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Synthesis and regioselective alkylation of 1,6- and 1,7-naphthyridines

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Abstract

A regioselective alkylation of naphthyridines **4a–d**, through the action of ethylchloroformate and benzylstannane **5**, afforded the benzyl substituted dihydronaphthyridines **3a–d**. These key intermediates **3a–d** were transformed into the desired targets **2a–d** in seven steps.

It has been established by these laboratories that 1,2,3,4-tetrahydroisoquinoline **1** acts as a novel β_3 adrenergic receptor (AR) agonist, which may be useful in the treatment of obesity.[1] As a result of our work with 3-pyridylethanolamines as β_3 AR agonists,[2] we envisioned that 5,6,7,8-tetrahydro-(1,6)- or -(1,7)-naphthyridines **2a–d** may serve as bioisosteric replacements for **1**. Thus, we were interested in preparing compounds **2a–d** for biological evaluation (Fig. 1).

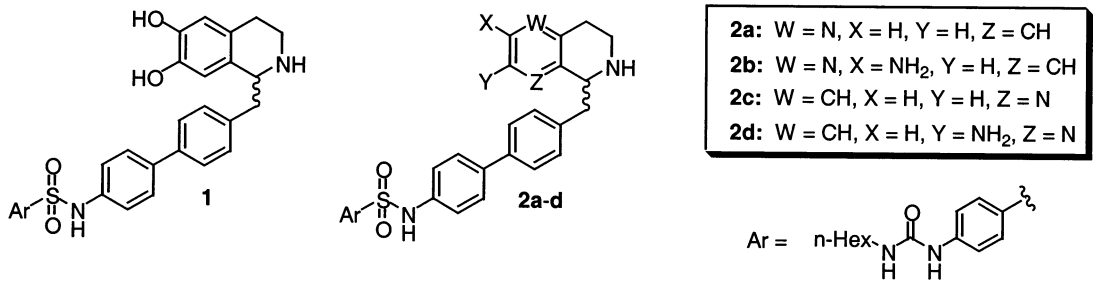

Figure 1.

Alkylation of pyridines via pyridinium salts is well documented.[3] Recently, this methodology has been extended to the alkylation of isoquinoline, using methylchloroformate and substituted benzylstannanes.[4] Inspired by these results, we planned to prepare compounds **2a–d** from

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dihydronaphthyridines **3a–d** (Fig. 2). Intermediates **3a–d** were proposed to arise from a regioselective alkylation of naphthyridines **4a–d** with benzylstannane **5**.

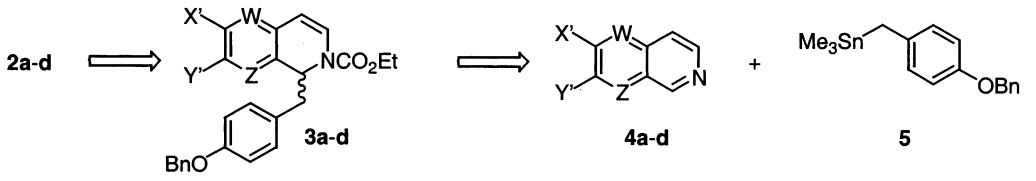
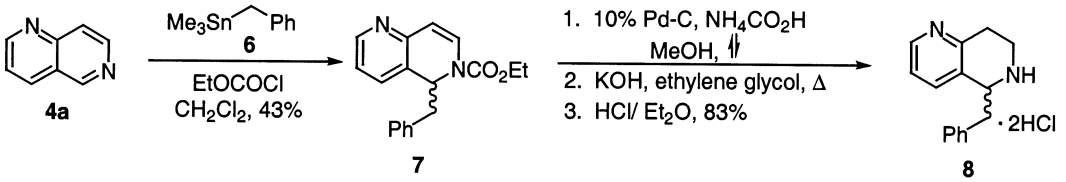


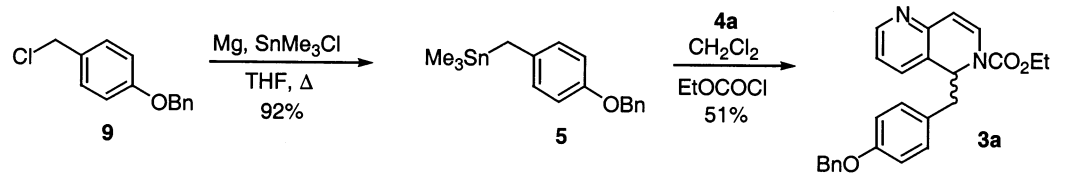
Figure 2.

To test this synthetic approach, we prepared benzyltrimethylstannane **6** and 1,6-naphthyridine **4a** by literature methods.[4,5] Treatment of naphthyridine **4a** and stannane **6** with ethylchloroformate gave one dihydronaphthyridine product (Scheme 1).[6] This material was tentatively assigned as **7**, but due to carbamate rotamers in the ^{1}H NMR spectrum, additional proof of structure was needed. Reduction of the olefin, followed by hydrolysis of the ethyl carbamate and HCl salt formation yielded a tetrahydronaphthyridine product in 83% overall yield. Through ^{1}H NMR coupling constants, we were able to unequivocally assign this product as **8**, proving that alkylation had occurred at the 5-position.[7]



Scheme 1.

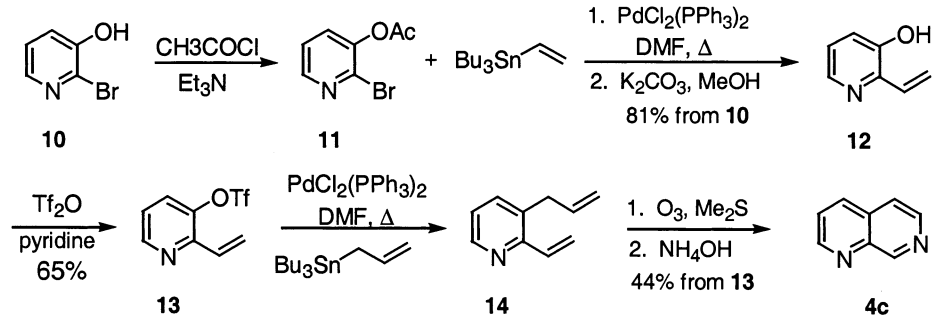
We next prepared 4-benzyloxybenzyltrimethylstannane **5** from commercially available 4-benzyloxybenzyl chloride **9**. Reaction of chloride **9** under Barbier conditions provided stannane **5** in 92% yield (Scheme 2). To our satisfaction, reaction of stannane **5** with 1,6-naphthyridine **4a** and ethylchloroformate vide supra gave rise to dihydronaphthyridine **3a** in 51% yield.



Scheme 2.

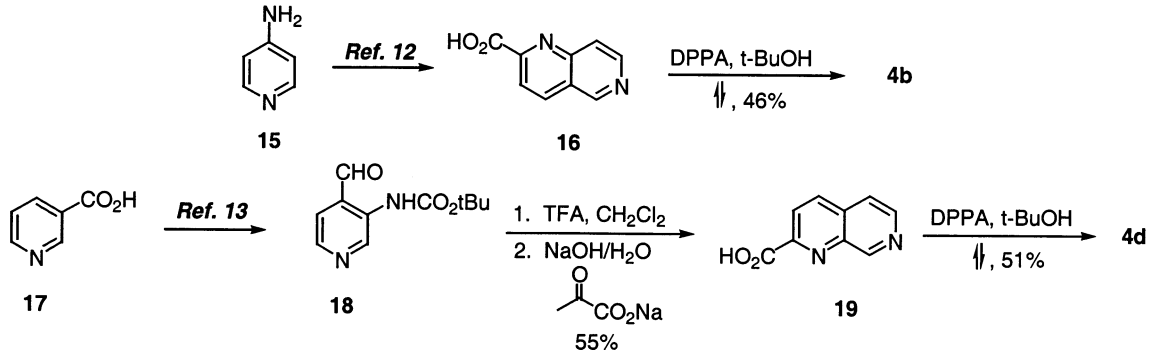
Having demonstrated that dihydronaphthyridine **3a** can be prepared via the acyl iminium salt of **4a**, we turned our attention toward the preparation of naphthyridines **4b–d**. A concise synthesis of 1,7-naphthyridine **4c** has been reported; however, we were unable to repeat this procedure.[8] Instead, an alternative route outlined in Scheme 3 was developed based upon an earlier naphthyridine synthesis.[9] The action of acetyl chloride on 2-bromo-3-hydroxypyridine **10** afforded acetate **11**, which underwent smooth palladium-catalyzed vinylation (Scheme 3).[10]

Deprotection of the crude reaction product with potassium carbonate afforded 3-hydroxy-2-vinylpyridine **12** in 81% overall yield. Treatment of **12** with triflic anhydride and pyridine gave triflate **13**, in 65% yield. Allylation of **13** under Stille conditions gave 3-allyl-2-vinylpyridine **14**. Ozonolysis of **14** under reductive conditions, followed by treatment with aqueous ammonia afforded 1,7-naphthyridine **4c** in 44% overall yield from **13**.



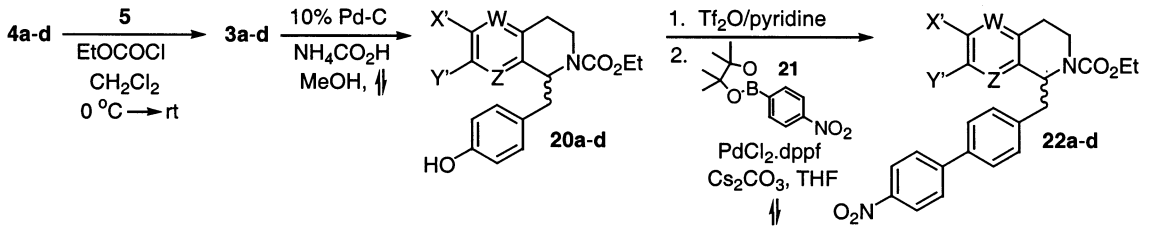
Scheme 3.

The synthesis of BOC-protected 2-aminonaphthyridines **4b** (X′ = NHBOC, Y′ = H) and **4d** (X′ = H, Y′ = NHBOC) was accomplished by a Curtius rearrangement of the appropriate naphthyridine carboxylic acids **16** and **19**, respectively (Scheme 4).[11] Following the work of Chan, we prepared 2-carboxy-(1,6)-naphthyridine **16** from 4-aminopyridine **15**.[12] Rearrangement of acid **16** using diphenylphosphoryl azide (DPPA) in *t*-butanol yielded naphthyridine **4b** in 46% yield. The synthesis of naphthyridine **4d** started with the nicotinic acid **17**. Using chemistry described by Venuti, aldehyde **18** was prepared in two steps from acid **17**.[13] Removal of the BOC moiety, followed by an aldol condensation with sodium pyruvate provided 2-carboxy-(1,6)-naphthyridine **19** in 55% overall yield. Treatment of **19** with DPPA in *t*-butanol at reflux afforded the naphthyridine **4d** in 51% yield.



Scheme 4.

With substrates **4b–d** in hand, conversion to dihydronaphthyridines **3b–d** was accomplished using the aforementioned alkylation conditions in moderate to good yields (Scheme 5 and Table 1). Phase transfer hydrogenolysis of dihydronaphthyridines **3a–d** effected concomitant removal of the benzyl group and hydrogenation of the olefin to give phenols **20a–d**, respectively. Treatment of phenols **20a–d** with triflic anhydride and pyridine gave the corresponding triflates, which were purified by chromatography. The triflates were then subjected to a palladium catalyzed biaryl cross-coupling with boronic ester **21**, as described by Miyaura.[14] The resulting biaryls **22a–d** were isolated in good overall yields from phenols **20a–d**.



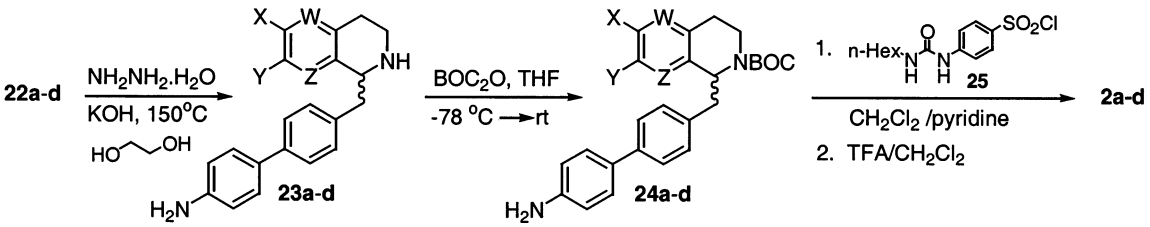
Scheme 5.

Table 1

Substrate	W	X′	Y′	Z	% Yield		
					3a–d[a]	**20a–d**[a]	**22a–d**[a]
4a	N	H	H	CH	51	90	82
4b	N	NHBOC	H	H	50	99	50
4c	CH	H	H	N	43	90	42
4d	CH	H	NHBOC	N	61	95	62

[a] Isolated yields.

The syntheses of compounds **2a–d** were realized in four steps from biaryls **22a–d** (Scheme 6). Reduction of **22a–d** with hydrazine hydrate and potassium hydroxide in ethylene glycol at 150°C with concomitant cleavage of protecting groups led to the amines **23a–d**, respectively.[15] A selective protection of the secondary amine was accomplished with di-*tert*-butyldicarbonate at low temperature to furnish anilines **24a–d**. Sulfonamide formation with sulfonyl chloride **25**, followed by removal of the BOC group with trifluoroacetic acid in dichloromethane afforded the desired targets **2a–d**[16] (Table 2).



Scheme 6.

Table 2

Substrate	W	X	Y	Z	% Yield		
					23a–d[a]	**24a–d**[a]	**2a–d**[a]
21a	N	H	H	CH	38	91	74
21b	N	NH_2	H	H	51	98	39
21c	CH	H	H	N	86	97	79
21d	CH	H	NH_2	N	76	90	39

[a] Isolated yields.

In conclusion, we have established that the acyl iminium salts of naphthyridines **4a–d** undergo a regioselective alkylation with benzylstannanes **5** and **6** to give dihydronaphthyridines **3a–d** and **8**. These key intermediates **3a–d** have been transformed into the desired targets **2a–d** in seven steps.

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6. **General procedure for alkylation of naphthyridines 4a–d**: to a solution of naphthyridines **4a–d** (1.0 mmol) and stannane **5** or **6** (1.1 mmol) in 2 mL of dry CH_2Cl_2 at 0°C, ethylchloroformate (1.1 mmol) was added dropwise. The reaction mixture was allowed to warm to ambient temperature and stirred for three days. Concentration in vacuo and purification by flash chromatography (eluent: 10–30% EtOAc/hexanes) on SiO_2 gave products **3a–d** and **7**.
7. Compound **8**: ^{1}H NMR (CD_3OD, 400 MHz), δ 3.31–3.36 (m, 1H), 3.47–3.66 (m, 4H), 3.79–3.83 (m, 1H), 5.13 (t, $J=7.7$ Hz, 1H), 7.37–7.42 (m, 5H), 7.84 (dd, $J=5.8$, 8.2 Hz, 1H), 8.08 (d, $J=8.2$ Hz, 1H), 8.81 (dd, $J=1.3$, 5.8 Hz, 1H).
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10. Attempted vinylation of pyridinol **10** resulted in recovered starting material.
11. The conversion of benzyl substituted dihydronaphthyridines **3a** and **3c** to their amino derivatives **3b** and **3d**, respectively, was unsuccessful.
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