Birch Reduction of Electron-Deficient Pyrroles

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The partial reduction of aromatic compounds using group I metals, ammonia solvent, and a proton source (usually *tert*-butyl alcohol) has become a powerful method for the preparation of complex organic molecules.[1] The scope of this reaction (the Birch reduction) has been extended beyond carbocyclic aromatics and onto many heteroaromatic systems.[2] However, the Birch reduction of pyrrole and its derivatives appears to have met with failure[3] and, to the best of our knowlege, is unknown in the literature. By analogy with both furan and thiophene, Birch reduction of the pyrrole nucleus should give the 3-pyrroline skeleton,[4] which is a useful and versatile synthetic intermediate (Figure 1).[5] This paper concerns extension of the Birch reduction to pyrroles.

We speculated that, in general terms, the pyrrole nucleus was too electron-rich to accept electrons and be reduced. Moreover, the presence of an acidic hydrogen atom on the pyrrole nitrogen presents the possibility of deprotonation under Birch-type conditions, and the resulting anion would be extremely resistant to reduction.

Initial studies began on the *N*-methylated pyrrole **2** (Scheme 1), which was readily prepared in two steps from commercially available 2-(trichloroacetyl)pyrrole.[6] Compound **2** was designed to overcome both of the barriers to reduction that are outlined above. The amide group at C-2 was specifically chosen not only as an electron-withdrawing group but also as a "handle" by which we could introduce substituents at C-2 by reductive alkylation. Accordingly, Birch reduction/alkylation of **2** with sodium in liquid ammonia (using 1 equiv of *tert*-butyl alcohol and quenching with methyl iodide) gave the pyrroline **3** (albeit in modest yield) (Scheme 1).[7] In this reaction, starting material was completely consumed, and the major product was the volatile aldehyde **4**, which had resulted from amide reduction rather than pyrrole reduction.[8]

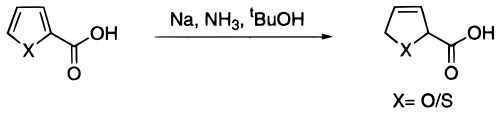


Figure 1.

Scheme 1

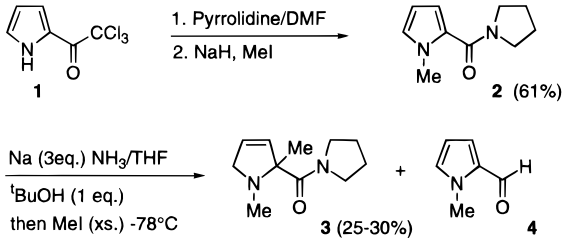
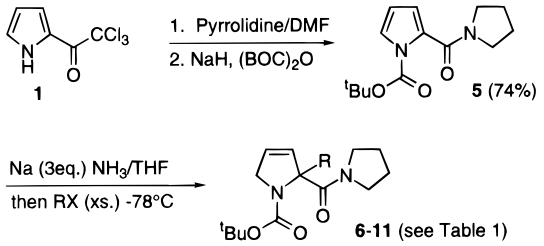


Table 1

entry	RX	R	yield (%)	compd
1	MeI	Me	85	**6**
2	BnBr	Bn	72	**7**
3	EtI	Et	81	**8**
4	BuI	Bu	86	**9**
5	^{i}BuI	^{i}Bu	73	**10**
6	NH_4Cl	H	71	**11**

Scheme 2



A solution to this problem was sought in the form of *N*-BOC amide **5**, which we suspected was sufficiently electron deficient to encourage reduction of the aromatic portion of the molecule. After an efficient synthesis of **5**, a versatile and high-yielding protocol for reductive alkylation was found by employing sodium metal (3 equiv) and omitting *tert*-butyl alcohol (Scheme 2). The results presented in Table 1 show that the enolate species that is quenched in the final step of the reaction is very reactive toward a series of primary alkyl halides, even those with branching at the β-position (entry 5, Table 1).[7] The 3,4-dehydroproline derivative **11** could be obtained by quenching the reaction with ammonium chloride (entry 6, Table 1).[7] Quenching of the enolate with secondary alkyl iodides also gave compound **11**, presumably formed *via* an E_2-type elimination from the alkyl halide: despite this limitation, the reactivity of the amide enolate is certainly great enough to open many opportunities for synthesis.

We propose that, under the conditions outlined above, compound **5** is able to accept two electrons and form a dianion:[1b] this would be protonated by ammonia at C-5, leaving an anion (enolate) at C-2 that can be quenched by addition of an electrophile.

Both the amide and BOC protecting groups should be removable if this chemistry is to become synthetically useful. Therefore, compound **6** was selected as a model and was subjected to the conditions outlined in Scheme 3. Removal of the BOC group was straightforward and proceeded under standard conditions to yield the free amine **12** (Scheme 3). Treatment of **6** with concentrated

(1) For general reviews of the Birch reduction see: (a) Mander, L. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Volume 8. (b) Rabideau, P. W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1. (c) Rabideau, P. W. *Tetrahedron* **1989**, *45*, 1579.

(2) (a) Siegel, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Volume 8. (b) Gribble, G. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Volume 8. (c) Donohoe, T. J.; Garg R.; Stevenson, C. A. *Tetrahedron: Asymmetry* **1996**, *7*, 317.

(3) Birch, A. J.; Slobbe, J. *Heterocycles* **1976**, *5*, 905.

(4) Reduction of the pyrrole nucleus to 3-pyrrolines under acidic conditions is well documented. (a) Evans, G. G. *J. Am. Chem. Soc.* **1951**, *73*, 5230. Schumacher, D. P.; Hall, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 6076. Cornforth, J.; Du, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1463. (b) Ketcha, D. M.; Carpenter, K. P.; Zhou, Q. *J. Org. Chem.* **1991**, *56*, 1318. (c) Scott, J. W.; Focella, A.; Hengartner, U. O.; Parrish, D. R.; Valentine, D., Jr. *Synth. Commun.* **1980**, *10*, 529. (d) Robertson, A. V.; Witkop, B. *J. Am. Chem. Soc.* **1962**, *84*, 1697.

(5) Ding, Z.; Turafiello, J. J. *Synth. Commun.* **1990**, *20*, 227.

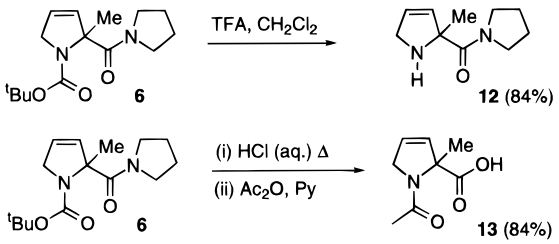
(6) Compound **1** can be prepared conveniently from pyrrole and trichloroacetylchloride: Harbuck, J. W.; Rapoport, H. *J. Org. Chem.* **1972**, *37*, 3618.

(7) All new compounds have been fully characterized. Compound **6** has been further characterized by X-ray crystallography. Donohoe, T. J.; Guyo, P. M. Unpublished work.

(8) See Kaiser, E. M. *Synthesis* **1972**, 391.

S0022-3263(96)01688-X CCC: $12.00

Scheme 3

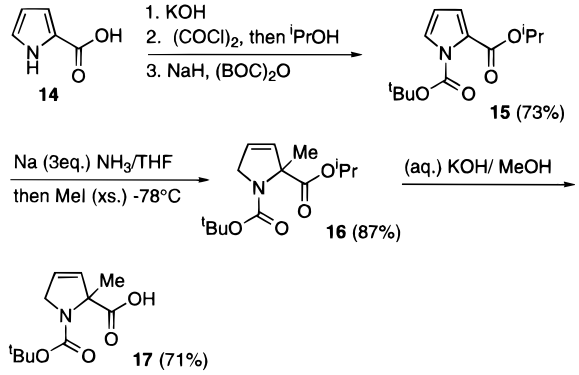


HCl(aq) at reflux secured removal of both the BOC and amide groups to yield the corresponding amino acid, which was conveniently purified as its *N*-acetyl derivative (**13**, Scheme 3). Notably, both of these transformations occurred without any detectable migration of the double bond at C-3.

Finally, we examined the Birch reduction of isopropyl ester **15**, which was prepared in two steps from the potassium salt of commercially available acid **14** (Scheme 4). The Birch reduction/alkylation of **15** proceeded well and gave the pyrroline ester **16** in excellent yield (Scheme 4). The advantage of carrying an ester through this sequence was realized when **16** was saponified to yield the acid **17** in 71% yield. This methodology provides a practicable alternative to the amide-substituted pyrrole reductions described earlier and means that the carboxylic acid at C-2 may be liberated without deprotection of the amine.

To conclude, we have developed a high-yielding and versatile method for the reduction of electron deficient pyrroles to 3-pyrrolines. This chemistry is compatible with several functional groups, which means that selective manipulation and deprotection of the reduced products is possible. Considering the large amount of chemistry in the literature regarding the synthesis of substituted pyrroles, we feel that this approach will have many useful applications in the preparation of important organic compounds, both natural and unnatural. Further work is continuing in this area.

Scheme 4



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Supporting Information Available: Experimental details and spectroscopic data for compounds **2**, **3**, **5**−**13**, and **15**−**17** (51 pages).

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