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SHORT SYNTHESIS OF AZAFLUORENONE ALKALOIDS USING TRANSITION METAL-CATALYZED CROSS COUPLING TACTICS

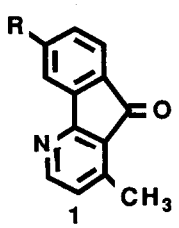
T. Alves,[1] A.B. de Oliveira,[1] and V. Snieckus*

Guelph-Waterloo Centre for Graduate Work in Chemistry

University of Waterloo, Waterloo, Ontario Canada N2L 3G1

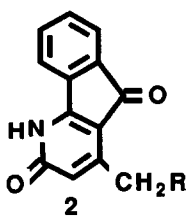
Summary: An efficient route to the azafluorenone alkaloids, onychine **(1a)** and 6-methoxyonychine **(1b)** based on Pd(0)-catalyzed cross coupling of arylboronic acids **4a, 4b** and arylstannane **4c** with a bromonicotinate ester **5** is described.

The 4-azafluorenone alkaloids **1** and **2** comprise a small but biogenetically intriguing group of alkaloids isolated from Brazilian *(Onychopetalum amazonicum, Guatteria dielsiana)* and African *(Cleistopholis patents)* **Annonaceae** species [2,3]. Together with the unique eupolauridine **(3)**, obtained from a botanically related **Eupomatiaceae** species [4] and two azaanthraquinones [2b], this class of alkaloids is speculated to be derived from aporphine precursors [2b]. Subsequent to an initial misassignment [2a], the structures of onychine and 6-methoxyonychine have been confirmed by synthesis in very low yield [3,5,6]. Unaware of its natural product stature, Taylor and co-workers prepared [4] onychine (< 5% yield) as an intermediate en route to eupolauridine. Herein we report a short and efficient synthesis of both alkaloids **1a** and **1b** as part of our inceptive efforts to develop the utility of the transition metal catalyzed cross coupling tactic [7] in natural product synthesis.



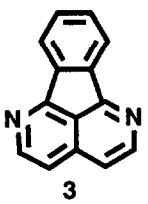
1

a: R=H (onychine)
b:R=OMe (6-OMe-onychine)



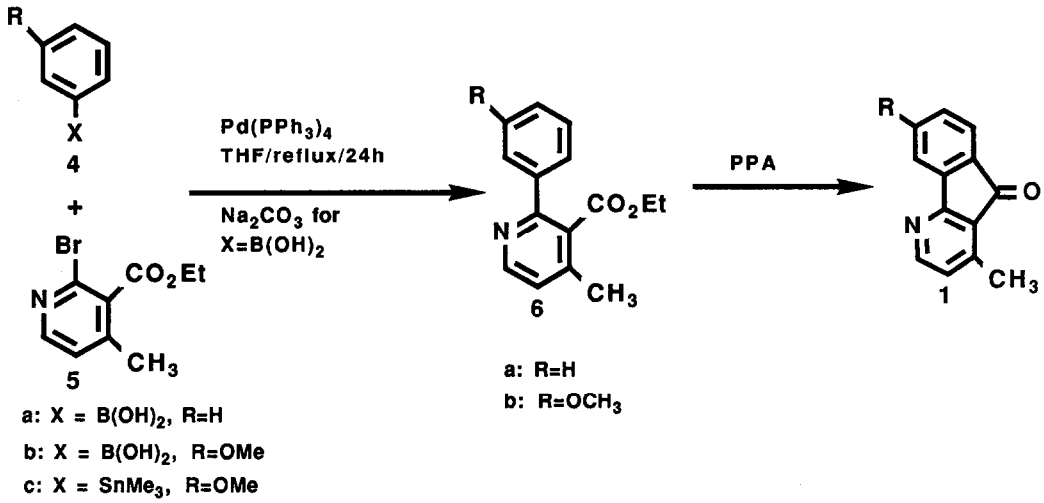
2

a: R=H (dielsine)
b:R=OH (dielsinol)



3

Commercial phenylboronic acid **4a** was coupled with the readily available bromonicotinic ester **5**, [8] using the previously established conditions [7,9a] to give the heterobiaryl **6a** in 58% yield [9b] which upon cyclization with



a: X = $B(OH)_2$, R=H

b: X = $B(OH)_2$, R=OMe

c: X = $SnMe_3$, R=OMe

a: R=H

b: $R=OCH_3$

polyphosphoric acid [6] provided onychine (80% yield) [10]. Similarly, coupling of m-methoxyphenylboronic acid **(4b)**[11] with **5** afforded **6b** (82% yield) [9b] which upon PPA cyclization led to 6-methoxyonychine (80% yield) [10]. The recent observations concerning the efficiency of heteroarylstannane-aryl halide couplings [12] gave impetus to attempt coupling reactions of **5** with the stannane **4c** [11]. Under the same conditions except excluding Na_2CO_3, the reaction proceeded more smoothly than that using **4b** and led to **6b** in 94.5% yield [9b].

In summary, the azafluorenone alkaloids **1a** and **1b** have been obtained in 27% and 44% overall yields, significant improvements over the previous routes [3,5]. In addition, the new synthesis of **1a** enhances the efficiency of the reported preparation of eupolauridine **(3)**. [4,13,14]

References and Footnotes

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9. a) An improvement in the yield of **6b** was achieved by refluxing a THF solution of **4b** and **5** and $Pd(PPh_3)_4$ for 1 h before adding aq Na_2CO_3 and then refluxing for a further 24 h. b) Yield is based on recovered **5**.
10. **1a**: mp 126-127°C; lit [2a] mp 133-135°C; NMR spectrum identical with that reported; [2a] **1b**: mp 95-98°C; lit [2a,3] gum; NMR specturm identical with that reported. [2a,3]
11. Prepared by metal-halogen exchange and treatment with $B(OMe)_3$/HCl or $(Me)_3SnCl$, see Jones, R.G.; Gilman, H. Org. React., **1951**, 6, 339.
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13. All new compounds shown analytical and spectral (IR, NMR, MS) data consistent with the indicated structures.
14. We are grateful to NSERC Canada and Merck Frosst Inc. for financial support. T. Alves is indebted to CAPES for a scholarship and material support for this work which was carried out at the University of Waterloo. We appreciate advice from Dr. Ponticello regarding the synthesis of **5**.

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