



# Decarbonylative Diarylation Reaction of *N*-Tosylated $\alpha$ -Amino Acids

Mi Ra Seong, Hong Jung Lee, and Jae Nyoung Kim\*

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

Received 19 May 1998; revised 18 June 1998; accepted 19 June 1998

## Abstract

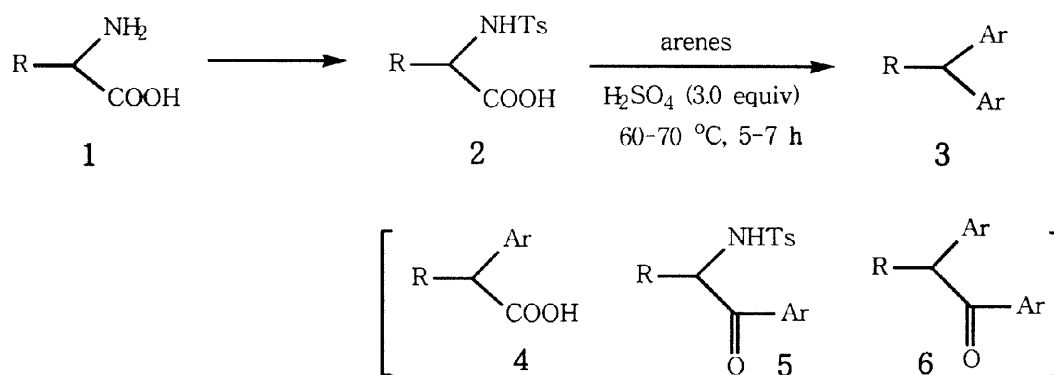
The reaction of various *N*-tosylated  $\alpha$ -amino acids with arenes in the presence of sulfuric acid afforded the corresponding diarylated derivatives in moderate yields, which were generated *via* decarbonylative arylation followed by Friedel–Crafts reaction of the generated tosylamide derivatives. © 1998 Elsevier Science Ltd. All rights reserved.

**Keywords:** Decarbonylative diarylation reaction;  $\alpha$ -Amino acids; Friedel–Crafts reaction

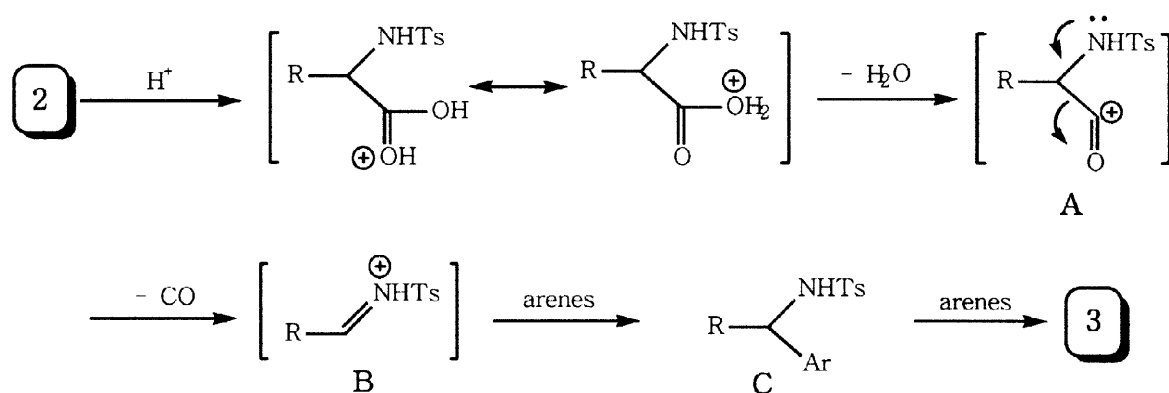
Recently, we have reported on the Friedel–Crafts type reaction of various kinds of nitrogen containing compounds including 1,3-dicyclohexylcarbodiimide, amides, sulfonamides, and urea derivatives [1–2]. In the reactions of the above compounds with benzene in the presence of acid catalyst such as  $\text{H}_2\text{SO}_4$  or  $\text{AlCl}_3$ , carbon–nitrogen single bond was broken and there must be generated carbocationic species. In the course of our program to develop a facile synthetic methods for the preparation of various 2-arylacetic acid derivatives, which could be used as starting materials for the preparation of nonsteroidal antiestrogen Tamoxifen derivatives [3–5], we intended to examine the reaction of *N*-tosylated  $\alpha$ -amino acids with aromatic compounds under the Friedel–Crafts reaction conditions.

As shown in Scheme 1, the reaction of *N*-tosylated  $\alpha$ -amino acids **2** with arenes in the presence of sulfuric acid (3.0 equiv) afforded the corresponding diarylated compounds **3** unexpectedly. In the reactions, 2-arylacetic acid derivatives **4** and Friedel–Crafts acylation products such as **5–6** were not obtained. Friedel–Crafts acylation of benzene with *N*-methyl-*N*-*p*-tosyl-L-alaninyl chloride in the presence of aluminium chloride was examined by Rapoport et al., where they observed a quantitative cleavage to *N*-methylalanine and *p*-toluenesulfonic acid [6].

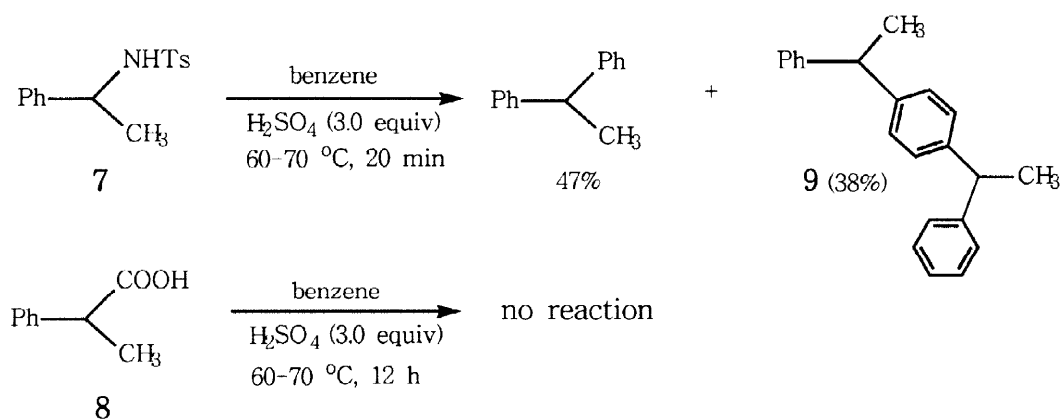
The mechanism for the formation of diarylated compounds **3** was proposed as follows (Scheme 2): After protonation at the hydroxyl group of carboxylic acid, elimination of water generates an unstable intermediate **A**. Subsequent elimination of carbon monoxide gives the key intermediate *N*-tosyliminium salt **B**. Addition of aromatic compound to this *N*-tosyliminium salt generates the corresponding sulfonamide derivative **C**. Successive Friedel–Crafts reaction of **C** affords the diarylated compounds **3** as expected from our previous report [2]. The representative results were summarized in Table 1. As shown in Table 1, from the reaction of *N*-tosylated derivatives of glycine (entry 1), alanine (entries



Scheme 1



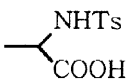

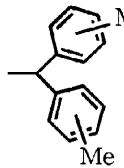
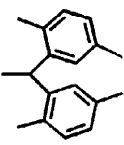
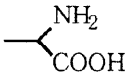
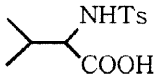
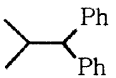
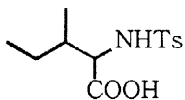
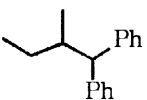
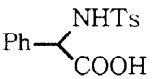
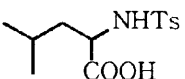
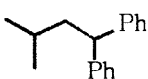
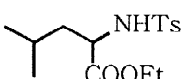
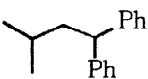
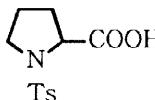
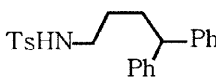


Scheme 2



Scheme 3

Table 1. Decarbonylative Diarylation Reaction of *N*-Tosylated  $\alpha$ -Amino Acids

entry	2	arene	product (3)	yields (%)
1	 <b>2a</b>	benzene		79
2	 <b>2b</b>	benzene		74
3	<b>2b</b>	toluene	 ( <i>p,p'</i> : <i>p,o</i> = 75:25)	77
4	<b>2b</b>	<i>p</i> -xylene		76
5	 <b>1b</b>	benzene	no reaction	
6	 <b>2c</b>	benzene	 (40:60)	67
7	 <b>2d</b>	benzene	 (50:50)	52
8	 <b>2e</b>	benzene	Ph-CH=N-Ts + Ph <sub>3</sub> CH (48%) (7%)	
9	 <b>2f</b>	benzene		68
10	 <b>2f'</b>	benzene		32
11	 <b>2g</b>	benzene		30

Reaction condition: **2** (5 mmol), arene (20 mL), H<sub>2</sub>SO<sub>4</sub> (3.0 equiv), 60–70 °C, 5–7 h.

2-4), valine (entry 6), isoleucine (entry 7), and leucine (entry 9) the corresponding diarylated compounds were obtained in moderate yields. The use of ethyl ester gave low yield of product as exemplified in the case of leucine (entry 10). Alanine (**1b**) itself did not react at all under the reaction conditions with benzene (entry 5). Due to the preferential protonation to free amino group in this case, elimination of water and carbon monoxide could not occur. In the cases of valine and isoleucine, rearranged products of the carbocation intermediates were also obtained. To our surprise the reaction of *N*-*p*-tosyl-2-phenylglycine and benzene (entry 8) gave the expected triphenylmethane in low yield (7%). The major product in the reaction is *N*-(*p*-toluenesulfonyl)benzaldimine. The diminished reactivity in this case might be due to the resonance stabilization of the electrophilic *N*-tosyliminium salt (the corresponding intermediate **B** in Scheme 2) by benzene ring. In the case of proline (entry 11), somewhat severe reaction conditions (5.0 equiv of H<sub>2</sub>SO<sub>4</sub>, 60–70 °C, 18 h) were required, and there was obtained ring-opened diarylated derivative in low yield.

In order to clarify the reaction pathway we examined the reaction of *N*-*p*-tosyl- $\alpha$ -methylbenzylamine (**7**) and 2-phenylpropionic acid (**8**) under the same reaction conditions in benzene as shown in Scheme 3. From the reaction of **7** we could obtain 1,1-diphenylethane (47%) together with **9** (38%), which was generated by the successive Friedel-Crafts reaction of initially formed 1,1-diphenylethane. However, from the reaction of **8** under the same reaction conditions, we could not detect 1,1-diphenylethane on tlc. These results showed that without the aid of the sulfonamide functionality decarbonylative arylation could not occur. Mechanistically similar reactions with our findings were reported in sulfonyliminium salt chemistry [6–9] and in 2-methoxypropionic acid system [10–11]. In certain cases there were obtained some Friedel-Crafts acylation products [6, 9]. However, in our reaction conditions, such acylation products were not observed at all.

In summary in this report we describe on the mechanistically interesting decarbonylative diarylation reaction of *N*-tosylated  $\alpha$ -amino acids. A study on the possibility of nucleophilic quenching of intermediate **A** in Scheme 2 before the elimination of carbon monoxide is currently undergoing.

## References and Notes

- [1] Kim JN, Chung KH, Ryu EK. *Tetrahedron Lett.* 1994;35:903–904.
- [2] Chung KH, Kim JN, Ryu EK. *Tetrahedron Lett.* 1994;35:2913–2914.
- [3] Hardcastle IR, Rowlands MG, Houghton J, Parr IB, Potter GA, Jarman M, Edwards KJ, Laughton CA, Trent JO, Neidle S. *J. Med. Chem.* 1995;38:241–248.
- [4] McCague R, Leclercq G, Legros N, Goodman J, Blackburn GM, Jarman M, Foster AB. *J. Med. Chem.* 1989;32:2527–2533.
- [5] Robertson DW, Katzenellenbogen JA. *J. Org. Chem.* 1982;47:2387–2393.
- [6] Buckley TF III, Rapoport H. *J. Am. Chem. Soc.* 1981;103:6157–6163.
- [7] Proctor GR, Thomson RH. *J. Chem. Soc.* 1957;2302–2311.
- [8] Negash K, Nichols DE. *Tetrahedron Lett.* 1996;37:6971–6972.
- [9] Schnur RC, Gallaschun RJ. *J. Org. Chem.* 1989;54:216–220.
- [10] Yonezawa N, Tokita Y, Hino T, Nakamura H, Katakai R. *J. Org. Chem.* 1996;61:3551–3552.
- [11] Yonezawa N, Hino T, Tokita Y, Matsuda K, Ikeda T. *Tetrahedron* 1997;53:14287–14296.