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LETTERS

An efficient method for the cleavage of *p*-methoxybenzylidene (PMP), tetrahydropyranyl (THP) and 1,3-dithiane protecting groups by Selectfluor™

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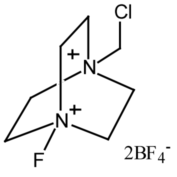
Abstract—A new and efficient method for the cleavage of the PMP, THP and 1,3-dithiane protecting groups with Selectfluor™ has been developed. © 2002 Elsevier Science Ltd. All rights reserved.

Selectfluor™ (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo [2,2,2] octane bis(tetrafluoroborate)) has recently been introduced commercially as a user-friendly electrophilic fluorinating reagent. It fluorinates a wide variety of electron-rich carbon centers, usually with high yield.[1] Our group has reported that Selectfluor™ can be easily used to make 2-deoxy-2-fluoroglycosides from glycals under mild conditions.[2] It also activates thioglycosides to form a reactive sulfonium intermediate which can be used for glycosidation or breakdown to glycosyl fluorides. In the presence of dimethyl sulfide, it converts the anomeric hydroxyl to glycosyl fluoride.[2] Mechanistic studies indicate that Selectfluor™ acts as an electrophilic fluorinating reagent in a two-electron process.[2b] The enantioselective fluorination can also be achieved when Selectfluor™ is used in combination with quinine derivatives.[3]



Selectfluor™

Considering its electrophilic and oxidative characters of Selectfluor™, we envision that this reagent could be used in the cleavage of some extensively used, electron-rich protecting groups.

p-Methoxybenzylidene (PMP) is a very useful protecting group for diols.[4] Its deprotection usually requires acidic (e.g. 80% AcOH) or oxidative conditions (e.g. DDQ). A mild cleavage condition to remove PMP is obviously needed when multifunctional groups are present, e.g. in complex carbohydrate synthesis. Selectfluor™ was examined in several PMP-protected compounds and the results are shown in Table 1 (entries 1–4).[5]

Both CH_3CN and CH_3NO_2 (5% H_2O content) can be used as solvents for the reaction. In the presence of 1.2 equiv. of Selectfluor™, deprotection usually goes to completion in 5 hours at room temperature and gives the desirable product in high yield.

The second protecting group we examined is the tetrahydropyranyl group (THP). Due to its low cost, ease of installation and stability, THP is a widely used protecting group.[6] We found that Selectfluor™ can smoothly cleave the THP group under the same mild conditions as in the PMP case (Table 1, entries 5–9).

Satisfied with the result, we further examined if 1,3-dithiane could be cleaved with Selectfluor™. 1,3-Dithiane can be easily prepared by reaction of the carbonyl compound with 1,3-propanedithiol in the presence of a Brönsted or a Lewis acid catalyst. Removal of 1,3-dithiane is, however, relatively difficult and often requires harsh conditions.[7] Because cleavage of the 1,3-dithiane group is usually performed in the late synthetic stage,[8] a new mild deprotection condition will be extremely useful. As shown in Table 2,[9] we have found that 1,3-dithianes can be cleaved in less than 5 minutes with very good yield by 2.5 equiv. of Selectfluor™ in CH_3CN or CH_3NO_2 (5% H_2O content).[10]

Keywords: cleavage reactions; dithianes; protecting groups.

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PII: S0040-4039(02)00740-2

Table 1. Deprotection of PMP and THP with Selectfluor™

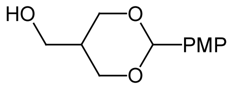
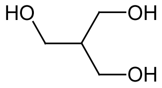
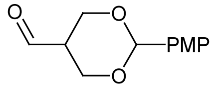
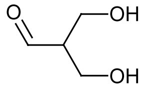
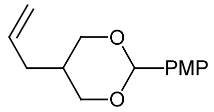
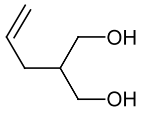
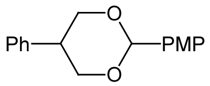
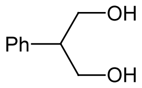
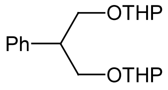
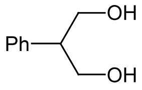
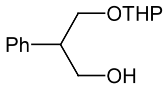
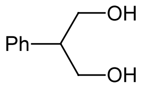
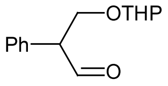
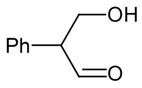
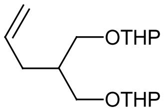
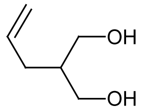
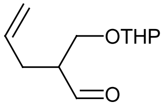
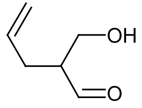
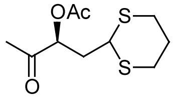
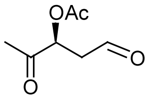
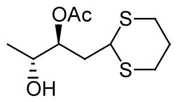
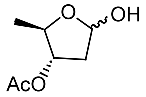
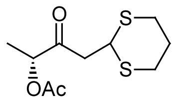
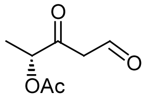
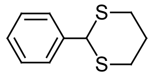
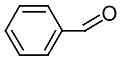
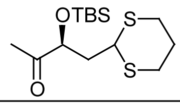
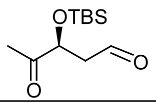
Entry	Substrates	Products	Yield
1			90%
2			87%
3			92%
4			90%
5			94%
6			89%
7			92%
8			95%
9			89%

Table 2. Deprotection of 1,3-dithiane with Selectfluor™

Entry	Substrates	Products	Yield
1			95%
2			85%
3			95%
4			85%
5			80%

We propose that the F group in Selectfluor™ plays a Lewis acid role in these deprotection reactions although other possibilities could not be ruled out.[11]

In summary, we have developed a new and efficient method to remove the PMP, THP and 1,3-dithiane protecting groups using Selectfluor™ in high yields and under very mild conditions. Because Selectfluor™ is very soluble in water (176 g/l at 20°C), a simple aqueous workup is enough to remove most byproducts. In addition, it is nontoxic and relatively inexpensive compared to other electrophilic fluorinating reagents. Further utility of this method is being investigated in our laboratory.

References

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5. **General procedure for the deprotection of PMP and THP groups**: substrate **5** (Table 1) (120 mg, 0.38 mmol) was dissolved in CH_3CN (10 ml, 5% H_2O). To the mixture was added Selectfluor™ (320 mg, 0.90 mmol) at room temperature. The mixture was stirred for 5 h. After the reaction went to completion, the solvent was remove in vacuo and the residue was purified by flash chromatography (silica, 1:1 hexanes:EtOAc) to afford the product as a colorless oil (53 mg, 94%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.27 (m, 1H), 7.23 (m, 2H), 3.93 (dd, $J=7.9$, 11.0 Hz, 2H), 3.87 (dd, $J=5.3$, 11.0 Hz, 2H), 3.02 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): 139.34, 128.66, 127.95, 127.06, 65.72, 49.57; ESI m/e Calcd for (M^+) $C_9H_{12}O_2$: 152; Found: 175 (M+Na), 151 (M–H), 187 (M+Cl).
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9. **General procedure for the deprotection of dithianes**: substrate **5** (Table 2) (54 mg, 0.17 mmol) was dissolved in CH_3CN (5 ml, 5% H_2O). To the mixture was added Selectfluor™ (150 mg, 0.42 mmol) at room temperature. The reaction went to completion in 5 min and was quenched by adding aqueous $NaHCO_3$ (sat. 5 ml). The mixture was extracted by CH_2Cl_2 (10 ml) twice. The combined organic layer was washed with H_2O (10 ml), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (silica, 8:1 hexanes:EtOAc) to afford the product as a colorless oil (31 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (br. s, 1H), 4.45 (t, $J=5.5$ Hz, 1H), 2.75 (dt, $J=1.8$, 5.2 Hz, 2H), 2.25 (s, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 210.59, 198.85, 73.97, 48.03, 25.99, 25.59, 18.31, –4.92, –5.02; HRMS m/e Calcd for (M^+) $C_{11}H_{22}O_3Si$: 230.1338; Found: 253.1223 (M+Na).
10. Deprotection of conjugated, cinnamaldehyde type 1,3-dithianes with Selectfluor™ usually gave a low yield.
11. We found that the pH of the aqueous solution of Selectfluor™ ($\sim$50 mg/ml) is about 3, which may implicate the formation of $\equiv N^{\oplus}$-H from the reaction between Selectfluor™ and H_2O. Whether other reactive species, e.g. HOF, are formed and also participate in the cleavage reaction is currently being investigated in our laboratory.