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Partial Reduction of Electron-Deficient Pyridines†

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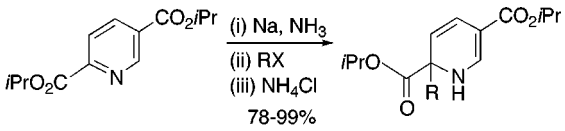
ABSTRACT



The partial reduction of electron-deficient pyridines is described herein. Mono- and disubstituted pyridines can be transformed into functionalized dihydropyridines using either Birch reduction conditions or sodium/naphthalene in THF. The compounds formed by these high-yielding reductive alkylation protocols have potential as synthetic intermediates, and we have shown that bicyclo compounds containing 6,5, 6,6, and 6,7 ring systems can be prepared in one step via a base-promoted cylization.

Reduction of the pyridine nucleus is a well-known transformation, with methods available for complete or partial addition of hydrogen.[1]

There are a few reagents capable of partially reducing pyridines to dihydropyridines, and the outcome is normally formation of 1,4-dihydro products.[2] Additionally, the formation of 1,2-dihydropyridines can be encouraged by addition of hydride sources to acylpyridinium salts formed in situ, although mixtures of regioisomers are sometimes formed.[3]

There are a handful of papers describing the Birch reduction of pyridines, and these describe the formation of 1,4-dihydropyridines that must be either stabilized by an electron-withdrawing group on nitrogen[4] or transformed in situ, presumably to prevent autoxidation.[5] It is fair to say that the Birch reductive alkylation reaction has not been applied to pyridine and also that this is a worthwhile goal as the products formed from such a reaction should prove to be useful synthetic intermediates for natural (and medicinal) products synthesis. Moreover, the regiochemistry that is obtained and the range of substituents that may be introduced by a reductive alkylation are difficult to match by any other method. Clearly, reductive alkylation procedures are expected to give products that are comparatively resistant to autoxidation and rearomatization.

Surprisingly, the Birch reduction of picolinic, nicotinic, and isonicotinic acids (or derivatives thereof) has not been reported in the literature. The successful Birch reduction of these substrates would elaborate a powerful methodology in organic chemistry, and as part of a study designed to explore the partial reduction of heterocycles,[6] we tested ester derivatives of the three acids. Birch reductive alkylation of isopropyl ester **1** was the most encouraging, Scheme 1.

† Dedicated to the late A. G. Schultz.
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(1) For a general review of the partial reduction of pyridines, see: Keay, J. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: 1991; Vol. 8, p 579.

(2) For examples, see: (a) Carelli, V.; Liberatore, F.; Scipione, L.; Musio, R.; Sciacovelli, O. *Tetrahedron Lett*. **2000**, *41*, 1235. (b) Comins, D.; Abdullah, A. H. *J. Org. Chem*. **1984**, *49*, 3392. (c) Yamada, S.-I.; Kuramoto, M.; Kikugawa, Y. *Tetrahedron Lett*. **1969**, 3101.

(3) For examples, see: (a) Sundberg, R. J.; Hamilton, G.; Trindle, C. *J. Org. Chem*. **1986**, *51*, 3672. (b) Booker, E.; Eisner, U. *J. Chem. Soc., Perkin Trans. 1* **1975**, 929. (c) Fowler, F. W. *J. Org. Chem*. **1972**, *37*, 1321.

(4) (a) Birch, A. J.; Karakhamor, E. A. *J. Chem. Soc., Chem. Commun*. **1975**, 480. (b) Olah, G. A.; Hunadi R. J. *J. Org. Chem*. **1981**, *46*, 715.

(5) (a) Danishefsky, S.; Cavanaugh, R. *J. Am. Chem. Soc*. **1968**, *90*, 520. (b) Danishefsky, S.; Cain P. Nagel, A. *J. Am. Chem. Soc*. **1975**, *97*, 380. (c) Danishefsky, S.; Cain, P. *J. Org. Chem*. **1975**, *40*, 3606. (d) Danishefsky, S.; Cain, P. *J. Steroid Biochem*. **1975**, *6*, 177. See also: Shaw, B. D. *J. Chem. Soc*. **1937**, 300.

(6) See: (a) Donohoe, T. J.; Ace, K. W.; Guyo, P. M.; Helliwell M.; McKenna, J. *Tetrahedron Lett*. **2000**, *41*, 989. (b) Donohoe, T. J.; Guillermin, J.-B.; Frampton, C.; Walter, D. S. *Chem. Commun*. **2000**, 465 and references therein.

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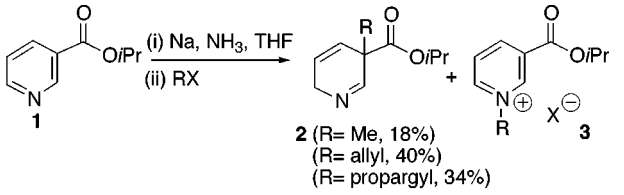
Scheme 1



Yields of reduced compound **2** (which is stable) were variable and depended on the electrophile used (methyl iodide, allyl bromide, and propargyl bromide are shown): these reactions were characterized by low mass recovery. A clue as to the fate of the pyridine was found when we isolated pyridinium salt **3** (R = Me) from the aqueous extract of one reaction quenched with MeI.

From the product distribution described above, we propose the following mechanism, Figure 1. Addition of two electrons

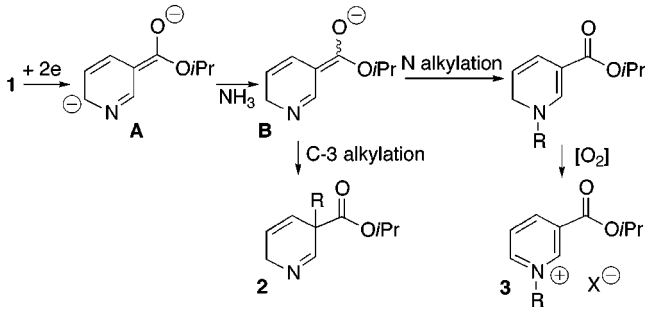


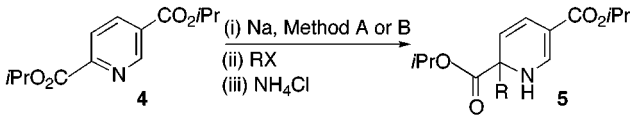
Figure 1.

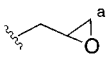
to **1** would form the dianion **A** which is basic enough to deprotonate ammonia (at C-6) and thus form extended enolate **B**. It appears that problems arise from a lack of regioselectivity during reaction of **B**, which can either alkylate at C-3 (to give **2**) or at nitrogen to give a dihydropyridine intermediate which autoxidizes directly to **3**.[7] Attempts to improve the regioselectivity of the Birch reduction reaction by further variation of the electrophile and reaction conditions were unsuccessful.

We concluded that reduction of diester **4** may avoid this problem of enolate regioselectivity and give a product that was relatively stable to autoxidation. This compound was prepared from the commercially available diacid in one step, (*i*PrOH, H_2SO_4, 65 g scale, 65%). Reductive alkylation of **4** under Birch-type conditions (Scheme 2, Method A, quenching the reaction with an electrophile followed by a proton source) gave excellent yields of the corresponding monoalkylated dihydropyridines **5**.[8] We were also pleased to note that the partial reduction could also be accomplished by using

(7) A control experiment whereby **1** was dissolved in NH_3 at −78 °C and treated with MeI gave no reaction; this showed that compound **3** was not formed by the addition of MeI to unreduced starting material **1** after a Birch reaction.

Scheme 2[a]



Entry	RX	R	Method	Yield (%)
1	MeI	Me	A	99
2	MeI	Me	B	86
3	EtI	Et	A	98
4	EtI	Et	B	78
5	*i*BuI	*i*Bu	A	93
6	epibromohydrin		B	84
7	allyl-Br	allyl[b]	A	90
8	$I(CH_2)_3Cl$	$(CH_2)_3Cl$	A	96
9	$I(CH_2)_3Cl$	$(CH_2)_3Cl$	B	96
10	$I(CH_2)_4Cl$	$(CH_2)_4Cl$	A	99
11	$I(CH_2)_4Cl$	$(CH_2)_4Cl$	B	91
12	$I(CH_2)_5Cl$	$(CH_2)_5Cl$	A	97
13	$I(CH_2)_5Cl$	$(CH_2)_5Cl$	B	94

[a] **Method A**: Na (3.5 equiv), NH_3/THF, −78 °C, then RX (3.5 equiv), then NH_4Cl after 5−30 s (time delay depends on the electrophile). **Method B**: Na (4.5 equiv), naphthalene (5 equiv), THF, −78 °C, then RX (3.5 equiv), then NH_4Cl after 5−30 s (time delay depends on the electrophile). a = formed as a mixture of diastereoisomers. b = this compound will aromatize in approximately 24 h at room temperature and should be stored in the freezer.

our recently reported conditions of sodium and naphthalene in THF, Scheme 2, Method B, thus avoiding the need for liquid ammonia.[9] Moreover, both sets of reducing conditions were compatible with a range of electrophiles.

We presume that the doubly activated pyridine **4** is capable of forming the stable dianion **C** after addition of two electrons, Figure 2.[10] The electrons are either "free" in

(8) Method A: to a deep blue solution of freshly distilled ammonia (100 mL), sodium (0.322 g, 1.40 mmol), and THF (10 mL) was added the pyridine **4** (0.803 g, 0.32 mmol) in THF (20 mL), and the reaction was stirred at −78 °C under an atmosphere of nitrogen for 30 min. Addition of isoprene (0.5 mL) followed by MeI (0.7 mL, 1.12 mmol) caused the reaction to turn light red in color. Stirring was continued for 8 s (timed from the start of electophile addition) before rapid addition of a saturated NH_4Cl solution (5 mL) [color change to light yellow]. The reaction was allowed to warm to room temperature overnight under an atmosphere of nitrogen. The reaction was diluted with CH_2Cl_2 (4 × 30 mL), dried (Na_2SO_4), and concentrated *in vacuo* to yield a yellow oil (0.966 g). Gradient column chromatography on silica eluting with 5:95 acetone/hexanes followed by 10:90 acetone/hexanes isolated the title compound as a pale yellow oil (0.843 g, 99%). We prefer to store these products in the freezer.

(9) Donohoe, T. J.; Harji, R. R.; Cousins, R. P. C. *Tetrahedron Lett.* **2000**, *41*, 1331. Method B: a solution of naphthalene (1.00 g, 0.78 mmol), sodium (0.172 g, 0.75 mmol), and THF (40 mL) was sonicated at room temperature for 1 h, by which time a deep green color had been formed. The reaction was cooled to −78 °C before addition of pyridine **4** (0.323 g, 0.13 mmol) in THF (20 mL). Stirring was continued for 45 min before addition of $I(CH_2)_3Cl$ (0.55 mL, 0.52 mmol) over a period of 10 s. The reaction was stirred for a further 10 s before rapid addition of a saturated NH_4Cl solution (5 mL), on which the reaction turned light yellow/orange with a white precipitate. The reaction was allowed to warm to room temperature and then absorbed on silica. Column chromatography (with reaction dry-loaded) on silica eluting with neat hexanes (to remove the naphthalene) followed by 5:95 acetone/hexanes furnished the title compound as a yellow oil (0.381 g, 96%).

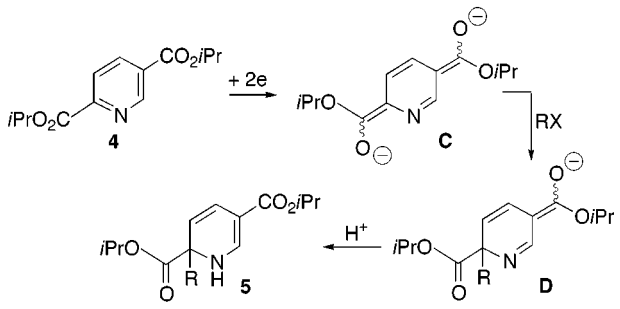


Figure 2.

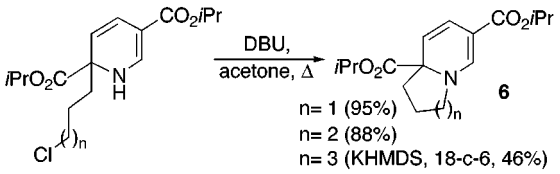
solution under Birch conditions (Method A) or donated from the radical anion of naphthalene under non-ammonia (Method B) conditions. Dianion **C** then reacts with the external electrophile fastest at C-2 to form the extended enolate **D** in solution. Finally, we add excess NH_4Cl solution to protonate **D** (added at a short interval after RX to avoid double alkylation of **C**).[11] In this scenario, the regiochemistry of protonation of enolate **D** is unimportant as the product tautomers will equilibrate to (what we presume is) the thermodynamically more stable isomer **5** as shown.

Some of the functionalized compounds described in entries 8−13, Scheme 2, were then subjected to cyclization conditions (DBU, acetone, Δ) and formed the corresponding bicyclo systems in high yields, Scheme 3. This chemistry offers an attractive and short route to bicyclo 5,6 and 6,6 ring systems. Not surprisingly, cyclization to form the seven-membered ring ($n = 3$) was slow under these conditions, and the best yield that we could obtain involved reaction of

(10) For an example of a stable dianion formed from reduction of a pyrrole, see: Donohoe, T. J.; Harji, R. R.; Cousins**,** R. P. C. *Tetrahedron Lett.* **2000**, *41*, 1327.

(11) Flooding dianion **C** with excess methyl iodide gave two compounds (93% combined yield) each with a methyl at C-2 and the second methyl either on nitrogen or on C-5.

Scheme 3



the corresponding chloride in THF with KHMDS and 18-crown-6. This method for the synthesis of such bicyclic ring systems has clear potential for elaboration into biologically active natural products. The identity of compound **6** ($n = 1$) was confirmed by X-ray crystallography.

We are currently investigating the reactivity pattern of the dihydro compounds descibed herein and expect that a wide variety of derivatization reactions will be possible. It should be possible to distinguish between the very different ester groups in the products. Preliminary experiments have shown that the NH group of these heterocycles can be Boc protected in excellent yield (>90%) under standard conditions (Boc_2O, DMAP, MeCN),[12] and this change is expected to alter the reactivity pattern of the diene and ester groups.

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Supporting Information Available: ^1H NMR spectra and detailed spectroscopic data for all new compounds and representative experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org

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(12) Grehn, L.; Ragnarsson, U. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 296.