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Synthesis of pyridine alkaloids via Pd-catalyzed coupling of 3-iodopyridine, 1,ω-dienes and nitrogen nucleophiles

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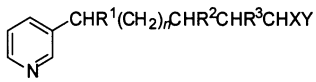
Abstract—The palladium-catalyzed cross coupling of 3-iodopyridine, long chain 1,ω-dienes, and benzylic amines or tosylamides provides a novel route to key intermediates for the synthesis of the naturally occurring, biologically active pyridine alkaloids theonelladins C and D, niphatesine C and xestamine D. © 2001 Published by Elsevier Science Ltd.

Recently, a number of pyridine alkaloids have been isolated from marine organisms and shown to exhibit interesting biological activity (Table 1). For example, the antileukemic and antineoplastic theonelladins C (**1**) and D (**2**) have been isolated from the Okinawan marine sponge *Theonella swinhoei*.[1] The antileukemic niphatesines C (**3**) and D (**4**), and the cytotoxic and antimicrobial niphatesine G (**5**) have been obtained from the Okinawan marine sponge *Niphates* sp.[1c,2] The antimicrobial xestamine C (**6**) comes from a Caribbean sponge *Xestospongia wiedenmayeri*, while the antimicrobial xestamine D (**7**) has been extracted from a Bahamian sponge *Calyx podatypa*.[3]

Some of these alkaloids have been synthesized. Rao et al. reported the first total synthesis of theonelladins A–D using a Wittig reaction for construction of the carbon skeleton.[1b] Six steps were required to complete the total synthesis of theonelladins C and D. The alkylation of a sulfone has also been utilized to prepare theonelladin D.[1d] Grignard or alkyne alkylation chemistry have also been employed to synthesize theonelladins C and D.[1c] Niphatesines C and D have been prepared by Friedel–Crafts acylation, Wittig, Heck and alkyne alkylation chemistry.[2c–e] There are apparently no syntheses of any of the xestamines. To date, no general synthetic strategy has been developed for the synthesis of a variety of these interesting alkaloids.

We have recently reported several palladium-catalyzed migration processes, which are extraordinarily efficient for the construction of long chain compounds with an aromatic ring on one end of the chain and some kind of functionality on the other end of the chain. For example, the palladium-catalyzed cross-coupling of aryl halides, 1,ω-dienes and amines[4] provides a highly efficient route to long chain amines (Eq. (1)). This chemistry appeared ideal for the synthesis of the pyri-

Table 1. Some naturally occurring pyridine alkaloids



	R^1	R^2	R^3	*n*	X, Y
Theonelladin C (**1**)	H	H	H	9	H, NH_2
Theonelladin D (**2**)	H	H	H	9	H, NHMe
Niphatesine C (**3**)	H	H	Me	8	H, NH_2
Niphatesine D (**4**)	H	Me	H	8	H, NH_2
Niphatesine G (**5**)	H	H	Me	9	=NOMe
Xestamine C (**6**)	Me	H	H	10	H, NMe(OMe)
Xestamine D (**7**)	H	H	H	10	H, NMe(OMe)

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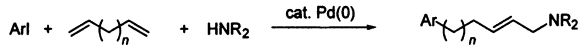
dine alkaloids discussed above. Indeed, we now wish to report very efficient syntheses of theonelladins C and D, niphatesine C, and xestamine D using this methodology.

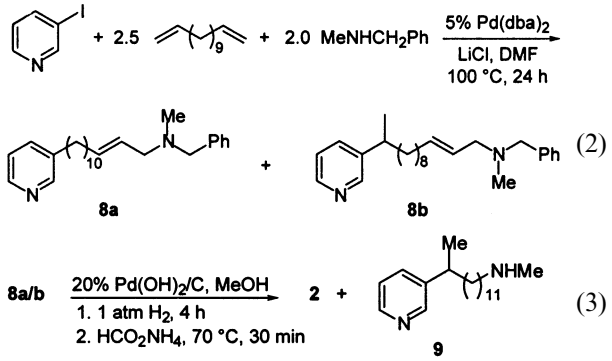


(1)

In order to prepare theonelladins C and D using the methodology outlined in Eq. (1), we required three major components—3-iodopyridine, 1,12-tridecadiene and an appropriate nitrogen nucleophile. 3-Iodopyridine is easily prepared from 3-aminopyridine by a literature procedure.[5] The requisite diene has been prepared from 10-decen-1-ol by conversion to the iodide with I_2 and imidazole[6] (88% yield), and the iodide has been cross-coupled with 1.3 equiv. of allylmagnesium bromide in the presence of 13 mol% CuI (60% yield).

The choice of nitrogen nucleophile turns out to be critical to the success of this approach. Unfortunately, ammonia and primary amines do not usually work well in our three component coupling process. However, secondary amines generally afford high yields of the desired long chain amines.[4] Since the benzyl group is often used as a protecting group for amines and is easily removed by a variety of methods,[7] benzylmethylamine and dibenzylamine were chosen as the most appropriate nucleophiles for synthesis of the theonelladins C and D.

For the synthesis of theonelladin D, 3-iodopyridine, 2.5 equiv. of 1,12-tridecadiene and 2 equiv. of benzylmethylamine were allowed to react in the presence of 5 mol% $Pd(dba)_2$ and 1.3 equiv. of LiCl in DMF at 100 °C for 24 h to produce an 85:15 mixture of regioisomers **8a** and **8b** in 78% yield (Eq. (2)). The hydrogenation and subsequent debenzylation was carried out by allowing this mixture to react with 1 atm of H_2 in the presence of 0.35 equiv. of Pearlman's catalyst[8] [20% $Pd(OH)_2/C$] in methanol for 4 h at room temperature and then adding 5 equiv. of ammonium formate and heating to 70 °C for 30 min (Eq. (3)). Theonelladin D (**2**) was obtained along with its isomer **9** in an 85:15 ratio in 70% combined yield.



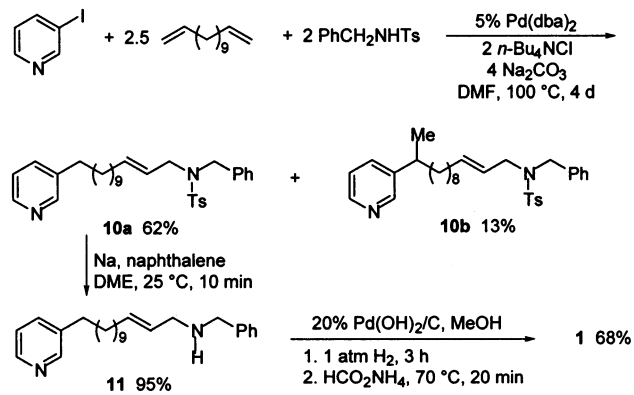
(2)

(3)

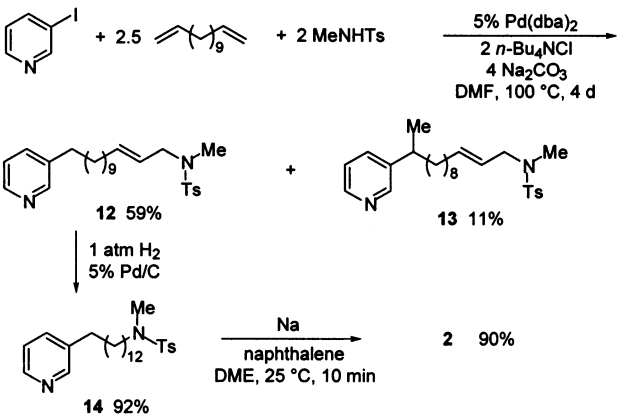
Theonelladin C, with an NH_2 group at the end of the long carbon chain, was our next synthetic target. As in the synthesis of theonelladin D, the key issue here is the choice of the nitrogen nucleophile to use in the palladium reaction. Unfortunately, in work on model systems, benzylamine gave none of the desired coupling product and dibenzylamine gave only very low yields for reasons we do not understand. It appeared that another protecting group was necessary.

The protecting group had to facilitate the palladium process itself and be easily removed after the palladium reaction. The tosyl group is a useful protecting group for amines,[7] and tosylamides are generally good nucleophiles in π-allylpalladium coupling processes,[9] so *N*-benzyl tosylamide was chosen as the nitrogen nucleophile. The coupling of 3-iodopyridine, 2.5 equiv. of 1,12-tridecadiene and 2 equiv. of *N*-benzyl tosylamide provided the desired product **10a** and isomer **10b** as readily separable isomers in 62 and 13% yields, respectively (Scheme 1). Compound **10a** was converted into benzylamine **11** in 95% yield upon treatment with sodium naphthalenide. Finally, theonelladin C (**1**) was obtained in 68% yield from the hydrogenation and debenzylation of **11** as described earlier.

The successful synthesis of pure theonelladin C using a tosylamide as a nucleophile in the palladium-catalyzed cross-coupling encouraged us to reexamine the synthesis of theonelladin D (**2**) by a similar process (Scheme 2). Commercially available *N*-methyl tosylamide was allowed to react with 3-iodopyridine and 1,12-tridecadiene for 4 days under the conditions shown in Scheme 2. The desired unsaturated tosylamide **12** was obtained in



Scheme 1.

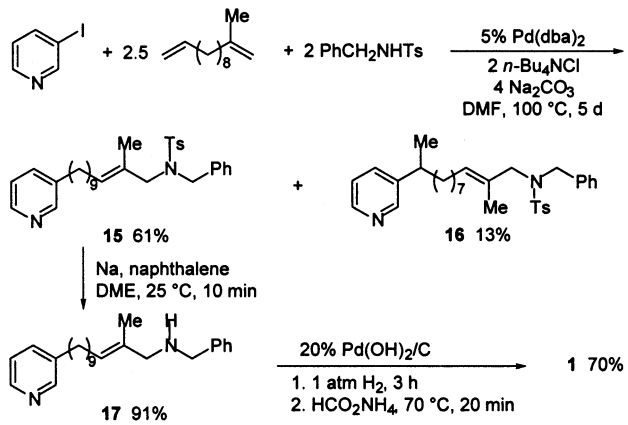


Scheme 2.

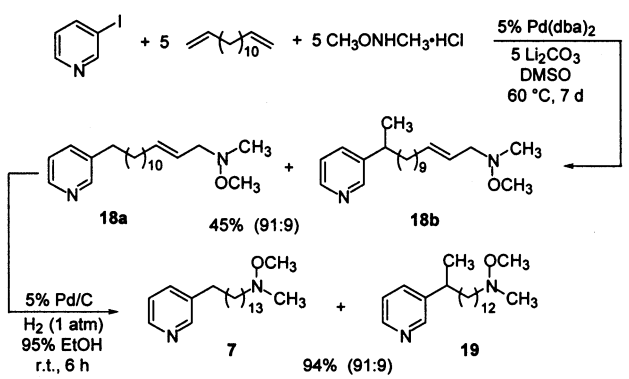
59% isolated yield as a pure isomer, along with 11% of the expected isomer **13**. Hydrogenation of the desired tosylamide under 1 atm of H_2 using 5% Pd/C as a catalyst and 95% ethanol as the solvent for 3 h afforded the saturated tosylamide **14** in 92% yield. Subsequent detosylation with Na and naphthalene provided theonelladin D (**2**) in 90% yield as a single pure product.

The similarity of niphatescine C and theonelladin C suggested that we ought to be able to prepare the former natural product using 2-methyl-1,11-dodecene with *N*-benzyl tosylamide as the nucleophile (Scheme 3). The required diene was prepared by the CuI-catalyzed coupling of 10-iodo-1-decene and isopropenylmagnesium bromide (97% yield). The palladium reaction was very slow and only after 5 days was a 61% yield of the desired tosylamide **15** obtained, along with 13% of the expected isomer **16**. The tosyl group was removed in 91% yield using Na and naphthalene, and the resulting product **17** was hydrogenated and the benzyl group removed using 20% $Pd(OH)_2$ in MeOH under 1 atm of H_2, followed by the addition of ammonium formate and heating for 20 min at 70 °C to afford the natural product niphatesine C (**3**) in 70% overall yield.

It appeared that the interesting alkaloid xestamine D (**7**) might also be easily synthesized using our palladium chemistry and *N*,*O*-dimethylhydroxylamine, 1,13-tetradecadiene and 3-iodopyridine, all of which are readily available (Scheme 4). Since *N*,*O*-dimethylhydroxylamine is only commercially available as the hydrochloride salt, a base is needed in the reaction system to release the hydroxylamine. After optimization work on model systems, the coupling of 3-iodopyridine, 1,13-tetradecadiene and the hydrochloride salt of *N*,*O*-dimethylhydroxylamine provided the desired coupling product **18a**, alongside a small amount of an isomer **18b**, in 45% overall yield. The efficient catalytic room temperature hydrogenation of this mixture afforded xestamine D (**7**) and its branched isomer **19** in a 91:9 ratio in 94% overall yield.



Scheme 3.



Scheme 4.

Acknowledgements

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