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Solid-phase synthesis of acyl biarylsulfonamides

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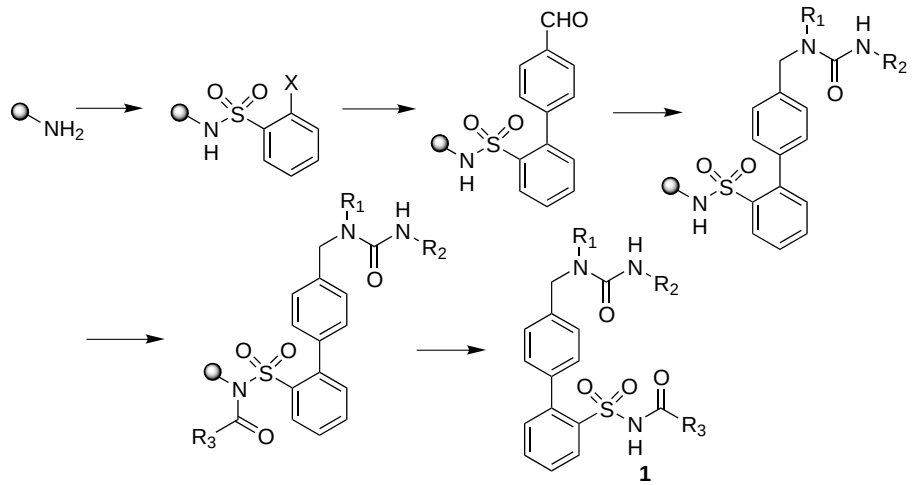
Abstract—A versatile solid-phase synthesis of acyl biarylsulfonamides is reported. The synthesis starts with sulfonylation of a solid bound aminomethyl linker group with arylsulfonyl chloride, followed by a Suzuki coupling to construct the biphenyl scaffold. Acylation of the sulfonamide and the proper choice of linker allows the acylsulfonamide to be cleaved as the product. © 2001 Published by Elsevier Science Ltd.

Acyl biarylsulfonamides such as **1** represent a structural class that includes compounds as potent angiotensin II antagonists,[1] and as well as compounds having moderate anti-HIV activity in the CXCR4 binding[2] and cell fusion assays.[3] A solid-phase synthesis of compound **1** that allows variations in many parts of the scaffold is desired.

There are a few solid-phase syntheses of acylsulfonamides reported that either anchor the compound through a separate functional group,[4] or are not versatile enough for our purposes.[5,6] The use of the aminoethyl sulfide linker,[5] which becomes base cleavable upon oxidation to the sulfone, has the drawback of the difficulty in removing the cleavage agent (NaOH). The traceless aryl silicon linker limits the number of available aryl compounds that can be anchored to resin. We designed a route that starts with sulfonylation of resin-bound amine, followed by a Suzuki coupling to form the biaryl core (Scheme 1). This route takes full advantage of solid-phase synthesis, providing many points for structural diversification. The only fixed structural feature is the acylsulfonamide function, which is used as an anchor point to the resin. The synthesis also calls for an acid labile linker that releases the acylsulfonamide upon cleavage.

We first tested the 4-aminomethylphenoxypropionic acid linker to prepare the acylsulfonamide (Scheme 2). The commercially available hydroxymethyl linker was



Scheme 1.

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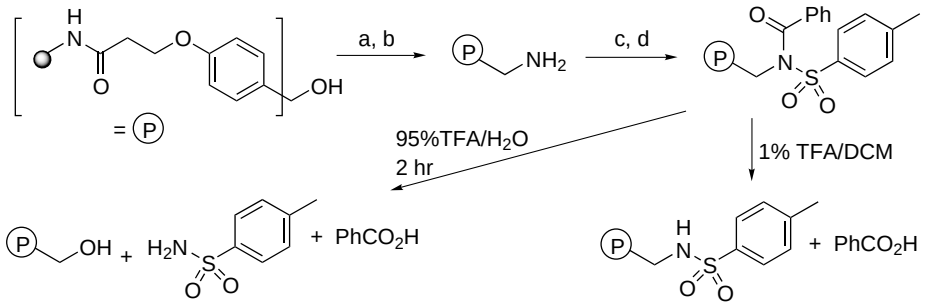


Scheme 2. (a) Phthalimide, Bu_3P, TMAD/THF–DCM, 5 h; (b) 1.0 M N_2H_4/THF, overnight; (c) TsCl, DIEA, cat. DMAP/THF–DCM 5 h; (d) PhCOCl, DIEA, cat. DMAP.

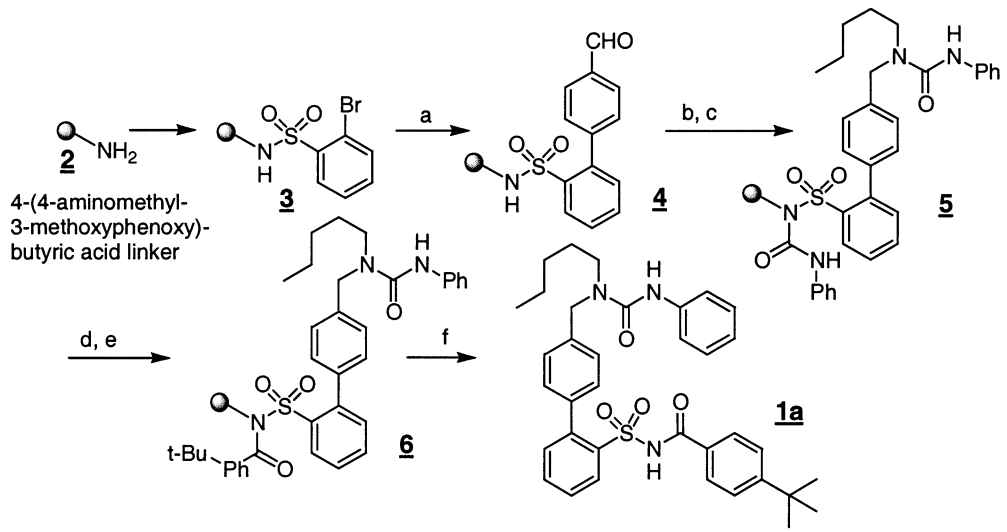
converted to the aminomethyl version via Mitsunobu reaction[7] with phthalimide and followed by hydrazinolysis. Other methods such as direct coupling of the alcohol with a primary sulfonamide[8] did not work well in the solid-phase system. Another approach, which involves conversion of the alcohol to halides (Br or Cl) and subsequent substitution with sodium sulfonamide salts,[9] produced less pure product. The phthalimide route provided good loading and product purity.

Sulfonylation of resin-bound amine to form sulfonamide was straightforward. Acylation of the sulfonamide proceeded with no difficulty; however, the cleavage was not that simple. With 95%TFA in water the cleaved product is not the desired acylsulfonamide, but the hydrolyzed sulfonamide and benzoic acid. The hydrolysis took place while the molecule was still resin-bound, since the acylsulfonamide was stable in the cleavage media 95%TFA/H_2O. Under mild cleavage conditions only hydrolysis occurred, resulting in the benzoic acid as the product.

To circumvent hydrolysis of the acylsulfonamide during cleavage we then turned to the more acid labile 4-(4 - hydroxymethyl - 3 - methoxyphenoxy) - butyric acid (HMPB) as linker.[10] The acylsulfonamide was prepared similarly as shown in Scheme 2. In this case cleavage in 50% TFA/DCM indeed produced the desired acylsulfonamide without any hydrolysis.

The next step was the construction of the biphenyl core via a Suzuki reaction. The bulky *ortho*-substitution presented an obstacle to a high yielding (and more importantly, a high purity) coupling reaction.[11] After some experimentation, we settled on the catalyst system of $Pd_2(dba)_3$/*t*-Bu_3P,[11a] but had to use higher levels of catalyst to drive the reaction to completion. Thus the *o*-bromophenyl sulfonamide on resin was coupled with 4-formylphenylboronic acid cleanly to form the biphenyl derivative (Scheme 3). A more recent report from Fu's group[12b] indicated that the commercially available $Pd[P(t\text{-}Bu)_3]_2$ catalyst is more effective and convenient to use. We found that at 0.2 equiv. of $Pd[P(t\text{-}Bu)_3]_2$ the coupling went equally well at similar reaction conditions (5 equiv. of $ArB(OH)_2$, 2 equiv. of Cs_2CO_3, 80°C 4 h).

Reductive amination with amylamine and $NaBH(OAc)_3$ in dichloroethane gave the secondary amine which was then acylated with phenylisocyanate to



Scheme 3. (a) HCO–PH–$B(OH)_3$, $Pd_2(dba)_3$, *t*-Bu_3P, Cs_2CO_3/DMF, 80°C, 4 h; (b) *n*-$C_5H_{11}NH_2$, $NaBH(OAc)_3$/1% HOAc in dichloroethane; (c) PhNCO/DIEA/THF–DCM; (d) Me_2NH/THF; (e) *t*Bu–Ph–COCl/DIEA/THF–DCM; (f) 50% TFA/DCM 2 h.

afford the desired urea **5**. Some degree of acylation of the sulfonamide nitrogen also took place even with a slight excess of PhNCO (1.5 equiv.). We chose to use a large excess of isocyanate (5 equiv.) to ensure complete acylation at the secondary amine position and then removed the unwanted acyl (aminocarbonyl) group at the sulfonamide position by treatment with dimethylamine, much like what happens to acylsulfonamide in the 'safety catch' linker.[13] The last acylation was accomplished with benzoyl chloride cleanly at the sulfonamide function. The final product was cleaved off in 50% TFA/DCM to give compound **1a** in >90% purity by HPLC (Fig. 1).

The urea formation (step c in Scheme 3) using isocyanates (method A) did not work well when R_1 is a less reactive aromatic. Aromatic isocyanates reacted well to form the desired ureas, entries 5, 6 and 9 in Table 1, but the less reactive aliphatic isocyanates (phenethyl and benzyl) failed to give any desired urea, even with the help of catalytic amount of DMAP (see entry 10). In cases where the urea formation failed, a bis-acylated by-product was obtained going through the last acylation step.

A more general two-step approach (method C) using triphosgene followed by reacting with amine gave better results (entries 11–15). Method C did not work when R_2 is a less nucleophilic aromatic. In this case, the desired urea can be obtained using the isocyanate approach (method A). Only when both R_1 and R_2 are aromatic amines did the urea formation not work in method C, giving the dimethylurea by-product going through the sequence d to f outlined in Scheme 3.

The acylation of solid anchored sulfonamide worked well with acid chloride or acid anhydride. Attempts to use carboxylic acid with DIC (in situ formation of acid anhydride) led to partial acylation. Other coupling agents like PyBOP, MSNT failed to produce any acylsulfonamide.

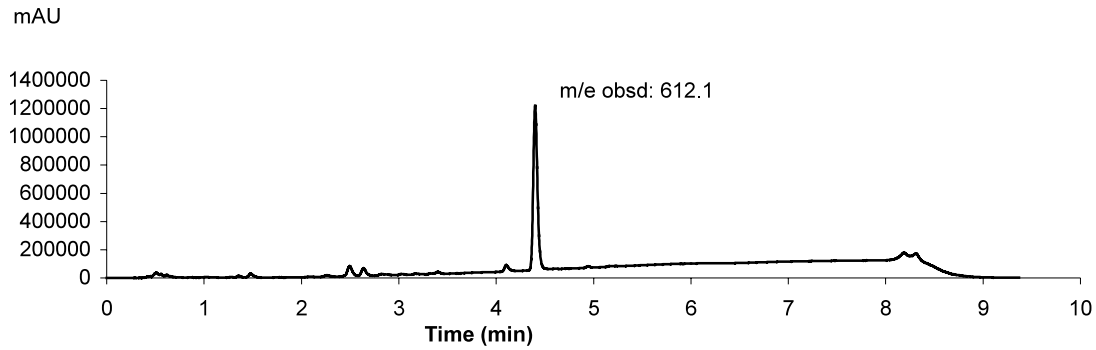


Figure 1. HPLC chromatograph of compound **1a**.

Table 1. List of acyl biphenylsulfonamides made as in Scheme 3

Entry	R_1	R_2	R_3	Product	Yield (%)	Purity (%)	Note[d]
1	n-C_5H_{11}	Ph	4-t-Bu-Ph	**1a**	66	90	Method A
2	n-C_5H_{11}	$PhCH_2CH_2$	4-t-Bu-Ph	**1b**	64	90	Method A
3	n-C_5H_{11}	3,4-Cl, Cl-Ph	4-t-Bu-Ph	**1d**	61	90	Method A
4[a]	Ph	Ph	4-t-Bu-Ph		1:1 **1d**:by-product		Method A
5	Ph	Ph	4-t-Bu-Ph	**1d**	89	90	Method A
6	Ph	3,4-Cl, Cl-Ph	4-t-Bu-Ph	**1e**	65	90	Method B
7	n-C_5H_{11}	1-Naphthyl	4-t-Bu-Ph	**1f**	85	90	Method B
8	n-C_5H_{11}	3-Me-$PhCH_2$	4-t-Bu-Ph	**1g**	86	90	Method B
9	Ph	1-Naphthyl	4-t-Bu-Ph	**1h**	86	90	Method B
10[b]	Ph	3-Me-$PhCH_2$	4-t-Bu-Ph		1:1 **1i**:by-product		Method B
11	4-NC-Ph	n-C_4H_9	4-t-Bu-Ph	**1j**	65	90	Method C
12	3-Cl-Ph	n-C_4H_9	4-t-Bu-Ph	**1k**	71	90	Method C
13	4,5-Cl, Cl-Ph	n-C_4H_9	4-t-Bu-Ph	**1m**	67	90	Method C
14	4-MeO_2C-Ph	n-C_4H_9	4-t-Bu-Ph	**1n**	67	90	Method C
15	3,5-Cl,Cl-Ph	n-C_4H_9	4-t-Bu-Ph	**1p**	70	90	Method C
16[c]	n-C_4H_9	Ph	CH_3	**1q**	65	90	Method A
17	n-C_4H_9	Ph	4-t-Bu-Ph	**1r**	68	90	Method A

[a] The by-product is the bisacylated compound.

[b] The by-product is the N,N-dimethylurea formed during step d (Me_2NH/THF treatment).

[c] The last acylation step was done with acetic anhydride/DIEA/DMAP.

[d] Reaction conditions are outlined in Scheme 3 except the urea formation (step c). Method A is the same as step c. Method B is method A with a catalytic amount of DMAP added. Method C is: (1) triphosgen/DIEA/THF–DCM (5/20 equiv., 1 h), wash with DCM 3×; (2) amine/DMAP/DMF (10 equiv./cat., 3 h).

All compounds listed in Table 1 were identified by LC–MS to have the correct molecular ion and purity as measure by HPLC similar to Fig. 1. When further purified by reverse-phase HPLC, the yield of the desired compound is about half of that listed in the table based on the estimated loading of the resin used. No other significant by product was isolated in prep. HPLC.

We have explored the scope of the solid-phase synthesis of biphenyl acylsulfonamides outlined in Scheme 3 and found this route suitable for generating a combinatorial library where structure variations can occur at many points.

Experimental

All reactions were done in polypropylene cartridges with PE frit when not specified. Washings were done four times with each solvent specified, each washing lasted about half a minute.

HMPB-AM resin (Novabiochem) 1.0 g (0.54 mmol/g loading), phthalimide (238 mg, 3 equiv.), *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (279 mg, 3 equiv.) were loaded in a cartridge and purged with nitrogen. A solution of *n*-Bu_3P (0.4 ml, 3 equiv.) in 1:1 THF–DCM (10 ml, dried over molecular sieves) was added. The resin suspension was agitated briefly and left undisturbed. After 3 h, the resin was washed with DCM, DMF, THF. The resin was then treated with 7 ml of a 1 M solution of hydrazine in THF for 15 h. It was washed with DMF, DMF–H_2O (2:1), DMF, DCM, then vacuum dried overnight to give 1.0 g of resin **2**. Nominal loading was 0.45 mmol/g based on weight change.

Sulfonylation. A solution of DIEA (0.25 ml, 7 equiv.), DMAP (5 mg), in THF–DCM (2 ml) was added to dry resin **2** (503 mg) in a cartridge, followed by a solution of 2-bromobenzenesulfonyl chloride (280 mg, 5 equiv.) in THF–DCM (2 ml). The resin suspension was agitated briefly and left undisturbed for 5 h. It is washed with DMF, DCM, and vacuum dried overnight to give 560 mg resin **3**. The loading was 0.35 mmol/g, measured by cleaving 53 mg of the resin in 95% TFA/H_2O to give 4.2 mg of 2-bromobenzenesulfonamide (white powder after lyophilization).

Suzuki coupling. Resin **3** (350 mg), 4-formylbenzene boronic acid (129 mg, 5 equiv.), $Pd_2(dba)_3$ 62 mg, 0.4 equiv.) and Cs_2CO_3 (111 mg, 2 equiv.) were weighed into a test tube. The test tube was evacuated/filled with nitrogen a few times. A solution of P(*t*-Bu)$_3$ (42 mg, 1.2 equiv.) in DMF (4 ml, nitrogen purged) was added to the resin mixture. The suspension was heated to 80°C for 4 h. The resin was washed with DMF, DMF–H_2O (1:1), DMF, MeOH, DMF, DCM and vacuum dried to give 350 mg of **4**. The loading was 0.34 mmol/g measured by cleaving 37 mg of **4** to give 3.3 mg product after lyophilization.

Similar results were obtained with the air stable catalyst Pd[P(*t*-Bu)$_3$]$_2$, used at 0.2 equiv. of the resin loading.

Compound **1a**. Resin **4** (200 mg) was treated with $NaBH(OAc)_3$ (84 mg, 5 equiv.), amylamine (46 μl, 5 equiv.) in dichloroethane (4 ml, contains 1% of HOAc) for 4 h. The resin was first washed with DMF, DCM and then treated with a solution of PhNCO/DIEA (3 equiv. each) in THF–DCM (1.5 ml) for 3 h, washed again with DMF to give resin **5**. Resin **5** was subsequently treated with a solution of Me_2NH/THF (2 ml, 2 M) for 1 h, washed with DMF, DCM and then acylated with a solution of 4-*t*-butylbenzoyl chloride/DIEA in THF–DCM (10 equiv. ~0.3 M, with a catalytic amount of DMAP) for 2 h to give resin **6**. After washing with DMF, DCM, resin **6** was treated with 50% TFA/DCM (2×3 ml, 2 h) to give, after lyophilization, 27.4 mg of product **1a** as an off-white powder. HPLC Fig. 1. MS, calcd: 612.3, obsd: 612.1; NMR (500 MHz, DMSO-d_6) 0.86 (t, 3H), 1.26 (s, 9H), 1.3 (m, 2H), 1.60 (p, 2H), 3.37 (t, 2H), 4.62 (s, 2H), 6.93 (t, 1H), 7.20–7.25 (m, 6H), 7.28 (dd, 1H), 7.42 (d, 2H), 7.51 (d, 2H), 7.56 (d, 2H), 7.63 (dt, 1H), 7.69 (dt, 1H), 8.16 (dd, 1H), 8.14 (s, 1H). Yield of 66% based on a loading of 0.22mmol/g of resin **4**.

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