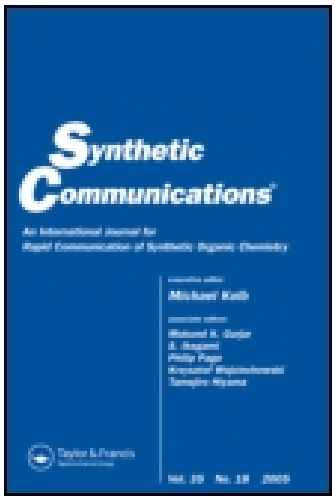


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Synthesis of Captopril Through a Baylis-Hillman Reaction

Melissa P. Feltrin [a] & Wanda P. Almeida [a]
[a] Instituto de Ciências da Saúde , Universidade Paulista , Campinas, SP, Brazil
Published online: 21 Aug 2006.

To cite this article: Melissa P. Feltrin & Wanda P. Almeida (2003) A Synthesis of Captopril Through a Baylis-Hillman Reaction, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:7, 1141-1146, DOI: 10.1081/SCC-120017189

To link to this article: http://dx.doi.org/10.1081/SCC-120017189

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 7, pp. 1141–1146, 2003

A Synthesis of Captopril Through a Baylis–Hillman Reaction

Melissa P. Feltrin and Wanda P. Almeida*

Instituto de Ciências da Saúde,
Universidade Paulista, Campinas, SP, Brazil

ABSTRACT

A synthesis of the antihipertensive amide **1**, named captopril, is described. The strategy is based on a Baylis–Hillman reaction between *N*-acryloylproline and formaldehyde. Subsequential diastereoselective hydrogenation step and functional group interconversion provided captopril in good overall yield.

Angiotensin-converting enzyme (ACE) inhibitors have been used for the treatment of high blood pressure.[1] Careful and extensive studies based on carboxypeptidase structure as a model for Zn^{2+} protease

*Correspondence: Wanda P. Almeida, Instituto de Ciências da Saúde, Universidade Paulista, Av. Comendador Enzo Ferrari 280, Swift, Campinas, SP, 13055-044–Brazil; E-mail: wciuffo@aol.com.

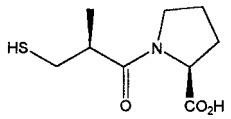
DOI: 10.1081/SCC-120017189 0039-7911 (Print); 1532-2432 (Online)

action[2] led to the synthesis of a small, potent and orally available inhibitor of ACE, named captopril (**1**, Fig. 1).[3]

In this work we report an alternative route (Sch. 1) to prepare **1**, based on a diastereoselective double bond hydrogenation of amide **2**, derived from *N*-acryloylproline **3**.

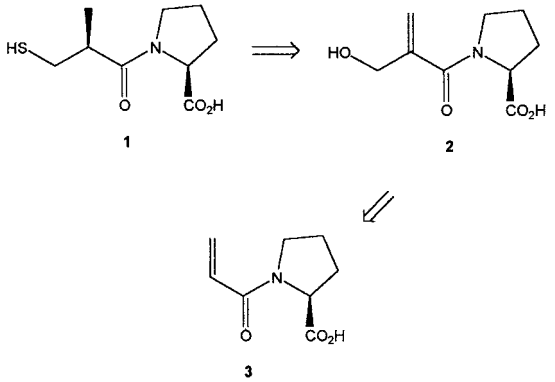
Captopril **1** contains two stereogenic carbon atoms. In our strategy, one of these is provided by (*S*)-proline, a natural aminoacid. The stereoselectivity in the hydrogenation step to generate the other chiral center is one of the synthetic challenges of this route. Our synthesis is illustrated in Sch. 2.

Amide **2** was readily prepared by a DABCO catalysed Baylis-Hillman reaction[4] between *N*-acryloylproline **3** and formaldehyde. *N*-acryloylproline **3** was obtained by treatment of acryloyl chloride with (*S*)-proline in the presence of potassium hydroxide[5] (Sch. 2). Compound **3** was then investigated as substrate for the Baylis–Hillman reaction. Acrylamides are reluctant substrates in this reaction.[4] After considerable experimentation under a variety of reaction conditions



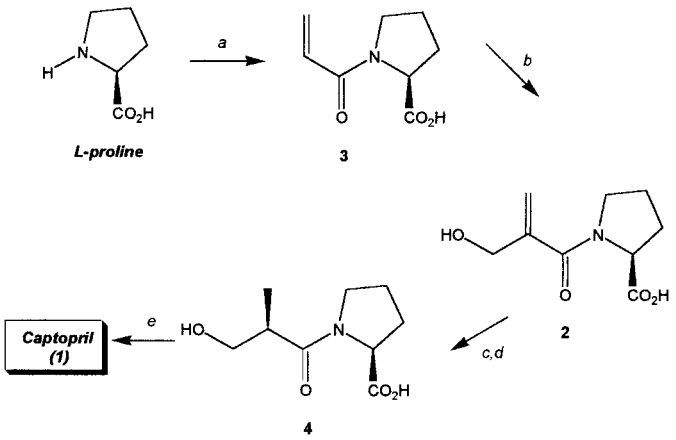
1

Figure 1. Captopril.



1 2 3

Scheme 1.



Scheme 2. Reagents and Conditions. *a:* KOH, H_2O-Acetone, $0^\circ \rightarrow$ r.t., 70%; *b:* aq. CH_2O 40%, H_2O, ultrasound, 47%; *c:* H_2, Pd/C, 92% (4:1 diastereomeric ratio); *d:* silica gel, 70% of the major isomer; *e:* $SOCl_2$, THF-H_2O; then NH_4SH/H_2O, 87%.

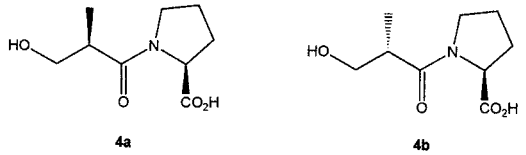


Figure 2. Diastereoisomers obtained from the hydrogenation step.

(reflux, stoichiometry of the catalyst, etc.), ultrasound technique at room temperature was found to be the most suitable condition. Hydroxyacrylamide **2** was obtained in 47% yield.

Hydrogenation of **2** was achieved at room temperature and atmospheric pressure, in the presence of Pd/C. Amide **4** was obtained as a diastereomeric mixture, in a 4:1 ratio (Fig. 2). Despite of the easy separation of the diastereoisomers (**4a/4b**), stereochemical assignments of the major compound could not be determined at this stage.

The major diastereoisomer treated with thionyl chloride followed by NH_4SH in H_2O/THF furnished the mercapto derivative **1**, in 87% yield. The α_D value of **1** (−129.5, *c*1.7, ethanol) is comparable to those reported in literature (−131.0, *c*1.7, ethanol)[6] and therefore, confirmed the configuration of the major diastereoisomer.

In conclusion we have synthesized the target compound **1** in four steps from (*S*)-proline in 20% overall yield. We believe that despite the moderate selectivity in the hydrogenation step, the simple and efficient synthetic strategy associated with the readily chromatographic separation of the diastereoisomers provided a valuable entry to captopril. In this work we have also observed that ultrasound technique could be improved the Baylis–Hillman reaction of *N*-acryloylproline.

EXPERIMENTAL

General

The ^{1}H NMR spectra were recorded on a Varian GEMINI BB-300 at 300 MHz. Purification and separations by column chromatography were performed on silica gel, using flash chromatography. Acryloyl chloride, (*S*)-proline and DABCO (1,4-diazabicyclo[2.2.2]octane) were purchased from Aldrich and used without purification. Formaldehyde was employed as a 40% aqueous solution. Thin Layer Chromatography visualization was achieved by spraying with 10% ninhydrin/acetone solution and heating.

***N*-acryloyl-(*S*)-proline 3.** A stirred solution of (*S*)-proline (5 g, 43 mmol) in 2 M aqueous KOH (26 mL, 52 mmol) was cooled in an ice-bath and diluted with acetone (26 mL). An acetone solution (26 mL) of acryloyl chloride (4.34 g, 48 mmol) and 2 M aqueous KOH solution (30 mL, 61 mmol) were simultaneously added over 40 min with good stirring to the aqueous proline in an ice-bath. After 3 h at room temperature the mixture was evaporated in vacuo to remove acetone. The residual solution was washed with ether and acidified (pH 3) with hydrochloric acid. The acidic mixture, after saturation with NaCl, was extracted with ethyl acetate and the combined extracts were washed with brine and evaporated. The residue was purified by column chromatography (CH_2Cl_2:CH_3OH:NH_4OH, 8:1.5:0.5). Amide **3** was obtained in 70% yield. IR (neat, λ_{max}): 3465–2621; 1728; 1688; 1641; 1452; 1196; 912; 735. ^{1}H NMR: δ 11.3 (br, 1H); 6.62–6.47 (br, 1H); 6.18–5.37 (m, 2H); 4.71(dd, $J = 8.2$ and 1.8 Hz; 1H), 3.66 (m, 2H); 2.45 (m, 1H); 2.09–1.89 (m, 3H). Anal. calcd. for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.61; H, 6.51; N, 8.18.

β-Hydroxy-α-methylene-*N*-acryloyl-(*S*)-proline 2. To a mixture of **3** (0.472 g, 1.89 mmol) and 10 mL of THF, 5 mL of a 40% aqueous formaldehyde were added. The suspension was sonicated for 48 h. The mixture was partionated with ethyl acetate (60 mL) and extracted. The

solid was washed with ether (50 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (100 mL), brine (100 mL) and dried over anhydrous sodium sulfate. Concentration under reduced pressure followed by flash chromatography on silica gel with hexane-ethyl acetate (9:1) gave compound **3** (0.32 g, 93%) as a yellow tinged oil. IR (neat, λ_{max}): 3444–2625; 1728; 1716; 1688; 1633; 1456; 1196 cm^{-1}. ^1H NMR: δ 10.7 (br, 1H); 6.27 (d, $J = 1.1$ Hz; 1H), 5.86 (d, $J = 1.5$ Hz, 1H); 4.75 (m, 1H); 4.34 (d, $J = 4.5$ Hz, 2H); 3.71 (m, 2H); 2.48 (m, 1H); 2.13–1.83 (m, 3H). Anal. calcd. for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.14; H, 6.53; N, 6.99.

β-Hydroxy-α-methyl-*N*-acryloyl-(*S*)-proline 4. A suspension of **2** (0.219 g, 1.21 mmol) and 5% Pd/C (21 mg) in ethyl acetate was hydrogenated at room temperature and atmospheric pressure for 4 h. After this period, the reaction mixture was filtered through a pad of celite. After concentration at reduced pressure, the residue was dried over anhydrous sodium sulfate. Filtration, concentration and flash chromatography (Hex-EtOAc-MeOH, 7:2:1) gave the major isomer (0.102 g, 70% from diastereomeric mixture). IR (KBr, λ_{max}): 3418, 3220, 1698, 1490, 1089, 827 cm^{-1}. ^1H NMR: δ 11.5 (br, 1H); 4.61 (m, 1H); 4.38 (m, 2H); 3.78 (m, 2H); 2.61 (m, 1H); 2.51 (m, 1H), 2.05–1.78 (m, 3H), 1.07 (d, $J = 7.7$ Hz, 3H). Anal. calcd. for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.54; H, 7.47; N, 6.98.

β-Mercapto-α-methyl-*N*-acryloyl-(*S*)-proline 1 (Captopril). To a solution of 0.160 mg (~0.8 mmol) of the major isomer obtained from hydrogenation step (amide **6**) in dry THF (10 mL), thionyl chloride (4.0 mmol) in 20 mL of dry THF was added. Stirring was kept at room temperature for 5 h. The reaction mixture was cooled to 0°C and a solution of 204 mg (~4 mmol) of NH_4SH in 15 mL H_2O-THF (1:1) was carefully added. Stirring was continuated at the same temperature for 30 min, and then warmed to room temperature. After 3 h, 15 mL of 5% aqueous $NaHCO_3$, were added and the reaction mixture was kept under stirring for 2 h. The mixture was washed with ether (2×20 mL), and the aqueous layer acidified with HCl (pH ~ 4) and extracted with ethyl acetate. The combined organic extracts were washed with brine (100 mL) and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave a white solid which was crystallized from ethyl acetate-hexane. Captopril was obtained in 87% yield. $[\alpha]_D$: −129.5 (*c*1.7, ethanol). Lit.[6b]: −131.0, (*c*1.7, ethanol). M.p.: 103–105°C: Lit.[6b]: 104–105°C. IR (KBr, λ_{max}): 3300–2197, 2560, 1744, 1741, 1646, 1590, 1445 cm^{-1}. ^1H NMR: δ 4.79 (m, 1H); 3.74 (m, 2H); 2.63 (m, 1H); 2.51 (m, 1H); 2.1–1.8 (m, 3H); 1.09 (d, $J = 7.7$ Hz, 3H). Anal. calcd. for $C_9H_{15}NO_3S$: C, 49.75; H, 6.96; N, 6.45; S, 14.75. Found: C, 49.62; H, 6.27; N, 6.42; S, 14.23.

ACKNOWLEDGMENTS

We wish to thank Prof. Dr. Fernando Coelho (IQ/UNICAMP) for ultrasound apparatus. The authors thank FAPESP for Melissa P. Feltrin's fellowship (99/10904-5).

REFERENCES

1. Greenlee, W.J.; Robertson, D.W.; Siegl, P.K.S. Angiotensin–renin modulators. Annu. Rep. Med. Chem. **1991**, *26*, 63.
2. Hooper, N.M. Angiotensin converting enzyme-implications from molecular biology for its physiological functions. Int. J. Biochem. **1991**, *23*, 641.
3. Ondetti, M.A.; Rubin, B.; Cushman, D.W. Design of specific inhibitors of angiotensin-converting enzyme: a new class of orally active antihipertensive agents. Science **1977**, *196*, 441.
4. (a) Basavaiah, D.; Rao, P.D.; Hyma, R.S. The Baylis–Hillman Reaction: a novel carbon-carbon bond forming reactions. Tetrahedron **1996**, *52*, 8001; (b) Ciganek, E. Morita–Baylis–Hillman–Reaction. In *Organic Reactions*; Paquette, L., Ed.; John Wiley and Sons Inc.: New York, 1997; 201; (c) Almeida, W.P.; Coelho, F. The Baylis–Hillman reaction: a strategy for the preparation of multi-functionalised intermediates for organic synthesis. Quimica Nova **2000**, *23*, 98. Chem. Abstr. **2000**, *132*, 236562e.
5. Effenberger, F.; Isak, H. Amino-acids 15. diastereoselective addition of thiocarboxylic acids to 1-(methacryloyl)proline and 1-(methacryloyl)prolinol derivatives. Chem. Ber. **1989**, *122*, 553.
6. (a) Cushman, D.W.; Cheung, H.S.; Sabo, E.F.; Ondetti, M.A. Design of potent competitive inhibitors of angiotensin-converting enzyme. Carboxyalkanoyl and mercaptoalkanoyl amino acids. Biochemistry **1977**, *16*, 5485; (b) The Merck Index, 12th Ed.; Merck & Co. In.: New Jersey, 1996; 1812.

Received in the USA May 15, 2002