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Efficient synthesis of 3-arylbutadiene sulfones using the Heck–Matsuda reaction

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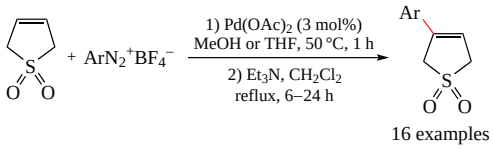
An efficient and practical method for a scalable synthesis of 3-arylbutadiene sulfones deals with the ligand-free Heck–Matsuda reaction of sulfolene with aryldiazonium tetrafluoroborates followed by triethylamine-promoted double bond shift.



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3-Sulfolenes[1] are valuable key intermediates widely used in the synthesis of sulfolanes,[2] polycyclic heterocycles[1(b),3] and conjugated unsaturated compounds[4] as well as in natural product synthesis.[5] 3-Sulfolenes are usually considered as 'protected dienes' where the electron-withdrawing properties of the sulfone group are responsible for the easy C^2 and C^5 deprotonation, along with the double bond shift, depending on reaction conditions. The alkylation at C^2 with C^3-substituted compounds readily occurs, except for cases when the carbanion is stabilized with a silyl or phenyl group.[6] Extrusion of SO_2 may be further easily carried out,[4(b),4(f),7] therefore sulfolenes are very beneficial in the syntheses of terpenes, for example (*E*)-ocimene[7(a)] obtained from 2-methylsulfolene, the commercially available isoprene adduct of SO_2. Although 3-sulfolene applications are very rewarding, it is all the more surprising that the synthesis of 3-arylbutadiene sulfones is documented scarcely.

Among the described methods for the synthesis of 3-arylbutadiene sulfones, SO_2 addition to these dienes is not easy.[8] The alternative transformation of 3-bromobutadiene sulfones requires the application of poorly accessible alkylcuprates[9] under inert atmosphere, whereas the Stille reaction[10] of exotic 3-stannylated butadiene is not environmental friendly.

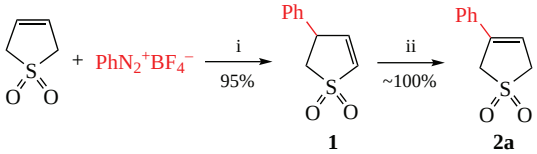
The Heck reaction resulting in 3-arylbutadiene sulfones as the products seems to be the most convenient and promising. The Heck reaction was earlier developed[2(d),11] on the narrow starting material scope, using expensive aryl iodides along with high loadings of Pd-catalyst (5 mol%). Since aryl halides in Heck reaction can be replaced with cheap and readily accessible aryldiazonium salts, we reasoned for improvement of the efficiency using the scalable Heck–Matsuda reaction. In general, the Heck–Matsuda reaction with aryldiazonium salts results in 3-aryl-4-sulfolenes of type **1** which can be quantitatively isomerized into desired 3-arylbutadiene sulfones (Scheme 1).

The only paper describing this approach[12] contains only six examples while steric and electronic effects of the substituents are not studied. In continuous search for efficient catalysts[13] for modern synthetic methods,[14] we report herein on the Heck–Matsuda reaction for the convenient synthesis of 3-arylbutadiene sulfones. Based on the abovementioned data,[12] we started our search for optimal conditions of the process (see Scheme 1 and Online Supplementary Materials, Table S1, entries 1–13).

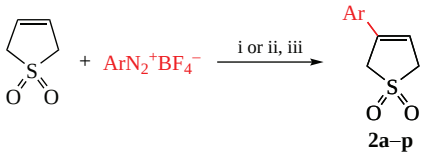
We used $PhN_2^+BF_4^-$ as a model substrate, $Pd_2(dba)_3 \cdot CHCl_3$ and $Pd(OAc)_2$ as a palladium source and examined various solvents. The highest yield of 95% was achieved in case of $Pd(OAc)_2$ and $Pd_2(dba)_3 \cdot CHCl_3$ at 50 °C in methanol. Decrease in temperature to the ambient one leads to a moderate decrease in the yield of product **1**. It should be noted that intermediate **1** (see Scheme 1) was isolated only for $PhN_2^+BF_4^-$ as a substrate, in case of all other aryldiazonium salts we performed one-pot process giving the target 3-sulfolenes of type **2** without the intermediate isolation.

We investigated the activity of the found catalytic system suitable for a variety of substrates (Scheme 2). Substrates, bearing various electron-donating and withdrawing groups at *ortho*-, *meta*- and *para*-positions along with the sterically hindered substituents, were systematically tested. Aryldiazonium salts containing electron-donating and electroneutral substituents react with 3-sulfolene under modified conditions in methanol to afford 3-arylbutadiene sulfones **2a**–**e** with the good to excellent yields (see Scheme 2). Also, aryldiazonium salts with such electron-withdrawing groups as Cl (**2f**,**h**), Br (**2g**) and CF_3 (**2i**) give the yields from 77 to 92% in methanol.

However, our attempt to introduce other electron-withdrawing (for products **2j**–**l**) or sterically hindered (for products **2m**–**p**) substituents into aryldiazonium salts caused serious drop in the cross-coupling yields up to 0%. Consequently, we continued search for optimal conditions for these substrates. We used



Scheme 1 *Reagents and conditions*: i, $Pd(OAc)_2$ (3 mol%), MeOH (2 ml mmol^{-1}), 50 °C, 1 h; ii, CH_2Cl_2 (5 ml mmol^{-1}), Et_3N (1 ml mmol^{-1}), reflux, 24 h.



2a–p

a Ar = Ph; 95% (i), 65% (ii)
b Ar = 4-MeC_6H_4; 99% (i), 71% (ii)
c Ar = 4-$Bu^tC_6H_4$; 65% (i), 72% (ii)
d Ar = 4-$MeOC_6H_4$; 72% (i), 40% (ii, 4 h)
e Ar = 2-naphthyl; 63% (i), 21% (ii, 4 h)
f Ar = 4-ClC_6H_4; 82% (i), 94% (ii)
g Ar = 4-BrC_6H_4; 77% (i), 88% (ii)
h Ar = 3-ClC_6H_4; 92% (i), 94% (ii)
i Ar = 3-$F_3CC_6H_4$; 79% (i), 82% (ii)
j Ar = 4-$F_3CC_6H_4$; 0% (i), 78% (ii)
k Ar = 4-$O_2NC_6H_4$; 56% (i), 90% (ii)
l Ar = 4-NCC_6H_4; 45% (i), 58% (ii, 4 h)
m Ar = 2-$MeOC_6H_4$; 0% (i), 70% (ii)
n Ar = 1-naphthyl; 44% (i), 61% (ii, 4 h)
o Ar = 2-FC_6H_4; 48% (i), 96% (ii)
p Ar = 2-BrC_6H_4; 34% (i), 77% (ii)

Scheme 2 *Reagents and conditions*: i, $Pd(OAc)_2$ (3 mol%), MeOH (2 ml $mmol^{-1}$), 50 °C, 1 h; ii, $Pd(OAc)_2$ (3 mol%), THF (5 ml $mmol^{-1}$), 50 °C, 1 or 4 h; iii, Et_3N (1 ml $mmol^{-1}$), CH_2Cl_2 (5 ml $mmol^{-1}$), reflux, 6–24 h.

4-$O_2NC_6H_4N_2^+BF_4^-$ as a model substrate, and $Pd(OAc)_2$ or $Pd_2(dba)_3 \cdot CHCl_3$ as a palladium source (see Table S1, entries 13–17) and found that the yields from good to almost quantitative of the desired 3-arylbutadiene sulfones **2j–p** were achieved using $Pd(OAc)_2$ and THF as the solvent (see Scheme 2). Carrying out the reaction in THF was also useful in cases of aryldiazonium salts with weak electron-withdrawing substituents (see Scheme 2, products **2f–i**). On the contrary, for substrates with electron-donating and electroneutral groupings the yields stayed better in methanol (products **2a–e**).

In conclusion, we have developed a simple and efficient method for the preparation of 3-arylbutadiene sulfones *via* the Heck–Matsuda reaction. The reactions can be carried out in a gram scale, using a bench stable and inexpensive aryldiazonium salts in methanol or THF in the presence of $Pd(OAc)_2$ under ligand-free conditions. In view of the readily available starting materials, simple operation of the process, as well as high regioselectivity, this methodology may become a useful tool for the synthesis of branched 3-arylbutadiene sulfones and their derivatives. The new method is expected to find applications in medicinal chemistry and organic synthesis.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.07.037.

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