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Technical Notes

Practical Syntheses of Neopentyl Alcohol and *sec*-Butyl Ethyl Ether Using Marukasol as a Solvent

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Abstract:

By using Marukasol, neopentyl alcohol and *sec*-butyl ethyl ether have been obtained in good yields with easy operations. Thus, neopentyl alcohol was obtained from *tert*-butylmagnesium chloride and paraformaldehyde in 76% isolated yield with >99% purity using Marukasol as an effective extraction solvent. On the other hand, *sec*-butyl ethyl ether was obtained from sodium *sec*-butoxide with ethyl iodide in Marukasol in 67% yield with >99% purity.

Introduction

Marukasol (trade name), produced by Maruzen Petrochemical Co., Ltd., contains 2,2,4,6,6-pentamethylpentane (*iso*-dodecane) as the main component (Figure 1) and has been employed as a useful solvent in many fields [see homepage of Maruzen Peterochemical Co., Ltd.; www.chemiway.co.jp/]. We have been studying the practical use of Marukasol and now report the efficient syntheses of neopentyl alcohol and *sec*-butyl ethyl ether, both of which are not sold as reagent grade, using Marukasol as an extraction or reaction solvent.

Neopentyl alcohol, 2,2-dimethyl-1-propanol (**1**), is known to be a useful raw material (Figure 2).[1] Many syntheses of **1** have been previously reported as follows; however, a practical synthesis of **1** has not been reported.

(i) Conant et al. have reported a method using formaldehyde and *tert*-butylmagnesium chloride in 42−50% yield.[2]

(ii) Whitemore et al. have reported the synthesis of **1** from *tert*-butylmagnesium chloride and *tert*-butyl acetyl chloride in 71% yield.[3]

(iii) Adkins et al. have reported the synthesis of **1** from the hydrogenation of *tert*-butyl acetic acid ethyl ester over copper chromate at 250 °C in 88% yield.[4]

(iv) Nystrom et al. have reported the synthesis of **1** from the reduction of *tert*-butyl acetic acid, ethyl *tert*-butyl acetate, or *tert*-butyl acetic chloride using lithium aluminum hydride.[5,6]

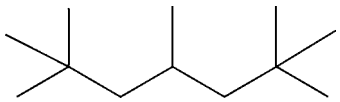
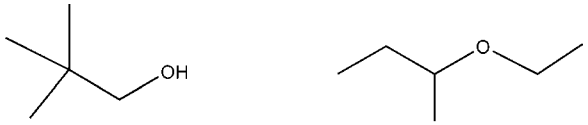


Figure 1. **Structure of main component of Marukasol.**



1 **2**

Figure 2. **Structures of Neopentyl alcohol 1 and *sec*-butyl ethyl ether 2.**

In these methods, the use of formaldehyde and *tert*-butylmagnesium chloride is considered suitable for economic reasons, but the purity and yield of **1** obtained are not satisfactory for large-scale production.

sec-Butyl ethyl ether (**2**) is useful as a flavoring material for dentrifices and mouthwashes and can be synthesized by the Williamson method.[7−9] This classical method is used more widely in ether synthesis at present; however, an efficient and practical synthesis of **2** has not been yet reported.

We have investigated a more practical synthesis of **1** using formaldehyde and *tert*-butylmagnesium chloride with Marukasol as an effective extraction solvent and of **2** using sodium *sec*-butoxide with ethyl iodide with Marukasol as the reaction solvent.

Results and Discussion

Initially, we attempted the synthesis of **1** from formaldehyde and *tert*-butylmagnesium chloride in diethyl ether according to the above-described literature.[2] The result was not practically acceptable with regard to the isolated yield of **1** which included residual water. Also, the use of formaldehyde and diethyl ether should be avoided for safety and environmental reasons. We tried using paraformaldehyde instead of formaldehyde, and *tert*-butyl methyl ether and

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(1) Faith, W. L. *Industrial Chemicals*, 2nd ed.; Wiley & Sons: New York, 1957; pp 107−114.
(2) Conant, J. B.; Webb, C. N.; Mendum, W. C. *J. Am. Chem. Soc.* **1929**, *51*, 1246.
(3) Greenwood, F. L.; Whitmore, F. C.; Crooks, H. M. *J. Am. Chem. Soc.* **1938**, *60*, 2028.
(4) Adkins, H.; Folkers, K. *J. Am. Chem. Soc.* **1931**, *53*, 1091.
(5) Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1947**, *69*, 1198.
(6) Salom, S.; Newman, M. S. *J. Am. Chem. Soc.* **1956**, *78*, 5416.
(7) Williamson, W. *J. Chem. Soc.* **1852**, *4*, 106, 229.
(8) Vogel, A. I. *J. Chem. Soc.* **1948**, 616.
(9) Patai, S. *The Chemistry of the Ether Linkage*; Wiley & Sons: New York, 1967; pp 446−448.

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Table 1. **Effect of extraction solvent upon the yield of 1[a]**

	solvent	isolated yield of **1** (%)
1	*n*-hexane	60
2	*p*-cymene	65
3	Marukasol	75

[a] *t*-BuCl (1.3 equiv), Mg (1.1 equiv), and $(CH_2O)_n$ (1.0 equiv) in THF were used.

diisopropyl ether instead of diethyl ether were investigated as reaction replacement solvents, but the reaction did not proceed. However, the reaction proceeded when using THF. Next, the amounts of *tert*-butyl chloride and magnesium for paraformaldehyde in THF were investigated. The use of 1.3 mol equiv of *tert*-butyl chloride and 1.1 mol equiv of magnesium for paraformaldehyde at 45 °C gave the best results. Neopentyl alcohol, which was obtained by removal of THF followed by distillation of the reactions, did not have high purity and included water. An appropriate extraction solvent is needed after the removal of THF. We tried using *n*-hexane, Marukasol, and *p*-cymeme as extraction solvents, which have either a low or a high boiling point, because it was considered that the purification of **1** could easily be performed by distillation. The results are shown in Table 1. The result using Marukasol which has a high boiling point and an effective solvent effect was preferred.

Second, we attempted the synthesis of **2** from sodium *sec*-butoxide with ethyl iodide using Marukasol. Metalic sodium and 3.3 mol equiv of *sec*-butanol were heated at 100 °C for 5 h to give sodium *sec*-butoxide. Excess *sec*-butanol was removed, and Marukazol was then added. Ethyl iodide was added dropwise at 85 °C for 1 h and allowed to react at 85−100 °C for 7 h. Ethyl iodide was found to be consumed completely by GC. After the workup, a high purity of **2** was obtained in 67% yield by distillation. When not using a solvent such as Marukazol, it is difficult to purify **2** from *sec*-butanol and ethyl iodide by distillation.

In a large-scale production, we have already produced 700 g of **1** with 99.5% purity in 75% yield from 1 kg of paraformaldhyde and 150 g of **2** with 99% purity in 67% yield from 50 g of metalic sodium using the above-described methods without difficulty.

Experimental Section

Marukasol was purchased from Maruzen Petrochemical Co., Ltd. All reagents and other solvents were obtained from commercial sources and used without further purification. For determining the melting points, a Yanagimoto micromelting apparatus was used, and the values are uncorrected values. Boiling points: uncorrected. NMR: Bruker DRX-500. ^{1}H and ^{13}C NMR were measured at 500 and 125 MHz, respectively. The NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard. The chemical shifts were given in δ (ppm). IR: Nicolet Avatar 360 FT-IR. MS: Hitachi M-80A mass spectrometer at 70 eV. GLC was done using a Shimadzu GC-17A with an FID detector (Column 1: Neutrabond-1 produced by GL Sciences, Inc., Japan; df = 0.25 mm ID × 30 m; carrier gas, N_2, 0.1 Mpa; oven temperature, 60−230 °C programmed at 5 °C/min; injection temperature, 230 °C; detector temperature, 250 °C. **1**, t_r: 3.84 min. Marukasol, t_r: 11.08−12.07 min. Column 2: TC-1, by GL Sciences, Inc., Japan; df = 0.25 mm ID × 30 m; carrier gas, N_2, 0.1 Mpa; oven temperature, 40 °C, isothermal 5 min and then 40−230 °C programmed at 5 °C/min; injection temperature, 230 °C; detector temperature, 250 °C. 2-Butanol, t_r: 3.40 min. Ethyl iodide, t_r: 3.54 min. **2**, t_r: 4.45 min. Marukasol, t_r: 17.71−19.90 min).

Scale-Up Procedure for Neopentyl Alcohol (1). In a 10-L glass vessel, magnesium (252.8 g, 10.4 mol) and THF (5.55 L) were added, and then *tert*-butyl chloride (1110.8 g, 12 mol) was added dropwise for 6 h at 35−40 °C. The mixture was allowed to stand overnight. 95% Paraformaldehyde (597.4 g, 9.45 mol) was added at 25 °C and stirred for 7 h at 45 °C. To the reaction mixture, Marukazol (5.55 L) was added, and 70% weight of THF was removed at 55−70 °C under reduced pressure (250 Torr). 20% H_2SO_4 solution (10 L) was added to the residue and stirred at 20−30 °C for 1 h. The organic layer was separated and washed with water (5.5 L), 5% Na_2CO_3 solution (1.5 L), and twice with 10% NaCl solution (2 L). The organic solution (6.25 Kg) was distilled at 100−145 °C under reduced pressure (240−260 Torr) to give neopentyl alcohol (**1**) (623.7 g, 75% vs paraformaldehyde). The distilled product was crystallized as clear white crystals. The purity was 99.5% by GC.

Bp 83−84 °C/245 Torr (lit.[2] 112−114 °C, lit.[3] 106−112 °C/737 mm). Mp 53 °C (lit.[2] 47−49 °C, lit.[3] 50 °C). The NMR, IR, and EI-MS data are identical with the ones from the literature.

Scale-Up Procedure for *sec*-Butyl Ethyl Ether (2). In a 3-L glass vessel, *sec*-butanol (532 g, 7.18 mol) was charged and heated at 55 °C. Metalic sodium (50 g, 2.175 mol) was introduced over 35 min at the same temperature. The mixture was stirred at 100 °C for 5 h. The reaction mixture was cooled to 55 °C, and 60% weight of *sec*-butanol was removed at 55−75 °C under reduced pressure (100 Torr). Marukazol (1.1 L) was added to the residue, and ethyl iodide (305.3 g, 1.957 mol) was then added dropwise at 85 °C for 1 h. The reaction mixture was stirred at 85−100 °C for 9 h. Ethyl iodide was found to be consumed completely by GC. The reaction mixture was cooled to 10 °C, and ice water (300 mL) was added. The organic layer was separated and washed with ice water (500 mL × 4). The organic solution was dried with anhydrous $MgSO_4$ and distilled by column distillation with a helipak No. 3 to give *sec*-butyl ethyl ether (**2**) (147.6 g, 67% vs metalic sodium). The purity was 99.4% by GC.

Bp 79−80 °C (lit.[10] 81°C). The NMR, IR, and EI-MS data are identical with the ones from the literature.

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(10) Lide, D. R.; Milne, G. W. A. *Handbook of Data on Organic Compounds*, 3rd ed.; CRC Press: 1993; p 1825.