

## Note

### Acid catalyzed condensation of pyroglutamic acid with arylaldehydes: Synthesis of (3*R*, 7*aS*)-3-aryldihydropyrrolo[1, 2-*c*] oxazol-1, 5(3*H*, 6*H*) dione

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A simple strategy for the synthesis of (3*R*, 7*aS*)-3-aryldihydropyrrolo [1, 2-*c*] oxazol-1, 5(3*H*, 6*H*)-diones as bicyclic hemiaminals through acid catalyzed condensation of pyroglutamic acid with arylaldehydes has been described. This could be useful for the synthesis of complex natural products requiring  $\alpha$ -substitution in proline or pyroglutamate skeleton.

**Keywords:** Pyroglutamic acid, aromatic aldehyde, acid catalyzed condensation reaction, bicyclic derivative.

Pyroglutamic acid has been acknowledged as a useful chiral synthon<sup>1</sup> for the synthesis of many of the bioactive natural products<sup>2-5</sup>, ACE inhibitors<sup>6-13</sup> and conformationally constrained peptides<sup>14,15</sup>. Pyroglutamic acid has two differential carbonyl groups, a carboxyl and a lactam carbonyl and the reactivity differences between these two carbonyl groups have well been exploited. Due to these reasons pyroglutamic acid has emerged as a starting material of choice in recent years for the synthesis of natural products such as salinosporamide-A<sup>3</sup>, anatoxin-a<sup>4</sup>, (-)-bulgecinine<sup>5</sup>, etc. While good synthetic routes are available for the chiral functionalization of pyroglutamates at C-3 (Ref 16), C-4 (Ref 17, 18) and C-5 (Ref 19-21), the behaviour of pyroglutamates towards chiral functionalization at C-2 has received less attention<sup>22,23</sup>. Earlier investigations reported the chiral synthesis of  $\alpha$ -substituted pyroglutamates<sup>23</sup> utilizing Seebach's procedure of self reproduction of chirality<sup>24,25</sup>, where pyroglutamic acid was condensed with trimethylacetaldehyde in the presence of trifluoroacetic acid (TFA) using dioxan as solvent, where the reaction was carried out in Parr SS pressure vessel and the resultant bicyclic compound was used for the stereo selective functionalization at C-2.

Even though quite a few reports are available where pyroglutamic acid has been condensed either with trimethyl acetaldehyde<sup>23</sup> leading to bicyclic hemiaminal, or with chloral<sup>26,27</sup> thereby furnishing hemi aminal/ bis- product, however the general behavior of pyroglutamic acid towards the acid catalyzed condensation with aromatic aldehydes has not yet been studied and this prompted to explore a simple methodology for the synthesis of bicyclic product **2**, which could avoid the use of oxygenated solvents as well as drastic conditions and then to look for desired chemical/ stereo chemical out come of the product.

### Results and Discussion

A comparatively simpler methodology for the acid catalyzed condensation of pyroglutamic acid with aromatic aldehydes, thereby leading to the synthesis of (3*R*, 7*aS*)-3-aryldihydropyrrolo [1, 2-*c*] oxazol-1,5(3*H*, 6*H*)-diones as chiral intermediates for the  $\alpha$ -substituted pyroglutamates and prolinates has been reported here. Further studies on the uses of these bicyclic chiral hemiaminals are under investigation in our laboratory and shall be reported in due course.

With a view to ascertain the structure and stereochemistry, an attempt was made to study the reaction of pyroglutamic acid with trimethylacetaldehyde in presence of trifluoroacetic acid (catalytic amount) and molecular sieves (4 Å), using toluene as the solvent and the reaction mixture was refluxed at 110°C for 48 hr, where compound **2a** was obtained. The data of compound **2a** were compared with earlier reported values<sup>23</sup> and were found to be identical. Lack of noe between H<sub>a</sub> proton and H<sub>b</sub> proton was the substantive evidence for the assigned stereochemistry, (**Figure 1**). The stereo chemical assignments were confirmed further by the comparison of optical rotation of **2a** with our previously reported values for this compound<sup>23</sup>, which provided conclusive evidence for the assigned stereochemistry.

Based on encouraging observations of the condensation of pyroglutamic acid with trimethyl acetaldehyde under simpler conditions as compared to previous report and to establish the versatility of our procedure, reactions of pyroglutamic acid with various aromatic aldehydes were carried out where in

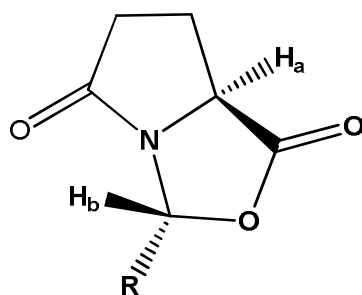
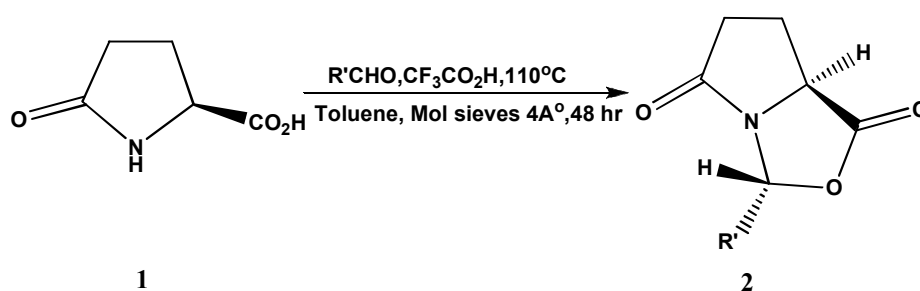


Figure 1 — Assigned structure for compound 2



Compd	R'
2a	-C(CH <sub>3</sub> ) <sub>3</sub>
2b	2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -
2c	4-F-C <sub>6</sub> H <sub>4</sub> -
2d	4-Cl-C <sub>6</sub> H <sub>4</sub> -
2e	4-MeO-C <sub>6</sub> H <sub>4</sub> -
2f	-Ph

Scheme I

each reaction bicyclic hemiaminals (**2b-f**) were obtained. In each of these aryl group acquired pseudo equatorial position. The results are summarized in (Scheme I).

### Conclusion

A unified and simple approach for the synthesis of (3*R*, 7*aS*)-3-aryldihydropyrrolo [1,2-*c*] oxazol-1, 5(3*H*, 6*H*)-diones through acid catalyzed condensation of pyroglutamic acid with various arylaldehydes has successfully been explored. The chiral bicyclic derivatives thus obtained shall be useful for the synthesis of complex natural products requiring C-2 substitutions in prolines or pyroglutamates.

### Experimental Section

Melting points are uncorrected, spectral data were recorded as follows: Perkin Elmer (FTIR); Jeol SX-102 (FAB) (MS); Bruker advance 400 (<sup>1</sup>H NMR), Rudolf Autopol III polarimeter (optical rotation),

Elementar Vario EL III (elemental analysis): Dry toluene was used for condensation reaction.

### General procedure for the synthesis of bicyclic compounds 2

To a solution of pyroglutamic acid **1** (1.30 g, 10 mmol) in dry toluene (20 mL) was added arylaldehydes (11 mmol, 1.1 equivalent), trifluoroacetic acid (2-3 drops, catalytic amount) and molecular sieves 4 Å (1.0g). The mixture was refluxed at 110°C with continuous stirring for 48 hr. The water formed during the reaction was removed azeotropically using a Dean-Stark water separator. Progress of the reaction was monitored by TLC. On the completion of the reaction, the reaction mixture was cooled up to RT and quenched with saturated sodium bicarbonate (NaHCO<sub>3</sub>) solution (5 mL) and filtered. The filtrate was concentrated under vacuum to remove the solvent, and the residual mixture was poured into water (15 mL) and extracted with ethyl acetate (2 × 20 mL). The combined ethyl acetate layer

was washed with saturated sodium chloride (NaCl) solution (10 mL), dried over anhydrous sodium sulfate (Na<sub>2</sub>SO<sub>4</sub>), concentrated and purified by column chromatography on silica gel using 20% EtOAc-hexane as eluent to afford the pure compounds **2a-f**.

**(3R, 7aS)-3-*t*-Butyldihydropyrrolo [1,2-*c*] oxazol-1, 5(3H, 6H)-dione, 2a**

The compound **2a** was synthesized from pyroglutamic acid (1.30 g, 10 mmol) and trimethylacetaldehyde (0.950 g, 11 mmol, 1.1 eq) according to procedure as described above and was obtained as white solid: Yield 1.05g (60.3%);  $[\alpha]_D^{25} +27.5$  (c 0.1 CHCl<sub>3</sub>)[reported: $[\alpha]_D^{25} +29.6$  (c 1.3 MeOH)] (Ref 23); All the other data of compound **2a** were compared, and found to be identical with reported values<sup>23</sup>.

**(3R, 7aS)-3-(2-Nitrophenyl) dihydropyrrolo [1,2-*c*] oxazol-1, 5(3H, 6H)-dione, 2b**

The compound **2b** was synthesized from pyroglutamic acid (1.30 g, 10 mmol) and *o*-nitrobenzaldehyde (1.66 g, 11 mmol, 1.1 eq) according to procedure as described above and was obtained as solid: Yield 1.67 g; (63.0%), m.p. 159-62°C;  $[\alpha]_D^{25} -25.16$  (c 0.1 CHCl<sub>3</sub>); IR (KBr): 1700, 1735, 2363, 2925 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.41-2.47(m, 1H, H-6), 2.76-2.83 (m, 1H, H-6'), 2.98-3.03 (m, 1H, H-7), 3.21-3.33 (m, 1H, H-7'), 4.09-4.14 (m, 1H, H-5), 5.30(s, 1H, C-2) 7.30-7.32 (d, 1H, ArH), 7.46-7.50 (d, 1H, ArH), 8.08-8.23 (m, 2H, ArH); MS: *m/z* 265(M+3), 221, 207, 147, 97, 91. Anal. Calcd for C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>O<sub>5</sub>: C, 54.96; H, 3.82; N, 10.68. Found: C, 55.44; H, 3.62; N, 10.34%

**(3R, 7aS)-3-(4-Fluorophenyl) dihydropyrrolo [1,2-*c*] oxazol-1, 5(3H, 6H)-dione, 2c**

The compound **2c** was synthesized from pyroglutamic acid (1.30 g, 10 mmol) and *p*-fluorobenzaldehyde (1.36 g, 11 mmol, 1.1eq) according to procedure as described above and was obtained as solid: Yield 1.27g (54.0%); m.p. 153-56°C;  $[\alpha]_D^{25} -29.0$  (c 0.1 CHCl<sub>3</sub>); IR (KBr): 1700, 1735, 2367, 2956 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.38-2.42 (m, 1H, H-6), 2.65-2.70 (m, 1H, H-6'), 2.90-2.95 (m 1H,H-7), 3.10-3.17 (m, 1H, H-7'), 4.56 (m 1H, H-5), 5.29 (s, 1H, C-2) 7.02-7.05 (m, 2H, ArH), 8.11-8.15 (m, 2H, ArH); MS: *m/z* 236(M+1), 221, 135, 109, 95 Anal. Calcd for C<sub>12</sub>H<sub>10</sub>NO<sub>3</sub>F: C, 61.28; H, 4.26; N, 5.95. Found: C, 61.12; H, 4.12; N, 5.64%

**(3R, 7aS)-3-(4-Methoxyphenyl) dihydropyrrolo [1,2-*c*] oxazol-1, 5(3H, 6H)-dione, 2d**

The compound **2d** was synthesized from pyroglutamic acid (1.30 g, 11.0 mmol) and *p*-methoxybenzaldehyde (1.49 g, 11.0 mmol, 1.1 eq) according to procedure as described above and was obtained as solid: Yield 1.21g (59.0%); m.p. 143-45°C;  $[\alpha]_D^{25} -12.4$  (c 0.1 CHCl<sub>3</sub>); IR (KBr): 1680, 1725, 2364, 2955 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.23-2.30 (m, 1H, H-6), 2.51-2.60 (m, 1H, H-6'), 2.80-2.90 (m, 1H, H-7), 3.0-3.07 (m, 1H, H-7'), 3.73-3.80 (m, 1H, H-5), 3.87 (s, 3H, OCH<sub>3</sub>) 5.29 (s, 1H, C-2) 6.93-6.95 (m, 2H, ArH), 8.05-8.07 (m, 2H, ArH); MS: *m/z* 256, 221, 147, 117. Anal. Calcd for C<sub>13</sub>H<sub>13</sub>NO<sub>4</sub>: C, 63.16; H, 5.26; N, 5.67. Found: C, 62.98; H, 5.12; N, 5.55%

**(3R, 7aS)-3-(4-Chlorophenyl) dihydropyrrolo [1,2-*c*] oxazol-1, 5(3H, 6H)-dione, 2e**

The compound **2e** was synthesized from pyroglutamic acid (1.30 g, 10.0 mmol) and *p*-chlorobenzaldehyde (1.55 g, 11.0 mmol, 1.1 eq) according to procedure as described above and was obtained as solid: Yield 1.46g, (58.0%); m.p. 143-45°C;  $[\alpha]_D^{25} -47.3$  (c 0.1 CHCl<sub>3</sub>); IR (KBr): 1690, 1735, 2367, 2955 cm<sup>-1</sup>; <sup>1</sup>H NMR: δ (CDCl<sub>3</sub>) 2.03-2.17 (m, 2H, H-6), 2.31-2.76 (m, 2H, H-7), 4.42-4.61 (m, 1H, H-5), 5.29 (s, 1H C-2) 7.20-7.46 (m, 2H, ArH), 7.83-8.04 (m, 2H, ArH); MS: *m/z* 254 (M+2), 216, 187, 125. Anal. Calcd for C<sub>12</sub>H<sub>10</sub>NO<sub>3</sub>Cl: C, 57.26; H, 4.05; N, 5.67. Found: C, 56.90; H, 3.95; N, 5.50%

**(3R, 7aS)-3-Phenyldihydropyrrolo [1,2-*c*] oxazol-1, 5(3H, 6H)-dione, 2f**

The compound **2f** was synthesized from pyroglutamic acid (1.30 g, 10.0 mmol) and benzaldehyde (1.16 g, 11.0 mmol, 1.1 eq) according to procedure as described above and was obtained as thick oil: Yield 1.11g, (55.0%);  $[\alpha]_D^{25} -18.91$  (c 0.1 CHCl<sub>3</sub>); IR (KBr): 1710, 1680, 1730, 2369, 2926 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.18-2.30 (1H, m, H-6), 2.61-2.77 (1H, m, H-6'), 2.80-2.92 (1H, m, H-7), 3.00-3.16 (1H, m, H-7'), 3.78-3.90 (1H, m, H-5), 5.00 (1H, s, C-2) 7.10-7.60 (5H, m, ArH); MS: *m/z* 218(M+1), 203, 207, 105, 91. Anal. Calcd for C<sub>12</sub>H<sub>11</sub>NO<sub>3</sub>: C, 66.36; H, 4.7; N, 5.98. Found: C, 66.32; H, 4.45; N, 5.72%

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