

SHORT SYNTHESIS OF AZAFLUORENONE ALKALOIDS USING TRANSITION METAL-CATALYZED

CROSS COUPLING TACTICS

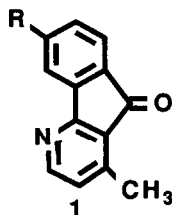
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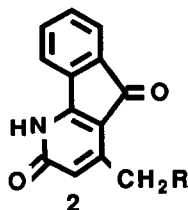
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Summary: An efficient route to the azafluorenone alkaloids, onychine (**1a**) and 6-methoxyonychine (**1b**) based on Pd(0)-catalyzed cross coupling of arylboronic acids **4a**, **4b** and arylstannane **4c** with a bromonicotinic ester **5** is described.

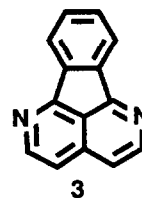
The 4-azafluorenone alkaloids **1** and **2** comprise a small but biogenetically intriguing group of alkaloids isolated from Brazilian (*Onychopetalum amazonicum*, *Guatteria dielsiana*) and African (*Cleistopholis patens*) **Annonaceae** species **2,3**. Together with the unique eupolauridine (**3**), 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.



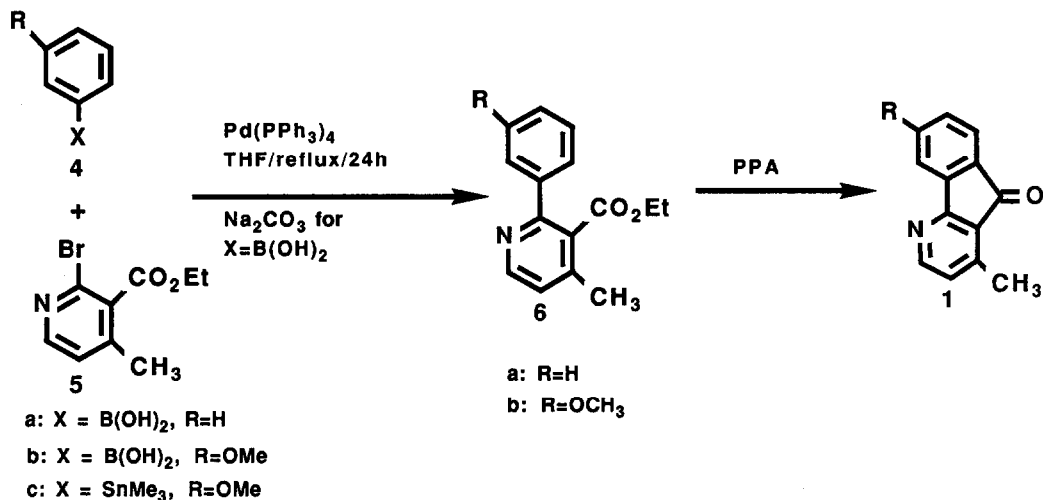
a: R=H (onychine)
b: R=OMe (6-OMe-onychine)



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



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



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 couplings¹² 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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- a) An improvement in the yield of **6b** was achieved by refluxing a THF solution of **4b** and **5** and $\text{Pd}(\text{PPh}_3)_4$ for 1 h before adding aq Na_2CO_3 and then refluxing for a further 24 h. b) Yield is based on recovered **5**.
- 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 spectrum identical with that reported. **2a**,³
- Prepared by metal-halogen exchange and treatment with $\text{B}(\text{OMe})_3/\text{HCl}$ or $(\text{Me})_3\text{SnCl}$, see Jones, R.G.; Gilman, H. *Org. React.*, **1951**, *6*, 339.
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- All new compounds shown analytical and spectral (IR, NMR, MS) data consistent with the indicated structures.
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