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Double Reduction of Cyclic Aromatic Sulfonamides: A Novel Method for the Synthesis of 2- and 3-Aryl-Substituted Cyclic Amines

Paul Evans,*,† Thomas McCabe,† Ben S. Morgan,‡ and Sophie Reau‡

Department of Chemistry, Trinity College, University of Dublin, Dublin 2, Ireland, and Department of Chemistry, University of Liverpool, Liverpool, L69 7ZD, United Kingdom

evansp@tcd.ie

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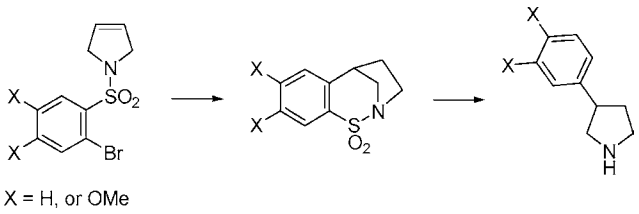
ABSTRACT



The facile double reduction of bicyclic aromatic sulfonamides was used to synthesize a variety of 2- and 3-aryl-substituted pyrrolidines and 2-phenylpiperidine. The method features a combined nitrogen protection and a traceless tether for the transposition of the aromatic moiety from nitrogen to carbon.

Sulfonamides constitute one of the main classes of N-protecting group used in modern-day organic synthesis.[1] They are attractive in this capacity because they are chemically robust, and because they can often be removed in high yield by reduction with various metals dissolved in liquid ammonia, or by metal naphthalenides. As a rule, the fate of the sulfonyl group is ignored during such deprotection reactions. However, mechanistic studies performed by Kovacs[2] in 1966 and Closson[3] in 1970 suggest that depending on the amount of reducing agent employed, both nitrogen−sulfur and carbon−sulfur bond scission do occur (i.e., double reduction). We became interested in the double-reduction process in the context of converting cyclic sulfonamides of type **1** into aryl-substituted amino compounds of type **2** (Figure 1).[4] Conceptually, the sulfonamide ring size could be varied ($n = 0$, 1, 2, etc.), and arguably the most useful manifestation of this sequence would be one in which the starting sulfonamide

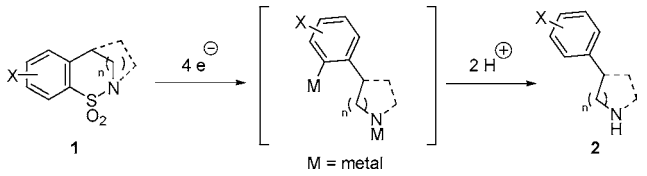


Figure 1. Possible pathway for the double reduction of cyclic sulfonamides.

† Trinity College.
‡ University of Liverpool.

(1) (a) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Thieme: Stuttgart, 2004. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999. (c) For a treatise on the general chemistry of sulfonamides, see: *The Chemistry of Sulphonic Acids Esters and their Derivatives*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1991.

(2) Kovacs, J.; Ghatak, U. R. *J. Org. Chem.* **1966**, *31*, 119.

(3) Closson, W. D.; Ji, S.; Schulenberg, S. *J. Am. Chem. Soc.* **1970**, *92*, 650.

(4) (a) Gautier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289. (b) Nájera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547.

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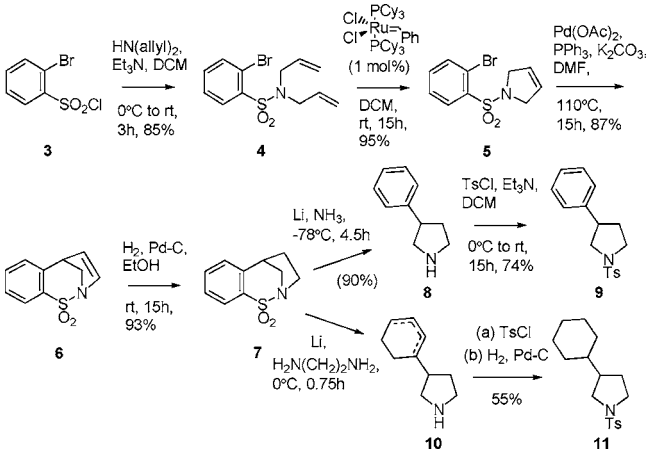
1 was polycyclic, thereby generating cyclic amines of the type **2**. Such molecules might be expected to have interesting biological effects.

Initial studies focused on the double reduction of the tricyclic sulfonamide **7**. This was prepared from **3** via the corresponding *N*-diallyl sulfonamide **4**, by ring-closing metathesis (RCM) with Grubbs' catalyst, intramolecular Heck reaction on the resulting product **5**, and double-bond reduction of **6** with H_2/Pd−C following a literature procedure (Scheme 1).[5]

Scheme 1. Synthesis of 3-Phenyl and 3-Cyclohexylpyrrolidines

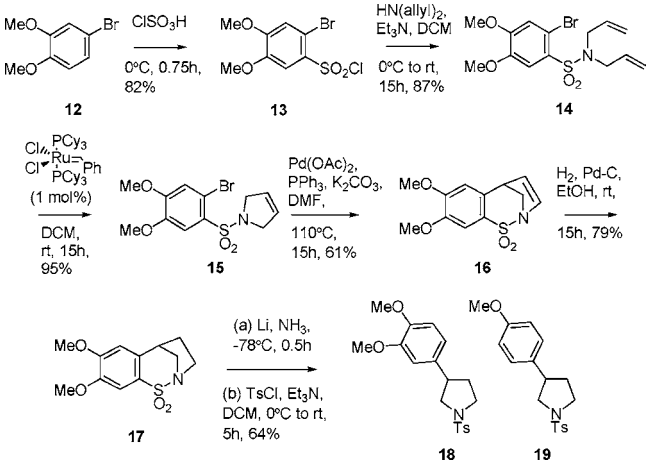


Pleasingly, under standard lithium/liquid NH_3 dissolving metal reaction conditions,[1,6] compound **7** was converted into 3-phenylpyrrolidine **8** in excellent yield (90%). Compound **8** was isolated by distillation, and as expected, without an alcohol additive, no further "Birch-like" reduction of the 3-aryl substituent was observed. The use of sodium in the place of lithium gave a similar outcome. However, with the radical anion sodium naphthalenide, only intractable materials were observed. Further optimization indicated that only 5 equiv of lithium were required, and in this case the resultant secondary amine was converted into the *N*-toluenesulfonamide **9** (74%) for characterization purposes.

The corresponding reduction performed under Benkeser conditions,[7] using ethylenediamine and an excess of lithium (24 equiv), afforded an inseparable mixture of three regioisomeric monoalkenes **10** in which both the sulfonamide tethering group and the aromaticity of the 3-phenyl substituent had been destroyed. N-Functionalization and double-bond reduction gave the 3-cyclohexyl pyrrolidine **11** in 55% yield over three steps.

Our double reduction could also be successfully applied to more electron-rich aromatic ring systems (Scheme 2). For

Scheme 2. Synthesis of 3,4-Dimethoxyphenylpyrrolidine **18** and 4-Methoxyphenylpyrrolidine **19**

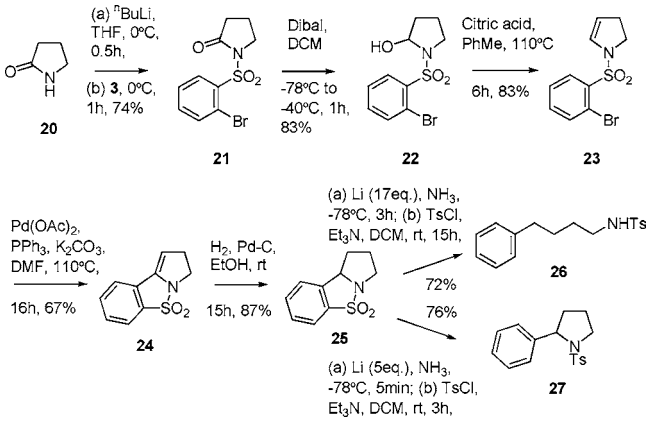


example, conversion of **12** to the corresponding sulfonyl chloride[8] and subsequent manipulation following the strategy described above gave **17** in 33% yield for the five steps. The successful Heck-type cyclization of the 1,2-dimethoxy aromatic bromide in this sequence is particularly notable.

Treatment of **17** with lithium in liquid ammonia followed by tosylation afforded a mixture of the expected 3-aryl pyrrolidine **18** (28%) and **19** (36%), the product of a regioselective aryl ether reduction. This type of aromatic ether cleavage under reductive conditions has been documented for several 1,2-dialkoxybenzenes.[9]

To further investigate the scope of this process, adduct **25** was prepared via a 5-*exo*-trig Heck cyclization−double-bond reduction sequence (Scheme 3). Thus, sulfonylation

Scheme 3. Synthesis of 2-Phenylpyrrolidine



of *N*-lithio pyrrolidinone[10] with **3** and subsequent lactam reduction[11] and dehydration[12] afforded the *N*-sulfonyl enamine Heck precursor **23** (Scheme 3). Interestingly, double-bond migration occurred during the Heck reaction under our

(5) (a) Grigg, R.; Sridharan, V.; York, M. *Tetrahedron Lett.* **1998**, *39*, 4139. (b) Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P.; Teasdale, A.; Thornton-Pett, M.; Worakun, T. *Tetrahedron* **1991**, *47*, 9703.

(6) Rabideau, P. W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1.

(7) Benkeser, R. A.; Robinson, R. E.; Suave, D. M.; Thomas, O. H. *J. Am. Chem. Soc.* **1955**, *77*, 3230. For a comparison between Birch-type and Benkeser reductions, see: Kaiser, E. M. *Synthesis* **1972**, 391.

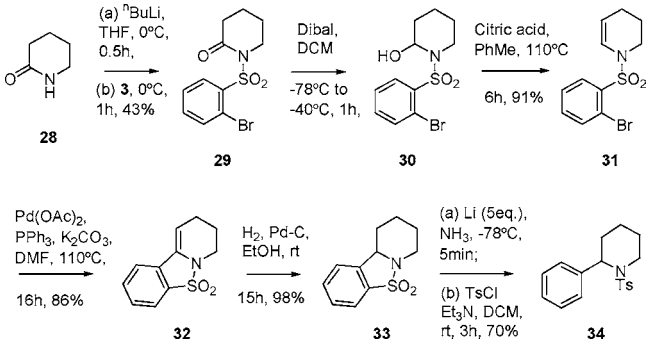
(8) Levi, A. A.; Smiles, S. *J. Chem. Soc.* **1931**, 520.

standard conditions, affording the trisubstituted alkene **24** alongside trace amounts of the expected disubstituted alkene. Following hydrogenation, the double reductive cleavage of **25** was investigated. It was found that when a large excess of lithium (17 equiv) was used, cleavage of the benzylic bond was observed, in addition to the desired double reductive cleavage. Following N-tosylation, compound **26** was isolated in 72% yield.

We reasoned that benzylic cleavage had occurred after the desired double sulfonamide reduction. Therefore, both the reaction period and the amount of reducing agent were optimized. It was subsequently found that use of 5 equiv of lithium completely reduced **25** after 5 min. 2-Phenylpyrrolidine was isolated in 76% yield as its *N*-toluenesulfonamide **27**.

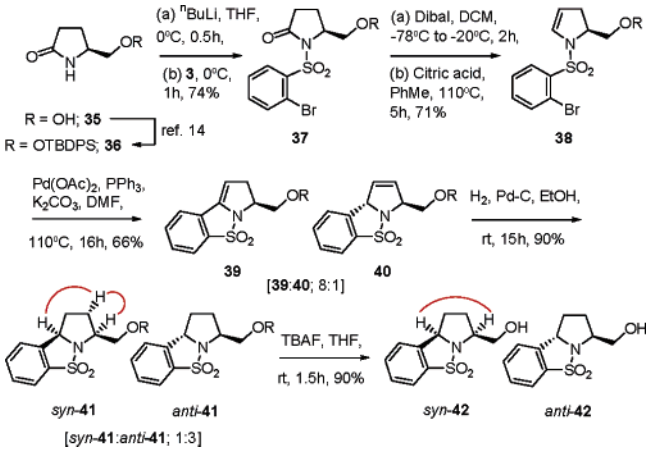
Studies with the corresponding piperidinyl system, accessed from piperidin-2-one **28** via an identical sequence of reactions, afforded precursor **33**, which smoothly underwent the desired double reduction, generating 2-phenylpiperidine **34** in 70% yield (Scheme 4).

Scheme 4. Synthesis of 2-Phenylpiperidine



The synthetic sequence described was adapted to prepare the enantioenriched 2-phenylpyrrolidine architecture exhibited by a series of natural and nonnatural aza sugars (Scheme 5).[13] The TBDPS group was chosen to protect the enantiopure primary alcohol **35**,[14] not only to withstand citric acid-facilitated dehydration but also to present a bulky group on one face of **39**. On the basis of the previous results we had obtained, the selective formation of **39** was expected. However, it was produced alongside appreciable amounts of **40** (single diastereomer on the basis of ^{1}H NMR spectroscopy), which proved to be inseparable by SiO_2 flash column chromatography. Somewhat surprisingly, reduction of this mixture gave a diastereoisomeric mixture (anti:syn = 3:1) of the saturated pyrrolidines **41**, which were now

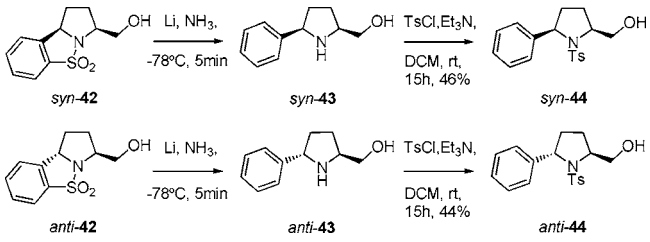
Scheme 5. Preparation of the Enantioenriched Double Reduction Precursors *syn*-**42** and *anti*-**42**



separable by careful SiO_2 flash column chromatography. Nuclear Overhauser (NOE) NMR spectroscopic studies indicated that the major isomer in this mixture possessed the anti ring architecture, indicating preferential hydrogenation from the same face as the substituent. Treatment of this mixture with TBAF in THF afforded a similar diastereoisomeric mixture of alcohols **42** (in 31 and 59% yields, respectively), which proved to be more readily separable by SiO_2 flash column chromatography.

Treatment of the major diastereomer *anti*-**42** with Li (6 equiv) in liquid NH_3 afforded the pyrrolidine product **43** of the desired double reduction, which was further converted to the sulfonamide *anti*-**44** (Scheme 6). Similarly, the minor

Scheme 6. Preparation of *syn*- and *anti*-[5*R*/*S*-Phenyl-1-(toluene-4-sulfonyl)pyrrolidin-2*S*-yl]methanol



diastereomer *syn*-**42** was converted into *syn*-**44**, whose spectroscopic data were in accord with that reported previously for racemic *syn*-**44**.[15] Additionally, X-ray crystallographic studies[16] demonstrated the syn-2,5-disubstituted ring architecture, thereby corroborating the stereochemical assignment made on the basis of the NOE studies indicated in Scheme 5.

In conclusion, we have described a novel method for the efficient preparation of aryl-substituted cyclic amines via the

(9) For example, see: Bunnett, J. F.; Jenvey, J. *J. Org. Chem.* **1996**, *61*, 8069 and references therein.
(10) Harkin, S. A.; Singh, O.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1489.
(11) Neipp, C. E.; Humphrey, J. M.; Martin, S. F. *J. Org. Chem.* **2001**, *66*, 531.
(12) Åhman, J.; Somfai, P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1079.
(13) For example, see: Severino, E. A.; Costenaro, E. R.; Garcia, A. L. L.; Correia, C. R. D. *Org. Lett.* **2003**, *5*, 305 and references therein.
(14) Cossy, J.; Cases, M.; Pardo, D. G. *Tetrahedron* **1999**, *55*, 6153.
(15) Gallagher, T.; Jones, S. W.; Mahon, M. F.; Molloy, K. C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2193.
(16) See Supporting Information for details.

double reduction of cyclic arylsulfonamides. Mechanistic studies aimed at probing the sequence of events suggested in Figure 1 and the application of this method toward the synthesis of naturally occurring aza sugars are currently under investigation.

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Supporting Information Available: Detailed descriptions of experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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