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

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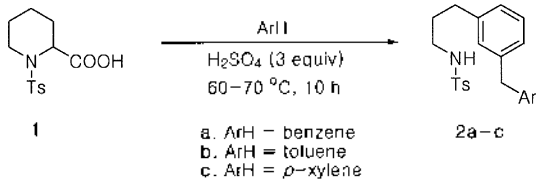
Recently, we have found that the reaction of arenes and *N*-tosylated α-amino acids in the presence of sulfuric acid gave the corresponding decarbonylative diarylation products.[1] When the α-amino acids were phenylalanine derivatives, we obtained 2-arylnaphthalene derivatives rather than the decarbonylative diarylation products.[2] As a continuous study on the reaction of *N*-tosylated α-amino acids, we examined on the reaction of cyclic amino acids such as proline,[1] 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.[1,2] 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.[3] 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 ^{1}H, ^{13}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.[1,2]

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,[2] (2) formation of nucleophilic component ***B*** *via* deprotonation,[2,4,5] (3) coupling reaction of *N*-tosyl enamine ***B*** and *N*-tosylimminium salt ***A*** to form another imminium 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[6] to produce the product **2**.

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



Scheme 1

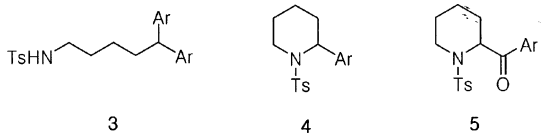
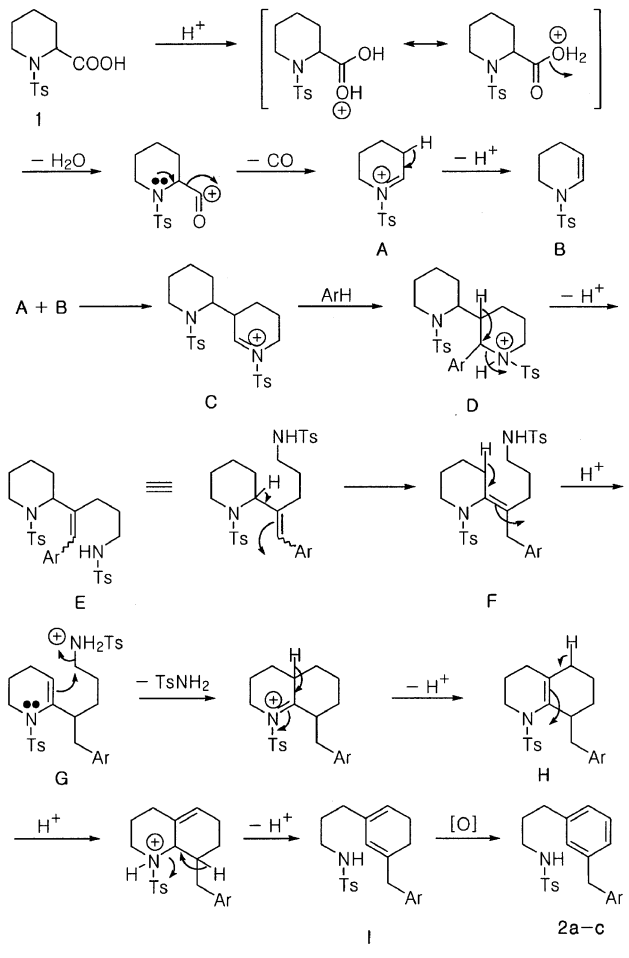


Figure 1



Scheme 2

undergoing.

Experimental

General procedure for the reaction of *N*-tosyl pipecolinic acid (1) and arenes in the presence of sulfuric acid. To a stirred suspension of *N*-tosyl pipecolinic acid (850 mg, 3 mmol) in corresponding arene (10 mL) was added concentrated sulfuric acid (890 mg, 9 mmol) and stirred vigourously 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 $MgSO_4$, 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_f (ether/hexane, 3 : 1) 0.55; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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^+, 18); HRMS Calcd. For $C_{23}H_{25}NO_2S$ 379.1606, Found 379.1626.

2b (190 mg, 16%, ortho/para = 3 : 7): R_f (ether/hexane, 3 : 1) 0.60; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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^+, 11); HRMS Calcd. For $C_{24}H_{27}NO_2S$ 393.1763, Found 393.1763.

2c (184 mg, 15%): R_f (ether/hexane, 3 : 1) 0.62; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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^+, 17); HRMS Calcd. For $C_{25}H_{29}NO_2S$ 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.
4. Maryanoff, B. E.; McComsey, D. F.; Leo, G. C.; Almond, H. R. Jr. *J. Org. Chem.* **1992**, *57*, 1190.
5. Kawase, M.; Hirabayashi, M.; Koiwai, H.; Yamamoto, K.; Miyamae, H. *J. Chem. Soc., Chem. Commun.* **1998**, 641.
6. It is uncertain of the nature of actual oxidizing agent.