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Convenient preparation of naphthyridines from halopyridines: sequential Heck coupling and cyclization

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Abstract—A simple method for the preparation of 1,7-naphthyridine and 1,6-naphthyridine from the corresponding aminopyridine starting materials is presented. © 2001 Elsevier Science Ltd. All rights reserved.

The *cis*-decalin scaffold had been identified as a flexible framework for the construction of a wide variety of interesting chiral ligands including diamines, diols, amino alcohols, phosphites and phosphines.[1] C_2-Symmetric 1,5-diaza-*cis*-decalin **2** and derivatives have been prepared, resolved, and employed in asymmetric lithiation/substitution reactions[2] and asymmetric oxidative biaryl coupling reactions.[3] As a continuation of our efforts in this area, we would like to investigate the conformational and ligand properties of non-C_2-symmetric diaza-*cis*-decalins such as 1,7-diaza-*cis*-decalin **4**[4] and 1,6-diaza-*cis*-decalin **6**. The most straightforward preparation of **4** and **6** would be by hydrogenation of the corresponding aromatic naphthyridines **3** and **5**, respectively following the procedure used to prepare **2** from **1** (Fig. 1). As such, efficient syntheses of **3** and **5** were sought.

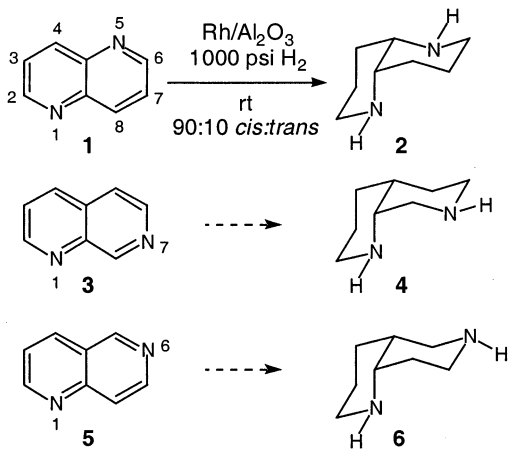
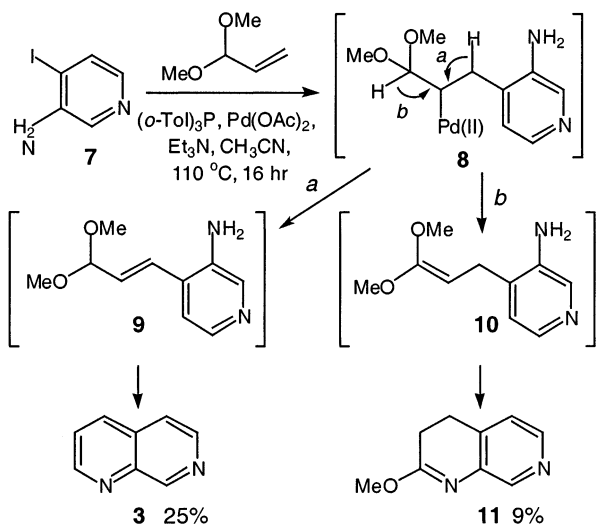


Figure 1.

Although **3**[5] has been prepared by various methods, most procedures were lengthy and low yielding. The synthesis by Giam[6] is short and high yielding, but produces a mixture of **3** and **5**. Furthermore, the starting material 2,3-cyclopentenopyridine is no longer commercially available. Colandrea[7] recently reported a selective seven-step synthesis of **3**; however, stoichiometric amounts of organotin materials are required. Herein, a new facile preparation of this seemingly uncomplicated heterocycle is reported.

We envisioned that **3** could arise from a 3-amino-4-iodo-pyridine **7**[8] and an acrolein equivalent via a Heck



Scheme 1.

Keywords: 1,7-naphthyridine; 1,6-naphthyridine; Heck reaction.

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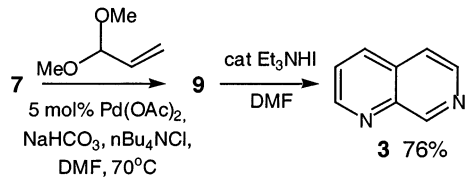
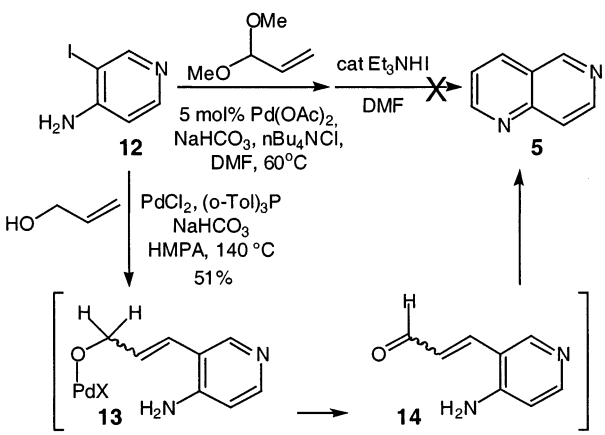
coupling[9] followed by an intramolecular condensation (Scheme 1). However, treatment of **7** with acrolein dimethylacetal in the presence of $(o\text{-Tol})_3P$, $Pd(OAc)_2$, and Et_3N in MeCN in a sealed tube at 110°C for 16 h provided none of the expected Heck product **9**. Instead, 25% of **3**, 9% of **11**, and 10% of starting material **7** were isolated. Hydroiodic acid, a byproduct of the reaction, was postulated to be responsible for the conversion of the initial Heck adduct **9** into **3** by causing hydrolysis of the acetal, isomerization of the *trans* alkene, and condensation. Competing β-hydride elimination of the acetal hydrogen in organopalladium **8** explains the formation of **11** via intermediate **10**. Encouraged by these results, a method was sought to suppress the formation of **11** and improve the yield of **3**.

After exploring a number of Heck reaction conditions, the Jeffery[10] protocol *with heating* was found to yield **9**[11] cleanly (Eq. (1)). After a quick aqueous workup, crude **9** was treated with DMF and a catalytic amount of triethylammonium iodide in ethyl ether (generated by mixing Et_3N and HI) and heated to 70°C for 16 h to cleanly provide **3**[12] in 76% yield over the two steps. Thus, **3** could be prepared in five steps starting from commercial 3-aminopyridine in 44% overall yield.



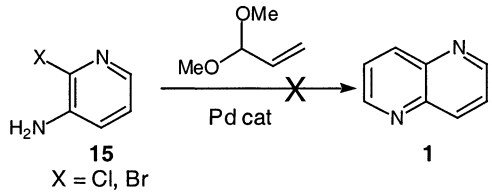
(1)

We sought to apply this reaction to prepare other naphthyridines, such as 1,6-naphthyridine. Surprisingly, treatment of 4-amino-3-iodopyridine **12**[13] with the conditions developed for **3** did not provide any products arising from Heck coupling (Scheme 2). The main complication appeared to arise from the 4-aminopyridine functionality in **12** competing as a ligand for palladium. A similar problem was observed even with the less basic *N*-pivaloyl derivative of **12**. However, when the protocol of Larock[14] using *allyl alcohol* was employed,[15] 1,6-naphthyridine **5** could be obtained directly in 51% yield. Formation of **5** under these conditions occurred via a multistep sequence involving Heck coupling, palladium-mediated oxidation of the allylic alcohol to the aldehyde, double bond isomerization, cyclization, and dehydration. With an overall yield of 38% from commercial 4-aminopyridine, this process provides **5** in a yield comparable to the reported Skraup procedure.[16]



Scheme 2.

To examine the general applicability of this approach, a synthesis of 1,5-naphthyridine was briefly investigated. However, various Heck reaction conditions with 2-halo-3-aminopyridines **15** did not yield **1** (Eq. (2)).



(2)

In short, a facile synthesis of 1,7-naphthyridine **3** has been achieved in five steps and 44% overall yield. The syntheses described for 1,7-naphthyridine **3** and 1,6-naphthyridine **5** may also be useful for the synthesis of substituted versions of these interesting heterocycles.

Acknowledgements

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8. Compound **7** can be prepared in 59% yield over three steps: (a) Malm, J.; Rehn, B.; Hornfeldt, A.; Gronowitz, S. *J. Heterocyclic Chem.* **1994**, *31*, 11–15; (b) Estel, L.; Marsais, F.; Queguiner, G. *J. Org. Chem.* **1988**, *53*, 2740–2744.
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11. A mixture of **7** (1.10 g, 5 mmol), dimethyl acetal acrolein (0.92 mL, 15 mmol), $Pd(OAc)_2$ (50 mg, 0.25 mmol), $NaHCO_3$ (1.05 g, 12.5 mmol), nBu_4NCl (1.39 g, 5 mmol) were heated to 70°C in DMF (25 mL) for 8 h. TLC indicated the disappearance of **7** and clean formation of **9**. The reaction mixture was cooled to rt, poured into ice water and extracted with EtOAc (3×50 mL). The combined extracts were dried over Na_2SO_4, and concentrated to yield crude **9**: ^1H NMR (500 MHz, $CDCl_3$): δ 3.37 (s, 6 H), 3.81 (bs, 2 H, NH), 4.97 (dd, $J=1.1$, 4.3 Hz, 1 H), 6.20 (dd, $J=4.4$, 16.0 Hz, 1H), 6.72 (dd, $J=15.9$ Hz, 1H), 7.11 (d, $J=5.0$ Hz, 1H), 7.97 (d, $J=4.9$ Hz, 1H), 8.08 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 52.7, 102.0, 120.7, 126.8, 128.5, 130.8, 138.7, 139.7, 140.1
12. To crude **9** in DMF (25 mL) was added ca. 5 drops of a preformed 1:1 complex of HI and Et_3N in Et_2O. After heating at 70°C for 16 h, the reaction mixture was cooled to rt, poured into ice water and extracted with EtOAc (3×50 mL). The combined extracts were dried over Na_2SO_4 and concentrated. The residue was chromatographed (9:1 CH_2Cl_2:MeOH) to afford **3** (0.50 g) in 76% overall yield from **7**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.56 (dd, $J=4.10$, 8.3 Hz, 1 H), 7.62 (d, $J=5.6$ Hz, 1H), 8.13 (d, $J=8.2$ Hz, 1H), 8.60 (d, $J=5.6$ Hz, 1H), 9.00 (dd, $J=1.3$, 4.0 Hz, 1H), 9.5 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 120.2, 125.4, 131.5, 135.0, 143.7, 144.1, 152.3, 154.7; MS (ES) m/z 153.1 (MNa^+)
13. Produced in 76% yield from 4-aminopyridine, see Ref. 8.
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15. A mixture of **12** (110 mg, 0.5 mmol), allyl alcohol (68 μL, 1 mmol), $PdCl_2$ (5 mg, 0.025 mmol), $NaHCO_3$ (126 mg, 1.5 mmol), $(o\text{-Tol})_3P$ (7.6 mg, 0.025 mmol) were heated to 140°C in HMPA (5 mL) for 4 h. The reaction mixture was cooled to rt, poured into ice water, and extracted with EtOAc (3 x 50 mL). The combined extracts were dried over Na_2SO_4 and concentrated. The residue was chromatographed (9:1 CH_2Cl_2:MeOH) to afford **5** (33 mg) in 51% yield: ^1H NMR (360 MHz, $CDCl_3$): δ 7.54 (dd, $J=4.2$, 8.3 Hz, 1 H), 7.91 (d, $J=5.8$ Hz, 1H), 8.29 (d, $J=8.2$, 1H), 8.75 (d, $J=6.0$ Hz, 1H), 9.08 (dd, $J=1.6$, 4.2 Hz, 1H), 9.27 (s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$): δ 22.5, 122.1, 135.7, 146.8, 150.3, 152.8, 154.8; MS (ES) m/z 153.1 (MNa^+)
16. 1,6-Naphthyridine has been synthesized by a Skraup reaction from 4-aminopyridine in 40% yield: Kress, T.; Pavoller, W. *J. Chem. Soc., Chem. Commun.* **1967**, 3.