RAPID PAPER

Facile Synthesis of 4-Alkoxy-2,3,6-trimethylphenols Using Trimethylhydroquinone with Aluminium Trichloride in Alcohols

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Trimethylhydroquinone was reacted with AlCl_3 in various alcohols to give the corresponding 4-alkoxy-2,3,6-trimethylphenols in good yields. In the case of CuCl_2 , FeCl_3 and ZnCl_2 , trimethyl-1,4-benzoquinone was obtained.

Much attention has been focused on the chemistry of metal mediated reactions from the viewpoints of synthetic reagents and biomimetic reaction¹⁾. On the other hand, 4-alkoxyphenols are also of interest in their connection with naturally occurring compounds such as libocedrol²⁾ and potent anti-oxidant BHA. However, no easy and simple method for the preparation of 4-alkoxyphenols has been known in strong acidic media. Recently, we reported a convenient method for synthesis of 2-alkoxy-5-methyl-1,4-benzoquinones by the oxidation of 4-methylcatechol with copper (II) chloride in alcohols³⁾. Then, we investigated the reaction of trimethylhydroquinone with metal salts and found a specific and interesting behavior of metal salts for reaction of trimethylhydroquinone. Here, we present a selective method for the synthesis of trimethyl-4-alkoxyphenols from trimethylhydroquinone with AlCl_3 in various alcohols.

Trimethylhydroquinone (3.3 mmol) in various alcohols (30 cm^3) was refluxed with anhydrous aluminium trichloride (4.5 mmol)

for 12 h to give the corresponding 4-alkoxy-2,3,6-trimethyl phenol⁴⁾ in high yield as shown in Table-1. Using *t*-butanol as solvent, only the starting material was recovered. From these results, the reaction mechanisms are thought as follows. The intermediary aluminium alkoxides were attacked by trimethylhydroquinone to produce the alkoxy phenols. The bulky aluminium alkoxides produced from sterically hindered alcohols were difficult to be attacked by trimethylhydroquinone, which is seen in the yields of the case of *t*-BuOH, *i*-AmOH and *i*-PrOH in Table-1.

When other metals such as cupric chloride, ferric chloride, and zinc chloride were used, trimethyl-1,4-benzoquinone was mainly produced. In this reaction Lewis acids were effective and among them, aluminium trichloride was most useful in selectivity and yield. In this reaction, when sulfonic acid and hydrochloric acid were used instead of aluminium trichloride, the yield of the reaction product was low and some by-products were produced. Other phenols such as hydroquinone, methylhydroquinone and dimethylhydroquinone did not react

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Table-1 Monoalkoxylation of trimethylhydroquinone with aluminium trichloride in alcohols.

2a : R=Methyl, 2b : R=Ethyl, 2c : R=*n*-Propyl,
2d : R=*i*-Propyl, 2e : R=*n*-Butyl, 2f : R=*i*-Amyl

Run	Solvent	Product	Mp/°C	Yield/% ^{a)}
1	MeOH	2a	97~98	96
2	EtOH	2b	84~85	91
3	<i>n</i> -PrOH	2c	77	68
4	<i>i</i> -PrOH	2d	48	44
5	<i>n</i> -BuOH	2e	79~80	60
6	<i>i</i> -AmOH	2f	49~50	44
7	<i>t</i> -BuOH	—		recovered ^{b)}

a) Isolated yield.

b) Starting material was recovered.

and starting material was recovered. This indicates that one hydroxy group of trimethylhydroquinone has sufficient basicity to attack various alcohols in the presence of Lewis acid. The hydroxy group which was alkoxyated in the product was the less sterically hindered one⁵⁾. In conclusion, this method was convenient and efficient preparation of 4-alkoxy-2,3,6-trimethylphenols in acidic media.

(Received June 5, 1995)

References and Note

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- 2) E. Zevarin and A. B. Andersson, *J. Org. Chem.*, **22**, 1122 (1957).
- 3) Y. Takizawa, Y. Iwasa, T. Suzuki, and H. Miyachi, *Chem. Lett.*, 1993, 1863.
- 4) All new compounds discussed in the text were fully characterized on the basis of spectral data and analysis. Some typical spectral data are as follows : 2e ; IR (KBr), 3420, 2960, 1240 cm⁻¹. ¹H-NMR, δ (CDCl₃) 0.98 (t, 3 H, *J*=6.0 Hz), 1.42–1.50 (m, 2 H), 1.68–1.75 (m, 2 H), 2.00 (s, 6 H), 2.10 (s, 3 H), 3.88 (t, 2 H, *J*=5.5 Hz), 4.02 (s, 1 H), 6.55 (s, 1 H). The distinct NOEs were observed on the aromatic proton (δ 6.55) by irradiation at the frequency of the oxymethylene proton (δ 3.88). MS. *m/z* 208 (M⁺) for C₁₃H₂₀O₂.
- 5) The alkoxylation of hydroxy group was confirmed spectroscopically by nuclear Overhauser enhancement (NOE) experiments on aromatic proton and alkoxy proton.

アルコール中でトリメチルヒドロキノンと塩化アルミニウムを用いる 4-アルコキシ-2,3,6-トリメチルフェノールの容易な合成法

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トリメチルヒドロキノンを種々のアルコール中で塩化アルミニウムと反応させることにより相当する 4-アルコキシ-2,3,6-トリメチルフェノールを収率よく与えた。他の金属塩 (CuCl₂, FeCl₃, ZnCl₂) を用いたときにはトリメチル-1,4-ベンゾキノンのみを与えた。

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