Enantioselective Synthesis of (*R*)-α-(*p*-Nitroaryl)prolines via Oxidative Nucleophilic Substitution of Hydrogen in Nitroarenes

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Abstract: Optically pure (*R*)-α-(*p*-nitroaryl)prolines are synthesized via oxidative nucleophilic substitution of hydrogen in nitroarenes using chiral carbanion of L-proline protected as *N*,*O*-acetal of pivalaldehyde.

Key words: amino acids, nitroarenes, oxidative substitution, carbanions

Enantiomerically pure unnatural α-amino acids are interesting intermediates for pharmaceutical and agrochemical industries so their synthesis attracts considerable attention. Of particular interest are α-substituted proline derivatives that are used in peptide research for manipulation of conformational flexibility of the peptide chain,[2] as chiral building blocks,[3] efficient organocatalysts,[4] etc.

Several methods for asymmetric synthesis of α-substituted prolines are reported. Alkylation and reactions with other electrophiles of the carbanion of proline protected as *N*,*O*-acetal of pivalaldehyde proceeds diastereoselectively thus assuring the synthesis of α-substituted prolines with self-reproduction of chirality.[5] Enantioselective introduction of aryl and benzyl groups into position α of *N*-methyl proline proceeds via Stevens and Sommelett–Hauser rearrangement of *N*-benzyl-*N*-methyl ammonium salts of proline *tert*-butyl ester.[6] Enantiomerically pure α-substituted prolines can be obtained via construction of the pyrrolidine ring in sequence of reactions: monoalkylation of chiral Schiff base of glycine with 1,3-diiodopropane followed by hydrolysis of the resulting imine and subsequent N-alkylation,[7] as well as via cyclization of enantiomerically pure α,ω-amino alcohols under Mitsunobu conditions.[8]

In this letter we report the synthesis of α-(*p*-nitroaryl)prolines in enantiomerically pure form via diastereoselective oxidative nucleophilic substitution of hydrogen, ONSH, in nitroarenes with carbanion of protected proline. We have shown previously that carbanions of some protected α-amino acids add to nitroarenes giving anionic σ^H adducts that after oxidation followed by hydrolytic deprotection produced racemic α-(*p*-nitroarylated)alanines and serines.[9] For enantioselective synthesis of α-(*p*-nitroaryl)prolines we have applied the approach developed by Seebach for self-reproduction of chirality, namely used as

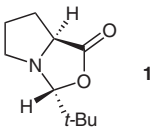

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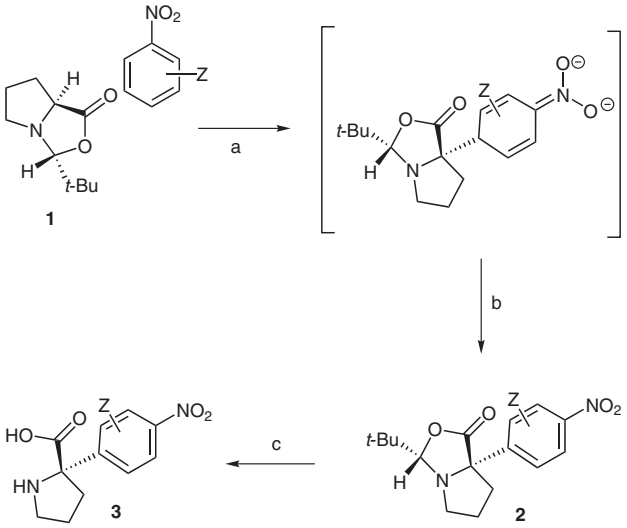
Figure 1 Precursor of carbanion **1** developed by Seebach



Scheme 1 *Reagents and conditions*: a) KHMDS, THF–DMF, –78 °C, 15 min; b) DDQ, THF, 5 min, –78 °C, then r.t.; c) 48% HBr, reflux, 20 h, then propylene oxide in EtOH.

the carbanion precursor, proline protected as *N*,*O*-acetal of pivalaldehyde **1** (Figure 1). It should be noted that reaction of **1** with benzenetricarbonylchromium complex followed by oxidation gave α-phenylproline, product of nucleophilic oxidative arylation in moderate yield.[5]

Compound **1** was prepared via direct reaction of pivalaldehyde with the trimethylsilyl ester of *N*-trimethylsilyl-L-proline according to slightly modified literature method.[10] In many reports on reaction of carbanion of **1**, its lithium salt generated by action of LDA was utilized.[5,11]

Taking into account that addition of carbanions to nitroarenes proceeds satisfactorily when they are in form of loose ion pairs,[12] we used the potassium salt of $\mathbf{1}^-$ generated by reaction of **1** with potassium hexamethyldisilazane (KHMDS) in a mixture of THF–DMF. When **1** and nitrobenzene in THF–DMF mixture was treated at –70 °C with KHMDS, and after some time the formed σ^H adduct oxidized with DDQ, expected *p*-nitrophenyl derivative **2a**[13] was obtained in good yield (72%) as a single diastereomer (Scheme 1). Due to bulkiness of $\mathbf{1}^-$, the addition

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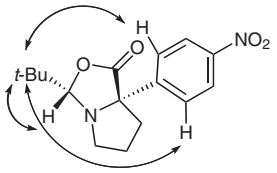

Figure 2 The NOE experiment of **2a**, irradiation of protons of *t*-Bu group

Table 1 Reaction of Compound **1** with Various Nitroarenes

Nitroarene	Product	Yield (%)	Product	Yield (%)
H	**2a**	72	**3a**	77
3-F	**2b**	29	**3b**	85
2-F	**2c**	37	–	–
2-Cl	**2d**	31	–	–
2-MeO	**2e**	43	**3e**[a]	55
2-Me	**2f**	15	–	–

[a] The product contains 4-nitro-3-hydroxyphenyl group due to O-demethylation.

took place selectively in the position *para* to the nitro group.

On the basis of NMR spectra, particularly NOE experiment of product **2a**, it was found that *tert*-butyl and *p*-nitrophenyl groups are in *cis* relation to each other (Figure 2). This means that the nucleophilic center is attacked by nitroarene from the *Re* face, giving product possessing *R*-configuration at the α-position.

Unfortunately the reaction of $\mathbf{1}^-$ with other nitroarenes under identical conditions gave products **2** only in moderate yields (Table 1).

Attempting to improve yields, we have checked the possibility to optimize the reaction conditions between $\mathbf{1}^-$ and *m*-fluoronitrobenzene. Thus, changing of the reaction time (addition and oxidation step), temperature (–40 °C and –60 °C instead of –78 °C), base (KO*t*-Bu, NaHMDS), and oxidant (*p*-chloranil, tetracyanoethylene, $KMnO_4$ in liquid ammonia, 1,1-dimethyldioxirane) does not improve the results. It should be noted that there is no correlation between electrophilic activity of nitroarenes and yields of the ONSH products. Thus, strongly deactivated and moderately activated 2-methoxy and 2-fluoronitrobenzene gave ONSH products in moderate yields, whereas the reaction with highly activated 2- and 3-nitrobenzonitrile failed. It was difficult to clarify which step – addition or oxidation – was responsible for the failure. One could suppose that an alternative process between $\mathbf{1}^-$ and nitroarenes takes place so that σ^H-adducts are not formed.

Final products **3**, free α-(*p*-nitroaryl)prolines, were obtained via hydrolysis of **2** according to the literature procedure using aqueous HBr,[5] followed by precipitation of **3** with propylene oxide in ethanol at room temperature.[14] Yields are presented in Table 1.

In summary, we have developed a new method for the synthesis of optically pure (*R*)-α-(*p*-nitroaryl)prolines via oxidative nucleophilic substitution of hydrogen in nitroarenes with carbanion of protected proline **1**.

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(10) (a) Synthesis of **1** was carried out according a literature procedure (see ref. 10b) with slight modification.
Preparation of Compound 1
To a solution of trimethylsilyl ester of *N*-trimethylsilyl-L-proline (28.8 g, 0.111 mol) in dry *n*-pentane (23 mL) under argon, pivalaldehyde (12.1 mL, 0.111 mol) was added very slowly. During the addition temperature must be kept below 20 °C cooling in water bath with ice, reaction is exothermic. Overheating the reaction mass above 30 °C cause partial decomposition of the product. After 1 h, the resulting solution was cooled to –70 °C and the crystalline product was filtered and dried; yield 20.3 g, 82%. (a) Annunziata, R.; Ferrari, M.; Papeo, G.; Resmini, M. *Synth. Commun.* **1997**, *27*, 23.
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(13) **General Procedure**
To a solution of **1** (1 mmol), nitroarene (2 mmol) in THF (10 mL), and DMF (2 mL), cooled to –78 °C, 0.5 M solution of KHMDS in toluene (3 mL, 1.5 mmol) was added dropwise during 10 min. The resulting dark-colored mixture was stirred for 30 min at the same temperature and then treated with a solution of DDQ (1.2 mmol) in THF (1 mL). After stirring for further 5 min at –78 °C, a brown slurry was slowly allowed to reach r.t. Aqueous workup gave crude product, which was purified by column chromatography.
Selected Analytical Data
Compound **2a**: mp 88–90 °C (MeOH); $[\alpha]_D^{22}$ +0.8 (*c* 1.000,

$CHCl_3$). IR (KBr): 2970, 2870, 1772, 1521, 1351, 1194, 1091, 853, 753 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 9.0 Hz, 2 H), 7.96 (d, *J* = 9.0 Hz, 2 H), 4.50 (s, 1 H), 3.36 (dt, *J* = 6.7, 11.5 Hz, 1 H), 3.09 (dt, *J* = 5.8, 11.5 Hz, 1 H), 2.56 (dt, *J* = 6.7, 12.8 Hz, 1 H), 2.00 (dt, *J* = 7.2, 12.8 Hz, 1 H), 1.90–1.80 (m, 2 H), 0.86 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.1, 149.0, 147.3, 126.6, 123.5, 106.3, 74.0, 58.9, 42.5, 36.8, 25.5, 24.3. MS (EI, 70 eV): *m/z* = 304 [M^+], 289, 261, 247, 219, 191, 145.

Compound **2b**: mp 94–96 °C (MeOH); $[\alpha]_D^{22}$ +2.1 (*c* 1.000, $CHCl_3$). IR (KBr): 2961, 2901, 1781, 1536, 1364, 1196, 895, 811, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.07–7.92 (m, 3 H), 4.49 (s, 1 H), 3.34–3.23 (m, 1 H), 3.13–3.03 (m, 1 H), 2.74–2.64 (m, 1 H), 2.36–2.24 (m, 1 H), 1.91–1.75 (m, 2 H), 0.89 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 160.2 (d, *J* = 250 Hz), 148.2 (d, *J* = 9 Hz), 135.8 (d, *J* = 12 Hz), 128.5 (d, *J* = 4 Hz), 118.5 (d, *J* = 3 Hz), 112.6 (d, *J* = 28 Hz), 105.4, 73.4 (d, *J* = 4 Hz), 57.4 (d, *J* = 1 Hz), 39.6 (d, *J* = 3 Hz), 36.8, 25.2, 24.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 105.5. MS (ESI^+): *m/z* = 323 [M + H]$^+$.

(14) **Hydrolysis – General Procedure**

A solution of **2** (0.5 mmol) in 48% aq HBr (1 mL) was heated to 100 °C for 20 h. The aq acid was removed in vacuo and the dry residue was dissolved in dry EtOH (1 mL). To this solution propylene oxide (5 mL) was added carefully, and stirred at r.t. for 2 h. Precipitated solid was filtered and washed with cold EtOH. Drying under reduced pressure gave product as a white, amorphous solid.

Selected Analytical Data

Compound **3a**: mp >320 °C; $[\alpha]_D^{22}$ +2.3 (*c* 0.667, 0.1 M HCl). IR (KBr): 3444 (bs), 3064 (bs), 1651, 1617, 1526, 1345, 854, 737 cm^{-1}. ^1H NMR (400 MHz, D_2O–DCl): δ = 8.34 (d, *J* = 9.1 Hz, 2 H), 7.77 (d, *J* = 9.1 Hz, 2 H), 3.74–3.65 (m, 1 H), 3.60–3.52 (m, 1 H), 3.10–3.05 (m, 1 H), 2.70–2.60 (m, 1 H), 2.40–2.29 (m, 1 H), 2.24–2.12 (m, 1 H). ^{13}C NMR (125 MHz D_2O–DCl): δ = 171.7, 148.5, 140.8, 128.1, 124.7, 74.7, 45.7, 33.5, 22.2. MS (ESI^+): *m/z* = 237 [M + H]$^+$.

Compound **3b**: mp >320 °C; $[\alpha]_D^{22}$ +86.5 (*c* 0.500, 0.1 M HCl). IR (KBr): 3107 (bs), 2720 (bs), 1634, 1624, 1348, 809 cm^{-1}. ^1H NMR (400 MHz, D_2O–DCl): δ = 8.21 (ddd, *J* = 0.8, 2.3, 8.8 Hz, 1 H), 8.17 (dd, *J* = 2.2, 10.9 Hz, 1H), 7.92 (t, *J* = 7.7 Hz), 3.82–3.60 (m, 1 H), 3.60–3.42 (m, 1 H), 3.00–2.87 (m, 1 H), 2.87–2.70 (m, 1 H), 2.43–2.25 (m, 1 H), 2.25–2.07 (m, 1 H). ^{13}C NMR (100 MHz D_2O–DCl): δ = 170.8, 159.7 (d, *J* = 250 Hz), 149.6 (d, *J* = 10 Hz), 130.4 (d, *J* = 4 Hz), 128.2 (d, *J* = 14 Hz), 120.5 (d, *J* = 3 Hz), 112.1 (d, *J* = 27 Hz), 70.9, 46.4, 33.9, 22.1. MS (ESI^+): *m/z* = 255 [M + H]$^+$.