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Application of Ugi three component reaction for the synthesis of quinapril hydrochloride

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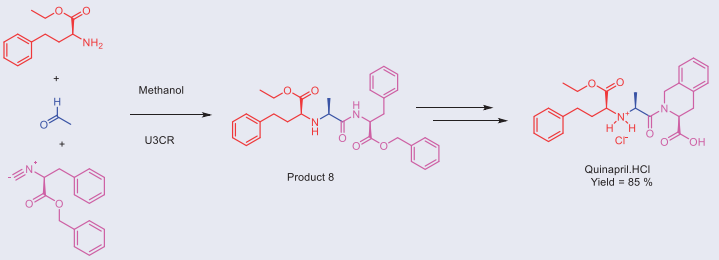
ABSTRACT

A novel, efficient and concise synthesis of chirally pure quinapril hydrochloride is described. The key step is the formation of α-amino amide backbone in one step using Ugi three component reaction. This method allows short access to α-amino amide chain which is a part of many drugs used for treatment of high blood pressure. A large molecular library can be synthesized by changing the components in Ugi reaction.

GRAPHICAL ABSTRACT



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KEYWORDS
α-amino amide; isocyanides; Ugi reaction

Introduction

Quinapril hydrochloride is an active pharmaceutical ingredient indicated for the treatment of high blood pressure (hypertension) and as an adjunctive therapy in the management of heart failure. It may be use for the treatment of hypertension by itself or in combination with thiazide diuretics and digoxin for heart failure. Phenyl acetamide, α-amino amide, α-amino acid chemotypes exhibits a wide range of biological activities and are building blocks to molecules like Etidocaine, Enalapril and Quinapril (Fig. 1). Multicomponent reactions (MCRs) have become very popular and a powerful strategy in modern organic synthesis.[1a,b,c] Among them, Ugi reaction provides a facile access to α-amino amide in one step.[2a,b] Hence, we turned our attention to exploring new synthetic routes for quinapril hydrochloride (ACE inhibitor) by using the U3CR.

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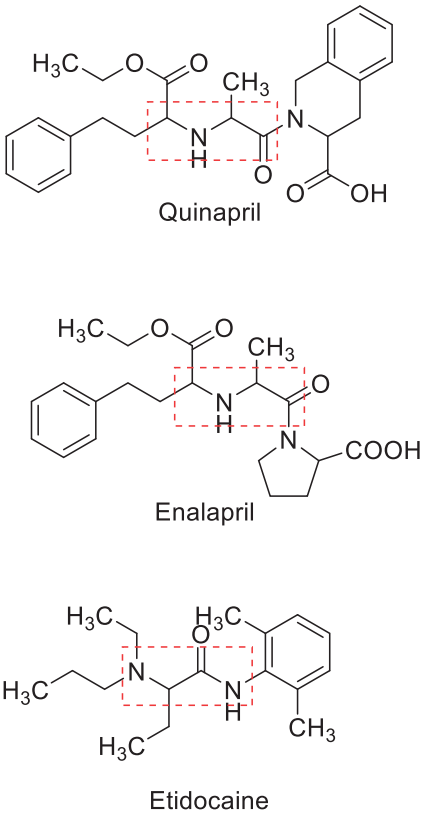
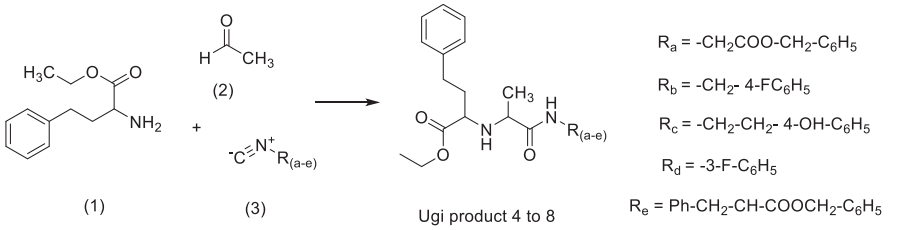


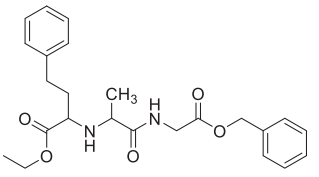
Figure 1. Representative examples of biologically active compounds containing α-amino amide and amino acid backbone.

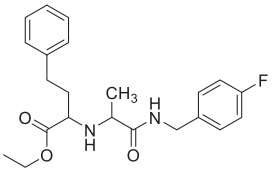
Results and discussion

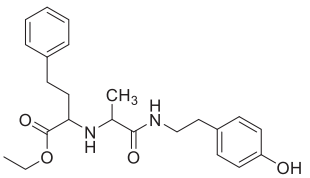
We report herein, the first synthesis of quinapril hydrochloride (Fig. 1) using Ugi 3CR through the intermediacy of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (TIQ). This method is superior to the prior art synthetic methods because the α-amino amide backbone of quinapril is synthesized in one-step. The subsequent steps followed by ring formation gave quinapril hydrochloride in good yield. In 1986, Klutchko et al., reported first multistep synthesis of quinapril hydrochloride.[3a] Later, few modified synthetic strategies were developed, which involved use of advance intermediates, acid chloride and amine approach, use of hazardous chemicals like benzsulfonamide, phosphorous pentachloride. The disadvantage of above method was handling of these hazardous chemicals in large scale synthesis faced various difficulties.[3b] Other synthetic methods involved use of acid amine coupling approach by using DCC and HOBt. Removal of insoluble DCU byproduct, low solubility of HOBt in water and formation of DKP impurity[3a] were demerits of this method. Some recent synthetic methods used carboxyanhydride prepared from poisonous phosgene.[3b] whereas our synthetic approach involved cheaper starting materials, cleaner and scalable reactions conditions.

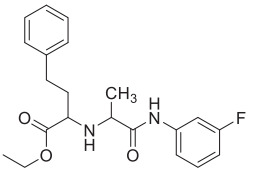
Table 1. Ugi product 4–8.

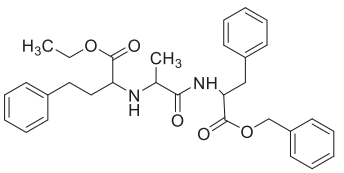



Ra (4) (70%)


Rb (5) (72%)


Rc (6) (65%)


Rd (7) (70%)


Re (8) (80%)

Reaction condition (a) Ethyl-2-amino-4-phenylbutanoate (b) Acetaldehyde, (c) Isonitrile (1 mmol each), catalyst $TiCl_4$, methanol, RT.

Initially, to examine the feasibility of the Ugi three-component reaction (U3CR), we conducted a model reaction using acetaldehyde, isonitrile of glycine benzyl ester, L-homophenyl alanine ethyl ester and $TiCl_4$ catalyst. The reaction gave the Ugi product **(4)** in good yield (Table 1).

Different Lewis acids like $TiCl_4$, phenyl phosphinic acid borox were screened as catalysts to increase the yield, and lower down reaction time. Among the Lewis acids tested, $TiCl_4$ gave the best results[4a,b,c,d] (Table 2).

Ugi products **(4–8)** were synthesized using optimized conditions and characterized by ^{1}H NMR, ^{13}C NMR, HRMS, and IR spectroscopy. A summary of above reactions and optimized conditions is depicted in Table 2. Yields were significantly higher and reaction times were considerably shorter relative to the un-catalyzed reactions run under Ugi's original conditions.[5a,b,c]

Inspired from the U3CR as above, we focused our efforts towards the search for a new efficient methodology for the synthesis of quinapril hydrochloride. Benzyl-2-isocyano-3-phenyl propanoate, acetaldehyde and ethyl-2-amino-4-phenylbutanoate were reacted in

Table 2. Identification of suitable catalyst for Ugi product 8.

Entry	Temp. (h)	Time (5 mol %)	Solvent	Lewis acid	Yield	dr
1	25 °C	48	MeOH	none	40%	70:30
2	25 °C	48	MeOH PPA	45%	70:30	
3	25 °C	48	MeOH	Borox	50%	60:40
4	25 °C	24	MeOH	TiCl4	80%	80:20

PPA = phenyl phosphinic acid.
Borox = BINOL + BH_3·SMe_2 + H_2O + 2, 4, 6-trimethylphenol complex.
$TiCl_4$ = Titanium Tetrachloride.
dr = Diastereomeric ratio.

methanol using $TICl_4$ catalyst (Table 2) to obtain mixture of diastereomers **(8)** and **(9)** with diastereomeric ratio 80:20. Diastereomeric mixture **(8)** and **(9)** was chromatographically inseparable. This mixture of diastereomers was further purified by reacting with maleic acid. Diastereomer **(8)** and **(9)** were characterized by ^{1}H NMR, ^{13}C NMR, HRMS, SOR, IR spectroscopy. Major diastereomer **(8)** was taken further for the synthesis of quinapril HCl (Scheme 1).

Alternatively, above reaction was performed in ethanol with L-homophenyl alanine, acetaldehyde and benzyl-2-isocyano-3-phenylpropanotae using $TiCl_4$ as a catalyst to yield mixture of diastereomers (**8**) and (**9**) (dr. 80:20) (Yield 40%)[4a,b,c,d] (Scheme 1).

After major diastereomer **(8)** in hand, it was thought to protect secondary amine –NH of diastereomer **(8)** with benzyl bromide. Accordingly, diastereomer **(8)** was reacted with benzyl bromide, Na_2CO_3 in DMF at room temperature to obtain compound **(10)** (60%) (Scheme 1).

Compound **(10)** was further subjected to TIQ ring formation using *p*-toluene sulfonic acid monohydrate, paraformaldehyde in toluene to furnish compound **(11)**. We have chosen this method because, *p*-toluene sulfonic acid monohydrate is mild, easy to handle, shorten reaction time and gave good yield (65–67%) (Scheme 1).

Alternatively, other conditions were tried mainly (HCHO)n/ethanol HCl, (HCHO)n/TFA, (HCHO)n/AcOH, (HCHO)n/H_2SO_4, and 1,3 dioxolane/HCl. Above listed methods gave yield of compound **(11)** in the range of 50–60%[6a,b,c,d] (Scheme 1).

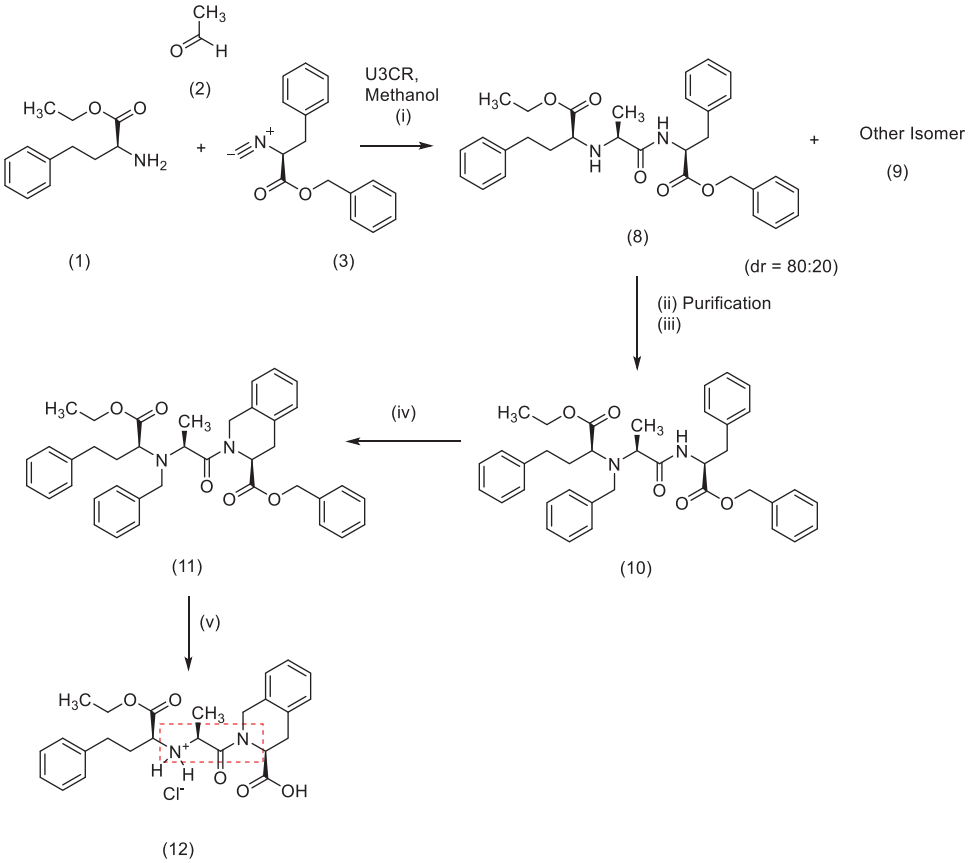
Debenzylation of compound **(11)** was achieved by using catalytic hydrogenation (20% $Pd(OH)_2$/C, conc. HCl) at 60 psi in autoclave to give quinapril hydrochloride **(12)**[7a,b,c,d,e,f] (Scheme 1).

The quinapril hydrochloride **(12)** thus obtained was characterized by ^{1}H NMR, ^{13}C NMR, HRMS, SOR, IR spectroscopy and data was in accordance with literature.[7a,b,c,d,e,f]

The synthetic method developed is described in Scheme 1.

Experimental details

All reagents were purchase from Sigma Aldrich, S D Fine and used without further purification. TLC Aluminum sheets Silica gel 60 F_{254}, Merck Life Science Pvt. Ltd. The NMR spectra recorded on a Bruker 500 MHz AVANCE III HD, Software –Topspin 3.5 at room temperature in $CDCl_3$, DMSO-d_6 using TMS as an internal reference. HRMS data acquired by Waters Xevo G2 QTOF mass spectrometer. Specific optical rotation recorded on Rudolph Research Analytical, Autopol V plus instrument. I.R. spectra (FTIR) recorded on Perkin spectrum 400 FTIR spectrometer. Waters HPLC, software chromeleon 6.80. Quinapril HCl checked on HPLC Diastereoisomers method as per



Scheme 1. Stepwise conversion of Ugi 3CR product 8 into quinapril (Entry 8–12). (i) Methanol, catalytic TiCl4, (80%) (ii) Purification (iii) Benzyl bromide, DMF, Na_2CO_3, (60%) (iv) p-TSA.1H_2O, (HCHO)n, toluene, reflux, (67%) (v) Pd $(OH)_2$/C, Ethanol. H_2 (g) 60 psi. Conc HCl. (85%).

European Pharmacopeia 9.0 page no. 3459-3461. Ugi reaction monitored on chiral method, mobile phase (80:20) ratio of n-Hexane: Ethanol, column used CHIRALPAK-AD-H, particle size 5 µm, dimensions 4.6 mmϕ × 250 mmL flow rate 1 mL min^{-1}, UV = 205 nm, Column Oven Temperature 25 °C, sampler temperature 15 °C.

General procedure for the ugi reaction: (Ugi products 4, 5, 6, 7, 8)

Procedure for ethyl-(benzyloxy)-1-oxo-3-phenylpropan-2-yl) amino)-1-oxopropan-2-yl) amino)-4-phenylbutanoate (8)

A solution of ethyl-2-amino 4-phenyl butanoate (1 g. 4.8 mmol), acetaldehyde (0.2 g, 4.8 mmol) in methanol was stirred for 20–30 min. To this solution, a solution benzyl-2-isocyno-3-phenyl propionate (1.27 g, 4.8 mmol) in methanol (5 mL) was added followed by $TiCl_4$ (5 mol %) (0.045 g). The reaction mixture was stirred for 24 h. The progress of the reaction was monitored by TLC (ethyl acetate: hexane, 1:1). After

completion of reaction, the reaction mixture was evaporated under reduced pressure at 45 °C. Residue was extracted with ethyl acetate (10 mL) and washed with brine. The organic layer was separated and dried over sodium sulfate. The organic layer was concentrated under reduced pressure at 40–45 °C to get mixture diastereomers **(8)** and **(9)** as thick oil (80%). The mixture of diastereomers was chromatographically inseparable. The mixture of diastereomers **(8)** and **(9)** was filtered through silica gel bed to remove other impurities[1–3] (Table 1).

The mixture of diastereomers **(8)** and **(9)** was dissolved in ethyl acetate (5 vol) and a solution of maleic acid (1 mmol) in ethyl acetate (5 vol) was added. The reaction mixture was stirred till solid formation observed. The solid obtained was filtered and washed with cold ethyl acetate to get maleate salt of diastereomer **(8)**.

A mixture of maleate salt of diastereomer **(8)** and aqueous saturated $NaHCO_3$ (5 vol) in ethyl acetate (5 vol) was stirred for 5–10 min. at room temperature. Organic layer was separated and dried over anhydrous Na_2SO_4. It was evaporated to get diastereomer **(8)** as thick yellow oil.

Ethyl-(benzyloxy)-1-oxo-3-phenylpropan-2-yl) amino)-1-oxopropan-2-yl) amino)-4-phenylbutanoate (8)

Yield 60%, 1.2 g. thick yellow oil. $[\alpha]_D^{25}$ – 19.8 (c 0.5, MeOH). IR (KBr) υ_{max} 699, 1182, 1247, 1505, 1604, 1682, 1732, 2928 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$), δ (ppm) 1.26–1.29 (m, 6 H), 1.66–1.74 (m. 2 H), 1.79–1.85 (m, 1 H), 2.42–2.60 (m, 2 H), 3.05 (q, $J = 7$ Hz, 1 H), 3.12–3.22 (m, 3 H), 4.11–4.20 (m, 2 H), 4.93–4.97 (m, 1 H), 5.15 (d, $J = 12$ Hz, 1 H), 5.19 (d, $J = 12$ Hz, 1 H), 7.03–7.05 (m, 2 H), 7.07–7.16 (m, 3 H), 7.19–7.22 (m, 3 H), 7.27–7.39 (m, 7 H), 7.68 (d, $J = 9$ Hz, 1 H, Amide). ^{13}C NMR (125 MHz) δ: 14.2, 20.2, 31.9, 35.5, 37.8, 52.2, 57.5, 60.4, 61.0, 67.2, 125.9, 127.1, 128.3, 128.3, 128.4, 128.5, 128.6, 128.6, 129.3, 135.1, 135.6, 141.4, 171.2, 174.4, 175.0. HRMS calculated (m/z) $[M + H]^+$: 517.2624; Found; 517.2623. Chiral HPLC = 100%.

Conclusion

In conclusion, we have demonstrated the effectiveness of $TiCl_4$ catalyzed Ugi three component reactions for the synthesis of quinapril HCl. A highly efficient, and atom economy methodology for the chirally pure quinapril hydrochloride (ACE inhibitor) synthesis has been established. Hence, these efficient procedures regarded as a new and time saving future method for the preparation of pharmaceutically relevant phenylacetimidamide, phenylacetamide, and α-amino acid derivatives (Fig. 1).

General experimental details, characterization of Ugi products 3 to 12 are available in Supporting information.

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