Unusual Behaviour of \textit{N}-Tosyl Pipecolinic Acid in Friedel-Crafts Reaction Conditions

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Recently, we have found that the reaction of arenes and \textit{N}-tosylated \(\alpha\)-amino acids in the presence of sulfuric acid gave the corresponding decarbonylative diarylation products.\(^1\) When the \(\alpha\)-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 \(\alpha\)-amino acids, we examined on the reaction of cyclic amino acids such as proline,\(^1\) 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 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\(^6\) to produce the product 2.

Further studies on the reaction mechanism and the conditions which produce products in higher yields are...
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 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 MgSO₄, 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; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 (30), 91 (100), 105 (51), 155 (32), 195 (31), 238 (67), 393 (M⁺, 11); HRMS Calcd. For C₂₃H₂₅NO₂S 393.1763, Found 393.1763.

2b (190 mg, 16%, ortho/para = 3 : 7): R_f (ether/hexane, 3 : 1) 0.62; ¹H NMR (CDCl₃) δ 1.74 (app quintet, J = 7.3 Hz, 2H), 2.22 (ortho isomer, s, 3H), 2.41 (s, 3H), 2.55 (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); ¹³C NMR (CDCl₃) 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, 138.59, 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 C₂₄H₂₇NO₂S 393.1763, Found 393.1763.

2c (184 mg, 15%): R_f (ether/hexane, 3 : 1) 0.62; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) δ 19.92, 21.44, 31.11, 32.67, 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 C₂₅H₃₀NO₂S 407.1919, Found 407.1921.

**References**

3. Many compounds were observed on tlc with no starting material. Thus, separation or identification of other compounds was impossible except 2a-c and tolyl disulfide.
6. It is uncertain of the nature of actual oxidizing agent.