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A simple deprotection of triflate esters of phenol derivatives

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Abstract—Efficient conversion of aryl triflates into the corresponding phenols has been accomplished with Et_4NOH. In contrast to other cleavage reactions, such functional groups as nitro, ketone, halogen, amide and sulfonamide groups were intact under the reaction conditions. This mild removal of the trifluoromethanesulfonyl group would serve a new protecting group of phenols.

The trifluoromethanesulfonyl group, a functional group possessing powerful electron-withdrawing effect, is widely used as an excellent leaving group rather than protecting group.[1] Aryl sulfonates such as aryl mesylates are highly stable under a wide range of reaction conditions, as compared with the corresponding alkyl sulfonates such as alkyl mesylates. Therefore, sulfonate esters have been adopted as protecting groups for the phenol system.[2,3] In addition, it is expected that the nucleophilic reactivity of the phenol system might effectively be decreased by adopting trifluoromethanesulfonyl group as a protecting group. As part of our ongoing synthetic studies using phenols as substrates,[4–7] we required cleavage of aryl triflates. Several examples of the cleavage reactions were found: solvolysis of aryl triflate in trifluoroethanol, followed by zinc reduction gave the corresponding phenol.[8] Schio investigated the reactivity of 4-cyanophenyl triflates towards various amines; the aryl–sulfonate bond was cleaved prior to the substitution reaction in the presence of octylamine.[9] However, the generality of these cleavage reactions has not been confirmed. On the other hand, Katzenellenbogen succeeded in cleavage of aryl triflates under strong reductive conditions with $LiAlH_4$ in good yield.[10,11] Interestingly, cleavage of aryl triflate with *n*-Bu_4NF was reported to give the corresponding phenol in moderate yield.[12] Cleavage of the aryl sulfonate ester has generally required the following conditions: reduction with Na in liquid NH_3,[13,14] Na-naphthanilide,[15,16] Mg in methanol,[17,18] hydrogenolysis with Raney-Nickel[19] and hydrolysis with alkaline metal hydroxide.[3] In addition to aryl triflates, tosylates and mesylates, other various functional groups might be susceptible under these conditions. Relatively mild conditions using KF on Al_2O_3 with a microwave were reported by Yadav and co-workers,[20] although the siloxy ether was spontaneously removed. We describe herein the selective cleavage condition of aryl triflates by Et_4NOH, which would be unprecedentedly simple and efficient methods.

As summarized in Table 1, the cleavage reaction of aryl triflates was performed using Et_4NOH in aqueous media (conditions A and B).

General procedure: To a solution of **1h** (entry 8; 271 mg, 1 mmol) in dioxane (3 mL) was added 10% aqueous Et_4NOH solution (3.0 g, 2 mmol) at ambient temperature; the mixture was stirred for 1 h. The reaction mixture was diluted with $CHCl_3$, washed with 1 M aq HCl, water and brine. The organic layer was dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC to yield **2h** (138 mg, 99%).

The data indicated that the cleavage reactions proceeded in excellent yields. Interestingly, no cleavage of methyl esters was observed under our reaction conditions (entries 1 and 2), although **1c** underwent selective hydrolysis of the ester moiety.[21] The well-known cleavage conditions of aryl sulfonates using a fluoride anion[12,20] resulted in undesired cleavage of siloxy ethers and sulfonamides. We also examined the cleavage reactions using *n*-Bu_4NF (conditions C and D), as contrastive

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Keywords: Protecting group; Aryl sulfonates; Trifluoromethanesulfonyl group; Et_4NOH.

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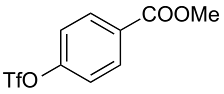
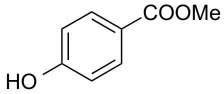
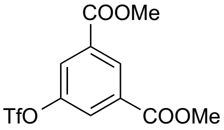
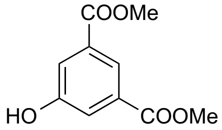
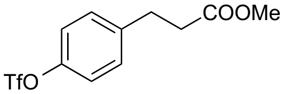
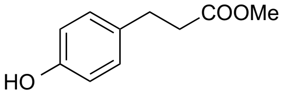
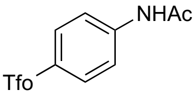
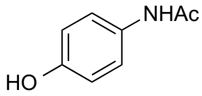
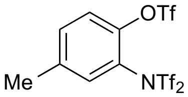
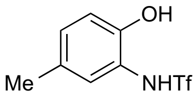
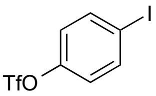
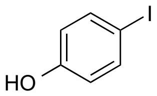
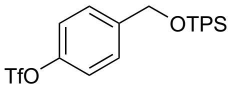
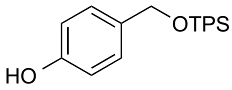
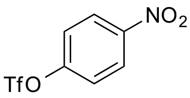
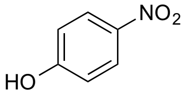
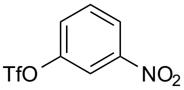
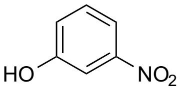
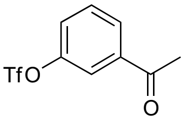
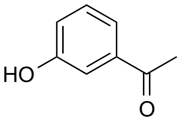
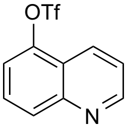
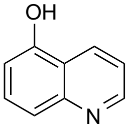
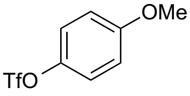
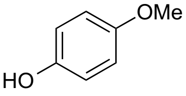
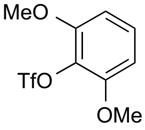
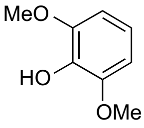
Table 1. Cleavage reaction of aryl trifluoromethanesulfonates

Entry	Substrates	Products	Method[a]	Temp	Time	Yield (%)
1	**1a**: 	**2a**: 	A C	rt rt	1 h 1 h	98 99
2	**1b**: 	**2b**: 	A	rt	1 h	95
3	**1c**: 	**2c**: 	A C	rt rt	1 h 3 days	Trace[b] 98
4	**1d**: 	**2d**: 	A	rt	1 h	87
5	**1e**: 	**2e**: 	B	50 °C	1 h	99
6	**1f**: 	**2f**: 	A	rt	1 h	99
7	**1g**: 	**2g**: 	A	rt	3 h	97
8	**1h**: 	**2h**: 	A C	rt rt	1 h 1 h	99 97
9	**1i**: 	**2i**: 	A	rt	1 h	99
10	**1j**: 	**2j**: 	A	rt	1 h	97
11	**1k**: 	**2k**: 	A	rt	1 h	99
12	**1l**: 	**2l**: 	A D	rt rt	1 h 5 days	99 70[c]
13	**1m**: 	**2m**: 	A A D	rt 60 °C rt	5 h 3 h 5 days	84 95 45[d]

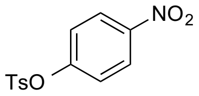
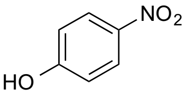
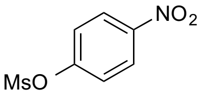
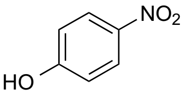
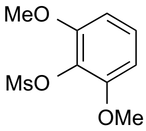
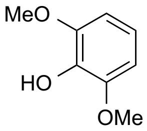
[a] Method A: 2 equiv of Et_4NOH was used in aq dioxane. Method B: 10 equiv of Et_4NOH was used in aq dioxane. Method C: 1 equiv of n-Bu_4NF was used in THF. Method D: 2 equiv of n-Bu_4NF was used in THF.

[b] Hydrolysis of methyl ester group was mainly observed.

[c] The starting material was recovered in 29% yield.

[d] The starting material was recovered in 53% yield.

Table 2. Cleavage of sulfonates using tetraethylammonium hydroxide

Entry[a]	Substrates	Products	Temp	Time	Yield (%)
1			rt	24h	92
2			rt	3h	97
3			rt	6days	37[b]

[a] 2equiv of Et_4NOH was used in aqueous dioxane.

[b] The starting material was recovered in 39% yield.

studies. Aryl compounds, **1a** and **1h**, having electron-withdrawing moieties, such as a methoxycarbonyl and nitro groups (entries 1 and 8), were susceptible to the n-Bu_4NF conditions to give the corresponding phenols, **2a** and **2h**. Despite a long reaction time, **1c** (entry 3) provide **2c** in quantitative yield, whereas **1l** and **1m** (entries 12 and 13) possessing electron-donating moieties exhibited low reactivity, and the starting materials were recovered in 29% and 53% yields, respectively. In contrast, our Et_4NOH-method did not affect the functional groups, such as nitro, ketone, halogen, amide, siloxy ether and sulfonamide (entries 4–10). Cleavage of the quinoline compound **1k** was also smoothly accomplished (entry 11). The substrate **1l**, possessing a methoxy group as an electron-donating moiety (entry 12), underwent smooth deprotection of an aryl trifluoromethanesulfonyl group even at ambient temperature, although the n-Bu_4NF method required a long reaction time. In the case of the 2,6-disubstituted phenol derivative **1m** (entry 13) possessing not only an electron-donating substituent in the aromatic ring, but also steric hindrance against the trifluoromethanesulfony group, the reaction quantitatively proceeded by using the elevated temperature (60 °C) to give **2m**. To compare with our method, we examined hydrolysis using NaOH, which has been reported to provide a similar cleavage.[3c,3d] Upon using NaOH (2equiv mol) in MeOH-dioxane at ambient temperature, **1b**, **1h**, **1j** afforded **2b** (72%), **2h** (87%) and **2j** (81%), along with their phenol methyl ether derivatives in 9%, 9% and 13% yields, which might be produced by the attack of MeOTf in situ generated. In the case of **1j**, a base-catalyzed coupling at the methyl ketone moieties was observed to give the corresponding dimmer in ca. 2% yield. These unexpected reactions were not observed under the Et_4NOH conditions (entries 2, 8 and 10). When NaOH (2equiv mol) in aq dioxane at ambient temperature, was used to avoid production of the phenol methyl ethers, yields of the corresponding phenols were slightly lowered (**2h**, 87%; **2j**, 87%) with the exception of **1b**, which provide **2b** in 32% yield, owing to hydrolysis of the methyl esters. In contrast, treatment under the Et_4NOH in aqueous dioxane conditions produced **2b** in 95% yield. Other aryl sulfonates, such as aryl tosylates and aryl mesylates, were hydrolyzed in a similar manner to those of triflates, although they required longer-reaction time (Table 2). Especially, in entry 3, the corresponding phenol was produced in low yield, owing to high electron density around the sulfonate moiety. Based on these observations, facility of the deprotection reaction would be in the following order: aryl triflates > aryl mesylates > aryl tosylates.

In conclusion, a new procedure to cleave aryl sulfonates under mild conditions was demonstrated. In contrast to such usual methods as reduction, hydrolysis and use of fluoride anion, our method was applicable to selective cleavage of aryl triflates. Other functional groups such as nitro, ketone, halogen, amide, siloxy ether and sulfonamide groups were intact under the reaction conditions.

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