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Efficient oxidative spirocyclization of phenolic sulfonamides

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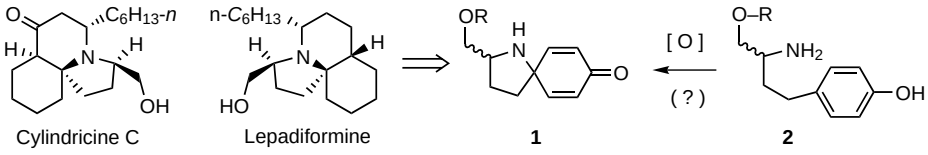
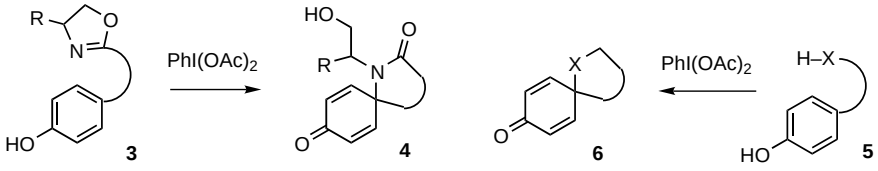
Abstract—Treatment of various homotyramine sulfonamides with iodobenzene diacetate in hexafluoroisopropanol induces oxidative spirocyclization in high yield. © 2002 Elsevier Science Ltd. All rights reserved.

Ongoing investigations on the synthesis of cylindricines and related alkaloids[1] mandated the development of an effective method for the oxidative cyclization of free primary amines such as **2**, or appropriately protected variants thereof, to intermediates of general structure **1** (Scheme 1). Recent work from this laboratory has established an avenue to spirolactams **4** via oxidative cyclization of phenolic *oxazolines* **3** (Scheme 2) with iodobenzene diacetate ('DIB').[2] The analogous oxidative cyclization of phenolic *secondary* amines (cf. **5**→**6**, X = *N*-alkyl) is possible,[3] but it remains problematic. Yields are often unsatisfactory, and the spirocyclic goals **6** are accompanied by a host of byproducts. Such shortcomings are magnified when the amino group in the substrate is primary (**5**, X = NH),[4] rendering the transformation entirely unsuitable for multistep synthetic operations. This has represented a major limitation of a valuable new technology. Efforts to resolve this problem led us to explore sulfonamides (cf. **5**, X = R-SO_2N) as equivalents of primary amines. This choice was motivated by a perceived analogy between the chemical behavior of sulfonamides and that of alcohols. For instance, sulfonamides undergo *N*-acylation at a rate comparable to that of primary alcohols.[5] Oxidative treatment of furylcarbinols[6] and *N*-sulfonyl furfurylamines[7] efficiently produces dihydro-β-pyranones and dihydro-β-pyridones, respectively, whereas *N*-acyl furfurylamines are not substrates for this reaction.[8] Because alcohols of the type **5** (X = O) cyclize efficiently to ethers **6** (X = O) upon exposure to DIB,[9] it seemed plausible that analogous sulfonamides may behave in a like manner. We now report that sulfonamide substrates indeed react with unprecedented efficiency in these heretofore problematic oxidative transformations.



Scheme 1.



Scheme 2.

Keywords: aminoacids; heterocycles; hypervalent iodine; phenols; sulfonamides.

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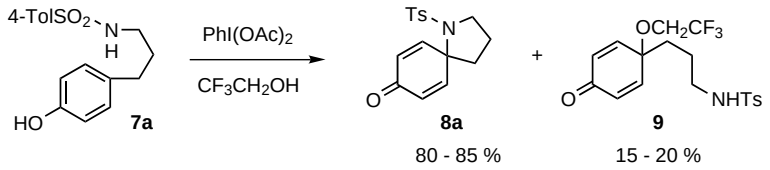
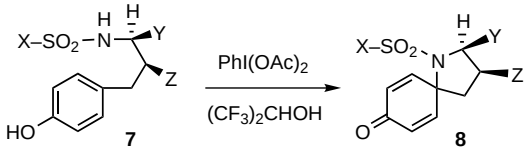


Scheme 3.

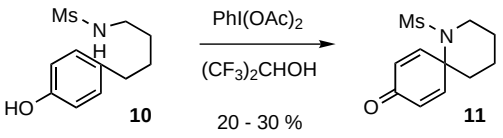
Substrates **7** were prepared by conventional methods,[10] and their DIB oxidation was studied in both trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP). As observed by Kita,[11] the use of such fluorinated alcohols as solvents is essential for the success of many DIB-mediated processes. A proclivity to form byproducts of the type **9** (Scheme 3) was observed when the reaction was carried out in TFE, signaling that this alcohol is an inappropriate solvent for the present transformation. An analogous problem was detected during our prior work with oxazoline substrates.[2c] On the other hand, clean, rapid, and efficient conversion to spirocycles **8** (Table 1) ensued upon reaction of **7** with DIB in HFIP. This is in strident contrast to the behavior of oxazolines, which normally afford moderate yields (45–50%) of spirocyclic products under similar conditions, let alone that of free secondary amines, for which yields are generally in the neighborhood of 30%.[12]

The reaction appears to be largely insensitive to the steric demand of the sulfonamide unit. Thus, *N*-mesyl and *N*-tosyl substrates **5a** and **5b** cyclized with equal efficiency. Especially significant is the cyclization of Fukuyama-type[13] 4-nitrobenzenesulfonamide **5c**, which may be elaborated to intermediates that are deblocked under mild conditions. The methyl ester of *N*-tosyl homotyrosine, **7d**, reacted normally and in high yield; however, the reaction of bis-sulfonamide **7e** proceeded less efficiently. The reasons for this remain unclear.

Table 1. Oxidative spirocyclizations of phenolic sulfonamide substrates



Entry	X	Y	Z	Yield (%)
a	4-Me-C_6H_4	H	H	97
b	Me	H	H	97
c	4-O_2N-C_6H_4	CH_2Br	H	84
d	4-Me-C_6H_4	COOMe	H	92
e	Me	H	$NHSO_2$-4-Tol	60



Scheme 4.

The oxidative cyclization of sulfonamide **10**, leading to spiropiperidine **11** (Scheme 4) occurred in a modest 20–30% yield (estimated by NMR and unoptimized), and induced formation of much polymeric material. Analogous difficulties with six-membered ring formation had also been observed with oxazolines substrates.[2c] Spiropiperidine synthesis thus remains problematic even via sulfonamide technology.

A typical experimental procedure to effect spirocyclization of phenolic sulfonamides is as follows. A 1 M solution of DIB in HFIP (1.05 equiv. of DIB) is added dropwise at room temperature to a 10% (w/w) solution of the substrate (1 equiv.) in HFIP, with good stirring. No inert atmosphere is necessary. The initially colorless solution changes to yellow and then to blue-green as the reaction progresses. After 30 min at rt, the solution is concentrated in vacuo and the crude residue is purified by chromatography.[14]

In summary, a practical and efficient new method for the creation of nitrogen spirocycles is now available. Synthetic applications of the methodology will be described in due course.

Acknowledgements

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References

1. For previous synthetic work and bibliography in this area, see for example: (a) Liu, J. F.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8263; (b) Molander, G. A.; Rönn, M. *J. Org. Chem.* **1999**, *64*, 5183; (c) Oppolzer, W.; Bochet, C. G. *Tetrahedon: Asymmetry* **2000**, *11*, 4761 (cylindricines); (d) Maeng, J. H.; Funk, R. L. *Org. Lett.* **2002**, *4*, 331; (e) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583 (fasicularine); (f) Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett.* **2001**, *3*, 3507; (g) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3511; (h) Pearson, W. H.; Ren, Y. *J. Org. Chem.* **1999**, *64*, 688 (lepadiformine; see also Ref. 1e).
2. (a) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534; (b) Ousmer, M.; Braun, N. A.; Ciufolini, M. A. *Org. Lett.* **2001**, *3*, 765; (c) Braun, N. A.; Bray, J. D.; Ousmer, M.; Peters, K.; Peters, E.-M.; Bouchu, D.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397 and references cited therein.

3. This noteworthy transformation may rightfully be termed the 'Sorensen reaction'. See: Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593.
4. Unpublished observations from this laboratory.
5. For instance, during our synthesis of FR901483 (Ref. 2a) we observed that a secondary sulfonamide and a primary alcohol are acylated at the same rate upon reaction with Ac_2O/pyridine.
6. For example, see: (a) Achmatowicz, O. In *Organic Synthesis Today and Tomorrow*; Trost, B. M.; Hutchinson, C. R., Eds.; Pergamon Press: Oxford, UK, 1981; (b) Gingerich, S. B.; Jennings, P. W. In *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 2.
7. For example, see: Zhou, W. S.; Lu, Z. H.; Xu, Y. M.; Liao, L. X.; Wang, Z. M. *Tetrahedron* **1999**, *55*, 11959 and references cited therein. See also Ref. 8.
8. For a review, see: Ciufolini, M. A.; Hermann, C. Y. W.; Dong, Q.; Shimizu, T.; Swaminathan, S.; Xi, N. *Synlett* **1998**, 105.
9. See: Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927.
10. Preparation of **7a**: From the dimesylate of *p*-hydroxydihydrocinnamyl alcohol by: (a) NaN_3/DMF; (b) PPh_3/THF/H_2O, 80% a–b; (c) TsCl/TEA/CH_2Cl_2; (d) aq. NaOH/dioxane, 90% c–d; **7b**: procedure as for **7a** except that MsCl was used in step (c); **7c**: from (*R*)-*p*-methoxyhomophenylalaninol [obtained by Evans azidation of 4-*p*-(methoxyphenyl)butyric acid followed by reduction. See: (a) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011] by: (a) TES-Cl/TEA/CH_2Cl_2; (b) 4-O_2N-C_6H_4-SO_2Cl/TEA/CH_2Cl_2, 85% a–b; (c) BBr_3, CH_2Cl_2, 69%; **7d**: by *N*-tosylation of methyl D-homotyrosinate [see: (b) Fischer, E.; Lipschitz, W. *Ber. Dtsch. Chem. Ges.* **1915**, *48*, 360; (c) McChesney, E. V.; Swann, W. K., Jr. *J. Am. Chem. Soc.* **1937**, *59*, 1116]; **7e**: from the *N*-tosyl derivative of methyl L-tyrosinate (see Refs. 10b,c above) by: (a) LAH; (b) MsCl/TEA/CH_2Cl_2, 78% a–b; (c) NaN_3/DMF; (d) H_2/Pd(c)/THF; (d) MsCl/TEA/CH_2Cl_2; (e) aq. NaOH/dioxane, 75% c–e.
11. See: Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991**, *56*, 435.
12. An efficient transformation of this type that proceeds in an exceptional 69% yield has recently been reported. See: Mizutani, H.; Takayama, J.; Soeda, Y.; Honda, T. *Tetrahedron Lett.* **2002**, *43*, 2411.
13. (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373; (b) Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831.
14. Physical data for compounds **8** [NMR: δ, $CDCl_3$, coupling constants J in Hz); IR (film, cm^{-1}); mass spectra (m/z)]. Compound **8a**: mp 106°C; ^{1}H NMR: 6.88 (d, 2H, $J=10.2$), 6.26 (d, 2H, $J=10.2$), 3.68 (t, 2H, $J=6.8$), 2.89 (s, 3H), 2.16 (m, 4H); ^{13}C NMR: 184.8, 149.4, 128.4, 63.4, 49.2, 40.3, 39.3, 23.6; IR: 1661; HRMS (CI) calcd for $C_{10}H_{14}NO_3S$ (M+H) 228.0694, found 228.0692. Compound **8b**: mp >300°C; ^{1}H NMR: 7.64 (d, 2H, $J=8.3$), 7.29 (d, 2H, $J=8.3$), 6.69 (d, 2H, $J=10.2$), 6.17 (d, 2H, $J=10.2$), 3.69 (t, 2H, $J=6.4$), 2.41 (s, 3H), 2.07 (m, 4H); ^{13}C NMR: 185.3, 150.1, 143.9, 136.2, 129.6, 127.9, 127.8, 63.7, 49.1, 40.4, 23.5, 21.6; IR: 1665; HRMS (CI) calcd for $C_{16}H_{18}NO_3S$ (M+H) 304.1007, found 304.1002. Compound **8c**: foam; ^{1}H NMR: 8.34 (d, 2H, $J=9.0$), 8.02 (d, 2H, $J=9.0$), 6.81 (dd, 1H, $J=3.4$, 10.2), 6.51 (dd, 1H, $J=3.4$, 10.2), 6.23 (dd, 1H, $J=2.0$, 10.7), 6.13 (dd, 1H, $J=2.0$, 10.7), 4.44 (m, 1H), 3.90 (dd, 1H, $J=2.6$, 10.6), 3.60 (dd, 1H, $J=8.7$, 10.6), 2.55 (m, 1H), 2.20–2.27 (m, 2H), 1.94 (m, 1H); HRMS (CI) calcd for $C_{16}H_{16}BrN_2O_5S$ (M+H) 426.9963, found 426.9961. Compound **8d**: oil; $[\alpha]_D=+30$ (c 1.5, EtOH, 20°C); ^{1}H NMR: 7.62 (d, 2H, $J=8.3$), 7.26 (d, 2H, $J=8.3$), 6.95 (dd, 1H, $J=3.2$, 10.9), 6.72 (dd, 1H, $J=3.2$, 10.9), 6.12 (d, 2H, $J=10.2$), 4.72 (d, 1H, $J=6.4$), 3.71 (s, 3H), 2.38 (m, 5H), 2.10 (m, 1H), 1.94 (m, 1H); ^{13}C NMR: 184.9, 172.5, 151.6, 148.9, 144.3, 136.6, 129.5, 128.1, 128.0, 64.2, 62.2, 52.7, 38.6, 28.7, 21.6; IR: 1734, 1688; HRMS (CI) calcd for $C_{18}H_{20}NO_5S$ (M+H) 362.1062, found 362.1069. Compound **8e**: ^{1}H NMR: 7.73 (d, 2H, $J=8.3$), 7.34 (d, 2H, $J=8.3$), 7.05 (dd, 1H, $J=2.6$, 10.6), 6.84 (dd, 1H, $J=2.6$, 10.6), 6.22 (d, 2H, $J=10.2$), 6.00 (d, 1H, $J=5.3$), 3.98 (m, 1H), 3.82 (dd, 1H, $J=6.8$, 10.2), 3.58 (dd, 1H, $J=5.3$, 10.2), 2.88 (s, 3H), 2.43 (s, 3H), 2.18 (m, 2H); ^{13}C NMR: 184.7, 149.1, 148.4, 144.3, 136.0, 130.0, 128.1, 128.0, 126.8, 62.3, 53.4, 50.5, 44.7, 39.4, 21.4; IR: 1667; HRMS (CI) calcd for $C_{17}H_{21}N_2O_5S_2$ (M+H) 397.0892, found 397.0897.