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Organocatalytic Synthesis of α,α–Diaryl Substituted α–Amino Acid Derivatives by an Interrupted Three-Component Ugi Reaction

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THIS PAPER IS DEDICATED TO PROF. KATA MLINARIĆ-MAJERSKI ON THE OCCASION OF HER 70TH BIRTHDAY

Abstract: An organocatalytic interrupted three-component Ugi reaction for the synthesis of α,α–diaryl α–amino acid derivatives is described. The transformation proceeds with a range of isocyanides and 3-aryl isoindolinone alcohols using Brønsted acid catalysts to afford products in good to excellent yields. Based on the obtained results, a reaction mechanism is proposed and discussed.

Keywords: organocatalytic synthesis, α,α–disubstituted amino acids, Ugi reaction.

INTRODUCTION

THE quaternary carbon stereocenter is a structure that represents a minimalistic molecular framework with enhanced (bio)chemical stability and embedded propensity to encode directionality in the three-dimensional space. Over the past decade, several efficient approaches addressing *de novo* construction of cyclic quaternary carbon stereocenters have been developed.[1] One of the most important class of non-natural compounds possessing quaternary carbon center are α,α–disubstituted α–amino acids.[2] Replacement of the α–hydrogen atom of α–amino acids with an alkyl or aryl substituent changes the properties of amino acids, such as increased chemical stability and hydrophobicity, the restriction of conformational freedom of amino acids' side chains, and the restriction of conformational freedom and metabolic stability of their peptides.[3] Due to these advantages, α,α–disubstituted α–amino acids have been in focus as non-proteinogenic amino acids in medicinal chemistry. Synthetically, the most efficient strategy is the addition of carbon nucleophiles to α–imino esters, since it can simultaneously construct a carbon skeleton and a quaternary carbon center,[4] and syntheses providing α,α–dialkyl and α,α–alkyl-aryl substituted α–amino acid derivatives have been developed.[5]

We were interested in the development of a general organocatalytic method for the synthesis of α,α–diaryl α–amino acid derivatives. Currently, there is a selected number of metal-catalyzed protocols for the generation of these compounds. It was reported that rhodium[6] and palladium[7] can catalyze the addition of arylboronic acids to five-membered cyclic *N*-sulfonyl ketimines substituted with an ester group to give α,α–diaryl α–amino acid derivatives. Recently, copper-catalyzed photoredox alkylations of imines[8] and CO_2 fixation with imines driven by visible light[9] have been reported.

We opted for the synthesis of isoindolinone-based units as α,α–diaryl α–amino acid surrogates, embedded in a formal dipeptide building block (Figure 1).

Isoindolinone cores are a common motif to a variety of compounds with potent biological activities. For example, these heterocycles have been established as precursors to anti–ischemic stroke agents,[10] MDM2–p53 protein–protein,[11] HIV–1 integrase,[12] and protein–tyrosine phosphatase inhibitors,[13] as well as antimicrobial[14] and antitumor[15] agents. In addition, molecules containing the 3–substituted isoindolinone unit are registered anxiolytic,[16] anticonvulsant[17] and antihypertensive[18] drugs.

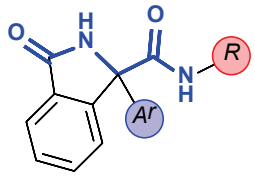


Figure 1. Peptide building block with an α,α–diaryl α–amino acid.

EXPERIMENTAL

General Information

Chemicals and solvents were purchased from commercial suppliers and used as received. Flash column chromatography was carried out using silica gel (Merck, 40–63 µm particle size). NMR spectra were recorded on Bruker Avance 600 and 300 MHz spectrometers, operating at 150.92 or 75.47 MHz for 13C and 600.13 or 300.13 MHz for 1H nuclei. Chemical shifts are quoted in ppm and are referenced to the residual nondeuterated solvent peak. Spectra were acquired at 298 K. Infrared spectra were recorded on a Varian UV/vis Cary 4000 spectrometer equipped with an attenuated total reflectance attachment with internal calibration. Absorbtion maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Mass spectrometry measurements were performed on an HPLC system coupled with a triple quadrupole mass spectrometer, operating in a positive electrospray ionization (ESI) mode. Melting points were determined using an Electro-thermal 9100 apparatus in open capillaries and are uncorrected. Compound names are those generated by ChemBioDraw Ultra 12.0 following IUPAC conventions. Substrates, 3-aryl 3-hydroxyisoindolinones, were synthesized in high yields from readily available starting materials, by employing addition of a Grignard or organolithium reagent to phthalimide or 5,6-dichlorophthalimide.[20]

General Procedure

To a flame-dried Schlenk tube containing 3-hydroxy 3-isoindolinone (0.1 mmol), benzoic acid (0.01 mmol) and phenylphosphinic acid (0.02 mmol) in acetonitrile (2 mL) was added isocyanide (0.2 mmol), and the reaction mixture was stirred overnight at 80 °C. Solvent was evaporated, and the crude reaction mixture was purified by flash column chromatography in petrol-ethyl acetate.

N-(TERT-BUTYL)-3-OXO-1-PHENYLISOINDOLINE-1-CARBOXAMIDE (1)

White solid. Yield: 27 mg (88 %). Column chromatography eluent: petrol-ethyl acetate 1 : 1. mp 125.8–129.1 °C. ^{1}H NMR (300 MHz, CDCl3) δ 8.05 (br s, 1H), 7.85–7.77 (m, 2H), 7.66–7.59 (m, 1H), 7.56–7.49 (m, 1H), 7.34–7.25 (m, 5H), 6.62 (br s, 1H), 1.33 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.4, 168.6, 146.9, 139.5, 133.0, 130.1, 129.1, 128.9, 128.4, 126.2, 125.3, 123.8, 71.8, 52.0, 28.5. ν_{max} 3231, 1655, 1469, 1306, 1145, 697, 563. ESI-MS: *m* / *z* 309 [M+H$^+$].

N-CYCLOHEXYL-3-OXO-1-PHENYLISOINDOLINE-1-CARBOXAMIDE (2)

Colorless oil. Yield: 25 mg (75 %). Column chromatography eluent: petrol-ethyl acetate 1 : 1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87–7.78 (m, 2H), 7.69–7.58 (m, 2H), 7.58–7.50 (m, 1H), 7.35–7.24 (m, 5H), 6.75 (d, *J* = 8.0 Hz, 1H), 3.86–3.69 (m, 1H), 2.04–1.95 (m, 1H), 1.77–1.67 (m, 2H), 1.64–1.53 (m, 2H), 1.43–0.97 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.2, 168.6, 146.8, 139.3, 133.1, 130.1, 129.2, 128.9, 128.5, 126.3, 125.2, 123.9, 71.5, 49.0, 32.9, 32.6, 25.4, 24.8, 24.7. ν_{max} 3228, 2933, 1641, 1478, 1291, 1101, 688. ESI-MS: *m* / *z* 335 [M+H$^+$].

METHYL 2-(3-OXO-1-PHENYLISOINDOLINE-1-CARBOXAMIDO)ACETATE (3)

Colorless oil. Yield: 16 mg (50 %). Column chromatography eluent: petrol-ethyl acetate 1 : 2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.66–7.62 (m, 1H), 7.57–7.53 (m, 1H), 7.44 (br t, *J* = 4.8 Hz, 1H), 7.31 (m, 5H), 7.26 (s, 1H), 7.25 (br s, 1H), 4.15 (dd, *J* = 18.1, 5.9 Hz, 1H), 3.96 (dd, *J* = 18.1, 5.2 Hz, 1H), 3.71 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 170.4, 169.9, 146.2, 138.8, 133.2, 130.3, 129.5, 128.9, 128.7, 126.6, 125.0, 124.1, 71.5, 52.4, 41.5. ν_{max} 3293, 2952, 1668, 1519, 1206, 694, 541. ESI-MS: *m* / *z* 325 [M+H$^+$].

5,6-DICHLORO-N-CYCLOHEXYL-3-OXO-1-PHENYLISOINDOLINE-1-CARBOXAMIDE (5)

White solid. Yield: 12 mg (29 %). Column chromatography eluent: petrol-ethyl acetate 1 : 1. mp 202.4–206.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.81 (s, 1H), 7.36–7.22 (m, 5H), 6.82 (br s, 1H), 3.88–3.71 (m, 1H), 2.02–1.93 (m, 1H), 1.80–1.70 (m, 2H), 1.61–1.50 (m, 2H), 1.37–1.14 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.1, 168.1, 146.1, 138.8, 133.9, 130.9, 128.9, 128.6, 128.4, 125.7, 125.7, 123.1, 71.8, 49.1, 32.7, 32.5, 25.8, 24.7, 24.6. ν_{max} 3206, 2931, 1638, 1530, 1305, 1015, 693. ESI-MS: *m* / *z* 403 [M+H$^+$].

N-CYCLOHEXYL-1-(4-METHOXYPHENYL)-3-OXOISOINDOLINE-1-CARBOXAMIDE (6)

Colorless oil. Yield: 19 mg (53 %). Column chromatography eluent: petrol-ethyl acetate 1 : 1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84–7.78 (m, 2H), 7.65–7.60 (m, 1H), 7.56 (br s, 1H), 7.55–7.52 (m, 1H), 7.21–7.18 (m, 2H), 6.84–6.80 (m, 2H), 3.78–3.75 (m, 4H), 1.99 (d, *J* = 11.6 Hz, 1H), 1.82–1.69 (m, 2H), 1.65–1.48 (m, 3H), 1.37–1.16 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.3, 168.8, 159.6, 147.1, 133.2, 131.2, 130.0, 129.2, 127.7, 125.2, 123.8, 114.3, 71.1, 55.3, 49.0,

32.9, 32.6, 25.4, 24.9, 24.8. ν_{max} 3281, 2931, 1667, 1509, 1249, 1178, 1027, 744. ESI-MS: *m* / *z* 365 [M+H$^+$].

N-CYCLOHEXYL-1-(3-METHOXYPHENYL)-3-OXOISOINDOLINE-1-CARBOXAMIDE (7)

White solid. Yield: 21 mg (59 %). mp 183.1–186.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88–7.81 (m, 2H), 7.70–7.60 (m, 2H), 7.59–7.50 (m, 1H), 7.27–7.20 (m, 1H), 6.94–6.82 (m, 3H), 6.76 (d, *J* = 8.0 Hz, 1H), 3.81–3.73 (m, 4H), 2.07–1.94 (m, 1H), 1.82–1.68 (m, 3H), 1.67–1.51 (m, 3H), 1.36–1.06 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 168.5, 159.9, 146.6, 140.7, 133.1, 130.1, 130.0, 129.3, 125.3, 123.9, 118.5, 113.54, 112.7, 71.4, 55.2, 49.0, 32.9, 32.6, 25.4, 24.8, 24.7. ν_{max} 3296, 2939, 1707, 1514, 1258, 1032, 740, 692, 545. ESI-MS: *m* / *z* 365 [M+H$^+$].

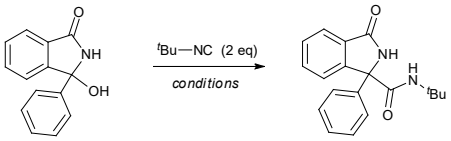
METHYL 2-(3-OXO-1-(4-(TRIFLUOROMETHYL)PHENYL)ISOINDOLINE-1-CARBOXAMIDO)ACETATE (8)

Colorless oil. Yield: 25 mg (64 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (br s, 1H), 7.84–7.74 (m, *J* = 12.4, 7.6 Hz, 3H), 7.70–7.61 (m, 1H), 7.60–7.50 (m, 5H), 4.10 (dd, *J* = 12.4, 5.6 Hz, 1H), 3.97 (dd, *J* = 12.2, 5.3 Hz, 1H), 3.68 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 170.0, 161.1, 145.7, 142.7, 133.5, 130.1 (d, *J* = 2.6 Hz), 129.8, 128.4, 127.2, 125.9 (q, *J* = 3.8 Hz), 125.0, 124.2, 71.1, 52.5, 41.6. ESI-MS: *m* / *z* 393 [M+H$^+$].

RESULTS AND DISCUSSION

Our strategy was based on the envisaged interruption of the Ugi reaction. In a classic four-component Ugi reaction, an imine (either preformed or generated *in situ* from an aldehyde or a ketone and an amine), a carboxylic acid and an isocyanide generate a formal dipeptide unit. If ketones are used, obtained products are *α,α*–disubstituted *α*–amino acid derivatives comprising a tertiary amide moiety. In order to generate *α,α*–diaryl *α*–amino acid derivatives, diaryl ketones are required as a carbonyl component. However, these species do not easily form imines with amines, and if they do, generated imines are very stable and usually unreactive. In our approach, diaryl-ketimine is generated *in situ* from 3-hydroxy 3-substituted isoindolinone. Thus formed

Table 1. Reaction optimization.



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Entry	Temp.	Solvent	Acid	Catalyst	Time (h)	Yield[a] / %
1	rt	MeCN	benzoic acid (1 eq)	–	16	–
2	rt	MeCN	benzoic acid (1 eq)	phenylphosphinic acid (1 eq)	16	77
3	rt	MeCN	–	phenylphosphinic acid (1 eq)	16	–
4	rt	Toluene	benzoic acid (1 eq)	phenylphosphinic acid (1 eq)	16	11
5	rt	DCM	benzoic acid (1 eq)	phenylphosphinic acid (1 eq)	16	traces
6	rt	MeOH	benzoic acid (1 eq)	phenylphosphinic acid (1 eq)	2	–[b]
7	rt	MeCN	benzoic acid (1 eq)	phenylphosphinic acid (20 mol%)	120	74
8	50 °C	MeCN	benzoic acid (1 eq)	phenylphosphinic acid (20 mol%)	16	83
9	50 °C	MeCN	benzoic acid (10 mol%)	phenylphosphinic acid (20 mol%)	72	71
10	**80 °C**	**MeCN**	**benzoic acid (10 mol%)**	**phenylphosphinic acid (20 mol%)**	**16**	**88**
11	80 °C	MeCN	benzoic acid (20 mol%)	phenylphosphinic acid (10 mol%)	72	39
12	80 °C	MeCN	benzoic acid (10 mol%)	toluenesulfonic acid (20 mol%)	4	traces[c]
13	80 °C	MeCN	acetic acid (10 mol%)	phenylphosphinic acid (20 mol%)	16	traces[c]
14	80 °C	MeCN	benzoic acid (5 mol%)	phenylphosphinic acid (10 mol%)	120	62
15	80 °C	MeCN	benzoic acid (10 mol%)	phenylphosphinic acid (20 mol%)	16	91[d]

[a] isolated yield of **1**.

[b] quantitative formation of 3-phenyl 3-methoxyisoindolinone.

[c] hydrolysis of ^{t}Bu–NC.

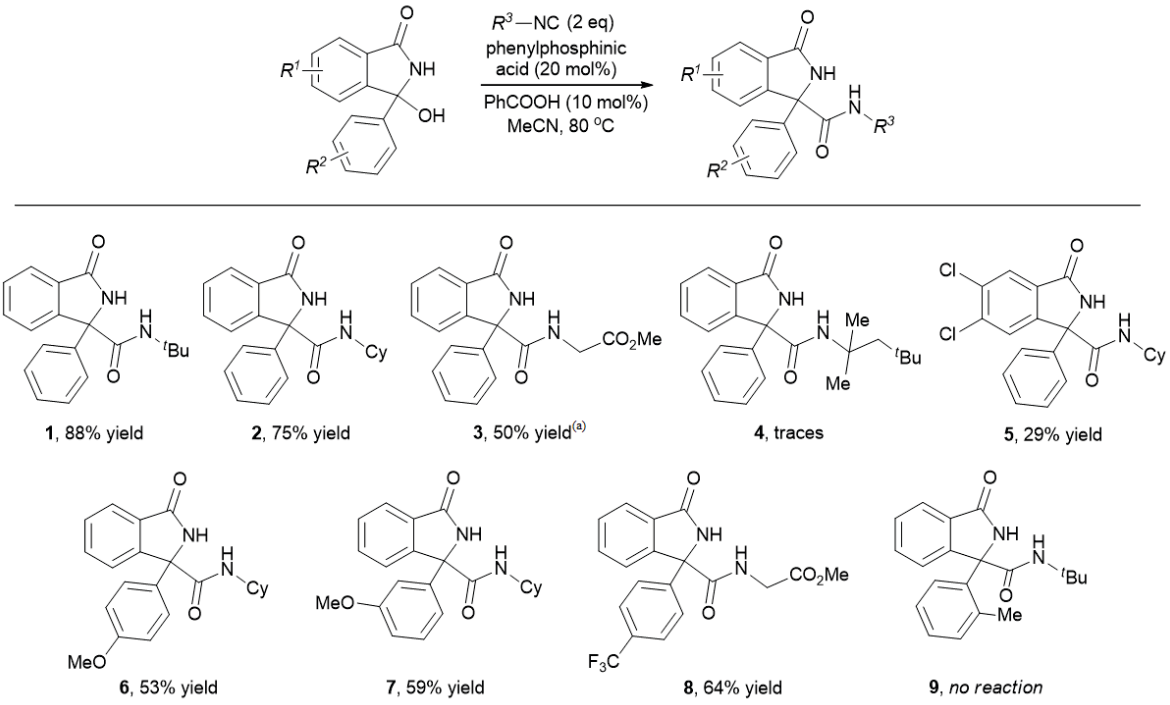
[d] ^{t}Bu–NC (5 eq).

N-acyl diaryl-ketimine is highly reactive, and readily reacts with nucleophiles. We reasoned that the acyl transfer in the last step of the Ugi reaction (Mumm rearrangement) would be prevented due to the fact that the amide is a very poor nucleophile. Instead, water would act as a nucleophile, leading to the desired product. Based on our previous results,[19] carboxylic acids are not acidic enough to induce the elimination of water. Hence, non-nucleophilic Brønsted acid organocatalyst would be have to be introduced for the successful formation of the ketimine intermediate.

We started our investigations by combining 3-phenyl 3-hydroxyisoindolinone and *tert*-butyl isocyanide in acetonitrile under various reaction conditions (Table 1).

Our initial attempt with benzoic acid (1 eq) at room temperature did not yield product (entry 1), confirming our hypothesis that benzoic acid could not protonate the hydroxy group. Hence, non-nucleophilic Brønsted acid was introduced into the reaction. When phenylphosphinic acid (1 eq) was employed, product **1** was obtained after 16 hours at room temperature in 77 % isolated yield (entry 2). We tested the possibility whether carboxylic acid is required for the transformation; the omission of benzoic acid from the reaction mixture did not yield desired product (entry 3). Next, we investigated the influence of various solvents on the reaction outcome. Conducting the reaction in toluene yielded product **1** in 11 % yield (entry 4), while the product was observed only in traces when the reaction was performed in dichloromethane (entry 5). These results suggest that non-polar solvents are not suitable for this transformation. When methanol was used, complete conversion of the substrate occured after 2 hours, though product **1** was not detected. Instead, 3-phenyl 3-methoxyisoindolinone was isolated in almost quantitave yield as a result of a nucleophilic attack of methanol to ketimine (entry 6).

Obtained results suggest that both carboxylic acid and non-nucleophilic Brønsted acid act as catalysts, since none of them are incorporated into the final product and the reaction does not occur without any of them (entries 1–3). First, the amount of phenylphosphinic acid was lowered to 20 mol%, and the product was obtained in 74 % yield after 5 days (entry 7). Performing the reaction at 50 °C accelerated the formation of the product, and in an overnight reaction it was isolated in 83 % yield (entry 8). Next, we tested the hypothesis whether benzoic acid could also be employed in the catalytic amount. Employing 10 mol% of benzoic acid with 20 mol% of phenylphosphinic acid at 50 °C resulted in product **1** in 71 % yield after 72 hours (entry 9). Increasing the temperature to 80 °C significantly accelerated the reaction, and the product was afforded in 88 % yield (entry 10). We also tested whether



(a) 89% yield with 10 eq of isocyanide added in 1 eq portions within 4 days

Figure 2. Substrate scope.

the amounts of catalysts in respect to each other have any influence on the reaction outcome. When catalyst loadings were switched (20 mol% of benzoic acid, and 10 mol% of phenylphosphinic acid), only 39 % of the product was isolated after 72 hours (entry 11).

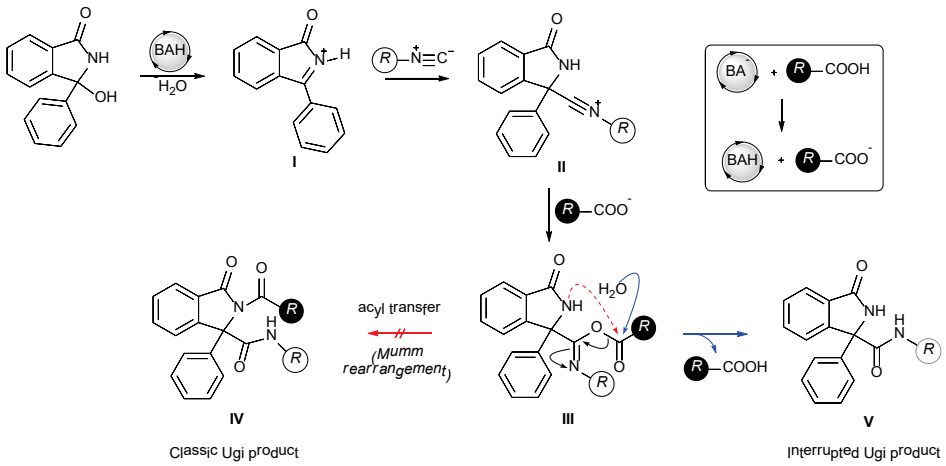
Stronger non-nucleophilic Brønsted acid catalyst was tested in order to see its impact on the reaction outcome. When toluenesulfonic acid was employed, after 4 hours only traces of the product were detected, and the reaction stopped. Most likely the isocyanide is hydrolized to its corresponding formamide, since it cannot be detected in the reaction mixture (entry 12). The same result, albeit after 16 hours, was obtained when benzoic acid was swapped with acetic acid (entry 13). Lowering catalysts loadings even further resulted in much slower formation of the product (entry 14), while increasing of the amount of isocyanide to 5 eq did not change the reaction time or the isolated yield of **1** (entry 15). Hence, the optimized procedure employed 3-aryl 3-hydroxyisoindolinone (1 eq), isocyanide (2 eq), benzoic acid (10 mol%) and phenylphosphinic acid (20 mol%) in acetonitrile at 80 °C.

With optimized reaction conditions in hand, we turned our attention to investigate the substrate scope and reaction limitations. We examined the formation of products with various isocyanides and 3-aryl 3-hydroxyisoindolinones (Figure 2).

3-phenyl 3-hydroxyisoindolinone reacted efficiently with several different isocyanides. Employing cyclohexyl isocyanide under the optimized reaction conditions yielded product **2** in 75 % isolated yield. In order to generate a formal dipeptide unit building block, methyl isocyanoacetate was introduced as a source of glycine. Though the product **3** was obtained in moderate yield, facile deprotection of methyl ester would enable further growth of the peptide chain. Considering isocyanide hydrolysis, additional portions of 1 eq of isocyanide were added sequentially until starting material was completely consumed. Although the yield was increased to 89 %, 10 eq of cyclohexyl isocyanide were required and the reaction time was prolonged to 4 days. Using 1,1,3,3-tetramethylbutyl isocyanide yielded only traces of product **4**. Most likely bulkiness of the isocyanide significantly increases steric hindrance around the reaction center, and thus hinders product formation. Futhermore, we investigated the reactivity of 3-aryl 3-hydroxyisoindolinone substrates. When 4,5-dichloro substituent was introduced on the isoindolinone ring, product **5** was obtained in poor yield, most likely due to the deactivation of the reaction center. The introduction of electron-donating groups at different positions on the 3-aryl ring of 3-hydroxyisoindolinone resulted in moderate yields (**6**, 53 % and **7**, 59 %). The substrate bearing a *para*-substituted trifluoromethyl group was also well tolerated and it furnished product **8** in 64 % yield. On the other hand, 3-hydroxyisoindolinone bearing an *ortho*-substituted aryl ring did not yield desired product **9**, most likely due to increased steric congestion around the reaction center.

Based on the observed results, we propose the following reaction mechanism of the developed interrupted Ugi reaction (Scheme 1).

Following the protonation of 3-hydroxy isoindolinone by non-nucleophilic Brønsted acid, water is eliminated, and a reactive ketimine intermediate **I** is formed. Nucleophilic addition of the isocyanide with its terminal carbon atom generates nitrilium ion **II**. Brønsted acid is reprotonated by the carboxylic acid, and the carboxylic acid anion reacts with intermediate **II** to generate species **III**. In a classic Ugi reaction, an acyl transfer would occur in this step, resulting in Ugi product **IV**. However, nitrogen in the intermediate **III** is part of the amide bond and, thus, a very poor nucleophile. Instead, intermediate **III** is trapped by water, followed by elimination of the carboxylic acid, which leads to the final product **V**.



Scheme 1. Proposed reaction mechanism.

CONCLUSION

In conclusion, we developed an interrupted Ugi reaction for the synthesis of α,α–diaryl amino acid derivatives. The reaction proceeds with various isocyanides and 3-aryl 3-hydroxyisoindolinones in moderate to excellent yields. Incorporation of these building blocks in a peptide chain, as well as developing an asymmetric variant of the reaction are currently under way and will be reported in due course.

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