Studies of the Selective O-Alkylation and Dealkylation of Flavonoids. XVI.[1] Demethylation of 2′-Methoxyacetophenones with Anhydrous Aluminum Chloride or Bromide in Acetonitrile

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Demethylation of 2′-methoxyacetophenones with anhydrous aluminum chloride in acetonitrile was studied to survey its scope and limitations. The mechanism which the reaction proceeds via sterically constrained intermediates was proposed from the substituent effects. Additionally, dealkylation of 2′-benzyloxy-, 2′-ethoxy-, and 2′-isopropoxyacetophenones with two demethylating reagents, hydrochloric acid in acetic acid and anhydrous aluminum bromide in acetonitrile, was studied. It was found that the reactivity was greatly affected by the steric factor between the alkoxyl group and reagent. This behavior may have wide application in selection of protecting groups in organic synthesis.

We have been studying the selective O-alkylation and dealkylation of flavonoids to establish new, convenient methods for synthesizing polyhydroxyflavones.[1] In these studies, it has been found that the cleavage of the 5-methoxyl group in 5,6,7-trioxygenated flavones is easier than that in 5,7,8-trioxygenated flavones with no substituent at the 6-position.[2,3] Furthermore, the 2-methoxyl group of 2,3,4,6-tetramethoxyacylbenzenes is selectively cleaved without cleavage of the 6-methoxyl group to give 2-hydroxyacylbenzenes only.[4] These results show that the cleavage of the methoxyl group adjacent to the carbonyl group is accelerated by a neighboring alkoxyl group. Discovery of the reason for this result would be useful for the application of the demethylation. Therefore, demethylation of substituted 2′-methoxyacetophenones with anhydrous aluminum chloride in acetonitrile was studied. In this paper, we wish to propose a mechanism for this demethylation reaction and report on the relative influence of different demethylating reagents (Chart 1).

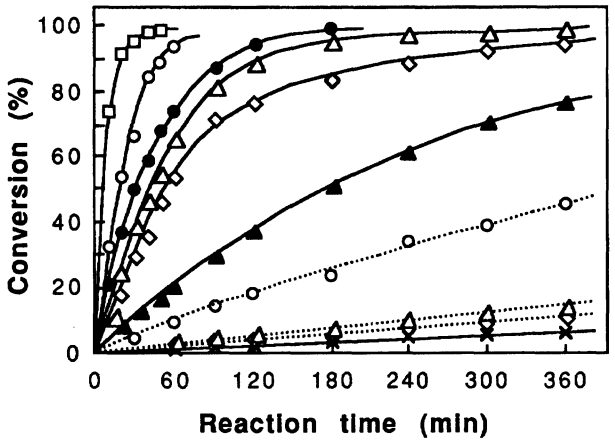


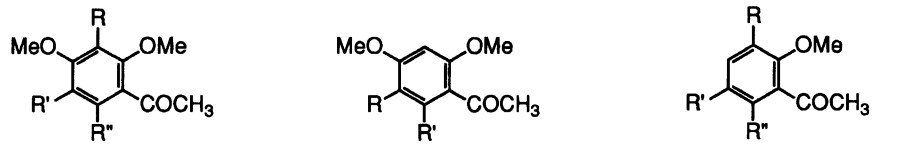
Fig. 1. Time conversion of the demethylation of 2′-methoxyacetophenones (50 mg) with 5% (w/v) anhydrous aluminum chloride–acetonitrile (5 cm^3) at 30 °C. **1a**, —□—; **1b**, —○—; **1e**, —●—; **1c**, —△—; **1d**, —◇—; **1f**, —▲—; **2a**, ---○---; **2b**, ---△---; **2c**, ---◇---; **3b**, —×—.

Results and Discussion

Demethylation of substituted 2′- methoxyacetophenones with 5% anhydrous aluminum chloride–acetonitrile was examined qualitatively using silica-gel TLC. TLC of products obtained from the reaction mixture after treatment with hot dilute hydrochloric acid showed that demethylation proceeds cleanly without formation of by-products. The result shows that the product can be measured by comparing the relative area of the product and starting material in the gas chromatogram. The reaction time dependency on demethylation of substituted 2′-methoxyacetophenones thus obtained are shown in Figs. 1 and 2.

In the demethylation of 2′, 4′- dimethoxyacetophenones, the reactivities decreased in the order **1a**, **1b**, **1e**, **1c**,[5] **1d**, **1f**, **2a**, **2b**, and **2c**. This suggests that demethylation is accelerated by an increasing number of electron-releasing substituents attached to the ring. Especially, the 3′-substituent accelerated greatly the rate of demethylation with increasing coordination ability of the substituent in the order Me, Cl, OMe, and SMe. However, the reactivities of other acetophenones with no substituent at the 4′-position were lower than those with the 4′-methoxyl group (**1** or **2** vs. **3**) and the rate acceleration by the 3′-methoxyl group on demethylation was not observed for 2′,3′,5′,6′-tetramethoxyacetophenone[6] (**3a**), suggesting that the 4′-methoxyl group participated greatly in the demethylation. Generally, it is considered that the cleavage of the methoxyl group adjacent to the carbonyl group proceeds via a cyclic aluminum complex[3,7] and these results may also be explained on the basis of the formation of a cyclic aluminum complex as shown in Scheme 1.

The nonbonded electron pairs associated with the 4′-methoxyl oxygen atom would be delocalized into the ring and the carbonyl group. This delocalization of electron density would facilitate the elimination of chlo-

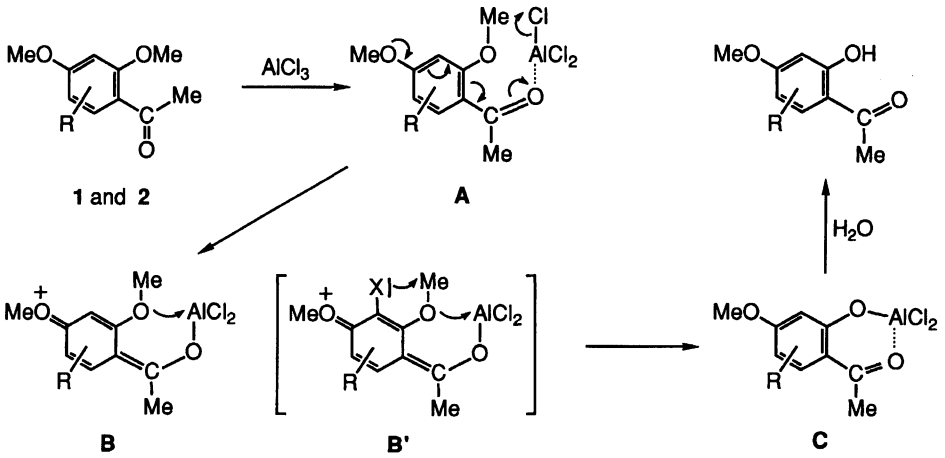


1a R=SMe, R'=H, R"=OMe
1b R=R"=OMe, R'=H
1c R=Cl, R'=H, R"=OMe
1d R=CH_3, R'=H, R"=OMe
1e R=OMe, R'=R"=H
1f R=R'=R"=OMe

2a R=H, R'=OMe
2b R=OMe, R'=H
2c R=R'=H

3a R=R'=R"=OMe
3b R=R'=H, R"=OMe
3c R=R"=H, R'=OMe
3d R=R'=R"=H

Chart 1.



Scheme 1.

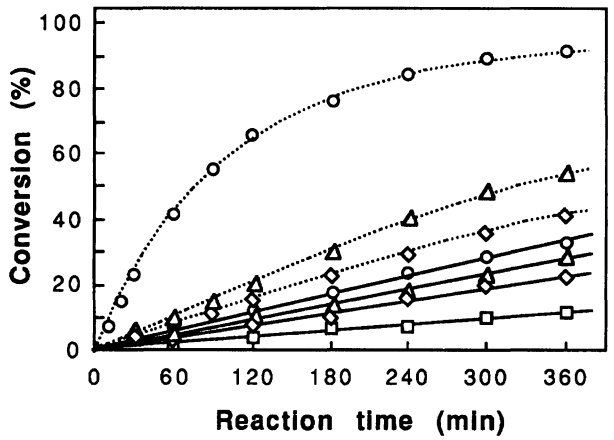


Fig. 2. Time conversion of the demethylation of 2′-methoxyacetophenones (50 mg) with 5% (w/v) anhydrous aluminum chloride–acetonitrile (5 cm^3) at 45 °C. **2a**, ---○---; **2b**, ---△---; **2c**, ---◇---; **3b**, —○—; **3a**, —△—; **3c**, —◇—; **3d**, —□—.

ride from aluminum-possibly with simultaneous coordination of the 2′-methoxyl oxygen atom to the aluminum atom. Coplanarity between the aromatic ring and carbonyl group is also enhanced by resonance. One result would be that cleavage of the 2′-methoxyl group becomes faster in acetophenones that have a 4′-alkoxyl group compared to those that have no substituent at the 4′-position.

In a study of the dealkylation of alkyl aryl ethers with metal halides in the presence of ethanethiol, Fujita et al.[8] reported that dealkylation is accelerated by nucleophilic attack of ethanethiol on the leaving group (pushing factor). Recently, Ozaki et al.[9] have reported that an iodo anion has also shown a similar effect in the demethylation of inositol derivatives with anhydrous aluminum chloride–sodium iodide. Our result that the 3′-substituent in 2′,4′-dimethoxyacetophenones (**1**) greatly accelerates the cleavage of the 2′-methoxyl group would be explainable by a similar effect. That is, the methyl group in the 2′-methoxyl group is acted on by a pushing force by the lone pair of electrons on the neighboring 3′-substituent (Scheme 1, **B′**). Demethylation is greatly accelerated as a result. Therefore, the rate acceleration caused by a 3′-substituent would be expected to increase with increasing coordination ability of the substituent as shown by the results in Fig. 1. An explanation for the fact that the 3′-methyl group in **1d** also accelerates demethylation may be that demethylation is accelerated by steric repulsion between the 3′-methyl group and the leaving methyl group in the complex **B′** (Scheme 1).

Reactivity of 2′, 3′, 4′, 5′, 6′-pentamethoxyacetophenone (**1f**) is less than that of **1b** or **1e** despite the

fact that **1f** has respectively one or two more methoxyl groups. A possible explanation for this result is that the resonance between the 4′-methoxyl oxygen atom and the carbonyl group in complex **A** is suppressed by steric hindrance involving the two methoxyl groups at the 3′- and 5′-positions. On the other hand, the fact that the rate of demethylation of **3a** is similar to that of **3b** is explained by considering that the coplanarity between the aromatic ring and carbonyl group in **3a** is reduced more than that in **3b** by increasing the steric hindrance against the carbonyl group.

To provide additional evidence for the above mechanism, reaction kinetics of some representative acetophenones (**1b**, **1f**, **2a**, **3b**, and **3c**) were studied and the results are shown in Table 1. Since only limited kinetic data are available, the isokinetic relationship is not clear. Kinetic parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, however, appear to compensate for each other in the opposite sense. This means that this structural change in the acetophenone results in a stronger interaction with aluminum chloride and consequent lowering of $\Delta H^{\ddagger}$. It would be accompanied by tighter binding in the transition state and more negative $\Delta S^{\ddagger}$. Fairly negative activation entropies were observed for the 4′-methoxyl substituted acetophenones, **1b**, **1f**, and **2a**. Considering the higher net pseudo-first-order reaction rate for reaction on **1b**, **1f**, and **2a**, it also suggests that the formation of the *p*-quinonoid structure in the intermediate permits an easier demethylation. Kinetic data from demethylation of these acetophenones show that the reaction proceeds via a sterically constrained intermediate and provide positive support for the mechanism in Scheme 1.

This mechanism clearly explains why the 2′-methoxyl group in the 3′-substituted 2′,4′,6′-trimethoxyacetophenones (**1a**—**1d**) is selectively cleaved without cleavage of the 6′-methoxyl group, and suggests also that cleavage of the 2′-alkoxyl group is greatly affected by variation of the reagent as expected from our previous studies.[2,4,10] Therefore, dealkylation of acetophenones with a methoxyl, ethoxyl, isopropoxyl, or benzyloxyl group at the 2′-position by two reagents was additionally examined and the representative results are shown in Figs. 3, 4, and 5. The reactivities among **2c**, **2c-Et**,[11] and **2c-Pr** are greatly affected by the nature

Table 1. Rate Constants and Kinetic Parameters for the Demethylation of 2′-Methoxyacetophenones with Aluminum Chloride–Acetonitrile

Compd	$\Delta G^{\ddagger}$ / kJ mol^{-1}	$\Delta H^{\ddagger}$ / kJ mol^{-1}	$\Delta S^{\ddagger}$ / J K^{-1} mol^{-1}
1b	93.3	75.5	−65.2
1f	96.0	72.3	−86.6
2a	100.1	80.9	−70.3
3b	105.6	95.3	−37.7
3c	106.7	100.6	−22.2

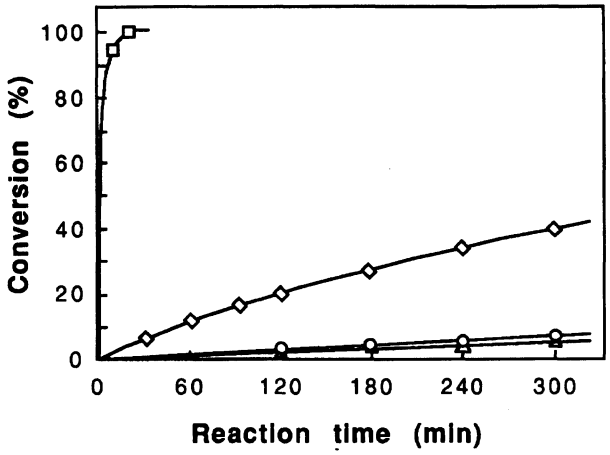


Fig. 3. Time conversion of the dealkylation of 2′-alkoxyacetophenones (50 mg) with conc. hydrochloric acid (0.5 cm^3) in acetic acid (5 cm^3) at 50 °C. **2c-Bz**, □; **2c-Pr**, ◇; **2c**, ○; **2c-Et**, △.

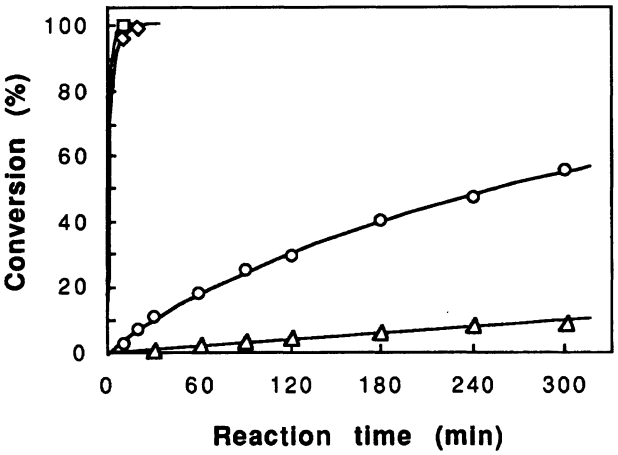
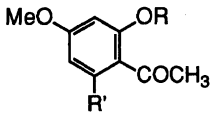


Fig. 4. Time conversion of the dealkylation of 2′-alkoxyacetophenones (50 mg) with 5% (w/v) anhydrous aluminum chloride–acetonitrile (5 cm^3) at 50 °C. **2c-Bz**, □; **2c-Pr**, ◇; **2c**, ○; **2c-Et**, △.

of the demethylating reagent, although the benzyloxyl group in **2c-Bz**[12] is easily cleaved with all reagents and thus the effect of the reagent is not observed under these reaction conditions (Chart 2).

In using the reagent hydrochloric acid–acetic acid, a difference in reactivities between **2c** and **2c-Et** is not observed, but it is clearly observed when using anhydrous aluminum chloride–acetonitrile where the rate of dealkylation decreases in the order **2c-Pr**, **2c**, and **2c-Et**. In using anhydrous aluminum bromide–aceto-



2a-Pr R=CH(CH$_3$)$_2$, R'=OMe
2c R=OMe, R'=H
2c-Et R=Et, R'=H
2c-Pr R=CH(CH$_3$)$_2$, R'=H
2c-Bz R=CH$_2$Ph, R'=H

Chart 2.

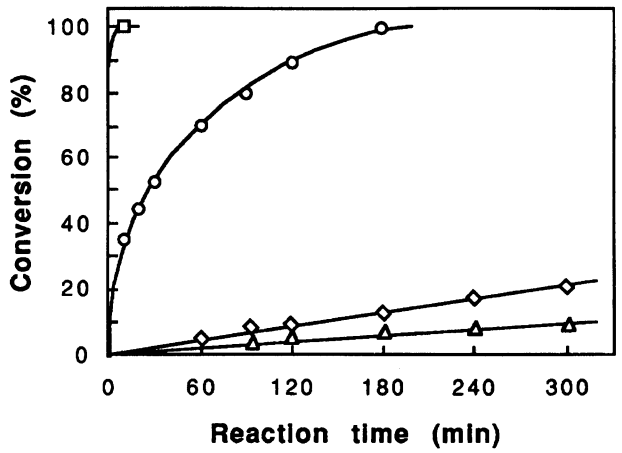


Fig. 5. Time conversion of the dealkylation of 2′-alkoxyacetophenones (50 mg) with 5% (w/v) anhydrous aluminum bromide–acetonitrile (5 cm^3) at 0 °C. **2c-Bz**, □; **2c**, ○; **2c-Pr**, ◇; **2c-Et**, △.

nitrile, cleavage of the isopropoxyl group is retarded and the cleavage of alkoxyl group decrease in the order methoxyl, isopropoxyl, and ethoxyl. The same result was observed in the dealkylation of alkyl ethers of 2′-hydroxyacetophenone and 2′-hydroxy-4′,6′-dimethoxyacetophenones. That is, in the dealkylation of 2′-isopropoxy-4′,6′-dimethoxyacetophenone (**2a-Pr**) with anhydrous aluminum bromide–acetonitrile, the cleavage of the 6′-methoxyl group is faster than that of the 2′-isopropoxyl group to give 2′-hydroxy-6′-isopropoxy-4′-methoxyacetophenone as the main product as shown in Fig. 6.

The cleavage of the methoxyl group with anhydrous aluminum bromide–acetonitrile proceeds much more rapidly than when anhydrous aluminum chloride–acetonitrile is used (Figs. 5 and 6). A possible reason is as follows: bromide, which is a softer base than chloride, binds more weakly to aluminum than chloride. As a result of formation of the cyclic complex of substrate with anhydrous aluminum bromide such as complex **B** in Scheme 1, the reaction rate is accelerated more with aluminum bromide than in the case of demethylation with aluminum chloride.[13] The dealkylation of the 2′-alkoxyl groups in **2c-Pr** and **2c-Et** with anhydrous aluminum bromide, however, is greatly retarded in contrast to demethylation. This result clearly shows that the rate of dealkylation is strongly influenced by a steric effect between the alkoxyl group and reagent: the formation of the intermediate such as complex **B** in Scheme 1 is suppressed due to steric interaction of a bulky alkoxyl group with a bulky reagent, and dealkylation is deterred as a result. This proposal is supported by our previous results[1,3,10] which showed that selective cleavage of 5- and/or 3-methoxyl groups in flavones bearing both methoxyl and benzyloxyl substituents can be achieved using aluminum bromide–acetonitrile. Furthermore, 3- or 5-methoxyl groups in the 5-hexyloxy-3-methoxyflavone and 3-hexyloxy-5-methoxyflavone derivatives are selectively cleaved with anhydrous aluminum bromide without cleavage of the hexyloxyl substituents.[4]

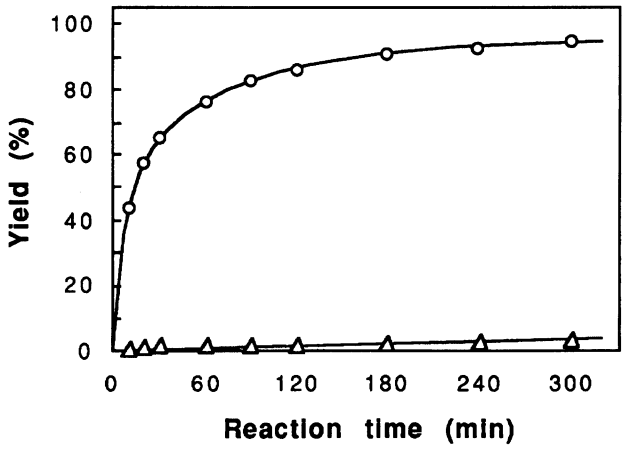


Fig. 6. Dealkylation of 2′-isopropoxy-4′,6′,-dimethoxyacetophenone (**2a-Pr**) (50 mg) with 5% (w/v) anhydrous aluminum bromide–acetonitrile (5 cm^3) at 0 °C. 2′-hydroxy-6′-isopropoxy-4′-methoxyacetophenone, ○; 2′-hydroxy-4′,6′-dimethoxyacetophenone, △.

These results are potentially useful in the selection of phenolic protecting groups and may have wide application in organic synthesis.

Experimental

All melting points were measured in glass capillaries and are uncorrected. Gas chromatographic analyses were done at 110—180 °C using a glass column (3.2 i.d.×2100 mm) packed with Silicone OV-101 (GL Science Co., Ltd.). 2′-Methoxyacetophenones were synthesized in the usual way. The dealkylating products were measured by comparisons with the authentic samples, except for 2′-isopropoxy-6′-hydroxy-4-methoxyacetophenone; mp 65—66 °C (from aq methanol) (Found: C, 64.39; H, 7.20%. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19%).

Synthesis of Acetophenones. 2′,4′,6′-Trimethoxy-3′-(methylthio)acetophenone (1a). To a solution of 1,3,5-trimethoxybenzene (5.0 g; 30 mmol) in tetrahydrofuran (THF) (40 cm^3), a solution of butyllithium in hexane (1.58 mol dm^{-3}; 19 cm^3) was added dropwise with stirring at 0 °C, and then a solution of dimethyl disulfide (2.9 cm^3; 32 mmol) in THF (20 cm^3) was added to the solution. Stirring was continued for another 30 min at 0 °C and the mixture was diluted with water and extracted with ethyl acetate. The extract was washed with 10% aqueous potassium hydroxide, dilute hydrochloric acid, and concentrated under reduced pressure. The residue was recrystallized from methanol to give 2,4,6-trimethoxy-1-(methylthio)benzene, mp 75—77 °C (from methanol) (Found: C, 56.07; H, 6.56%. Calcd for $C_{10}H_{14}O_3S$: C, 56.07; H, 6.59%); yield, 3.36 g (53%).

A solution of the methylthiobenzene (2.0 g) in dry ether (40 cm^3) was mixed with a solution of anhydrous aluminum chloride (1.3 g) in dry ether (20 cm^3) at 0 °C. Acetyl chlo-

ride (1.3 g) was added with stirring to the mixture at 0 °C and the mixture left for 30 min. The resulting semisolid was separated from the ether layer by decantation and treated with ice-cold dilute hydrochloric acid. The precipitate was collected and recrystallized from methanol to give 2′-hydroxy-4′,6′-dimethoxy-3′-(methylthio)acetophenone, mp 143—145 °C (from methanol) (Found: C, 54.64; H, 5.71%. Calcd for $C_{11}H_{14}O_4S$: C, 54.54; H, 5.83%); yield, 540 mg (24%). Additionally, the starting material (1.0 g) was recovered from the ether layer by treatment with dilute hydrochloric acid.

A mixture of the 2′-hydroxyacetophenone (250 mg), dimethyl sulfate (1 cm^3), and anhydrous potassium carbonate (5 g) in acetone (25 cm^3) was refluxed with stirring for 5—6 h. The mixture was diluted with water (30 cm^3) and then refluxed for 30 min, and worked up in the usual way to give **1a**, mp 96—97 °C (from methanol) (Found: C, 56.07; H, 6.19%. Calcd for $C_{12}H_{16}O_4S$: C, 56.24; H, 6.29%); yield, 230 mg (87%).

2′,4′,6′-Trimethoxy-3′-methylacetophenone (1d). 2,4,6-Trimethoxybenzaldehyde (5.0 g) was hydrogenated with 10% palladium on charcoal (0.8 g) in methanol (200 cm^3) at room temperature (about 1.5 h) to give crude 2,4,6-trimethoxytoluene (oil, 4.25 g). To a solution of the toluene (3.9 g) and anhydrous aluminum chloride (5.0 g) in dry ether (50 cm^3), acetyl chloride (1.9 g) was added with stirring. The mixture was stirred at room temperature for 10 h and treated with dilute hydrochloric acid to give 2′-hydroxy-4′,6′-dimethoxy-3′-methylacetophenone, mp 141.5—143 °C (from chloroform–methanol) (lit,[14] mp 141—142 °C), yield 2.3 g (51%). The product was methylated with dimethyl sulfate and potassium carbonate in acetone to give (**1d**) quantitatively, mp 48.5—50 °C (from hexane) (lit,[15] mp 44—45 °C).

2′-Isopropoxyacetophenones (2a-Pr and 2c-Pr). The compounds were synthesized from the corresponding 2′-hydroxyacetophenones in 80—85% yields by isopropylation with isopropyl bromide, potassium iodide, and anhydrous potassium carbonate in acetone–*N*,*N*-dimethylformamide (DMF) at 120—130 °C: **2a-Pr**; mp 66—68 °C (from hexane) (Found: C, 65.45; H, 7.54%. Calcd for $C_{13}H_{18}O_4$: C, 65.53; 7.61%): **2c-Pr**; bp 138—139 °C/3 mmHg (1 mmHg=133.322 Pa) (Found: C, 68.92; H, 7.72%. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%).

General Method for Analysis of the Demethylated Products. In a test tube (18 i.d.×150 mm) fitted with a calcium chloride tube was dissolved the 2′-methoxyacetophenone (50 mg) in 5% (w/v) solution of anhydrous aluminum chloride–acetonitrile (5 cm^3), and the solution was heated at the definite temperature in a thermostat-controlled oil bath. A small amount of the reaction mixture (0.1—0.2 cm^3) was removed at intervals, diluted with 2—3% hydrochloric acid (1—2 cm^3), heated at 40—50 °C for 20—30 min, and then extracted with ether. The extract was directly analyzed by gas chromatography and the yield of the products was calculated from the chromatogram.

The demethylated products obtained using anhydrous aluminum bromide–acetonitrile or hydrochloric acid–acetic acid were analyzed by a similar method.

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