

The partial reduction of heterocycles: an alternative to the Birch reduction

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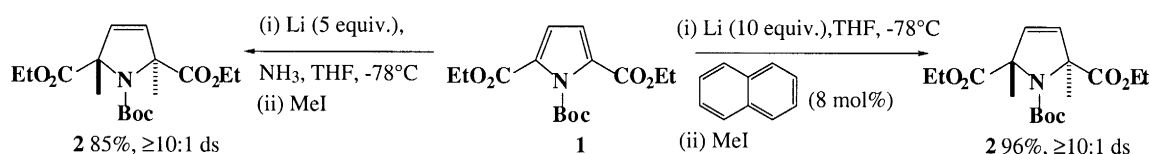
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Abstract

The partial reduction of a series of heterocycles in THF is described. By adding amine **3** as a proton source and naphthalene as an electron carrier, we were able to produce reductively alkylated pyrrolines and dihydrofurans in moderate to good yields. This reaction does not require liquid ammonia as a solvent, which may have interesting ramifications for large-scale synthesis. Moreover, we were also able to quench the reduction reactions with an acid chloride so performing a reductive acylation reaction. © 2000 Elsevier Science Ltd. All rights reserved.

In the preceding paper we described the double reductive alkylation of 2,5-diester **1** under Birch type conditions (Scheme 1).¹ Later, we discovered that the same reduction could be performed in THF (no ammonia) with lithium metal and catalytic amounts of naphthalene used as an electron shuttle.¹ We feel that removing the need for ammonia solvent will make the partial reduction reaction more practicable, especially on a large scale, and may also allow us to quench reduction reactions with sensitive electrophiles that would otherwise react with ammonia itself.



Scheme 1.

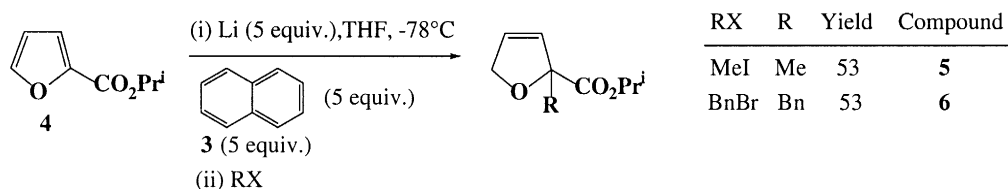
The reduction of other electron-deficient heterocycles using this method would prove a potentially useful extension to this methodology. However, there are some problems that need to be addressed first. Reduction of **1** with naphthalene is straightforward because the pyrrole acquires two electrons to form a stable dianion that is subsequently alkylated twice. Most of the pyrroles and furans that we have reduced previously have only one ester activating group and form relatively unstable dianions that are

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basic enough to deprotonate ammonia (protonation of this dianion forms an enolate which can then be alkylated). Thus, a proton source is needed if the reaction is to become widely applicable.

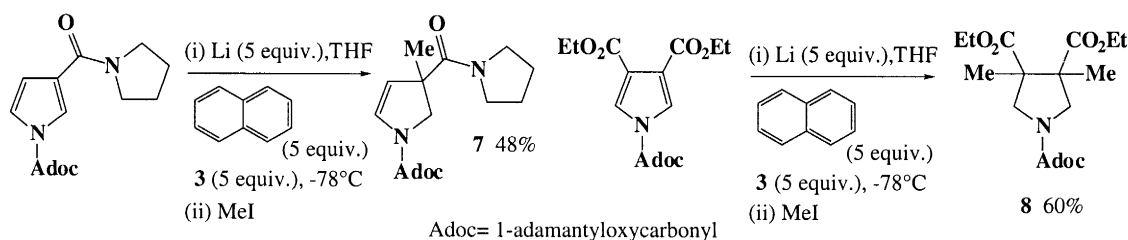
Previously we have added an excess of $(\text{MeOCH}_2\text{CH}_2)_2\text{NH}$ **3** to the Birch reduction of heterocycles because it improves the yields.³ We suppose that the amine would either protonate the heterocyclic dianion itself, or react favourably with LiNH_2 to form $(\text{MeOCH}_2\text{CH}_2)_2\text{NLi}$ in situ. The advantage of having this anion present, rather than LiNH_2 , lies in its reduced nucleophilicity (presumably the anion is chelated) and basicity: this means that the anion is not so aggressive towards both starting material and product and the yields are increased. One essential property of this amine is its inability to protonate the enolate formed after protonation of the dianion: this means that we can add excess **3** with impunity and makes its role distinctly different from conventional proton sources used in the Birch reduction (e.g. *t*-BuOH).⁴

Clearly, the properties of this amine make it an ideal substitute for ammonia. Therefore, we took the electron deficient furan **4** and reduced it with lithium in THF with naphthalene (5 equiv.) and amine **3** (5 equiv.). Sonication during formation of lithium naphthalenide was found to be beneficial to the yield.⁵ After 2 h at -78°C , the reaction was quenched with two electrophiles (Scheme 2). We were delighted to find that the reductive alkylation reaction proceeded well and gave products identical to those observed in liquid ammonia. However, the yields of reduced products were not quite as high as that observed in a bona fide Birch reduction.⁶



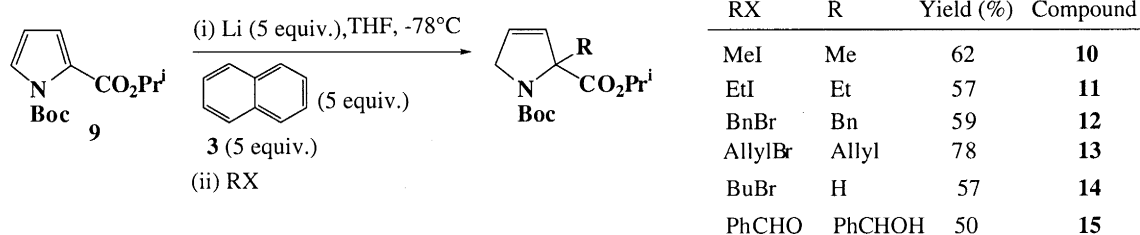
Scheme 2.

We then set about reducing 3-substituted and 3,4-disubstituted pyrroles under identical conditions to assess the scope of the reduction method (Scheme 3). In both cases, reductive alkylation products were isolated in reasonable yields.

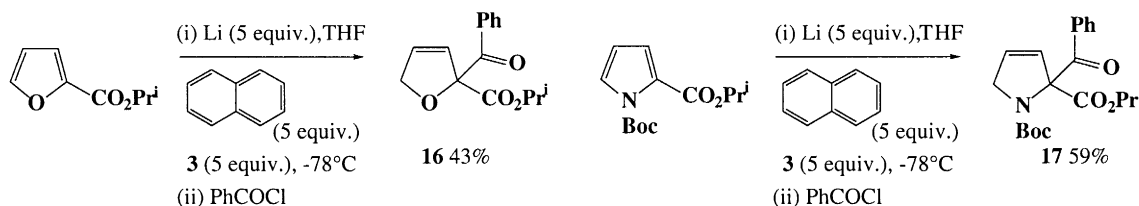
Scheme 3. Compound **8** was formed as a 1:1 mixture of diastereoisomers

Pyrrole **9** is one of the most useful heterocyclic systems we can partially reduce and a study was therefore undertaken (Scheme 4). In each case, the reduction reaction worked well to produce substituted pyrrolines. Formation of **15** via a reductive aldol reaction is noteworthy.⁷

The only example in which the product was at variance with that observed under Birch conditions in ammonia involved butyliodide as an electrophile. In this case, the protonated material **14** (which is a protected form of dehydropyrroline) was isolated in 57% yield; this result implies that the enolate generated under these conditions is not as nucleophilic as that formed in the Birch reduction.

Scheme 4. Compound **15** was formed as a 1:1 mixture of diastereoisomers

Remarkably, we were able to quench reduction reactions with benzoyl chloride to form β -ketoesters (Scheme 5); we have previously found that this type of electrophilic quench does not work at all in liquid ammonia, presumably because the acid chloride reacts with ammonia and the HCl by-product protonates the enolate.⁸



Scheme 5.

The mechanism of this reduction has not been studied in detail. However, we presume that the (green) radical anion derived from naphthalene (Li Np) is formed in solution (Fig. 1). Two equivalents of this reagent should form the corresponding dianion from the relevant heterocycle (only small amounts need be generated at any given time). Presumably, only this dianion is basic enough to deprotonate amine **3** to yield an enolate **A** and the amide anion **18**. With the exception of reaction with butyl iodide, this enolate behaves as if it were generated in liquid ammonia and reacts at the α -position with a variety of different electrophiles.

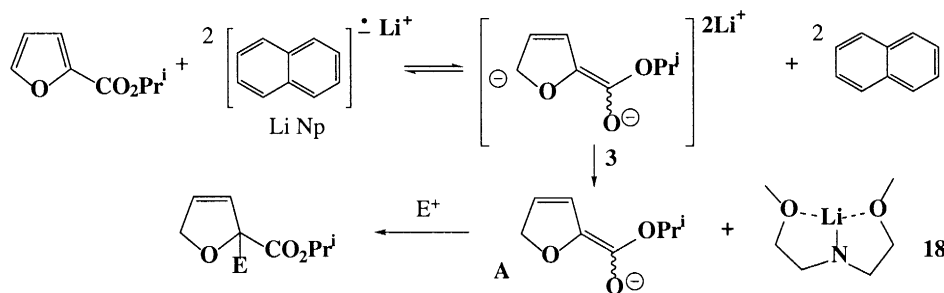


Fig. 1.

Attempts to optimise this reaction are underway and we have made the following observations regarding the reaction of **9** $\rightarrow$ **10** (Scheme 4).⁸

- The product **10** can be isolated in 57% yield using sodium, rather than lithium, metal.
- Addition of the pyrrole substrate over 2 h, using a syringe pump, increased the yield of **10** to 81% (however, not all heterocycles examined gave this increase in yield and further investigation is called for).
- The reaction was successful in diethylether (71% yield) using lithium metal and a syringe pump.

To conclude, we have developed an interesting method for the partial reduction of heterocycles that does not require ammonia as solvent. Replacing ammonia with THF and amine **3** means that a wider range of electrophiles can be tolerated in the reduction which obviously increases its scope. Efforts are currently underway to explore this reaction further.

Representative experimental procedure: A mixture of lithium metal (28 mg, 3.9 mmol) and naphthalene (506 mg, 3.9 mmol) in THF (25 mL) was placed in a sonic bath at room temperature for 1.5 h under an atmosphere of argon. The dark green solution was then cooled to -78°C and a premixed solution of pyrrole **9** (200 mg, 0.8 mmol) and amine **3** (0.59 mL, 3.9 mmol) was added. After 1 h, benzoyl chloride (1 mL, 8.6 mmol) was added and the reaction stirred at -78°C for 10 min before being quenched with aq. NH_4Cl . The crude mixture was evaporated to dryness and purified by chromatography on silica (eluting with EtOAc: petrol, 1:10) to afford **17** as a pale yellow oil (315 mg, 59%): ^1H NMR (200 MHz, CDCl_3) δ 7.90–7.75 (m, 2H, ArH), 7.60–7.30 (m, 3H, ArH), 6.24–6.03 (m, 2H, $2\times\text{CH}$), 5.20–5.03 (m, 1H, $\text{HC}(\text{CH}_3)_2$), 4.58–4.30 (m, 2H, NCH_2), 1.50–1.00 (m, 15H, $\text{C}(\text{CH}_3)_3$, $\text{HC}(\text{CH}_3)_2$).

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