Pergamon

Tetrahedron Letters, Vol. 38, No. 20, pp. 3535-3538, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00696-5

An Efficient Protocol for the Selective Reduction of Benzenesulfonyllactam to Benzenesulfonyl Cyclic Amine

Toshihiro Hosaka, Yasuhiro Torisawa, and Masako Nakagawa*

Faculty of Pharmaceutical Sciences, Chiba University, 1-33, Yayoi-cho, Inage-ku, Chiba-shi, 263, Japan

Abstract: The selective reduction of *N*-benzenesulfonylpiperidin-2-one to *N*-benzenesulfonylpiperidine was accomplished through the use of $NaBH_4$ with either $ZrCl_4$ or $SnCl_4$ and by silane-mediated two-step reductions. © 1997 Elsevier Science Ltd.

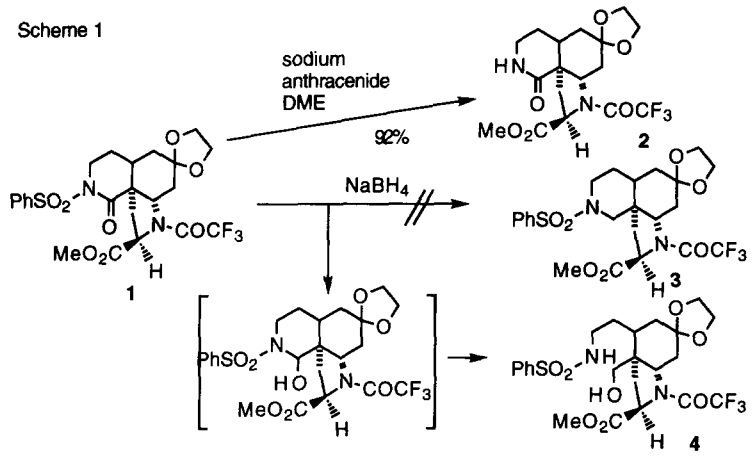
Sulfonamides are some of the most stable forms of amines, and are frequently used in various synthetic operations, despite the drastic conditions required for their reductive elimination.[1] Therefore, considerable effort has recently been devoted to the development of new methods for deprotection to their parent amines.[2] We previously reported the successful deprotection of benzenesulfonyllactam **1** to the corresponding lactam **2** through the use of sodium anthracenide in the presence of both an ester and a ketal functionality.[3d,3h]

On the other hand, very few methods have been reported for the selective reduction of the amide carbonyl group of *N*-acylsulfonamides to the corresponding sulfonamides including such reagents as BH_3•THF, BH_3•Me_2S,[4] and $NaBH_3(OCOCF_3)$.[5] In our work on the synthesis of manzamines,[3] we used an arenesulfonyl group for nitrogen protection to activate dihydropiperidine-2-one as a dienophile, and a method is now required for the selective conversion of **1** to benzenesulfonylamide **3** under conditions that would not cause ring-opening into the amino alcohol **4**. The choice of appropriate reagents is a major problem for the selective reduction of *N*-acylsulfonamides to the corresponding *N*-sulfonamides. This prompted us to look for a new and efficient protocol for selective reduction of the amide carbonyl group of a *N*-arylsulfonyllactam to the protected cyclic amine. In this paper, we report the reaction of *N*-benzenesulfonylpiperidone **5** with various reducing agents.

We started our survey with typical Al-based reducing agents. Thus, treatment of **5** with $LiAlH_4$ in ether at r.t. gave *N*-benzenesulfonyl-2-hydroxypiperidine **7** [6] in 52% yield together with the ring-opened amino alcohol **8** in 37% yield (run 1).

On the other hand, DIBALH reduction of **5** proceeded at –78°C within 30 min to selectively give **7** in an almost quantitative yield (run 2). Compound **7** proved to be stable towards normal work-up conditions, but was dehydrated to *N*-benzenesulfonyl-enamine **9** with pyridinium *p*-toluenesulfonate.[7] The conditions in runs 1 and 2 did not provide the desired sulfonamide **6**.

Scheme 1



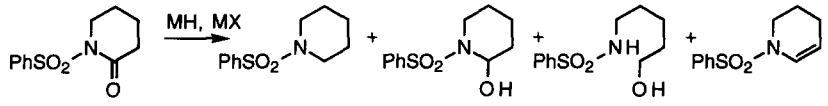


Table 1: Reduction of *N*-Benzenesulfonylpiperidin-2-one (5) wiht Various Metal Hydrides

run	reagent				conditions			yield (%)			
	MH (mol eq)		MX (mol eq)		solvent	temp.	time	6	7	8	9
1	$LiAlH_4$	0.5			ether	rt	20 min		52	37	
2	DIBALH	3			toluene	-78°C	30 min		97		
3	$Zn(BH_4)_2$	3			ether	rt	12 h	25	14	49	
4	nBu_4NBH_4	3			1,2-dichloro ethane	reflux	30 min	62		34	
5	$NaBH_4$	2			MeOH	rt	2 h			96	
6	$NaBH_4$	4	$SnCl_4$	1	THF	rt	20 min	95			
7	$NaBH_4$	4	$ZrCl_4$	1	DME	rt	5 h	92			
8	$NaBH_4$	6	$FeCl_3$	2	THF	rt	1 d	trace			
9	$NaBH_4$	6	$NiCl_2$	2	THF	rt	2 h			trace	
10	$NaBH_4$	6	$CoCl_2$	2	THF	rt	2 h	NR			
11	$(EtO)_3SiH$	5.4	$Ti(OiPr)_4$	0.7	no solvent	rt	5 h		~100		
12	Ph_2SiH_2	6	$Ti(OiPr)_4$	0.7	no solvent	rt	5 h		85		
13	$(EtO)_3SiH$	11	$Zr(OiPr)_4$	1	no solvent	100°C	1 h				90

The carbonyl group of *N*-arylsulfonyllactam is anticipated to be susceptible toward nucleophilic ring opening. Thus, the reduction of **5** in MeOH at r.t. resulted in reductive ring opening to give **8** in 96% yield (run 5). Meanwhile, the reaction of **5** with $Zn(BH_4)_2$ or nBu_4NBH_4 gave the desired sulfonamide **6** [8] in moderate yield along with considerable amounts of **8** (runs 3 and 4).

To attain the efficient reduction of the amide carbonyl group of **5** into the methylene group, we next investigated the combined use of $NaBH_4$ with a metal halide, such as $SnCl_4$[9a], $ZrCl_4$[9b], or $CoCl_3$[9c], which have been applied to the reduction of various other functional groups, including amides.

Among the combined reducing agents examined, a $NaBH_4/SnCl_4$ or $NaBH_4/ZrCl_4$ system proved to be the reagent of choice, and gave a high yield (92%) of **6** (run 6 and 7), although the reaction with $NaBH_4/ZrCl_4$ proceeded sluggishly and required a prolonged reaction time. The addition of stannic tetrachloride enhanced the selective reduction of the carbonyl group of **5** to **6**, while $FeCl_3$, $NiCl_2$, and $CoCl_2$ were all ineffective. *N*-Benzenesulfonyl-2-hydroxypiperidine **7** was readily converted to **6** in 92% yield when treated with Et_3SiH (3 equiv.) in CH_2Cl_2 in the presence of TFA (0.25 mol.equiv.) at -78°~-29°C for 40 min. However, direct conversion of **5** into **6** by Et_3SiH failed.

In contrast to the mild reducing ability of Et_3SiH/TFA, Buchwald reported the effective reduction of ester to alcohol using $(EtO)_3SiH/Ti(OiPr)_4$.[10]

An inexpensive reagent system was recently developed by the same research group[11] and others.[12] We examined the reduction of **5** by these Buchwald systems. The results are summarized in run 11~12, which shows that **7** is the major product in these reductions. This result indicates that the Buchwald system is as effective as DIBALH in the reduction of *N*-acylbenzenesulfonamides. As described above, **7** was easily converted to the *N*-protected cyclic amine **6** by treatment with Et_3SiH/TFA. On the other hand, the reaction of 5 with excess $(EtO)_3SiH$ at 80-100°C in the presence of $Zr(OiPr)_4$ resulted in the formation of 9 as the only detectable product (run 13).

In summary, a rapid and convenient procedure has been developed for the conversion of *N*-benzenesulfonyllactams into *N*-benzenesulfonamides.

The present results are currently being applied to the synthesis of **3**.

Acknowledgements: This study was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture. We also thank the Naito Foundation, Research Foundation of Optically Active Compounds, Japan Tabacco Inc., and Dr. H. Seki, Ms. R. Hara, and Mr. T. Kuramochi of the Chemical Analysis Center of our University for mass spectroscopy measurement, microanalysis, and NMR measurement.

References

1) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis* second ed., John Wiley & Sons, Inc., New York, **1991**, p.309. (b) Kociénski, P. J. *Protecting Groups*, Thieme, New York, **1994**, p.209.

2) (a) Vedejs, E.; Lin, S. *J. Org. Chem.* **1994**, *59*, 1602-1603. (b) Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127-3128. (c) Goulaouic-Dubois, C.; Guggisberg, A.; Hesse, M. *J. Org. Chem.* **1995**, *60*, 5969-5972. (d) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373-6374.

3) (a) Nakagawa, M.; Lai, Z.; Torisawa, Y.; Hino, T. *Heterocycles* **1990**, *36*, 999-1002. (b) Torisawa, Y.; Nakagawa, M.; Hosaka, T.; Tanabe, K.; Lai, Z.; Ogata, K.; Nakata, T.; Oishi, T.; Hino, T. *J. Org. Chem.* **1992**, *57*, 5741-5747. (c) Nakagawa, M.; Torisawa, Y.; Hosaka, T.; Tanabe, K.; Tavet, F.; Aikawa, M.; Hino, T. *Heterocycles* **1993**, *34*, 4543-4546. (d) Nakagawa, M.; Torisawa, Y.; Hosaka, T.; Tanabe, K.; Da-te, T.; Okamura, K.; Hino, T. *Tetrahedron Lett.* **1993**, *34*, 4543-4546. (e) Ma, J.; Nakagawa, M.; Torisawa, Y.; Hino, T. *Heterocycles* **1994**, *38*, 1609-1618. (f) Torisawa, Y.; Motohashi, Y.; Ma, J.; Hino, T.; Nakagawa, M. *Tetrahedron Lett.* **1995**, *36*, 5579-5580. (g) Torisawa, Y.; Ayman Ali, Mohamed; Tavet, F.; Kageyama, A.; Aikawa, M.; Fukui, N.; Hino, T.; Nakagawa, M. *Heterocycles* **1996**, *42*, 677-689. (h) Torisawa, Y.; Hosaka, T.; Tanabe, K.; Suzuki, N.; Motohashi, Y.; Hino, T.; Nakagawa, M. *Tetrahedron* **1996**, *52*, 10597-10608.

4) (a) Belletire, J. L.; Fry, D. L. *Synthetic Commun.* **1988**, *18*, 29-35. (b) Camoutsis, C.; Catsoulacos, P. J. *Heterocyclic Chem.* **1992**, *29*, 569-570.

5) Morris, J.; Wishka, D. G. *J. Org. Chem.* **1991**, *56*, 3549-3556.

6) Compound **7**, mp 110 °C ($CHCl_3$-hexane): ^{1}H-NMR(500 MHz) d 1.47-1.89(6H, m), 2.30(1H, dd, *J*=3.90 Hz, 1.40 Hz, OH), 3.15(1H, dd, *J*=12.08, 2.74 Hz), 3.57-3.64(1H, m), 5.56(1H, dd-like, *J*=3.12, 2.74 Hz), 7.49-7.63(3H, m), 7.84-7.89(2H, m). LREIMS m/e 241 (M^+), 224 (M^+-OH).; *Anal.* Calcd. for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.27; N, 5.81; S, 13.29. Found: C, 54.86; H, 6.28; N, 5.85; S, 13.08.

7) Ahman, J.; Somfai, P. *Tetrahedron* **1992**, *48*, 9537-9544.

8) *N*-Benzenesulfonylpiperidine **6**, mp 89-90°C; Hurd, C. D.; Sherwood, L. T. *J. Org. Chem.* **1948**, *13*, 471-476.

9) (a) Kano, S.; Yuasa, Y.; Shibuya, S. *J. Chem. Soc. Chem. Commun.* **1979**, 796. (b) Ituno, S.; Sakurai, Y.; Shimizu, K.; Ito, K. *J. Chem. Soc. Perkin Trans. I* **1990**, 1859-1863. (c) Satoh, T.; Suzuki, S. *Tetrahedron Lett.* **1969**, 4555-4558.

10) Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 3751-3753.

11) (a) Reding, M. T.; Buchwald, S. L. *J. Org. Chem.* **1995**, *60*, 7884-7890. (b) Bower, S.; Kreutzer, K. A.; Buchwald, S. L. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1515-1516.

12) (a) Nicolaou, K. C.; Shreiner, E. P.; Stahl, W. *Angew. Chem. Int. Ed. Engl* **1991**, *30*, 585-588. (b) Breeden, S. W.; Lawrence, N. J. *Synlett*, **1994**, 833-835.

(*Received in Japan* 10 *March* 1997; *revised* 7 *April* 1997; *accepted* 10 *April* 1997)