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# The reductive cleavage of picolinic amides

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ABSTRACT

Treatment of picolinic amides with excess zinc in aqueous hydrochloric acid at room temperature affords the corresponding amines in good to excellent yields. The mild reaction conditions exhibit useful functional group tolerance and facilitate the application of the picolinic amide moiety as a protecting group which can be easily introduced and selectively removed.



## Introduction

The picolinic amide group has been used as a ligand,[1] as a protecting group,[2] and more recently as a directing group for transition-metal catalysed CH activation reactions.[3] However, few general methods for the mild and selective conversion of picolinic amides to the corresponding amines have been reported. The most widely used procedures employ strongly hydrolytic or nucleophilic conditions at elevated temperatures,[4] leading to poor functional group tolerance and limiting the utility of these methods in the context of complex molecule synthesis, where selectivity is desirable. Another reported cleavage reaction suggests the use of Cu (II) salts to promote the cleavage of picolinic amides,[2b] however in our hands we found the reported conditions to afford little or no reactivity for a variety of substrates.

We therefore sought to develop a simple, high-yielding procedure to convert picolinic amides to the corresponding amines under mild reaction conditions. We were inspired by an earlier study in which Barrière et al. reported the reductive cleavage of the 3-hydroxy-picolinamide group within the polyamide antibiotic pristinamycin.[5] However, in spite of detailed mechanistic investigations by the same authors,[6] there have been no further Letters on the reductive cleavage of picolinic amides exhibiting high chemical yields and broad functional group tolerance.

## Results and discussion

Our studies began with the preparation of a collection of diverse picolinic amides. The conversion of amines to the corresponding picolinic amides is trivial; many methods have been reported, including amide coupling procedures such as DCC or EDCI coupling,[7] mixed anhydride methods[8] and Schotten–Baumann methods.[9] In order to expedite our studies, we chose the HATU amide coupling procedure[10] to afford a series of picolinic amides in good to excellent yields. Treatment of these amides with excess zinc dust in aqueous HCl (1.5 M) at room temperature led to regeneration of the parent amines in good to excellent yield for most substrates (Table 1).

The reaction tolerates a broad range of functional groups including aryl halides (entry 1), ethers (entry 2), alcohols (entry 4) and nitrogenous heterocycles (entries 5 and 6). As evidenced by entry 6, even acid sensitive substrates such as methyl esters can be successfully converted to the parent amine with careful control of the reaction time. Notably, entries 6 and 8 also necessitated the addition of tetrahydrofuran as a co-solvent as the parent amides were insoluble in water alone; this demonstrates that even substrates with poor aqueous solubility can be used in this reaction.

Entry 8 resulted in a complex mixture from which the desired product was isolated in just 30% yield. It is likely that facile reduction of the aromatic ketone moiety competes with the desired reaction; this suggests that the Zn/HCl cleavage procedure is poorly compatible with other readily-reduced functional groups.

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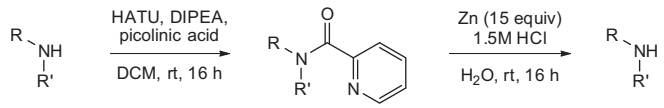
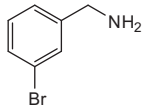
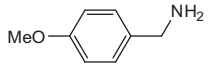
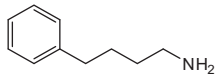
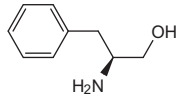
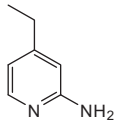
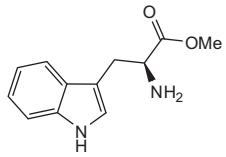
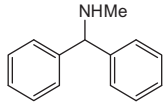
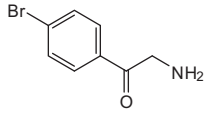
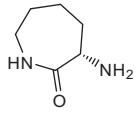
**Table 1**
Protection and deprotection of amines as picolinic amides

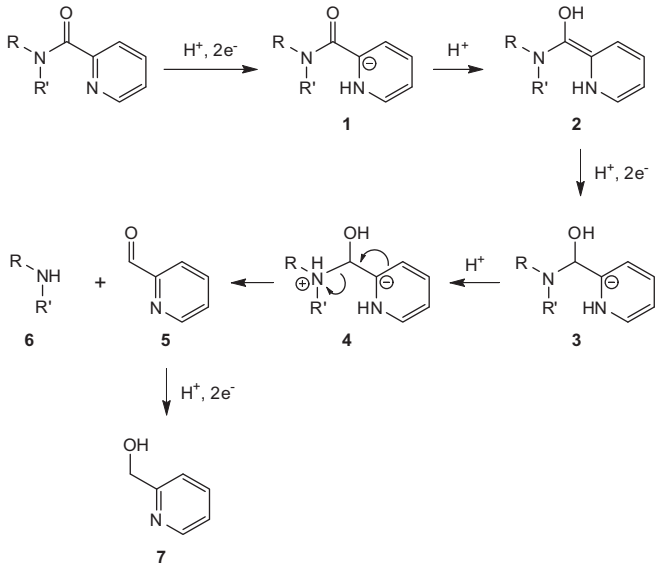



| Entry | Substrate | Step 1 % isolated yield | Step 2 % yield by internal standard[a] (isolated yield) |
|---|---|---|---|
| 1 |  | 85 | 79 (65)[b] |
| 2 |  | 98 | 94 (91) |
| 3 |  | 94 | 99 (96) |
| 4 |  | 92 | 69 (60) |
| 5 |  | 82 | 99 (95) |
| 6 |  | 99 | 67 (57)[c] |
| 7 |  | 96 | 63 (59) |
| 8 |  | 86 | 31 (30)[c] |
| 9 |  | 75 | 20 (not isolated) |

[a] Determined by $^1$H NMR using $(MeO)_3Ph$ as internal standard.
[b] No evidence of the debrominated product was observed by $^1$H NMR analysis of the crude reaction mixture.
[c] Solvent changed to 1:1 THF/$H_2O$, reaction time 1.5 h.

In the case of entry 9, the poor yield for selective cleavage in the presence of the lactam functionality is consistent with the earlier Letter on the polyamide pristinamycin[5] in which the authors also observed a complex mixture of products; this suggests that these conditions have limited compatibility with compounds containing other sensitive amide functional groups.

The reaction mechanism is likely to proceed via a sequence of protonation/reduction steps as outlined in Scheme 1; the proposed mechanism is supported by an earlier work by Fleury and co-workers.[6] Protonation of the pyridine nitrogen facilitates zinc reduction within the aromatic ring **1** followed by protonation of the resulting anion **2**. A further protonation/reduction sequence leads to hemiaminal **4** which dissociates under acidic conditions to afford the product amine **6** and pyridine-2-carboxaldehyde **5**, which is further reduced under the reaction conditions to pyridin-2-ylmethanol **7**.[11]




**Scheme 1.** Proposed mechanism for the Zn/HCl reductive cleavage of picolinic amides.

In summary, we have demonstrated a facile procedure for the Zn/HCl promoted cleavage of picolinic amides. The mild conditions and broad functional group tolerance suggest that this reaction should be useful in complex molecule synthesis and related synthetic applications.

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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.2016.05.068.

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