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A one-pot tandem oxidation–reduction protocol for the synthesis of cyclic ethers from their diols

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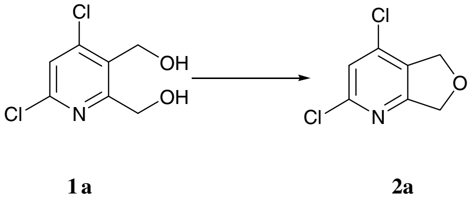
ABSTRACT

A novel and an efficient one-pot cyclization method for the preparation of cyclic ethers from their diols via a tandem oxidation–reduction protocol using a cocktail of $MnO_2/Et_3SiH/CF_3COOH$ is reported.

In conjunction with a project underway in our laboratory, we faced the problem of synthesizing, in quantity, the halogeno-substituted heterocyclic ether **2a** from the corresponding diol **1a** under non-basic conditions (Scheme 1). To date, four main approaches have been reported for such a transformation: (i) acid catalyzed cyclodehydration using HCl[1,2]/H_3PO_4[3]/PTSA,[4] etc. (ii) TPP-CCl_4[5] promoted cyclodehydration of diols via intramolecular displacement of TPPO, (iii) base promoted[6] mono-tosylate formation and elimination[7] and (iv) intramolecular cyclization of diols via a Mitsunobu reaction.[8]

Unfortunately, none of the above conditions proved useful in the transformation of **1a**–**2a** (Table 1). Thus, we deemed it necessary to develop a new methodology that would allow ready one-pot conversion of **1a**–**2a**.

Our strategy to effect this transformation is summarized in Scheme 2. The success of this protocol hinges on clean monoxidation of the *ortho* diols **3** to the corresponding lactols **4** unaccompanied by any of the over-oxidized products, for example, lactones **6**, and further transformation of the lactols **4** to the cyclic ethers **5** via reduction of the corresponding oxonium ion intermediates. Active MnO_2 appeared to be the oxidant of choice in this protocol, and for the reduction step, we selected a combination of Et_3SiH and CF_3COOH. Our choice of the oxidant was dictated by a literature report which indicated that MnO_2 oxidation of *ortho* diols to lactols proceeds faster than the corresponding oxidation of lactols to lactones.[9] Furthermore, MnO_2 should be compatible with the use of the reductant, Et_3SiH, in the presence of CF_3COOH.


1 a **2a**

Scheme 1.

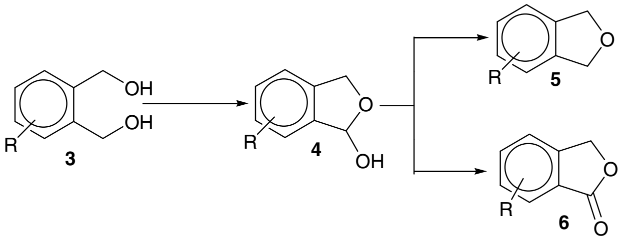
In this Letter, we report the successful development of a new methodology for efficient one-pot transformation of *ortho* diols, for example, **3** to the cyclic ethers **5** based on the above concept.

Thus, exposure of the diol **1a** in DCM to active MnO_2[13] (5 equiv) followed by addition of Et_3SiH (4.5 equiv) and CF_3CO_2H (15 equiv) at −5→0 °C for 1 h and then 1 h at rt gave **2a** in 93% isolated yield. We then applied this methodology to a series of *ortho* diols, and the

Table 1
Preparation of ether **2a** from diol **1a** according to the literature conditions

Conditions	Yield (%)	Recovery (%) of diol **1a**
HCl-MeOH, heat	0	25
H_3PO_4, PhMe, heat	0	0
PTSA, C_6H_6, reflux	0	0
PPh_3-CCl_4, reflux	<5	0
TsCl, py	0	0
PPh_3, DEAD	17[a]	62

[a] The product was obtained after a reaction time of 12 h at rt.



Scheme 2.

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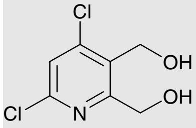
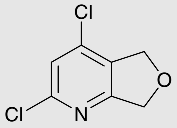
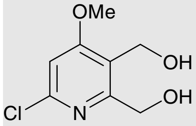
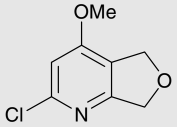
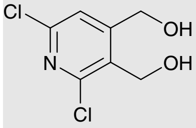
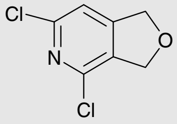
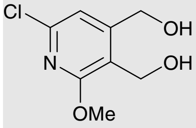
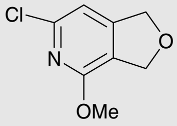
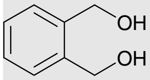
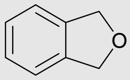
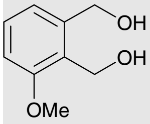
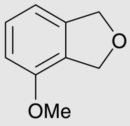
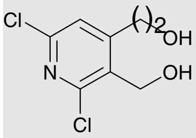
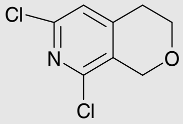
results are presented in Table 2. As can be seen from Table 2, the yields of the cyclic ethers in almost all the cases are excellent. Only in the case of **1g** did we isolate some staring material (16%). Furthermore, in the absence of both MnO_2 and Et_3SiH, addition of CF_3COOH in DCM did not lead to the cyclic ethers even after a reaction time of over 30 h at rt, only starting materials were recovered.

This methodology is also applicable to the synthesis of acyclic ethers[14] **7–9** (Table 3). For example, while benzyl alcohol gave dibenzyl ether **7** (93%), a mixture of benzyl alcohol and 3-phenylpropan-1-ol (1:1.2, respectively) gave only the mixed ether **8** in high yield (88%); no dibenzyl ether could be detected (TLC) in the latter case in the crude reaction product. Furthermore, this reaction could also be carried out by addition of a mixture of benzyl alcohol and 3-phenylpropan-1-ol (1:1.2, respectively) to a cocktail of active MnO_2 (5 equiv), Et_3SiH (4.5 equiv) and CF_3COOH (15 equiv) in DCM, but with a lower yield of **8** (60%); in this case also, no dibenzyl ether could be detected in the crude reaction product by TLC. As can be seen from Table 3 this protocol is also applicable to the synthesis of the heterocyclic ether **9**.

Table 2

Synthesis of cyclic ethers from their diols[10–12]

Diol[a]	Ether	Yield[b] (%)
 **1a**	 **2a**	93
 **1b**	 **2b**	88
 **1c**	 **2c**	91
 **1d**	 **2d**	89
 **1e**	 **2e**	91
 **1f**	 **2f**	86
 **1g**	 **2g**	73[c]

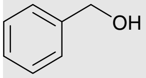
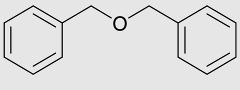
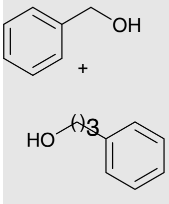
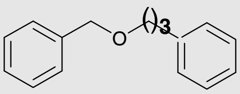
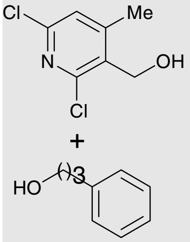
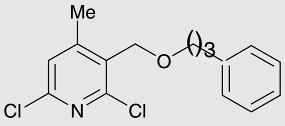
[a] The preparation of the diols will be published elsewhere.

[b] Isolated yield of purified product.

[c] 16% of 1 g was isolated after a 3 h reaction period at rt.

Table 3

Synthesis of acyclic ethers from alcohols[10,11]

Alcohol	Ether	Yield (%)
	 **7**	93
	 **8**	88
	 **9**	86

In conclusion, we have developed a tandem oxidation–reduction protocol for the highly effective etherification of diols and alcohols using a combination of active $MnO_2/Et_3SiH/CF_3COOH$.

Typical experimental procedure: To diol **1a** 208 mg (1 mmol) in 7 ml of dry DCM was added 435 mg of active MnO_2 (5 mmol) in one portion at −5→0 °C (ice-salt bath). Then, triethylsilane (0.72 ml, 4.5 mmol) was added dropwise followed by trifluoroacetic acid (1.2 ml, 15 mmol) over a period of 15 min. The reaction mixture was stirred at the same temperature for 1 h, and for 1 h at room temperature. Water (5 ml) was added and the reaction mixture was filtered through a sintered funnel over a celite-450 bed. The organic layer was separated from the filtrate and the aqueous layer was extracted with DCM (3 × 5 ml). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo and the crude product was purified by chromatography over silica gel to afford **2a** (176 mg, 93%).

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.046.

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10. All compounds reported in the Table have been fully characterized by ^{1}H and^{13}C NMR spectroscopy as well as mass spectral data.
11. All reactions were carried out on a 1 mmol scale.
12. *Spectral data of selected compounds*: **1a**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.36 (1H, s), 4.87 (2H, s), 4.81 (2H, s), 3.80 (1H, s), 2.61 (1H, s). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.3, 149.9, 146.6, 129.8, 123.7, 63.0, 57.2. *Compound* **2a**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.26 (1H, s), 5.18 (2H, s), 5.1 (2H, s). ^{13}C NMR($CDCl_3$, 50 MHz) δ 162.4, 151.7, 139.9, 130.3, 122.2, 73.3, 71.5.
13. Fatiadi, A. J. In *Organic syntheses by oxidation with metal compounds*; Mijs, W. J., De Jonge, C. R. H., Eds.; Plenum press, 1986; p 122. MnO_2 prepared in this way was further dried at 120 °C overnight everytime before use.
14. Publications on the synthesis of acyclic ethers via reductive etherification of carbonyl compounds with alkoxysilanes and triethylsilane promoted by Lewis acids are numerous, see: Iwanami, K.; Seo, H.; Tobita, Y.; Oriyama, T. *Synthesis* **2005**, 183 and references cited therein.