Decarbonylative Diarylation Reaction of *N*-Substituted α-Amino Acids

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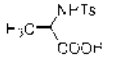
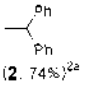
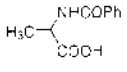
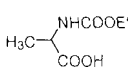
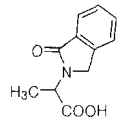
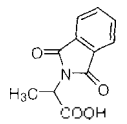
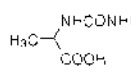
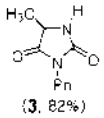
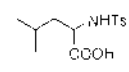
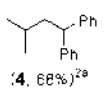
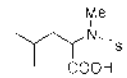
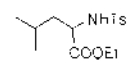
Recently, we have reported on the Friedel-Crafts type reaction of arenes with various kinds of nitrogen containing compounds such as 1,3-dicyclohexylcarbodiimide and sulfonamides.[1] Application of the above reaction to *N*-tosylated α-amino acids results in decarbonylative diarylation reaction to give the corresponding diarylated derivatives in moderate to good yields.[2] In the reactions we did neither alter the *N*-substituent nor optimize the conditions. Thus, we intended to examine the effects of *N*-substituent on the reaction and report herein the results.

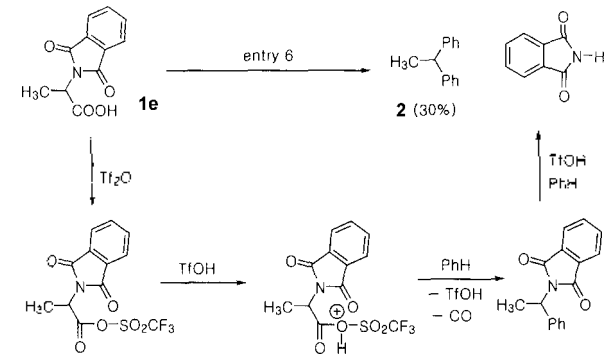
As shown in Table 1, we examined the reaction of *N*-substituted alanine derivatives **1a-f** and three leucine derivatives **1g-i** in the presence of sulfuric acid with benzene as a representative arene nucleophile.

Table 1. Effects of *N*-substituent in the decarbonylative diarylation reaction

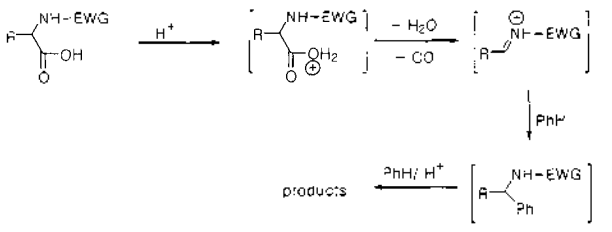
Entry	Substrate (**1**)	Conditions	Product (yield)
1	 (**1a**)	H_2SO_4 (3 equiv) 60–70 °C, 7 h	 (**2**, 74%)[2a]
2	 (**1b**)	H_2SO_4 (5 equiv) 60–70 °C, 20 h	no reaction
3	 (**1c**)	H_2SO_4 (3 equiv) 60–70 °C, 7 h	**2** (41%)
4	 (**1d**)	H_2SO_4 (5 equiv) 60–70 °C, 12 h	no reaction
5	 (**1e**)	H_2SO_4 (3 equiv) 60–70 °C, 7 h	no reaction
6	**1e**	Tf_2O (1.5 equiv) 60–70 °C, 15 h	**2** (30%)
7	 (**1f**)	H_2SO_4 (3 equiv) 60–70 °C, 4 h	 (**3**, 82%)
8	 (**1g**)	H_2SO_4 (3 equiv) 60–70 °C, 7 h	 (**4**, 68%)[2a]
9	 (**1h**)	H_2SO_4 (3 equiv) 60–70 °C, 7 h	**4** (32%)
10	 (**1i**)	H_2SO_4 (3 equiv) 60–70 °C, 7 h	**4** (39%)

By using the *N*-tosyl derivative **1a**, 1,1-diphenylethane (**2**) was obtained in 74% yield as reported.[2a] However, we could not isolate or detect any arylated compounds in the cases of **1b**, **1d**,[3a] and **1e**.[3b] In the case of ethoxycarbonyl derivative **1c**, **2** was obtained in 41%. Urea derivative **1f** gave *N*-phenyl-4-methylimidazolidine-2,5-dione (**3**) in 82% yield instead of **2** *via* the intramolecular amide bond formation. As mentioned above, **2** was not obtained from **1e** by using sulfuric acid, however, we could obtain **2** in 30% yield by trifluoromethanesulfonic anhydride *via* the mixed carboxylic sulfonic anhydride as shown in Scheme 1.[2,4]

The differences in reactivity between the sulfonyl derivative **1a** and the carbonyl derivatives **1b-e** might be explained as follows. As shown in Figure 1, the non-bonding electrons on nitrogen atom of **A** (protonated sulfonyl derivative **1a**)



Scheme 1



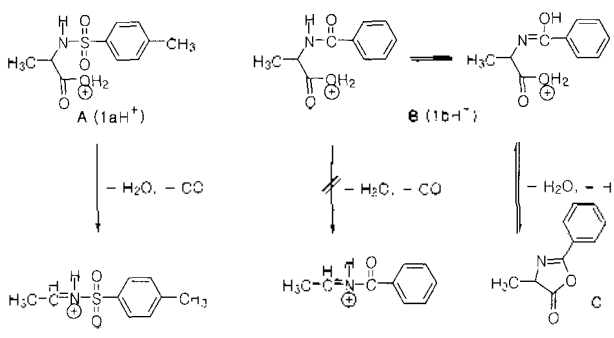


Figure 1

are less delocalized than those of **B** (protonated **1b** as an example of carbonyl derivatives) due to insufficient overlap between *N* and *S* atom,[5] and consequently are more available to trigger the elimination of water and carbon monoxide from **A**. Thus, the corresponding reactive intermediate, *viz* *N*-tosylimminium salt, could be generated much more efficiently in the case of *N*-tosyl α-amino acids, and subsequently the decarbonylative diarylation could be conducted *via* the imminium salt. In the case of benzoyl derivative **1b**, formation of oxazolinone derivative **C** might be the more preferable pathway than the formation of *N*-acylimminium salt.[6]

As shown in entries 9-10, *N*-methyl-*N*-tosyl leucine (**1h**) or ethyl ester derivative **1i** gave the corresponding product **4** with diminished yields as compared with **1g** (entry 8).

In this report we could conclude that in the decarbonylative diarylation reaction of *N*-substituted α-amino acids, tosyl group is the best *N*-substituent of choice.

Experimental Section

The starting materials **1a-c**, and **1f** were prepared from L-alanine by using *p*-toluenesulfonyl chloride, benzoyl chloride, ethyl chloroformate, phenyl isocyanate respectively according to the normal experimental procedures. **1d-e** were synthesized by phthalic dicarboxaldehyde and *N*-carbethoxyphthalimide respectively by using the literature methods.[3] **1g** was synthesized from L-leucine as in the case of **1a**. **1h** was prepared from **1g** by *N,N*-dimethylformamide dimethylacetal in good yield. **1i** was prepared from **1g** by bromoethane and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile.

General procedure. To a stirred suspension of **1** (1 mmol) in dry benzene (5 mL) was added sulfuric acid (0.3-0.5 g, 3-5 mmol) and stirred vigorously at 60-70 °C for the time indicated in Table 1. The reaction mixture was poured into cold water and extracted with ethyl acetate. The organic layers were washed with water, dried with $MgSO_4$, evaporated to dryness to obtain crude products. After flash column chromatograpy we could obtain analytically pure products. Physicochemical data of **2-4** was as follows.

2: yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.55 (d, J = 7.2 Hz, 3H), 4.06 (q, J = 7.2 Hz, 1H), 7.06-7.21 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.83, 44.76, 125.99, 127.60, 128.33, 146.35; MS (70 eV) *m/z* (rel intensity) 77 (23), 149 (22), 152 (21), 164 (52), 167 (100), 182 (M^+, 37).

3: white solid; mp 169-171 °C; ^{1}H NMR (DMSO-d_6) δ 1.35 (d, J = 7.0 Hz, 3H), 4.25 (q, J = 7.0 Hz, 1H), 7.31-7.49 (m, 5H), 8.45 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 17.20, 52.03, 126.68, 127.65, 128.65, 132.22, 155.34, 174.05; MS (70 eV) *m/z* (rel intensity) 41 (32), 64 (75), 77 (24), 91 (100), 119 (71), 190 (M^+, 5).

4: yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 6.6 Hz, 6H), 1.37-1.51 (m, 1H), 1.92 (app t, J = 7.5 Hz, 2H), 4.01 (t, J = 8.0 Hz, 1H), 7.11-7.31 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 22.64, 25.53, 45.05, 48.90, 125.98, 127.88, 128.37, 145.30; MS (70 eV) *m/z* (rel intensity) 91 (7), 152 (10), 165 (21), 167 (100), 168 (15), 224 (M^+, 20).

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