

## Unusual Behaviour of *N*-Tosyl Pipecolinic Acid in Friedel-Crafts Reaction Conditions

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Recently, we have found that the reaction of arenes and *N*-tosylated  $\alpha$ -amino acids in the presence of sulfuric acid gave the corresponding decarbonylative diarylation products.<sup>1</sup> When the  $\alpha$ -amino acids were phenylalanine derivatives, we obtained 2-arylnaphthalene derivatives rather than the decarbonylative diarylation products.<sup>2</sup> As a continuous study on the reaction of *N*-tosylated  $\alpha$ -amino acids, we examined on the reaction of cyclic amino acids such as proline,<sup>1</sup> pipecolinic acid, pyroglutamic acid, and indoline-2-carboxylic acid. In this paper, we describe on the unusual behaviour of *N*-tosyl pipecolinic acid (**1**) toward some arene nucleophiles in the Friedel-Crafts reaction conditions.

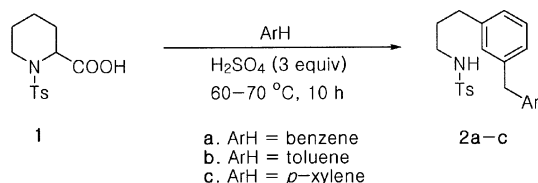
As shown in Scheme 1, *N*-tosyl pipecolinic acid (**1**) in the presence of sulfuric acid (3 equiv) in benzene gave the unexpected aromatized derivative **2a**. Although the yield of **2a** was low (18%), the generation of this compound seems quite interesting as compared with our previous results.<sup>1,2</sup> Thus, we examined the reaction in toluene and *p*-xylene. In these cases compounds **2b-c** were also obtained in similar yields (**2b** = 16%, **2c** = 15%). There were many spots on tlc of the reaction mixtures, however, we could isolate **2a-c** and tolyl disulfide (8-10% isolated yields) in all cases.<sup>3</sup> We could not isolate any of the expected compound **3** from the reaction mixtures nor the plausible products **4-5**.

The products **2a-c** were characterized from their <sup>1</sup>H, <sup>13</sup>C, and mass spectra. The reaction mechanism for the formation of **2** could be proposed as shown in Scheme 2 based on our previous paper.<sup>1,2</sup>

As shown in Scheme 2, the reaction mechanism is composed of somewhat complicated steps: (1) formation of electrophilic component **A** via consecutive protonation,

elimination of water and carbon monoxide as in the cases of *N*-tosyl phenylalanine derivatives,<sup>2</sup> (2) formation of nucleophilic component **B** via deprotonation,<sup>2,4,5</sup> (3) coupling reaction of *N*-tosyl enamine **B** and *N*-tosyliminium salt **A** to form another iminium salt **C**, (4) Friedel-Crafts type arylation of **C** to give **D**, (5) protonation, ring opening to generate **E**, (6) successive acid catalyzed isomerization of **E** to **F** to **G**, (7) intramolecular cyclization followed by deprotonation gave **H**, (8) acid catalyzed isomerization of **H** followed by ring opening reaction gave cyclohexadiene derivative **I**, (9) finally, oxidation<sup>6</sup> to produce the product **2**.

Further studies on the reaction mechanism and the conditions which produce products in higher yields are



Scheme 1

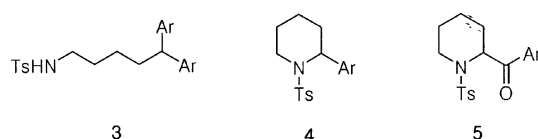
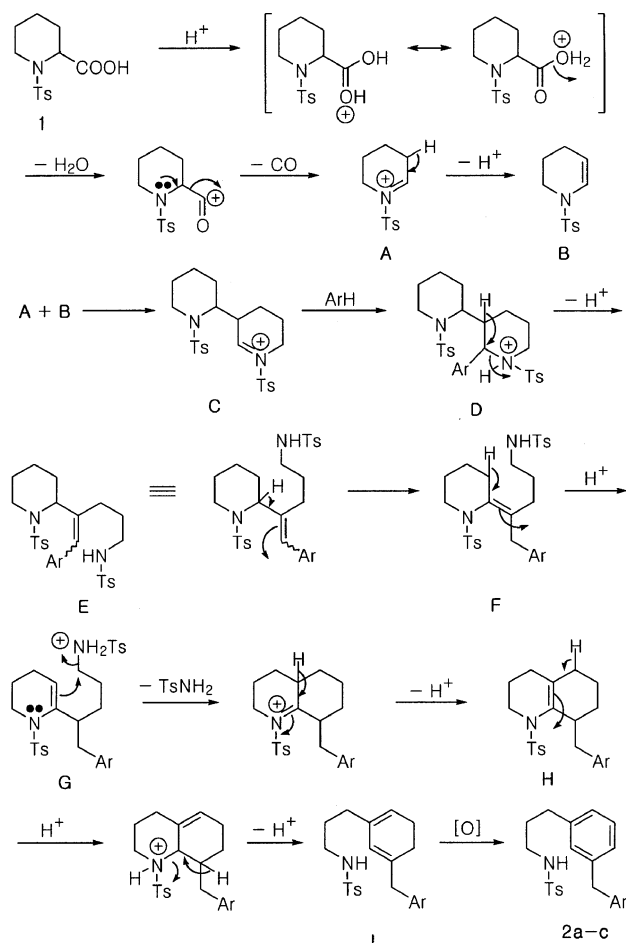


Figure 1



Scheme 2

undergoing.

### Experimental

**General procedure for the reaction of *N*-tosyl pipercolinic acid (1) and arenes in the presence of sulfuric acid.** To a stirred suspension of *N*-tosyl pipercolinic acid (850 mg, 3 mmol) in corresponding arene (10 mL) was added concentrated sulfuric acid (890 mg, 9 mmol) and stirred vigorously at 60–70 °C for 10 h. The reaction mixture was poured into cold water (50 mL) and diluted with ether (100 mL). The organic layers were washed with brine, dried with MgSO<sub>4</sub>, and evaporated to dryness. After flash column chromatography, the corresponding products were obtained as colorless oils. Their spectroscopic data are as follows.

**2a** (250 mg, 18%): R<sub>f</sub> (ether/hexane, 3 : 1) 0.55; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.75 (app quintet, *J* = 7.3 Hz, 2H), 2.41 (s, 3H), 2.55 (t, *J* = 7.6 Hz, 2H), 2.94 (app q, *J* = 6.7 Hz, 2H), 3.92 (s, 2H), 4.51 (t, *J* = 6.2 Hz, NH), 6.89–7.74 (m, aromatics, 13H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 21.47, 31.14, 32.67, 41.85, 42.68, 126.04, 126.25, 126.72, 127.08, 128.43, 128.55, 128.85, 128.96, 129.67, 129.80, 137.04, 141.12, 141.28, 143.33; Mass (70 eV) *m/z* (rel intensity) 65 (23), 91 (100), 117 (22), 155 (26), 165 (22), 166 (11), 167 (8), 181 (25), 224 (73), 379 (M<sup>+</sup>, 18); HRMS Calcd. For C<sub>23</sub>H<sub>25</sub>NO<sub>2</sub>S 379.1606, Found 379.1626.

**2b** (190 mg, 16%, ortho/para = 3 : 7): R<sub>f</sub> (ether/hexane, 3 : 1) 0.60; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.74 (app quintet, *J* = 7.3 Hz, 2H), 2.22 (ortho isomer, s, 3H), 2.31 (para isomer, s, 3H), 2.42 (s, 3H), 2.54 (t, *J* = 7.6 Hz, 2H), 2.94 (app q, *J* = 6.6 Hz, 2H), 3.88 (para isomer, s, 2H), 3.92 (ortho isomer, s, 2H), 4.54 (brs, NH), 6.88–7.74 (m, aromatics, 12H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 19.67, 21.00, 21.51, 31.16, 32.70, 39.35, 41.45,

42.71, 125.35, 125.94, 125.99, 126.43, 126.56, 126.69, 127.11, 128.52, 128.55, 128.76, 128.83, 128.94, 129.16, 129.71, 129.86, 130.27, 135.54, 136.58, 137.03, 138.02, 138.89, 140.61, 140.98, 141.02, 143.37; Mass (70 eV) *m/z* (rel intensity) 65 (30), 91 (100), 105 (51), 155 (32), 195 (31), 238 (67), 393 (M<sup>+</sup>, 11); HRMS Calcd. For C<sub>24</sub>H<sub>27</sub>NO<sub>2</sub>S 393.1763, Found 393.1763.

**2c** (184 mg, 15%): R<sub>f</sub> (ether/hexane, 3 : 1) 0.62; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.73 (app quintet, *J* = 7.3 Hz, 2H), 2.17 (s, 3H), 2.27 (s, 3H), 2.41 (s, 3H), 2.53 (t, *J* = 7.8 Hz, 2H), 2.93 (app q, *J* = 6.5 Hz, 2H), 3.88 (s, 2H), 4.73 (t, *J* = 6.2 Hz, NH), 6.87–7.75 (m, aromatics, 11H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 19.14, 20.92, 21.44, 31.11, 32.65, 39.31, 42.65, 125.81, 126.42, 126.75, 127.05, 128.28, 128.41, 128.74, 129.10, 129.63, 129.76, 130.12, 130.66, 137.02, 140.70, 140.90, 143.27; Mass (70 eV) *m/z* (rel intensity) 65 (28), 91 (100), 105 (28), 117 (36), 119 (35), 132 (49), 155 (38), 209 (20), 252 (68), 407 (M<sup>+</sup>, 17); HRMS Calcd. For C<sub>25</sub>H<sub>29</sub>NO<sub>2</sub>S 407.1919, Found 407.1921.

### References

1. Seong, M. R.; Lee, H. J.; Kim, J. N. *Tetrahedron Lett.* **1998**, 39, 6219.
2. Seong, M. R.; Song, H. N.; Kim, J. N. *Tetrahedron Lett.* **1998**, 39, 7101.
3. Many compounds were observed on tlc with no starting material **1**. Thus, separation or identification of other compounds was impossible except **2a-c** and tolyl disulfide.
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6. It is uncertain of the nature of actual oxidizing agent.