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Aqueous Heck Reaction of Amino Acid Derived Arenediazonium Salts : Semisynthetic Modification of Phenylalanine and Tyrosine.†

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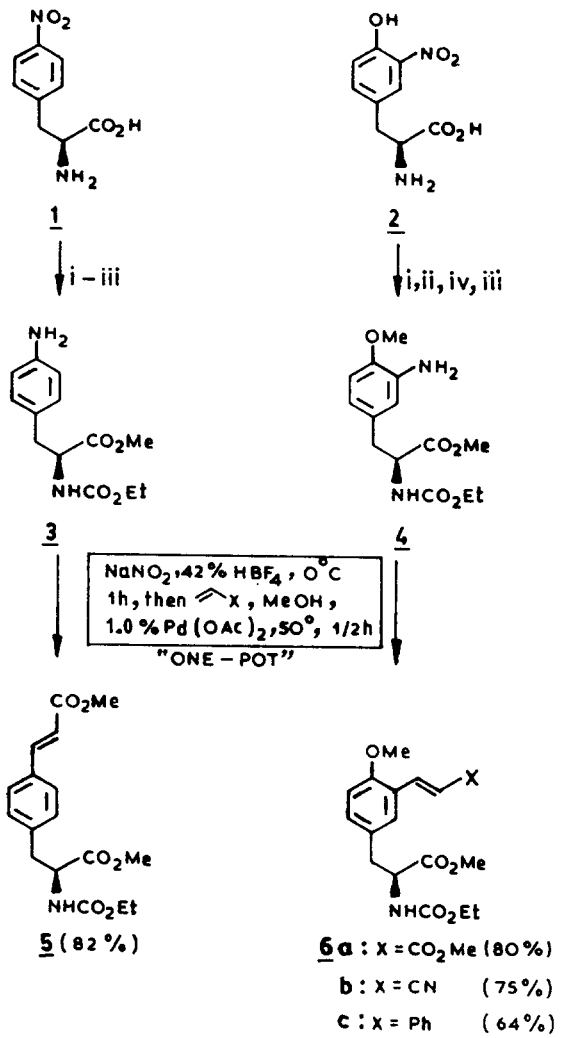
Abstract : Aqueous Heck reaction of arenediazonium salts derived from L-Phe and L-Tyr produced styryl amino acids in high yields.

Recently,[1] we have described an aqueous Heck reaction in which arenediazonium salts were used as opposed to conventional aryl halides/triflates. The process scores over the usual Heck reactions[2] on several counts : short reaction times, high catalytic turnover, superior reactivity of the diazonium nucleofuge and most significantly, the use of aqueous[3] reaction conditions. We have also shown that instead of using the isolated diazonium salts, one could directly start with the respective anilines and perform a 'one-pot' diazotization - Heck reaction in water without even isolating the diazonium salts.[1] This one-pot recipe offers several advantages especially in those cases where the salts are unstable and/or difficult to isolate. We now describe a novel utilization of this process in which aniline derivatives of L-phenylalanine and L-tyrosine were induced to one-pot Heck reaction towards semisynthetic modification of these amino acids.

In the rapidly expanding field of unnatural amino acids, synthesis of ring-modified phenylalanines have gained considerable attention.[4] However, synthesis of such derivatives directly via nuclear carbo-functionalization of phenylalanine, although an attractive proposition, has not been actively pursued. A few Pd-catalyzed reactions on the expensive tyrosine triflate remain as the only development in this area.[5,6] We envisioned that one-pot Heck reaction of anilino-alanines (e.g. **3** and **4**), readily available from L-Phe or L-Tyr via ring nitration and reduction sequence, would expand this repertoire and constitute a new semisynthetic route towards ring-modified (in this case, vinylated) phenylalanine and tyrosine.

Towards this end, the required anilino-alanines (**3** and **4**) were prepared as shown in **Scheme 1**. Thus 4-nitrophenylalanine (**1**), easily available from nitration of L-Phe,[7] was N-protected as the ethylcarbamate followed by esterification and the nitro group was subsequently reduced by transfer hydrogenation (Pd/C, NH_4O_2CH, MeOH, RT)[8] to give the 4-aminophenylalanine derivative **3** in high overall yield (88%). Similar set of operations on the commercial 3-nitrotyrosine (**2**) led to the

†Dedicated to Prof. A.R. Katritzky on his glorious 'Fifty Years of Heterocyclic Chemistry'.



i) EtO_2CCl, aq. NaOH ; ii) CH_2N_2, iii) NH_4O_2CH, Pd/C, MeOH ; iv) K_2CO_3, MeI, Acetone

SCHEME 1

corresponding aniline derivative **4**, also in high yield (84%). The anilines **3** and **4** upon diazotization ($NaNO_2$, 42% HBF_4, 0°), however, gave diazonium salts which were appreciably soluble in the medium and were difficult to isolate in good yields. Hence, **3** and **4** were subjected to our one-pot diazotization - Heck reaction protocol which, most gratifyingly, afforded the desired styrylalanines (**5** and **6**) in good yields (64-82%) (**Scheme 1**).[9,10] Methyl acrylate, acrylonitrile and styrene all reacted with equally high efficacy in this Heck reaction. The high yield of **5** clearly shows the superiority of this aqueous Heck protocol since Heck reaction of tyrosine triflate reportedly produced only moderate yields (54%) and that too, under harsher and prolonged reaction conditions (90°, 24h).[5] Other attractive features of this method include operational simplicity,[9] short reaction times and mild conditions which are ideally suited for sensitive substrates like amino acids. The Heck products, especially the cinnamates (**5** and **6a**) are also biologically significant being stable, nonpolar mimics of tyrosine phosphates and sulfates[5] whereas the stilbene derivative **6c** can potentially lead to polyaromatic amino acids via photocyclization.

In summary, we have developed a simple semisynthetic route towards modified phenylalanines via Heck reaction of arenediazonium salts derived from L-Phe and L-Tyr. Extension of this methodology to other aromatic amino acids is currently in progress.

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9. Typical procedure (**4** → **6a**) : A solution of $NaNO_2$ (0.11g, 1.7 mmol) in water (1 ml) was added dropwise to an ice cold mixture of **4** (0.5g, 1.7 mmol) and 42% HBF_4(0.68 ml, 4.2 mmol). After 30 min at 0°, MeOH (4ml), methyl acrylate (0.3g, 3.4 mmol) and $Pd(OAc)_2$ (5.0mg) were added and the mixture heated on a waterbath for 30 min. It was then filtered through celite, washed with CH_2Cl_2 and the filtrate extracted with CH_2Cl_2. Removal of solvent followed by chromatography over silica gel (20-25% EtOAc/Pet ether) gave **6a** as a pale yellow solid (0.48g, 80%); m.pt. 63-64°; $|\alpha|_D^{25}$ +18.54 (c, 1.3, EtOH); ^{1}HNMR($CDCl_3$) : 1.24(3H, t, J 7Hz), 3.08(2H, m), 3.70(3H, s), 3.86(3H, s), 3.94(3H, s), 4.16(2H, q, J 7Hz) 4.67(1H, m), 5.14(1H, broad), 6.63(1H, d, J 16Hz), 6.90(1H, d, J 10.2Hz), 7.16(1H, d, J 10.2Hz), 7.30(1H, d, J 2Hz), 8.0(1H, d, J 16Hz).

10. **5** (82%); m.pt.90° ; $|\alpha|_D^{25}$ + 71.461 (c, 0.44, EtOH); ^{1}HNMR($CDCl_3$):1.20 (3H, t, J 8.2 HZ), 3.1(2H, m), 3.73(3H, s), 3.82(3H, s), 4.1(2H, q, J 7.2 HZ), 4.65(1H, m), 5.1(1H, broad), 6.41(1H, d, J 16.4 HZ), 7.2(2H, t, J 8.2 HZ), 7.43(2H, d, J 11 HZ) 7.69(1H, d, J 16.4 HZ). **6b** (75%); oil; $|\alpha|_D^{25}$ + 46.113 (c, 1.86, EtOH); ^{1}HNMR($CDCl_3$) : 1.20(3H, t, J 8.2 HZ), 3.03(2H, m), 3.73(3H, s), 3.88(3H, s), 4.10(2H, q, J 8.2 HZ), 4.6(1H, m), 5.14(1H, broad), 6.04(1H, d, J 16.4 HZ), 6.86(1H, d, J 9.0 HZ), 7.1-7.2(2 H, m), 7.57(1H, d, J 16.4 HZ). **6c** (64%); m.pt. 67° ; $|\alpha|_D^{25}$ + 54.515 (c, 1.18, EtOH); ^{1}HNMR($CDCl_3$) : 1.20(3H, t, J 8.2 HZ), 3.10(2H, m), 3.73(3H, s), 3.88(3H, s), 4.12(2H, q, J 7.3 HZ), 4.63(1H, m), 5.12(1H, broad), 6.86-7.62(10H, m).

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