Total Synthesis of Horsfiline: A Palladium-Catalyzed Domino Heck-Cyanation Strategy

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Received 20 July 2009

Abstract: A total synthesis of horsfiline has been accomplished featuring a key intramolecular palladium-catalyzed domino Heck–cyanation sequence for the formation of the 3,3′-disubstituted oxindole.

Key words: domino reaction, palladium, Heck, cyanation, oxindole, horsfiline

The spiropyrrolidinyloxindole skeleton is present in a growing number of natural products presenting various biological activities.[1] This class of compound can be as simple as elacomine (**1**)[2] or present additional structural complexity as in spirotryprostatine A (**2**)[3] or alstonisine (**3**)[4] (Figure 1). The stereogenic quaternary spiro center is usually well defined, but some natural compounds have been isolated as racemate.[5] It has also been established that both enantiomers of some synthetic analogues of **2** presented biological activities with equal potency.[6]

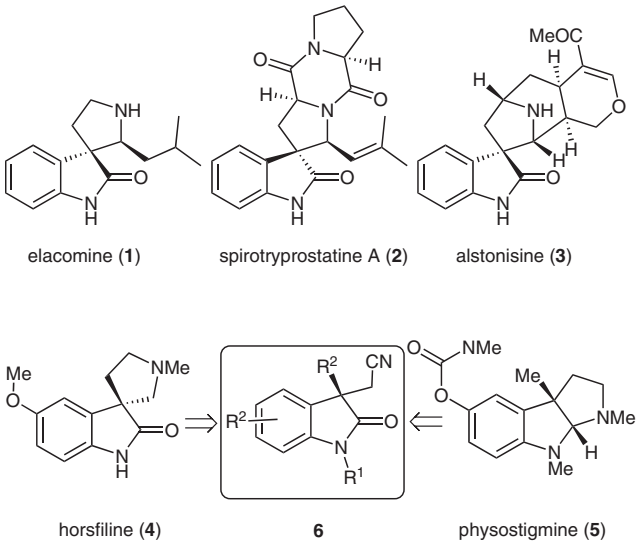


Figure 1 Examples of naturally occurring spiroxoindoles

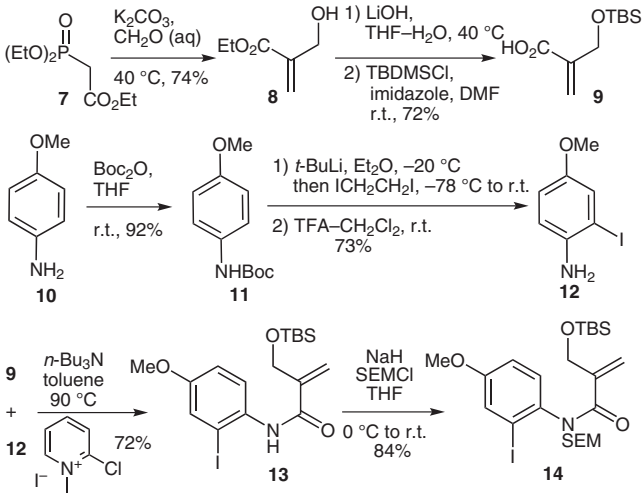
Horsfiline (**4**) is an oxindole alkaloid isolated from the roots of *Horsfieldia superba* by Bodo and co-workers.[7] Due to its structural simplicity, it has often been targeted to illustrate the power of novel synthetic methodologies/strategies and indeed a number of total synthesis have been accomplished to date.[8]

As part of our interest in developing novel approaches to indolinones based on transition-metal-catalyzed transformations[9] and domino processes,[10,11] we have recently reported a facile access to functionalized 3-alkyl-3-cyanomethyl-2-oxindole **6** by a palladium-catalyzed domino intramolecular Heck–cyanation process.[12] In this transformation, the nontoxic potassium ferro(II)cyanide, $K_4[Fe(CN)_6]$, was used as a cyanide source to trap the σ-alkylpalladium intermediate.[13] This strategy allowed us to develop a concise total synthesis of physostigmine (**5**). Based on the same strategy, we report herein a total synthesis of horsfiline (**4**).

Our synthesis began with the preparation of protected α-hydroxymethylacrylate **9**. The Baylis–Hillman reaction between acrylate and formaldehyde was initially examined for the synthesis of hydroxymethylacrylate **8**.[14] However, the yield of **8** never exceeded 35%. Alternatively, reaction of triethyl phosphonoacetate with formaldehyde in the presence of potassium carbonate following a procedure described by Villieras et al. provided **8** in a reliable 74% yield.[15] Hydrolysis of the ester (LiOH, THF–H_2O) followed by protection of the primary alcohol as a *tert*-butyldimethylsilyl ether afforded compound **9** in 72% yield. On the other hand, double deprotonation of *N*-Boc *p*-anisidine **11**, prepared in 92% yield from *p*-anisidine (**10**), with *t*-BuLi followed by addition of 1,2-diiodoethane and removal of *N*-Boc under mild acidic conditions afforded the desired iodide **12** in 67% yield over three steps.[16] Coupling of **9** and **12** was best realized in the presence of Mukaiyama's reagent (2-chloro-*N*-methyl pyridinium iodide, tributylamine in refluxing toluene)[17] to afford the desired amide **13** in 74% yield. Finally, protection of the secondary amide **13** with SEM group afforded the *ortho*-iodoanilide **14** in 84% yield (Scheme 1).

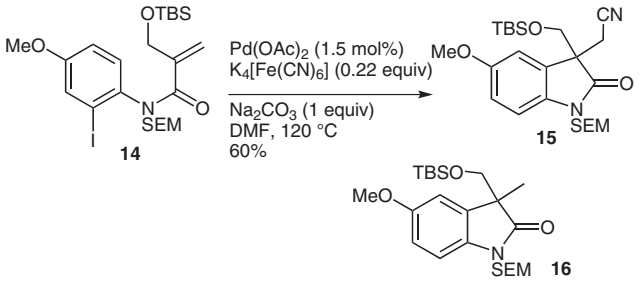
With the properly functionalized amide in hand, we set out to examine the pivotal domino Heck–cyanation reaction. When *ortho*-iodoanilide **14** was submitted to previously established reaction conditions {$Pd(OAc)_2$ (1.5 mol%), $K_4[Fe(CN)_6]$ (0.22 equiv), Na_2CO_3 (1 equiv), DMF, 120 °C}, we were delighted to isolate the desired oxindole **15** in 60% yield (Scheme 2).[18] Three points deserved further comment regarding this transformation: 1) by-product **16**, which could be easily separated from **15**,

SYNLETT 2009, No. 18, pp 2997–2999
Advanced online publication: 08.10.2009
DOI: 10.1055/s-0029-1218004; Art ID: G23709ST



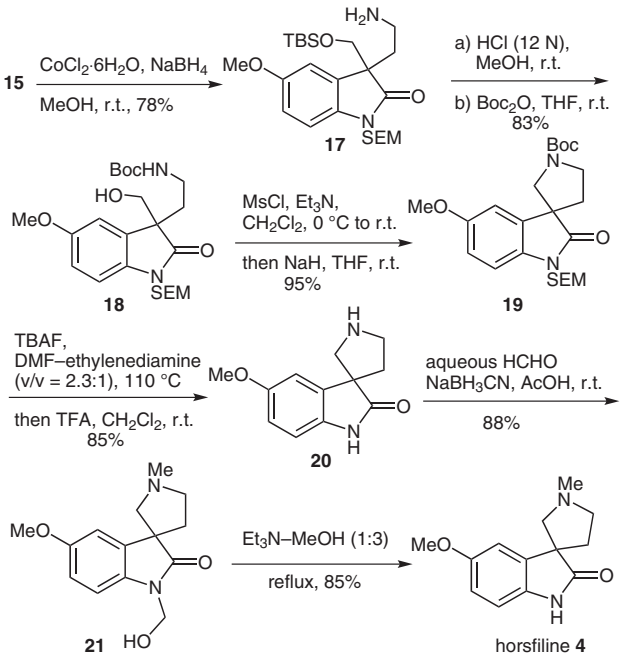
Scheme 1 Synthesis of *ortho*-iodoanilide **14**

was isolated in 20% yield. This compound probably arises from the reduction of the intermediate σ-alkylpalladium.[19] It is well known that DMF decomposes to some extent under thermal conditions furnishing dimethylamine, which could then reduce the σ-alkylpalladium intermediate.[20] 2) Protection of the hydroxyl group was mandatory in this transformation as extensive degradation was observed otherwise. 3) Attempted enantioselective Heck–cyanation of **14** under our previously established conditions [$Pd(dba)_2$ (0.05 equiv), (*S*)-difluorophos (0.12 equiv), Ag_3PO_4 (2.0 equiv), K_2CO_3 (1.0 equiv), $K_4[Fe(CN)_6]$ (0.22 equiv)] afforded **15** in low yield and negligible ee. It is interesting to note that the related *N*-methyl anilide cyclized to afford the oxindole in 78% yield with 72% ee.[12] The presence of chelating *N*-SEM group had apparently negative impact on the reaction outcome under these conditions.



Scheme 2 Palladium-catalyzed domino Heck–cyanation for the construction of oxindole

Construction of the pyrrolidine ring was next undertaken. Selective reduction of the nitrile function in **15** ($CoCl_2·6H_2O$, $NaBH_4$, MeOH, r.t.)[21] afforded amine **17** in 78% yield. Removal of *O*-TBS protecting group from **17** under acidic conditions afforded the amino alcohol in quantitative yield. Direct cyclization of this amino alcohol using Appel's conditions (CBr_4, PPh_3)[22] was sluggish and we therefore adopted a three-step sequence. A *tert*-butyloxycarbonylation of the primary amine under standard conditions afforded **18**. Treatment of **18** with methanesulfonyl chloride (MsCl, Et_3N, CH_2Cl_2) afforded the corresponding mesylate, which without purification was cyclized upon treatment with NaH in THF to afford the spirooxindole **19** in 95% yield. This advanced intermediate has been converted by Murphy et al. to horsfiline in three steps with 41% overall yield.[8m] However, removal of the Boc protecting group (the first step) was low yielding in their synthesis. We therefore slightly modified the reaction sequence. Removal of the *N*-SEM group (TBAF in DMF–ethylenediamine at 110 °C, 24 h) followed by deprotection of the *N*-Boc function afforded compound **20** in 85% yield. To complete the synthesis, a selective methylation of the secondary amine over the amide functionality had to be effected. This reaction proved to be more difficult than expected. After having examined a variety of methylation conditions, it was finally realized in two steps. Treatment of **20** with an excess of formaldehyde in acetic acid in the presence of $NaBH_3CN$ furnished **21** (88% yield) in which the secondary amine was *N*-methylated whereas the secondary amide was hydroxymethylated. Hydrolysis of the hemiaminal function under basic reaction condition (Et_3N, MeOH) afforded the horsfiline (**4**) in 85% yield (Scheme 3). Thus, we were able to convert the compound **19** into **4** in 64% overall yield which appears to be more efficient than the literature procedure.



Scheme 3 Total synthesis of horsfiline

In conclusion, we have reported a total synthesis of horsfiline featuring a key palladium-catalyzed domino intramolecular Heck–cyanation sequence. This work further demonstrated the synthetic potential of oxindole of general structure **6** which is readily prepared in one step from simple anilides by a palladium-catalyzed domino sequence.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

Financial support from the CNRS and the Bayer CropScience (Doctoral fellowship to S.J.) is gratefully acknowledged.

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(18) **Experimental Procedure**: To a degassed solution of iodoanilide **14** (1.90 g, 3.29 mmol, 1.0 equiv) in DMF (16 mL) were added $K_4Fe(CN)_6{\cdot}3H_2O$ (306.0 mg, 0.72 mmol, 0.22 equiv), Na_2CO_3 (350.0 mg, 3.30 mmol, 1.0 equiv) and $Pd(OAc)_2$ (22.0 mg, 0.1 mmol, 0.03 equiv). After being stirred at 120 °C under an argon atmosphere for 3 h, the reaction mixture was quenched with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, heptane–EtOAc, 95:5 → 90:10) to give the corresponding oxindole **15** (0.94 g, 60%) as a light orange solid.
Compound **15**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.06 (d, *J* = 2.6 Hz, 1 H), 7.02 (d, *J* = 8.6 Hz, 1 H), 6.88 (dd, *J* = 8.6, 2.6 Hz, 1 H), 5.17 (d, *J* = 11.0 Hz, 1 H), 5.11 (d, *J* = 11.0 Hz, 1 H), 3.92 (d, *J* = 9.7 Hz, 1 H), 3.80 (s, 3 H), 3.73 (d, *J* = 9.7 Hz, 1 H), 3.62–3.51 (m, 2 H), 3.02 (d, *J* = 16.7 Hz, 1 H), 2.79 (d, *J* = 16.7 Hz, 1 H), 0.92 (t, *J* = 8.2 Hz, 2 H), 0.84 (s, 9 H), 0.00 (s, 3 H), –0.01 (s, 3 H), –0.03 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.4, 156.4, 135.4, 129.1, 116.2, 114.3, 111.2, 110.6, 69.9, 66.5, 66.1, 55.8, 51.9, 25.7, 21.7, 18.1, 17.7, –1.4, –5.6, –5.7. HRMS (ES+): *m/z* $[M + Na]^+$ calcd for $C_{24}H_{40}N_2O_4Si_2Na$: 499.2424; found: 499.2415.

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