Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7727–7730

Highly efficient two-step selective synthesis of 2,6-dimethylnaphthalene

Byung Hyun Kim, Jong Gil Lee, Taeeun Yim, Hyo-Jin Kim, Hyun Yeong Lee and Young Gyu Kim*

School of Chemical and Biological Engineering, Seoul National University, Seoul 151-744, Republic of Korea

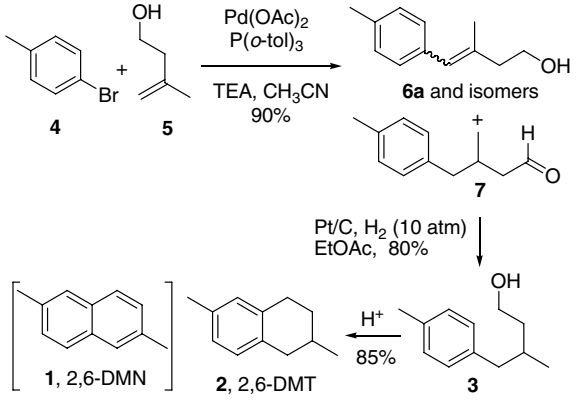
Received 21 July 2006; accepted 25 August 2006
Available online 15 September 2006

Abstract—2,6-Dimethylnaphthalene (2,6-DMN), a key raw material for poly(ethylene naphthalate) (PEN), was selectively synthesized via a two-step process in an overall 66% yield from commercially available 4-bromotoluene and 3-methyl-3-buten-1-ol. The ligand-free Heck reaction of the starting materials produced γ-(*p*-tolyl)-substituted aldehyde that was cyclized with an acid to give 2,6-DMN after in situ oxidation. No other isomers of 2,6-DMN were found.

2,6-Dimethylnaphthalene (2,6-DMN) is an important raw material for the synthesis of a high performance polyester, poly(ethylene naphthalate) (PEN).[1] PEN has many superior properties such as gas barrier, mechanical, thermal, and electrical properties compared with those of poly(ethylene terephthalate) (PET). Thus, it has a high market potential in a variety of applications including films, fibers, and packaging. However, PEN has been slow in expanding its market share because of a short supply of the monomer, 2,6-naphthalenedicarboxylic acid (2,6-NDA), which is closely related to the price and availability of 2,6-DMN. 2,6-NDA is prepared from the catalytic oxidation of 2,6-DMN.

There have been several synthetic processes designed for the mass production of 2,6-DMN. BP Amoco has already commercialized the 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.[1,2] Mitsubishi Gas Chemical,[3] Optatech,[4] Kobe Steel, and Mobil Technology Company[5] have also reported some useful routes to 2,6-DMN. However, many of them 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 suffer from the low yields of the desired product. Thus, it is worthwhile to develop an efficient synthetic method for 2,6-DMN without any other isomers.[6]

We have recently reported the three-step selective synthesis of 2,6-dimethyltetralin (2,6-DMT, **2**) that is a precursor to 2,6-DMN (**1**) (Scheme 1).[7] The process has an advantage over the established processes in that 2,6-DMT is obtained as the only isomer but it requires an extra oxidation step[8] to give 2,6-DMN. In continuation of our investigation on 2,6-DMN, we have developed a highly efficient two-step and selective process for 2,6-DMN, where 2,6-DMN is obtained as the only isomer



Scheme 1. The three-step selective synthesis of 2,6-DMT (**2**).[7]

Keywords: 2,6-Dimethylnaphthalene; Heck reaction; Aromatic electrophilic cyclodehydration; In situ oxidation.
* Corresponding author. Tel.: +82 2 880 8347; fax: +82 2 885 6989; e-mail: ygkim@snu.ac.kr

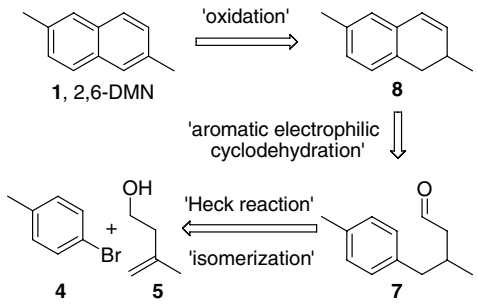
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.08.102

and the isomerization and/or the separation steps are not required. We wish to report the results as follows.[9]

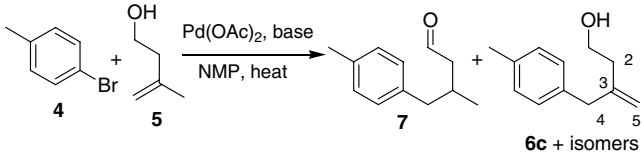
In Scheme 1, the Heck reaction of **4** and **5** produced aldehyde **7** as a minor product together with a mixture of olefinic isomers **6**. Both **6** and **7** were reduced without separation to give alcohol **3**.[7] We have envisioned here that an aromatic electrophilic cyclodehydration reaction[10] of **7** followed by oxidation[8] would produce 2,6-DMN more efficiently without the reduction step. An additional advantage of the formation of dihydronaphthalene **8** would be a more facile oxidation of **8** into **1** (Scheme 2) because of its more oxidized structure compared to that of tetralin **2**. The aldehyde product **7** could be formed as a major or the only product by the known in situ isomerization of olefinic alcohols into aldehydes.[11] Our retrosynthetic scheme for the more efficient process of **1** via the aldehyde intermediate **7** is shown in Scheme 2.

In the present study, a ligand-free Heck reaction was carried out for both operational and economical advantage, which would reduce both the separation process of the phosphorus ligand and the amount of the palladium catalyst (Scheme 3).[12] It has been shown that nature of the base is often an important factor to determine the fate of the ligand-free Heck coupling reactions. The screening results of some bases are shown in Table 1. The use of bromide **4** required a higher reaction temperature of 130–140 °C.

The combination of $Pd(OAc)_2$ and Na_2CO_3 in *N*-methyl-2-pyrrolidinone (NMP) as solvent constituted a highly active catalyst system for the present ligand-free Heck reaction and gave almost exclusively aldehyde **7** in good yield (Table 1, entry 5). Interestingly enough, only alcohols **6** were obtained in low yield with K_3PO_4 as a base and NMP as a solvent here (entry 2) in contrast to the high yield of the ligand-free Heck reactions as reported in the literature.[12c] However, the solvent



Scheme 2. Retrosynthetic analysis for 2,6-DMN via aldehyde **7**.



Scheme 3. The ligand-free Heck reactions of alcohol **5** for aldehyde **7**.

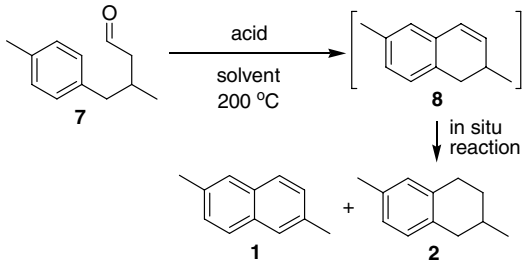
Table 1. Effect of the base on the Heck reaction

Entry	Base	Yield (%)	
		7	**6**
1	$NaHCO_3$	67	5
2	K_3PO_4	—	10
3	NaOAc	60	10
4	K_2CO_3	9	5
5	Na_2CO_3	80	Trace

change from NMP to *N*,*N*-dimethylacetamide (DMA) resulted in a large increase in the yield of both products (45% of **7** and 32% of **6**, not shown). Aldehyde **7** is most likely obtained from the corresponding enol tautomer derived from the Pd-catalyzed isomerization of the double bond that is facilitated by the heterogeneous inorganic base.[11b] Formation of the olefinic mixture **6** can also 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.

We then tried to cyclize aldehyde **7** to yield 2,6-dimethyl-1,2-dihydronaphthalene (**8**) under the cyclodehydration conditions with an acid (Scheme 4). We were concerned here about the stability of **8**. It has been reported that 1,2-dihydronaphthalene is thermolyzed to produce tetralin (15%), naphthalene (19%), and some C_{20} compounds (19%) with the starting material, 1,2-dihydronaphthalene (45%), recovered.[13]

Several Lewis and Brønsted acids were examined for the electrophilic cyclodehydration reactions (Table 2). We were pleased to find that the target product **1** was obtained directly together with some 2,6-DMT (**2**). The expected dihydronaphthalene intermediate product **8** was not detected with most of the acids used at 200 °C, while the use of 10-camphorsulfonic acid (CSA) resulted in **8** as a major product (entry 8). It is to be noted that the in situ aromatization of **8** is facile in the present study because the aromatic cyclodehydration reactions generally need a hydroxyl group or a double bond at the α- or β-position to the carbonyl group in the starting material to generate a fully aromatic ring.[10] It is presumed that the disproportionation reaction of dihydronaphthalene **8** facilitated the in situ oxidation reaction of **8** to give the fully aromatic product **1**, while its reduced product, tetralin **2**, is obtained as a byproduct (entries 1–3). $FeCl_3$ and $TiCl_4$ were most effective to give the fully aromatized product **1** predominantly with a



Scheme 4. Synthesis of 2,6-DMN by electrophilic cyclodehydration of **7**.

Table 2. Electrophilic cyclodehydration reactions with Lewis and Brønsted acids[a]

Entry	Acid/equiv	Yield (%)[b]		
		8	**2**	**1**
1	$AlCl_3$/2	—	12	23
2	$SnCl_4$/2	4	8	59
3	$BF_3{\cdot}OEt_2$/2	—	17	16
4	$FeCl_3$/2	—	Trace	79
5	$TiCl_4$/2	—	2	75
6	H_2SO_4/2	—	1	61
7[c]	H_3PO_4/2	—	—	38
8	CSA/1.5	50	—	26

[a] In a pressure tube, 200 °C, 2 h with 1,1,2-trichloroethane.
[b] Isolated as a mixture and the ratio was determined by GC/MSD.
[c] 40% of the starting material was recovered.

minute amount of **2** (entries 4 and 5). In all cases, any rearranged or isomerized products such as 2,7-DMN were not observed.

We have also screened several solid acids because they can be easily separated from the reaction mixture and reused to make the process economically favorable (Table 3). It is apparent that Amberlyst® 15 and Amberlite® IR 120 that are sulfonic acid resins were very effective in the cyclodehydration reactions and provided a good yield of **1** with a tiny amount of **2** at a higher reaction temperature (entries 1 and 3). At a lower temperature of 100 °C with Amberlyst® 15, **8** was obtained as a major product in 42% yield, whereas **1** was produced in only 5% with 50% of the starting material recovered (not shown). Here, **2** was not detected at all. Production of **8** at a lower reaction temperature is also significant in entry 2. All of the solid acids used in Table 3 including the Nafion® resins and zeolite H-Y produced a mixture of **1** and **2** or/and **8** in reasonable yields. In the case of zeolite H-Y, however, a large amount of the expected dihydronaphthalene product **8** was obtained (entry 6).

Next, we have examined the effect of various solvents with Amberlyst® 15 and the results are shown in Table 4. Among the solvents, chlorobenzene, bromobenzene and 1,1,2-trichloroethane were quite effective to give the target compound **1** in high yield. 1,1,2-Trichloroethane appeared the best choice as the reaction solvent because its boiling point (110–115 °C) is low enough to be removed easily under low vacuum and thus could be recycled. When the heating method was changed from conventional heating to microwave flash heating[14] (120–140 °C, 20 min) under the similar conditions to those of entry 3 in Table 4, the reaction also gave **2** as a major product together with a small amount of **8** (entry 4).

Table 3. Aromatic electrophilic cyclodehydration with solid acids[a]

Entry	Solid acid	Yield (%)[b]		
		8	**2**	**1**
1	Amberlyst® 15	—	3	80
2[c]	Amberlyst® 15	27	—	50
3	Amberlite® IR 120	—	Trace	83
4	Nafion® NE 450	—	6	69
5	Nafion® 1035	6	4	53
6	Zeolite H-Y	56	4	18

[a] In a pressure tube at 200 °C for 2 h.
[b] Isolated as a mixture and the ratio was determined by GC/MSD.
[c] The reaction was conducted under the reflux conditions.

Table 4. Effect of the solvent on the electrophilic cyclodehydration[a]

Entry	Solvent	Yield (%)[b]	
		2	**1**
1	1,4-Dioxane	2	70
2	Toluene	4	66
3	Cl_2CHCH_2Cl	3	80
4[c]	Cl_2CHCH_2Cl	46	34
5	PhBr	4	81
6	PhCl	Trace	80

[a] In a pressure tube at 200 °C for 2 h.
[b] Isolated as a mixture and the ratio was determined by GC/MSD.
[c] Microwave flash heating (120–140 °C, 20 min). **8** (4%) was also obtained.

In summary, we have developed an efficient and selective two-step process for 2,6-DMN starting from commercially available 4-bromotoluene (**4**) and 3-methyl-3-buten-1-ol (**5**). The two-step process comprises the ligand-free Heck coupling reaction of the starting materials to give aryl substituted aldehyde **7** that underwent the acid-catalyzed cyclodehydration reaction to give directly the target compound **1** after in situ oxidation of the initially expected intermediate **8**. Because no other isomers of 2,6-DMN were produced during the process, neither the isomerization step nor the separation step was necessary. The active catalytic system of $Pd(OAc)_2$ developed here without using a phosphine ligand should enhance the economy of the present process as well. The overall yield was 66% based on the starting material, 4-bromotoluene. Although the yield was not optimized in the present study, the high efficiency and selectivity of this process should be valuable for developing a novel and competitive industrial process for 2,6-DMN. In addition, the synthetic pathway developed for 2,6-DMN could be easily extended to an efficient and selective synthesis of other isomers of DMN and other substituted polyaromatic compounds, which are now underway in our laboratory.

Representative procedure. 3-Methyl-4-(*p*-tolyl)butanal (**7**): To a solution of 4-bromotoluene (**4**, 3.42 g, 20.0 mmol) in NMP (5 mL) in a pressure tube was added $Pd(OAc)_2$ (4.49 mg, 0.02 mmol), Na_2CO_3 (4.24 g, 40.0 mmol) and 3-methyl-3-buten-1-ol (**5**, 3.44 g, 40.0 mmol). The resulting mixture was heated at 130–140 °C for 24 h. After the reaction mixture was cooled to room temperature, water (100 mL) was added to the residue and then the aqueous layer was extracted with diethyl ether (2×100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on a silica gel column using a mixture of hexane and EtOAc (from 16:1 to 4:1) to give 2.83 g of **7** (80%) as

a pale yellow oil. $R_f = 0.4$ (hexane:EtOAc = 4:1); ^{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), 7.04 (d, 2H, $J = 7.8$ Hz), 7.10 (d, 2H, $J = 7.8$ Hz), 9.70 (t, 1H, $J = 2.3$ Hz); ^{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; Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15; O, 9.08. Found: C, 81.70; H, 9.01; O, 9.29.

2,6-Dimethylnaphthalene (**1**): To a solution of 3-methyl-4-(*p*-tolyl)butanal (**7**) (2.83 g, 16.1 mmol) in 1,1,2-trichloroethane (5 mL) in a pressure tube was added Amberlite® IR 120 (2,83 g, 100 wt %). The reaction mixture was heated at 200 °C for 2 h. The resulting mixture was then filtered and the filtrate was concentrated. The crude residue was chromatographed on a silica gel column with hexane to give 2.10 g of **1** (83%) as a white solid. All the analytical and the spectroscopic data of **1** were identical with those of commercially available 2,6-DMN.

Acknowledgements

This work was financially supported by KOSEF through the Research Center for Energy Conversion and Storage and by the Division of Advanced Batteries in NGE Program (Project No. 10016439) and by the Agency for Defense Development of Korea. We also thank Professor Young Keun Chung at the Department of Chemistry, Seoul National University for the microwave reactor.

References and notes

1. For a review, see: Lillwitz, L. D. *Appl. Catal. A* **2001**, *221*, 337.
2. (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.
3. (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.
4. Vahteristo, K.; Halme, E.; Koskimies, S.; Csicsery, S. M.; Laatikainen, M.; Niemi, V. U.S. Patent 5,952,534, 1999.
5. (a) Sumitani, K.; Shimada, K. Japan Patent JP 4,013,637, 1992; (b) Motoyuki, M.; Yamamoto, K.; McWilliams, J. P.; Bundens, R. G. U.S. Patent 5,744,670, 1998.
6. For recent efforts for the production of 2,6-DMN, see: (a) Millini, R.; Frigerio, F.; Bellussi, G.; Pazzuconi, G.; Perego, C.; Pollesel, P.; Romano, U. *J. Catal.* **2003**, *217*, 298; (b) Iwai, Y.; Higuchi, M.; Nishioka, H.; Takahashi, Y.; Arai, Y. *Ind. Eng. Chem. Res.* **2003**, *42*, 5261; (c) 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; (d) Tsutsui, T.; Ijichi, K.; Inomata, T.; Setiadi; Kojima, T.; Sato, K. *Chem. Eng. Sci.* **2004**, *59*, 3993.
7. (a) Kim, B. H.; Kim, W. K.; Lee, J. G.; Kim, Y. G. *Org. Process Res. Dev.* **2005**, *9*, 814; (b) Kim, Y. G.; Kim, W. K.; Kim, B. H.; Lee, J. G. International Application No. PCT/KR2005/000507, 2005.
8. For a review, see: (a) Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, *78*, 317; (b) Neumann, R.; Lissel, M. *J. Org. Chem.* **1989**, *54*, 4607; (c) Minisci, F.; Recupero, F.; Gambarotti, C.; Punta, C.; Paganelli, R. *Tetrahedron Lett.* **2003**, *44*, 6919; (d) Amelse, J. A. U.S. Patent 5,189,234, 1993.
9. Kim, Y. G.; Kim, W. K.; Kim, B. H.; Lee, J. G.; Yim, T. Korean Application No. 10-2005-0115139, 2005.
10. Bradsher, C. K. *Chem. Rev.* **1987**, *87*, 1277.
11. For a review, see: (a) Muzart, J. *Tetrahedron* **2005**, *61*, 4179; For non-allylic olefinic alcohols, (b) Melpolder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265; (c) Larock, R.C.; Leung, W.-Y.; Stolz-Dunn, S. *Tetrahedron Lett.* **1989**, *30*, 6629; For allylic alcohols, (d) Chalk, A. J.; Magennis, S. A. *J. Org. Chem.* **1976**, *41*, 273; (e) Tamaru, Y.; Yamada, Y.; Yoshida, Z. *J. Org. Chem.* **1978**, *43*, 3396; (f) Smadja, W.; Czernecki, S.; Ville, G.; Georgoulis, C. *Organomettalics* **1987**, *6*, 166; (g) Jeffery, T. *Tetrahedron Lett.* **1991**, *32*, 2121; (h) Kang, S.-K.; Jung, K.-Y.; Park, C.-H.; Namkoon, E.-Y. *Tetradedron Lett.* **1995**, *36*, 6287.
12. For reviews, see: (a) Reetz, M. T.; Vries, J. G. *Chem. Commun.* **2004**, 1559; (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771; For other examples, see: (c) Yao, Q.; Kinney, E. P.; Yang, Z. *J. Org. Chem.* **2003**, *68*, 7528, and references cited therein; (d) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285.
13. Franz, J. A.; Camaioni, D. M.; Beishline, R. R.; Dalling, D. K. *J. Org. Chem.* **1984**, *49*, 3563.
14. (a) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002; (b) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.