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Communications to the Editor

Regioselective Synthesis of 2,6-Dimethyltetralin: Key Precursor to 2,6-Dimethylnaphthalene

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Abstract:

A novel regioselective synthesis for 2,6-dimethyltetralin (2,6-DMT), a key precursor to 2,6-dimethylnaphthalene (2,6-DMN), is described. The synthesis comprises the following three steps; the Heck reaction between commercially available 4-bromotoluene and 3-methyl-3-buten-1-ol, the catalytic reduction of the coupling products, and the acid-catalyzed cyclization of the alcohol intermediate. The process has an advantage over the established processes in that 2,6-DMT is obtained as the only isomer, and the isomerization and/or the complicated separation and purification steps are not required to produce pure 2,6-DMT. 2,6-DMN could be also obtained as a major product depending on the cyclization conditions.

Introduction

2,6-Dimethylnaphthalene (2,6-DMN) is an important raw material in industry for the synthesis of poly(ethylene naphthalate) (PEN) and liquid crystalline polymers.[1] PEN is a high performance polyester superior to poly(ethylene terephthalate) (PET) in many properties such as mechanical, thermal, and electrical properties. Therefore, it has received continual attention since the late 1950s because of its high growth potential in a variety of applications including packaging. However, PEN has been slow in expanding its market share because of short monomer supply that is related to the price and availability of 2,6-DMN.

The mass production of 2,6-DMN by separation from naphtha oil did not look feasible,[2] and various synthetic methods aimed at its economical production have been proposed.[1,3] BP Amoco has commercialized a four-step process for 2,6-DMN that involves the isomerization of 1,5-DMN derived from 5-(*o*-tolyl)pent-2-ene into 2,6-DMN and the separation between them.[4] Mitsubishi Gas Chemical has also explored several potential routes to 2,6-DMN.[5] Optatech has studied a well designed process using base-catalyzed addition of *p*-xylene to butene or butadiene to generate a mixture of adducts and then cyclodehydrogenation to furnish 2,6-DMN.[6] Kobe Steel and Mobil Technology Company have investigated the process in which naphthalene or methylnaphthalene is used as a starting material to produce 2,6-DMN.[7,8] However, most of the above processes yield a mixture of DMN isomers and have to go through an extra separation and/or purification step to produce pure 2,6-DMN. Some of them are suffering from low yield of the desired product.

There are 10 possible isomers of DMN, and it is difficult to obtain pure 2,6-DMN free from other DMN isomers using conventional separation methods such as distillation or solvent extraction. In particular, it is troublesome to cleanly separate 2,6-DMN from 2,7-DMN because they are very similar in some physical properties.[9] Therefore, it is worthwhile to develop a synthetic method for 2,6-DMN free from other isomers. We have recently developed a regioselective synthetic process for 2,6-dimethyltetralin (2,6-DMT) whose conversion to 2,6-DMN by catalytic oxidation is well established[10] and report the results as follows.[11]

Results and Discussion

Our retrosynthetic analysis for the regioselective synthesis of 2,6-DMT is shown in Scheme 1. The Heck reaction between commercially available compounds, 4-halotoluene (**4**) and 3-methyl-3-buten-1-ol (**5**), would provide the key precursor **3** with an excellent regioselectivity after catalytic reduction of the coupling product. The regioselectivity in the Heck reaction of aryl halides with 1,1-disubstituted alkenes is known to be nearly exclusive to yield the substitution products at the terminal carbon of the alkenes

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(1) For a review, see: Lillwitz, L. D. *Appl. Catal. A* **2001**, *221*, 337.
(2) (a) Iwai, Y.; Higuchi, M.; Nishioka, H.; Takahashi, Y.; Arai, Y. *Ind. Eng. Chem. Res.* **2003**, *42*, 5261 and references therein. (b) Kim, S. J.; Kim, S. C.; Kawasaki, J. *Sep. Sci. Technol.* **2003**, *38*, 179.
(3) (a) Chen, T.; Kang, N. Y.; Lee, C. W.; Kim, H. Y.; Hong, S. B.; Roh, H. D.; Park, Y.-K. *Catal. Today* **2004**, *93*, 371. (b) Millini, R.; Frigerio, F.; Bellussi, G.; Pazzuconi, G.; Perego, C.; Pollesel, P.; Romano, U. *J. Catal.* **2003**, *217*, 298. (c) Pu, S.-B.; Inui, T. *Appl. Catal. A* **1996**, *146*, 305.
(4) (a) Lillwitz, L. D.; Karachewski, A. M. U.S. Patent 5,198,594, 1993. (b) Sikkenga, D. L.; Zaenger, I. C.; Williams, G. S. U.S. Patent 5,030,781, 1991. (c) Choo, D. H.; Kim, H. J.; Kong, B. H.; Choi, I. S.; Ko, Y. C.; Lee, H. C.; Kim, J. C.; Lee, J. S. *J. Catal.* **2002**, *207*, 183.
(5) (a) Abe, T.; Uchiyama, S.; Ojima, T.; Kida, K. U.S. Patent 5,008,479, 1991. (b) Abe, T.; Ebata, S.; Machida, H.; Kida, K. U.S. Patent 5,023,390, 1991.
(6) Vahteristo, K.; Halme, E.; Koskimies, S.; Csicsery, S. M.; Laatikainen, M.; Niemi, V. U.S. Patent 5,952,534, 1999.
(7) Sumitani, K.; Shimada, K. Japan Patent JP 4,013,637, 1992.
(8) Motoyuki, M.; Yamamoto, K.; McWilliams, J. P.; Bundens, R. G. U.S. Patent 5,744,670, 1998.
(9) Kim, Y. D.; Lee, J. K.; Cho, Y. S. *Korean J. Chem. Eng.* **2001**, *18*, 971.
(10) Amelse, J. A. U.S. Patent 5,189,234, 1993.
(11) (a) Presented at the 229th American Chemical Society National Meeting, ORGN No. 881, San Diego, CA, March 13−17, 2005. (b) Kim, Y. G.; Kim, W. K.; Kim, B. H.; Lee, J. G. International application No. PCT/KR2005/000507, 2005.

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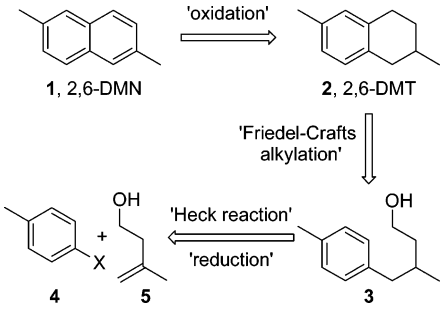
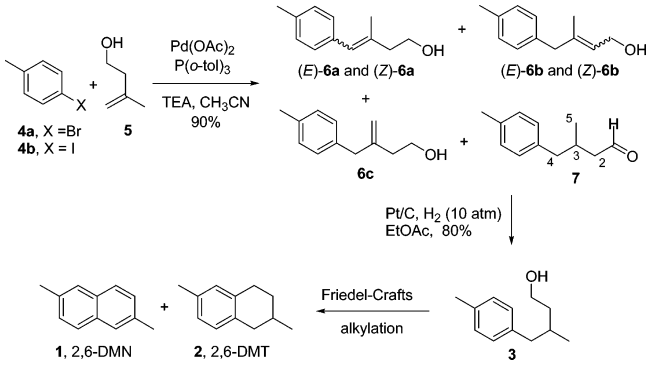
Scheme 1. **Retrosynthetic analysis for the regioselective synthesis of 2,6-DMT and 2,6-DMN**



Scheme 2. **Regioselective synthesis of 2,6-DMT**



as the only isomeric products.[12,13] Cyclization of *para*-aryl substituted alcohol **3** under the conditions of a Friedel−Crafts alkylation reaction should produce the desired isomer **2**.

In reality, the Pd-catalyzed coupling reaction of 4-bromotoluene (**4a**) and **5** resulted in the expected *para*-substituted product as an isomeric mixture of alkenes **6** together with aldehyde **7** in a combined yield of 90% (Scheme 2). Formation of the olefinic mixture **6** can be explained by the β-hydrogen elimination of the different hydrogens at C-2, C-4, or C-5 with the initial Pd adduct at C-3. Aldehyde **7** is most likely obtained from the corresponding enol isomer derived from the in situ Pd-catalyzed isomerization of the double bond at C-2 and C-3.[13] The ratio of **6** to **7** was about 3:2. The same Heck reaction with 4-iodotoluene (**4b**) gave a low yield (25%) of the desired coupling products, and the major byproduct was a homocoupling product, 4,4′-dimethylbiphenyl. Although the olefinic mixture **6** and aldehyde **7** were separable by conventional methods, they were reduced together to the desired key intermediate **3** under the Pt-catalyzed hydrogenation conditions. The higher yield in the hydrogenation was obtained at higher hydrogen gas pressure. Separate reduction reactions of **6** and **7** with different reducing agents were also possible to give **3**. The Pd-catalyzed hydrogenation of **6** under atmospheric pressure of hydrogen gas at room temperature gave **3** in 90% yield and the sodium borohydride ($NaBH_4$) reduction of **7** in methanol at 0 °C produced **3** in 75% yield.

We then investigated the cyclization reaction of **3** under the Friedel−Crafts alkylation conditions with various acids

Table 1. **Intramolecular Friedel−Crafts alkylations of 3 with acid[a]**

		yield[b] (%)	
entry	acid (equiv)	**2**	**1**
1	$SnCl_4$ (2)	22	
2	$BF_3{\cdot}OEt_2$ (2)	6	
3	$FeCl_3$ (2)	70	8
4	$TiCl_4$ (2)	76	10
5	H_2SO_4 (2)	60	
6	H_3PO_4 (2)	40	1
7	CSA[c] (1.5)	34	

[a] In a pressure tube, 200 °C, 2 h in chlorobenzene (PhCl). [b] Isolated as a mixture and the ratio determined by GC. [c] 10-Camphorsulfonic acid.

Table 2. **Intramolecular Friedel−Crafts alkylations of 3 with solid acid[a]**

		yield[b] (%)	
entry	solid acid	**2**	**1**
1	Amberlyst 15	85	2
2	Amberlite IR 120	74	2
3	Nafion NE 450	44	33
4	Nafion 1035	65	10
5	Zeolite H-Y	71	6

[a] In a pressure tube, 200 °C, 2 h in PhCl. [b] Isolated as a mixture and the ratio determined by GC.

(Table 1). We were concerned here about the stability and reactivity of the primary alcohol in the presence of acid. If the lifetime of the cationic primary carbon is long enough, a rearrangement problem would complicate the reaction results.[14] There also might be further difficulty by migration of the methyl group on 2,6-DMT. We were pleased to find that some of the acids were effective to provide 2,6-DMT as the only isomeric product. No other isomers were noticeable. With aluminum chloride ($AlCl_3$) or *p*-toluenesulfonic acid (*p*-TsOH), however, no product was detected (not shown). Interestingly, a small amount of 2,6-DMN was produced with iron(III) chloride ($FeCl_3$) and titanium(IV) chloride ($TiCl_4$) (entries 3 and 4), probably because of the in situ air oxidation of 2,6-DMT. Commonly used acids in the Friedel−Crafts alkylation reaction of alcohols such as sulfuric acid (H_2SO_4) and phosphoric acid (H_3PO_4) were not as effective as the Lewis acids, $FeCl_3$ and $TiCl_4$ (entries 5 and 6).[15]

We have also screened some solid acids because they can be easily separated from the reaction mixture and reused to make them be catalytic in amount (Table 2). The use of solid acids also would minimize the tendency of the methyl group migration.[16] It is shown that Amberlyst 15, a sulfonic acid resin, is the most effective in the cyclization reaction and provides a good yield of 2,6-DMT with a minute amount of 2,6-DMN (entry 1). No rearranged or isomerized adduct was observed. All of the solid acids used in Table 2 including Nafion (perfluorinated sulfonic acid resin)[17] and acid zeolite (aluminosilicate)[18] produce a mixture of 2,6-DMT and 2,6-

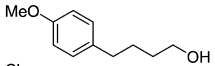
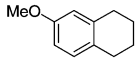
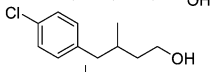
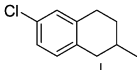
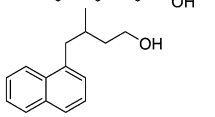
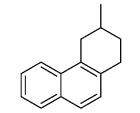
(12) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: Chichester, 2004; pp 105−176.
(13) Larock, R. C.; Leung, W.-Y.; Stolz-Dunn, S. *Tetrahedron Lett.* **1989**, *30*, 6629.
(14) Olah, G. A. *Friedel−Crafts Chemistry*; Wiley: New York, 1973; p 68.
(15) Olah, G. A. *Friedel−Crafts Chemistry*; Wiley: New York, 1973; p 47.
(16) (a) Olah, G. A.; Kaspi, J.; Bukala, J. *J. Org. Chem.* **1977**, *42*, 4187. (b) Sohn, J. R. *J. Ind. Eng. Chem.* **2004**, *10*, 1.

Table 3. **Effect of solvent on the intramolecular Friedel−Crafts alkylations of 3[a]**

		yield[b] (%)	
entry	solvent	**2**	**1**
1	PhCl	85	2
2	PhBr	79	2
3	toluene	73	1
4	Cl_2CHCH_2Cl	84	2
5	1,4-dioxane	73	3

[a] In a pressure tube, 200 °C, 2 h, Amberlyst 15. [b] Isolated as a mixture and the ratio determined by GC.

Table 4. **Application of the intramolecular Friedel−Crafts alkylations to alcohols[a]**

entry	alcohol	time (h)	product	yield (%)
1		3		77
2		24		62
3		3		78

[a] In a pressure tube, 200 °C, PhCl, Amberlyst 15.

DMN in reasonable yields. It is also worth noting that production of 2,6-DMN is considerable with the Nafion resins (entries 3 and 4).

With the results from the solid acids in hand, the effect of the reaction solvent was examined with Amberlyst 15 as acid and the results are described in Table 3. Although all the solvents shown in Table 3 look quite effective to give 2,6-DMT, chlorobenzene (PhCl) and 1,1,2-trichloroethane (Cl_2CHCH_2Cl) give better yields than the rest (entries 1 and 4). With every case in Table 3, a very small quantity of 2,6-DMN is always present in the product.

Next, we tried to find milder reaction conditions with Amberlyst 15 in PhCl. At a lower temperature of 150 °C, however, the reaction rate became very slow and the reaction was not complete in 2 h. Only 2,6-DMT was obtained in 33% yield, and no 2,6-DMN was noticed. At higher temperature of 250 °C, on the other hand, the composition of the products dramatically changed and 2,6-DMN became a major product. The yield of **2** was 5%, and that of **1** was 78%. This result indicates a possible pathway for direct conversion of compound **3** to 2,6-DMN, but the solid acid was damaged during the reaction because of high temperature.

The intramolecular Friedel−Crafts alkylation conditions in the present study were applied to some compounds with different functional groups (Table 4). The compounds with an electron-donating group such as a methoxy group were readily reacted to generate the expected cyclized products. However, an electron-withdrawing group retarded the reaction rate (entry 2), and the reaction with 4-(4-nitrophenyl)butan-1-ol gave only the dehydrated products (not shown in Table 4).

Finally, we attempted to change the heating method to a microwave reactor. Automated and focused microwave flash heating has been recently proven to enhance the preparative efficiency and to dramatically reduce the reaction time for various types of organic transformations.[19] In the present study, the microwave assisted alkylation was also successful to give the expected cyclization product efficiently. Even at a lower temperature of 150 °C, most of the starting material was converted to 2,6-DMT in 85% yield only in 10 min and only a trace of 2,6-DMN was observed.

Conclusion

In summary, we have developed a novel and highly regioselective synthetic route for 2,6-DMT starting from commercially available **4a** and **5**. The Pd-catalyzed coupling reaction of **4a** and **5** produced a mixture of olefins **6** together with aldehyde **7** that were both *para*-aryl and terminally substituted products. The mixture of both **6** and **7** was then catalytically reduced without separation to the key precursor **3**. Finally, *para*-aryl substituted alcohol **3** was cyclized with acid to give the desired product, 2,6-DMT, without any other regioisomers. Some Lewis acids and solid acids were very effective in the intramolecular Friedel−Crafts alkylation of the primary alcohol substrate without rearrangement or migration. At higher temperature, considerable amount of 2,6-DMN was obtained as a major product. Although the yields in the present study were not optimized, the highly regioselective method for 2,6-DMT shown here should be useful for developing an economical and practical process for 2,6-DMN.

Experimental Section

Materials were obtained from commercial suppliers and used without further purification. Reactions were monitored by TLC. Commercially available TLC plates (silica gel 60 F_{254}) were visualized under UV light (254 or 365 nm) followed by molybdophosphoric acid staining. Column chromatography was performed on silica gel 60 (70−230 mesh, Merck). The microwave-assisted reaction was performed with a microwave reactor (Discover LabMate, CEM). ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 and 75 MHz (JEOL JNM-LA 300), respectively, unless stated otherwise. High-resolution mass spectra were obtained with a JEOL JMS-AX505WA gas chromatography−mass spectrometer.

Olefinic Mixture 6 and 3-Methyl-4-(*p*-tolyl)butyraldehyde (7). To a solution of 4-bromotoluene (**4a**) (2.5 g, 14.6 mmol) in acetonitrile (100 mL) were added palladium(II) acetate (164 mg, 0.73 mmol), tri(*o*-tolyl)phosphine (445 mg, 1.46 mmol), triethylamine (6.1 mL, 43.8 mmol), and 3-methyl-3-buten-1-ol (**5**) (4.5 mL, 43.8 mmol). The mixture was heated under reflux for 24 h. After the resulting mixture was

(17) Yamato, T.; Hideshima, C.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1991**, *56*, 2089.
(18) Espeel, P. H.; Janssens, B.; Jacobs, P. A. *J. Org. Chem.* **1993**, *58*, 7688.
(19) For reviews: (a) Loupy, A., Ed. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, 2002. (b) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.

cooled to room temperature, the solvent was evaporated under reduced pressure. Distilled water (100 mL) was added to the residue, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was chromatographed on a silica gel column with hexane/ethyl acetate (from 16:1 to 4:1 v/v) to give the olefinic mixture **6** (1.42 g, 55%) and aldehyde **7** (0.90 g, 35%). The major isomer of **6** was (*E*)-3-methyl-4-(*p*-tolyl)-3-buten-1-ol ((*E*)-**6a**); ^{1}H NMR (500 MHz) δ 1.89 (s, 3H), 2.34 (s, 3H), 2.43 (t, 2H, J = 6.3 Hz), 3.79 (t, 2H, J = 6.3 Hz), 6.33 (s, 1H), 7.05−7.16 (m, 4H); ^{13}C NMR δ 17.6, 21.1, 43.7, 60.4, 127.6, 128.7, 128.8, 134.2, 134.9, 135.8; HRMS (EI) calcd for $C_{12}H_{16}O$ 176.1201, found 176.1199. Data of **7**: ^{1}H NMR δ 0.98 (d, 3H, J = 6.6 Hz), 2.32 (s, 3H), 2.18−2.47 (m, 3H), 2.54 (d, 2H, J = 6.8 Hz), 7.01−7.13 (m, 4H), 9.68−9.71 (m, 1H); ^{13}C NMR δ 19.8, 20.8, 30.1, 42.6, 50.0, 128.9, 128.9, 135.4, 136.7, 202.4; HRMS (CI) calcd for $C_{12}H_{15}O$ $[M - H]^+$ 175.1123, found 175.1126.

3-Methyl-4-(*p*-tolyl)-1-butanol (3). To a solution of the olefinic mixture **6** (1.42 g, 8.07 mmol) and aldehyde **7** (0.90 g, 5.11 mmol) in ethyl acetate (50 mL) in an autoclave was added 5% Pt/C (5.14 g, 1.32 mmol) at room temperature. The mixture was stirred under 10 atm of hydrogen gas for 24 h at room temperature. The resulting mixture was filtered through Celite. The clear solution was concentrated, and the residue was chromatographed on a silica gel column with 4:1 hexane/ethyl acetate to give **3** (1.88 g, 80%) as a colorless oil. ^{1}H NMR: δ 0.89 (d, 3H, J = 6.8 Hz), 1.12 (br, 1H), 1.37−1.46 (m, 1H), 1.60−1.71 (m, 1H), 1.82−1.96 (m, 1H), 2.32 (s, 3H), 2.41 (dd, 1H, J = 13.4 and 7.7 Hz), 2.59 (dd, 1H, J = 13.4 and 6.4 Hz), 3.60−3.77 (m, 2H), 7.01−7.11 (m, 4H); ^{13}C NMR δ 19.5, 21.0, 31.7, 39.4, 43.3, 61.1, 128.8, 129.0, 135.2, 137.9; HRMS (EI) calcd for $C_{12}H_{18}O$ 178.1358, found 178.1356.

2,6-Dimethyltetralin (2). To a solution of 3-methyl-4-(*p*-tolyl)-1-butanol (**3**) (50 mg, 0.28 mmol) in chlorobenezene (2.8 mL) in a pressure tube was added Amberlyst 15 (50mg, 100 wt %), and the reaction mixture was heated at 200 °C for 2 h. The reaction mixture was then filtered and concentrated, and the resulting residue was chromatographed on a silica gel column with hexane as an eluent to afford 39 mg (87%) of mixture of **1** and **2** (**1**:**2** = 2:85). Data of **2**: ^{1}H NMR δ 1.05 (d, 3H, J = 6.4 Hz), 1.30−1.43 (m, 1H), 1.76−1.92 (m, 2H), 2.21−2.40 (m, 1H), 2.28 (s, 3H), 2.72−2.83 (m, 3H), 6.87−6.98 (m, 3H); ^{13}C NMR δ 20.9, 22.0, 29.2, 29.4, 31.6, 37.7, 126.2, 128.9, 129.4, 133.8, 134.8, 136.4; HRMS (EI) calcd for $C_{12}H_{16}$ 160.1252, found 160.1258.

Pretreatment of Amberlyst 15: Amberlyst 15 is an acidic resin (4.7 meq of H^+/g), and it was washed sequentially with methanol, an aqueous solution of 2 N HCl, and distilled water before use. Afterward, the resin was rinsed using acetone and dried at room temperature to enhance the catalyst activity.

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