Solid-Phase Synthesis of Structurally Diverse 1,4-Benzodiazepine Derivatives Using the Stille Coupling Reaction

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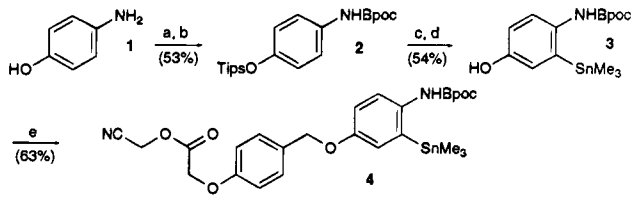
In the past few years, major efforts have focused on the construction and evaluation of compound libraries, including libraries of several classes of nonpolymeric compounds.[1] However, libraries of nonoligomeric molecules of complexity comparable to those targeted in many of the current medicinal chemistry efforts have not yet been described. Previously we reported methods for the solid-phase synthesis of a library of 1,4-benzodiazepine derivatives,[2,3] one of the most important classes of bioavailable therapeutic agents with widespread biological activities.[4] Three building blocks may be employed to construct the 1,4-benzodiazepine derivatives: alkylating agents, Fmoc amino acid fluorides, and 2-aminobenzophenones or 2-aminoacetophenones. The 2-aminoaryl ketone building block introduces an essential determinant of activity or specificity for many benzodiazepine-based therapeutic agents or candidates including HIV Tat/Tar inhibitors, selective cholecystokinin receptor subtype A or B antagonists, and platelet activating factor antagonists.[5] Unfortunately, the small number of commercially available 2-aminoaryl ketones limits the rapid synthesis of benzodiazepine derivatives that display diverse functionality upon this important region of structure. Here we report a general and high-yielding method for the solid-phase synthesis of 2-aminoaryl ketone derivatives that display diverse chemical functionality, and we demonstrate the direct incorporation of these molecules into structurally complex 1,4-benzodiazepines.

For the solid-phase synthesis of 2-aminoaryl ketone derivatives we chose the palladium-mediated Stille coupling reaction[6,7] between an acid chloride and a support-bound N-protected (2-aminoaryl)stannane as the key bond-forming step because it proceeds under mild and general reaction conditions and is tolerant of a wide range of functionality. This approach provides rapid access to hundreds of diverse 2-aminoaryl ketone derivatives, since over 500 acid chlorides are commercially available.

The first issue to be addressed to achieve a successful synthesis sequence was selection of the N-protecting group of the (2-aminoaryl)stannane. The protecting group must be stable to preparation of the stannane, to coupling of the stannane to the solid support, and to the palladium-mediated Stille coupling step, which rules out the use of base labile and allyl protecting group strategies. After the Stille coupling step is completed, the product aminobenzophenone must be unmasked for benzodiazepine synthesis without any cleavage of the alkoxybenzyl ether linker, preventing the use of protecting groups removed by strong acid or hydrogenation conditions. One protecting group that fulfilled all of these requirements is the 2-(4-biphenyl)isopropyloxycarbonyl (Bpoc) group[8] since it is stable to both basic and Stille coupling conditions, yet can be cleaved under very mild acidic conditions, to which the linker is completely stable.[9]

Scheme 1[a]



[a] (a) *i*-Pr_3SiCl, imidazole, CH_2Cl_2; (b) THF, 2-(4-biphenyl)isopropyl phenyl carbonate, KH; (c) (i) Et_2O, 1.1 equiv of *n*-BuLi, (ii) 1.2 equiv of *t*-BuLi, (iii) Me_3SnCl; (d) Bu_4NF/THF; (e) THF, (4-(hydroxymethyl)phenoxy)acetic acid cyanomethyl ester, PPh_3, DEAD.

The *N*-Bpoc-protected (2-aminoaryl)stannane was prepared as shown in Scheme 1. The triisopropylsilyl ether of 4-aminophenol was treated with 2-(4-biphenyl)isopropyl phenyl carbonate in THF followed by addition of excess KH to provide the Bpoc derivative **2**. The trimethyltin group was then introduced by directed ortho metalation followed by reaction with trimethyltin chloride.[10] Subsequent treatment with Bu_4NF provided the free phenol **3**, which was then coupled to the cyanomethyl ester of 4-(hydroxymethyl)phenoxyacetic acid under standard Mitsunobu reaction conditions.[11] The preactivated ester **4** was employed for direct acylation to the aminomethylated solid support to expedite the synthesis sequence and to minimize exposure of the acid sensitive Bpoc group and stannane to the phenoxyacetic acid functionality or the acidic coupling reagents that are often employed in conventional amide bond-forming methods.

Solid-phase synthesis was initiated by coupling active ester **4** to aminomethylated polystyrene resin in *N*-methyl-2-pyrrolidinone with *i*-Pr_2EtN as base and DMAP as an acylation catalyst (Scheme 2). Stille reactions of the support-bound stannane **5** with aromatic and aliphatic acid chlorides were performed with the "ligandless" catalyst $Pd_2dba_3{\cdot}CHCl_3$. To minimize protodestannylation and premature carbamate deprotection, K_2CO_3 and *i*-Pr_2EtN were added as acid scavengers. (While the ligandless catalyst provided a rapid reaction at room temperature, coupling with $Pd(PPh_3)_4$ required elevated temperature and some cleavage of the Bpoc group was observed.) After the reaction solution was rinsed away, palladium black that had precipitated on the resin during the coupling step was removed by brief treatment of the resin with dilute KCN in DMSO.[12] The Bpoc protecting group was then cleaved by brief treatment with 3% TFA in CH_2Cl_2 to provide the support-bound 2-aminoaryl ketone **6**.[13]

The support-bound 2-aminoaryl ketones were then incorporated directly into 1,4-benzodiazepine derivatives according to published procedure.[2] The aniline was acylated with an α-*N*-Fmoc amino acid fluoride,[14] and the Fmoc protecting group was

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(6) Labadie, J. W.; Tueting, J.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634–4642.

(7) Stille reactions have recently been reported between support-bound aryl iodides and stannane derivatives in solution. Deshpande, M. S. *Tetrahedron Lett.* **1994**, *35*, 5613–5614.

(8) Sieber, P.; Iselin, B. *Helv. Chim. Acta.* **1968**, *51*, 622–632.

(9) The amine packaged as the nitro group also fulfills all of these requirements. However, Stille coupling reactions of (2-nitroaryl)stannanes were found to be less general. Coupling reactions with aliphatic acid chlorides and electron poor aroyl chlorides proceeded in low yields.

(10) (a) Stanetty, P.; Koller, H.; Mihovilovic, M. *J. Org. Chem.* **1992**, *57*, 6833–6837. (b) Salituro, F. G.; McDonald, I. A. *J. Org. Chem.* **1988**, *53*, 6138–6139.

(11) Hughes, D. L. *Org. React. (N.Y.)* **1992**, *42*, 335–656.

(12) Backes, B. J. Unpublished observation.

(13) No cleavage of material from the support was observed during the Bpoc deprotection step as determined by concentration of the 3% trifluoroacetic acid CH_2Cl_2 solution.

(14) Carpino, L. A.; Satat-Aalaee, D.; Chao, H. G.; DeSelms, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 9651–9652.

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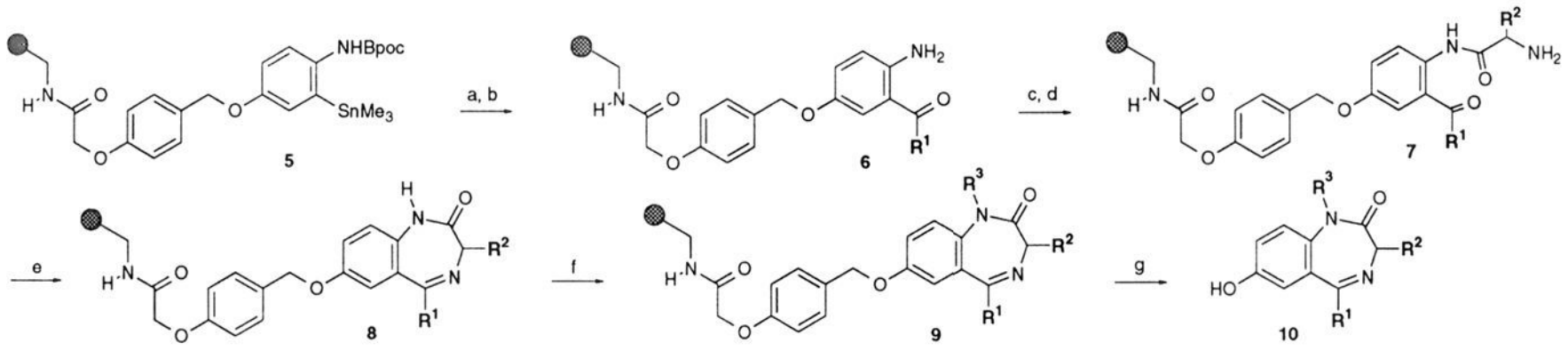
Scheme 2[a]



[a] (a) THF, K_2CO_3, *i*-Pr_2EtN, Pd_2dba_3•$CHCl_3$, aroyl or alkyl acid chloride; (b) 97:3 CH_2Cl_2/TFA; (c) Fmoc amino acid fluoride, 2,6-di-*tert*-butyl-4-methylpyridine; (d) 20% piperidine in DMF; (e) 5% AcOH in DMF, 65 °C, 4−8 h; (f) (i) lithiated 5-(phenylmethyl)-2-oxazolidinone in THF, 0 °C, (ii) alkylating agent, DMF; (g) TFA/Me_2S/H_2O (85:10:5).

removed by treatment with 20% piperidine in DMF to give **7**. Treatment of the free amine with 5% acetic acid in DMF at 65 °C gave the cyclic product **8**. Deprotonation followed by alkylation afforded the fully functionalized support-bound derivative **9**. The benzodiazepine was cleaved from the support by treatment with 85:10:5 trifluoroacetic acid/dimethyl sulfide/water to give the derivatives **10a**−**o**. The unpurified 1,4-benzodiazepine derivatives were isolated in greater than 80% purity as judged by ^{1}H NMR analysis. The yields reported for the eight-step process were determined from the mass balance of pure material after column chromatography, based on the initial aminomethyl substitution level of the resin.[15] Although the efficiency of the initial loading step (the acylation to give **5**) could not be determined directly,[16] treatment of **5** with 3% trifluoroacetic acid, acetylation of the resulting aniline with acetic anhydride, and cleavage from the solid support gave 4-hydroxyacetanilide in 92% overall yield based on the aminomethyl loading level of the resin.

Most of the benzodiazepine derivatives were synthesized incorporating the amino acid alanine and the alkylating agent ethyl iodide in order to facilitate direct comparison of the efficiency of the Stille coupling step and to evaluate the compatibility of the product 2-aminoaryl ketone with the 1,4-benzodiazepine synthesis sequence. These included benzodiazepines incorporating 2-aminobenzophenones prepared from acid chlorides that were electron rich, electron poor, alkyl substituted, polyaromatic, heterocyclic, and ortho substituted, as well as benzodiazepines from 2-aminoacetophenones prepared from several aliphatic acid chlorides displaying diverse functionality. In addition, benzodiazepine derivatives **10k** and **10n** were also synthesized to demonstrate that more highly functionalized alkylating agents and amino acids can also be incorporated[17] to access architecturally complex 1,4-benzodiazepine derivatives.

In conclusion, we have developed a rapid and efficient method for performing the Stille coupling reaction on a solid support to prepare 2-aminoaryl ketones that display diverse chemical functionality, and we have demonstrated the direct incorporation of these derivatives into 1,4-benzodiazepine structures in high yield. Using this methodology, the construction of a large library of 1,4-benzodiazepines and biological evaluation of the library against a number of therapeutically relevant targets are in progress.

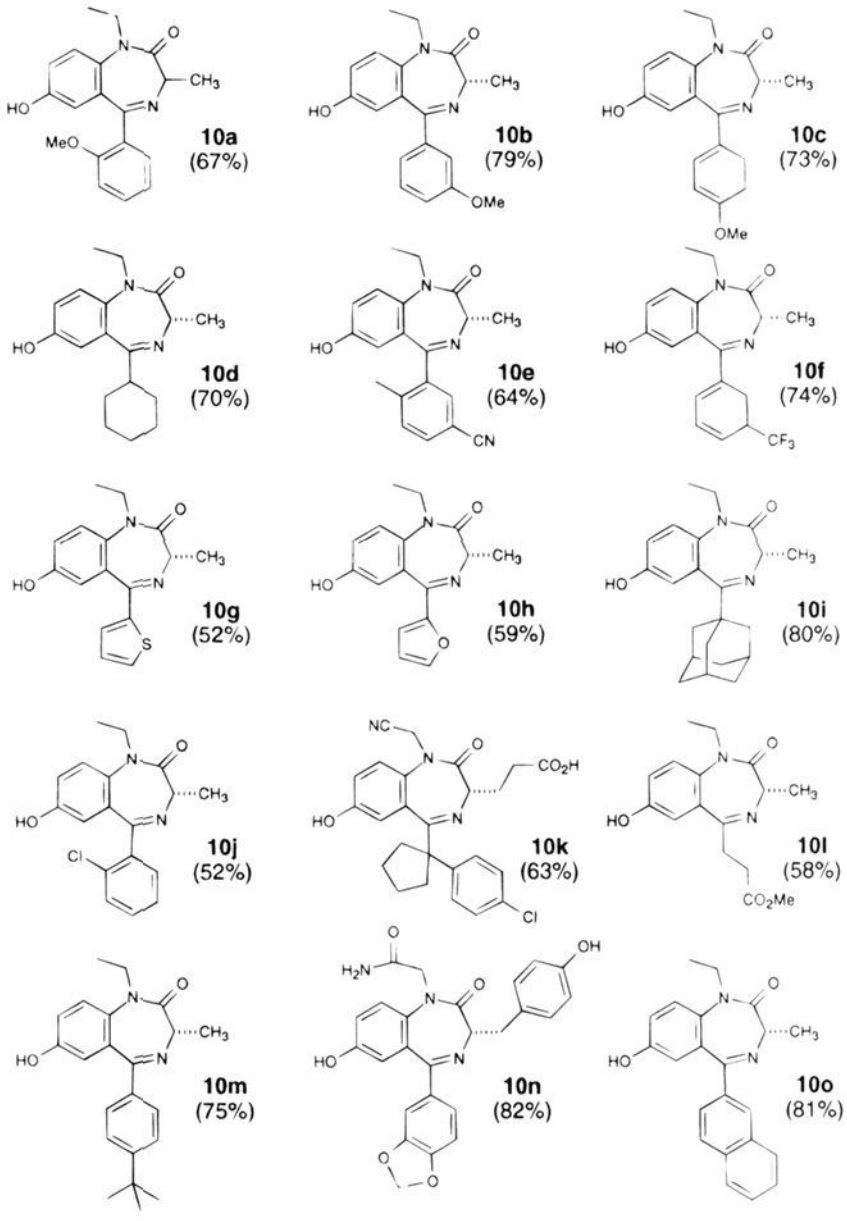


Figure 1. 1,4-Benzodiazepine derivatives synthesized on a solid support. Yields were determined from mass balance of purified material based upon initial aminomethyl loading level of the solid support.

Acknowledgment. We appreciate the reviewer's suggestion to check the stated substitution level of the commercially available resin. The NIH, the Burroughs Wellcome Fund, the A. P. Sloan Foundation, Affymax, Hoffman La Roche, Eli Lilly, and Tularik provided support for this work. Barry Bunin and Eddie Song gave synthetic assistance in these investigations. Structure searches were performed using the ACD and the MDL Drug Data Report (MDDR), MDL Information Systems, Inc., 14600 Catalina St., San Leandro, CA 94577.

Supplementary Material Available: Experimental details for the synthesis and characterization of all compounds (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(15) Substitution level was determined by two independent methods as described in the supplementary material.

(16) Loading could not be determined by direct submission of **5** to the trifluoroacetic acid cleavage because 4-aminophenol cleaves slowly and degrades under those conditions.

(17) We have previously demonstrated that a range of functionality, including amides, esters, ethers, indoles, carbamates, phenols, acids, alcohols, and amines, can be incorporated into 1,4-benzodiazepines employing the reported solid-phase synthesis methods.