Tetrahedron Letters 52 (2011) 1882–1887

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A general route to unsubstituted *N*-aryl and heteroarylaminobenzenesulfonamides

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ARTICLE INFO

Article history:
Received 10 January 2011
Revised 3 February 2011
Accepted 7 February 2011
Available online 12 February 2011

Keywords:
Buchwald–Hartwig coupling
Sulfonamide
Paramethoxybenzyl
Protecting group

ABSTRACT

Starting from suitably protected 3- and 4-aminobenzenesulfonamides, a practical two-step strategy for the synthesis of unsubstituted *N*-aryl and heteroarylaminobenzenesulfonamides was devised. Strong bases are tolerated during the *N*-arylation step. Overall moderate to excellent yields are reported.

There are an abundant number of molecules that contain the sulfonamide moiety. Chiral auxiliaries,[1] peptidomimetics,[2] modified oligonucleotides,[3] amines synthons,[4] and therapeutics[5–7] illustrate the diverse application for the sulfonamide group. Their ability to serve as amide surrogates and also as zinc-chelators, with unique physical properties, has made them ideal functional groups for the development of pharmaceutical and agricultural agents. More specifically, unsubstituted *N*-aryl and heteroarylaminobenzenesulfonamide compounds with 3- or 4-aminobenzesulfonamide (sulfanilamide) motifs have found extensive applications in oncology, CNS, diabetes, and cardiovascular disease areas but also as analgesic and anti-inflammatory compounds[8–22] (Fig. 1). In particular, a whole class of carbonic anhydride inhibitors belongs to the sulfonamide family.[23,24]

Standard protocols to access unsubstituted *N*-heteroarylaminobenzenesulfonamides from **1** or **2** include transition metal catalyzed C–N bond formation, direct H^+-catalyzed SNAr or nucleophilic substitution under weakly basic conditions (Scheme 1, Approach A). These methods mostly refer to activated heterocyclic partners with a chlorine/idodine atom at C-2 position (e.g., pyrimidines,[25–28] pyridines,[29,30] oxazoles,[31] pyrazines[14,32]) or C-4 (e.g., quinolines,[33] phtalazines[34]) and moderate to good yields have been reported. Alternatively, unsubstituted *N*-aryl and heteroarylaminobenzenesulfonamides can be delivered in a variable yield by 'reverse' Buchwald–Hartwig[13,20,22,35,36] or Ullmann-type coupling[12] (Scheme 1, Approach B), using commercially available halides **3** and **4** with corresponding anilines or aminoheterocycles.

Inconsistency in the outcome of approaches A and B and lack of a general process applicable to both aryl and heteroaryl series independent of the electronic nature of the ring systems prompted us to consider a strategy based on a direct Buchwald–Hartwig coupling (following route A) with a suitably protected sulfonamide. We were confident that this alternative would favorably compete with previous routes while affording higher solubility of the sulfonamide moiety in organic solvents and preventing the likely competitive side-reaction of the more acidic sulfonamide NH_2 group for the C–N bond formation. Although many methods exist for the manipulation of sulfonamide functional group, there is a general dearth of protecting groups for this functionality.[37] In principle, the benzyl group could serve as a useful protecting group for primary sulfonamides. However, *N,N*-dibenzylsulfonamide dealkylation requires either high pressure hydrogenolysis that can be quite problematic,[38,39] harsh acidic conditions leading to variable recovery,[11,40] or toxic chromium(III) salts in the presence of periodic acid.[41] Sulfonamides protected as acetimidates have also been reported,[42,43] but these groups will probably not survive the basic coupling conditions. Eventually, derivatisation as dimethylaminoformamidine[10,44–49] or *N,N*-bis-*p*-methoxybenzylsulfonamide seemed more appropriate to our case. Although very little is known in the literature about primary sulfonamides protection using a bis-PMB strategy,[50,51] this option was retained based on the ease in both the protection and removal steps. Thus, key synthons **7** and **8** were prepared in high yield by first alkylation of the corresponding 3- and 4-nitrobenzenesulfonamides **5** and **6** using PMBCl, followed by the nitro-function reduction step. Conveniently, none of the stages required any purification (Scheme 2).

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0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.02.034

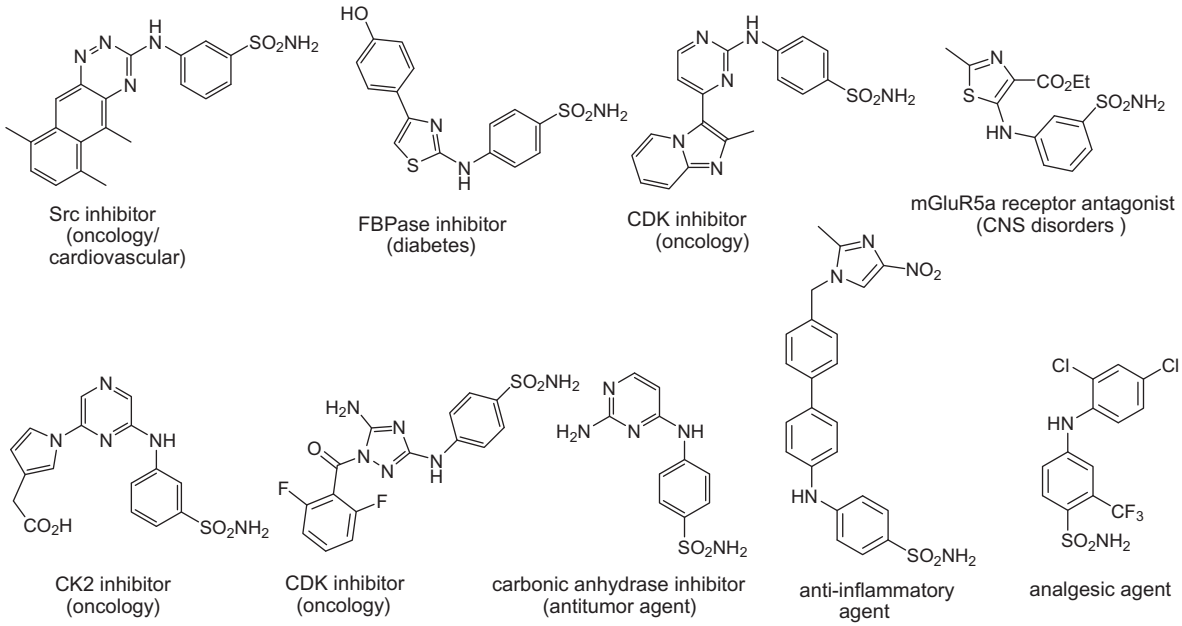
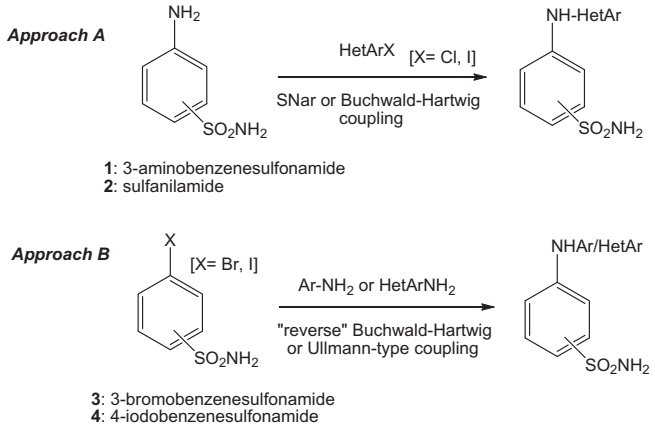
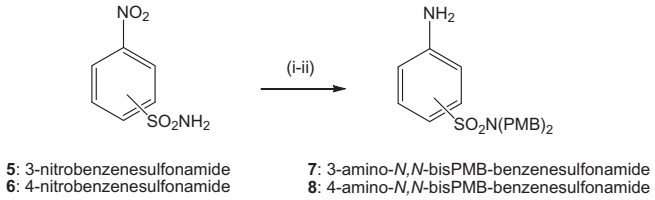


Figure 1. Biologically active unsubstituted *N*-aryl and heteroarylaminobenzenesulfonamides compounds with the 3-aminobenzesulfonamide and sulfanilamide framework.

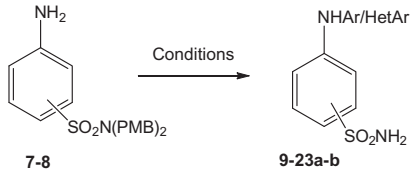


Scheme 1. Synthetic paths to unsubtituted *N*-aryl and heteroarylaminobenzenesulfonamides compounds with 3-aminobenzesulfonamide and 4-aminobenzesulfonamide framework.



Scheme 2. Synthesis of key synthons **7** and **8**. Reagents and conditions: (i) PMB-Cl, K_2CO_3, NaI, 2-butanone, 80 °C, 16 h, 95%; (ii) H_2, PtO_2, ethanol, 1 atm, 60 min, quant.

The first step positively compares in terms of yield and cost with the alternative treatment of commercially available 3- or 4-nitrobenzenesulfonyl chlorides with quite expensive *N,N*-bis-*p*-methoxybenzylamine.[52] Key anilines **7** and **8** were reacted next with a wide range of aryl/heteroaryl halides substrates under Buchwald conditions (Scheme 3) to deliver after PMB cleavage the expected compounds **9a–b** to **28a–b** with moderate to excellent yield (32–96%, Table 1).[53] The optimized telescoped process required a simple aqueous workup after *N*-arylation, followed by a solvent switch from dioxane to dichloromethane. Final compounds were isolated after adsorption and purification by flash silica gel chromatography.



Scheme 3. Synthesis of various unsubstituted *N*-aryl and heteroarylaminobenzene sulfonamides compounds using our protecting group strategy.

Our protocol readily applies to the aryl series and accommodates both electron withdrawing and electron donating substituents (entries 1–10). Encouragingly, both activated (entries 11–14, 21–25) and unactivated heterocyclic halides (entries 15–20, 26–32) were efficiently coupled under applied conditions. In the course of this study, the bidendate chelating ligand Xantphos in combination with the weak base Cs_2CO_3 was generally used because it limits diarylation, increases reductive elimination rate, and prevents catalyst deactivation by the co-ordination of pyridine-containing substrates.[54] Still, the problematic direct amination of 3-bromothiophene[55] was conducted using the third-generation monodendate ligand P^tBu_3 in the presence of NaO^tBu to deliver compounds **27ab** in acceptable yield (entries 30 and 31). Following the same trend, poorly reactive substrates, such as **12**, **19,** and **28** were easily coupled using the sterically demanding biaryl monophosphine ligand XPhos (entries 6, 17 and 32), which favors LPd and LPd(Ar)amido intermediates facilitating the oxidative addition and reductive elimination steps of the catalytic cycle. In addition, XPhos in combination with strong bases (NaO^tBu, LiHMDS) was found to promote the chemoselective *N*-arylation of the aniline NH_2 group (substrate **8**) over a primary amide (entry 10) or a 2-aminopyridine motif (entry 17).

Eventually, as a proof of concept, we embarked on a direct comparison of our process with standard routes A–B. On the one hand, unsubstituted sulfonamides **1** or **2** were randomly *N*-arylated under microwave-heating Buchwald conditions using aryl/hetero-

Table 1
Unsubstituted *N*-aryl and heteroarylaminobenzenesulfonamides **9–28ab** produced via Scheme 3 (with selected comparative examples according to Scheme 1)

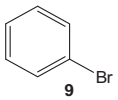
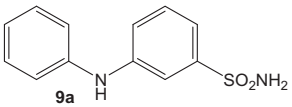
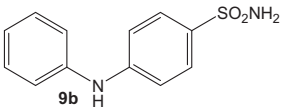
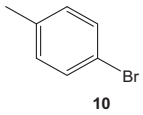
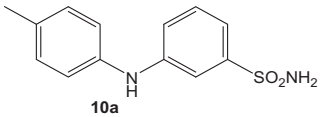
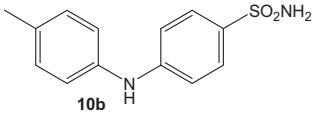
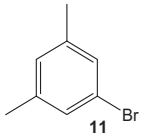
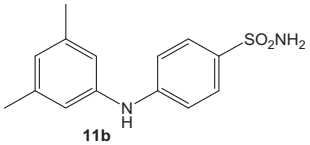
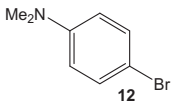
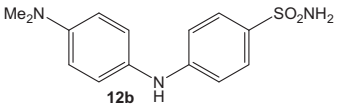
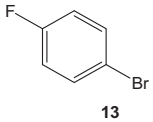
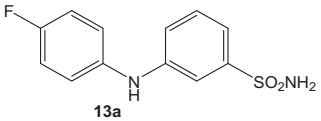
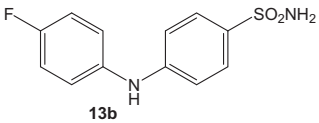
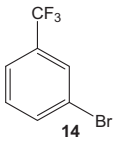
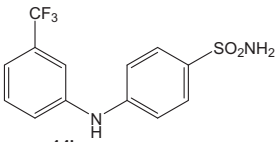
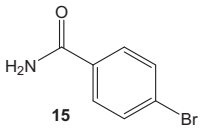
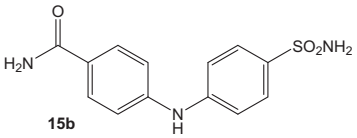
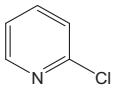
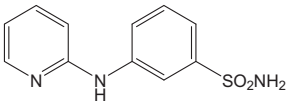
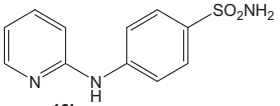
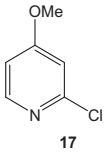
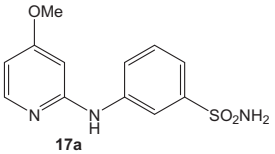
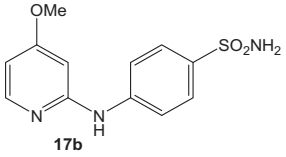
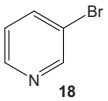
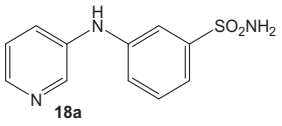
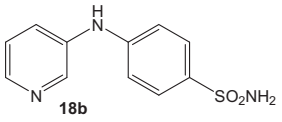
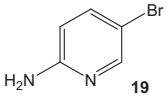
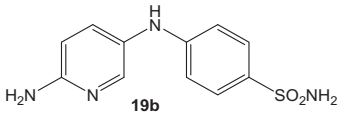
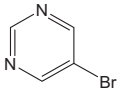
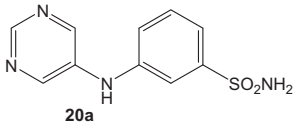
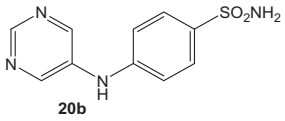
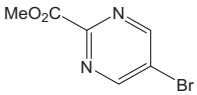
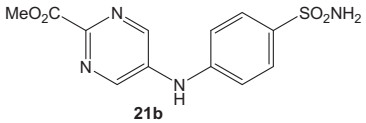
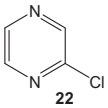
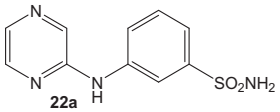
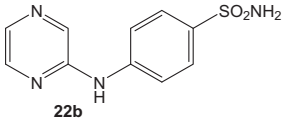
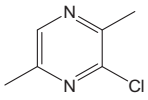
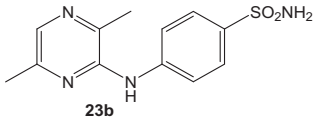
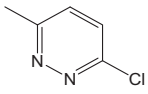
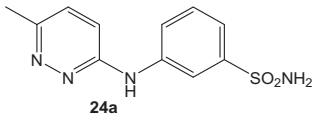
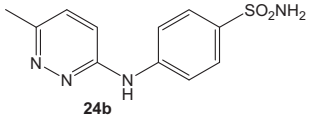
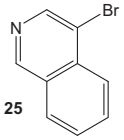
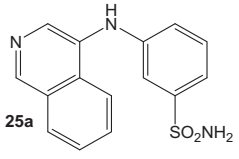
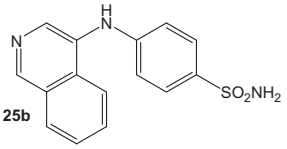
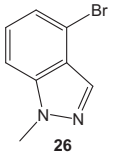
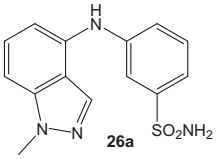
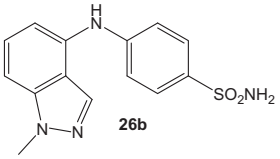
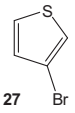
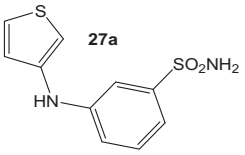
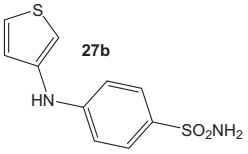
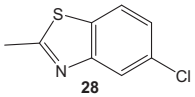
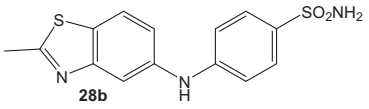
Entry	Sulfonamide	Aryl/hetaryl halide	Product	Isolated yield (%)
1	**7**	 **9**	 **9a**	65[a]
2	**8**		 **9b**	70[a] (27)[e]
3	**7**	 **10**	 **10a**	83[a] (13)[f]
4	**8**		 **10b**	59[a]
5	**8**	 **11**	 **11b**	68[a]
6	**8**	 **12**	 **12b**	83[b]
7	**7**	 **13**	 **13a**	45[a] (11)[f]
8	**8**		 **13b**	66[a]
9	**8**	 **14**	 **14b**	83[a]
10	**8**	 **15**	 **15b**	94[b]
11	**7**	 **16**	 **16a**	71[a] (17)[f]
12	**8**		 **16b**	38[a]
13	**7**	 **17**	 **17a**	43[a]

Table 1 (*continued*)

Entry	Sulfonamide	Aryl/hetaryl halide	Product	Isolated yield (%)
14	**8**		 **17b**	70[a] (0)[e]
15	**7**	 **18**	 **18a**	50[a]
16	**8**		 **18b**	63a (13)[e]
17	**8**	 **19**	 **19b**	47[c]
18	**7**	 **20**	 **20a**	60[a] (18)[e]
19	**8**		 **20b**	38[a]
20	**8**	 **21**	 **21b**	40[a]
21	**7**	 **22**	 **22a**	96[a] (38)[e]
22	**8**		 **22b**	38[a]
23	**8**	 **23**	 **23b**	80[a]
24	**7**	 **24**	 **24a**	32[a]
25	**8**		 **24b**	32[a]
26	**7**	 **25**	 **25a**	80[a]

(*continued on next page*)

Table 1 (*continued*)

Entry	Sulfonamide	Aryl/hetaryl halide	Product	Isolated yield (%)
27	**8**		 **25b**	62[a]
28	**7**	 **26**	 **26a**	86[a]
29	**8**		 **26b**	88[a]
30	**7**	 **27** Br	 **27a**	45[d]
31	**8**		 **27b**	33[d] (0)[e]
32	**8**	 **28**	 **28b**	54[b]

[a] Method A: (i) **7** or **8** (1 equiv), Ar–Br or HetArX (1 equiv), Cs_2CO_3 (2 equiv), $Pd(OAc)_2$ (0.02 equiv), Xantphos (0.05 equiv), dioxane, 85 °C, 4 h; (ii) TFA, CH_2Cl_2, anisole (3.5 equiv), 25–45 °C.

[b] Method B: (i) **8** (1.2 equiv), **12**, **15** or **28** (1 equiv), NaO^{t}Bu (1.4 equiv), Pd_2dba_3 (0.04 equiv), XPhos (0.12 equiv), toluene, 100 °C, 16 h; (ii) TFA, CH_2Cl_2, anisole (3.5 equiv), 25–45 °C.

[c] Method C: (i) **8** (1.2 equiv), **19** (1 equiv), LiHMDS (2.8 equiv), Pd_2dba_3 (0.04 equiv), XPhos (0.12 equiv), dioxane, 85 °C, 16 h; (ii) TFA, CH_2Cl_2, anisole (3.5 equiv), 25–45 °C.

[d] Method D: (i) **7** or **8** (1 equiv), **27** (1.2 equiv), NaO^{t}Bu (1.2 equiv), Pd_2dba_3 (0.02 equiv), P^{t}Bu$_3$ (0.04 equiv), toluene, 100 °C; (ii) TFA, CH_2Cl_2, anisole (3.5 equiv), 25–45 °C.

[e] Method E: **1** or **2** (1 equiv), Ar–Br or HetArX (1 equiv), Cs_2CO_3 (1.2 equiv), $Pd(OAc)_2$ (0.04 equiv), Xantphos (0.08 equiv), DMA, 130–150 °C, 15–30 min, microwave.

[f] Method F: **3** (1 equiv), *p*-toluidine, *p*-fluoroaniline or 2-aminopyridine (1 equiv), Cs_2CO_3 (1.2 equiv), $Pd(OAc)_2$ (0.04 equiv), Xantphos (0.08 equiv), DMA, 150 °C, 15–30 min, microwave.

aryl halides **9** (entry 2), **17** (entry 14), **18** (entry 16), **20** (entry 18), **22** (entry 21), and **27** (entry 31) with overall marked lower yields than using our protective group strategy. Furthermore, attempts to prepare final compounds **10a**, **13a,** and **16a** from 3-bromobenzenesulfonamide **3** by 'reverse Buchwald coupling' under similar microwave-heating conditions, respectively, with *p*-toluidine (entry 3), *p*-fluoroaniline (entry 7) or 2-aminopyridine (entry 11), did not give satisfactory outcomes (poor yields ranking 11–17%).

In summary, a practical synthesis of unsubstituted *N*-aryl and heteroaryl aminobenzenesulfonamides has been validated. In particular, the sulfonamide protecting group strategy tolerates the use of strong bases for the *N*-arylation step, whereas the unsubstituted sulfonamide group would certainly be deprotonated leading to unchemoselective C–N bond formation. Besides, our protocol specially applies to substrates not amenable toward nucleophilic aromatic substitution.

Acknowledgments

The authors would like to acknowledge Craig Harris, Rémy Morgentin, Richard Ducray for revising the manuscript and Christian Delvare for analytical support.

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53. *Representative procedure for the synthesis of **22b** (Method **A**):* A mixture of **8** (200 mg, 0.48 mmol), **22** (0.060 mL, 0.48 mmol), diacetoxy-palladium (6 mg, 0.02 mmol), cesium carbonate (316 mg, 0.97 mmol), and Xantphos (28 mg, 0.05 mmol) in degassed dioxane (4.0 mL) was heated at 85 °C in a sealed vessel under inert atmosphere for 4 h. The resulting mixture was diluted with dichloromethane and ethanol, extracted with a saturated aqueous solution of $NaHCO_3$. The organics were dried over $MgSO_4$ and concentrated in vacuo. TFA (5 mL) and anisole (0.32 mL, 2.9 mmol) were added to a solution of the crude product in dichloromethane (7 mL). The mixture was stirred at 25–40 °C for 24 h and slowly quenched with a saturated aqueous solution of Na_2CO_3. Extractive workup (at pH 8–9) with ethyl acetate and then dichloromethane afforded a residue which was adsorbed on silica gel and purified by flash chromatography (2/100 to 5/100 EtOH/DCM + 0.5% NH_4OH) to yield **22b** (108 mg, 80%) as a pale yellow solid.^{1}H NMR (500 MHz, DMSO) δ 8.56 (NH), 7.87 (s, 1H), 7.86 (d, J = 8.6 Hz, 2H), 7.71 (d, J = 8.6 Hz, 2H), 7.17 (SO_2NH_2), 2.49 (s, 3H), 2.36 (s, 3H). ESIMS (m/z): 279.3 (MH^+).
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