An Efficient Approach to α-Aryl β-Amino Esters through 1,2-Aryl Migration of *p*-Toluenesulfonic Acid Mediated Diazo Decomposition

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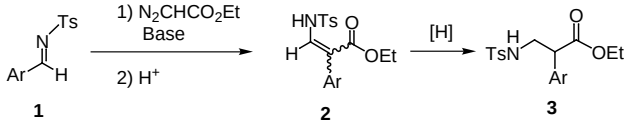
Abstract: A new method for the synthesis of α-aryl β-amino esters has been developed. The key step in this preparation is the chemoselective 1,2-aryl migration of diazo carbonyl compounds catalyzed by TsOH.

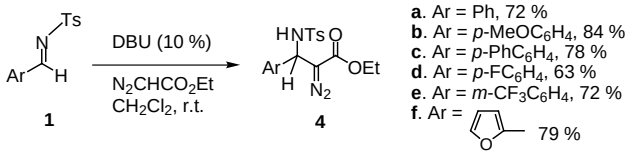
Key words: diazo compounds, 1,2-aryl migration, amino acids, hydrogenations, α-aryl β-amino esters

Considerable efforts have been directed to the synthesis of β-amino acids and their derivatives in recent years, because of their occurrence in biologically active natural products, such as alkaloids and antibiotics.[1] β-Amino acids also find application in the synthesis of β-lactams,[2] piperidines,[3] indolizidines,[4] and β-peptides.[5] α-Aryl β-amino acids have been found in some biologically important products. For example, (*S*)-3-Amino-2-phenylpropionic acid is the side chain of penicillin betacine, and its ethyl ester derivatives has neurological activity.[6] The synthesis of α-aryl β-amino acids and their derivatives are particularly challenging and there are only few methods now available.[7] In this communication, we report an efficient approach to the synthesis of this type of β-amino acid derivatives through *p*-toluenesulfonic acid (TsOH) catalyzed 1,2-aryl migration of α-diazo carbonyl compounds, as shown in Scheme 1.



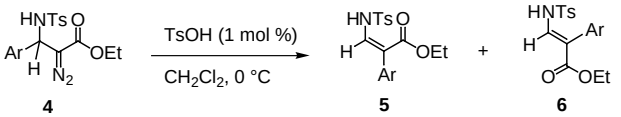
Scheme 1

We have recently reported that the α-diazo carbonyl compounds **4a–f** can be prepared by nucleophilic addition of diazo ethylacetate (EDA) anion to the *N*-tosyl protected imine **1**.[8] The EDA anion was generated through deprotonation by lithium diisopropylamide (LDA) or NaH. In the later investigation, we find that this nucleophilic addition can be promoted by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) under catalytic condition. The reaction condition is milder and the yields are moderate to good (Scheme 2).



Scheme 2

In our previous investigation, the α-diazo carbonyl compounds are decomposed with Rh(II) or copper catalysts to give α-aryl-β-enamino esters (Scheme 3).[8]



Scheme 3

Table TsOH-Catalyzed Diazo Decomposition of **4a**– **f**

Entry	Substrate	Product ratio (**5**:**6**)[a]	Yield (5)[b]
1	**4a**	71:29	89
2	**4b**	62:38	90
3	**4c**	78:22	95
4	**4d**	>95:5	87
5	**4e**	75:25	85
6	**4f**	70:30	79

[a] Product ratio was determined by ^{1}H NMR (400 MHz).
[b] Yields after column chromatography.

We now find that the α-diazo carbonyl compounds, which are in general quite stable at room temperature, can be efficiently decomposed at 0 °C with catalytic TsOH (~ 1 mol%).[9] As in the reaction with Rh(II) or copper catalysts, the 1,2-aryl products are predominate in all cases (Table). However, in Rh(II) or Cu(I) catalyzed reaction, *trans* α-aryl-β-enamino esters are predominant, while the TsOH promoted reaction gave predominately *cis* products. The *cis* isomer is more stable than the *trans* isomer because of the intramolecular hydrogen bonding. We have observed

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that *trans* products could isomerize to their *cis* isomer in silica gel column. Therefore it is likely that the predominant formation of the *cis* products under TsOH catalysis condition is due to the acid-catalyzed isomerization during the reaction.[9] To test this point, the diazo decomposition of **4a** was carried out with 10% TsOH at room temperature. As expected, the ratio of the *cis* to *trans* increased from 71:29 to 95:5.

β-Enamino esters are reported to be easily reduced to the corresponding β-amino esters with $NaBH(OAc)_3$.[10] However, the α-aryl-β-enamino esters obtained in our investigation did not react with $NaBH(OAc)_3$ under identical condition. On the other hand, the *cis* and *trans* mixture of α-aryl-β-enamino esters **5a**–**f** and **6a**–**f** can be easily converted to α-aryl β-amino esters by hydrogenation with 1 atm H_2 and 10% Pd/C as the catalyst (Scheme 4).[11,12]

For the acid catalyzed 1,2-aryl migration, we can propose a possible reaction mechanism. The diazo compound was first protonated at the negatively polarized carbon to which the diazo group is attached, following the extrusion of N_2 to give a highly reactive α-carbonyl cation. The neighboring phenyl group migrates through a bridged phenylium ion (Scheme 5).

In summary, we have developed an efficient route to the synthesis of α-aryl-β-amino esters. Efforts toward the synthesis of enantiomerically pure α-aryl-β-amino esters by asymmetric hydrogenation is currently under the way and the results will be report in due course.

Acknowledgement

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(9) **General procedure for the TsOH catalyzed diazo decomposition:** To a solution of TsOH (1 mg) in anhydrous CH_2Cl_2 (20 mL) at 0 °C under N_2, was added dropwise a solution of diazo compound in anhydrous CH_2Cl_2 (5 mL). The reaction was complete within 30 min as indicated by TLC check. Solvent was removed by evaporation, and the residue was purified by flash column chromatography to give *cis* and *trans* α-aryl-β-enamino esters as a mixture.

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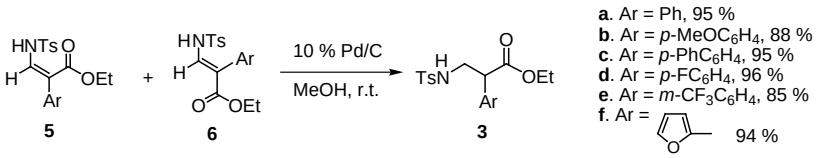
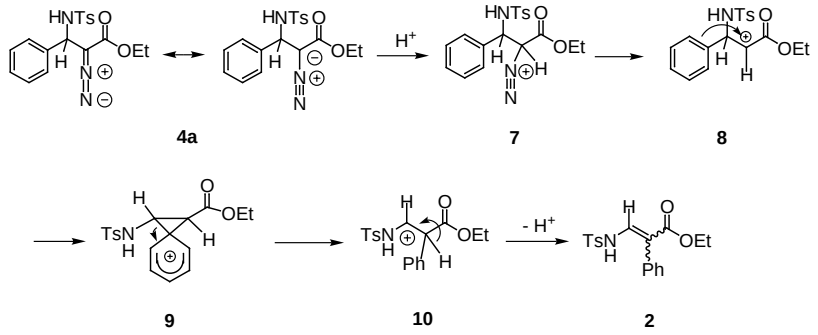
(11) **General procedure for the hydrogenation of α-aryl-β-enamino esters:** To a solution of α-aryl-β-enamino esters (50 mg, *cis* and *trans* mixture) in absolute MeOH (25 mL) was added 10% Pd/C catalyst (10 mg). The reaction mixture was stirred for 10 h under 1 atm hydrogen atmosphere. Then catalyst was removed by filtration and solvent was evaporated to give a residue, which was purified by flash column chromatography.
3a: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.13 (t, 3 H), 2.36 (s, 3 H), 3.19–352 (m, 2 H), 3.79–3.86 (q, 1 H), 4.04–4.17 (m, 2 H), 5.13 (t, 1 H), 7.13 (m, 7 H), 7.72 (d, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.88, 21.42, 45.62, 51.72, 61.27, 126.91,



Scheme 4



Scheme 5

127.82, 127.84, 128.88, 129.68, 135.63, 136.86, 143.40, 172.34; MS *m/z* (relative intensity): 347 (M^+, 17%), 118 (100%).

3b: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18 (t, 3H), 2.42 (s, 3 H), 3.16–3.50 (m, 2H), 3.77–3.81 (m, 1 H), 3.79 (s, 3H), 4.04–4.17 (m, 2 H), 5.07 (t, 1 H), 6.83 (d, 2 H), 7.06 (d, 2 H), 7.29 (d, 2 H), 7.72 (d, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.90, 21.41, 45.67, 50.82, 55.14, 61.18, 114.25, 126.91, 127.60, 128.90, 129.65, 136.90, 143.36, 159.14, 172.56; MS *m/z* (relative intensity): 377 (M^+, 10%), 194 (100%).

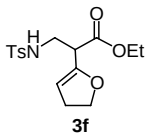
3c: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.19 (t, 3 H), 2.39 (s, 3 H), 3.21–3.55 (m, 2 H), 3.84–3.91(q, 1 H), 4.04–4.20 (m, 2 H), 5.07 (t, 1 H), 7.20–7.57 (m, 1 1H), 7.71 (d, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.96, 21.45, 45.65, 51.40, 61.39, 126.95, 127.45, 127.60, 128.30, 129.71, 134.60, 136.89, 140.26, 140.82, 143.45, 172.36. *m/z* (relative intensity): 423 (M^+, 11%), 240 (100%).

3d: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.17 (t, 3 H), 2.42 (s, 3 H), 3.15–3.50 (m, 2 H), 3.78–3.85 (q, 1 H), 4.04–4.18 (m, 2 H), 5.20 (t, 1 H), 6.92–7.30 (m, 6 H), 7.70 (d, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.87, 21.41, 45.57, 50.92, 61.37, 115.55, 115.98, 126.89, 129.44, 129.60, 129.69, 136.79, 143.47, 172.19. *m/z* (relative intensity): 365 (M^+, 24%), 182 (100%).

3e: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18 (t, 3 H), 2.42 (s, 3 H), 3.20–3.55 (m, 2 H), 3.87–3.94 (q, 1 H), 4.04–4.17 (m, 2 H), 5.13 (t, 1 H), 7.29 (m, 2 H), 7.31–7.56 (m, 4 H), 7.70 (m, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.84, 21.42, 45.44, 51.55, 61.61, 124.74, 124.81, 126.91, 129.42, 131.44, 136.68, 136.78, 143.62, 171.70. *m/z* (relative intensity): 415 (M^+, 8%) 184 (100%).

3f: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22 (t, 3 H), 1.97 (m, 2 H), 2.39 (s, 3 H), 2.83 (t, 2 H), 3.89 (d, 2 H), 4.02–4.20 (m, 4 H), 5.15 (t, 1 H), 7.23 (d, 2 H), 7.68 (d, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.32, 21.40, 23.74, 31.15, 39.35, 59.84, 72.16, 76.36, 76.99, 77.63, 98.03, 127.10, 129.11, 137.59, 142.79, 167.55, 173.76. *m/z* (relative intensity): 339 (M^+, 14%), 184 (100%).

(12) For the α-aryl-β-enamino esters **5f** and **6f**, the hydrogenation gave a product with the furanyl moiety being partially hydrogenated. The structure of the **3f** (Figure) is as follows.



3f

Figure