Tetrahedron Letters xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Preparation of highly functionalized 1,5-disubstituted tetrazoles via palladium-catalyzed Suzuki coupling

Edward J. Hennessy *, Mark Cornebise, Lakshmaiah Gingipalli, Tyler Grebe, Sudhir Hande, Valerie Hoesch, Hoan Huynh, Scott Throner, Jeffrey Varnes, Ye Wu

IMED Oncology, Innovative Medicines & Early Development, AstraZeneca, 35 Gatehouse Drive, Waltham, MA 02451, United States

ARTICLE INFO

Article history:
Received 2 March 2017
Accepted 17 March 2017
Available online xxxx

Keywords:
Tetrazoles
Heterocycles
Suzuki coupling
Biologically-active Molecules

ABSTRACT

The preparation of a range of 1,5-disubstituted tetrazoles has been achieved through palladium-catalyzed Suzuki coupling. Using appropriately substituted 5-*p*-toluenesulfonyltetrazoles as substrates (obtained by cycloaddition of a substituted azide with *p*-toluenesulfonyl cyanide), this methodology provides access to a variety of highly substituted tetrazoles that would be difficult to access otherwise. The procedure is compatible with functional groups commonly found in drug-like molecules, and has been used to generate a number of compounds of potential biological interest.

Aromatic heterocycles are ubiquitous in synthetic compounds designed to have biological activity, in large part due to the ability of the heteroatoms within these ring systems to interact favorably with functional groups in the biological target of interest. In addition, the ability to modulate the properties (such as lipophilicity, aqueous solubility, etc.) of a scaffold through the inclusion of heterocyclic rings is commonly exploited in the drug discovery process. For example, the replacement of carbocyclic rings with heterocyclic moieties in general results in quantifiably improved physical properties, lowered risk of drug-drug interactions, and improved overall developability.[1]

Amongst the heterocycles commonly encountered in medicinal chemistry programs, tetrazoles are often used to modulate binding affinity or physical properties of a series.[2] N—H tetrazoles, by virtue of the electron-deficient nature of the heterocyclic ring, are ionized at physiological pH and are thus often employed as non-classical carboxylic acid isosteres in the design of biologically active compounds.[3] Indeed, this ring system can be found in various approved medicines, such as in a number of angiotensin II receptor blockers (sartans).[4]

Tetrazoles in which the carbon atom as well as one of the nitrogen atoms are substituted have also found applications in the construction of biologically-active motifs. For example, 1,5-disubstituted tetrazoles have been successfully employed as an isosteric replacement for *cis*-amide bonds in peptidomimetics.[5] 2,5-Disubstituted tetrazoles have similarly been utilized as components of synthetic nucleotides and oligonucleotides.[6]

As part of a drug discovery program aimed at identifying compounds with activity against a biological target of interest, we postulated that an *ortho*-disubstituted phenyl ring common to compounds within the lead series could be replaced with a 1,5-disubstituted tetrazole ring, thus largely maintaining the overall shape of the scaffold but with a substantial beneficial reduction in lipophilicity. To test this hypothesis, we designed a series of compounds containing such a disubstituted tetrazole ring to assess whether this change would be compatible with the desired biological activity. Synthetic access to many of these compounds proved troublesome, however, as it has been established repeatedly throughout the literature that the alkylation of N—H tetrazoles proceeds to give mixtures of the 1,5- and 2,5-disubstituted isomers, with product ratios largely dependent upon the nature of the 5-substitutent.[7] Thus, we sought a synthetic methodology that would provide a reliable route to a variety of tetrazoles with the desired substitution pattern.[8]

In devising a strategy to address this problem, we were inspired by a publication from the Sharpless group describing the regiospecific preparation of 1-substituted 5-sulfonyltetrazoles through the cycloaddition of an organic azide with commercially available *p*-toluenesulfonyl cyanide.[9] This operationally-simple reaction was shown to be high-yielding, providing access to a relatively broad scope of substituted tetrazoles. Moreover, the 5-*p*-toluenesulfonyl group of these adducts can be readily displaced by heteroatom-based nucleophiles, thus offering the

* Corresponding author.
E-mail address: edward.hennessy@astrazeneca.com (E.J. Hennessy).

http://dx.doi.org/10.1016/j.tetlet.2017.03.056
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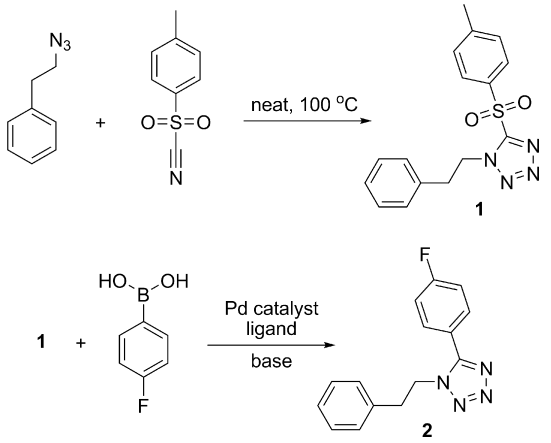
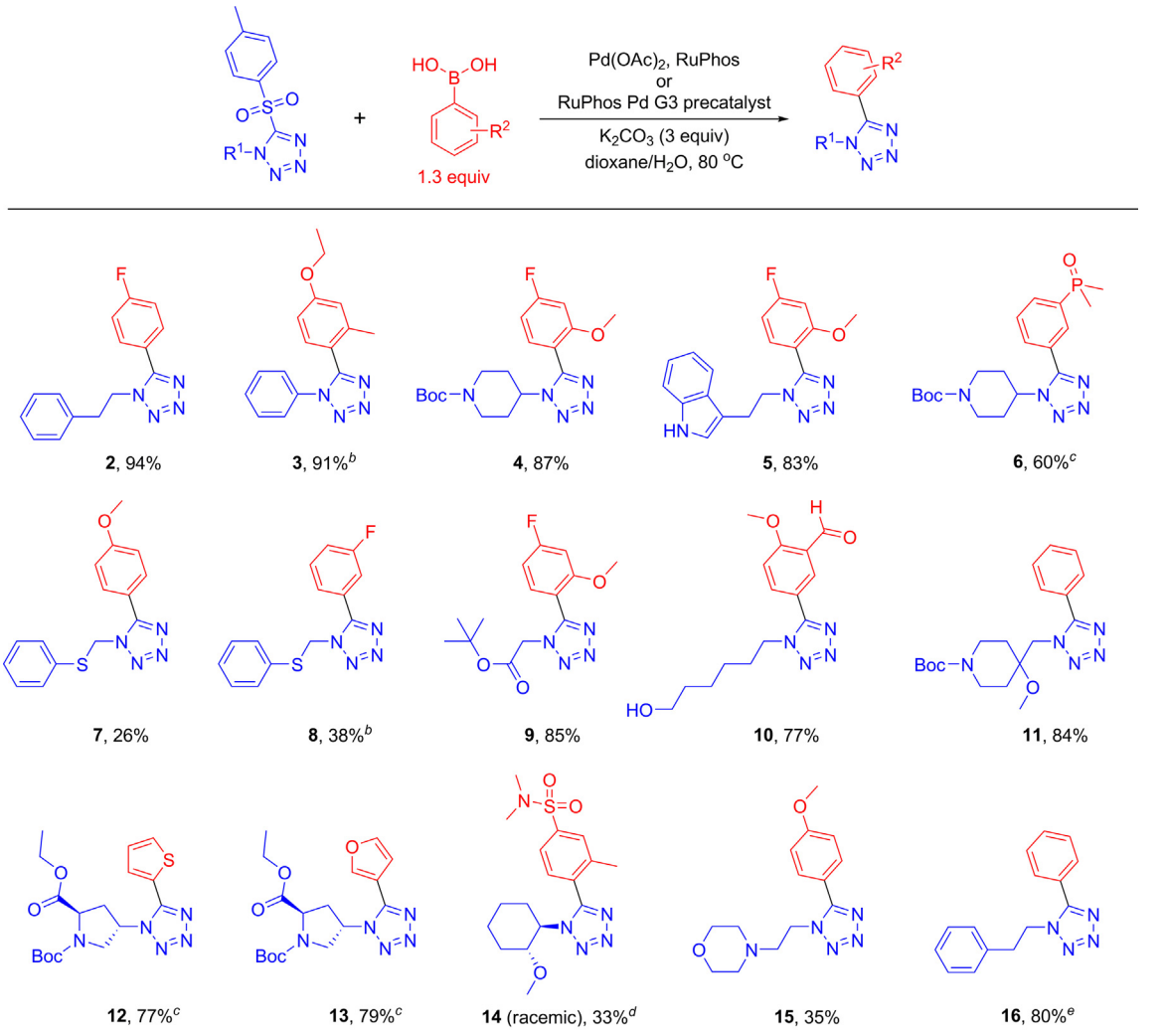


Scheme 1. Preparation of 1-phenethyl-5-*p*-toluenesulfonyltetrazole (**1**) and coupling with 4-fluorophenylboronic acid to yield tetrazole **2**.

opportunity to prepare a diverse array of 1,5-disubstituted tetrazoles. While this methodology was useful for the construction of some of our designed targets, we also desired compounds in which a carbon atom was bound to the 5-position of the tetrazole ring, which would be derived from reaction with carbon-based nucleophiles. At the time of our studies, however, there were only a few reports of the use of activated carbon nucleophiles (such as ethyl cyanoacetate) to displace a 5-sulfonyl group from a tetrazole.[10] In addition, an aryl Grignard reagent has similarly been shown to undergo this reaction.[11] Given the modest reported yield of this transformation, however, along with limited functional group compatibility expected with the use of organomagnesium reagents, we sought an alternative method to construct carbon–carbon bonds within this scaffold that would be more generally applicable to a range of functionalized substrates.

While palladium-catalyzed Suzuki couplings employing 5-chloro or 5-bromotetrazole substrates have been described in the literature,[12] preparation of these substrates typically requires multiple synthetic steps, often using reagents incompatible with

Table 1
Pd-catalyzed synthesis of 1,5-disubstituted tetrazoles.



[a]Reported yields are for analytically pure material isolated following the reaction, and unless otherwise indicated are the average of two independent runs. [b]$NaHCO_3$ used as base. [c]Aryl or heteroarylpinacolboronate ester used instead of boronic acid. [d]Isolated yield from single run. [e]Aryl potassium trifluoroborate used instead of arylboronic acid.