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REGULAR ARTICLE

# Use of convertible isocyanides for the synthesis of benazepril hydrochloride

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**Abstract.** Herein, we have described a novel and concise synthesis of the potent angiotensin-converting enzyme (ACE) inhibitor, benazepril hydrochloride (**7**) in trifluoroethanol *via* an Ugi three-component reaction in shorter reaction times. The key step is the trifluoroacetic acid-mediated hydrolysis of secondary amides (**4a** and **4b**) followed by esterification as a domino process to form corresponding ethyl ester (**6**). Mainly two universal convertible isocyanides (**1a** and **1b**) were used for the synthesis of benazepril hydrochloride.

**Keywords.** Ugi reaction; convertible isocyanides; α-amino amide; esterification.

## 1. Introduction

Multicomponent reactions (MCRs)[1] are the most powerful methods in which at least three starting materials react to each other to form compounds with a diverse skeleton in one pot. MCRs are widely used synthetic tool to manufacture different pharmaceutical compounds due to their high atom economy, high efficiency with low cost. The Ugi reaction is one of the most applied multicomponent reactions due to easy access to different scaffolds in shorter reaction times. A classical Ugi three-component reaction (U-3CR) combines an amine, carbonyl compound and isocyanide to get α-amino amides. There are numerous pharmaceutical compounds used as angiotensin-converting enzyme (ACE) inhibitor contains α-amino amides structural frameworks like benazepril, lisinopril, quinapril and enalapril (Figure 1).

ACE inhibitors used to lower high blood pressure, prevent heart failure and to treat diabetic kidney diseases.

We recently reported[3e] efficient synthesis of quinapril hydrochloride using Ugi multicomponent reaction. We thought to develop a synthesis of benazepril hydrochloride. Literature survey revealed that there are many synthetic approaches reported for the synthesis of benazepril HCl. These methods involved multiple steps[2b, 2e] for the synthesis of benazepril HCl. Use of costly advance intermediates like L-Homophenyl alanine ethyl ester (LHPE), 4-(2-nitrophenyl)-4-oxo-but-2-enoic acid methyl ester,[2a] ethyl-(R)-2-hydroxy-4-phenylbutyrate,[2c] (S)-3-amino-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one, critical asymmetric Aza-Michael reaction and cumbersome chiral separations[2a] are some of the demerits of prior art synthesis.

Herein we describe an efficient synthesis of angiotensin-converting enzyme (ACE) inhibitor, benazepril hydrochloride (**7**) in trifluoroethanol *via* an Ugi three-component reaction in shorter reaction times using cheaper starting materials with good yields.

## 2. Experimental

### 2.1 *Raw materials and physical measurement*

All reagents purchased from Sigma Aldrich, S. D. Fine chemical. NMR data recorded on Bruker 500 MHz,

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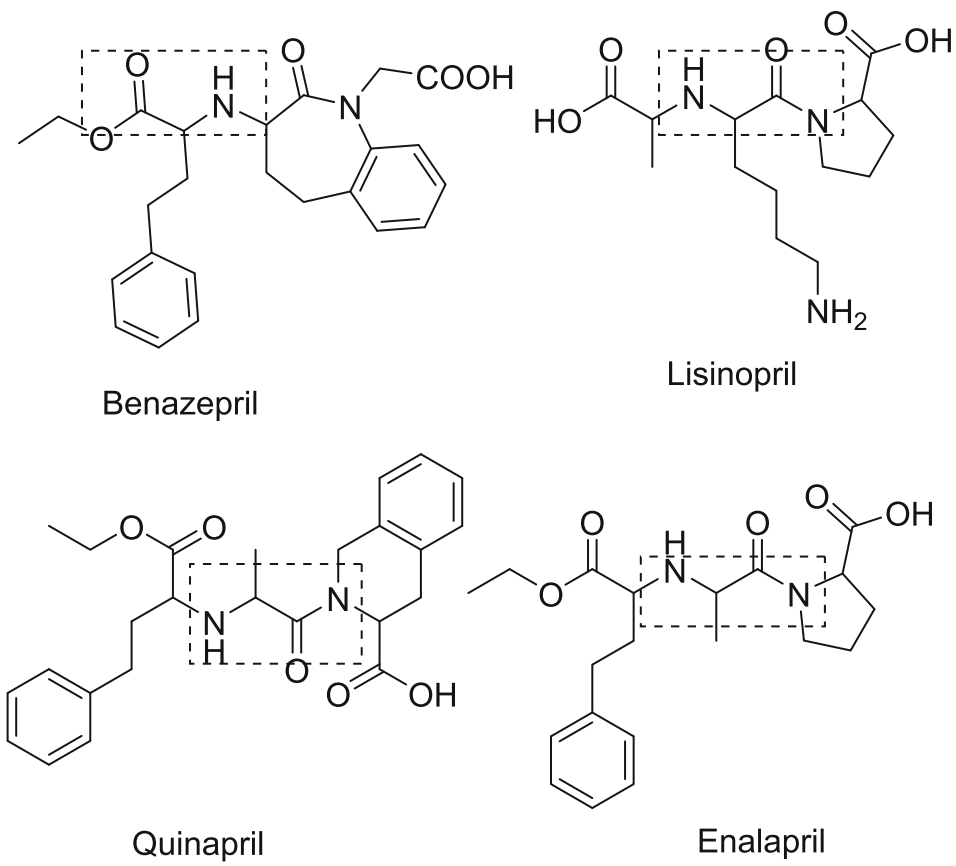


**Figure 1.** Representative examples of pharmaceutical compounds containing α-amino amide and amino acid structural frameworks.

AVANCE III HD and Software Topspin at room temperature in $CDCl_3$ and DMSO $d_6$ using TMS as an internal reference standard. HRMS data recorded on Waters Xevo G2 QTOF mass spectrometer. Specific optical rotation recorded on Rudolph Research Analytical, Autopol V plus instrument. IR spectra recorded on Perkin spectrum 400 FTIR spectrophotometer. Isonitriles are commercially available, were outsourced. All compounds were analyzed by Chiral HPLC, SHIMADZU LC-2010 CHT, CHROMELEON version 6.80, CHIRALPACK AD-H column, Particle size 5 μm, Dimensions 4.6 mmϕ x 250 mmL. Oven temperature 30 °C, mobile phase ethanol: n-Hexane (20:80) ratio. Flow rate 1 mL/min.

### 2.2 *General procedure for Ugi three-component reaction (**4a, 5a**)*

A solution of 3-phenylpropanal (**2**) (4.1gm, 30.85 mmol, 1 eq.), (S)-2-(3-amino-2-oxo-2, 3, 4, 5-tetrahydro-1Hbenzo[b]azepin-1-yl) acetate (**3**)[3f] (10 gm, 30.85 mmol, 1 eq.) in 2, 2, 2 trifluoroethanol (50 mL) was stirred for 30 min. To this reaction mixture, 2-nitrobenzyl isocyanide (**1a**) (4.9 gm, 30.85 mmol, 1 eq.) and catalyst $TiCl_4$ (0.30 gm, 0.0015 mmol, 0.05 eq.) was added. The reaction was monitored using thin-layer chromatography (ethyl acetate/hexane, 70:30). After completion of the reaction (7 h), the reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and the organic layer was washed with aqueous (5%) $NaHCO_3$ solution (100 mL). The organic layer was dried over sodium sulphate (10 gm), filtered it and evaporated under reduced pressure to get compound (**4a** and **5a**) crude showing (dr = 91:9) 18 gm. After column chromatography (Yield 4a = 78%, 5a = 5%). Similarly, compound (**4b** and **5b**) was synthesized by the same procedure described above. Crude showing (dr =87:13). After column chromatography (Yield **4b** = 72%, 5b = 9%), these diastereomeric mixture was column chromatographically separated. Silica 100–200 mesh, Mobile phase Ethyl acetate: Hexane (70:30)

2.3 *Benzyl 2-((S)-3-(((S)-1-((2-nitrobenzyl) amino)-1-oxo-4-phenylbutan-2-yl) amino)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)acetate (**4a**)*

Yield 15 gm, 78%, Yellow Oil. $[\alpha]_D^{25}$ – 145.0° (c 0.9, EtOH). IR (KBr) ν *max* 696, 735, 1184, 1521, 1660, 1746, 2930, 3326 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$), δ (ppm) 1.87–2.02 (m, 4H), 2.28–2.33 (m, 1H), 2.49–2.53 (m, 1H), 2.69–2.74 (m, 2H), 2.96–3.01 (m, 2H), 3.19–3.26 (m, 1H), 4.38 (d, *J* = 17.5 Hz, 1H), 4.54–4.62 (m, 2H), 4.79 (d, *J* = 17.5 Hz, 1H), 5.15 (s, 2H), 7.01 (d, *J* = 8 Hz, 1H), 7.16–7.48 (m, 16H), 7.97 (d, *J* = 8 Hz, 1H), 8.00 (t, *J* = 6 Hz, 1H). $^{13}C$ NMR (125 MHz) δ: 28.2, 31.9, 35.9, 38.1, 40.6, 50.3, 57.7, 62.1, 67.2, 122.5, 125.0, 125.8, 126.9, 127.8, 128.3, 128.4, 128.4, 128.5, 128.6, 129.5, 131.9, 133.6, 133.9, 135.1, 135.9, 140.3,141.4, 148.0, 168.5, 173.8, 174.2. HRMS calculated (m/z) $[M+H]^+$: 621.2635; Found; 621.2635.

2.4 *Benzyl 2-((S)-3-(((S)-1-(tert-butylamino)-1-oxo-4-phenylbutan-2-yl) amino)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)acetate (**4b**)*

Yield 12 gm, 72%, Yellow Oil. $[\alpha]_D^{25}$ – 146° (c 0.9, EtOH). IR (KBr) ν *max* 701, 1032, 1751, 2973, 3707 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$), δ (ppm) 1.22 (s, 9 H), 1.82–1.89 (m, 1H), 1.94–2.06(m, 3H), 2.22–2.31 (m, 1H), 2.52–2.56 (m, 1H), 2.67–2.79 (m, 2H), 2.83–2.86 (m, 1H), 3.08–3.11 (m, 1H), 3.24–3.31 (m, 1H), 4.43 (d, *J* =17 Hz, 1H), 4.81 (d, *J* =17 Hz, 1H), 5.17 (s, 2H), 7.04–7.38 (m, 15H).$^{13}C$ NMR (125 MHz) δ: 28.3, 28.6, 32.0, 36.0, 38.4, 50.2, 50.3, 57.5, 62.9, 67.2, 122.6, 125.8, 127.0, 127.9, 128.3, 128.4, 128.4, 128.4, 128.6, 129.3, 135.1, 135.8, 140.4, 141.7, 168.6, 173.0, 173.8. HRMS calculated (m/z) $[M+H]^+$: 542.2941; Found; 542.2941.

2.5 *Benzyl 2-((R)-3-(((S)-1-((2-nitrobenzyl) amino)-1-oxo-4-phenylbutan-2-yl)amino)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)acetate (**5a**)*

Yield 1.0 gm, 5%, Yellow Oil. $[\alpha]_D^{25}$ + 141.0° (c 0.9, EtOH). IR (KBr) ν *max* 699, 762, 1254, 1742, 2980, 3467 $cm^{-1}$. $^1H$ NMR (500 MHz, MeOD), δ (ppm) 1.88–1.97 (m, 3H), 2.0–2.31 (m, 1H), 2.47–2.51 (m, 1H), 2.64–2.69 (m, 2H), 3.00–3.12 (m, 3H), 4.43–4.46 (m, 1H), 4.56–4.68(m, 3H), 5.12 (q, *J*= 12.5 Hz), 7.11–7.46 (m, 16H), 7.95–7.97 (m, 1H). $^{13}C$ NMR (125 MHz) δ:29.1, 32.9, 36.9, 38.5, 41.2, 51.4, 58.7, 62.9, 68.0, 123.5, 125.9, 126.9, 128.2, 129.0, 129.3, 129.3, 129.4, 129.4, 129.5, 130.4, 131.4, 134.7, 134.7, 136.9, 137.1, 142.0, 142.8, 149.5, 170.4, 175.5, 176.7. HRMS calculated (m/z) $[M+H]^+$: 621.2635; Found; 621.2633.

2.6 *Benzyl 2-((R)-3-(((S)-1-(tert-butylamino)-1-oxo-4-phenylbutan-2-yl) amino)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)acetate (**5b**)*

Yield 1.5 gm, 9%, Yellow Oil. $[\alpha]_D^{25}$ + 140° (c 0.9, EtOH). IR (KBr) ν *max* 701, 1262, 1418, 1736, 2983 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d^6$), δ (ppm) 1.08 (s, 9 H), 1.63–1.73 (m, 2H), 1.90–1.97(m, 1H), 2.12–2.17 (m, 1H), 2.50–2.57 (m, 2H), 2.59–2.65 (m, 1H), 2.69–2.71 (m, 1H), 2.96–3.00 (m, 1H), 3.03–3.10 (m, 1H), 7.10–7.38 (m, 15H).$^{13}C$ NMR (125 MHz) δ:27.5, 28.1, 31.4, 35.4, 37.2, 49.4, 49.8, 56.4, 61.4, 66.1, 122.6, 125.6, 126.4, 127.5, 128.0, 128.1, 128.2, 128.2, 128.3, 128.4, 128.9, 135.6, 140.7, 141.9, 169.0, 172.3, 173.0. HRMS calculated (m/z) $[M+H]^+$: 542.2941; Found; 542.2944.

2.7 *Ethyl(S)-2-(((S)-1-(2-(benzyloxy)-2-oxoethyl)-2-oxo-2, 3, 4, 5-tetrahydro-1H-benzo[b]azepin-3-yl) amino)-4-phenylbutanoate (Benzyl Benazepril) (**6**)*

A solution of compound (**4a**) (15 gm, 24.19 mmol, 1eq.), TFA (5.5 gm, 48.38 mmol, 2 eq.) in ethanol (60 mL) was refluxed for 5 h. The reaction was monitored using TLC (ethyl acetate/hexane, 7:3). After completion reaction, the mixture was evaporated under reduced pressure at 40–45 °C. The residue was extracted with ethyl acetate and the organic layer was washed with aqueous saturated $NaHCO_3$ (60 mL). The organic layer was separated and dried over sodium sulphate. Organic layer was filtered and evaporated to get compound (**6**) as a thick yellow oil (Yield 11 gm, 77%).

Similarly, (**4b**) (12 gm, 22.18mmol, 1 eq.), TFA (5 gm, 44.36 mmol, 2 eq.), ethanol (60 mL) was converted to (**6**) using above process and (Yield 10.5 gm, 92%).

2.8 *Ethyl(S)-2-(((S)-1-(2-(benzyloxy)-2-oxoethyl)-2-oxo-2, 3, 4, 5-tetrahydro-1H-benzo[b]azepin-3-yl) amino)-4-phenylbutanoate (Benzyl Benazepril) (**6**)*

Yield 11 gm, 77%, thick yellow oil. $[\alpha]_D^{25}$ – 140° (c 0.9, EtOH). IR (KBr) ν *max* 738, 1026, 1186, 1667,

3030, 3435 $cm^{-1}$. $^{1}H$ NMR (500 MHz, $CDCl_3$), δ (ppm) 1.14 (t, $J$ = 7 $H_Z$, 3H), 1.90–2.07 (m, 4H), 2.36–2.44 (m, 1H), 2.52–2.56 (m, 1H), 2.66–2.76 (m, 2H), 3.18–3.25 (m, 2H). 3.28–3.31 (m, 1H), 4.01–4.12 (m, 2H), 4.49 (d, $J$ = 17 $H_Z$, 1H), 4.75 (d, $J$ = 17 $H_Z$, 1H), 5.17 (s, 2H), 7.11 (d, $J$ = 7.5 Hz, 1H), 7.17–7.22 (m, 5H), 7.26–7.37 (m, 8H). $^{13}C$ NMR (125 MHz) δ: 14.1, 28.3, 32.0, 35.0, 37.7, 50.4, 56.9, 60.1, 60.6, 67.1, 122.3, 125.9, 126.9, 127.7, 128.3, 128.4, 128.4, 128.4, 128.6, 129.6, 135.2, 136.1, 140.7, 141.4, 168.7, 174.0, 174.1. HRMS calculated (m/z) $[M+H]^+$: 515.2468; Found; 515.2468.

### 2.9 *2-((S)-3-(((S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl) amino)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)acetic acid (**7**): (benazepril HCl)*

A solution of compound (**6**) (11 gm, 21.4 mmol, 1 eq.) was subjected for hydrogenation in ethanol using 10% Pd/C (2 gm) under 60 psi for 3 h at room temperature. The reaction was monitored by TLC (ethyl acetate/hexane, 7:3). After completion of the reaction, the reaction mixture was filtered over a celite bed and the bed was washed with ethanol (5 mL). The filtrate was concentrated under reduced pressure. A residue was dissolved in ethyl acetate and treated with HCl gas for 1 h to form a white slurry. It was filtered, solid refluxed in ethyl acetate and acetone (95: 5 ratio) (50 mL) for 20 min, then filtered, and dried under vacuum at 40–45 °C to get benazepril HCl (**7**).

### 2.10 *2-((S)-3-(((S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl) amino)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)acetic acid (**7**): (benazepril HCl)*

Yield 9.0 gm, 91%, (lit 7[c, d] M. p. = 188–190 °C) M. p. = 185–189 °C, White Solid, (lit 7[c, d] $[\alpha]_D$ = -141° (c 0.9, EtOH), $[\alpha]_D^{20}$ = -141° (c 0.9, EtOH). IR (KBr) ν *max* 732, 751, 1209, 1389, 1523, 1672, 1737, 2434, 3121 $cm^{-1}$. $^{1}H$ NMR (500 MHz, $CD_3OD$), δ (ppm) 1.22 (t, $J$ = 7.5 Hz, 3H), 2.24–2.29 (m, 2H), 2.39–2.65 (m, 1H), 2.69–2.79 (m, 1H), 2.80–2.87 (m, 3H), 3.32–3.37 (m, 1H), 3.93–4.0 (m, 2H), 4.13–4.24 (m, 2H), 4.62 (d, $J$ = 17.5 Hz, 1H), 4.66 (d, $J$ = 17.5 Hz, 1H), 7.23–7.41 (m, 9H). $^{13}C$ NMR (125 MHz) δ: 14.2, 28.1, 31.8, 33.1, 34.7, 51.4, 59.0, 60.2, 63.9, 124.1, 127.6, 128.9, 129.4, 129.7, 130.7, 135.5, 141.0, 141.1, 168.2, 169.7, 171.8. HRMS calculated (m/z) $[M+H]^+$: 425.1998; Found; 425.1998.

## 3. Results and Discussion

We reported the use of Ugi three-component reaction for the synthesis of quinapril HCl.[3e] We used these optimized conditions to design new methodology for the synthesis of benazepril HCl. A novel synthetic route designed for the preparation of benazepril HCl which began with Ugi three-component reaction involved the reaction of amine, carbonyl compound and convertible isocyanide (Figure 2).

The selection of convertible isocyanides is the key parameter to obtain the desired product in which

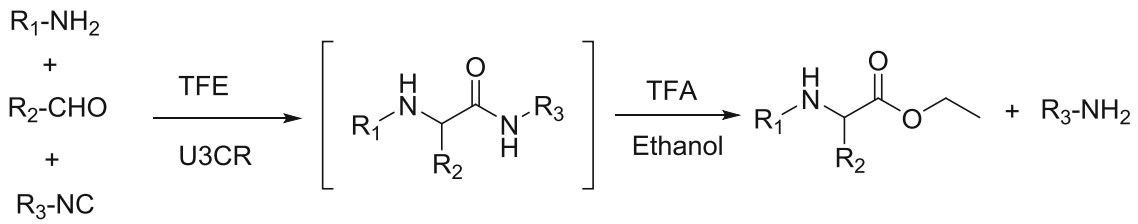


**Figure 2.** General schematic representation of the proposed synthesis.

**Table 1.** Screening of Lewis acid and Solvent for Ugi reaction (**4a**, **5a**).

| Sr. No. | Lewis acid | Solvent | Time (h) | Temp (°C) | Yield (4a:5a) | dr (4a: 5a) |
|---|---|---|---|---|---|---|
| 1 | None | MeOH | 40 | 25 | 57%, 26% | 67:33 |
| 2 | PPA | MeOH | 45 | 25 | 57%, 26% | 66:34 |
| 3 | $TiCl_4$ | TFE | 7 | 25 | 78%, 25% | 91:9 |

**Table 2.** Screening of Lewis acid and Solvent for Ugi reaction (**4b**, **5b**).

| Sr. No. | Lewis acid | Solvent | Time (h) | Temp (°C) | Yield (4a:5a) | dr (4a: 5a) |
|---|---|---|---|---|---|---|
| 1 | None | MeOH | 38 | 25 | 65%, 17% | 76:23 |
| 2 | $TiCl_4$ | MeOH | 24 | 25 | 71%, 11% | 81:18 |
| 3 | $TiCl_4$ | TFE | 7 | 25 | 71%, 9% | 87:13 |

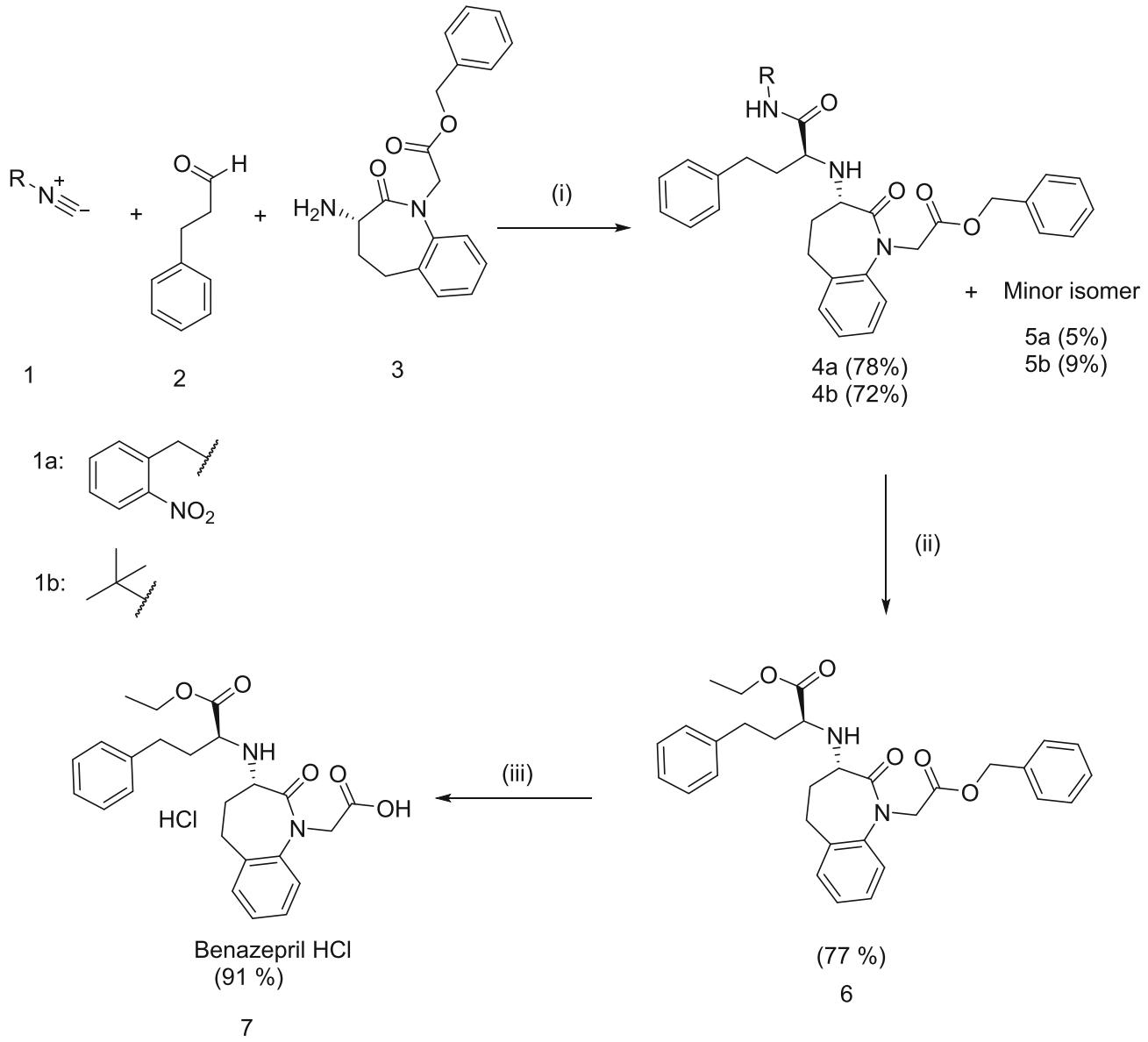


**Figure 3.** Stepwise conversion of Ugi 3CR product **4a** and **4b** into benazepril HCl.

secondary amide needs to be converted into ethyl ester to yield benazepril HCl.

Accordingly, isocyanides were chosen in Ugi reaction such that resulting amides could be easily converted into corresponding ethyl ester. The rational to choose these convertible isocyanides were its commercial availability and easy conversion of secondary amides obtained from Ugi reaction to corresponding ethyl ester.

There are many convertible isocyanides reported in the literature.[4–6] We screened two isocyanides namely

2-nitrobenzyl isocyanide (**1a**),[5] tertiary butyl isocyanide (**1b**).[5b] These convertible isocyanides were chosen due to their commercial availability. The conversion of secondary amides obtained from these isocyanides to the corresponding ester was achieved using sulfuric acid.[5b]

Initially, 2-nitrobenzyl isocyanide (**1a**), 3-phenylpropanal (**2**) and benzyl (S)-2-(3-amino-2-oxo-2, 3, 4, 5- tetrahydro-1H-benzo[b]azepin-1-yl) acetate (**3**) was reacted in methanol furnished major diastereomer (**4a**) along with minor diastereomer (**5a**), (dr 67:33). The reaction was completed in 40 h. The use of phosphoric acid (PPA) did not improve reaction time and yield.

The results of screening different reactions conditions are shown below Table 1.

Literature report revealed that 2,2,2, trifluoroethanol (TFE) was widely used solvent for Ugi reaction hence we thought to use TFE as a solvent for the above reaction. $TiCl_4$ was also known for such kind of Ugi reaction. Accordingly, we conducted the reaction of 2-nitrobenzyl isocyanide (**1a**), 3-phenylpropanal (**2**) and benzyl (S)-2-(3-amino-2-oxo-2, 3, 4, 5- tetrahydro-1H-benzo[b]azepin-1-yl) acetate (**3**) using $TiCl_4$ as a catalyst in 2,2,2, trifluoroethanol (TFE). The reaction was completed in 7 h yielding major diastereomer (**4a**) along with minor diastereomer (**5a**), (dr 91:9).

The enhanced reaction rate of Ugi reaction could be attributed to the formation of iminium ion by the high ionizing ability of 2,2,2, trifluoroethanol.[5b] This diastereomeric mixture was chromatographically separated to get chirally pure major diastereomer (**4a**) and minor diastereomer (**5a**).

The major diastereomer (**4a**) was subjected for esterification using TFA in ethanol to furnish ethyl (S)-2-(((S)-1-(2-(benzyloxy)-2-oxoethyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)amino)-4-phenylbutanoate (**6**). Debenzylation of benazepril ester (**6**) was carried out using 10% Pd/C and 60 psi $H_2$ (g) in ethanol to give required benazepril HCl. (**7**). It was confirmed and characterized by SOR, HRMS, IR, $^{13}$C NMR, $^{1}$HNMR and Chiral HPLC.[7]

The spectral and analytical data of benazepril HCl (**7**) suggest that major diastereomer (**4a**) has a sense of diastereoinduction (*S, S*). The observed (*S, S*) stereoinduction of major diastereomer (**4a**) could be due to existing chiral center in benzyl (S)-2-(3-amino-2-oxo-2, 3, 4, 5- tetrahydro-1H-benzo[b]azepin-1-yl) acetate (**3**) that facilitates the stereoselective attack of isocyanide nucleophile to chiral imine which was formed in the reaction from 3-phenylpropanal (**2**) and benzyl (S)-2-(3-amino-2-oxo-2,3,4,5- tetrahydro-1H-benzo[b]azepin-1-yl) acetate (**3**).

Similarly, tertiary butyl isocyanide (**1b**), 3-phenylpropanal (**2**) and (S)-2-(3-amino-2-oxo-2, 3, 4, 5-tetrahydro-1H-benzo[b]azepin-1-yl) acetate (3) was reacted in 2,2,2, trifluoroethanol (TFE) in presence of catalyst $TiCl_4$, gave corresponding major diastereomer (**4b**) along with minor diastereomer (**5b**) (Table 2). (dr 87:13). This diastereomeric mixture was chromatographically separated.

Major diastereomer (**4b**) was successfully converted to (S)-2-(((S)-1-(2-(benzyloxy)-2-oxoethyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)amino)-4-phenylbutanoate (**6**) by using TFA in ethanol. Subsequent debenzylation of benazepril ester (**6**) was carried out using 10% Pd/C and 60 psi $H_2$ (g) in ethanol to give required benazepril HCl. (**7**). It was confirmed and characterized by SOR, HRMS, IR, $^{13}$C NMR, $^{1}$HNMR and Chiral HPLC.[7]

The spectral and analytical data of benazepril HCl (**7**) suggest that major diastereomer (**4b**) has a sense of diastereoinduction (*S, S*). The synthetic scheme developed for benazepril HCl is depicted in Figure 3.

**Reagents and conditions**: (i) 2, 2, 2 Trifluroethanol, $TiCl_4$, Purification (ii) TFA, Ethanol (iii) Ethanol, Pd/C, Conc HCl, $H_{2\ (g)}$ 60 psi.

## 4. Conclusions

In summary, we have developed a novel and efficient synthesis of ACE inhibitor, benazepril HCl using convertible isocyanides. The present method offers the following competitive advantages: i) shorter reaction time ii) higher yields.

## Supplementary Information (SI)

$^{1}$HNMR, $^{13}$CNMR, I.R. spectra, HRMS, HPLC data associated with this work is available in the supplementary file, can be accessed at https://www.ias.ac.in/chemsci.

## Acknowledgements

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