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Synthesis of 2-substituted pyrrolidines from nitriles

P. Veeraraghavan Ramachandran *, Wataru Mitsuhashi, Daniel R. Nicponski

Herbert C. Brown Center for Borane Research, Department of Chemistry, Purdue University, 560 Oval Dr. West Lafayette, IN 47907, USA

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ABSTRACT

A novel and synthetically facile production of 2-substituted pyrrolidines from commercially available nitriles is reported herein. This methodology is operationally simple, and only requires the use of an extraction and a single chromatographic purification to furnish the title compounds in high purity and very good yields.

Alkaloids are one of the most important classes of natural products, often exhibiting outstandingly potent biological activities.[1] Pyrrolidine-containing compounds are an especially important subclass of this group, as a variety of synthetic pharmaceuticals and natural toxins have been reported which contain this structural motif. For example, cocaine,[2] lepadiformine,[3] ptilomycalin A,[4] and lapidilectine B[5] are natural products with pyrrolidine derivatives in their structures (Fig. 1). Furthermore, pyrrolidine derivatives many times serve as the building blocks for ligands in catalysis chemistry.[6] We have been especially interested in 2-substituted pyrrolidines, as they have been shown to possess a variety of physiological and pharmacological effects (e.g., nicotine, proline derivatives, ONO-1603,[7] and racetam drugs[8]).

A variety of methods have been reported in the literature detailing the construction of this important functionality. In certain cases, they can provide access to these compounds with a variety of different functional groups at the 2-position, without requiring an N-protection strategy. For example, Xu and co-workers have described the preparation of pyrrolidines from amino alcohols, without a protection-deprotection sequence, via the formation of the amino chlorides, followed by cyclization.[9] The asymmetric hydrogenation of 2-substitued pyrrolines has been described,[10] but this strategy requires the preemptive synthesis of these same pyrrolines. In another report, 1,4-butanediol derivatives have been directly converted to pyrrolidine scaffoldings without protection under the conditions of iridium(III) catalysis using elevated temperatures.[11] Similarly, Singaram and co-workers described the benzylamination of the bismesylate derivatives of 1,4-diols as a route to pyrrolidines.[12]

We recently reported a convenient synthesis of 2-substituted and 2,3-disubstituted tetrahydrofurans in a one-pot procedure that involved Brown's allyl/crotylboration of aldehydes, followed by iodination and cyclization.[13] Additionally, we previously described the production of homoallylic amines through an allyl/crotylboration strategy, using in situ-produced imines.[14] We posited that the application of a strategy similar to these two transformations would allow direct access to these 2-substituted pyrrolidines directly from commercially available nitriles. Specifically, we envisaged using a one-pot procedure that would employ a sequence involving: reduction, allylation, hydroboration, iodination, and cyclization (Scheme 1, top pathway).

To determine the feasibility of this synthetic route, we chose to study this sequence using benzonitrile as the model substrate. To this end, an achiral allylation of the produced *N*-aluminoimine with the simple Grignard reagent allylmagnesium bromide was performed. Due to its difficult preparation, inherent instability, and the fact that it did not offer improved conversions, the equivalent reaction with allyldicyclohexylborane was found to be inferior. Additionally, we successfully extended this one-pot procedure to include the hydroboration of the formed homoallylic amine using a variety of boranes, thereby providing 4-amino-4-substitued-butan-1-ols, which were isolated by simple extraction in high enough purity to carry forward without additional purification. Unlike our previous report describing the synthesis of tetrahydrofurans,[13] the iodine-promoted cyclization did not provide the expected pyrrolidine product under any of the screened conditions. As such, we sought to modify our approach, and discovered that the use of thionyl chloride in a reverse addition[9] provided,

* Corresponding author. Tel.: +1 765 494 5303; fax: +1 765 494 0239.
E-mail address: chandran@purdue.edu (P.V. Ramachandran).

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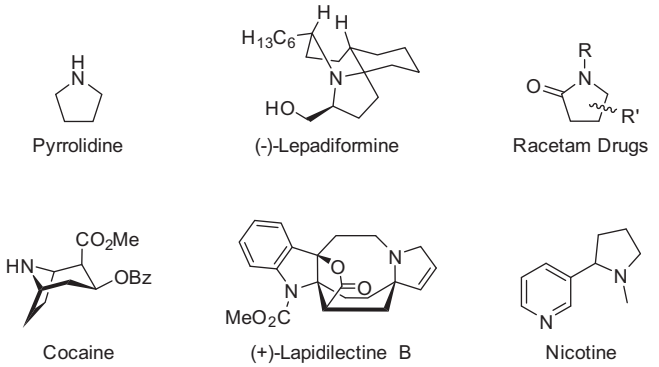
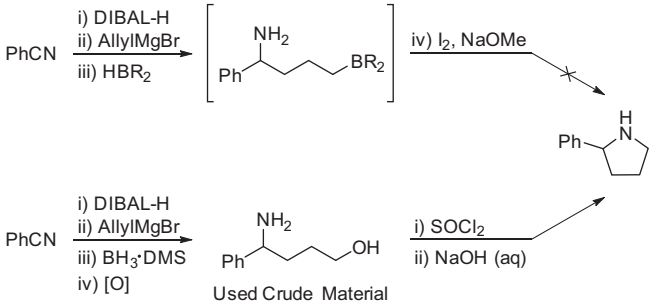


Figure 1. Pyrrolidine and several molecules containing its structural derivatives.



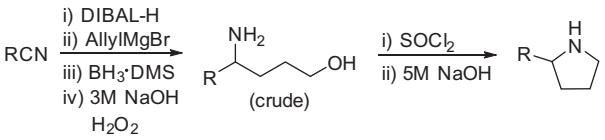
Scheme 1. Initial (upper) and modified (lower) approaches to pyrrolidines from nitriles.

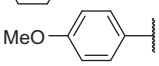
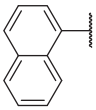
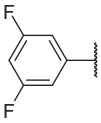
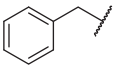
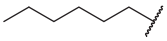
upon subsequent aqueous workup, the desired pyrrolidine products. (Scheme 1, bottom pathway). We were gratified to discover that the application of these conditions allowed for the formation of these pyrrolidines from nitriles in six synthetic steps, but which required only two purifications (one of them being extractive, the other chromatographic).

With the optimized conditions for this six-step, high-yielding transformation in hand, we applied this protocol to a series of nitriles of varying steric and electronic properties (Table 1). As can be seen from the table, a variety of nitrile derivatives were tolerated under these conditions, including both electron-rich (entry 2) and electron-poor aromatic ones (entry 4), as well as heteroaromatic (entry 5) and polyaromatic nitriles (entry 3). In accord with our previous observation that aliphatic nitrile reductions/allylations using similar processes furnish lower yields than do their aromatic counterparts,[15] the use of heptanonitrile (entry 7) and cyclohexancarbonitrile (entry 8) furnished lower overall yields. In contrast, the use of benzyl cyanide provided the corresponding pyrrolidine in excellent yield (entry 6). Overall, this six-step procedure provided very high isolated yields, averaging 75% for each step, and 18% (average) overall.

Through the incorporation of our previously reported reduction–allylboration–hydroboration sequence parameters,[15] the application of this methodology to the asymmetric synthesis of pyrrolidines was next attempted. (In this case, we have found that the use of DIBAL-H is superior to that of lithium triethylborohydride, and opted for the use of the former in the present study.) In this manner, we obtained the expected 2-phenylpyrrolidine product. The incorporation of Brown's isopinocampheyl ligand during the allylation step provided the expected stereoinduction, but necessitated the use of an additional acid-base extraction of the aminol derivative to rid said product of the formed isopinocampheol byproduct. Unexpectedly, a degradation of the chirality occurred, as a decrease in the enantiomeric ratio from 94:6 to 81:19 occurred during the oxidation–cyclization protocol, as determined by ^{1}H NMR analysis of the N-menthylated product [formed by the reaction of 2-phenylpyrrolidine with (−)-menthyl chloroformate]. Further work in obtaining enantioenriched pyrrolidines through this sequence, along with the extension of this methodology to the crotylation and alkoxyallylboration analogs, is ongoing, and will be reported at a later date.

Table 1
Application of six-step procedure to a variety of nitriles



Entry	R=	Pyrrolidine	Yield[a] %
1		**1**	36
2		**2**	17
3		**3**	25
4		**4**	17
5		**5**	17
6		**6**	22
7		**7**	4
8		**8**	4

[a] Isolated overall yield of analytically pure product after column chromatography.

In conclusion, we have developed a straightforward, synthetically facile procedure for the production of 2-substituted pyrrolidines,[16] which starts from commercially available nitriles, and proceeds in very good yields. In contrast to other reported methods, this route does not require any tedious purifications, requiring instead only a single performance of column chromatography.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.075.

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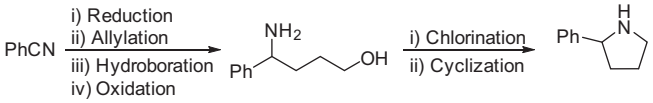
16. *Representative experimental*:



To a round bottom flask containing 0.10 mL benzonitrile (0.98 mmol, 1.0 equiv) in 2 mL Et_2O was added 0.18 mL DIBAL-H (1.03 mmol, 1.05 equiv) at 0 °C, and the reaction mixture was stirred for 1 h. After this , 1.47 mL allylmagnesium bromide (1.0 M in Et_2O, 1.47 mmol, 1.5 equiv) was then added at −78 °C, and the mixture was stirred for 24 h, then slowly warmed to 25 °C. After this , 0.15 mL BH_3·DMS (∼10 M, 1.47 mmol, 1.5 equiv) was then added to the solution at 0 °C, followed by 2 mL THF (added to help solvate the reaction mixture). After stirring for 24 h at 25 °C, 0.2 mL MeOH, 1 mL 3 M aqueous NaOH, and 1 mL 30% H_2O_2 were slowly and sequentially added to the mixture at 0 °C. The product was then extracted with Et_2O (3 × 15 mL), then solvent was removed under reduced pressure. The crude mixture was then dissolved in 5 mL 1,2-DME, and was subsequently transferred into another round bottom flask that had been charged with 0.14 mL $SOCl_2$ (1.96 mmol, 2 equiv) at 0 °C. The reaction mixture was stirred for 3 h at 25 °C, then 1 mL aqueous 5 M NaOH was added at 0 °C. After stirring for an additional 4 h at 0 °C, the product was extracted with Et_2O (3 × 15 mL), then the solvent was removed under reduced pressure. The crude product was purified via column chromatography to furnish 2-phenylpyrrolidine.