Pergamon

Tetrahedron Letters, Vol. 38, No. 19, pp. 3373-3376, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00652-7

Solid Phase Synthesis of Sulfonamides Using a Carbamate Linker

B. Raju* and Timothy P. Kogan
Department of Chemistry & Biophysics
Texas Biotechnology Corporation, 7000 Fannin, Houston TX 77030

Abstract: A method for the synthesis of sulfonamides on a solid support by immobilizing amines through the nitrogen atom using a carbamate linkage is described.

In 1963 Merrifield conducted amide bond formation on a solid support in a heterogeneous medium.[1] For the past several years, the above methodology has been successfully utilized in the construction and evaluation of individual compounds or compound libraries of biopolymers (oligomeric compounds, polypeptides, oligonucleotides) and small organic molecules to develop molecular diversity.[2] Unlike biopolymers, development in the area of synthesis of small organic molecules on a solid support is in its infancy. However, a significant number of organic reactions on solid support and a variety of new linkers have been developed recently.[3] In addition, combinatorial or parallel organic synthesis have been successfully used to identify nonpeptide leads and the further optimization of these against a target protein.[4] In our own effort to develop focused libraries of small molecules, we have developed a method for the synthesis of sulfonamides on a solid support as described herein.

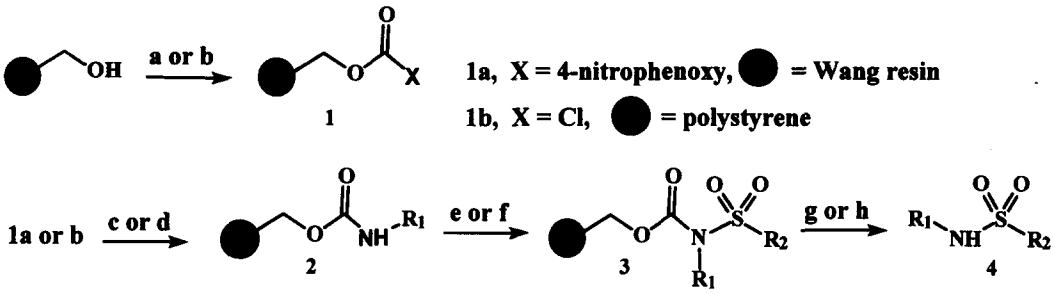
Sulfonamides (R_1SO_2-NHR_2) are a common pharmacophoric feature in various biologically active molecules, enzyme inhibitors and receptor antagonists.[5] The existing methods of solid phase synthesis of sulfonamides uses an additional heteroatom, present in functional group such as -COOH, -NH_2, -SH, and -OH, as an anchoring point for attachment to the solid support.[6] In another approach, a resin bound -NH_2 group was used to tether sulfonyl chlorides. The nitrogen atom was further functionalized by alkylation, and subsequent cleavage gave the desired sulfonamides.[6c] The obvious disadvantage in this methodology is the lack of ability to synthesize aryl-, vinyl-, and hindered sulfonamide linkages. We considered that tethering of an amine moiety through the nitrogen atom to a polymer and then functionalization to the desired sulfonamide would lead to a more general method of synthesis of sulfonamides on a solid support.

The choice of a linker was based on the observation that urethane and sulfonamide groups attached to the same nitrogen atom when exposed to basic conditions resulted in the cleavage of the urethane linkage rather than the stronger sulfonamide bond.[7] Thus, we used a polymer bound chloroformate or its equivalents to immobilize an amine through the nitrogen atom.

The activated carbonate **1a**, prepared from Wang resin,[8a,b] was treated with benzylic amines to afford the carbamates **2a-j** (Scheme I). To avoid incomplete deprotonation,[9] the carbamate **2a** was treated with LHMDS in THF at -70 °C followed by quenching of the anion with excess sulfonyl chloride to give the resin bound sulfonamide[10] **3a**. Treatment of the resin bound sulfonamide **3a** with saturated LiOH in water and THF gave the sulfonamide **4a** in 42% yield, whereas by using freshly prepared sodium methoxide in THF afforded **4a** in 88% yield, with identical purity. The IR spectrum of the resin obtained after cleavage using LiOH in water/THF showed a carbonyl absorption. Resubjection of this resin to hydrolysis using NaOMe in THF gave **4a** in an additional 43% yield, consistent with the earlier low yield being due to incomplete hydrolysis. Further IR analysis of the cleaved resin showed the absence of a carbonyl group. Using the above set of optimized reactions conditions, deprotonation with LHMDS in THF at -78 °C followed by cleavage using NaOMe in THF, sulfonamides **4b-j** were synthesized in excellent purity and good overall yield for the 4 step process (Table 1).

The treatment of the activated carbonate **1a** with *p*-anisidine in the presence of diisopropylethylamine[11a] (DIEA) using DMF as a solvent gave the polymer bound carbamate **2n**. However, under similar reaction conditions the

Scheme I



Reagents: (a) 4-nitrophenyl chloroformate, 4-methylmorpholine, CH_2Cl_2, 24 h, rt; (b) 2 M phosgene[12] in toluene, dry THF, 8 h, rt; (c) R_1NH_2, DIEA, THF, 8 h, rt; (d) R_1NH_2, DMF, 24 h, rt; (e) NaH, DMA, 8 h, rt, then R_2SO_2Cl; (f) LiHMDS, THF, 45 minutes, -78 °C, then R_2SO_2Cl; (g) LiOH, water/THF, 54 h, rt; (h) 3 M NaOMe in methanol, THF, 16 h, rt.

Table 1 [$R_2 = (p\text{-}CH_3)C_6H_4$-]

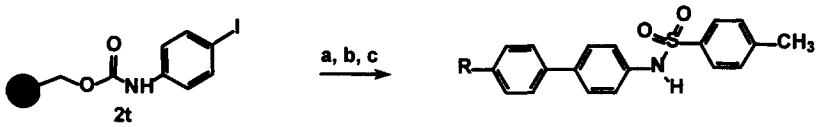
		IR absorbance (cm^{-1})[a]		Sulfonamide[13] 4		
	R_1	Resin 2	Resin 3	% Yield[b]	% Purity(R_t)[c]	Method[14]
a	$C_6H_5CH_2$-	1676, 1719, 3350, 3416	1726	88	98 (23.2)	A
b	$(o\text{-}CH_3)C_6H_4CH_2$-	1671, 1719, 3343, 3420	1726	69	99 (24.7)	A
c	$(m\text{-}CH_3)C_6H_4CH_2$-	1674, 1718, 3338, 3420	1730	70	94 (24.5)	A
d	$(p\text{-}CH_3)C_6H_4CH_2$-	1674, 1714, 3352, 3416	1725	88	95 (24.6)	A
e	$(o\text{-}OCH_3)C_6H_4CH_2$-	1674, 1718, 3346, 3418	1726	71	82 (19.9)	A
f	$(m\text{-}OCH_3)C_6H_4CH_2$-	1674, 1717, 3340, 3416	1732	79	99 (23.0)	A
g	$(p\text{-}OCH_3)C_6H_4CH_2$-	1674, 1719, 3342, 3414	1724	70	96 (23.2)	A
h	2-pyridylmethyl-	1670, 1718, 3425	1734	83	98 (13.7)	A
i	3-pyridylmethyl-	1674, 1718, 3333, 3418	1720	67	94 (13.6)	A
j	4-pyridylmethyl-	1669, 1719, 3329,3412	1720	68	99 (13.8)	A
k	C_6H_5-	1670, 1734, 3292, 3402	1676, 1734	63	96 (22.5)	B
l	$(o\text{-}OCH_3)C_6H_4$-	1678, 1734, 3433	1737	48	88 (23.1)	B
m	$(m\text{-}OCH_3)C_6H_4$-	1734, 3281, 3394	1680, 1736	61	95 (22.3)	B
n	$(p\text{-}OCH_3)C_6H_4$-	1734, 3402	1734	55	97 (22.1)	B
o	$(o\text{-}CH_3)C_6H_4$-	1676, 1734, 3418	1734	55	94 (23.6)	B
p	$(m\text{-}CH_3)C_6H_4$-	1734, 3395	1734	50	96 (23.7)	B
q	$(p\text{-}CH_3)C_6H_4$-	1732,3287, 3395	1734	57	96 (23.5)	B
r	$(o\text{-}I)C_6H_4$-	1737, 3389	1680, 1739	41	93 (25.0)	B
s	$(m\text{-}I)C_6H_4$-	1734, 3277, 3387	1676, 1736	42	94 (25.5)	B
t	$(p\text{-}I)C_6H_4$-	1736, 3261, 3394	1676, 1736	51	97 (25.8)	B
u	$(o\text{-}CO_2CH_3)C_6H_4$-	1691, 1736, 3300	1676, 1734	13[d]	82 (22.3)	B
v	$(m\text{-}CO_2CH_3)C_6H_4$-	1728, 3350	1676, 1726	41[d]	91 (19.1)	B
w	$(p\text{-}CO_2CH_3)C_6H_4$-	1715, 1738, 3383	1719	45[d]	98 (18.7)	B
x	$(o\text{-}CN)C_6H_4$-	1743, 1739, 2222, 3414	1742, 2224	49	89 (21.0)	B
y	$(m\text{-}CN)C_6H_4$-	1738, 2230, 3383	1740, 2232	66	85 (21.8)	B
z	$(p\text{-}CN)C_6H_4$-	1740, 2224, 3383	1740, 2224	51	92 (21.7)	B
aa	$(o\text{-}NO_2)C_6H_4$-	1736, 2230, 3385	1739, 2232	**	**	B
bb	$(m\text{-}NO_2)C_6H_4$-	1667, 1734, 3261	1655, 1739	41	96 (23.0)	B
cc	$(p\text{-}NO_2)C_6H_4$-	1743, 3378	1655, 1740	45	50 (23.1)	B

[a] Resins were dried and IR spectra recorded as sodium chloride pellets; [b]Yields of the cleaved product are based on the theoretical loading of commercial resins; [c]Analytical HPLC of the products after cleavage using a C18 reverse phase column (250 mm X 4.6 mm) eluting with a water/acetonitrile mixture containing 0.1 % TFA from 5% to 95% acetonitrile (linear gradient) over 30 minutes; [d] final product was isolated as the corresponding acid derivative; ** product not detected.

less nucleophilic anilines such as *p*-aminobenzonitrile, *p*-nitroaniline, *p*-iodoaniline, and *p*-carbomethoxyaniline did not yield their respective carbamates as judged by IR, consistent with an earlier report.[8c] Treatment of the activated carbonate **1a** with anthranilic acid in the presence of HOBt and DIEA gave the desired carbamate[8d] but in our hands this failed to afford the carbamate **2u** by reacting the activated carbonate **1a** with methyl anthranilate under similar reaction conditions. To circumvent this problem, the more reactive resin bound chloroformate[10f] was prepared by reacting the hydroxymethyl resin with phosgene[12] using 1:1 mixture of toluene and THF, and this was reacted with a variety of substituted anilines in the presence of DIEA[11b] to afford carbamates[10] **2k-z**, **2bb**, and **2cc**. However, *o*-nitroaniline failed to give the corresponding carbamate **2aa** under these reaction conditions. Deprotonation of the carbamate in **2k-z**, **2bb**, and **2cc** by use of NaH in DMA at ambient temperature or LHMDS[11c] in THF at -70 °C followed by quenching of the anions with excess of sulfonyl chloride gave the resin bound sulfonamides **3k-z**, **3bb**, and **3cc**. Treatment of the resin bound sulfonamides **3k-z**, **3bb**, and **3cc** with LiOH in THF/water mixture or with NaOMe[11d] in THF gave the sulfonamides. The resin bound carbamate **2y** was subjected to the above sequence of reactions, (1. NaH/DMA, rt, then $ArSO_2Cl$; 2. LiOH, water, THF, rt) using a set of aromatic sulfonyl chlorides to afford the sulfonamides **5-8**.

To increase structural diversity, the functional groups present on the resin bound carbamate **2** can be transformed under a variety of reaction conditions. As an example, the resin bound carbamate **2t** was subjected to Suzuki couplings[3] using aryl boronic acids and a palladium catalyst. The resulting carbamates were transformed to the anticipated sulfonamides **9** and **10** using the standard set of reactions conditions as described above for anilines.

Scheme II



Reagents: a. $Pd(PPh_3)_4$, DME, $ArB(OH)_2$, 2M Na_2CO_3, 90 °C, 24 h.
b. NaH, DMA, rt, 8 h, ; then p-toluenesulfonyl chloride.
c. LiOH, water, THF, rt, 2 days.

No.	R	% Yield	% Purity
9	$-CH_3$	33	92
10	$-OCH_3$	32	94

In conclusion, an efficient and general method for the solid phase synthesis of sulfonamides using a carbamate linker has been developed. Functionalization of suitably substituted resin bound carbamates to a required template followed by the introduction of a sulfonyl group and cleavage as a last step, in parallel to the safety-catch principle,[15] can lead to the synthesis of structurally diversified sulfonamides.[16]

References and Notes:

1. Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149.
2. Gallop, M. A.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233. (b) Gordon, E. M.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1233.
3. (a) Balkenhohl, F.; Bussche-Hunnefeld, C.; Lanskt, A.; Zechel, C. *Angew. Chem. Int. Ed.* Engl **1996**, *335*, 2288. (b) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1996**, *52*, 4527. (c) Thompson, L.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555, and references cited therin. (d). Morphy, J. R.; Rankovic, Z. Rees, D. C. *Tetrahedron Lett.* **1996**, *37*, 3209. (e) Bannwarth, W.; Huebscher, J.; Barner, R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1528. (f) Jung, K. W.; Zhap, X.; Janda, K. *Tetrahedron Lett.* **1996**, *37*, 6491. (f) Boehm, T.; Showalter. H. D. *J. Org. Chem.* **1996**, *61*, 6498.
4. (a) Dewitt, S. H.; Czarnik, A. W. *Acc. Chem. Res.* **1996**, *29*, 114. (b) Armstrong, R. W.; Combus, A P.; Tempest, P. A.; Brown, D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 1123. (c) Ellman, J. A.; *Acc. Chem. Res.* **1996**, *29*, 132. (d) Gordon, E. M.; Gallop. M.A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*, 144.
5. Lendnicer, D.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis*, Wiley, New York, **1977**, *Vol. 1*, pp 120-132.; 1980, Vol. 2, pp 112-119. (b) Raju, B.; Wu, C.; Kois, A.; Verner, E. J.; Castillo, R.; Okun, I.; Stavors, F. D.; Chan, M.F. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2651. and references cited therein. (c) Yoshino, H.; Vedan, N.; Niijima, J.; Sugumi, H.; Kotake, Y.; Koyanagi, N.; Yoshimatsu, K.; Asada, M.; Watanabe, T.; Nagasu, T.; Tsukahara, K.; Iijima, A.; Kitch, K. *J. Med. Chem.* **1992**, *35*, 2496. (d) Ellingobe, J. W.; Spinelli, W.; Winkley, M. W.; Nguyen, T. T.; Parsons, R. W.; Moubarak, I. F.; Kitzen, J. M.; Vonengen, D.; Bagli, J. F. *J. Med. Chem.* **1992**, *35*, 707. (e) Klar, U.; Kuhnke, A.; Pletsch, H.; Rehwinkel.; Schreyer, R. *Bioorg. Med. Chem. Lett.* **1996**, *5*, 1219.
6. (a) Han, H.; Wolfe, H. M.; Brenner, S.; Janda, K. D. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 6419. (b) Meyers, H. V.; Dilley, G. J.; Durgin, T. L.; Powers, T. S., Winssinger, N. A.; Zhu, H.; Pavia, M. R. *Molecular Diversity* **1995**,

1, 13. (c) Beaver, K. A.; Siegmund, A. C.; Spear, K. L. *Tetrahedron Lett.* **1996**, *37*, 1145.
7. Finch, H.; Pegg, N. A.; Evans, B. *Tetrahedron Lett.* **1993**, *37*, 8353.
8. (a) Dressman, B. A.; Spangle, L. A; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937. (b) Hauske, J. R.; Droff, P. *Tetrahedron Lett.* **1995**, *36*, 1589. (c) Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1994**, *35*, 4055. (d) Gouilleux, L.; Fehrentz, J. A.; Winternitz, F. F.; Martinez, J. *Tetrahedron Lett.* **1996**, *37*, 7030.
9. Deprotonation of the carbamate **2a** using sodium hydride (NaH) in dimethylacetamide (DMA) at ambient temperature, followed by quenching of the reaction mixture with excess sulfonyl chloride gave the resin bound sulfonamide[10] **3a**. Hydrolysis of the resin bound sulfonamide **3a** with a saturated solution of LiOH in a mixture of water and THF gave the sulfonamide **4a** in a modest 30% yield, while under similar reaction conditions the carbamates **2e-g** gave sulfonamides **4e-g** in less than 5% yield. Acidic cleavage (TFA/CH_2Cl_2, 1:1) of the resin bound sulfonamide **3a** gave the sulfonamide and benzylamine as a 1:1 mixture, as determined by NMR, suggesting incomplete deprotonation using NaH. Cleavage under basic conditions avoided possible contamination resulting from unreacted urethane.
10. Procedure: (a) Carbamates **2a-j and 2n**: To a suspension of the resin **1a** (600 mg, 0.92 mmol/g, 0.552 mmol) in dry DMF (7 mL) was added 10 equivalents of an amine [DIEA (1.5 equiv.) used in the case of p-anisidine]. This was stirred at room temperature for 16 h. The resin was filtered and washed successively with DMF (10 mL), CH_2Cl_2 (10 mL), MeOH (10 mL), CH_2Cl_2 (5 mL), and MeOH (10 mL). The resin was dried under vacuum and the IR spectrum recorded (NaCl); (b) Carbamate **3** (NaH): To a stirred suspension of resin **2** (300 mg, 0.74 mmol/g, 0.222 mmol) in DMA was added NaH (53 mg, 2.22 mmol) and vortexed for 8 h. To this was added solid *p*-toluenesulfonyl chloride (0.4218 g, 2.22 mmol) in one lot and vortexing continued for 8 h. The resin was filtered and washed successively with DMF (10 mL), CH_2Cl_2 (10 mL), MeOH (10 mL), CH_2Cl_2 (5 mL), and MeOH (10 mL). The resin was dried under vacuum and the IR spectrum recorded (NaCl); (c) Carbamate **3** (LHMDS): To a stirred suspension of resin **2** (200 mg, 0.92 mmol/g, 0.184 mmol) in dry THF (2 mL) at -70 °C was added LHMDS (1.1 mL of 1 M solution, 6 equiv.) dropwise and stirred for 45 min. To this was added the THF solution of *p*-toluenesulfonyl chloride (209 mg, 1.104 mmol) and the reaction mixture was slowly allowed attain rt and stirring continued for 8 h. The remainder of the procedure and workup were as in (10b); (d) Cleavage using LiOH/water/THF: To a suspension of resin **3** (100 mg, 0.74 mmol/g) in water/THF (ratio 1:2, 4 mL) was added a saturated solution of LiOH in water (2 mL). After being vortexed for 54 h the mixture was filtered and the resin was washed with water (1 mL) and methanol (2 mL). The filtrate was concentrated under reduced pressure. The residue was neutralized with HCl to pH 2-3 and was extracted with ethyl acetate (8 mL). The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure to afford the sulfonamides **4**; (e) Cleavage using NaOMe/THF: To a suspension of resin **3** (200 mg, 0.74 mmol/g) in THF (2 mL) was added freshly prepared sodium methoxide in methanol (2 mL, 3M, prepared using sodium granules and 95% methanol) which was vortexed for 16 h. The remainder of the procedure and workup were same as in (10d); (f) Resin bound chloroformate **1b**: To a stirred suspension of hydroxymethyl resin (0.74 mmol/g, 15 g, 11.1 mmol) in THF (100 mL) was added phosgene[12] in toluene (2 M, 55.6 mL, 111 mmol, 10 equiv.) and the mixture was stirred at rt for 6 h. The resin was filtered, washed with dry THF (200 mL), and dried under vacuum in a desiccator; (g) Carbamate **2k-z and 2a1, 2b1, 2c1**: To a suspension of the resin **1b** (700 mg, 0.74 mmol/g, 0.518 mmol) in dry THF (7 mL) was added 10 equivalent of an aniline and DIEA (135 mL, 0.777 mmol, 1.5 equiv.) and the mixture was stirred rt for 8 h. The remainder of the procedure was as in (10a).
11. (a) DIEA was distilled over ninhydrin and then over calcium hydride. (b) Using triethylamine as a base instead of DIEA failed to yield the carbamates from methyl anthranillate (**2u**), *o*-aminobenzonitrile (**2x**), and the three regioisomeric nitroanilines (**2aa**, **2bb**, and **2cc**). (c) The purity of the sulfonamides derived from anilines using LHMDS as a base was significantly lower than that obtained using NaH as a base. (d). The purity of the sulfonamides obtained by using the LiOH cleavage protocol was superior.
12. Commercial 1.93 M solution in toluene was used. **WARNING**: Phosgene is highly toxic and should only be handled in a hood with appropriate safety equipments.
13. All the sulfonamides gave satisfactory high resolution PMR spectra and Fab mass spectra on a sub set of samples.
14. Optimum conditions: **Method A (for benzylamines):** (a) chloro 4-nitrophenylcarbonate, 4-methylmorpholine, CH_2Cl_2, 24 h, rt; (d) R_1NH_2, DMF, 24 h, rt; (f) LiHMDS, THF, 45 minutes, -78 °C, then R_2SO_2Cl; (h) 3 M NaOMe in methanol, THF, 16 h, rt.; **Method B (for anilines):** (b) 2 M phosgene[12] in toluene, dry THF, 8h, rt; (c) R_1NH_2, DIEA, THF, 8 h, rt; (e) NaH, DMA, 8 h, rt, then R_2SO_2Cl; (g) LiOH, water/THF, 54 h, rt.
15. Backes, B. J.; Virgilio, A. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 3055 and references cited therein.
16. Use of acid labile Wang or related linkers to synthesize sulfonamides and related analogs is under progress and will be reported in the near future.

(*Received in USA* 19 *February* 1997; *accepted* 1 *April* 1997)