Sulfamide Synthesis via Pd-Catalysed Cross-Coupling

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Abstract: A novel efficient procedure for the improved synthesis of aryl-substituted sulfamides via a Pd-catalysed arylation of sulfamide is reported.

Key words: amines, amides, sulfur compounds, catalysis, palladium

Sulfamides (Figure 1) constitute an interesting functional group for organic chemistry. While on first sight the structure reminds one of related sulfonamides, its two amino moieties, which are connected via an electron-acceptor functionality, render it reminiscent of ureas. In contrast to the latter, the inherent electronic properties of the sulfonyl bridge do not induce mesomeric amide interactions.

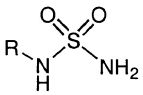


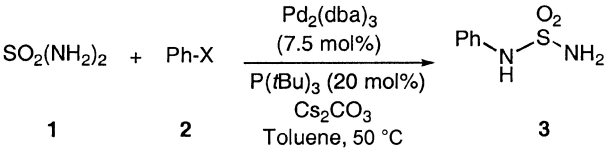
Figure 1 General structure of sulfamides

In view of these rather unique properties, there has been a broad interest on sulfamides including their use in the synthesis of heterocycles[2] and incorporation in molecules of pharmaceutical interest.[3]

While the parent sulfamide (**1**, R = H) is commercially available, there does not exist a general access to higher substituted derivatives of **1**.[4] Over the last decades, several reports have appeared which include synthesis from amination reaction of sulfamoyl chloride[5] and sulfamate esters,[6] transamidation on sulfamide[7] or aminolysis of stable sulfamoyl salts.[8] A solid-phase protocol on the basis of the latter was reported recently.[9]

We here describe preliminary results toward a convenient synthetic procedure for the rapid and high-yielding synthesis of these compounds, which is based on a novel palladium-catalysed amination of arenes.

Within this context of synthesising aryl sulfamides, a palladium(0)-catalysed amination of arenes[10] was examined (Scheme 1, Table 1). Preliminary experiments with triflates and chlorides gave rather low conversion and/or complex reaction mixtures. However, when bromo- or iodobenzene were treated with a catalyst derived from a combination of tris(*tert*-butyl)phosphine and a palladium(0) source, the expected amination reaction occurred as major pathway. Still, the crude reaction mixture contained several compounds which supposedly included *N*,*N*- and *N*,*N*′-diarylated and higher arylated derivatives as well. In order to accomplish clean mono-phenylation, three equivalents of **1** were employed and the aniline-derivative **3** was obtained in 73% yield after work-up and crystallisation (Scheme 1).[11]



Scheme 1 Pd-catalysed phenylation of sulfamide **1**

Table 1 Hartwig–Buchwald Coupling of Sulfamide **1**[11]

Entry	Ph-X	Ratio **1**/ Ph-X	Product	Yield of **3** (%)[a]
1	**2** (X = Cl)	3:1	**3**	14
2	**2** (X = OTf)	3:1	**3**	Ca. 10[b]
3	**2** (X = Br)	1:1	**3**	Ca. 15[b]
4	**2** (X = Br)	2:1	**3**	Ca. 35[b]
5	**2** (X = Br)	3:1	**3**	73
6	**2** (X = I)	3:1	**3**	57

[a] Isolated yield after crystallisation.
[b] Estimated from the NMR spectra of the crude reaction mixture.

For all these coupling reactions, a catalyst derived from combination of $Pd_2(dba)_3$ and the basic phosphine P(*t*-Bu)$_3$ turned out to be best. Related catalysts from this palladium source and ligands such as BINAP, dppf, dppp or triphenylphosphine gave more complex reaction mixtures and yields in the range of 22–51% for the isolated product **3**. Preformed tetrakis(triphenylphosphine)palladium(0) gave comparable results.

To the best of our knowledge, these examples represent the first successful examples of a Hartwig–Buchwald coupling employing sulfamide **1** as nitrogen source.[12,13]

Within this context, the comparable reavtivity of iodo- and bromobenzene is somewhat surprising. Generally, bromo arenes tend to give significantly higher reactivity

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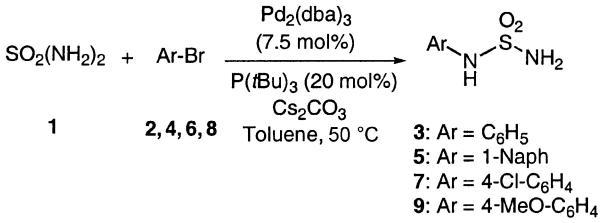
in this type of coupling reactions.[10,12] The requirement of over-stoichiometric amounts of sulfamide in these couplings in order to facilitate mono-arylated sulfamide **3** matches well with a recent report by Moreno-Mañas on Pd-catalysed Tsuji–Trost reactions with **1** as nucleophile.[14] Here, an excess of 4 equivalents was necessary in order to prevent more than one allylation to occur.



Scheme 2 Pd-catalysed arylation of sulfamide **1**

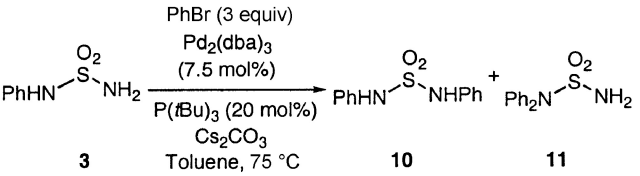
Table 2 General Hartwig–Buchwald Coupling of Sulfamide **1**[11]

Entry	Ar-Br	Ratio **1**/ Ar-Br	Product	Yield (%)[a]
1	**2** (Ar = C_6H_5)	3:1	**3**	73
2	**4** (Ar = 1-Naph)	3:1	**5**	65
3	**6** (Ar = 4-Cl-C_6H_4)	3:1	**7**	79
4	**8** (Ar = 4-MeO-C_6H_4)	5:1[b]	**9**	61

[a] Isolated yield after crystallisation.
[b] Reaction at 75 °C.

In an identical manner, naphthalene derivative **5** was obtained in 65% yield after crystallisation from the crude reaction mixture (Scheme 2, Table 2, entry 2). Substitution pattern at the aromatic ring are tolerated by the present protocol (Table 2, entries 3, 4), however, a preference for the electron-acceptor substituent over the electron-donating one was observed. Apparently, the latter one decreases the rate for the initial oxidative insertion in the aryl bromide bond leading to lower chemical yields. A satisfying yield of 61% could only be obtained at a higher **1/8** ratio of 5:1 and at a temperature of 75 °C. Substituted sulfamides such as **3** undergo non-position selective arylation (Scheme 3). For example, when **3** was submitted to phenylation under the standard conditions, the crude reaction mixture consisted of the three compounds **3**, **10** and **11** in a ratio of 1:3:2.2. Apparently, steric factors lead to preference for the arylation at the free NH_2 terminus over the arylated one. Attempts to improve the respective ratios for **10** and **11** by altering the amounts of phenyl bromide **2** did only lead to lower reactivity and isolation of larger amounts of unreacted starting material **3**.

All reaction products gave satisfying ^{1}H NMR, ^{13}C NMR, MS, and HRMS data. These data were compared to the one from authentical samples obtained through a variation of standard synthetic procedures. To this end, commercially available chloro sulfonylisocyanate was converted to chloro sulfonamide by reaction with formic acid as



Scheme 3 Arylation of sulfamide **3**

previously reported.[5a] While the nucleophilic direct substitution at sulfur with amines to yield N-substituted sulfamides had been established before, we found this procedure less attractive for the application of more elaborated amines since an excess of these compounds is usually required.[5,6] The overall synthetic efficiency could be significantly enhanced when the reaction was carried out in the presence of 20–25 mol% of DMAP (*N*,*N*-dimethylamino pyridine) and stoichiometric amounts of triethylamine.[15,16]

In view of the convenient process of the described transition metal coupling, compound **3** was submitted to X-ray structure determination.[17] As expected, the central sulfur atom displays a nearly tetrahedral environment with the expected bond lengths and angles for such an arrangement. With regards to the crystal packing, significant intermolecular hydrogen bonding between the sulfonyl oxygen and the NH moieties are present.[17]

In summary, we have reported the use of sulfamide as substrate for palladium-catalysed amination of halo arenes. The reaction proceeds under relatively mild conditions to furnish *N*-aryl sulfamides.

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(11) **Typical Synthetic Procedure for Amination of Haloarenes via Pd-Coupling**: A solution of compound **1** (3.3 mmol) and bromo benzene **2** (1.0 mmol) in freshly distilled toluene are treated with dipalladium(0)–dba complex (0.075 mmol), tris(*tert*-butyl)phosphine (0.2 mmol) and caesium carbonate (1 mmol) and heated to 50 °C overnight. The reaction mixture is cooled to r.t., filtered over celite and evaporated under reduced pressure. The pure product was usually obtained by crystallization from methanol. Analytical data for compound **3**: ^{1}H NMR (DMSO-d_6): δ = 4.05 (d, *J* = 1.2 Hz, 2 H, CH_2), 6.55 (br s, 2 H, NH_2), 6.92 (t, *J* = 1.2 Hz, 1 H, N*H*), 7.11–7.40 (m, 5 H, arom.). ^{13}C NMR (DMSO-d_6): δ = 46.5 (*C*H$_2$), 127.3, 128.1, 128.5 (arom. *C*H), 139.0 (C_{ipso}). Anal. Calcd for $C_7H_{10}N_2O_2S$: C, 45.15; H, 5.41; N, 15.04; S, 17.22. Found: C, 45.29; H, 5.09; N, 14.81; S, 17.50.
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(16) **Typical Procedure for DMAP-Mediated Synthesis of Sulfamides:** A solution of sulfamoyl chloride (5 mmol) in CH_2Cl_2 (10 mL) is treated with an additional amount of dry toluene (10 mL) and stirred at 0 °C. To this solution, DMAP (1.0 mmol) is added in one portion followed by addition of Et_3N (5.5 mmol) and the respective aniline (1.0 mmol). The resulting yellow solution is stirred first at 0 °C, then at r.t. for 5 h. The solvents are removed to a remaining volume of approx. 4 mL and extracted with boiling water. Evaporation of the aqueous phase yields the respective sulfamides. Alternatively, some of the products can be distilled directly from the crude reaction mixture.
(17) **Data on the X-Ray Analysis of Compound 3**. Crystallographic data (excluding structure factors) for the structure reported have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-241627. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ UK (fax: +44(1223)336033; email: deposit@ccdc.cam.ac.uk).