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Synthesis of Functionalized Pseudopeptides through Five-Component Sequential Ugi/Nucleophilic Reaction of *N*-Substituted 2-Alkynamides with Hydrazides

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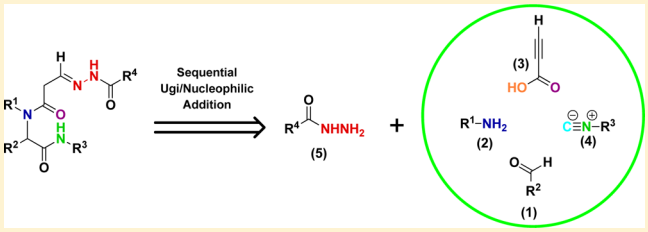
Supporting Information

ABSTRACT: Five-component sequential Ugi/nucleophilic addition reaction of aromatic aldehydes, primary amines, propiolic acid, isocyanides, and hydrazides has been developed in order to access polyfunctional pseudopeptides. The reaction may proceed through formation of *N*-substituted 2-alkynamides as intermediates. This process is found to be mild and operationally simple with broad substrate scope.



INTRODUCTION

Development of strategies for the facile construction of highly functionalized molecules with a diverse range of complexity via multicomponent reactions has recently attracted much attention and is now widely recognized as a first choice opportunity in the preparation of macromolecules with a high bond-forming efficiency (BFE) under simple and mild reaction conditions.[1] To accomplish this purpose, a combination of multicomponent reaction with an efficient post transformation, typically a ring formation process or nucleophilic addition,[2] has been proven to be a powerful tool for the synthesis of highly functionalized compounds.

To develop an efficient sequential multicomponent reaction, selecting functionalized starting materials has an essential role. For example, in light of our recent research reports, Ugi 4-CR reaction of aromatic aldehydes, primary amines, propiolic acid, and isocyanides leading to *N*-substituted 2-alkynamides has further applications in nucleophilic addition and stereoselective synthesis of enaminones and dithiocarbamates.[3]

We have recently initiated a research program to develop transition-metal-free efficient sequential Ugi/nucleophilic addition reactions as a promising approach for nucleophilic addition of hydrazides to *N*-substituted 2-alkynamides. The direct addition of primary or secondary amines to alkynes is known as hydroamination reaction, which needed metal catalysts.[4] This approach is an atom-efficient route to new, synthetically useful, and biologically significant organonitrogen compounds.[5,6]

Although it is thermodynamically favorable, the high activation barrier for the hydroamination reaction under normal conditions means a catalyst is required to make the reaction practical.[7] Several catalysts have been utilized for this reaction such as calcium,[8] rhodium,[9] palladium,[10] iridium,[6,11] ruthenium,[12] lanthanides,[13] actinides,[14] and titanium.[15] Restrictions in these previous works include lack of generality, limited functional group tolerance, lengthy synthetic sequences, and harsh reaction conditions.

To the best of our knowledge, there are a limited number of reports of direct addition of hydrazides to alkynes in the literatures.[6,16] In continuation of our research for the construction of new polyfunctional compounds through multicomponent reactions, we became interested in synthesis of pseudopeptides via the addition of hydrazides to alkynamides. Herein we report a novel approach for the synthesis of functionalized psedopeptides through sequential Ugi/nucleophilic addition reactions. The reactions were carried out in a "one-pot" two-step process (Scheme 1).

RESULTS AND DISCUSSION

The transition-metal-catalyzed hydroamination of alkynes with amines is a well-known process, which represents a promising arena for initial studies toward the development of a sequential process between activated alkynamides and hydrazides. In the first step, we tried to obtain our desired product by direct addition of benzhydrazide (**6a**) to Ugi 4-CR intermediate **5a** in the presence of DIEA in MeOH, without any catalyst or separation of intermediate. Unfortunately, neither strategy was ultimately successful. The results indicate that methanol in the presence of base was added as nucleophile to the active triple bond and functionalized methyl vinyl ether was produced instead of expected product **I** (Scheme 2).

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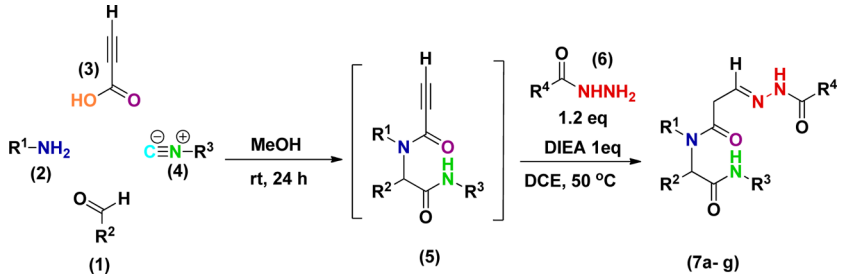
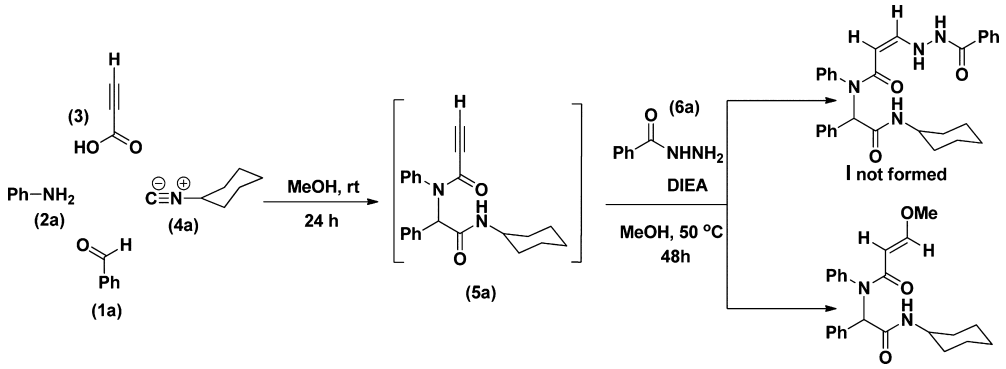
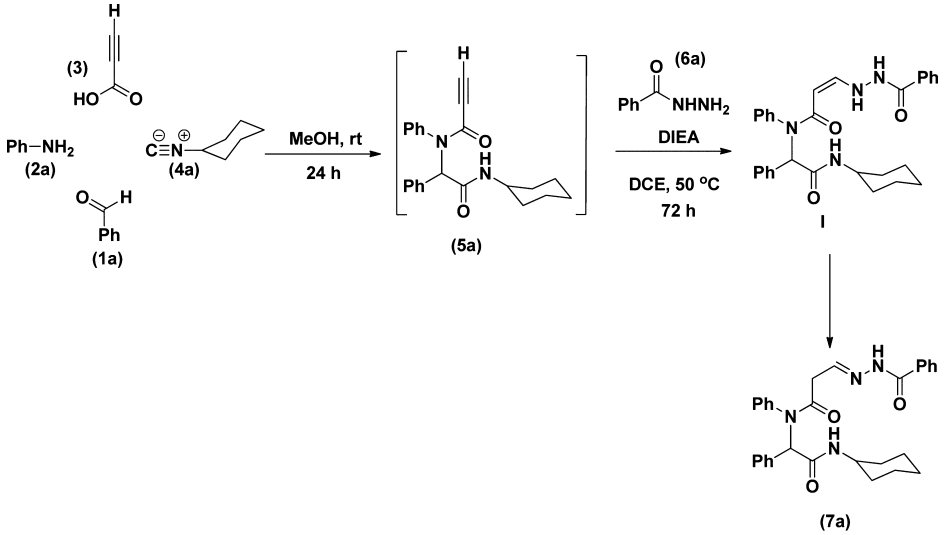
Scheme 1. Synthesis of Pseudopeptides (7a–g) via Sequential Ugi/Nucleophilic Addition Reactions



Scheme 2. Attempted Addition of Benzhydrazide to *N*-Substituted 2-Alkynamides 5a



Scheme 3. Synthesis of Pseudopeptide (7a) via Addition of Benzhydrazide to *N*-Substituted 2-Alkynamide (5a)



After failing to conduct this reaction in MeOH, we sought to replace the solvent of the nucleophilic addition sequence with a non-nucleophilic solvent. Fortunately, use of DCE as solvent leads to completion of the reaction. Ugi 4-CR was carried out in MeOH, and after evaporation of the solvent, without separating the Ugi 4-CR intermediate (**5a**), addition of benzhydrazide (**6a**, 1.2 equiv) was performed in the presence of (1equiv) DIEA as the base in DCE.

We envisioned the functionalized vinyl hydrazide **I** (Scheme 2) produced from hydroamination of *N*-substituted 2-alkynamide **5a** with benzhydrazide (**6a**) but ^{1}H NMR and X-ray crystallographic analysis proved structure of hydrazone **7a** as the sole product (Scheme 3).

The proposed mechanism for the synthesized of hydrazone **7a** is shown in Scheme 4. The Ugi-4CR with an active triple bond has high affinity toward nucleophilic addition, and the reaction could proceed without any catalyst or separation of intermediate **5a**. Following the formation of Ugi 4-CR intermediate (**5a**), benzhydrazide (**6a**) was added as nucleophile to the active triple bond and substrate **I** was formed. Then enamine–imine tautomerization converted compound **I** to hydrazone **7a** as sole product. Structure of compound **7a** was assigned by ^{1}H NMR spectroscopy with highly characteristic peaks with ABX pattern at 2.91–3.09 ppm for diastereotopic hydrogens.

X-ray crystallographic data confirmed the structure of the product **7a**. Figure 1 shows ORTEP structure of the compound **7a** and molecular associations which were caused by the intramolecular hydrogen bondings.

After optimization of reaction conditions, the scope of the reaction was extended to other *N*-substituted-2-alkynamides and

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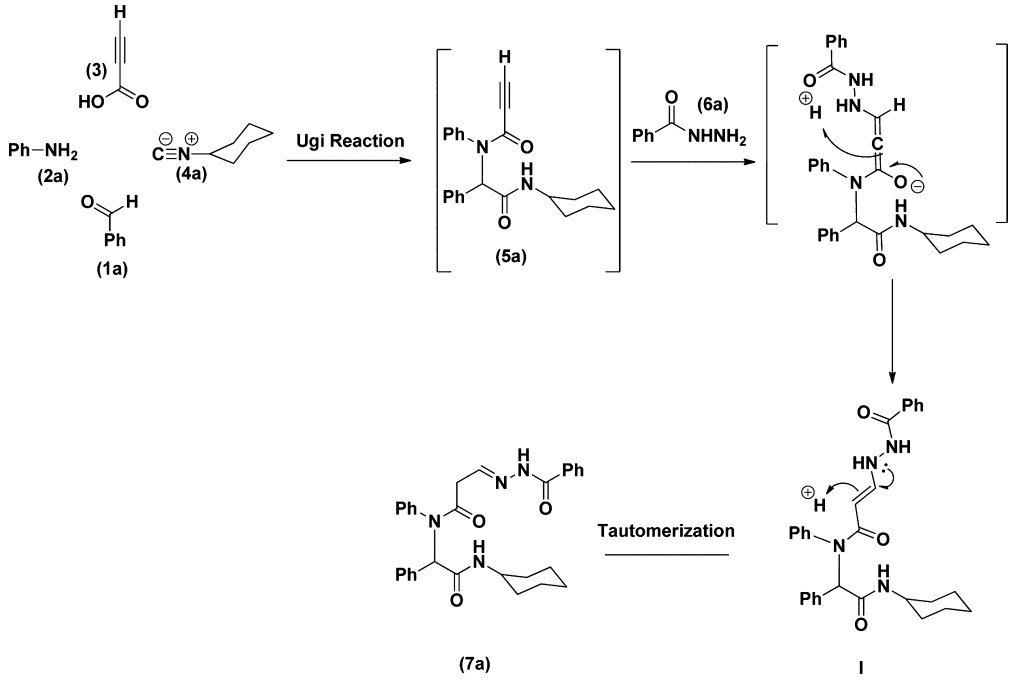
Scheme 4. Proposed Mechanism for Synthesis of Pseudopeptide (7a)



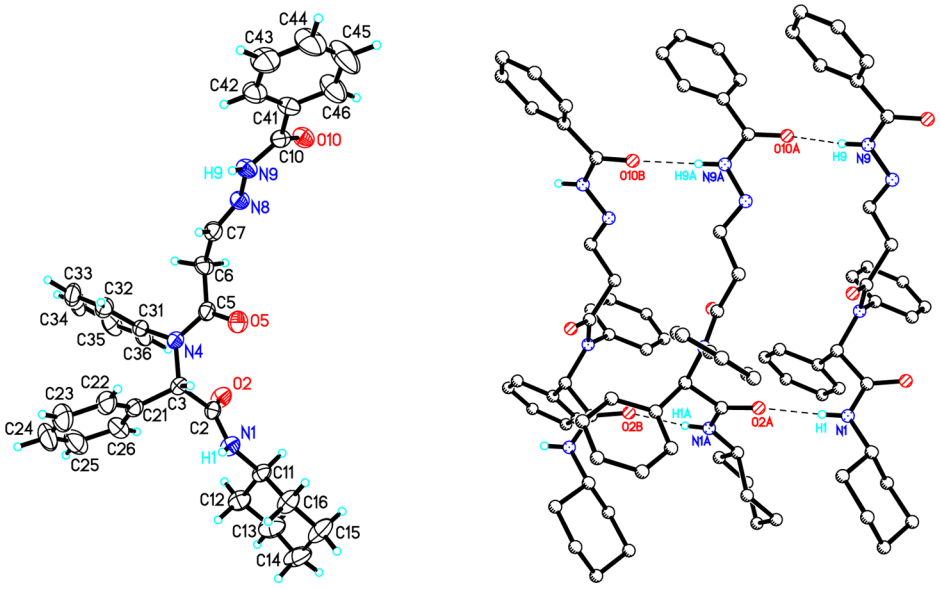


Figure 1. ORTEP structure and intramolecular association of compound **7a**.

different types of hydrazides as nucleophiles. The results are summarized in Table 1.

In another attempt, phenylpropiolic acid and methylpropiolic acid were used for the synthesis of desired *N*-substituted 2-alkynamides, but addition of hydrazides as nucleophiles was not successful and the Ugi-4CR was unactive to nucleophilic addition.

The products **7a**−**g** are functionalized hydrazones which are the same as the metal-catalyzed hydroamination reaction product.[6] Under metal-free reaction conditions, the formation of hydrazones could be obtained with good yields because of intramolecular hydrogen bondings and stabilized molecular associations. Next, to gain more insight into the reaction mechanism and broaden the chemical library of products, we investigated the addition of 3-phenylpropiolhydrazide and *p*-toluenesulfonhydrazide to the Ugi-4CR **5a** intermediate, which leads to vinyl hydrazides with different configurations (Scheme 5).

As can be seen in Scheme 5, addition of 3-phenylpropiolhydrazide (**6d**) to Ugi-4CR intermediate **5a** produced pseudopeptide **7h**, which contained the vinyl hydrazide group with *Z* configuration. The appearance of doublets at 5.22 and 6.22 ppm with J = 7.3 Hz for vinylic protons and also the deshielded chemical shift (δ 10.51 ppm) for NH reveals the formation of the *Z* configuration of compound **7h**. This data could confirm efficient intermolecular hydrogen bondings. When *p*-toluenesulfonhydrazide was used as nucleophile, the product showed characteristic peaks at δ 5.15 and 7.88 ppm with J = 12.9 Hz, which confirms the *E* configuration of compound **7i**. It seems that selective formation of *E* configuration is due to the

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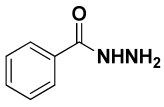
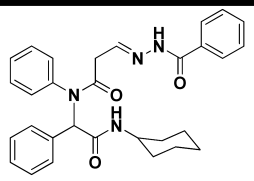
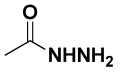
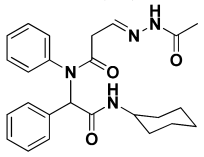
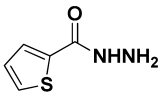
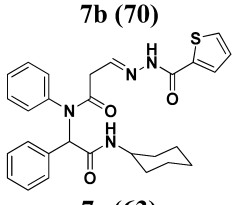
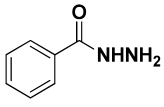
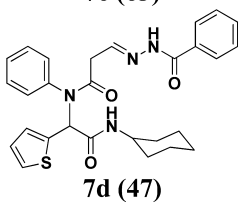
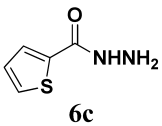
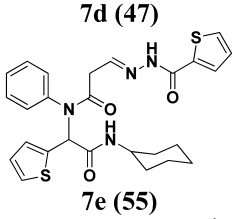
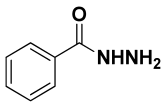
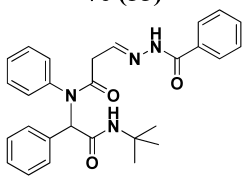
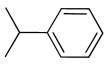
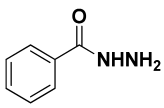
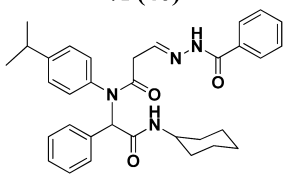
Table 1. Synthesis of Pseudopeptides via 5-Component Sequential Ugi/Nucleophilic Addition[a]

R^1	R^2	R^3	Hydrazide	Product (yield%)[b]
Ph	Ph	Cyclohexyl	 6a	 7a (72)
Ph	Ph	Cyclohexyl	 6b	 7b (70)
Ph	Ph	Cyclohexyl	 6c	 7c (63)
Ph	2-Thienyl	Cyclohexyl	 6a	 7d (47)
Ph	2-Thienyl	Cyclohexyl	 6c	 7e (55)
Ph	Ph	*t*-Bu	 6a	 7f (40)
	Ph	Cyclohexyl	 6a	 7g (52)

[a]Reactions condition: aromatic aldehydes (1 mmol), primary amines (1 mmol), propiolic acid (1 mmol), isocyanides (1 mmol), hydrazide (1.2 mmol), DIEA (1 mmol). [b]Monitored after 3−4 days.

thermodynamically more stable intermediate and there is not intermolecular hydrogen bonding.

Seemingly, the nature of hydrazides plays an important role in the appearance and type of hydrogen bondings and intramolecular associations and leads to formation of products with different stereoselectivity.

The proposed mechanism for the synthesis of compounds **7h,i** is shown in Scheme 6.

CONCLUSIONS

We have introduced a facile and efficient free-metal-catalyzed approach for nucleophilic addition of hydrazide to *N*-substituted-2-alkynamides which leads to functionalized psudopeptides containing hydrazones (**7a−g**) and vinyl hydrazide (**7h−j**) groups with high diversity and different stereoselectivity. The type of hydrazide could affect the configuration of vinyl

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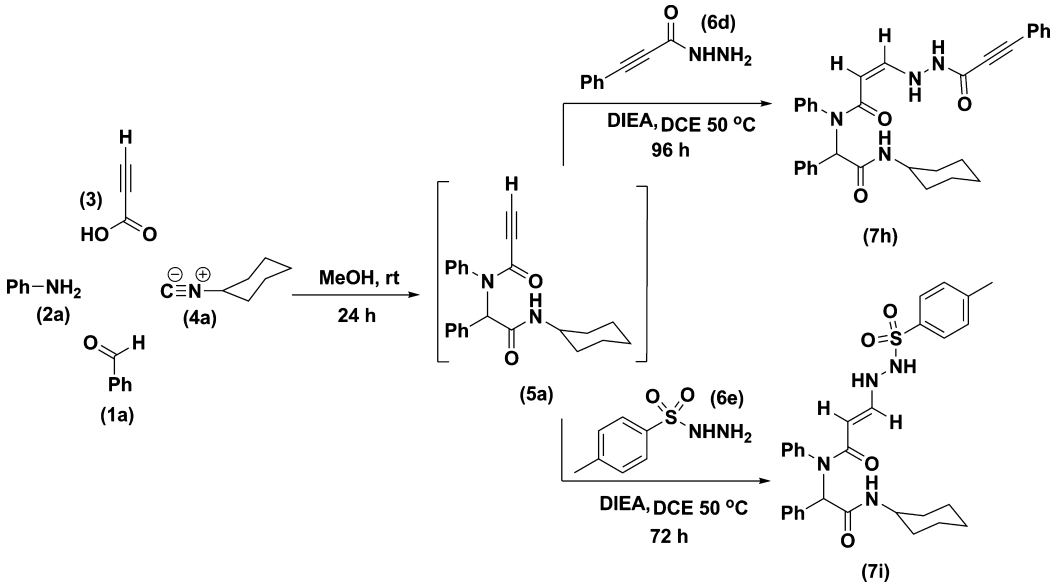
Scheme 5. Synthesis of Vinyl Hydrazide Pseudopeptides 7h−i



hydrazides. These features were exploited through the development of five-component sequential Ugi/Nucleophilic addition reaction. Several advantages, such as mild reaction conditions, simple and easy workup procedure, atomic economy, and high BFE are discussed.

EXPERIMENTAL SECTION

General Experimental Details. Commercially available materials were used without further purification. High-resolution mass spectra were recorded on a Mass-ESI-POS (Apex Qe-FT- ICR instrument) spectrometer.

General Procedure for the Synthesis of the Pseudopeptides 7a−j. To a solution of aldehyde **1** (1 mmol) in methanol (5 mL) was added the primary amine **2** (1 mmol), and the reaction mixture was stirred at room temperature for 1 h. Then, propiolic acid **3** (1 mmol) was added, and stirring was continued for 15 min, followed by addition of isocyanides **4** (1 mmol); the solution was stirred for 24 h at room temperature. The solvent was removed in vacuo, and DCE was added to the residue. Then hydrazide **7** (1.2 mmol) and DIEA (1 mmol) were added to the mixture. The reaction mixture was stirred at 50 °C for 3−4 days. The progress of the reaction was monitored using TLC (*n*-hexane−EtOAc 1:2). The precipitate which formed in the mixture of reaction was filtered off and washed with CH_2Cl_2.

*(E)-3-(2-Benzoylhydrazono)-N-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)-N-phenylpropanamide (**7a**):* isolated yield 72% (357 mg); mp 210−213 °C; IR (KBr, cm^{-1}) ν = 3255, 3071, 2931, 1553; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.96−1.23 (m, 5H), 1.50−1.76 (m, 5H), 3.00 (ABX, 2H, J = 16.7, 4.5 Hz), 3.48−3.70 (m, 1H), 6.05 (s, 1H), 7.05−7.14 (m, 10H), 7.37−7.55 (m, 3H), 7.78−7.84 (m, 3H), 7.12 (d, 1H, J = 7.1 Hz), 11.62 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.5, 24.6, 25.7, 32.2, 48.0, 63.6, 127.6, 128.0, 128.4, 130.1, 130.9, 131.7, 133.3, 135.2, 139.2, 146.9, 162.8, 168.5, 168.7; HR-MS (ESI) calcd for $C_{30}H_{33}N_4O_3$ $[M + H]^+$ 497.25510, found 497.25518, calcd for $C_{30}H_{32}N_4NaO_3$ $[M + Na]^+$ 519.23689, found 519.23685.

Colorless crystal (needle): dimensions 0.24 × 0.15 × 0.07 mm^3, crystal system orthorhombic, space group *Aba*2, Z = 8, a = 17.2631(12) Å, b = 35.327(3) Å, c = 8.9843(6) Å, α = 90°, β = 90°, γ = 90°, V = 5479.1(7) $Å^3$, ρ = 1.204 g/cm^3, T = 200(2) K, θ_{max}= 26.52 deg, radiation Mo Kα, λ = 0.71073 Å, 0.5 deg ω-scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 9.18 and a completeness of 99.5% to a resolution of 0.80 Å, 28519 reflections measured, 3028 unique (R(int) = 0.0363), 2670 observed ($I > 2\sigma(I)$). Intensities were corrected for Lorentz and polarization effects; an empirical absorption correction was applied using SADABS[17] based on the Laue symmetry of the reciprocal space, μ = 0.08 mm^{-1}, T_{min} = 0.98, T_{max} = 0.99; structure solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm using the SHELXTL (Version 2008/4) software package;[17] 342 parameters refined; hydrogen atoms were treated using appropriate riding models, except for the hydrogens at the nitrogen atoms N1 and N9, which were refined isotropically, Flack absolute structure parameter 0.0(15), goodness of fit 1.08 for observed reflections; final residual values R1(F) = 0.038, wR(F^2) = 0.095 for observed reflections, residual electron density −0.15 to 0.14 e $Å^{-3}$. CCDC 922255 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

*(E)-3-(2-Acetylhydrazono)-N-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)-N-phenylpropanamide (**7b**):* isolated yield 70% (303 mg); mp 210−211 °C; IR (KBr, cm^{-1}) ν = 3267, 3062, 1676, 1553; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95−1.22 (m, 5H), 1.49−1.81 (m, 5H), 1.95 (s, 3H), 2.79− 2.99 (ABX, 2H, J = 16.9 Hz), 3.54−3.67 (m, 1H), 6.02 (s, 1H, CH), 7.02−7.43 (m, 11H, CH), 7.99 (d, 1H, J = 6.3 Hz), 10.95 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.2, 21.4, 24.5, 24.7, 25.2, 25.3, 32.2, 47.9, 63.5, 127.6, 127.8, 128.4, 129.1, 130.1, 130.9, 135.2, 139.2, 141.6, 167.0, 168.5, 171.3; HR-MS (ESI) calcd for $C_{25}H_{31}N_4O_3$ $[M + H]^+$ 435.23983, found 435.23969, calcd for $C_{25}H_{30}N_4NaO_3$ $[M + Na]^+$ 457.22142, found 457.22135.

*(E)-N-(2-(Cyclohexylamino)-2-oxo-1-phenylethyl)-N-phenyl-3-(2-(thiophene-2-carbonyl)hydrazono)propanamide (**7c**):* isolated yield 63% (316 mg); mp 205−207 °C; IR (KBr, cm^{-1}) ν = 3267, 3064, 1657, 1552; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.98−1.17 (m, 5H), 1.40−1.75 (m, 5H), 2.95−3.22 (m, 2H), 3.50−3.80 (m, 1H), 6.07 (s, 1H), 6.66−7.11 (m, 10H), 7.41 (brs, 1H), 7.79−7.94 (m, 4H), 11.50 (brs, 1H, NH, *pro-Z*), 11.62 (brs, 1H, NH, *pro-E*); ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.5, 24.6, 25.1, 32.2, 47.9, 63.6, 127.2, 127.6, 127.8, 128.4, 128.7, 130.1, 130.9, 131.7, 135.2, 138.2, 139.2, 146.7, 168.5, 168.9, 169.8; HR-MS (ESI) calcd for $C_{28}H_{31}N_4O_3S$ $[M + H]^+$ 503.21193, found 503.21180, calcd for $C_{28}H_{30}N_4NaO_3S$ $[M + Na]^+$ 525.19340, found 525.19335.

*(E)-3-(2-Benzoylhydrazono)-N-(2-(cyclohexylamino)-2-oxo-1-(thiophene-2-yl)ethyl)-N-phenylpropanamide (**7d**):* isolated yield 47% (235 mg); mp 215−217 °C; IR (KBr, cm^{-1}) ν = 3245, 3065, 2932, 1654; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.00−1.23 (m, 5H), 1.50−1.80 (m, 5H), 3.00 (ABX, 2H, J = 17.0, 5.4 Hz), 3.47−3.60 (m, 1H), 5.74 (s, 1H), 6.90−7.45 (m, 10H), 7.50−7.53 (m, 1H), 7.75−7.84 (m, 2H), 8.08 (d, 1H, J = 7.2 Hz), 11.63 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.5, 24.6, 25.1, 31.7, 32.1, 35.3, 48.1, 66.1, 127.1,127.6, 127.8, 128.4,128.8, 130.1, 130.8, 131.7, 135.2, 138.2, 139.2, 146.7, 166.5, 167.7, 168.4; HR-MS (ESI) calcd for $C_{28}H_{31}N_4O_3S$ $[M + H]^+$

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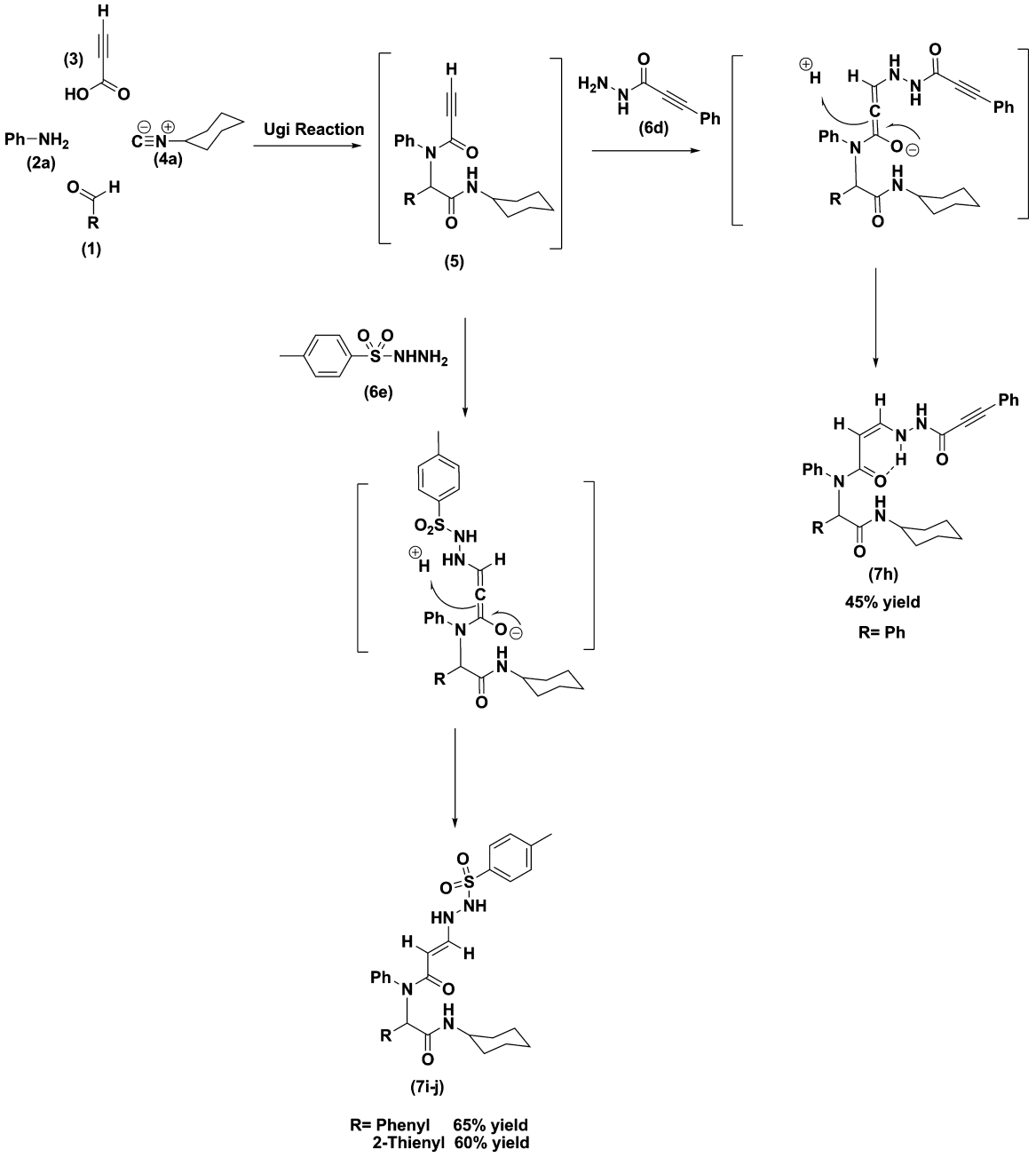
Scheme 6. Proposed Mechanism for Synthesis of Pseudopeptides 7h−j



503.21155, found 503.21148, calcd for $C_{28}H_{30}N_4NaO_3S$ $[M + Na]^+$ 525.19355, found 525.19331.

*(E)-N-(2-(Cyclohexylamino)-2-oxo-1-(thiophene-2-yl)ethyl)-N-phenyl-3-(2-(thiophene-2-carbonyl)hydrazono)propanamide (**7e**):* isolated yield 52% (279 mg); mp 228−230 °C; IR (KBr, cm^{-1}) ν = 3359, 3267, 3075, 2933, 1685, 1527;[1] H NMR (300 MHz, DMSO-d_6) δ 1.00−1.35 (m, 5H), 1.40−1.90 (m, 5H), 2.49−2.69 (m, 2H), 3.72 (m, 1H), 5.84 (s, 1H), 6.70−6.85 (m, 1H), 6.90−7.00 (m, 3H), 7.11−7.18 (m, 5H), 7.41 (d, 1H, J = 4.6 Hz), 7.63 (d, 1H), 7.75 (d, 1H, J = 4.8 Hz), 7.99 (d, 1H, J = 7.3 Hz), 9.98 (s, 1H, NH, *pro-Z*), 9.99 (s, 1H, NH, *pro-E*); ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.7, 25.3, 31.7, 32.0, 35.4, 49.3, 65.7, 126.2, 126.4, 127.3, 127.5, 127.9, 128.3, 129.3, 130.9, 136.8, 137.5, 140.7, 161.3, 166.5, 171.3; HR-MS (ESI) calcd for $C_{26}H_{29}N_4O_3S_2$ $[M + H]^+$ 509.16909, found 509.16884, $C_{26}H_{28}N_4NaO_3S_2$ $[M + Na]^+$ 531.15104, found 531.15080.

*(E)-3-(2-Benzoylhydrazono)-N-(2-(tert-butylamino)-2-oxo-1-phenylethyl)-N-phenylpropanamide (**7f**):* isolated yield 40% (188 mg); mp 200−201 °C; IR (KBr, cm^{-1}) ν = 3359, 3267, 3075, 2933, 1655, 1527; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.22 (s, 9H), 2.9−3.00 (ABX, 2H,16.5 Hz), 6.00 (s, 1H), 6.10−7.30 (m, 11H), 7.40−7.92 (m, 6H), 11.61 (s, 1H); ^{13}C NMR(75 MHz, DMSO-d_6) δ 28.4, 50.30, 63.8, 127.1, 127.5, 127.8, 128.4, 129.9, 130.1, 130.9, 131.6, 131.6, 133.3, 135.5, 139.3, 147.0, 162.7, 168.5, 168.9, 169.8; HR-MS (ESI) calcd for $C_{28}H_{31}N_4O_3$ $[M + H]^+$ 471.23953, found 471.23945, calcd for $C_{28}H_{30}N_4NaO_3$ $[M + Na]^+$ 493.22129, found 493.22124.

*(E)-3-(2-Benzoylhydrazono)-N-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)-N-(4-isopropylphenyl)propanemide (**7g**):* isolated yield 63% (279 mg); mp 187−190 °C; IR (KBr, cm^{-1}) ν = 3270, 3060, 2930, 1655, 1540; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.82−1.50 (m, 5H), 1.08 (d, 6H, J = 6 Hz,), 1.50−1.90 (m, 5H), 2.74−2.78 (m, 1H), 2.70−3.20 (ABX, 2H, J = 17.1, 4.4 Hz), 3.48−3.60 (m, 1H), 6.00 (s, 1H), 7.90−7.30 (m, 7H), 7.45−7.55 (m, 5H), 7.70−7.90 (m, 3H), 7.96 (d, 1H, J = 7.1 Hz), 11.62 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.7, 24.5, 24.6, 25.2, 30.9, 32.1, 47.9, 63.5, 126.2, 127.0, 127.5, 127.7, 128.2, 128.4, 129.8, 130.1, 130.6, 131.6, 133.2, 135.4, 136.8, 147,.0 147.9, 162.7, 168.4, 168.8; HR-MS (ESI)

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calcd for $C_{33}H_{39}N_4O_3$ [M + H]$^+$ 539.30347, found 539.30320, calcd for $C_{33}H_{38}N_4NaO_3$ [M + Na]$^+$ 561.28481, found 561.28463.

*(Z)-N-(2-(Cyclohexylamino)-2-oxo-1-phenylethyl)-N-phenyl-3-(2-(3-phenylpropioloyl)hydrazinyl)acrylamide (**7h**):* isolated yield 45% (234 mg); mp 217−220 °C; IR (KBr, cm^{-1}) ν = 3255, 3071, 2931, 2175, 1650, 1553; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.9−1.40 (m, 5H), 1.50−1.90 (m, 5H), 3.50−3.65 (m, 1H), 5.22 (d, 1H, J = 7.2 Hz), 5.84 (brs, 1H), 6.11 (s, 1H), 6.22 (d, 1H, J = 7.4 Hz), 6.96−7.52 (m, 15H), 8.05 (brs, 1H), 10.51 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.6, 24.8, 25.2, 32.2, 48.0, 63.4, 94.3, 126.9, 127.7, 127.6, 128.6, 128.7, 130.2, 130.7, 135.9, 139.8, 144.3, 161.8, 166.3, 168.6; HR-MS (ESI) calcd for $C_{32}H_{33}N_4O_3$ [M + H]$^+$ 521.25634, found 521.25608, calcd for $C_{32}H_{32}N_4NaO_3$ [M + Na]$^+$ 543.23691, found 543.23799.

*(E)-N-(2-(Cyclohexylamino)-2-oxo-1-phenylethyl)-N-phenyl-3-(2-tosylhydrazinyl)acrylamide (**7i**):* isolated yield 65% (354 mg); mp 214−217 °C; IR (KBr, cm^{-1}) ν = 3271, 3085, 2929, 1653, 1599; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.93−1.30 (m, 5H), 1.50−1.80 (m, 5H), 2.38 (s, 3H), 3.55−3.58 (m, 1H), 4.87 (s, 2H), 5.15 (d, 1H, J = 12.9 Hz), 6.13 (s, 1H), 6.90−7.01 (m, 10H), 7.43 (d, 2H, J = 8.1 Hz), 7.67 (d, 2H, J = 8.2 Hz), 7.88 (d, 1H, J = 12.9 Hz), 7.95 (d, 1H, J = 7.7 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.1, 24.5, 24.7, 25.2, 32.1, 32.3, 47.9, 63.5, 99.5, 127.3, 127.4, 127.7, 127.7, 128.1, 130.1, 131.1, 132.9, 135.8, 139.3, 141.0, 144.7, 165.4, 168.8; HR-MS (ESI) calcd for $C_{30}H_{35}N_4O_4S$ [M + H]$^+$ 547.23916, found 547.23888, $C_{30}H_{34}N_4NaO_4S$ [M + Na]$^+$ 569.22079, found 569.22057.

*(E)-N-(2-(Cyclohexylamino)-2-oxo-1-(thiophene-2-yl)ethyl)-N-phenyl-3-(2-tosylhydrazinyl)acrylamide (**7j**):* isolated yield 60% (331 mg); mp 223−225 °C; IR (KBr, cm^{-1}) ν = 3271, 3085, 2929, 1653, 1599; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.94−1.30 (m, 5H), 1.40−1.80 (m, 5H), 3.33 (s, 3H), 3.40−3.60 (m, 1H), 4.87 (s, 2H), 5.13 (d, 1H, J = 12.8 Hz), 6.35 (s, 1H), 6.76−6.78 (m, 2H), 7.04−7.15 (m, 5H), 7.29 (d, 2H, J = 4.2 Hz), 7.43 (d, 2H, J = 7.9 Hz), 7.66 (d, 2H, J = 8.1 Hz), 7.88 (d, 1H, J = 12.9 Hz), 8.00 (d, 1H, J = 7.7 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.1, 24.5, 24.6, 25.2, 32.1, 48.0, 58.4, 99.2, 126.1, 127.4, 127.7, 128.3, 129.1, 129.8, 130.1, 130.3, 130.8, 132.9, 137.6, 141.1, 144.7, 165.3, 168.0; HR-MS (ESI) calcd for $C_{28}H_{33}N_4O_4S_2$ [M + H]$^+$ 553.19531, found 553.19515, calcd for $C_{28}H_{32}N_4NaO_4S_2$ [M + Na]$^+$ 575.17729, found 575.17709.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, X-ray crystallographic data, and copies of IR, ^{1}H NMR,^{13}C NMR, and also HRMS (ESI) spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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