Med Chem Res (2012) 21:321–324
DOI 10.1007/s00044-010-9536-6

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

An efficient and straight forward synthesis of (5S)-1-benzyl-5-(1H-imidazol-1-ylmethyl)-2-pyrrolidinone (MM1): a novel antihypertensive agent

Jagdish Prasad · Manoher Bhushan Pathak · Sharad Kumar Panday

Received: 12 January 2010 / Accepted: 3 December 2010 / Published online: 4 January 2011

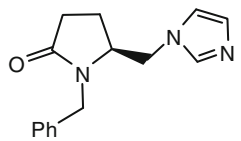
Abstract (5S)-1-benzyl-5-(1H-imidazol-1-ylmethyl)-2-pyrrolidinone and its closely related analog was synthesized from (S)-pyroglutaminol and imidazole or substituted imidazole using Mitsunobu reaction as the key step.

Keywords Hypertension · Angiotensin-II · AT_1 antagonists · MM1 · Mitsunobu reaction · *N*-benzyl-5(S)-pyroglutaminol

Introduction

Hypertension is a major health risk factor in the developed as well as developing countries and has been the target of recent trends in the rational drug design (Laragh, 1980). One of the biological mechanisms playing key role in controlling hypertension is the renin-angiotensin system. Angiotensin-II (A-II), a potent vasoconstructive octapeptide, is formed in the renin-angiotensin system and plays vital role in regulating blood pressure (Burnier and Brunner, 1999; Corvol, 1989; Gavras *et al*., 1978).

The observations prompted researchers to study and control hypertension by competing Ang II binding to AT_1 receptors and that led to the development of Losartan (Duncia *et al*., 1990; Carini *et al*., 1990; Polevaya *et al*., 2001; Roumelioti *et al*., 2002), Sartans, and several other analogs as AT_1 antagonists (Abston, 1994; De Casparo *et al*., 2000; Easthope and Jarvis, 2002; Millard *et al*., 2000; Rippin *et al*., 2002). Further studies taking into account the stereochemical considerations have led to the discovery of some other A-II antagonists such as Sarmesin, Sarilesin, and various other peptides (Matsoukas *et al*., 1994; Mavromoustakos *et al*., 2004). Recent studies based on Losartan and the model proposed for Sarmesin led to the discovery of (5S)-1-benzyl-5-(1H-imidazol-1-ylmethyl)-2-pyrrolidinone (MM1) **1** as novel AT_1 antagonist (Mavromoustakos *et al*., 2006). The synthesis and biological properties of MM1 **1** have been reported where it was observed that MM1 mimics conformational characteristics of His6-Pro7-Phe8 and It has been claimed undoubtedly as the first lead compound in controlling hypertension.



MM1, 1

The only reported synthesis (Moutevelis-Minakakis *et al*., 2003; Mavromoustakos *et al*., 2006) of MM1 involved conversion of (S)-pyroglutaminol to its *o*-tosyl derivative followed by reaction with lithium imidazole thereby furnishing MM1 through nucleophilic/substitution elimination sequences. However, an alternate synthetic pathway which could be easily accessible was still demanding and therefore, it was of particular interest to explore an alternate synthetic pathway for MM1 which could furnish the target molecule in a simple and straight forward manner avoiding unnecessary steps in between and in turn should be more useful. These observations coupled with the novel antihypertensive activity associated with AT_1 antagonist MM1, encouraged the authors to develop a simple and efficient synthetic strategy for such an important bioactive molecule.

J. Prasad · M. B. Pathak · S. K. Panday (✉)
Department of Chemistry, Faculty of Engineering and Technology, M. J. P. Rohilkhand University, Bareilly, UP, India
e-mail: skpandey@mjpru.ac.in; drsharadpandey@yahoo.com

Chemistry

The proposed plan of this study was to investigate a simple approach starting with (2S)-pyroglutamic acid derivative whose synthetic potential has been well documented (Panday *et al*., 2009).

It was thought of interest to obtain **1** involving Mitsunobu reaction (Hughes, 1992; But and Toy, 2006; Lepore and He, 2003; Olofsson *et al*., 2002; Sen and Roach, 1995) of *N*-benzyl-5(S)-pyroglutaminol with imidazole or substituted imidazole. Mitsunobu reaction offers a unique methodology for the reaction of alcohols with amines, acids, or other nucleophiles, thereby furnishing a wide variety of compounds. Eventhough various literature reports exist where primary amines, secondary amines, or amides have been used in Mitsunobu reaction with alcohols, but there is no report till date where imidazole (Kim *et al*., 2005) has been used in place of amines in the above reaction with pyroglutaminol (Altman *et al*., 1993) and therefore, it was interesting to study the Mitsunobu reaction of *N*-benzyl-5(S)-pyroglutaminol with imidazole and to observe the out come of the resultant reaction.

Based on above analogy, the reaction of *N*-benzyl-(5S)-pyroglutaminol with imidazole in presence of diethylazodicarboxylate (DEAD) and triphenylphosphine (Ph_3P) under Mitsunobu conditions was attempted, where MM1 **1** was obtained in 71% yield (Scheme 1). The structural assignment of compound **1** was done based on ^1H NMR which was in agreement to the assigned structure as well as to the reported values (Moutevelis-Minakakis *et al*., 2003; Mavromoustakos *et al*., 2006). The assigned structure was confirmed further by IR, MASS, and microanalysis.

To standardize the methodology, the reaction of *N*-benzyl-5(S)-pyroglutaminol with 2-methyl imidazole was also carried out under similar conditions as described for **1**, where (5S)-1-benzyl-5-(1H-2-methylimidazol-1-ylmethyl)-2-pyrrolidinone **5** was obtained in reasonable yield.

Conclusion

Thus, the authors have successfully explored for the first time the use of imidazole/substituted imidazole in Mitsunobu reaction with *N*-benzyl pyroglutaminol coupled with an efficient synthetic pathway for the novel antihypertensive agent MM1. These results of the above study clearly demonstrate the investigation of a simple and straight forward strategy for the synthesis of a potent antihypertensive agent MM1 (Mavromoustakos *et al*., 2006) and its closely related analog. These results would certainly be useful for exploiting further the application of this simple approach toward the synthesis of other closely related analogs as well.

Experimental section

Spectral data were recorded as follows: Perkin Elmer (FTIR); Jeol SX-102 (FAB) (MS); Bruker advance 300 (^1H NMR), Rudolf Autopol III polarimeter (optical rotation); Elementar Vario EL III, Elemental analysis. Dry THF was used in the reactions.

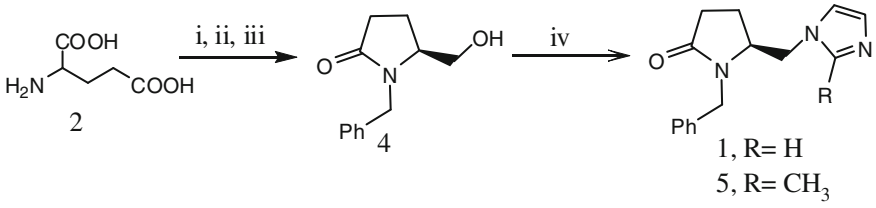
N-benzyl-(2S)-pyroglutamic acid (**3**)

N-benzyl-(2S)-pyroglutamic acid **3** was synthesized from L-glutamic acid **2** (14.7 g, 0.1 mol) and benzaldehyde (25.4 g, 0.24 mol,) using 2 N NaOH (170 ml) and $NaBH_4$ (1.2 equivalent, 4.6 g, 0.12 mol) accordingly to procedure as described in literature and obtained as white solid (Peterson *et al*., 1984). Yield: 15.3 g, 70%.

N-benzyl-(5S)-pyroglutaminol (**4**)

A solution of *N*-benzyl-(2S)-pyroglutamic acid **3** (6.5 g, 0.3 mol) was taken in MeOH (25 ml) and 2–3 drops of conc. H_2SO_4 were added. The solution was refluxed for 12 h. At the completion of the reaction, the reaction mixture was neutralized with saturated $NaHCO_3$ (15 ml), concentrated to remove excess methanol, and extracted with EtOAc. The combined organic layer was washed with saturated NaCl (15 ml), dried over Na_2SO_4, and concentrated under vacuum to get *N*-benzyl-(2S)-methyl pyroglutamate which was subsequently reduced to *N*-benzyl-(5S)-pyroglutaminol **4** as discussed below.

$NaBH_4$ (1.1 equivalent) was taken in THF and a solution of *N*-benzyl-(2S)-methyl pyroglutamate in THF (20 ml) was added dropwise. Once addition was complete, the reaction mixture was stirred at room temperature for 3 h. Progress of the reaction was monitored by TLC. At the



Scheme 1 *i* PhCHO, NaOH, and $NaBH_4$. *ii* H_2O, Heat, 15 h. *iii* MeOH/H^+, $NaBH_4$, and THF. *iv* DEAD, Ph_3P, imidazole or 2-methyl imidazole

completion of reaction, the mixture was quenched with acetic acid (20%) at −0°C. Excess of the acid was neutralized with saturated $NaHCO_3$ (15 ml) and extracted with EtOAc (20 ml). The organic layer was washed with water (20 ml), dried over Na_2SO_4, and evaporated to get *N*-benzyl-(5S)-pyroglutaminol **4**. Yield: 4.50 g, 73%, Spectral data were compared and found to be identical with reported values (Peterson *et al*., 1984).

General procedure for the Mitsunobu reaction of *N*-benzyl-(5S)-pyroglutaminol with imidazole/ substituted imidazole

N-benzyl-(5S)-pyroglutaminol **4** (1.0 equivalent) was dissolved in dry THF (5 ml), Diethylazodicarboxylate (DEAD) (1.4 equivalent) and triphenyl phosphine (Ph_3P) (1.4 equivalent) were added to the solution of **4** and stirred at room temperature for 30 min. After 30 min, imidazole or substituted imidazole (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^2). 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 compound **1** and **5**.

(5S)-1-benzyl-5-(1H-imidazol-1-ylmethyl)-2-pyrrolidinone (**1**)

It was prepared from *N*-benzyl-(5S)-pyroglutaminol **4** (1.0 g, 3.75 mmol) and imidazole (0.281 g, 4.13 mmol) as described above and was obtained as an oil. Yield: 678 mg (71%), $[\alpha]_D^{25}$ + 9.21 (c 0.1 $CHCl_3$); IR (KBr): 1666, 1720, 3019, and 3406 cm^{-1}; ^{1}H NMR($CDCl_3$): δ 1.86–2.12 (2H, m, H-4), 2.35–2.45 (1H, m, H-3), 2.51–2.57 (1H, m, H-3′), 3.78 (1H, m, H-5), 3.96 [1H, dd (J = 2.5 and 10 Hz, respectively), CH_2N], 4.05 (2H, m, CH_2^1 N, and CH_2Ph), 5.10 [1H, d (J = 15.1 Hz) CH_2^1Ph], 6.80 (1H, s, aromatic), 7.11–7.41 (7H, m, ArH); MS(*m*/*z*): 256(M + 1), 190, 91; Analysis for $C_{15}H_{17}N_3O$; Calculated: C,70.59; H, 6.67; N, 16.47; Found: C,70.49; H, 6.57; N, 16.67.

(5S)-1-benzyl-5-(1H-2-methylimidazol-1-ylmethyl)-2-pyrrolidinone (**5**)

It was prepared from *N*-benzyl-(5S)-pyroglutaminol **4** (1.0 g, 3.75 mmol) and 2-methyl imidazole (0.337 g, 4.10 mmol) as described above and was obtained as an oil. Yield: 675 mg (67%); $[\alpha]_D^{25}$ − 7.21 (c 0.1 $CHCl_3$); IR (KBr): 1660, 1710, 3020, and 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.95–2.12 (2H, m, H-4), 2.34–2.45 (1H, m, H-3), 2.52–2.63 (1H, m, H-3′), 3.47–3.60(4H, m, H-5 and CH_3), 3.76–3.80 [1H, dd (J = 2.5 and 10.5 Hz, respectively), CH_2N], 4.16–4.21 (2H, m, CH_2N and CH_2Ph), 4.93 [1H, d (J = 15.5 Hz), CH_2^1Ph], 7.20–7.60 (7H, m, ArH); MS(*m*/*z*): 270 (M + 1), 190, 91, 83; Analysis for $C_{16}H_{19}N_3O$; Calculated: C,71.38; H, 7.06; N, 15.61; Found: C,71.51; H, 7.23; N, 15.86.

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

References

Abston WT (1994) Non-peptide angiotensin II receptor antagonists. Expert Opin Invest Drugs 3:1105–1142

Altman J, Ben-Ishai D (1993) Synthesis of chiral 1,2,4-triaminobutanes. Tetrahedron: Asymmetry 4:91–100

Burnier M, Brunner HR (1999) Comparative antihypertensive effects of angiotensin II receptor antagonists. J Am Soc Nephrol 10(Suppl 12):S278–S282

But TYS, Toy PH (2006) Organocatalytic Mitsunobu reaction. J Am Chem Soc 128:9636–9637 (and references cited therein)

Carini DJ, Dunica JV, Johnson AL, Chiu AT, Price WA, Wong PC, Timmermans PBMWM (1990) Non-peptide angiotensin II receptor antagonists: *N*-[(benzyloxy) benzyl] imidazole and related compounds as potent antihypertensives. J Med Chem 33:1330–1336

Corvol P (1989) New therapeutic prospects of renin angiotensin system inhibition. Clin Exp Hypertens A 11(Suppl.2):463–470

De Casparo M, Catt KJ, Inagami T, Wright JW, Unger T (2000) The angiotensin II receptor antagonists. Pharmacol Rev 52:415–472

Duncia JV, Chiu AT, Carini DJ, Gregory GB, Johnson AL, Price WA, Wells GJ, Wong PC, Calabrese JC, Timmermans PBMWM (1990) The discovery of potent nonpeptide angiotensin II receptor antagonists: a new class of potent antihypertensives. J Med Chem 33:1312–1329

Easthope SE, Jarvis B (2002) Candesartan cilexetil: an update of its use in essential hypertension. Drugs 62(8):1253–1287

Gavras H, Brunner HR, Turini GA, Kershaw GR, Tifft CP, Cuttelod S, Gevras I, Vukovich RA, McKinstry DNN (1978) Antihypertensive effects of the oral angiotensin converting enzyme inhibitor SQ 14225 in man. New Eng J Med 298(18):991–995

Hughes DL (1992) The Mitsunobu reaction. Org React 42:335–656

Kim EJ, KO SY, Dziadulewicz EK (2005) Mitsunobu alkylation of imidazole: a convenient route to chiral ionic liquids. Tetrahedron Lett 46(4):631–633

Laragh JH (1980) In: Case DB (ed) Captopril and hypertension. Plenum, New York, p 173

Lepore SD, He Y (2003) Use of sonication for the coupling of sterically hindered substrates in the phenolic Mitsunobu reaction. J Org Chem 68:8261–8263

Matsoukas JM, Hondrelis J, Keramida M, Mavromoustakos T, Makriyannis A, Yamdagni R, Wu Q, Moore GJ (1994) Role of the NH2-terminal domain of angiotensin II (ANG II) and [Sar1]angiotensin II on conformation and activity. NMR evidence for aromatic ring clustering and peptide backbone folding compared with [des-1, 2, 3]angiotensin II. J Biol Chem 269:5303–5312

Mavromoustakos T, Zervou M, Zoumpoulakis P, Kyrikou I, Benetis NP, Polevaya L, Roumelioti P, Giatas N, Zoga A, Minakakis PM, Kolocouris A, Vlahakos D, Golic GS, Matsoukas J (2004) Conformation and bioactivity. Design and discovery of novel antihypertensive drugs. Curr Top Med Chem 4:385–401

Mavromoustakos T, Minakakis PM, Kokotos CG, Kontogianni P, Politi A, Zoumpoulakis P, Findlay J, Cox A, Balmforth A, Zoga A, Iliodromitis E (2006) Synthesis, binding studies, and in vivo biological evaluation of novel non-peptide antihypertensive analogues. Bioorg Med Chem 14:4353–4360

Millard MP, Rossat J, Beunner HR, Burnier M (2000) Tasosartan, Enoltasosartan, and angiotensin II receptor blockade: the confounding role of protein binding. J Pharmacol Exp Ther 295(2):649–654

Moutevelis-Minakakis P, Gianni M, Stougiannou H, Zoumpoulakis P, Zoga A, Vlahakos D, Iliodromitis E, Mavromoustakos T (2003) Design and synthesis of novel antihypertensive drugs. Bioorg Med Chem Lett 13:1737–1740

Olofsson B, Wijtmans R, Somfai P (2002) Synthesis of N–H vinylaziridines: a comparative study. Tetrahedron 58:5979–5982

Panday SK, Prasad J, Dikshit DK (2009) Pyroglutamic acid: a unique chiral synthon. Tetrahedron: Asymmetry 20:1581–1632 (and references cited therein)

Peterson JS, Fels G, Rapoport H (1984) Chirospecific synthesis of (+) and (−)-anatoxin a. J Am Chem Soc 106:4539–4547

Polevaya L, Mavromoustakos T, Zoumboulakis P, Golic GS, Roumelioti P, Giatas N, Mutule I, Keivish T, Vlahakos DV, Iliodromitis EK, Kremastinos DT, Matsoukas J (2001) Synthesis and study of a cyclic angiotensin II antagonist analogue reveals the role of pi*–pi* interactions in the C-terminal aromatic residue for agonist activity and its structure resemblance with AT(1) non-peptide antagonists. Bioorg Med Chem 9:1639–1647

Rippin J, Bain SC, Barbett AH (2002) Rationale and design of diabetics exposed to telmisartan and enalapril (DETAIL) study. J Diabet Complicat 16(3):195–200

Roumelioti P, Polevaya L, Zoumpoulakis P, Giatas N, Mutule I, Keivish T, Zoga A, Vlahakos D, Iliodromitis E, Kremastinos D, Grdadolnik SG, Mavromoustakos T, Matsoukas J (2002) Design, synthesis and biological evaluation of cyclic angiotensin II analogues with 3, 5 side-chain bridges. Role of C-terminal aromatic residue and ring cluster for activity and implications in the drug design of AT1 non-peptide antagonists. Bioorg Med Chem Lett 12:2627–2633

Sen SE, Roach SL (1995) A convenient two step procedure for the synthesis of allylic amines from allylic alcohols. Synthesis 756–758