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An Efficient Two-Step Total Synthesis of the Quaterpyridine Nemertelline

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Received June 11, 2003

Abstract: Regioselective and univocal Suzuki cross-coupling reactions performed on halopyridinyl boronic acids provide a flexible and versatile route to a multigram scale synthesis of 2,2′-dichloro-3,4′-bipyridine **14**, which allows couplings with excess pyridin-3-yl boronic acid to give a new and efficient two-step rapid synthesis of nemertelline, the quaterpyridine neurotoxin isolated from a Hoplonemertine sea worm.

Pyridine-based neurotoxic substances have been isolated from the phylum of marine worms called nemertines.[1] Extracts from the Hoplonemertine *Amphiporus angulatus* contain anabaseine (3,4,5,6-tetrahydro-2,3′-bipyridine), 2,3′-bipyridine, and a quaterpyridine named nemertelline (3,2′:3′,2″:4″,3‴-quaterpyridine, **1**)[2] whose structure was not easy to determine. The structure originally proposed by Kem et al. in 1976 was revised in 1995 by Cruskie et al.[3] to the correct structure of **1** (Figure 1).[4] For in vitro and in vivo testing on nicotinic receptors, larger quantities of **1** were required.

The overall strategy of Cruskie allowed the synthesis and the whole spectral characterization of nemertelline. However, some aspects of this synthesis seem problematic to us: (i) the use of tin derivatives generates prohibitive toxic wastes and traces, (ii) the regioselectivity for the synthesis of bipyridine **7** is somewhat difficult to control, (iii) the use of pyridin-3-yldiethylborane is not satisfactory in terms of handling of materials and optimization of the reaction,[5] (iv) the whole synthesis is complex, (v) overall yield of this convergent synthesis is low (40% calculated on **6** and 34% calculated on **2**, respectively), and (vi) the synthesis is only described on a milligram scale (Scheme 1).

Faced with the difficulties above and experienced in the synthesis of halopyridinyl boronic acids and in their multiple possibilities in Suzuki[6] cross-coupling reactions, we decided to set up an "all-Suzuki" synthesis. Among many strategies that could be envisaged, some are presented here.

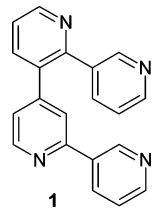

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FIGURE 1. Correct structure of nemertelline, as proven by Cruskie et al. in 1995.

An all-Suzuki version of Cruskie's synthesis, although avoiding several of the problems discussed above, was not attempted because of the limited access to the required bipyridine boronate **I**[7,8] and the lack of synthetic flexibility to generate molecular diversity (Scheme 2).

As some results concerning selective C(2) lithiation of 3- and 4-chloropyridine rings have recently been described by Fort et al.,[9] we have attempted the synthesis of chlorinated derivatives of **IV**, following their procedure. However, we did not manage to obtain the desired boronic derivatives at all, probably because of the instability of pyridin-2-yl boron derivatives.[10]

The last approach, which will appear to be obviously the best, is a disconnection of the two pyridin-3-yl extremities of **1**. Thus the resulting synthetic approach becomes a one-step [2 + (1 + 1)] method (Scheme 3).

In this case, the key component is the 2,2′-dihalogeno-3,4′-bipyridinyl moiety **VII**, whose synthesis could be imagined from the adequate halopyridinyl boronic acids we previously described.[11] This strategy has also the advantage to use the same boronic acid in the last step. Further, **VII** could be a very versatile key intermediate to prepare nemertelline isomers or derivatives.

Having recently published the synthesis of a range of pyridinyl boronic acids and esters usable in efficient Suzuki cross-couplings,[11] we realized that the synthesis of nemertelline can come from an inexpensive commercial starting material 3-amino-2-chloropyridine **8** (Scheme 4). Sandmeyer reaction allows the synthesis of 2-chloro-3-iodopyridine **9** and 3-bromo-2-chloropyridine **10**. These

(1) Kem, W. R.; Scott, K. N.; Duncan, J. H. *Experimentia* **1976**, *32*, 684−686.
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(5) Ripin, D. H. EP 1288217 A2, 2003. Ishikura, M.; Kamada, M.; Terashima, M. *Heterocycles* **1984**, *22*, 265−268. Terashima, M.; Kakimi, H.; Ishikura, M.; Kamata, K. *Chem. Pharm. Bull.* **1983**, *31*, 4573−4577.
(6) For recent reviews on uses of Suzuki cross-coupling, see: (a) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633−9695. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (c) Suzuki, A.; Brown, H. C. *Organic Syntheses Via Boranes*; Aldrich Chemical Co.: Milwaukee, WI, 2003; Vol. 3, Suzuki Coupling.
(7) In some extend, Stille cross-coupling can leave boronic esters unchanged, giving oligopyridinyl boronic esters. See: Lehmann, U.; Henze, O.; Schlüter, A. D. *Chem. Eur. J.* **1999**, *5*, 854−859.
(8) Very few reactions involving bipyridines and lithiated bases are known. See: Zoltewicz, J. A.; Dill, C. D. *Tetrahedron* **1996**, *52*, 14469−14474.
(9) (a) Gros, P.; Fort, Y. *Eur. J. Org. Chem.* **2002**, *20*, 3375−3383. (b) Choppin, S.; Gros, P.; Fort, Y. *Eur. J. Org. Chem.* **2001**, *3*, 603−606.
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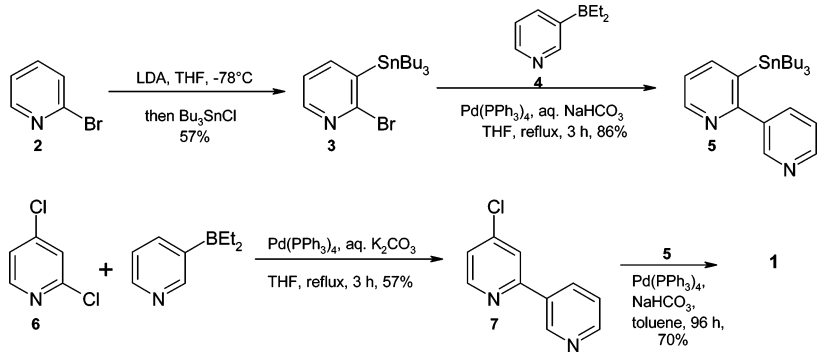
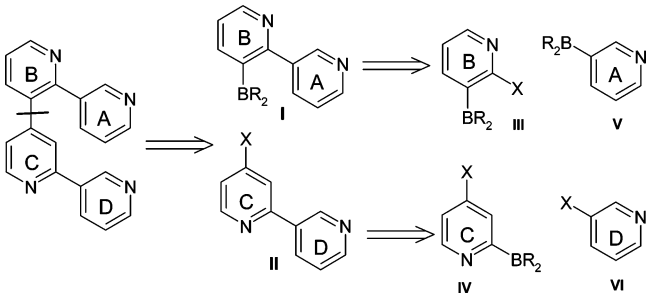
(11) (a) Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 3323−3328. (b) Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 4369−4373.

10.1021/jo034805b CCC: $25.00
Published on Web 11/25/2003

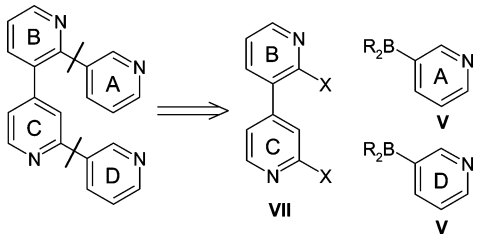
SCHEME 1. Synthesis of Cruskie et al.



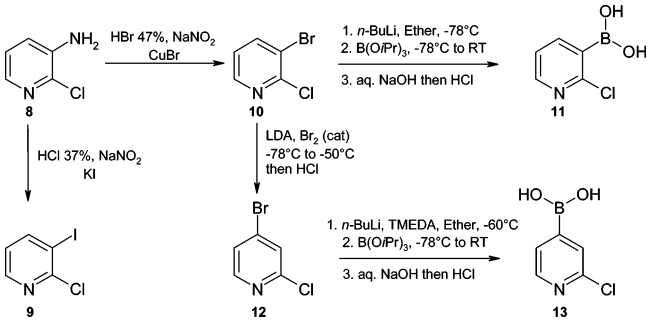
SCHEME 2. [2 + 2] Strategy, a Boron Version of Cruskie's Synthesis



SCHEME 3. [2 + (1 + 1)] Strategy



SCHEME 4. Synthesis of Starting Materials



latter can be subjected to selective halogen−metal exchange followed by triisopropylborate quench to give the corresponding boronic acid **11**.[11]

Dihalogenopyridine **10** can also undergo a regioselective halogen dance to make bromine migrate from the 3- to the 4-position allowing a facile synthesis of 4-bromo-2-chloropyridine **12** following a reported procedure.[12] Selective halogen−metal exchange using *n*-BuLi−TMEDA chelate[13] provided cleanly boronic acid **13**.[11]

Newly, these boronic acids **11** and **13** are commercially available. Another aspect of their potential stands in their clean coupling ability, very recently exploited by two groups[14,15] who have highlighted that no reactivity of halogen of halopyridinyl boronic acids or esters was observed.

Thus, we have been able to prepare efficiently, on a multigram scale, the key component 2,2′-dichloro-3,4′-bipyridine **14**. Its structure has been confirmed univocally by two different syntheses (Scheme 5). The first route was a Suzuki cross-coupling of 4-bromo-2-chloropyridine **12** with 2-chloropyridin-3-yl boronic acid **11**. The target compound **14** was obtained exclusively after refluxing for 18 h with aqueous sodium carbonate as a base and catalytic amounts of $Pd(PPh_3)_4$ in 1,4-dioxane. The 4-position is more reactive toward nucleophilic substitution, because the bromine atom exhibits a greater ability to undergo oxidative addition than the chlorine atom.

The second route consisted of a Suzuki cross-coupling of 2-chloro-3-iodopyridine **9** with 2-chloropyridin-4-yl boronic acid **13**. This reaction led also unambiguously to compound **14**, thus confirming the selectivity of our first coupling reaction, as well as the structure of **14** to be 2,2′-dichloro-3,4′-bipyridine. Again, obviously no coupling occurs on the chlorine atoms, because of the much higher reactivity of the other halogen in this Suzuki cross-coupling reaction.

The results of some comparative attempts are not so different to definitively choose one or another method for the synthesis of **14**. Both are efficient and high-yielding, affording only the desired compound with limited purification step.

With key component **14** in hand, we were finally able to prepare nemertelline in only one step. On one hand, it has been reported that 2-chloro-pyridines can be good substrates in Suzuki cross-coupling because of the π-deficiency of these heteroaromatics.[16] On the other hand, pyridin-3-yl boronic acid **15** is commercially available, but

(12) For recent use of halogen dance in total synthesis of natural compounds, see: Sammakia, T.; Stangeland, E. L.; Whitcomb, M. C. *Org. Lett.* **2002**, *4*, 2385−2388. For mechanistic studies and synthesis of 2,4-dihalogenopyridines, see: (a) Mallet, M. Quéguiner, G. *Tetrahedron* **1985**, *41*, 3433−3340. (b) Mallet, M. Quéguiner, G. *Tetrahedron* **1986**, *42*, 2253−2262.

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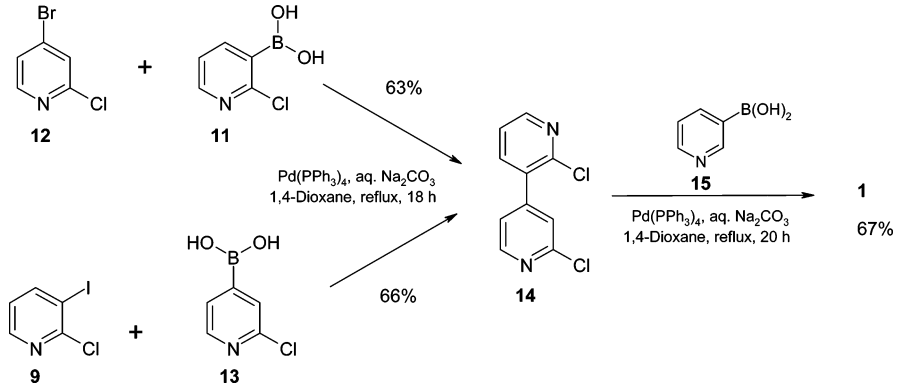
SCHEME 5. Total Synthesis of Nemertelline



it is expensive (>$100/g) and often only small quantities can be obtained. To solve this problem, Cai et al. have recently reported an effective protocol for the synthesis of **15**.[17a] This reaction was then modified in a Barbier-type procedure.[17b]

However, concomitantly to these works, we prepared pure pyridin-3-yl boronic acid **15** using the conventional method. Slight modification of Cai's methods (*n*-BuLi, toluene, −50 °C) using ether as the solvent at −60 °C gave pure pyridin-3-yl boronic acid **15** in 79% yield. Finally, the Suzuki cross-coupling of **14** with an excess of **15** under optimized conditions (1,4-dioxane, aqueous sodium carbonate, $Pd(PPh_3)_4$, reflux, 20 h) gave nemertelline in good yields. The oil isolated after purification by column chromatography slowly crystallized to a solid with satisfactory analytical data. Overall yield from now commercially available dihalogenopyridines **9** or **12** and halogenopyridinyl boronic acids **11** or **13** is 42−44% for two steps.

Using this very versatile methodology, we are now working to produce new derivatives of nemertelline.

Experimental Section

Representative Cross-Coupling Procedure. A mixture of 4-bromo-2-chloropyridine **12** (2.7 g, 14 mmol), 2-chloropyridin-3-yl boronic acid **11** (1.68 g, 1.1 equiv) and tetrakis(triphenylphosphine)palladium(0) (0.405 g, 0.025 equiv) are dissolved in 100 mL of 1,4-dioxane. After 10 min of stirring, aqueous sodium carbonate (1.854 g, 2.5 equiv/acid) is added. The mixture is gradually heated to reflux and allowed to react for 18 h (the end of the reaction is visualized with TLC). After cooling to room temperature, the mixture is poured into an Erlenmeyer flask containing 500 mL of a 1:1 mixture of water/ethyl acetate. The organic layer is removed, and the aqueous layer is further extracted with 50 mL of ethyl acetate twice. The combined organic layers are dried over $MgSO_4$, filtered, and concentrated to dryness. The residue is crystallized from diethyl ether and can be used without further purification.

2,2′-Dichloro-3,4′-bipyridine (14). Beige solid (66%), mp 153 °C. IR (KBr): 3433, 3050, 1560, 1374, 1093, 807, 678 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.50 (m, 2H, H_6, $H_{6'}$), 7.68 (dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.9 Hz, 1H, H_4), 7.44 (d, $^4J_{HH}$ = 1.4 Hz, 1H, $H_{3'}$), 7.39 (dd, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 4.8 Hz, 1H, H_5), 7.35 (dd, $^3J_{HH}$ = 5.0 Hz, $^4J_{HH}$ = 1.4 Hz, 1H, H_4). MS ($CDCl_3$) 224−226−228 [$M^{+\cdot}$], 189−191 [M^+ − Cl], 153 [M^+ − 2Cl].

3,2′:3′,4″:2″,3‴-Quaterpyridine Nemertelline (1). Following the representative general procedure for Suzuki cross-coupling, 1.0 g of **14** is reacted with 2.40 g of **15** (2.2 equiv/chlorine to be exchanged) in the presence of $Pd(PPh_3)_4$ (0.257 g, 0.05 equiv) and aqueous Na_2CO_3 (2.5 equiv/acid). The mixture is then refluxed for 20 h and treated as described in the representative procedure. The crude product is purified by column chromatography, with a gradient of solvent from 80/20 cyclohexane/AcOEt to 80/20 AcOEt/MeOH, giving 0.924 g of an oil that slowly crystallized on standing. Beige solid (67%), mp 155 °C. IR (KBr): 1600, 1589, 1574, 1537, 1453, 1428, 1412, 1390, 1190, 1011, 818, 778, 718, 616 cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.00 (s, 1H), 8.83 (d, J_{HH} = 4.1 Hz, 1H), 8.66 (d, J_{HH} = 4.9 Hz, 1H), 8.64−8.62 (m, 2H), 8.56 (d, J_{HH} = 4.3 Hz, 1H), 8.18 (d, J_{HH} = 7.9 Hz, 1H), 7.85 (d, J_{HH} = 7.6 Hz, 1H), 7.78 (d, J_{HH} = 7.9 Hz, 1H), 7.56 (s, 1H), 7.49 (dd, J_{HH} = 4.8 Hz, J_{HH} = 7.6 Hz, 1H), 7.38 (dd, J_{HH} = 4.8 Hz, J_{HH} = 7.7 Hz, 1H), 7.27 (dd, J_{HH} = 5.0 Hz, J_{HH} = 7.9 Hz, 1H), 7.14 (d, J_{HH} = 4.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 155.21, 154.02, 150.53, 150.27, 150.08, 149.93, 149.29, 148.10, 148.06, 138.22, 136.98, 134.89, 134.26, 134.22, 133.62, 123.49, 123.20, 122.99, 122.92, 121.11. HRMS (EI, 70 eV) calcd for $C_{20}H_{14}N_4$ 310.12183, found 310.12181.

Acknowledgment. Mélanie Celant is gratefully acknowledged for a helpful synthetic hand. The authors thank Conseil Régional de Basse-Normandie and FEDER (Fonds Européens de Développement Economique Régional) for their financial support.

JO034805B

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