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Formation of 2-Arylnaphthalenes from *N*-Tosylated Phenylalanine Derivatives

Mi Ra Seong, Hyun Nam Song, and Jae Nyoung Kim*

Department of Chemistry, Chonnam National University, Kwangju 500-757, Korea

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Abstract

N-Tosylated phenylalanine derivatives in benzene in the presence of sulfuric acid afforded 2-arylnaphthalene derivatives in moderate yields. The reaction might proceed *via* the corresponding decarbonylated *N*-tosylimine derivatives. Aldol type reaction of *N*-tosylimines followed by intramolecular Friedel-Crafts reaction and elimination of *p*-toluenesulfonamide gave 2-arylnaphthalenes. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: 2-Arylnaphthalenes; Friedel-Crafts reaction; *N*-Tosylated phenylalanine

Much attention has recently been focused on the regioselective synthesis of substituted naphthalene derivatives [1]. Since these compounds have the basic skeleton of many biologically important natural products and pharmaceuticals [2], synthetic methods for the naphthalene moiety are highly desired.

In the course of our recent studies on the Friedel-Crafts reaction we have found that the reaction of *N*-tosylated α-amino acids and arenes afforded the corresponding decarbonylative diarylated derivatives [3]. However, we could not obtain the corresponding diarylated compound from the reaction of *N*-*p*-tosyl-L-phenylalanine (**1a**) and benzene in the presence of sulfuric acid. Instead, there was obtained nonpolar hydrocarbon derivative, which was identified as 2-phenylnaphthalene (**2a**) by its ^{1}H NMR, ^{13}C NMR, mass, and melting point [4]. The reaction of **1a** in chlorobenzene or *p*-xylene gave the same 2-phenylnaphthalene (**2a**) in good yields. In other words, in the formation of **2a** arenes did not incorporated in any way. Thus, we prepared some *N*-tosylated phenylalanine derivatives **1** and examine the unusual formation of this naphthalene skeleton. As shown in Scheme 1, the reactions of *N*-tosylated phenylalanine derivatives **1** in the presence of sulfuric acid (2.2 equiv) in appropriate arene solvents gave the corresponding 2-arylnaphthalene derivatives **2** in moderate yields. In certain cases, diarylated derivatives **3** were also obtained as in our previous paper [3] (*vide infra*), and the representative results were summarized in Table 1.

The reaction mechanism for the formation of 2-arylnaphthalenes **2** could be proposed as depicted in Scheme 2. As proposed in our previous report [3] the formation *N*-tosyliminium salt **A** is crucial. **A** is a protonated form of *N*-tosylimine and can act as an electrophilic component in the formation of **2**. Loss of proton from **A** and isomerization [5] generates the actual nucleophilic part of this reaction *viz* *N*-tosylenamine **B**. It is important to note that the presence of the phenyl group is crucial for the formation of resonance stabilized *N*-tosylenamine **B**. Aldol type reaction between **A** and **B** gives tosylimminium salt **C**.

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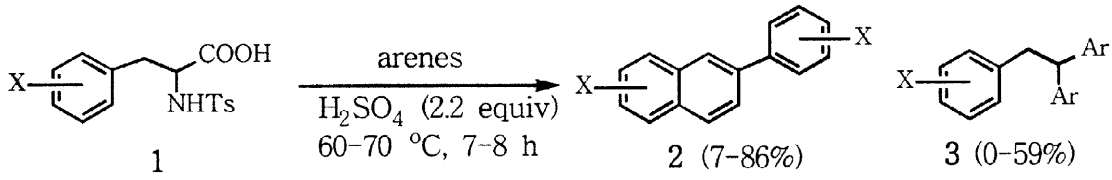
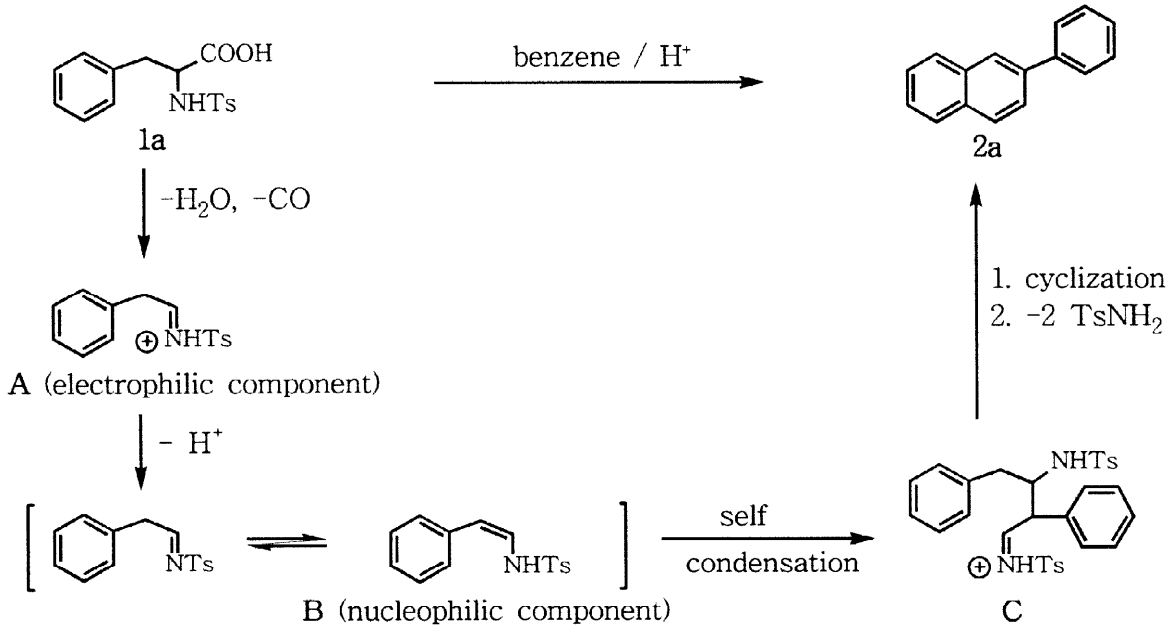
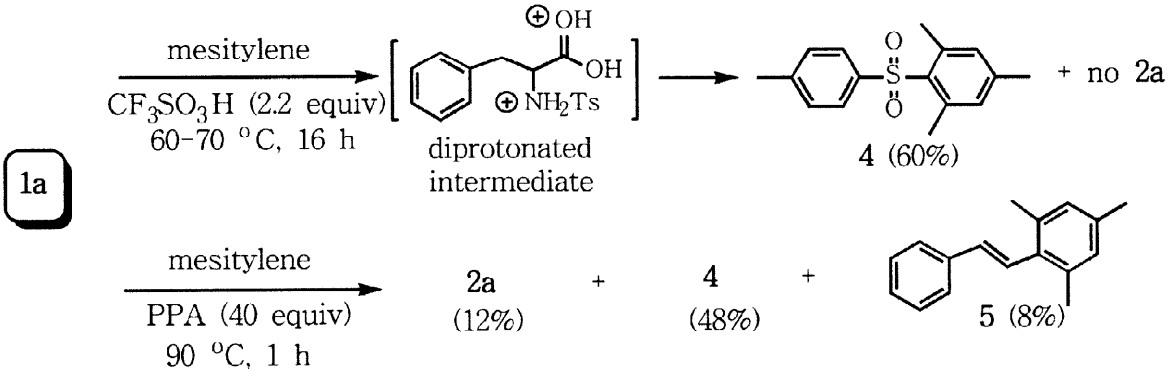


Scheme 1

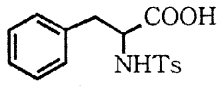
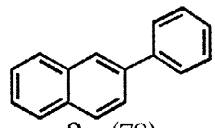
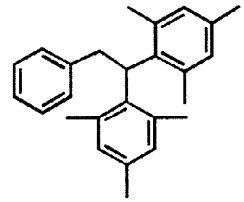
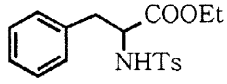
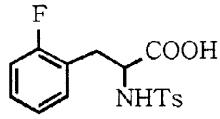
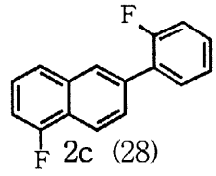
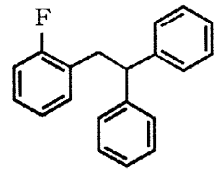
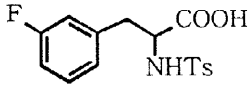
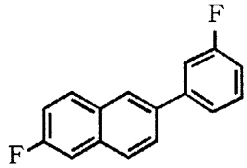
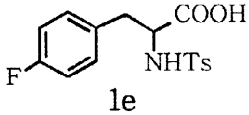
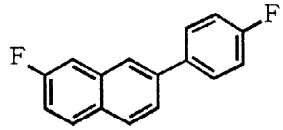
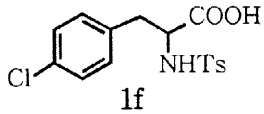
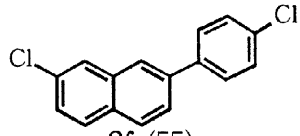


Scheme 2



Scheme 3

Table 1. The Reactions of *N*-Tosylated Phenylalanine Derivatives.

entry	1	arene	2 (% yield)	3 (% yield)
1	 1a	benzene	 2a (79)	nd
2	1a	chlorobenzene	2a (86)	nd
3	1a	*p*-xylene	2a (72)	trace[#]
4	1a	mesitylene	2a (7)	 3a (59)
5	 1b	benzene	2a (38)	nd
6	 1c	benzene	 2c (28)	 3c (25)
7	 1d	benzene	 2d (62)	trace[#]
8	 1e	benzene	 2e (53)	nd
9	 1f	benzene	 2f (55)	trace[#]

[#]In ^{1}H NMR spectrum of2, the characteristic peaks (triplet and doublet) of 1,1,2-diarylethane derivatives3 were observed (<5%).

Intramolecular Friedel-Crafts type reaction of **C** and subsequent loss of two molecules of tosylamide affords 2-arylnaphthalenes **2**. Although we could not detect phenylacetaldehyde in the reaction mixtures, we could not exclude entirely the mechanism involving phenylacetaldehyde as a key intermediate. Actually, the formation of 2-phenylnaphthalene in less than 5% yield from the self condensation reaction of phenylacetaldehyde in acidic conditions was reported [6]. Repeated reaction of phenylacetaldehyde under the same reaction conditions in benzene or chlorobenzene afforded 2-phenylnaphthalene (**2a**) in low yields (17-20 % at best) in our hands. Thus, the reaction mechanism involving phenylacetaldehyde might contribute as a minor pathway, if possible. In the cases where the nucleophilicity of arenes is good enough to compete with that of the *N*-tosylenamine **B** as *p*-xylene or mesitylene, there were also obtained decarbonylated diarylation products **3** in variable amounts (entries 3-4). The reaction of halogen substituted phenylalanine derivatives (**1c-1f**) in benzene gave the corresponding 2-arylnaphthalenes in moderate yields. In the case of *N*-*p*-tosyl-DL-2-fluorophenylalanine (**1c**), there were obtained appreciable amounts of diarylated derivative **3c** (25%) *via* decarbonylative diarylation. The formation of **3c** was presumably due to the fact that the corresponding nucleophilic component **B** in this case might be generated in small amounts partly because of the intramolecular hydrogen bonding between ortho-fluorine atom and the hydrogen atom of protonated tosylamide group in the electrophilic component **A** in Scheme 2.

The reaction of **1a** in anisole or 1-methylpyrrole instead of benzene gave neither 2-phenylnaphthalene nor the corresponding diarylated derivatives. As shown in entry 5, ethyl ester **1b** gave the same product **2a** in low yield. The use of aluminium chloride instead of sulfuric acid was not effective to our surprise. The use of trifluoromethanesulfonic acid or polyphosphoric acid resulted somewhat different reaction pathway as shown in Scheme 3. Diarylsulfone derivative **4** was obtained as a major product, which might be formed *via* the diprotonated intermediate [7-8]. Besides of **4**, 2-phenylnaphthalene (**2a**) and stilbene derivative **5** were obtained by using polyphosphoric acid.

In summary, we have prepared some 2-arylnaphthalenes from *N*-tosylated phenylalanine derivatives. Further studies on the formation of alkoxy-substituted 2-arylnaphthalenes from tyrosine or L-DOPA are currently undergoing.

References and Notes

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[4] Spectroscopic data of **2a**: mp. 99-102 °C (lit [4a], 103 °C); ^{1}H NMR ($CDCl_3$) δ 7.11-8.05 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 125.57, 125.78, 125.90, 126.26, 127.32, 127.41, 127.62, 128.18, 128.39, 128.83, 132.61, 133.67, 138.54, 141.11; Mass (70 eV) *m/z* (rel intensity) 41 (76), 43 (65), 55 (100), 57 (76), 69 (69), 83 (45), 149 (25), 202 (23), 203 (21), 204 (M^+, 54).

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