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Synthesis of 7-Substituted Tetracycline Derivatives

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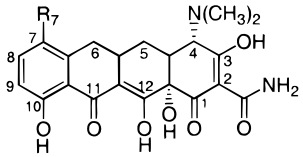
ABSTRACT



The synthesis of 7-substituted tetracycline derivatives has been accomplished in high yield from 7-halotetracyclines by modified Suzuki and Stille coupling protocols. These novel derivatives may serve as a new class of tetracycline antibiotics effective against multi-antibiotic-resistant bacteria.

The first tetracycline to be discovered, chlortetracycline, was isolated from *Streptomyces aurefaciens* in 1944.[1] Subsequently, numerous tetracycline analogues have been introduced including oxytetracyline,[2] tetracycline, and demeclocycline.[3] In the past, tetracyclines have been the antibiotics of choice against a wide variety of microorganisms. The overuse of this class of antibiotics has led to widespread bacterial resistance and eventual replacement with more effective antibiotics such as fluoroquinolones and penicillins.[4] However, tetracyclines have many distinct advantages despite current bacterial resistance. Clinically, tetracyclines are much safer than other antibiotics and chemical modification should lead to compounds with enhanced antibiotic properties, low toxicity, and clinical effectiveness against a broad spectrum of microorganisms.[5] Thus, synthetic modification of tetracyclines continues to hold promise in the development of antibiotics effective against resistant microorganisms.

Numerous D ring modifications have been reported in the literature.[6−8] This is due to the activation of the aryl ring by the presence of the phenolic hydroxyl at C-10. This ortho−para directing group enriches the electron density at C-7 and C-9. All reactions in the D ring reported to date have involved electrophilic substitution in these two positions.[9] C-7 bromo substitution has been accomplished through the 11α-chloro derivative with bromonium ion generated from *N*-bromosuccinimide followed by careful reductive removal of the 11α-halo group.[10] However, when sancycline is treated with *N*-iodosuccinimide in concentrated sulfuric acid the extreme lability of the 11α-iodo group readily leads to a rearrangement of the halo group to the C-7 position. The intermolecular nature of the rearrangement has been demonstrated by trapping experiments with α-naphthol as an alternate halogen acceptor. Biotesting of these various derivatives leads to the general conclusion that C-7 substitution is more favorable for bioactivity than C-9. Thus, additional work on C-7 compounds should prove fruitful in the search for a tetracycline compound which shows potent activity against resistant bacteria.

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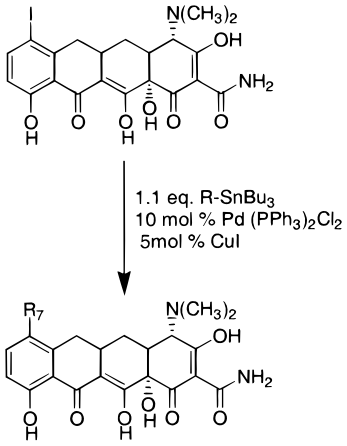
The absence of reported modifications to the 7-iodo tetracyclines is surprising in light of current efforts toward carbon−carbon bond formation by transition metal-catalyzed reactions.[11,12] Despite the polyhydroxylated nature of the substrate, a number of cross-coupling reactions have proven valuable for the incorporation of aryl moieties. The cross coupling of organotin reagents with organic electrophiles has been shown to be versatile and tolerant of a wide variety of functional groups.[13] Stille coupling has been applied to the synthesis of a large number of complex molecules, and its application to the synthesis of novel 7-substituted tetracycline derivatives produces an exciting new class of tetracycline derivatives.

Aryl iodides and bromides undergo oxidative addition to palladium(0) complexes at moderate temperatures. Thus, these halides are suitable for coupling with tin reagents.

The reaction of 7-iodosancycline with 1.1 equiv of tri-*n*-butylstannyl reagent (Scheme 1) in the presence of a

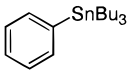
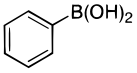
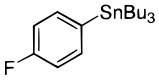
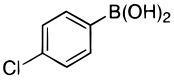
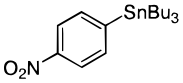
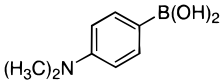
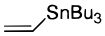
Scheme 1



palladium catalyst and copper iodide affords excellent yields of the cross-coupled product. No significant side products or homocoupling products are observed. This reaction has been extended to the synthesis of a variety of phenyl, alkenyl, and alkynyl derivatives in good yield (Table 1). The reaction conditions are mild, and the products are easily isolated.

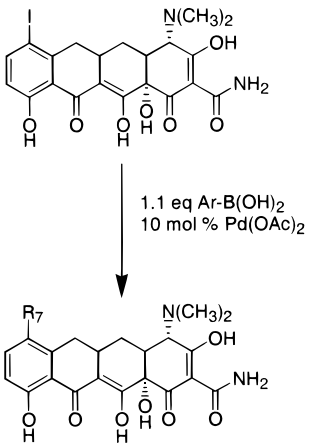
The application of Suzuki coupling in the synthesis of complex natural products is well documented in the literature.[14,15] This cross-coupling protocol has been successfully applied to a wide variety of substrates and also has the advantages of high yields, mild conditions, and facile product isolation. Additionally, the reaction can be successfully carried out in solvents such as methanol which provides better solubility for the 7-iodosancycline. Phenylboronic acid

Table 1. Synthesis of 7-Substituted Tetracyclines via Suzuki and Stille Cross Coupling

entry	starting material	product	yield
1		7-phenylsancycline	87%
2		7-phenylsancycline	48%
3		7-(4-fluorophenyl)sancycline	91%
4		7-(4-chlorophenyl)sancycline	42%
5		7-(4-nitrophenyl)sancycline	83%
6		7-(4-dimethylamino)sancycline	28%
7		7-ethylenylsancycline	94%
8		7-ethynylsancycline	90%

(Scheme 2) reacts with 7-iodosancycline in the presence of 10 mol % palladium acetate to afford 7-phenylsancycline in 67% yield (Table 1). Despite the lower yields associated with the Suzuki couplings when compared to Stille coupling, the two couplings are complementary in that some boronic acids are easier to synthesize than their organotin counterparts. This

Scheme 2



allows the incorporation of a wide variety of functionalized substituents at this position of the tetracycline molecule.

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A simple and expeditious synthesis of 7-substituted tetracyline derivatives has been described. With appropriate modifications, this methodology could be applied to other tetracycline antibiotics such as doxycycline, methacycline, and oxytetracycline, providing new class of tetracycline antibiotics for evaluation against tetracycline-resistant bacteria.

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Supporting Information Available: General procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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