Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7203–7206

Solid-phase synthesis of tertiary-amino linked benzamides: a versatile method for forming C–N bonds with electron-rich and electron-poor anilines

Kevin W. Gillman,* Danielle Bocchino, Jeffrey W. Noonan, Milind Deshpande and Weixu Zhai

Richard L. Gelb Center for Pharmaceutical Research and Development, Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, PO Box 5100 Wallingford, CT 06492-7660, United States

Received 6 July 2007; revised 26 July 2007; accepted 27 July 2007
Available online 2 August 2007

Abstract—There currently are a wide variety of methods for forming C–N bonds on solid support. Two preferred methods are reductive aminations with resin bound amines or aldehydes as well as standard alkylation strategies. We herein disclose the scope and application of the Mitsunobu reaction of 2,4-dinitro-*N*-phenylbenzenesulfonamides derived from both electron-rich and electron-poor anilines as a practical and versatile addition to the repertoire of solid phase C–N bond forming reactions.

Developing robust synthetic methods is of paramount importance for combinatorial applications of solid phase chemistry. Synthesis of diverse arrays of compounds without the necessity for isolation of synthetic intermediates or purification of final products requires that the following criteria be met: minimization of side reactions; progression of reactions to >95% completion; tolerance for a diverse array of starting materials. Herein we disclose the results of the application of Fukuyama's[1] novel 2,4-dinitrobenzenesulfonamide Mitsunobu methodology as a linchpin for the formation of a diverse library of tertiary-amino linked benzamides. The scope of this reaction was investigated by employing a variety of electron-poor and electron-rich benzenesulfonamides in the key coupling reaction.

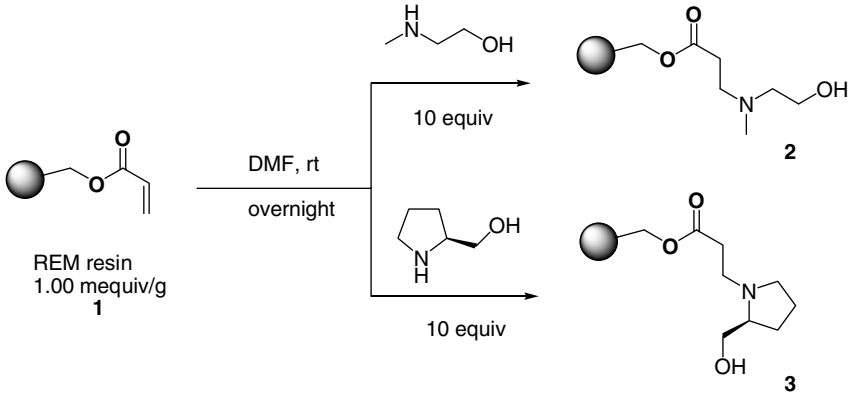
The synthetic sequence started with Michael addition of excess 2-methylamino-ethanol or L-prolinol to commercially available REM resin **1** (1 mmol/g),[2] to provide the initial substrates **2** and **3** for the Mitsunobu reaction (Scheme 1). The scope of the Mitsunobu reaction was studied using electronically diverse 2,4-dinitro-*N*-phenylbenzenesulfonamides[3] under conditions that were slightly modified from those described by Fukuyama.[4]

The Mitsunobu reaction was carried out by addition of 5 equiv of 2,4-dinitro-*N*-phenylbenzenesulfonamide **4** and triphenylphosphine to the resin bound amino-alcohols **2** and **3** (1 mmol/g) in THF at −78 °C, affording sulfonamides **5** and **6**. Use of diisopropyl azodicarboxylate (5 equiv) rather than diethyl azodicarboxylate was critical for obtaining superior yields and purity of the final products.[5] Following standard washout of the Mitsunobu reagents from the resin bound amine, the 2,4-dinitrophenylsulfonyl group was cleaved by treatment with excess *n*-propylamine in THF, producing the resin bound anilines **7** and **8** (Scheme 2).[6]

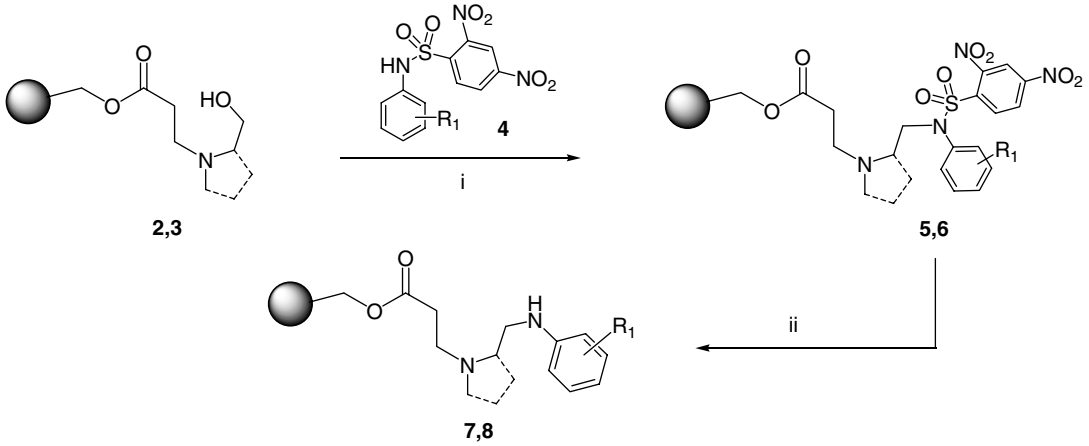
Anilines **7** and **8** were subsequently benzoylated with 4-(trifluoromethyl)benzoyl chloride producing their corresponding benzamides **9** and **10** ready for cleavage.[7] Cleavage of the resin bound amine was accomplished via a two-step quaternization/Hoffmann elimination sequence. Treatment of **9** and **10** with excess methyl iodide in the absence of base, followed by washing of the resin to remove excess methyl iodide, afforded the quaternary ammonium salts **11** and **12**. Addition of Hunig's base to induce the Hoffman elimination was followed by removal of the cleaved resin by filtration to afford the final products **13** and **14**. In order to remove the ammonium salt side-products that are formed in the Hoffman elimination reaction, the literature method incorporates an aqueous work-up step.[2] We wanted to

* Corresponding author. Tel.: +1 203 677 6785; fax: +1 203 677 7702; e-mail: Kevin.Gillman@bms.com

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.07.192

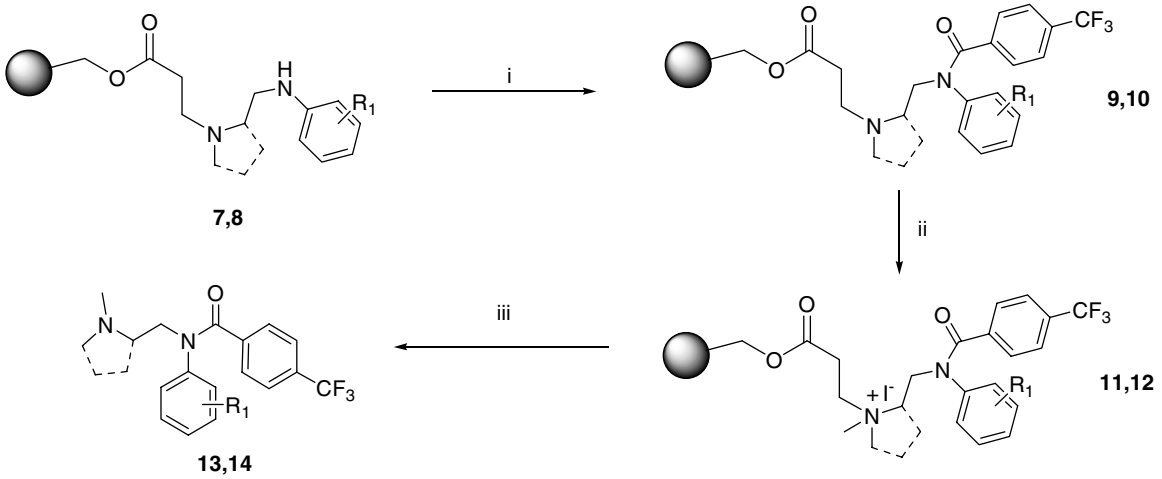


Scheme 1.



Scheme 2. Reagents and conditions: (i) 2,4-dinitro-*N*-phenylbenzenesulfonamide (5 equiv), PPh_3 (5 equiv), DIAD (5 equiv), THF, −78 °C to rt, overnight; (ii) *n*-propylamine (10 equiv), THF, rt, overnight.

avoid the work-up step and thereby simplify isolation of the final products. We found that addition of Argonaut MP-carbonate resin[8] was effective in removing any trace inorganic or amine-based salts and thereby eliminating the necessity for an aqueous work-up. Thus, addition of Argonaut MP-carbonate resin to the reaction mixture, followed by filtration and evaporation of the reaction solvent enabled isolation of the free base of tertiary-amine benzamides **13** and **14** in good yields and purity (Scheme 3).[9]



Scheme 3. Reagents and conditions: (i) 4-(trifluoromethyl)benzoyl chloride (5 equiv), Et_3N (10 equiv), DCM, rt, overnight; (ii) MeI (10 equiv), DMF, rt, overnight; (iii) Hunigs base (10 equiv), Argonaut MP-carbonate resin (5 equiv), DMF, rt, overnight.

The scope of the C–N bond forming reaction was tested using a selection of electron-rich and electron-deficient anilines in the Mitsunobu reaction (Table 1). In general the C–N bond forming reaction, and overall synthetic sequence worked well for both electron-rich and electron-deficient aniline substrates, affording the desired tertiary-amine linked benzamides **13** and **14** (Fig. 1). Overall yields from six synthetic steps on resin, and compound purities are in the desirable range for combinatorial chemistry applications without the need for purification. More importantly, the generality of this methodology to incorporate electron-rich and electron-poor anilines as substrates for analog design is an advantage over standard reductive amination[10] strategies, which do not work well for electron-deficient anilines.

We have extended this methodology toward the synthesis of several thousand analogs in split-pool fashion,[11] for in vitro screening against a variety of CNS targets in-house. Library production incorporating additional amino-alcohols, anilines, and differentially substituted benzoylchlorides gave similar results to that outlined above, and afforded sufficient amounts of compound with purities >80% necessary for in vitro screening. The results of our in-house in vitro screening effort

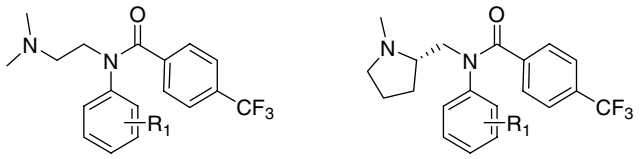
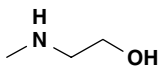
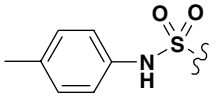
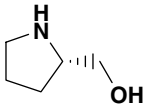
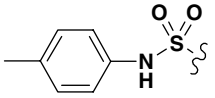
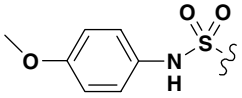
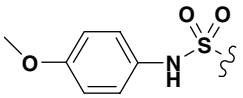
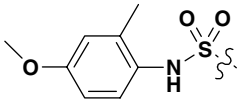
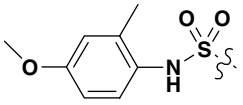
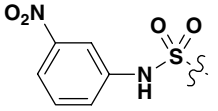
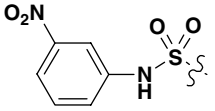
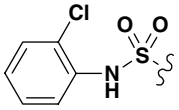
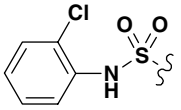
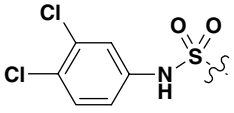
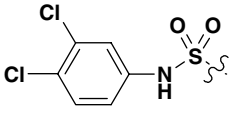
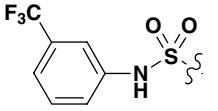
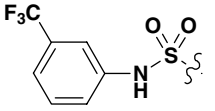
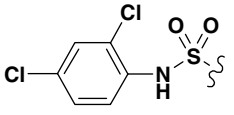
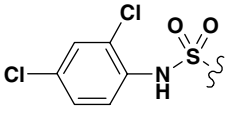


Figure 1. Final products cleaved from resin. All compounds were isolated as their corresponding free base without the need for purification.

Table 1. Purity and yields of final products (six synthetic steps) cleaved from resin based on 1 mmol/g of REM resin

Amine	Sulfonamide	Purity (%)	Yield (%)	Amine	Sulfonamide	Purity (%)	Yield (%)
		99	80			99	48
		96	77			99	51
		99	86			99	40
		60[a]	26			87	54
		86	68			94	38
		94	42			91	76
		93	47			96	28
		77	42			87	52

[a] Minor product (30%$_{\lambda=220\ nm}$ by area relative to the desired product) was the des-4-(trifluoromethyl)benzoylated aniline.

and subsequent biological impact will be reported in the near future.

Acknowledgments

The authors wish to thank Drs. Edward Petrillo and Graham Johnson for the opportunity to develop this methodology, explore the scope, and potential for library design.

References and notes

1. Kobayashi, S.; Peng, G.; Fukuyama, T. *Tetrahedron Lett.* **1999**, *40*, 1519–1522.
2. Surman, M. D.; Mulvihill, M. J.; Miller, M. J. *Org. Lett.* **2002**, *4*, 139–141.
3. Morphy, J. R.; Rankovic, Z.; Rees, D. C. *Tetrahedron Lett.* **1996**, *37*, 3209–3212.
4. To a 7 mL vial was added resin bound aminoalcohol (0.1 g, 0.10 mmol), PPH_3 (0.131 g, 0.5 mmol), and 2,4-dinitro-*N*-*p*-tolylbenzenesulfonamide (0.168 g, 0.5 mmol) in anhydrous THF (1.5 mL). The solution was cooled to −78 °C and DIAD (0.101 g, 0.5 mmol) was added. The reaction vial was allowed to warm to rt and shaken overnight. The resin was filtered away from the reaction solution, and washed with THF (3×) and CH_2Cl_2 (3×). The resin was then dried overnight in vacuo. Single bead IR analysis displayed no detectable trace of the OH stretching peak at 3500 cm^{-1}.
5. Diethylazodicarboxylate demonstrated a significant percentage of nucleophilic addition to the alcohol not detected with diisopropylazodicarboxylate.
6. To a 7 mL vial was added resin bound sulfonamide (0.1 g, 0.10 mmol), *n*-propylamine (0.059 g, 1.0 mmol) in anhydrous THF (1.5 mL). The reaction vial was sealed and shaken overnight at rt. The resin was filtered away from the reaction solution, and washed with THF (3×), CH_2Cl_2 (3×), followed by Et_2O (3×). The resin was then dried overnight in vacuo.
7. To a 7 mL vial was added resin bound aniline (0.1 g, 0.10 mmol) and Et_3N (0.101 g, 1.0 mmol), in anhydrous CH_2Cl_2 (1.5 mL). 4-(Trifluoromethyl)benzoyl chloride (0.104 g, 0.5 mmol) was added, and the reaction vial was sealed and shaken overnight at rt. The resin was filtered away from the reaction solution, and washed with CH_2Cl_2 (3×), THF (3×), followed by Et_2O (3×). The resin was then dried overnight in vacuo. Single bead IR analysis displayed a strong peak at 1730–1765 cm^{-1} (C=O stretch) representative of a benzamide carbonyl.
8. For ordering information and product specifications see: www.biotage.com.
9. To a 7 mL vial was added resin bound benzamide (0.1 g, 0.10 mmol), MeI (0.141 g, 1.0 mmol) in anhydrous DMF (1.5 mL). The reaction vial was sealed and shaken overnight at rt. The resin was filtered away from the reaction solution, and washed with DMF (3×) and CH_2Cl_2 (3×). The resin was then dried overnight in vacuo. The final product was isolated by adding the resin bound quaternary ammonium salt (0.1 g, 0.10 mmol) to a 7 mL vial. Hunigs base (0.129 g, 1.0 mmol), MP-carbonate resin (0.190 g, 0.5 mmol) in anhydrous DMF (1.5 mL) was added, and the reaction vial was sealed and shaken overnight at rt. The reaction solution was filtered away from the resin, and the resin was washed with CH_2Cl_2 (3×). The filtrates were combined and evaporated in vacuo. The crude product was dried overnight under high vacuum (0.05 torr) affording the desired product. ^1H NMR (400 MHz) and LC/MS analysis of the desired products confirmed the structural integrity and purity for all compounds.
10. El-Araby, M.; Guo, H.; Pottorf, R. S.; Player, M. R. *J. Comb. Chem.* **2004**, *6*, 789–795.
11. (a) Furka, A.; Sebestyen, F.; Asgedom, M.; Dibo, G. *Int. Pept. Protein Res.* **1991**, *37*, 487–493; (b) Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J. *Nature* **1991**, *354*, 82–84; (c) Houghten, R. A.; Pinilla, C.; Blondelle, S. E.; Appel, J. R.; Dooley, C. T.; Cuervo, J. H. *Nature* **1991**, *354*, 84–86.