SHORT PAPER

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Soft cleavage of THP protected estradiols mediated by TMSI

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Treatment of 3-tetrahydropyranyloxy-17α-aryl estradiols, dissolved in acetonitrile or acetonitrile/THF/pentane mixture, with trimethylsilyl iodide resulted in the soft deprotection of THP ether in good yields without side dehydratation.

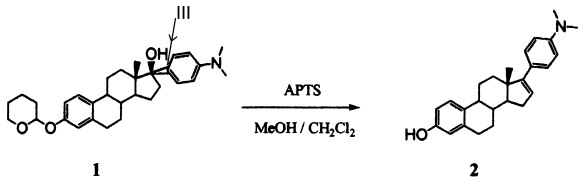
Keywords: 3-tetrahydropyranyloxy-17α-aryl estradiols, cleavage, trimethylsilyl

Since we described novel routes to protected arylestradiols[1,2] we have encountered some problems with the choice and removal of the prominent phenol-protecting group.

The THP is one of the most widely used protective group for phenols, and can be removed in mild acidic medium.[3]

During our investigations, we became interested in the conversion of triazene moiety into aryl iodide through the use of trimethylsilyl iodide (TMSI).[4] While applying this approach, we have discovered that treatment of 3-tetrahydropyranylated estradiols results in the deprotection of phenol groups.

The deprotection of the arylestradiol (**1**) by classical methods[5] using mild acidic medium leads to the effective cleavage of the THP ether. Nevertheless, an undesirable side dehydratation reaction of the particularly sensitive tertiary and benzylic alcohol, in 17β position, take place to give (**2**) (Scheme 1), which is characterised by ^{1}H NMR signal at 5.80-5.90 ppm.

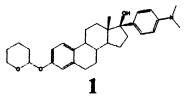
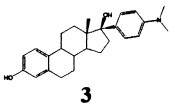
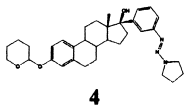
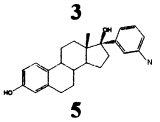
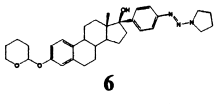
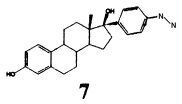
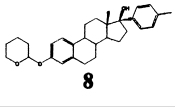
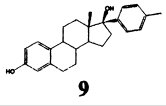


Scheme 1

When a tetrahydropyranyl protected estradiol was reacted with excess of TMS1 in acetonitrile at room temperature quantitative conversion into the corresponding deprotected estradiol occurred as shown in Table 1.

The TMSI was generated, *in situ*, by reacting TMSCl with an excess of NaI in acetonitrile.[4] The substrates (**1**, **4**, and **6**), in dispersion in acetonitrile, were reacted with 1.2 to 2.2 equiv. of TMSI which resulted in formation of the corresponding estradiols shown in Table 1, in good yields, after hydrolysis with saturated $NaHCO_3$. The products resulting from dehydratation of 17-hydroxyl group were not detected by ^{1}H NMR. The estradiol **(8)** is soluble in acetonitrile and has a great tendency to dehydrate when reaction is carried out in acetonitrile. The use of an acetonitrile/THF/pentane mixture minimizes its solubility and avoids this dehydratation. We suppose that compounds in dispersion are first solubilised by silylation of the 17-hydroxyl group before THP is cleaved by a pathway similar to thus proposed by Jung.[6] The protection of the 17-OH group may avoid the dehydratation. The alcohol

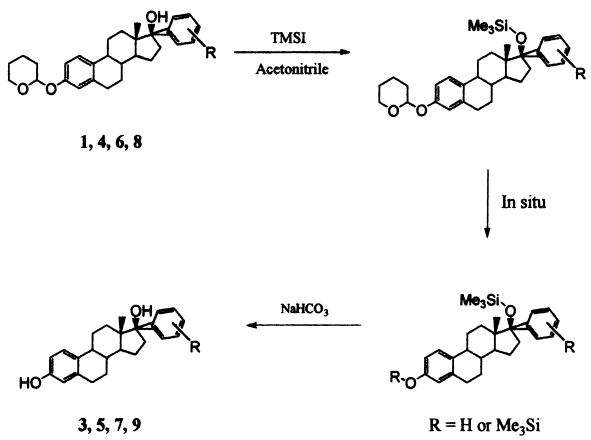
Table 1 Deprotection of THP with TMSI

Substrate	Product	Yield (%)[a]
 1	 3	90[b]
 4	 5	80[c]
 6	 7	90[c]
 8	 9	77[d]

[a]Isolated yield
[b]The reaction were carried out in acetonitrile for 1 h.
[c]The reaction was carried out in acetonitrile for 17 h.
[d]The reaction was carried out in acetonitrile/THF/pentane for 45 min.

and the phenol are then regenerated during the hydrolysis with saturated $NaHCO_3$ (Scheme 2).

The reaction reported herein expand the scope of synthetic deprotections known to be accomplished by TMSI[7] and offers a new and convenient method for the deprotection of THP ethers in mild conditions.



Scheme 2

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Experimental

Deprotection of THP. General procedure: NaI (190 mg, 1.26 mmol) and TMSCl (0.080 ml, 0.63 mmol) were dissolved in CH_3CN (1.5 ml) and stirred under argon at 40°C for 15 min. The reaction medium is allowed to return at room temperature and the starting steroid (0.28 mmol) is suspension in acetonitrile or acetonitrile/THF/pentane (2:4:10) mixture (9 ml) was then added all at once. The reaction was stirred for additional time (see Table 1, notes b–d) at room temperature and the reaction mixture was hydrolysed with saturated $NaHCO_3$ (10 ml), stirred for 5 min and water (10 ml) was added. The CH_3CN was evaporated and the residue was extracted with AcOEt, washed with water, dried over $MgSO_4$ and concentrated to afford crude products. Flash chromatography afford pure products as shown in Table 1: m.p. **3**, 191°C; m.p. **5**, > 300°C; m.p. **7**, > 300°C; m.p. **9**, 211°C.

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