv showed desired product in over 80% yield by NMR of the crude reaction mixture indicating that indeed multiple (three) reactions had taken place under the chosen reaction conditions. Use of weaker base (NaHCO₃) or organic base (triethylamine) resulted in lower percent conversions of the Heck coupling (penultimate step of the synthesis). This was confirmed by the presence of potassium vinyl sulfonate peaks (and complete absence of 2-chloroethanesulfonyl chloride peaks) in the crude reaction mixture. Use of sodium carbonate instead of potassium carbonate gave slightly less yield (69% Na vs 85% K). Bromobenzene gave the desired styrene sulfonate salt in only 52% yield, while chlorobenzene was unreactive under the reaction conditions. Phosphine free palladium catalysts, such as the one used here (palladium(II) acetate), have been shown to be very reactive and more efficient for Heck coupling prompting for the minimum catalyst loading in the reaction. However, in the absence of any ligands, deactivation of the Pd(0) species to generate ineffective palladium black in the reaction mixture is a well-known process.²² This could be due to various reasons such as difference in the reaction rates of the individual steps of the catalytic cycle, temperature and change in concentration, and composition of the reaction mixture.²² Indeed, we observed Pd black in some of our initial reactions. However, addition of fresh catalyst (1 mol %) to the same reaction mixture followed by heating in microwave for 10 min at 180 °C was found to be very useful in overcoming the catalyst deactivation issue to obtain higher conversions to the desired product, and hence, this protocol was adopted for further reactions. Importantly, all

Received: December 21, 2010

Published: January 26, 2011

Scheme 1. Domino Hydrolysis/Dehydrohalogenation/Heck Coupling Pathway for the Synthesis of Potassium Styrene Sulfonates

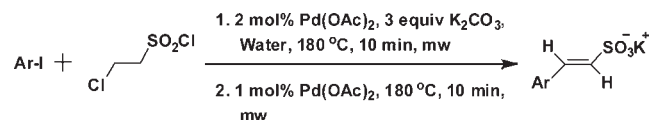
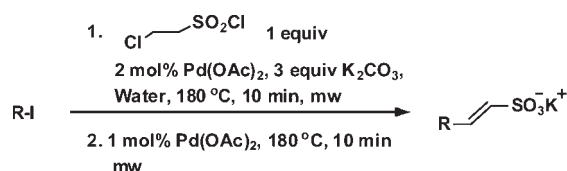


Table 1. Substrate Scope of Domino (Hydrolysis/Dehydrohalogenation/Heck) Coupling Reaction



entry	substrate/product R =	% yield
1	C ₆ H ₅ -	85
2	3-NO ₂ -C ₆ H ₄ -	89
3	2-OCH ₃ -C ₆ H ₄ -	83
4	3-CH ₃ -C ₆ H ₄ -	83
5	2-COOH-C ₆ H ₄ -	0 ^a
6	2-CH ₃ -C ₆ H ₄ -	85
7	2,6-diMe-C ₆ H ₃ -	61
8	3-NO ₂ ,4-OCH ₃ -C ₆ H ₃ -	74
9	Naphthyl-	89
10	4-Vinyl-C ₆ H ₄ -	25 ^b
11	2-F-C ₆ H ₄ -	63
12	3-OH-C ₆ H ₄ -	0 ^a
13	4-F-C ₆ H ₄ -	80
14	3-CF ₃ -C ₆ H ₄ -	80
15	3,5-(CF ₃) ₂ -C ₆ H ₃ -	65
16	3-COOH, 4-OH-C ₆ H ₃ -	69 ^c
17	2-NH ₂ -C ₆ H ₄ -	20 ^b
18	2-pyridyl-	10 ^b
19	3-pyridyl-	66
20	2-thiophenyl-	38 ^b
21	5-indolyl	47
22	2-pyrazinyl	17 ^b

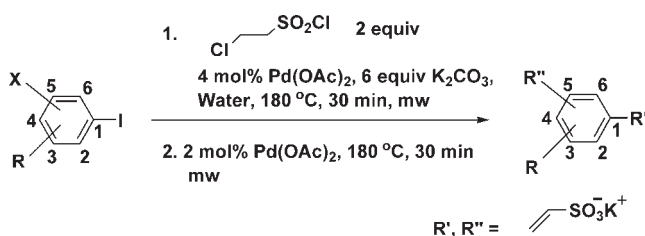
^a 4 equiv of base used. ^b NMR conversions. ^c 5 equiv of base used.

reactions were carried out in environmentally friendly and economically cheap solvent, water in the absence of any additives.

With the optimized conditions in hand, we applied this method to a variety of iodoarenes with different substituents on the aromatic ring in order to study the steric and electronic effects on the outcome of the reaction (Table 1).

Iodobenzene gave desired styrene sulfonate salt in excellent yield (85%, entry 1). Substituted iodobenzenes, with both electron withdrawing and electron donating groups are also well tolerated in this domino Heck chemistry yielding the corresponding styrene sulfonate salts in moderate to excellent yields (Table 1).

Table 2. Synthesis of Disulfonate Salts



entry	substrate/product R =	X =	R''	% yield
23	H	2-I	2-R''	75 ^a
24	H	3-I	3-R''	68
25	H	4(4'-Iodo-C ₆ H ₄)	R''-C ₆ H ₄	29
26	2,3,5,6-Tetra-F	4-I	4-R''	41
27	2,3,5,6-Tetra-Me	4-I	4-R''	59

^a Percent conversion based on potassium vinylsulfonate (product of hydrolysis and dehydrohalogenation), 1:2.5 ratio of bis-/monosubstituted product.

2-Aminoiodobenzene does not seem to work well because of the poisoning of the Pd catalyst by the electron rich amine nitrogen. Same could be true in the case of 2-iodobenzoic acid, which completely fails to react. 2,6-Dimethyl iodobenzene also gave inferior yields, probably because of the steric hindrance of two methyl groups during or after the palladium insertion into the aryl-I bond and subsequent coordination of the palladium species to vinyl sulfonate. On the other hand, iodonaphthalene produced the desired sulfonate salt in excellent yield (89%, entry 9). Heterocyclic sulfonate salts were also synthesized using this method albeit, in lower yields. 2-Iodopyridine (entry 18), 2-iodopyrazine (entry 22), and 2-iodothiophene (entry 20) gave complex mixtures and were difficult to purify. Again, in all these cases, low yields could be due to catalyst poisoning because of presence of heteroatom at the *ortho* position of C-I bond. Both, 3-iodopyridine (entry 19) and 5-iodoindole (entry 21), where the heteroatom is present farther away from the C-I bond, gave desired product in moderate yields.

We also extended this methodology to disubstituted iodobenzenes and the results are shown in Table 2. While 1,2-diiodobenzene gave a mixture of the desired disulfonate salt and monosulfonate product, 1,3-diiodobenzene gave the corresponding product in good yield (entry 24). In the case of 1,2-diiodobenzene, formation of two simultaneous palladium insertion complexes at the 1 and 2 positions could be sterically demanding. Because of this steric hindrance, both Pd σ -complexes cannot undergo β -hydride elimination, which probably results in a side reaction to produce the monosubstituted product.

Surprisingly, biphenyl system (entry 25) gave the desired product only in 29% yield. Substituted diiodobenzenes such as 2,3,5,6-tetrafluoro- (entry 26) and 2,3,5,6-tetramethyl-1,4-diiodobenzene (entry 27) gave corresponding products in moderate to good yields. However, for all the diiodo substrates, longer reaction times (30 min) were required to obtain better conversions. Unfortunately, 2-bromo-4,5-dichloroimidazole and 5-chloro-8-hydroxy-7-iodoquinoline did not react.

Mechanistically, it is reasonable to understand that hydrolysis of the sulfonyl chloride to the sulfonate salt would be an initial

step under aqueous basic conditions. This is followed by the base induced elimination (dehydrohalogenation) of corresponding chlorosulfonate at higher temperatures to generate vinyl sulfonate *in situ*, which would be inserted into the well-known Heck coupling catalytic cycle to give the desired Heck-coupled product in an overall three-step reaction.⁴⁵

To make proton exchange membranes/electrolytes for fuel cell and battery applications, we intend to synthesize ethane sulfonate salts, which can be accessed by hydrogenation of the styrene sulfonate salts obtained in Table 1. We were able to hydrogenate⁴⁶ compounds **1**, **11**, and **14** (see Supporting Information) to obtain the corresponding ethanesulfonate salts in excellent yields.⁴⁷ Further application of this novel Heck coupling method to synthesize polymeric materials containing ethanesulfonate salts is underway.

In summary, we have shown that various styrenesulfonates can be synthesized by a novel domino approach, where the alkene is made *in situ* prior to Heck coupling. This synthetic protocol is quite environmentally friendly as it involves phosphine free catalysis, water as a solvent, and it does not require addition of any additives.

■ ASSOCIATED CONTENT

S Supporting Information. General experimental procedure along with spectroscopic data of all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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■ ACKNOWLEDGMENT

Financial support for our work by Loker Hydrocarbon Research Institute is greatly acknowledged. Dr. M. Czaun is thanked for useful discussions.

■ REFERENCES

- (1) Oestreich, M.; Ed. *The Mizoroki-Heck Reaction*; Wiley-VCH Verlag GmbH: Weinheim, 2009.
- (2) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH Verlag GmbH: Weinheim, 2006.
- (3) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.
- (4) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131–163.
- (5) Previous synthesis of styrene sulfonate salts can be found at: Bader, A.; Arlt, D.; Fiedel, D.; Meier, S.; U. S. Patent 5 231 223, **1992**; *Chem. Abstr.* **1993**, *118*, 101659.
- (6) Watanabe, M.; Kiuchi, H.; Hosaka, S.; Toyo Rayon, C.; *Chem. Abstr.* **1965**, *62*, 82298.
- (7) Rondestvedt, C. S., Jr.; Bordwell, F. G. *Org. Synth.* **1954**, *34*, 85.
- (8) Terent'ev, A. P.; Gracheva, R. A.; Shcherbatova, Z. F. *Dokl. Akad. Nauk SSSR* **1952**, *84*, 975–977.
- (9) Terent'ev, A. P.; Dombrovskii, A. V. *Zh. Obshch. Khim.* **1950**, *20*, 1875–1880.
- (10) Bordwell, F. G.; Rondestvedt, C. S., Jr. *J. Am. Chem. Soc.* **1948**, *70*, 2429–2433.
- (11) Bordwell, F. G.; Suter, C. M.; Holbert, J. M.; Rondestvedt, C. S. *J. Am. Chem. Soc.* **1946**, *68*, 139–140.
- (12) Suter, C. M.; Milne, H. B. *J. Am. Chem. Soc.* **1943**, *65*, 582–584.
- (13) Kharasch, M. S.; Schenck, R. T. E.; Mayo, F. R. *J. Am. Chem. Soc.* **1939**, *61*, 3092–3093.

- (14) Quilico, A.; Fleischner, E. *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.* **1928**, *7*, 1050–1056.
- (15) Ermaganbetov, M. E.; Shaikhutdinov, E. M.; Elikbaeva, T. Z.; Asaubekov, M. A. *Dokl. Minist. Nauki-Akad. Nauk Resp. Kaz.* **1997**, *46–49*. *Chem. Abstr.* **1997**, *130*, 4115.
- (16) Bader, A.; Arlt, D.; Fiedel, D.; Meier, S.; EP 105452 508264, **1992**; *Chem. Abstr.* **1993**, 101659.
- (17) Toyo Soda Mfg. Co., Ltd., Japan.: Application: JP, 136314 55064565, **1978**; *Chem. Abstr.* **1978**, *93* 204267.
- (18) Makarova, S. B.; Roizen, K. M.; Vlasov, L. G.; Aptova, T. A.; Korovina, T. N.; Makovskaya, V. I.; Lavrikov, E. S.; Bazhenov, V. I.; (USSR). SU 1974-2082463 530024, **1974**; *Chem. Abstr.* **1974**, *86*, 43406.
- (19) Negishi, E.-i.; Coperet, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365–394.
- (20) Brenner, M.; Mayer, G.; Terpin, A.; Steglich, W. *Chem.—Eur. J.* **1997**, *3*, 70–74.
- (21) Tietze, L. F.; Heitmann, K.; Raschke, T. *Synlett* **1997**, 35–37.
- (22) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.
- (23) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2964.
- (24) Battistuzzi, G.; Cacchi, S.; De Salve, I.; Fabrizi, G.; Parisi, L. M. *Adv. Synth. Catal.* **2005**, *347*, 308–312.
- (25) Jacobi von Wangelin, A.; Neumann, H.; Goerdes, D.; Huebner, S.; Wendler, C.; Klaus, S.; Struebing, D.; Spannenberg, A.; Jiao, H.; El Firdoussi, L.; Thurow, K.; Stoll, N.; Beller, M. *Synthesis* **2005**, 2029–2038.
- (26) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442–4489.
- (27) Oestreich, M. *Eur. J. Org. Chem.* **2005**, 783–792.
- (28) Storsberg, J.; Yao, M.-L.; Ocal, N.; de Meijere, A.; Adam Arnold, E. W.; Kaufmann Dieter, E. *Chem. Commun.* **2005**, 5665–5666.
- (29) Bernini, R.; Cacchi, S.; Fabrizi, G.; Sferazza, A. *Heterocycles* **2006**, *69*, 99–105.
- (30) Yolacan, C.; Bagdatli, E.; Ocal, N.; Kaufmann, D. E. *Molecules* **2006**, *11*, 603–614.
- (31) Giguere, D.; Patnam, R.; Juarez-Ruiz, J. M.; Neault, M.; Roy, R. *Tetrahedron Lett.* **2009**, *50*, 4254–4257.
- (32) Mao, H.; Wan, J.-P.; Pan, Y.; Sun, C. *Tetrahedron Lett.* **2010**, *51*, 1844–1846.
- (33) Namyslo, J. C.; Storsberg, J.; Klinge, J.; Gaertner, C.; Yao, M.-L.; Ocal, N.; Kaufmann, D. E. *Molecules* **2010**, *15*, 3402–3410.
- (34) Saiyed, A. S.; Bedekar, A. V. *Tetrahedron Lett.* **2010**, *51*, 6227–6231.
- (35) Use of palladium(II) chloride instead of palladium(II) acetate gave nearly identical conversion in a test reaction; however, we chose palladium(II) acetate as a precatalyst for all further reactions.
- (36) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582–9584.
- (37) Lew, A.; Krutzyk, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2001**, *4*, 95–105.
- (38) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283.
- (39) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717–727.
- (40) Bergbreiter, D. E.; Furyk, S. *Green Chem.* **2004**, *6*, 280–285.
- (41) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771–11835.
- (42) Arvela, R. K.; Leadbeater, N. E. *J. Org. Chem.* **2005**, *70*, 1786–1790.
- (43) Botella, L.; Nájera, C. *J. Org. Chem.* **2005**, *70*, 4360–4369.
- (44) Gil-Moltó, J.; Karlström, S.; Nájera, C. *Tetrahedron* **2005**, *61*, 12168–12176.
- (45) Heating the reaction mixture containing only chloroethanesulfonyl chloride and K₂CO₃ (2 equiv) at 180 °C for 10 min in microwave produced potassium vinyl sulfonate (by ¹H NMR). Addition of palladium(II) acetate, iodobenzene, and 1 equiv of K₂CO₃ to the same reaction mixture followed by heating under identical conditions gave **1** in 82% yield.

(46) Nardello, V.; Aubry, J.-M.; Johnston, P.; Bulduk, I.; de, V. A. H. M.; Alsters, P. L. *Synlett* **2005**, 2667–2669.

(47) Hydrogenation of the reaction mixture (obtained during the synthesis of **1**), using palladium(black) obtained in the reaction mixture itself as a catalyst (6 bar H₂, rt, 24 h), unfortunately, did not produce the corresponding hydrogenated product (**28**). This could be due to the catalytic amount (2 mol%) of Pd being used for the Heck coupling versus 0.5 equiv used for the hydrogenation based on ref 46.