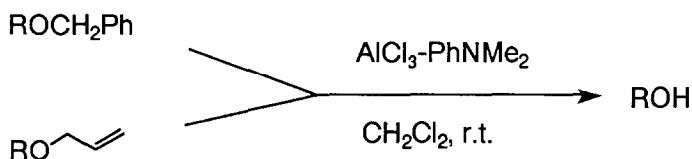


AlCl₃-N,N-DIMETHYLANILINE: A NEW BENZYL AND ALLYL ETHER CLEAVAGE REAGENT.

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Summary: Benzyl and allyl ethers have been cleaved readily on treatment with AlCl₃ and N,N-dimethylaniline to give parent alcohols in high yields. Comparisons of N,N-dimethylaniline and anisole are also described.

A certain combination system of a Lewis acid and a Lewis base shows unique reactivity not exerted by a Lewis acid itself. For the cleavage of carbon heteroatom bond, various combination systems have been developed.¹⁾ A combined system of AlCl₃ and anisole was used to cleave benzyl ester,²⁾ and we recently reported that the system cleaved N-3 imide *p*-methoxybenzyl (PMB) group of uridine moiety without affecting N-glycosidic bond.³⁾ This time we have found that AlCl₃-N,N-dimethylaniline readily cleaves benzyl as well as allyl ethers at room temperature. In addition to catalytic hydrogenolysis, a number of debenzylating reagents such as TMSI,⁴⁾ TMSCl-NaI,⁵⁾ SiCl₄-NaI,⁶⁾ BBr₃,⁷⁾ BF₃-EtSH,⁸⁾ and BF₃-Me₂S⁹⁾ have been reported;¹⁰⁾ these systems, however, have drawbacks such as instability of the reagent, nasty smell, long reaction time. Ready availability as well as ease of handling of the reagent provide a particular advantage of the present system.



In the first place, 3-phenylpropanol benzyl ether (**1a**) was treated with AlCl₃ (3 equiv) and anisole (4 equiv) in CH₂Cl₂ at room temperature for 40 min to obtain 3-phenylpropanol in high yield. This combined system of AlCl₃ and anisole worked well for the cleavage of benzyl ether, but tediousness in the removal of anisole prompted us to screen other additives and the results are shown in Table 1. Without an additive, the starting material was disappeared readily and messy products were obtained. (Run 6) As expected, the debenzylation underwent smoothly by use of electron rich aromatic compounds, among which we selected N,N-dimethylaniline as the additive for this reaction because it can be easily washed out from organic layers. A typical experimental procedure for the cleavage of benzyl ether is as follows: To a solution of **1a** (100 mg, 0.443 mmol) and N,N-dimethylaniline (0.18 ml, 1.33 mmol) in CH₂Cl₂ (1.0 ml) was added powdered AlCl₃ (239 mg, 1.79 mmol) at room temperature. Stirring was continued for 30 min. The reaction mixture was

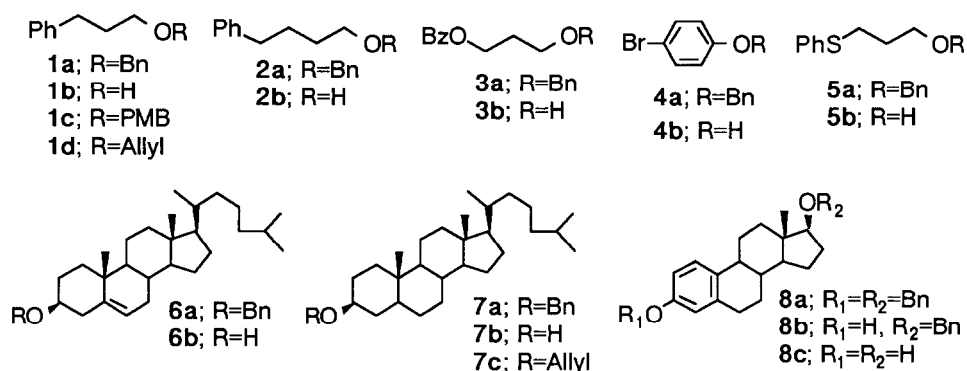


Table 1 Results of the cleavage of **1a** with AlCl₃ (3 equiv) and additive (4 equiv) in CH₂Cl₂ at room temperature.

Run	Additive	Reaction time/ h	Yield of 1b / %
1	PhOCH ₃	0.7	100
2	PhNMe ₂	0.5	93
3	PhOH	0.75	87
4	NEt ₃	2.5	0 ^{a)}
5	Pyridine	2.5	0 ^{a)}
6	None	4.0	0

a) Starting material was recovered quantitatively.

quenched by addition of 1N HCl (3 ml) and the aqueous layer was extracted with ethyl acetate (3 x 7 ml). The combined organic layers were successively washed with 5% NaHCO₃ solution and brine, dried over anhydrous Na₂SO₄, and the solvent was removed under reduced pressure. The remaining residue was purified by short column chromatography (SiO₂, hexane:ethyl acetate (v/v) = 4:1) to afford 3-phenylpropanol (56.1 mg, 0.412 mmol, 93%). Deprotection of varieties of aliphatic and aromatic benzyl ethers were examined by use of AlCl₃ (3 equiv) and *N,N*-dimethylaniline in CH₂Cl₂ at room temperature and the results are shown in Table 2. Although no reaction took place at 0 °C, the cleavage reaction was accomplished mostly in less than 1 h at room temperature to obtain parent alcohols in high yield. For the cleavage of an aromatic benzyl ether (**4a**), slightly larger amount of *N,N*-dimethylaniline was necessary to obtain *p*-bromophenol in a good yield. (Run 4) When 4 equiv of *N,N*-dimethylaniline was used, *o*-benzyl-*p*-bromophenol was obtained as the main product. Functional groups such as ester, sulfide, and olefinic double bond were compatible with this reaction conditions. The aromatic benzyl ether of β-estradiol dibenzyl ether (**8a**) was cleaved selectively in preference to the aliphatic one.¹¹⁾ (Run 9) *p*-Methoxybenzyl (PMB) ether was cleaved readily at 0 °C. (Run 11)

The present debenzylolation reaction is considered to proceed via initial coordination of AlCl₃ to ether oxygen followed by attack of an aromatic compound, such as *N,N*-dimethylaniline or anisole, to benzylic carbon.¹²⁾ Although the combined system of AlCl₃ and anisole also cleaved benzyl ethers smoothly to give

Table 2 Results of the cleavage of benzyl ethers with AlCl₃ (3 equiv) and Additive in CH₂Cl₂ at room temperature.

Run	Starting material	Additive (equiv)	Reaction time / h	Product	Yield / %
1	1a	PhNMe ₂ (4.0)	0.5	1b	93
2	2a	PhNMe ₂ (4.0)	0.5	2b	86
3	3a	PhNMe ₂ (4.0)	1.0	3b	88
4	4a	PhNMe ₂ (10.0)	0.5	4b	91
5	5a	PhNMe ₂ (4.0)	1.0	5b	96
6		Anisole (4.0)	3.0	5b	8
7	6a	PhNMe ₂ (4.0)	1.0	6b	88
8	7a	PhNMe ₂ (8.0)	2.5	7b	96 ^{a)}
9	8a	PhNMe ₂ (4.0)	1.0	8b	80
10		Anisole (4.0)	1.0	8c	73
11	1c	PhNMe ₂ (4.0)	0.75	1b	91 ^{b)}

a) Six equiv of AlCl₃ was employed. b) Reaction was carried out at 0°C.

parent alcohols in good yields, it occasionally gave different results from AlCl₃-N,N-dimethylaniline. A remarkable contrast between the two systems are exemplified in the cleavage reaction of 5a. (Runs 5, 6) The results suggests that the intramolecular attack by the sulfide moiety, which acts as a cation scavenger,¹³⁾ took place in preference to the intermolecular attack upon benzylic carbon by anisole. Consequently, nucleophilicity of N,N-dimethylaniline has proven to be much stronger than that of anisole, in agreement with the reactivity order as Friedel-Crafts substrates.¹⁴⁾ Selective cleavage of the aromatic benzyl ether of 8a effected by AlCl₃-N,N-dimethylaniline can also be attributed to its high reactivity of N,N-dimethylaniline, thereby the reaction with N,N-dimethylaniline is displaced toward S_N2 end of the mechanism spectrum in comparison to that with anisole.

Next we studied the cleavage reaction of allyl ethers and the results are shown in Table 3. AlCl₃-N,N-dimethylaniline cleaved allyl ethers more smoothly than AlCl₃-anisole to afford parent alcohols in good yield.

Table 3 Results of the cleavage of allyl ethers with AlCl₃ and additive in CH₂Cl₂.

Run	Starting material	Equiv of AlCl ₃	Additive (equiv)	Reaction conditions	Product	Yield / %
1	1d	3.0	PhNMe ₂ (4.0)	reflux 1 h	1b	83
2	1d	6.0	PhOCH ₃ (8.0)	reflux 2 h	1b	65
3	7c	6.0	PhNMe ₂ (8.0)	r.t. 2.5 h	7b	96

The AlCl_3 -*N,N*-dimethylaniline system is superior to AlCl_3 -anisole in the cleavage of benzyl as well as allyl ethers. The features of the system are; 1) short reaction times; 2) mild reaction conditions; 3) ease of handling of the reagent; 4) compatibility of the functional groups such as ester, sulfide and olefinic double bond. The present method will be a new entry into the removal of benzyl as well as allyl ether protecting groups.

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