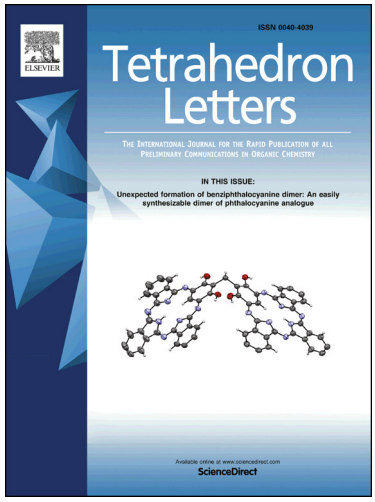

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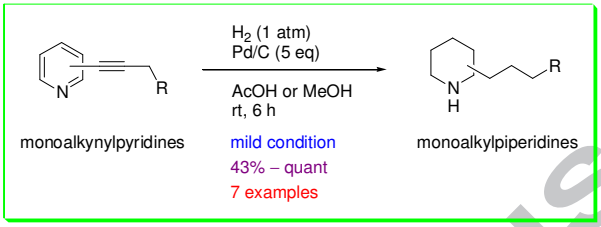

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Preparation of monoalkylpiperidines via the mild hydrogenation of monoalkynylpyridines

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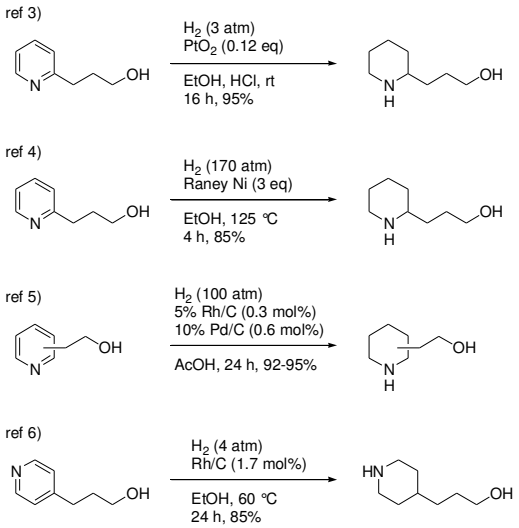
ABSTRACT

Monoalkynylpyridines were prepared via a Sonogashira cross-coupling reaction between monoiodopyridines and alkynes. Mild hydrogenation of the obtained monoalkynylpyridines was then conducted to produce the corresponding monoalkylpiperidines in moderate to excellent yields. The hydrogenation reaction was carried out under H_2 (1 atm) in the presence of 10 wt% Pd/C (5 eq) in either AcOH or MeOH at room temperature. The present method is therefore useful for the quick and easy preparation of monoalkylpiperidines.

Introduction

Alkylpiperidines and their derivatives are important industrial materials, building blocks for pharmaceutical compounds, and core structures in biologically active natural products such as deoxocassine[1] and azimine.[2] The direct synthesis of monoalkylpiperidines from monoalkynylpyridines has been reported via a hydrogenation reaction under intensive conditions and/or in the presence of rare metal catalysts.[3-7] For example, as shown in Scheme 1, the following reaction conditions have been reported to generate monoalkylpiperidines from monoalkynylpyridines: H_2 (3 atm) with PtO_2 (0.12 eq) in EtOH at room temperature for 16 h in 95% yield;[3] H_2 (170 atm) with Raney Ni (3 eq) in EtOH for 4 h in 85% yield;[4] H_2 (100 atm) with 5% Rh/C (0.3 mol%) and 10% Pd/C (0.6 mol%) in AcOH for 24 h in 92-95% yield;[5] and H_2 (4 atm) with Rh/C (1.7 mol%) in EtOH at 60 °C for 24 h in 85% yield.[6] It is therefore apparent that these previously reported methods required extremely high pressures, relatively long reaction times, and the use of expensive rare metal catalysts.

In our previous synthesis of the tetrasubstituted pyridinium amino acid isodesmosine, one of the elastin crosslinkers, the hydrogenation of 2-alkynylpyridine was investigated to produce the corresponding 2-alkylpyridine.[8] The reaction conditions were as follows: H_2 (1 atm) with 10 wt% Pd/C (5 eq) in MeOH at room temperature for 3 days, which constituted relatively milder conditions compared to the examples described above. Thus, we herein investigate the hydrogenation of simple model monoalkynylpyridine substrates, prepared by a Sonogashira cross-coupling reaction between monohalopyridines and alkynes, to afford the corresponding monoalkylpiperidines under mild conditions.



Scheme 1. Literature examples of the synthesis of monoalkylpiperidines from monoalkylpyridines via hydrogenation.

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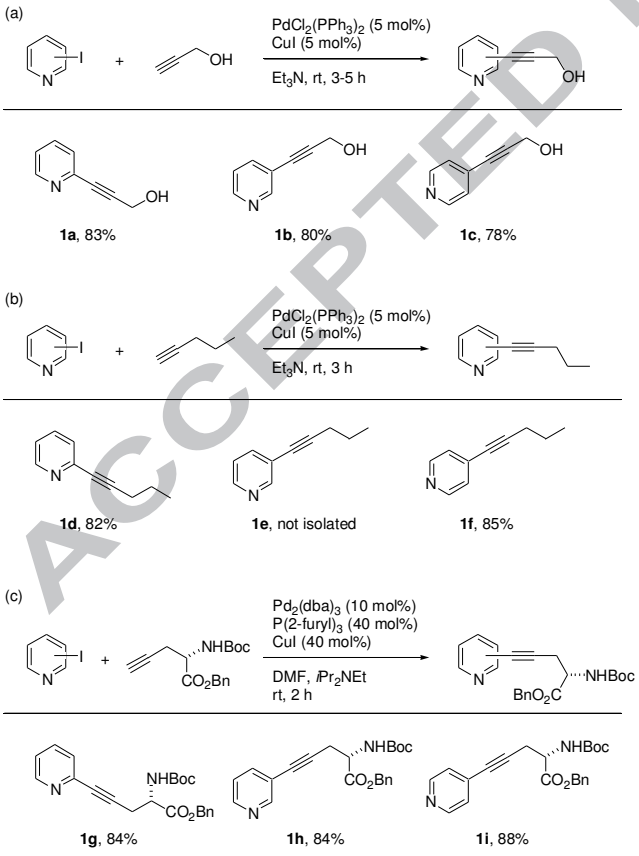
Results and discussion

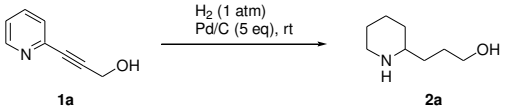
Preparation of a number of monoalkynylpyridines was firstly examined. 3-(2'-Pyridinyl)-2-propyn-1-ol **1a**, 3-(3'-pyridinyl)-2-propyn-1-ol **1b**, and 3-(4'-pyridinyl)-2-propyn-1-ol **1c** were synthesized using Sonogashira cross-coupling reaction between iodopyridines and 2-propyn-1-ol under the conditions of 5 mol% $PdCl_2(PPh_3)_2$ and 5 mol% CuI in Et_3N for 3 – 5 h in 83%, 80%, and 78% yield, respectively (Scheme 2a). In addition, 2-(pent-1'-ynyl)-pyridine **1d** and 4-(pent-1'-ynyl)-pyridine **1f** were prepared starting from iodopyridine and 1-pentyne using the above reaction conditions in 82% and 85% yield (Scheme 2b), whilst inseparable products were obtained in the attempted synthesis of 3-(pent-1'-ynyl)-pyridine **1e**, (data not shown).[9] Furthermore, 2-(*S*)-[(*tert*-butoxycarbonyl)amino]-5-(pyridin-2'-yl)-pent-4-ynoic acid benzyl ester **1g**, 2-(*S*)-[(*tert*-butoxycarbonyl)amino]-5-(pyridin-3'-yl)-pent-4-ynoic acid benzyl ester **1h**, and 2-(*S*)-[(*tert*-butoxycarbonyl)amino]-5-(pyridin-4'-yl)-pent-4-ynoic acid benzyl ester **1i** were synthesized from the Sonogashira cross-coupling reaction between the appropriate iodopyridine and benzyl 2-(*S*)-[(*tert*-butoxycarbonyl)amino]pent-4-ynoate, which was prepared from Garner's aldehyde (Scheme 2c).[10] The conditions employed for these transformations were as follows: 10 mol% $Pd_2(dba)_3$, 40 mol% P(2-furyl)$_3$,[11] and 40 mol% CuI in DMF and *i*Pr_2NEt at room temperature for 2 h. The yields of the corresponding products **1g**-**1i** were 84%, 84%, and 88%, respectively. However, when 10 mol% $Pd_2(dba)_3$, 40 mol% P(2-furyl)$_3$, and 40 mol% CuI in DMF and *i*Pr_2NEt was employed for the synthesis of 3-pyridinyl-2-propyn-1-ols, the yield decreased along with the production of undetermined byproducts (data not shown), likely due to the relatively harsher conditions of the $Pd_2(dba)_3$/P(2-furyl)$_3$ system for the substrates.



Scheme 2. Preparation of monoalkynylpyridines using the Sonogashira cross-coupling reaction.

The reaction conditions were then optimized using 3-(2'-pyridinyl)-2-propyn-1-ol **1a** as a model substrate (Table 1). The use of 1 atm of H_2 and 5 eq of the relatively cheap 10 wt% Pd/C at room temperature was fixed for the hydrogenation. When the reaction was run in either MeOH or EtOH yielded the desired product, 3-piperidin-2'-yl-propan-1-ol **2a**, in 24% and 36% yield, respectively (entries 1 and 2). Since the hydrogenation reaction proceeded under acidic conditions, as shown in Scheme 1,[3,5] we then examined the addition of an acid source to the reaction. Interestingly, the addition of glycine and AcOH improved the yield slightly to 43% entries 3 and 4), while the use of HCl was unsuccessful (entry 5), with only the alkyne-reduced product, i.e. the monoalkylpyridine being observed (data not shown). Upon changing the solvent from EtOH to AcOH, the reaction yield improved significantly to 57% (entry 6). In contrast, increasing the reaction time from 6 to 24 h caused the lower yield to 45% (entry 7). Stepwise addition of 2 × 2.5 eq Pd/C led the decrease of yield to 34% (entry 8), suggesting that 5 eq Pd/C at least are required for the hydrogenation from the beginning of reaction. Based on the above results, the influence of a weak acid such as AcOH can be explained as follows: 1) activation of the π-system in the substrate may be promoted by AcOH protonation, enhancing substrate reactivity;[12] 2) Coordination to the metal Pd/C by pyridine and/or piperidine was likely prevented by the increased acidity of AcOH in the reaction system, and so the presence of a strong acid such as HCl may interfere with the activity of the Pd/C catalyst.

Table 1. Hydrogenation of 3-(2'-pyridinyl)-2-propyn-1-ol



Entry	Solvent	Additive	time/h	yield/%
1	MeOH	-	6	24
2	EtOH	-	6	36
3	EtOH	glycine[a]	6	43
4	EtOH	AcOH[b]	48	43
5	EtOH	HCl[c]	6	-
6	AcOH	-	6	57
7	AcOH	-	24	45
8[d]	AcOH	-	6	34

[a] 1.2 eq of glycine was employed.

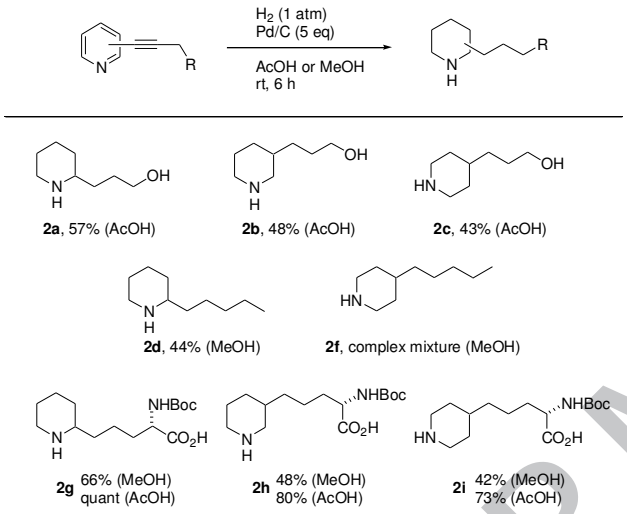
[b] Ratio of EtOH to AcOH was 1:1 (v/v).

[c] Ratio of 6 M HCl in EtOH to EtOH was either 2:1 (v/v) or 1:10 (v/v).

[d] 2.5 eq of Pd/C were added at the beginning of the reaction and after 3 h.

Hydrogenation of the prepared substrates was then carried out using of H_2 (1 atm) and 10% Pd/C (5 eq) at room temperature (Scheme 3). In the case of the 3-(pyridinyl)-2-propyn-1-ols **1a**-**1c**, hydrogenation in AcOH was achieved to afford 3-piperidin-2'-yl-propan-1-ol **2a**, 3-piperidin-3'-yl-propan-1-ol **2b**, and 3-piperidin-4'-yl-propan-1-ol **2c** in yields of 57% (see also Table 1,

entry 6), 48%, and 43% yields, respectively. In addition, the hydrogenation of 2-(pent-1'-ynyl)-pyridine **1d** in MeOH[13] produced the corresponding alkylpiperidine **2d** in 44% yield, while a complex mixture was obtained in the case of 4-(pent-1'-ynyl)-pyridine **1f**. Furthermore, for 2-, 3-, and 4-substituted pyridines bearing alkynyl amino acids, hydrogenation of pyridine ring and the alkyne moiety with removal of the benzyl group at the carboxylic acid moiety gave 2-(*S*)-[(*tert*-butoxycarbonyl)-amino]-5-(piperidin-2'-yl)-pentanoic acid **2g**, 2-(*S*)-[(*tert*-butoxycarbonyl)-amino]-5-(piperidin-3'-yl)-pentanoic acid **2h**, and 2-(*S*)-[(*tert*-butoxycarbonyl)-amino]-5-(piperidin-4'-yl)-pentanoic acid **2i** in 66%, 48%, and 42% yield in MeOH, and 100%, 80%, and 73% yield in AcOH, respectively. The yields obtained in AcOH were significantly higher than those obtained for the pyridine moieties bearing alkynyl alcohol groups.



Scheme 3. Hydrogenation of monoalkynylpyridines in AcOH or MeOH

The above results therefore indicate that the presence of an acidic proton promotes the hydrogenation reaction. In addition, it appears that the reactivity of the substituents on the pyridine rings follows the order: 2 > 3 > 4. This tendency is probably due to the closer distance between the nitrogen atom of the pyridine moiety and the alkyne group of the 2-alkynylpyridines, which results in strong π-electron interactions, thereby promoting the simultaneous hydrogenation of the pyridine ring and the alkyne moiety. Compared with the substrates shown in Scheme 1, the conjugated π-electron system present in the alkynylpyridines promoted the hydrogenation reaction even under the mild conditions examined herein (i.e., H_2 (1 atm) with Pd/C at room temperature). Furthermore, based on the improved yield obtained following the addition of glycine (entry 3, Table 1) and the improved yields observed for the pyridine substrates bearing alkynyl amino acids (Scheme 3, bottom), it appears that the presence of an intramolecular amino acid function is crucial for enhancing the hydrogenation of alkynylpyridines and improving product yields.

Conclusion

In conclusion, the hydrogenation of the monoalkynylpyridines prepared via a Sonogashira cross-coupling reaction between monoiodopyridines and alkynes was successfully conducted to produce the corresponding monoalkylpiperidines in moderate to excellent yields. The optimal conditions for the hydrogen reaction were H_2 (1 atm) and 10 wt% Pd/C (5 eq) in either AcOH or MeOH at room temperature, rendering our conditions milder than those of similar previously reported hydrogenation reactions. We therefore expect that these mild conditions will be suitable for the quick and easy preparation of other monoalkylpiperidines both in the laboratory and in industry. Further synthetic studies of preparation of alkylpiperidines are now in progress in our laboratory.

Acknowledgments

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Supplementary Material

Supplementary data (experimental procedures and characterization data) associated with this article can be found, in the online version, at http://

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13. As 2-(pent-1'-ynyl)-pyridine and 4-(pent-1'-ynyl)-pyridine were not soluble in AcOH, the reaction was conducted in MeOH.

- Monoalkynylpyridines were prepared via Sonogashira cross-coupling reaction.
- Monoalkylpiperidines were prepared via mild hydrogenation of monoalkynylpyridines.
- The reactions proceeded in moderate to excellent yields.