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Remote protection prevents unwanted cyclizations with 2-aminopyridines

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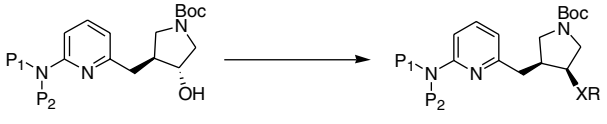
Abstract—The pyridine nitrogen of the 2-aminopyridine group is sufficiently nucleophilic to undergo intramolecular cyclizations, thereby preventing competing Mitsunobu and other substitution reactions from proceeding at a remote site. Double protection of the 2-amino group effectively blocked reaction at the pyridine nitrogen. This is a rare example of the use of a remote protecting group to block another group from reacting.

In our ongoing search for selective inhibitors of nitric oxide synthase, a method for converting a *trans*-alcohol having general structure **1** into compounds of general structure **2** with cis stereochemistry was desired (Scheme 1).

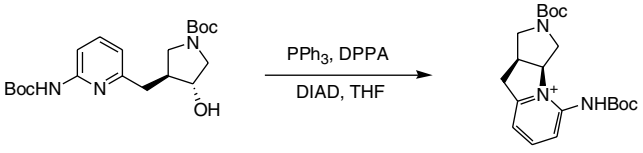
When **1a** was submitted to Mitsunobu conditions,[1] an intramolecular cyclization occurred instead of the desired addition by an external nucleophile. The pyridine nitrogen is sufficiently nucleophilic to displace the activated alcohol of the Mitsunobu intermediate, forming **3** (Scheme 2).[2] None of the desired product was detected, despite numerous attempts to vary the reaction conditions. Furthermore, attempts to activate the hydroxyl group as a tosylate, mesylate, or triflate followed by displacement with a nucleophile met with a similar undesired fate.



1 **2**

a, P_1, P_2 = Boc, H
b, P_1, P_2 = Boc, Boc
c, P_1, P_2 = dimethylpyrrole
d, P_1, P_2 = Boc, Bn

Scheme 1.

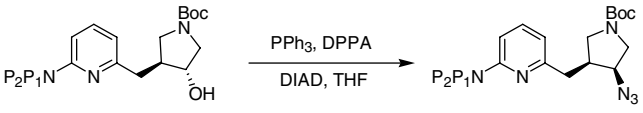


1a (±) **3 (±)**

Scheme 2.

It would be impractical to protect the pyridine ring nitrogen itself, but it was believed that different protecting groups on the primary amino group attached to the

Table 1. Yields of Mitsunobu product **4** when different protecting groups are used



1a-d (±) **4a-d (±)**

Compound	P_1, P_2	Yield of **4** (%)
1a	Boc, H	0
1b	Boc, Boc	85
1c	Dimethylpyrrole	31
1d	Boc, Bn	86

Keywords: 2-Aminopyridines; Remote protection; Prevent cyclization; Side reaction; Mitsunobu reaction.
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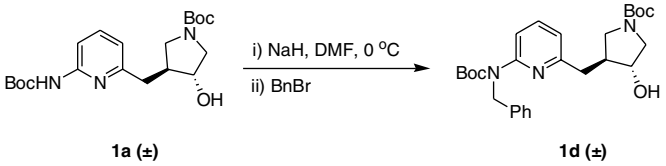

1a (±) 1d (±)

Scheme 3.

pyridine ring might result in different rates of intramolecular cyclization. We were pleased to find that double protection of the amino group completely prevented the intramolecular side reaction and allowed for successful remote Mitsunobu coupling. In Table 1, the results of performing a Mitsunobu reaction using DPPA as the source of nucleophilic azide are displayed.[3,4]

Subjecting the mono-Boc protected aminopyridine to Mitsunobu conditions resulted exclusively in undesired cyclization. Attempts to add another Boc group to **1a** resulted in reaction at the hydroxyl group and formation of the *tert*-butyl carbonate instead. Protection of the alcohol group of **1a** as a TBS ether, followed by addition of a second Boc group to the aminopyridine, then deprotection of the silyl ether resulted in tri-Boc protected **1b**. Amino group diprotection prevented intramolecular cyclization at the pyridine nitrogen and allowed the Mitsunobu reaction to proceed as desired to give **4b** in excellent yields.[5] The drawback of this method was that it required multiple additional steps to synthesize **1b**.

Protection of the aminopyridine as a dimethylpyrrole to give **1c**[6] gave some of the desired product **4c**,[7] but the reaction did not proceed cleanly, and the product yield was low. However, there was no evidence of formation of an analog of **3**.

Conversion of **1a** to the benzyl protected analog **1d** proved most straightforward (Scheme 3).[8] Because the carbamate proton of **1a** is significantly more acidic than the hydroxyl proton, treatment of **1a** with one equivalent of sodium hydride in DMF followed by quenching with benzyl bromide gave exclusively alkylation of the nitrogen and not the oxygen. When **1d** was submitted to Mitsunobu conditions, the desired product **4d** was formed in excellent yields with no detectable intramolecular cyclization.[9] The success of the Mitsunobu reaction with both **1b** and **1d** is most likely the result of a remote steric effect that prevents the pyridine nitrogen from displacing the activated hydroxyl group during the reaction.

The same trend was observed when other nucleophiles (phthalimide and acetate) were used, and this approach is believed to be general for any nucleophile that is compatible with Mitsunobu conditions. The protection strategy may also be general for other aminoheterocycles that might undergo analogous intramolecular reactions, such as aminoimidazoles and aminooxazoles, although this has not been attempted.

The use of protecting groups to affect the stereochemical course at a remote site is well documented.[10] However, the use of a protecting group to block an undesired reaction at a remote site is rare; protection of the 2-amino group in our reaction blocks the reaction of the pyridine nitrogen and allows the desired substitution reaction at a remote site to proceed.

In conclusion, intramolecular cyclization by the ring nitrogen of a protected 2-aminopyridine was found to be favored over displacement of the activated alcohol by an external nucleophile during the Mitsunobu reaction. Simply adding a benzyl protecting group or a second Boc group to the already Boc protected amino group prevented the pyridine nitrogen from interfering in the reaction and gave the desired product in good yields. Remote protection is rarely seen; usually the reactive groups themselves must be protected. This chemistry should prove useful whenever an S_N2 reaction is desired four or five atoms away from the ring nitrogen of a 2-aminopyridine ring.

Acknowledgments

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Supplementary data

Synthetic procedures for all intermediates. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.091.

References and notes

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4. *Typical experimental conditions for the preparation of* **4**. Diisopropylazodicarboxylate (66 μL, 0.35 mmol) was added to a solution of triphenylphosphine (79 mg, 0.3 mmol) in dry THF (5 mL) under nitrogen at room temperature. The mixture was stirred for 5 min, then a solution of **1** (0.25 mmol) in dry THF (5 mL) was added via cannula. After 5 min of stirring, diphenylphosphoryl-

azide (76 μL, 0.35 mmol) was added dropwise. The mixture was stirred overnight at room temperature. The organic layer was diluted with ethyl acetate and washed with 1 N HCl and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with hexanes/ethyl acetate 8:2. In the case of **1a** and **1c** different reaction conditions, order of addition, reagent concentrations and temperatures failed to have any significant effect on product yield. Compound **3** was eluted with ethyl acetate/methanol 9:1.

5. Compound **4b**; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (m, 1H), 7.54 (m, 1H), 7.24 (m, 5H), 6.85 (d, $J = 7$ Hz, 1H), 5.18 (s, 2H), 3.76 (m, 1H), 3.59–3.29 (m, 3H), 3.00 (m, 1H), 2.90 (m, 1H), 2.77 (m, 1H), 2.61 (m, 1H), 1.45 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.3, 154.6, 154.1, 139.9, 137.8, 128.4, 126.9, 118.8, 116.9, 81.7, 79.8, (63.4+62.7), (51.7+51.4), 50.1, (49.1+48.7), (42.7+42.1), 35.3, 28.7, 28.4. ESMS $m/z = 531$ ($[M+Na]^+$). Compound **4b** was also analyzed by COSY and NOESY. A strong NOE was seen between the protons at the 3 and 4 positions of the pyrrolidine ring, indicating that the stereochemistry is indeed cis. Only one diastereomer is produced in the formation of **4b**, indicating that the Mitsunobu reaction proceeded with complete inversion of stereochemistry.
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9. Compound **4d**; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (m, 1H), 7.10 (m, 2H), 4.03 (m, 1H), 3.71–3.49 (m, 3H), 3.08 (m, 2H), 2.89 (m, 2H), 1.45 (s, 27H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.7, 154.6, 154.3, 152.1, 151.5, 138.6, 121.9, 119.4, 83.1, 79.9, (63.3+62.7), (51.8+51.5), (48.9+48.6), (43.2+42.5), 35.4, 28.7, 28.1. ESMS $m/z = 519$ ($[M+H]^+$), 541 ($[M+Na]^+$).
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