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Hard Acid and Soft Nucleophile System. IV.[1] Removal of Benzyl Protecting Group with Boron Trifluoride Etherate and Dimethyl Sulflide

KAORU FUJI, TAKEO KAWABATA, and EIICHI FUJITA

Institute for Chemical Research, Kyoto University[2]

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A new combination system consisting of boron trifluoride etherate and dimethyl sulfide has proved to be useful especially for the selective removal of the benzyl protecting group in a molecule having a Michael acceptor or carbonyl group(s).

Keywords——hard acid; soft nucleophile; debenzylation; boron trifluoride etherate; ethanethiol; dimethyl sulfide; Michael addition

The combination system of a hard acid and a soft nucleophile has proved to be effective for a variety of carbon-oxygen bond cleavage reactions. They include demethylation of aliphatic methyl ethers with boron trifluoride etherate-ethanedithiol,[3] removal of the benzyl protecting group with boron trifluoride etherate-ethanethiol,[4] and demethylation of methyl ethers and demethylenation of the methylenedioxy group with aluminum halide-ethanethiol.[5] The last system has also been applied to nonsaponificative cleavage of the alcoholic oxygen-carbon bond of methyl and benzyl esters[1,6] and lactones.[6] The more active dealkylation of esters has been performed with aluminum halide and dialkyl sulfide.[1] Demethylation of an aromatic methyl ether with methanesulfonic or trifluoromethanesulfonic acid-methionine[7] or trifluoromethanesulfonic acid-thioanisole[8] falls into this category, though the scope is rather limited. All of the above carbon-oxygen bond cleavage reactions are based on the balance between the coordination of a hard acid with the oxygen atom (pulling factor) and the nucleophilic attack of a soft nucleophile at the carbon atom (pushing factor), and illustrate that a slight variation of the balance can cause a remarkable change of reactivity. We report here another type of variation involving the use of dimethyl sulfide as a nucleophile for debenzylation, which has more attractive feafures than the former system.[4]

Though the wide range of synthetic utility of the boron trifluoride etherate-ethanethiol system for deblocking of the benzyl protecting group has been well demonstrated,[4] the application of this system to a molecule having a Michael acceptor or carbonyl group(s) is of little value owing to the intrusion of undesired reactions such as the addition of thiol to the α,β-unsaturated double bond or dithioacetal formation. These side reactions were eliminated by changing the nucleophile from ethanethiol to dimethyl sulfide. The results summarized in the table clearly show the advantage of the present system.

The benzyl ether **1** afforded the Michael adduct **1b** with system B (boron trifluoride etherate–ethanethiol), while the benzyl ethers **4** and **5** were debenzylated to give the corres-

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[2] Location: *Uji, Kyoto-Fu 611, Japan.*

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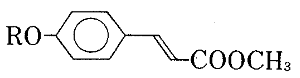
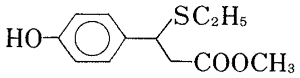
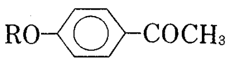


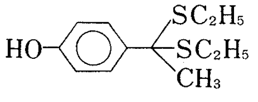
1 : R=CH$_2$Ph
1a : R=H



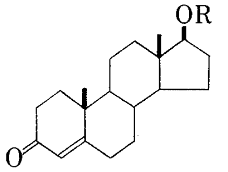
1b



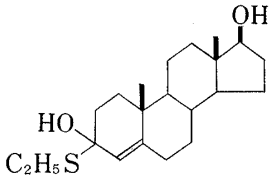
2 : R=CH$_2$Ph
2a : R=H



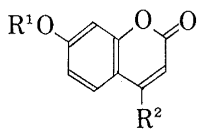
2b

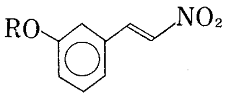


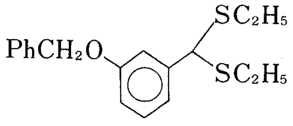
3 : R=CH$_2$Ph
3a : R=H



3b







4 : R^1=CH$_2$Ph, R^2=H
4a : R^1=R^2=H
5 : R^1=CH$_2$Ph, R^2=CH$_3$
5a : R^1=H, R^2=CH$_3$

6 : R=CH$_2$Ph
6a : R=H

6b

TABLE. Debenzylation by $BF_3 \cdot OEt_2$–Me_2S System (A) and $BF_3 \cdot OEt_2$–EtSH System (B)

Compound	System	Reaction Time hr	Product	Yeild %
1	A	4	**1a**	88.9
	B	1.5	**1b**	89.2
2	A	15	**2a**	97.1
	B	16	**2b**	83.9
3	A[a]	19	**3a**	94.4
	B	18	**3b**	84.5[b]
4	A[c]	24	**4a**	97.5
	B[d]	72	**4a**	98.8
5	A	47	**5a**	93.2
	B	46	**5a**	94.3
6	A	1.5	**6a**	97.8
	B[e]	0.5	**6b**	47.7

a) After 14 hr, a further 10 eq. of boron trifluoride etherate was added.
b) Testosterone (**3a**) was obtained in 11.2% yield.
c) Fifty eq. of boron trifluoride etherate was used.
d) After 48 hr, a further 48 eq. of boron trifluoride etherate was added.
e) At 0° in N_2.

ponding parent phenols **4a** and **5a**, respectively, by both systems A (boron trifluoride etherate–dimethyl sulfide) and B. The contribution of the resonance formes **7a** and/or **7b** involving the ten π-electron system, which is not expected for **1**, might prevent the attack of ethanethiol on the double bond in the cases of **4** and **5**.

Debenzylation of **2** and **3** with system B gave the unstable products **2b** and **3b** respectively, whose spectroscopic data (see experimental section) are clearly consistent with the assigned structures. Unambiguous confirmation of the structures **2b** and **3b** was obtained by the subsequent conversion to the original ketones **2a**[9] and **3a**.

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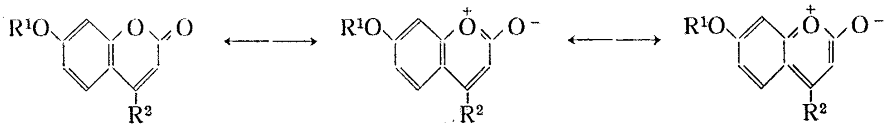

4 or 5 7a 7b

Unexpected cleavage of the carbon-carbon double bond of the α,β-unsaturated nitro compound **6** was observed instead of the Michael addition with system B.

Experimental

The IR spectra were recorded with a JASCO A-202 diffraction grating infrared spectrometer and the NMR spectra were obtained with either a Varian T-60 spectrometer or a JEOL-FX-100 spectrometer. Chemical shifts are reported relative to internal tetramethylsilane.

Material——The known benzyl ethers **1**—**6**[10] were prepared from the parent phenols or alcohols according to the standard method.[11]

General Procedure for Debenzylation——Me_2S (1 ml; System A) or EtSH (1 ml; System B) and boron trifluoride etherate (0.63 ml, 5 mmol) were added to a solution of substrate (0.5 mmol) in dichloromethane (1 ml), and the mixture was stirred at 30°. The reaction mixture was poured into water and extracted with ethyl acetate or dichloromethane. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and evaporated to dryness to leave a crude material which was purified by chromatography on a silica gel column and/or by recrystallization. The products and the yields are given in the table.

Physical Data for New Products——**1b**: mp 62—64° (from Et_2O–hexane). NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7 Hz, $SCH_2C\underline{H}_3$), 2.33 (2H, q, J=7 Hz, $SC\underline{H}_2CH_3$), 2.84 (2H, d, J=8 Hz, $C\underline{H}_2COOCH_3$), 3.61 (3H, s, $COOCH_3$), 4.25 (1H, t, J=8 Hz, -CH<), 6.75 (2H, d, J=9 Hz, aromatic H), 7.20 (2H, d, J=9 Hz, aromatic H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1730, 1610, 1520. *Anal.* Calcd for $C_{12}H_{16}O_3S$: C, 59.97; H, 6.71. Found: C, 59.72; H, 6.59. **2b**: NMR ($CDCl_3$) δ: 1.16 (6H, t, J=7 Hz, $SCH_2C\underline{H}_3$), 2.00 (3H, s, CH_3), 2.51 (4H, q, J=7 Hz, $SC\underline{H}_2CH_3$), 6.76 (2H, d, J=8 Hz, aromatic H), 7.57 (2H, d, J=8 Hz, aromatic H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1610, 1520. **3b**: NMR ($CDCl_3$) δ: 0.76 (3H, s, CH_3), 1.02 (3H, s, CH_3), 1.22 (3H, t, J=7 Hz, $SCH_2C\underline{H}_3$), 2.62 (2H, q, J=7 Hz, $SC\underline{H}_2CH_3$), 3.62 (1H, br. t, J=8 Hz, C-17-H), 5.31 (1H, s, C-4-H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 2970, 1670. **6b**: NMR ($CDCl_3$) δ: 1.20 (6H, t, J=7 Hz, $SCH_2C\underline{H}_3$), 2.54 (4H, q, J=7 Hz, $SC\underline{H}_2CH_3$), 4.87 (1H, s, -CH<), 5.06 (2H, s, OCH_2Ph), 6.8—7.5 (9H, m, aromatic H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1600, 1490, 1260. *Anal.* Calcd for $C_{18}H_{22}OS_2$: C, 67.88; H, 6.96. Found: C, 68.13; H, 6.92.

Conversion of 2b into 2a——Isoamyl nitrite (102 mg, 0.86 mmol) and H_2O (40 μl, 2.2 mmol) were added to a solution of **2b** (174 mg, 0.72 mmol) in dichloromethane (10 ml), and the mixture was stirred at room temperature. After 80 min, a further 440 mg (3.7 mmol) of isoamyl nitrite and 100 μl (5.6 mmol) of H_2O were added. After 1 hr, ethyl acetate was added and the mixture was worked up as usual to give an oily crude product, which was chromatographed on a silica gel column to afford *p*-hydroxyacetophenone (**2a**) (61 mg, 62.3%).

Conversion of 3b into 3a——A mixture of **3b** (137 mg, 0.39 mmol) and acidic aqueous acetone (8 ml; containing 5% of HCl) was stirred for 1 hr at room temperature. Usual work-up and purification (silica gel column chromatography) of the crude product afforded testosterone **3a** (94 mg, 83.3%).

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