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An Original One-Pot Synthesis of 5-(4-Pyridyl)-Benzo[c]-2,7-Naphthyridine as Key Intermediate in the Synthesis of Amphimedine by Metalation Connected with Cross-Coupling Reaction.

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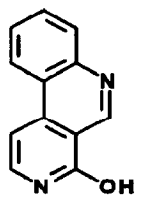
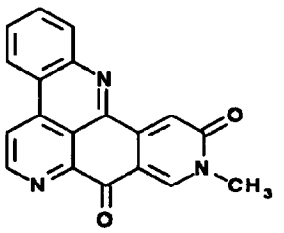
Abstract : A short new route to 4,5-disubstituted-benzo[c]-2,7-naphthyridines has been developed. The strategy involves directed ortho metalation of pyridines following by an halogen dance reaction and biaryl cross-coupling as key steps. A concise and efficient one-pot synthesis of 4-chloro-5-(4-pyridyl)-benzo[c]-2,7-naphthyridine, as a key intermediate in the synthesis of amphimedine is described.

A wide range of polycyclic alkaloids which contain a common benzo[c]-2,7-naphthyridine structure have been isolated, during the last ten years, from marine organisms.[1] A general and efficient methodology using metalation in connection with cross-coupling reaction has been developed in our laboratory for the synthesis of natural products.[2] In the benzo[c]-2,7-naphthyridine series, we synthesized perlolidine **1**.[3] Gronowitz has recently published a synthesis of some benzo[c]-2,7-naphthyridines.[4] This prompted us to report the synthesis of the 5-(4-pyridyl)-benzo[c]-2,7-naphthyridine ring system, a subunit of two marine alkaloids : amphimedine **2** and petrosamine **3**.



1



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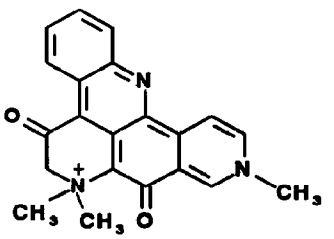
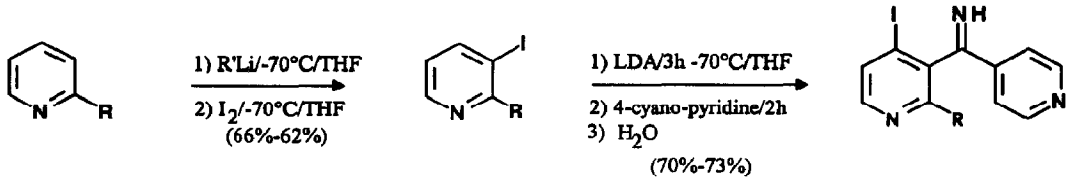


3

2-Chloro and 2-diisopropylcarboxamido-3-iodopyridine **5a** and **5b** are readily prepared from the corresponding 2-substituted pyridines **4a** and **4b** by a metalation iodination sequence.[5,3] Metalation of iodopyridines **5a** and **5b** with LDA is successfully performed at -75°C. Lithiation is ortho directed by the iodo group wich subsequently ortho migrates to give the more stabilized 2-substituted-3-lithio-4-iodo-pyridine. The lithiated product was quenched with an electrophile to provide imines **6a** and **6b** in high yields. (70% and 73% respectively).

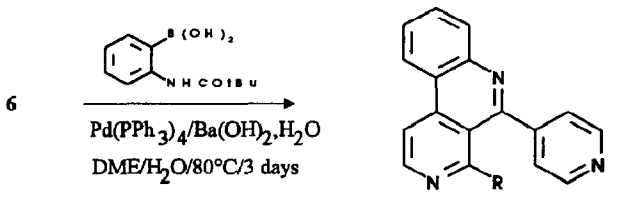


4a R=Cl
4b R=CONiPr_2

5a R=Cl
5b R=CONiPr_2

6a R=Cl
6b R=CONiPr_2

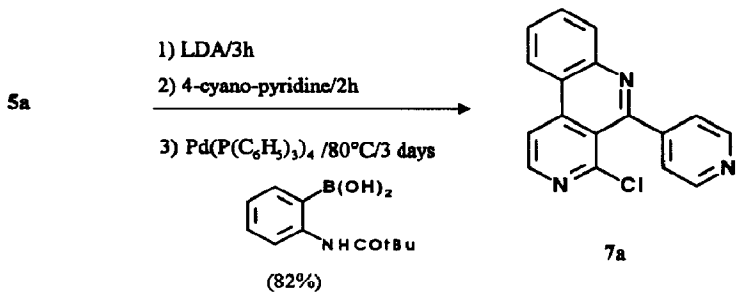
This convenient synthesis of 4-iodopyridine derivatives is followed by cross-coupling reaction with aryl boronic acid under Suzuki's procedure.[6] In these conditions, a spontaneous cyclisation afforded the target system. 4-chloro-5-(4-pyridyl)-benzo[c]-2,7-naphthyridine **7a** and 4-diisopropylcarboxamido-5-(4-pyridyl)-benzo[c]-2,7-naphthyridine **7b** are thus obtained in good overall yields : 33% and 37% starting from the monosubstituted pyridines.



7a R = Cl
7b R = CONiPr_2

It should be noted that amphimedine can be obtained via Prager's route[7] from **7a**. The latter compound **7a** has been obtained by Prager in five steps via a totally different route from an acetophenone derivative in 25% overall yield. For this reason we carefully studied the synthesis of compound **7a**[8] by our methodology.

We found that the overall yield could be greatly improved if the reactions were carried out by a one-pot procedure.[9] Metalation, isomerisation, cross-coupling and cyclisation were performed without isolation of any intermediate products. Cross-coupling was carried out after addition of 4-cyano-pyridine and hydrolysis by addition of $Pd(P(C_6H_5)_3)_4$ and aryl boronic acid. It is noteworthy that the coupling reaction of a iodopyridine and phenylboronic acid takes place in different conditions from that usually described.



3,4-Disubstituted-benzo[c]-2,7-naphthyridine is thus conveniently and rapidly obtained through a metalation and cross-coupling one-pot reaction. Generalization of this strategy to marine alkaloids synthesis promises overall advantages compared to classical methods. The synthesis of alkaloids of this series was hence carried out using the methodology described in this paper.

References and Notes

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8 **7a** : ^{1}H NMR ($CDCl_3$) δ 7.50 (2H, dd, J=1.5Hz J'=4.5Hz, H-3', H-5'), 7.79 (1H, dt, J=1.5Hz J'=5.5Hz, H-9), 7.92 (1H, dt, J=1.5Hz J'=8Hz, H-8), 8.24 (1H, dd, J=1.5Hz J'=8Hz, H-7), 8.45 (1H, d, J=5.5Hz, H-1), 8.55 (1H, dd, J=1.5Hz J'=5.5Hz, H-10), 8.70 (1H, d, J=5.5Hz, H-2), 8.76 (2H, dd, J=1.5Hz J'=4.5Hz, H-2', H-6'); mp 236°C; EI M^+=291/293

9. General reaction procedure : 2-Chloro-3-iodo-pyridine 5a (2.09 mmol) in THF solution (5 ml) was slowly added to a cold (-75°C) solution of LDA (2.3 mmol) in THF (10 ml). The resulting mixture was stirred for 3h at -75°C before addition of 4-cyano-pyridine (2.95 mmol) in THF solution (5 ml). Stirring was continued for 2h at the same temperature before hydrolysis at -75°C by water (3 ml). The mixture is stirred and argon is bubbled 1h at room temperature. $Pd(P(C_6H_5)_3)_4$ (5% mol) and aryl boronic acid (2.3 mmol) were added and the mixture was warmed at 80°C for 72h. After 48h a further addition of $Pd(P(C_6H_5)_3)_4$ (3% mol) and aryl boronic acid (0.21 mmol) was performed. Cooling, filtration, extraction with dichloromethane, drying over $MgSO_4$, and solvant removal afforded a crude product which was purified by flash chromatography on silica gel (ether).

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