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Solid Phase Synthesis of Biphenyltetrazole Derivatives

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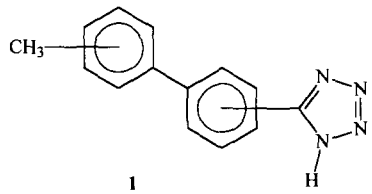
Abstract: A dihydropyran carboxylic acid type linker is suitable for the solid phase Suzuki type aryl-aryl coupling reaction for the preparation of various biphenyltetrazole derivatives.

In recent years there have been enormous interests in the combinatorial synthetic approach to build various small molecule libraries particularly using a solid phase methodology.[1] In connection with our research program on the development of angiotensin II receptor antagonists,[2] we needed to prepare all possible regioisomers of biphenyltetrazole derivatives of type 1 and herein we would like to report a preliminary result on the selection of a proper linker and the subsequent solid phase Suzuki reaction for the synthesis of biphenyltetrazole derivatives.



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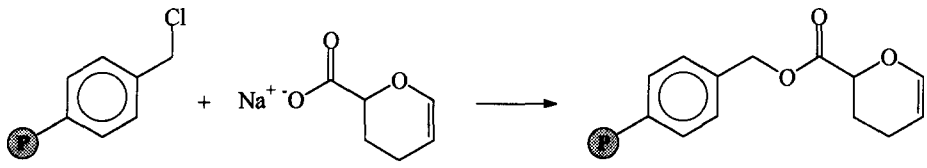
To synthesize biphenyltetrazole derivatives of type 1, there are few things to consider. First of all, it is strategically desirable to introduce the tetrazole ring as early as possible due to the harsh reaction conditions generally required to prepare tetrazoles from nitriles and azides.[3] However, with a prebuilt tetrazole group, then it is necessary to protect the tetrazole moiety due to the fact the acidic nature of the native tetrazole group usually interferes subsequent reactions.[4] Finally with a properly protected tetrazole moiety, the biphenyl part can be prepared by the palladium catalyzed aryl-aryl coupling reactions such as Stille[5] or Suzuki reaction.[6]

Taking these considerations into the solid phase chemistry, it is important to select a proper linker which is suitable for not only attaching the tetrazole part onto the solid support but also protecting the tetrazole group at the same time. Although one can think of attaching the tetrazole unit directly onto the Merrifield resin by simple alkylation, there are several problems with this approach. First, even in a typical solution chemistry a benzyl group is sometimes difficult to remove. Second, if the benzyl group is cleaved reductively then the resin becomes no longer recyclable.

Therefore, we decided to examine an aminal type of protecting group which we have found, in our solution chemistry, quite useful for the protection of a tetrazole group. To this end we selected dihydropyran carboxylic acid **2** as an enol ether type of a linker which also contains a carboxylic group which can be used to attach the



2 3

group on the polymer.

The group can be easily attached to the Merrifield resin by simple alkylation reaction (dimethylacetamide, rt, 24 hrs) to give **3**. We then examined conditions for attaching the tetrazole group to the polymer **3** and found that the condition using trifluoroacetic acid as a catalyst was satisfactory. The efficiency of this reaction was determined by monitoring the amount of tetrazole freed from the resin by treating the resin with 50% of trifluoroacetic acid in water (Table 1). Next we examined conditions for removing the tetrazole moiety from the resin and found that 3% HCl in methanol was effective (Table 2). These processes for the attachment and detachment of the tetrazole group are quite general as demonstrated with various tetrazole derivatives (Table 3). In order to definitely confirmed that the tetrazole group is in fact attached to the polymer, the polymer was hydrolyzed with LiOH and the resulting acid was treated with diazomethane to give the product which was identified as **4**.

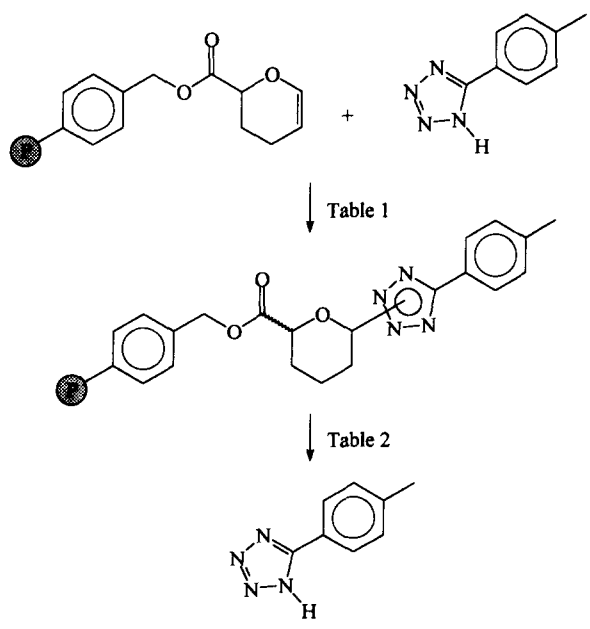


Table 1

Condition (1,2-dichloroethane, 80°C, 24 hr)	Yield*
p-TsOH (1 eq.)	6.3 %
PPTS (2.5 eq.)	17 %
TFA (1 eq.)	25 %

* Two-step yield after the treatment of the resin with TFA:H_2O (1:1) and measuring the amount of tetrazole isolated

Table 2

Condition	Yield*
TFA:H_2O (1:1), 1 hr	25 %
3% HCl in methanol, 24 hr	58 %

* Tolyltetrazole was attached to the resin by TFA (1 eq.). The yield is for two steps based on tolyltetrazole recovered under the condition

Finally we carried out actual palladium catalyzed Suzuki reaction[7] with the polymer containing ortho bromotetrazole and arylboronic acids to demonstrate this solid phase approach is practical and found that a typical Suzuki reaction condition provided the desired coupled products in good overall yield as shown in Table 4.

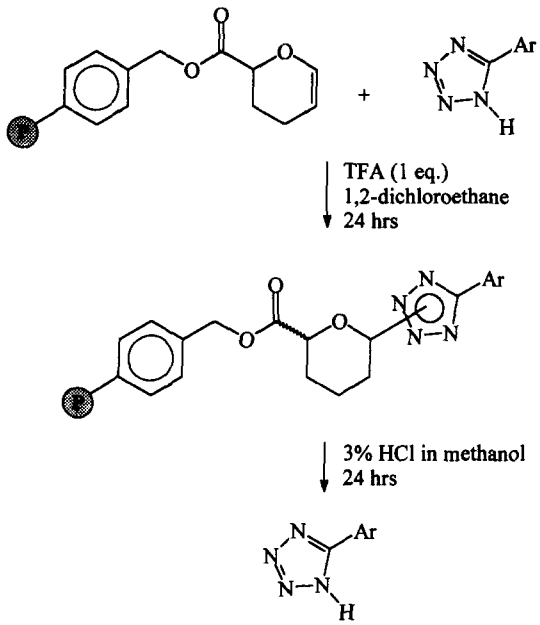
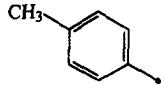
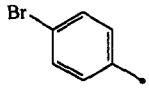
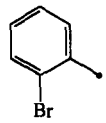
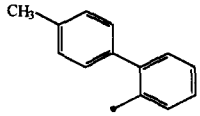
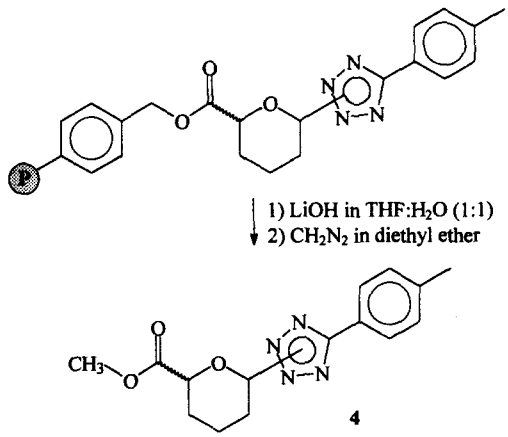


Table 3

Ar	Yield*
	58 %
	40 %
	40 %
	41 %

* two-step yield

In conclusion we have demonstrated that dihydropyran carboxylic acid type linker is suitable for attaching and detaching the tetrazole unit and also demonstrated that this system is suitable for the solid phase Suzuki type of C-C coupling reaction for the preparation of biphenyltetrazole derivatives. The preparation of various polymer bound biphenyltetrazole derivatives and a subsequent utilization of these intermediates for the synthesis of biologically interesting compounds are the subjects for our current research.



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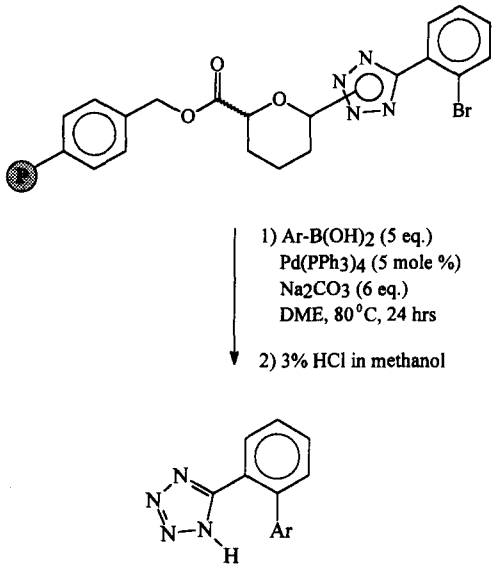
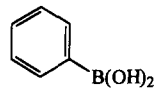
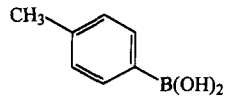


Table 4

Ar-B(OH)$_2$	Yield*
	53 %
	57%

* two-step yield from polymer bound ortho bromophenyltetrazole

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