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CYCLOFUNCTIONALIZATION OF UNSATURATED ALCOHOLS, PHENOLS, ACIDS, AND SULFONAMIDES WITH 1-BENZENE-SULFINYL PIPERIDINE AND TRIFLUOROMETHANESULFONIC ANHYDRIDE*

*** Dedicated with respect to Professor Leo A. Paquette on the occasion of his 70th birthday**

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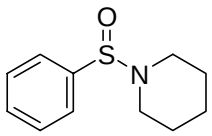
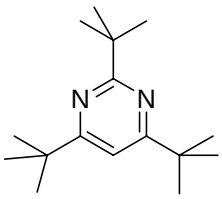
Abstract - The combination of a benzenesulfinamide, trifluoromethanesulfonic anhydride, and Hünig's base brings about the cyclofunctionalization of unsaturated alcohols, phenols, acids, and sulfonamides to give the corresponding α-phenylsulfanylmethyl cyclic ethers, lactones and sulfonamides, respectively. In an unanticipated twist the products are isolated at the sulfur (II) oxidation state denoting an overall reduction in the oxidation state of the sulfur based electrophile in the course of the reaction.

INTRODUCTION

1-Benzenesulfinyl piperidine (**1**, BSP)[1,2] was developed to bring about the rapid, low temperature conversion of a wide range of thioglycosides to glycosyl triflates when activated with triflic anhydride (Tf_2O) in the presence of the convenient non-nucleophilic base 2,4,6-tri-*tert*-butylpyrimidine (**2**, TTBP).[3] The same combination of reagents is also suitable for the hydrolysis of a wide range of mono- and dithioacetals to the corresponding aldehydes and ketones under very mild conditions.[4] We report here that the BSP/Tf_2O couple may also be used for cyclization of a range of ω-unsaturated alcohols, phenols, carboxylic acids, and sulfonamides to give the corresponding α-phenylsulfanylmethyl cyclic ethers, lactones, and *N*-sulfonyl cyclic amines, in a process involving overall reduction from S(IV) to S(II).



1: BSP



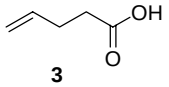
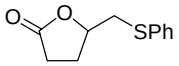
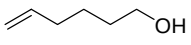
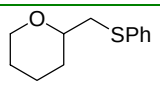
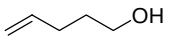
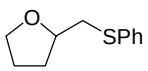
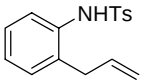
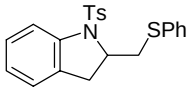
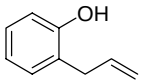
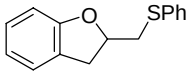
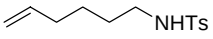
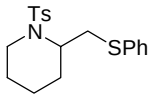
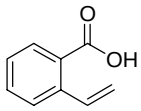
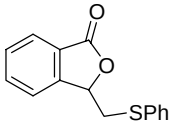
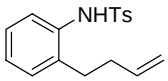
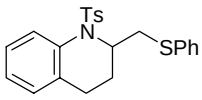
2: TTBP

RESULTS AND DISCUSSION

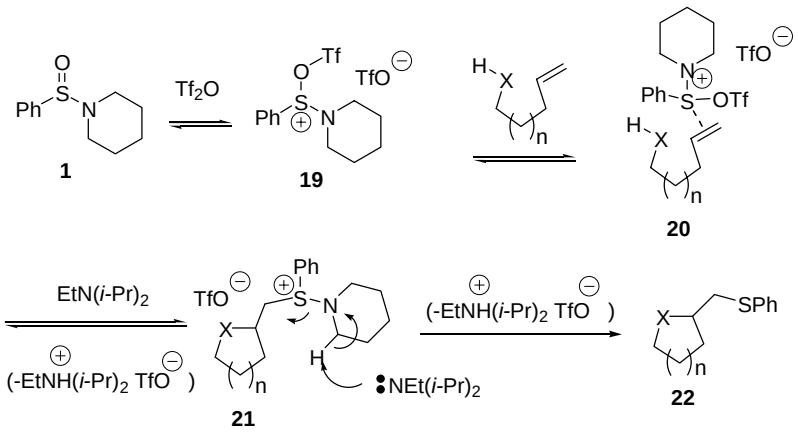
It was previously reported that *N*-phenylthiomorpholine brings about the thioetherification of ω-unsaturated alcohols leading to the formation of α-phenylsulfanylmethyl cyclic ethers.[5-7] We reasoned that reaction of the BSP/TTBP/Tf_2O with similar compounds would afford cyclization to give not the thioethers but rather the corresponding sulfoxides. Accordingly, the cyclization of 4-pentenoic acid with the BSP/TTBP/Tf_2O system was attempted in dichloromethane at -60 ^oC. Surprisingly, under these conditions conversion was poor, even after allowing the reaction mixture to warm to room temperature, and reaction mixtures were complex. We hypothesized that the activated BSP was reversibly forming an adduct with the alkene and that more effective cyclizations would result from the use of a stronger nucleophile. Accordingly, the very weak base TTBP was exchanged for ethyldiisopropylamine (Hünig's base) which resulted in the formation of the α-phenylsulfanylmethyllactone (**4**) in 79% yield (Table 1). Although cyclization was affected under these conditions, the product was not the anticipated sulfoxide but rather the thioether as was confirmed by mass spectrometry, microanalysis, and comparison of the NMR data with the literature.[8] In spite of the unexpected change in oxidation state in the course of the reaction we considered the white stable crystalline nature of BSP to afford considerable advantages over the use of more familiar but less convenient phenylsulfanyl electrophiles such as benzenesulfenyl chloride and, indeed, the benzenesulfenamides previously employed. Accordingly, a number of simple alkenyl phenols, carboxylic acid, and sulfonamides were prepared by standard means and subjected to reaction with a mixture of BSP, Hunig's base and Tf_2O with the results reported in Table 1. It is noteworthy that carboxylic acids, alcohols, phenols, and sulfonamides are suitable nucleophiles in these cyclofunctionalization reactions, and that the formation of five and six membered rings has been demonstrated.

The results are best explained by the mechanism set out in Scheme 1 whereby the function of the stronger base is seen to be one of deprotonating the intermediate (**21**). This key step both diverts a series of equilibria in the forward direction and brings about the reduction observed at sulfur.

Table 1. Cyclofunctionalizations with 1-Benzenesulfinylpiperidine and Tf_2O.

Substrate	Product (yield %)	Substrate	Product (yield %)
 **3**	 **4** (79)	 **11**	 **12** (76)
 **5**	 **6** (70)	 **13**	 **14** (78)
 **7**	 **8** (80)	 **15**	 **16** (68)
 **9**	 **10** (81)	 **17**	 **18** (79)

Scheme 1. Mechanism for Cyclization with BSP/Tf_2O.



EXPERIMENTAL

Typical Cyclization Protocol: 2-Phenylsulfanylmethyltetrahydrofuran (6). To a stirred, cooled (- 60 ºC) solution of BSP (**1**) (0.75 mmol, 157 mg), and Hünig's base (1.0 mmol, 175 μL) containing 4Å molecular sieves (5.0 mg) in dry CH_2Cl_2 (22.0 mL) was added freshly distilled Tf_2O (0.75 mmol, 127 μL). After 5 min, 4-pentenol (**5**) (0.5 mmol, 51.3 μL) was added to the blood red reaction mixture which was

maintained at -60 ºC for 15 min and then allowed to warm up to rt gradually over 2 h. The reaction was quenched with saturated $NaHCO_3$ (5.0 mL). The dark brown organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography over silica gel using 1:3 EtOAc-hexane to yield **6** as a pale brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.56-2.18 (m, 4 H), 2.96 (dd, *J* = 12.9, 6.9 Hz, 1 H), 3.15 (dd, *J* = 12.9, 6.0 Hz, 1 H), 3.74-3.94 (m, 2 H), 4.03 (p, *J* = 6.6 Hz, 1 H), 7.16-7.42 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.93, 31.11, 38.99, 68.50, 77.74, 126.14, 129.04, 129.33, 136.52. ESI-MS m/z 195.1 $[MH]^+$. Anal. Calcd for $C_{11}H_{14}OS$: C 68.00, H 7.26. Found C 68.22, H 7.34.

ACKNOWLEDGEMENTS

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4. D. Crich and J. Picione, *Synlett*, 2003, 1257.
5. P. Brownbridge, *J. Chem. Soc., Chem. Commun*., 1987, 1280.
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