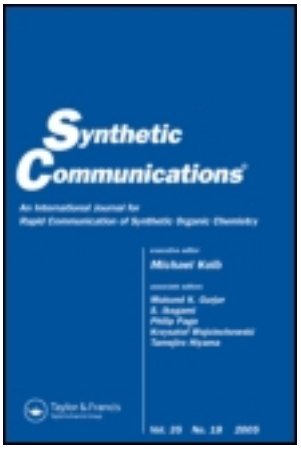


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Straightforward and Facile Approach Toward the N-Derivatization of Pyroglutamates Through Mitsunobu Reaction: Synthesis of N-Alkyl/N-Acyl Pyroglutamates

Sharad Kumar Panday [a], Jagdish Prasad [a] & Manoher Bhushan Pathak [a]

[a] Department of Chemistry, Faculty of Engineering and Technology, M. J. P. Rohilkhand University, Bareilly, India

Accepted author version posted online: 30 Jun 2011.Published online: 08 Jun 2011.

To cite this article: Sharad Kumar Panday , Jagdish Prasad & Manoher Bhushan Pathak (2011) Straightforward and Facile Approach Toward the N-Derivatization of Pyroglutamates Through Mitsunobu Reaction: Synthesis of N-Alkyl/N-Acyl Pyroglutamates, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:24, 3654-3661, DOI: 10.1080/00397911.2010.519844

To link to this article: http://dx.doi.org/10.1080/00397911.2010.519844

Synthetic Communications®, 41: 3654–3661, 2011

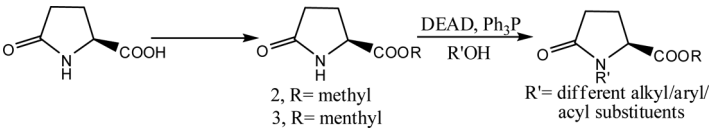
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.519844

STRAIGHTFORWARD AND FACILE APPROACH TOWARD THE N-DERIVATIZATION OF PYROGLUTAMATES THROUGH MITSUNOBU REACTION: SYNTHESIS OF N-ALKYL/N-ACYL PYROGLUTAMATES

Sharad Kumar Panday, Jagdish Prasad, and Manoher Bhushan Pathak

Department of Chemistry, Faculty of Engineering and Technology, M. J. P. Rohilkhand University, Bareilly, India

GRAPHICAL ABSTRACT



Abstract *Pyroglutamates have been acknowledged as useful chiral synthons for the synthesis of many bioactive natural products, ACE inhibitors, and conformationally constrained peptides. Though the reactivity differences between two differential carbonyl groups have been well exploited, there is still a dearth of publications on the N-alkylation/acylation of native pyroglutamate as such, due to the relatively low reactivity of NH of pyroglutamates. In the present communication, we report for the first time a simple and efficient methodology for the N-alkylation/acylation of pyroglutamate via Mitsunobu reaction.*

Keywords Acylation; alkylation; lactam NH; Mitsunobu reaction; pyroglutamates

INTRODUCTION

Pyroglutamates/N-substituted pyroglutamates have emerged as useful chiral synthons for the synthesis of many bioactive natural products such as anatoxin,[1] bulgecinine,[2] salinosporamide,[3] ACE inhibitors,[4,5] and conformationally constrained peptides.[6,7] Pyroglutamic acid has two differential carbonyl groups, a carboxyl and a lactam carbonyl, and the reactivity differences between these two differential carbonyl groups have been well investigated. Although good synthetic procedure are available for the synthesis of 2,[8,9] 3,[10] 4,[11,12] or 5[13–15] substituted pyroglutamates, the same is not true for the N-alkylation/acylation of

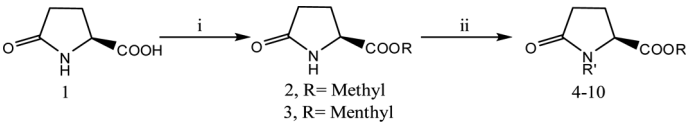
Received December 18, 2009.
Address correspondence to Sharad Kumar Panday, Department of Chemistry, Faculty of Engineering and Technology, M. J. P. Rohilkhand University, Bareilly, U. P., India. E-mail: skpandey@mjpru.ac.in; drsharadpandey@yahoo.com

pyroglutamates.[16] Even though N-acylated/alkylated pyroglutamates are essential components of many bioactive products, such as fosinopril,[17–20] and have been used efficiently as chiral auxiallaries[21] pertaining to the synthesis of variety of natural/bioactive compounds, yet a facile synthetic route for the N-acylation/alkylation of lactam NH of pyroglutamate is still in demand. That prompted us to study the Mitsunobu reaction of pyroglutamates with acids and alcohols with the objective of exploring the possibility of developing an efficient procedure for the N-acylation/alkylation of pyroglutamates.

In our ongoing program toward the synthesis of bioactive molecules from pyroglutamates, we were interested in investigating a simple strategy for the N-derivatization of pyroglutamates, especially so when earlier literature procedures for N-acylation of pyroglutamates were not very encouraging in our case.[22] Further, because racemization at C-2 of pyroglutamate or other centers in substituted pyroglutamates was also a distinct possibility under the usual basic conditions, it was truly demanding to develop a procedure for N-alkylation/acylation of pyroglutamates that would give satisfactory results at room temperature and not require drastic basic conditions, thereby eliminating the possibility of any racemization. Based on these presumptions, we attempted N-alkylation/acylation of pyroglutamate through the Mitsunobu reaction.

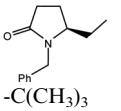
The Mitsunobu reaction offers a unique methodology for the condensation of various nucleophiles with alcohols in the presence of diethylazodicarboxylate (DEAD) and triphenyl phosphine (Ph_3P), leading to esters, phenyl ethers, and various other compounds, and it has been well documented.[23–26] However, to the best of our knowledge, there has been no report describing this reaction between lactam NH of pyroglutamate and alcohol or carboxylic acids under Mitsunobu conditions,[27] which prompted us to explore the possibility of alkylation/acylation of lactam NH of pyroglutamate where the amine part was replaced by pyroglutamate.

In the present communication, we describe our attempts at the N-alkylation/acylation of pyroglutamates, taking advantage of Mitsunobu reaction, where we modified the reactants by replacing the amine component in the usual Mitsunobu reaction with pyroglutamates. Thus, pyroglutamate, was allowed to react with alcohols/acids in the presence of DEAD and Ph_3P using tetrahydrofuran (THF) as a solvent. To check the feasibility of the reaction, methyl (2S)-pyroglutamate **(2)** (1 eq) was allowed to react with benzyl alcohol (1.2 eq) in the presence of DEAD (1.4 eq) and Ph_3P (1.4 eq) using THF as a solvent, and N-benzyl-methyl (2S)-pyroglutamate **(4)** was obtained in 52% yield. The structural assignment was made on the basis of ^{1}HNMR, which was in consonance with the reported values.[28] The absence of a signal for NH proton and the presence of peaks in ^{1}H NMR at δ 4.0 ppm and δ 5.03 ppm respectively for benzylic protons was clear evidence for the successful replacement of the NH proton of pyroglutamate by a benzylic moiety under Mitsunobu conditions. Comparison of optical rotation with the reported value excluded the possibility of any racemization during the reaction. To ascertain further that no racemization/epimerization had occurred during the reaction, chiral high-performance liquid chromatography (HPLC) was also performed for compound (4), which showed the presence of exclusively one enantiomer with more than 90% overall purity. This eliminated the possibility of any racemization/epimerization during the reaction.



Scheme 1. Reactions and reagents: 1, $SOCl_2$, THF and M_eOH for **2** or menthol for **3**; 2, DEAD, Ph_3P, THF, and R^1-OH.

Table 1. Various N-alkyl/acyl pyroglutamates

Compound	R	R^1
4	Methyl	$-CH_2Ph$
5	Methyl	$-COCH_2Ph$
6	Menthyl	$-CH_2Ph$
7	Menthyl	
8	Menthyl	$-C(CH_3)_3$
9	Menthyl	$-COCH_2Ph$
10	Menthyl	-COPh

To standardize the methodology and explore the scope of this reaction, various N-alkylation/acylations using different alcohol/acids were attempted, where the desired N-alkyl/acyl derivatives were obtained in reasonable yields. The results of different N-alkylation/acylations attempted on pyroglutamates have been summarized in Scheme 1 and Table 1.

These results demonstrate the simple and efficient approach for the N-alkylation/acylation of pyroglutamates for which not many reports are available in literature because of the relatively low reactivity of NH of pyroglutamate toward further reactions. Further studies on the development of bioactive molecules taking advantage of this N-alkylation/acylation procedure are in progress and shall be reported in due course.

EXPERIMENTAL

Spectral data were recorded as follows: Perkin-Elmer (FTIR), Jeol SX-102 (FAB) (MS), Bruker Advance 400 (^{1}H NMR and ^{13}C), Rudolf Autopol III polarimeter (optical rotation), Elementar Vario EL III. Dry THF was used wherever required. Chiral HPLC was performed on a D-7000 HPLC manager report system-using column chiral 1C and hexane as solvent.

Methyl (2S) Pyroglutamate (2)

Methyl (2S)-pyroglutamate (**2**) was prepared from pyroglutamic acid (**1**) (6.45 g, 0.05 mol, 1.0 equivalent) according to procedure described in literature and was obtained as a colorless oil. Yield: 5.75 g (80%). Data of this compound were identical with the reported values.[28]

Menthyl (2S)-Pyroglutamate (3)

Pyroglutamic acid (6.45 g, 0.05 mol, 1.0 equivalent) was dissolved in dry THF (15 mL), and thionyl chloride (4 mL, 0.55 mol, 1.1 equivalent) was added dropwise at 0 °C while stirring the reaction mixture. When addition was complete, the mixture was stirred at room temperature for 2 h, and the solvent was evaporated under vacuum to get crude pyroglutamoyl chloride (7.35 g), which was used as such for esterification. In another flask, menthol (8.2 g, 0.053 mol, 1.1 eq) was dissolved in dry THF (10 mL), and triethylamine was added to it, followed by dropwise addition of a solution of pyroglutamoyl chloride (7.35 g, 0.048 mol, 1.0 equivalent) in THF at 0 °C. When the addition was complete, the mixture was stirred at room temperature for 2 h. Progress of the reaction was monitored by thin-layer chromatography (TLC). At the completion of reaction, the solvent was evaporated under vacuum and the reaction was quenched with water (10 mL). The reaction mixture was extracted twice with ethyl acetate (2×25 mL). The combined ethyl acetate layer was washed with saturated NaCl solution (15 mL), dried over Na_2SO_4, concentrated, and purified by column chromatography using 20% EtOAc–hexane as eluent to afford the pure compound **3** as a colorless oil, Yield: 9.0 g (70%); IR (KBr): 1695, 1705, 2985, 3018 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.78 (3H, d, $\underline{J} = 7.5$ Hz,C$\underline{H}_3$), 0.93 (6H, m, C$\underline{H}_3$), 1.0–1.97 (9H, m, menthyl), 2.08–2.12 (1H, m, H-3), 2.26–2.43 (1H, m, H-3′), 3.28–3.36 (1H, m, H-4), 3.48–3.58 (1H, m, H-4′), 4.00–4.18 (1H, m, H-2), 4.66 (1H, m, OCH) 6.90 (br s, NH); MS (m/z): 268 (M + 1), 221, 154, 130 128.

General Procedure for N-Acylation/Alkylation of Pyroglutamates

Methyl (2S)-pyroglutamate (**2**) or menthyl (2S)-pyroglutamate (**3**) (1.0 equivalent) was dissolved in dry THF (5 mL), DEAD (1.4 equivalent), and Ph_3P (1.4 equivalent) and then added to the solution of **2** or **3** and stirred for 30 min at room temperature. After 30 min alcohol or acid (1.2 equivalent) in THF (5 mL) was added to it, and the reaction mixture was stirred at room temperature for 7 h. Progress of the reaction was monitored by TLC. At the completion of the reaction, the solvent was evaporated under vacuum, poured into water (15 mL), and extracted twice with ethyl acetate (2×20 mL). The combined ethyl acetate layer was washed with saturated NaCl solution (10 mL), dried over Na_2SO_4, concentrated and purified by column chromatography on silica using 20% EtOAc–hexane as eluent to afford the pure compounds **4**–**10**. Chiral purity of the reaction product was ascertained by performing chiral HPLC experiment for compounds **4** and **6** using column chiral 1C where only one single prominent peak was observed in the spectrum. That was enough evidence to ascertain the desired stereochemistry without any racemization or epimerization.

Methyl (2S)-N-Benzyl Pyroglutamate (4)

Compound **4** was prepared from methyl (2S)-pyroglutamate **(2)** (1.0 g, 7.0 mmol) and benzyl alcohol (0.910 g, 8.43 mmol) and was obtained as an oil. Yield: 830 mg (52%); $[\alpha]_D^{25} + 2.85$ (c 0.1, $CHCl_3$), reported $[\alpha]_D^{25} + 3.5$ (c 1, MeOH);[28] IR (KBr): 1680, 1745, 2920 and 3450 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.02–2.12 (1H, m, H-3),

2.19–2.32 (1H, m, H-3′), 2.37–2.45 (1H, m, H-4), 2.52–2.63(1H, m, H-4′), 3.63 (3H, s, OCH_3), 3.95–4.05 (2H, m, H-2 + PhC$\underline{H}_2$), 5.03 (1H, d, $\underline{J}$ = 16.0 Hz, PhC$\underline{H}_2$′) 7.16–7.35 (5H, m, Ar$\underline{H}$); MS: m/z 233 (M^+) Analysis for $C_{13}H_{15}O_3N$, calculated: C, 66.95; H, 6.44; N, 6.00. Found: C, 66.73; H, 6.28; N, 6.24.

Methyl (2S)-N-Phenyl Acetyl Pyroglutamate (5)

Compound **5** was prepared from methyl (2S)-pyroglutamate **(2)** (1.0 g, 7.0 mmol) and phenyl acetic acid (1.141 g, 8.38 mmol) and was obtained as an oil. Yield: 445 mg (39%); $[\alpha]_D^{25}$ − 3.34 (c 0.1, $CHCl_3$); IR (KBr): 1687, 1732, 2957 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.02–2.12 (1H, m, H-3), 2.19–2.32 (1H, m, H-3′), 2.37–2.45 (1H, m, H-4), 2.52–2.63 (1H, m, H-4′), 3.64 (3H, s, OCH_3), 4.18–4.31 (2H, m, H-2 + PhC$\underline{H}_2$), 4.38–4.43 (1H, d, J = 16.5, PhC$\underline{H}_2$′), 7.24–7.36 (5H, m, Ar$\underline{H}$); MS: m/z 267 (M+), 221, 207, 118. Analysis for $C_{14}H_{15}O_4N$, calculated: C, 64.37; H, 5.75; N, 5.36. Found: C, 64.55; H, 5.91; N, 5.29.

Menthyl (2S)-N-Benzyl Pyroglutamate (6)

Compound **6** was prepared from menthyl (2S)-pyroglutamate **(3)** (1.0 g, 3.75 mmol) and benzyl alcohol (0.487 g, 4.50 mmol) as described perviously and was obtained as an oil. Yield: 775 mg (58%); $[\alpha]_D^{25}$ − 18.91 (c 0.1 $CHCl_3$); IR (KBr): 1710, 2985, 3018 cm^{-1}; ^{1}H NMR ($CDCl_3$): ^{1}H NMR ($CDCl_3$): δ 0.78 (3H, d, J = 7.5 Hz,C$\underline{H}_3$), 0.82 (6H, m,C$\underline{H}_3$), 1.0–1.91 (9H, m, menthyl), 1.97–2.05 (1H, m, H-3), 2.19–2.30 (1H, m, H-3′), 2.35–2.45 (1H, m, H-4), 2.51–2.57 (1H, m, H-4′), 3.84–3.87 (1H, d, J = 16.5 Hz, PhC$\underline{H}_2$), 3.89–3.92 (1H, m, H-2) 4.70–4.78 (1H,m, OC$\underline{H}$) 5.13–5.17 (1H, d, J = 16.5 Hz, PhC$\underline{H}_2$′), 7.18–7.37 (5H, m, Ar$\underline{H}$); ^{13}C NMR ($CDCl_3$): δ 16.19, 20.69, 21.93, 22.84, 23.23, 26.31, 29.62, 31.34, 34.05, 40.58, 45.49, 46.85, 58.68, 75.43, 127.79, 128.35, 128.72, 135.79, 171.33, 175.01; MS (m/z): 358 (M + 1), 356 (M−1) 220, 218, 174, 91. Analysis for $C_{22}H_{31}O_3N$, calculated: C, 73.95; H, 8.68; N, 3.92. Found: C, 74.02; H, 8.76; N, 4.13.

Menthyl (2S)-N-[N′-Benzyl-meth-5′-yl-pyrrolidine-2′-one] Pyroglutamate (7)

Compound **7** was prepared from menthyl (2S)-pyroglutamate **(3)** (1.0 g, 3.75 mmol) and N-benzyl pyroglutaminol (0.922 g, 4.5 mmol) and was obtained as an oil. Yield: 700 mg, (41%); $[\alpha]_D^{25}$ − 111.32 (c 0.1, $CHCl_3$); IR(KBr): 1702, 1732, 2958, 3017 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.73–0.79(3H, d, $\underline{J}$ = 7.5 Hz, C$\underline{H}_3$), 0.84–1.14 (9H, m, C$\underline{H}_3$+menthyl), 1.23–1.56 (6H, m, menthyl), 1.65–2.05 (4H, m, H-3 and H-3′ of menthyl pyroglutamate as well as H-4 and H-4′ of N-benzyl meth-5′-yl pyrrolidine-2-one), 2.13–2.24 (1H, m, H-5 of N-benzyl pyrrolidine-2-one), 2.34–2.40 (2H, m, H-4 of menthyl pyroglutamate H-3 of N-benzyl meth-5′-yl pyrrolidine-2-one), 2.43–2.54 (2H, m, H-4′ of menthyl pyroglutamate as well as H-3′ of N-benzyl meth-5′-yl pyrrolidine-2-one), 3.97–4.04 (2H, m, H-2 + PhC$\underline{H}_2$), 4.18–4.26 (2H, m, N-C$\underline{H}_2$), 4.71–4.78 (1H, m, OCH), 4.97–5.04(1H, d, J = 16.5, PhC$\underline{H}_2$′); 7.18–7.35 (5H, m, Ar$\underline{H}$); MS (m/z): 536, 268, 266, 207, 130, 128, 91. Analysis for $C_{27}H_{38}O_4N_2$, calculated: C,71.37; H, 8.37; N, 6.17. Found: C, 71.21; H, 8.47; N, 6.10.

Menthyl (2S)-N-*t*-Butyl Pyroglutamate (8)

Compound **8** was prepared from menthyl (2S)-pyroglutamate **(3)** (1.0 g, 3.75 mmol.) and t-butyl alcohal (0.335 g, 4.50 mmol) as described previously and was obtained as an oil. Yield: 581 mg (48%); $[\alpha]_D^{25} - 134.24$ (c 0.1 $CHCl_3$); IR (KBr): 1734, 2959, 3022 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.78 (3H, d, $J = 7.5$ Hz,C$\underline{H}_3$), 0.82 (6H, m,C$\underline{H}_3$), 1.0–1.89, (18H, m, menthyl + *t*-butyl), 1.92–2.08 (2H, m, H-3), 2.31–2.47 (1H, m, H-4), 2.51–2.64 (1H, m, H-4′), 4.63–4.67 (1H,m, H-2) 4.73–4.82 (1H, m, OC$\underline{H}$); MS (*m/z*): 340 ($M + H_2O$), 324 (M+), 278, 267, 202. Analysis for $C_{19}H_{33}O_3N$, calculated: C, 70.58; H, 10.21; N, 4.33. Found: C, 70.70; H, 10.11; N, 4.50.

Menthyl (2S)-N-Phenyl Acetyl Pyroglutamate (9)

Compound **9** was prepared from menthyl (2S)-pyroglutamate **(3)** (1.0 g, 3.75 mmol) and phenyl acetic acid (0.622 g, 4.50 mmol) and was obtained as an oil. Yield: 950 mg (66%); $[\alpha]_D^{25} - 33.74$ (c 0.1 $CHCl_3$); IR (KBr): 1720, 1754, 3023 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.78 (3H, d, $J = 7.5$ Hz,C$\underline{H}_3$), 0.93(6H, m, C$\underline{H}_3$), 1.0–1.91, (9H, m, menthyl), 1.97–2.05 (1H, m, H-3), 2.19–2.30 (1H, m, H-3′), 2.35–2.45 (1H, m, H-4), 2.51–2.57 (1H, m, H-4′), 3.62–3.68 (1H, d, $J = 24$ Hz, PhC$\underline{H}_2$), 4.17–4.24 (2H,m, H-2, OC$\underline{H}$), 4.38–4.42(1H, d, $J = 16.5$, PhC$\underline{H}_2$′); 7.23–7.35 (5H, m, Ar$\underline{H}$); MS (*m/z*): 413, 295, 118, 91. Analysis for $C_{23}H_{31}O_4N$, calculated: C, 71.68; H, 8.05; N, 3.74, Found: C, 71.90; H, 7.91; N, 3.89.

Menthyl (2S)-N-Phenyl Carbonyl Pyroglutamate (10)

Compound **10** was prepared from menthyl (2S)-pyroglutamate **(3)** (1.0 g, 3.75 mmol) and benzoic acid (0.550 g, 4.50 mmol) as described previously and was obtained as an oil. Yield: 723 mg (52%); $[\alpha]_D^{25} - 109.37$ (c 0.1 $CHCl_3$); IR (KBr): 1710, 2985, 3018 cm^{-1}; ^1H NMR ($CDCl_3$): ^1H NMR ($CDCl_3$): δ 0.85 (3H, d, $J = 7.5$ Hz,C$\underline{H}_3$), 0.91 (6H, m,C$\underline{H}_3$), 1.0–1.86, (9H, m, menthyl), 2.06–2.12 (2H, m, H-3), 2.33–2.45 (1H, m, H-4), 2.52–2.56 (1H, m, H-4′), 4.15–4.22 (2H, m, H-2 + OC$\underline{H}$); 7.41–8.06 (5H, m, Ar$\underline{H}$); MS (*m/z*): 385, 383, 356, 327, 251, 237, 207, 191, 105. Analysis for $C_{22}H_{29}O_4N$, calculated: C, 71.16; H, 7.82; N, 3.77. Found: C, 71.35; H, 8.00; N, 3.67.

ACKNOWLEDGMENTS

We are extremely thankful to the University Grants Commission for financial assistance in form of a major research project and to SAIF, Central Drug Research Institute, Lucknow, for providing all the spectral data.

REFERENCES

1. Peterson, J. S.; Fels, G.; Rapoport, H. Chirospecific synthesis of (+) and (−)-anatoxin a. *J. Am. Chem. Soc.* **1984**, *106*, 4539–4547.
2. Panday, S. K.; Langlois, N. An efficient straight forward synthesis of (−)-bulgecinine. *Synth. Commun.* **1997**, *27* (8), 1373–1384.

3. Caubert, V.; Masse, J.; Retailleau, P.; Langlois, N. Stereoselective formal synthesis of the potent proteasome inhibitors: Salinosporamide A. *Tetrahedron Lett*. **2007**, *48*, 381–384 and references cited theirin.
4. Imaki, K.; Sakuyama, S.; Okada, T.; Toda, M.; Hayashi, M.; Miyamoto, T.; Kawasaki, A.; Okegawa, T. Potent orally active inhibitors of angiotensin-converting enzyme (ACE). *Chem. Pharm. Bull* **1981**, *29*, 2210–2214.
5. Panday, S. K.; Dikshit, M.; Dikshit, D. K. Synthesis of N-[30-(acetylthio)alkanoyl] and N-[30-mercaptoalkanoyl]-4-*a*(s)-(phenylmethyl) pyroglutamic acids and prolines as potent ACE inhibitors. *Med. Chem. Res.* **2009**, *18*, 566–578.
6. Thaisrivongs, S.; Pals, D. T.; Turner, S. R.; Kroll, L. T. Conformationally constrained rennin inhibitory peptides: Gammalactam-bridged dipeptide isostere as conformational restriction. *J. Med. Chem.* **1988**, *31*, 1369–1376.
7. Yu, K. L.; Rajakumar, G.; Srivastava, L. K.; Mishra, R. K.; Johnson, R. L. Dopamine receptor modulation by conformationally constrained analogues of Pro-Leu-gly-NH_2. *J. Med. Chem.* **1988**, *31*, 1430–1436.
8. Stevens, C. V.; Rammeloo, T.; Kimpe, N. D. Directing the resioselectivity of the alkylation of pyroglutamates carbamates by formation of a stable counter-ion complex. *Synlett.* **2001**, *10*, 1519–1522.
9. Dikshit, D. K.; Maheshwari, A.; Panday, S. K. Self-reproduction of chirality in pyroglutamates: Reactions at α-position with electrophiles. *Tetrahedron Lett.* **1995**, *36*, 6131–6134.
10. Herdeis, C.; Kelm, B. A stereoselective synthesis of 3-substituted(S)-pyroglutamic and glutamic acids via OBO ester derivatives. *Tetrahedron* **2003**, *59*, 217–219.
11. Dikshit, D. K.; Panday, S. K. Aldol reactions of pyroglutamates: Chiral synthesis of 4-α (S)-and 4-β(R)-arylmethyl pyroglutamates. *J. Org. Chem.* **1992**, *57*, 1920–1924.
12. Dieltiens, N.; Stevens, C. V.; Masschelein, K. G. R.; Rommeloo, T. [1,2] Boc migration during pyroglutamate alkylations. *Tetrahedron* **2005**, *61*, 6749–6756 and references cited their in.
13. Hussaini, S. R.; Moloney, M. G. 2,5-Disubstituted pyrrolidines: Synthesis by enamine reduction and subsequent regioselective and diastereoselective alkylations. *Org. Biomol. Chem.* **2006**, *4*, 2600–2615.
14. Hussaini, S. R.; Moloney, M. G. CIS-selective synthesis of 2,5-disubstituted pyrrolidines. *Tetrahedron Lett.* **2004**, *45*, 1125–1127.
15. Agarwal, V. K.; Astle, C. J.; Iding, H.; Werz, B.; Evans, M. R. Separation of pyrrolidines allylation products by diastereoselective enzymatic hydrolysis. *Tetrahedron Lett.* **2005**, *46*, 945–947.
16. Bourry, A.; Rigo, B.; Sanz, G.; Couturier, D. Studies on pyrrolidinones: Some attempts to improve the anticancer properties of methyl N-(3,4,4′,5-tetramethoxybenzhydryl) pyroglutamate (HEI81). *J. Heterocyclic Chem.* **2002**, *39*, 119–124 and references cited their in.
17. Krapcho, J.; Turk, C.; Cushman, D. W.; Powell, J. R.; Deforrest, J. M.; Spitzmiller, E. R.; Karanewsky, D. S.; Duggan, M.; Rovnyak, G.; Schwartz, J.; Natrajan, S.; Godfrey, J. D.; Ryono, D. E.; Neubeck, R.; Atwal, K. S.; Petrillo, E. W. Jr. Angiotensin-converting enzyme inhibitors, mercaptan, carboxyalkyl dipeptide and phosphinic acid inhibitors incorporating 4-substituted prolines. *J. Med. Chem.* **1988**, *31* (6), 1148–1160.
18. Smith, E. M.; Swiss, G. F.; Neustadt, B. R.; McNamara, P.; Gold, E. H.; Sybertz, E. J.; Baum, T. Angiotensin converting enzyme inhibitors: spirapril and related compounds. *J. Med. Chem.* **1989**, *32*, 1600–1606.
19. Smith, E. M.; Swiss, G. F.; Neustadt, B. R.; Gold, E. H.; Sommer, J. A.; Brown, A. D.; Chiu, P. J. S.; Moran, R.; Sybertz, E. J.; Baum, T. J. Synthesis and pharmacological activity of angiotensin-converting enzyme inhibitors: N-(Mercaptoalkanoyl)-4-substituted-(S)-prolines. *J. Med. Chem.* **1988**, *31* (4), 875–885.

20. Thottahil, J. K.; Moniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P. J. Conversion of L-pyroglutamic acid to 4-alkyl substituted-L-prolines: The synthesis of trans-4-cyclohexyl-L-proline. *J. Org. Chem.* **1986**, *51*, 3140–3143.
21. Panday, S. K.; Prasad, J.; Dikshit, D. K. Pyroglutamic acid: A unique chiral synthon. *Tetrahedron Asymmetry* **2009**, *20*, 1581–1632 and references sited therein.
22. Rigo, B.; Lespagnol, C.; Pauly, M. Studies on pyrrolidinones: Synthesis of N-acyl pyroglutamic esters with bactericide and fungicide properties. *J. Heterocycl. Chem.* **1988**, *25* (1), 49–59.
23. Hughes, D. L. The Mitsunobu Reaction. *Org. React.* **1992**, *42*, 335–656.
24. But, T. Y. S.; Toy, P. H. Organocatalytic mitsunobu reaction. *J. Am. Chem. Soc.* **2006**, *128*, 9636–9637 and references cited there in.
25. Lepore, S. D.; He, Y. Use of sonication for the coupling of sterically hindered substrates in the phenolic Mitsunobu reaction. *J. Org. Chem.* **2003**, *68*, 8261–8263.
26. Olofsson, B.; Wijtmans, R.; Somfai, P. Synthesis of N-H vinylaziridines: A comparative study. *Tetrahedron* **2002**, *58*, 5979–5982.
27. Sen, S. E.; Roach, S. L. A convenient two - step procedure for the synthesis allylic amines from allylic alcohols. *Synthesis* **1995**, 756–758.
28. Mavromoustakos, T.; Minakakis, P. M.; Kokotos, C. G.; Kontogianni, P.; Politi, A.; Zoumpoulakis, P.; Findlay, J.; Cox, A.; Balmforth, A.; Zoga, A.; Iliodromitis, E. Synthesis, binding studies, and in vivo biological evaluation of novel nonpeptide antihypertensive analogues. *Bioorg. Med. Chem.* **2006**, *14*, 4353–4360.