ORGANIC LETTERS

2004
Vol. 6, No. 7
1143−1146

Solid-Phase Synthesis of 5-Biphenyl-2-yl-1*H*-tetrazoles

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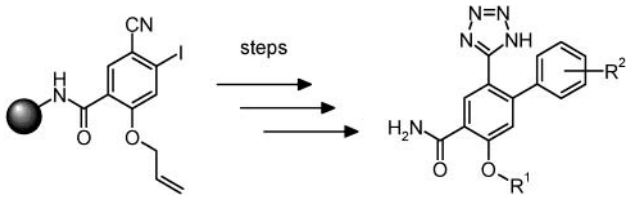
Received January 19, 2004

ABSTRACT



The combinatorial synthesis of novel biphenyl tetrazoles is described. Key steps include the simultaneous biphenyl formation and phenol deallylation under Suzuki cross-coupling conditions as well as the tetrazole ring formation on solid support. A representative library of 20 biphenyl tetrazoles was synthesized.

The combinatorial synthesis of low-molecular-weight compounds along with high-throughput screening continues to be a promising strategy for the discovery of new pharmaceutical lead structures.[1] Within this context, the synthesis of combinatorial libraries based on so-called "privileged structures"[2] is of considerable interest, because such structures combine druglike properties with the ability to address various biological targets, depending on their substitution pattern. Examples include the combinatorial synthesis of benzodiazepines,[3] benzopyrans,[4] biphenyls,[5] phenyl piperazines,[6] and spiro-piperidines.[7]

In the course of our ongoing efforts directed toward the solid-phase synthesis of general-purpose screening libraries, we were interested in the combinatorial diversification of the biphenyl tetrazole scaffold, another example of a "privileged structure".[8] Biphenyl tetrazoles, when appropriately substituted, exert potent and selective actions at diverse sets of protein targets, including G protein-coupled receptors, enzymes, and ion channels. Besides their well-known antihypertensive activity found in therapeutics such as Losartan (**1**),[9] biphenyl tetrazoles have also demonstrated activities

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10.1021/ol0498848 CCC: $27.50
Published on Web 03/02/2004

as stimulators of growth hormone release (**2**),[10] metalloprotease inhibitors (**3**, **4**),[11,12] and chloride channel blockers (**5**)[13] (Figure 1).

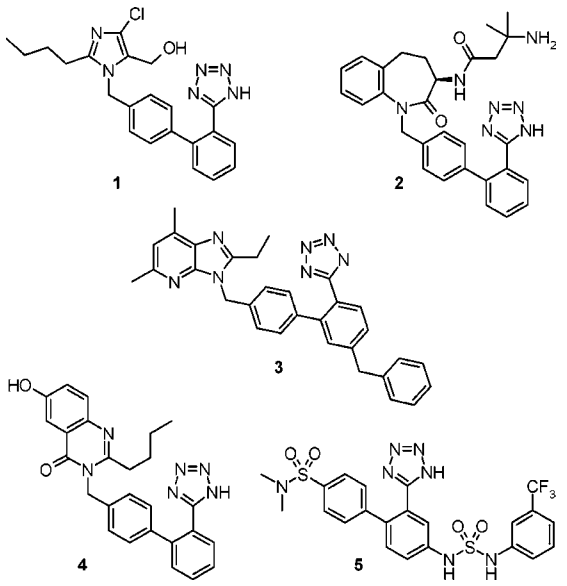
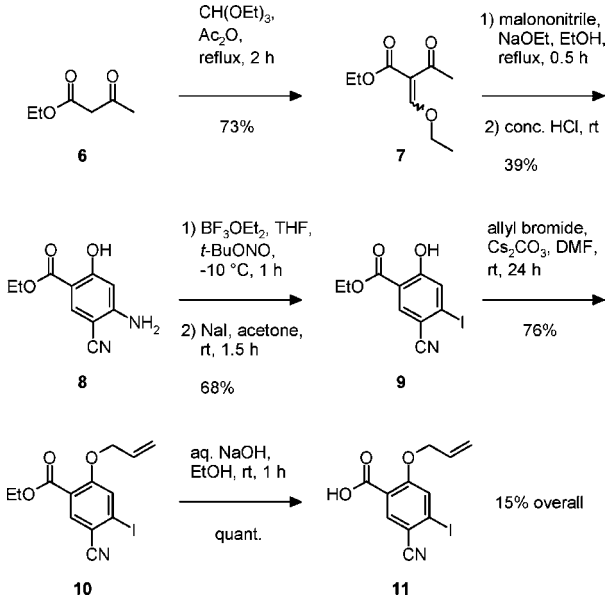


Figure 1. Examples of pharmaceutically relevant biphenyl tetrazoles.

A literature survey revealed two reports describing the solid-phase synthesis of biphenyl tetrazoles.[14] In both methods, a preformed phenyl tetrazole derivative was attached to the resin and elaborated further via Suzuki cross-coupling to the biphenyl core. Thus, diversity is limited to one of the phenyl rings. With the aim of synthesizing biphenyl tetrazoles with points of diversity at both phenyl rings, we considered the synthesis of the 2-allyloxy-5-cyano-4-iodobenzoic acid **11** as a key intermediate for the solid-phase synthesis. The scaffold offers three sites of diversification: the carboxylic acid, the iodo substituent, and the allyl-protected phenol. The carboxylic acid should serve as a solid-phase attachment point via an amide linkage while the aromatic iodine functionality allows the construction of the biphenyl core by Suzuki cross-coupling with boronic acids. Further diversification of the scaffold could be accomplished by the elaboration of the deprotected phenolic group via the Mitsunobu reaction with alcohols. It was envisaged further that the Suzuki cross-coupling reaction and the allyl deprotection could be accomplished under the same conditions simultaneously. Finally, the nitrile group of scaffold **11** was expected to be a suitable precursor for tetrazole formation. The scaffold **11** was synthesized in five linear steps and 15% overall yield from ethyl acetylacetate (**6**) as outlined in Scheme 1.

Scheme 1. Scaffold Synthesis



The amino salicylate **8** was prepared according to the published method.[15] Thus, the ethyl acetylacetate (**6**) was treated with triethyl orthoformiate to give the acrylic acid ester **7** as an *E/Z* mixture,[16] which was subsequently subjected to a sodium ethanolate mediated addition of malononitrile. An acidic workup gave the amino salicylate **8**. Conversion of the amino functionality of **8** via anhydrous diazotation[17] followed by treatment with NaI in acetone[18] afforded the iodo salicylate **9**. Typical aqueous Sandmeyer conditions gave a significantly lower yield (48%). Treatment of **9** with allyl bromide in the presence of Cs_2CO_3 gave the allyl-protected ester **10**, which was subsequently saponified providing scaffold **11**.

The solid-phase synthesis of biphenyl tetrazoles using **11** is outlined in Scheme 2. Initially, Rink amide polystyrene resin[19] was Fmoc-deprotected with 25% piperidine in DMF to give the free amine resin, which was loaded with the

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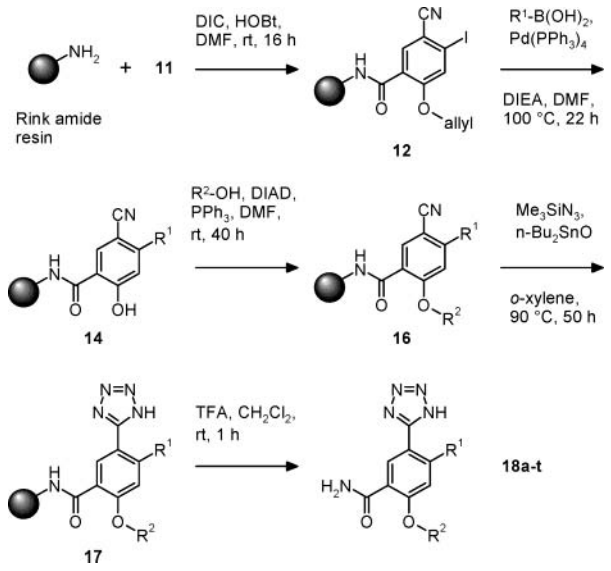
Scheme 2. Solid-Phase Synthesis of Biphenyl Tetrazoles



scaffold **11** using the DIC/HOBt/DMF procedure. The completion of loading was verified by the ninhydrin test.[20] With the scaffold **11** successfully loaded onto the resin, our efforts focused on the elaboration of the aromatic iodine functionality to the biphenyl core via the Suzuki cross-coupling reaction.

Thus, cross-coupling of the resin-bound scaffold **12** was investigated using either the standard aqueous[21] or anhydrous[22] reaction conditions. Initially 2.5 equiv of boronic acid **13a**, 5 mol % of $Pd(PPh_3)_4$, and 2.5 equiv of aqueous Na_2CO_3 or excess of neat DIEA as base at 100 °C in DMF were used. The resin was then subjected to the TFA/CH_2Cl_2 cleavage procedure to determine the extent of the coupling reaction via HPLC analysis of the crude product. Both protocols led predominately to deallylation at the phenol, whereas only little biphenyl formation was observed. Therefore, higher equivalents of reagents were used to drive the reaction to completion. Best results were obtained when 20 mol % of catalyst and 10 equiv of phenyl boronic acid as well as 10 equiv of aqueous Na_2CO_3 or excess of DIEA as base were used. Consequently, the resin-bound biphenyl **14** (R^1 = Ph) was obtained in high purity in both cases. Using the anhydrous reaction conditions, further boronic acids **13b**−**f** were investigated in the Suzuki cross-coupling reaction. The crude products cleaved from the resin showed good to excellent purities as outlined in Figure 2.

Diversification of the deprotected phenolic group was investigated with the resin-bound biphenyl **14** (R^1 = Ph)

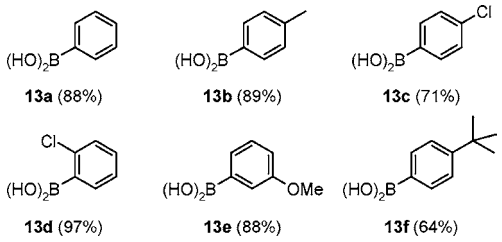


Figure 2. Phenylboronic acids **13a**−**f** used in the Suzuki cross-coupling reaction. Purities (in %) correspond to the deallylated biphenyls **14** cleaved from the resin and were based on the peak area of HPLC traces at 214 nm.

using the standard Mitsunobu reaction protocol with 5 equiv of the alcohols **15a**−**e** as well as 5 equiv of DIAD and PPh_3 in DMF as solvent.[23] Using these reaction conditions, primary and secondary alcohols afforded the ethers **16** in good purity, as indicated by HPLC analysis of the detached products (Figure 3).

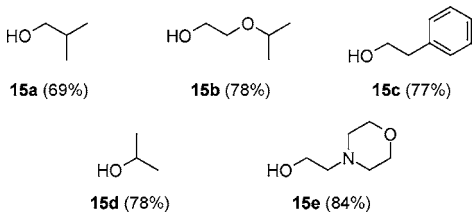


Figure 3. Alcohols **15a**−**e** used in the Mitsunobu reaction. Purities (in %) correspond to the detached ethers **16** and were calculated from the peak areas recorded by HPLC analysis at 214 nm of the crude products.

Tetrazole ring formation from the resin-bound nitrile **16** (R^1 = Ph, R^2 = *i*-Bu) was accomplished with Me_3SiN_3 and catalytic *n*-Bu_2SnO for 50 h at 90 °C in *o*-xylene.[24] Compared with previously reported solid-phase protocols using azidotrimethyltin[4] or sodium azide,[25] the method described herein allows for the use of less toxic and hazardous reagents.[24] Finally, cleavage from the resin with the TFA/CH_2Cl_2 procedure provided the fully functionalized tetrazole **18a** in 74% purity.

To illustrate the versatility of this chemistry, a library of 20 compounds **18a**−**t** was prepared, using a representative set of five boronic acids **13a**−**e** and four alcohols **15a**−**d**. All products were obtained in good to high purities as well as moderate yields after HPLC purification,[26] as shown in Table 1.

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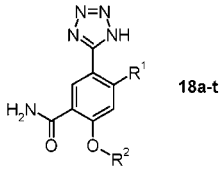
Table 1. Examples of Biphenyl Tetrazoles Synthesized on Solid Support



18a-t

compound	R^1	R^2	purity[a] (%)	yield[b] (%)	compound	R^1	R^2	purity[a] (%)	yield[b] (%)
18a	phenyl	isobutyl	74	44	**18k**	phenyl	2-phenylethyl	73	36
18b	4-methylphenyl	isobutyl	77	25	**18l**	4-methylphenyl	2-phenylethyl	81	42
18c	4-chlorophenyl	isobutyl	70	14	**18m**	4-chlorophenyl	2-phenylethyl	73	41
18d	2-chlorophenyl	isobutyl	93	36	**18n**	2-chlorophenyl	2-phenylethyl	84	25
18e	3-methoxyphenyl	isobutyl	76	24	**18o**	3-methoxyphenyl	2-phenylethyl	88	27
18f	phenyl	2-isopropoxy-ethyl	68	29	**18p**	phenyl	isopropyl	75	39
18g	4-methylphenyl	2-isopropoxy-ethyl	66	21	**18q**	4-methylphenyl	isopropyl	75	44
18h	4-chlorophenyl	2-isopropoxy-ethyl	65	23	**18r**	4-chlorophenyl	isopropyl	59	24
18i	2-chlorophenyl	2-isopropoxy-ethyl	81	27	**18s**	2-chlorophenyl	isopropyl	91	32
18j	3-methoxyphenyl	2-isopropoxy-ethyl	81	30	**18t**	3-methoxyphenyl	isopropyl	74	18

[a] Calculated from integrated peak areas recorded by HPLC analysis (214 nm) of the crude products. [b] Yields of the purified material were calculated on the basis of the initial loading of the resin.

In conclusion, we have developed a straightforward procedure for the synthesis of structurally diverse biphenyl tetrazoles. The synthesis includes a novel one-step procedure for biphenyl formation and phenol deprotection under Suzuki cross-coupling reaction conditions, as well as a convenient synthesis protocol for tetrazole formation on solid support. The further elaboration of the scaffold **11** at the carboxylic acid using amine-loaded resins as an additional point of diversity is ongoing. In addition, the preparation and biological screening of a larger library is in progress.

Acknowledgment. The authors thank Dr. Franz v. Nussbaum and Dr. Leila Telan (Bayer AG) for helpful discussion and critical reading of the manuscript.

Supporting Information Available: Detailed experimental procedure and analytical data for compounds **7**−**11** and **18a**−**t**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0498848