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ARTICLE

Synthesis of Passerini adducts from aldehydes and isocyanides under the auxiliary of water†

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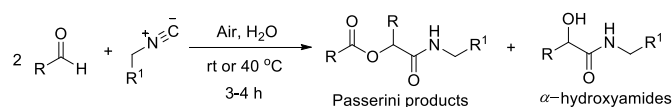
An efficient protocol for the synthesis of the Passerini adducts α -acyloxy-carboxamides from aldehydes, isocyanides and water in molecular ratio of 3:1:3 was described. The possible mechanism for the reaction was discussed by employing cross condensation and H_2^{18}O isotope labeling experiment. This method offers a straightforward access to α -acyloxy-carboxamides bearing two identical functional groups in high yields under mild conditions.

Introduction

Isocyanides have long proved themselves to be irreplaceable building blocks in modern organic chemistry.¹ Its application in pharmaceutical and academic research underwent a dramatic increase over the past years.² Along with the Ugi reaction,³ the Passerini reaction is particularly attractive, and coupling of isocyanides with aldehydes and carboxylic acids represents the most important use of isocyanides in organic synthesis.⁴

Water, as the sole medium for organic reactions, has advantages of being low cost, safe, and environmentally friendly that make it an ideal reaction medium in synthetic chemistry.⁵ The use of water could accelerate rate of reaction and also lead to selectivity changes.⁶ Recently, reactions of water-insoluble organic compounds that take place in aqueous suspensions have received a great deal of attention because of their high efficiency and straightforward synthetic protocols.⁷ A. Vigalok⁸ reported a highly efficient aqueous three-component Passerini reaction (Scheme 1), where one of the components, carboxylic acid, is generated in situ via the aerobic oxidation of hydrophobic aldehydes upon stirring with water in the presence of air. However, the method often gave both the Passerini adducts α -acyloxyamides and α -hydroxyamides, and the role of water is still unclear.

By taking note of the Vigalok's report, we have two questions: (1) Since the water-solubility of reactants, especially the aldehydes, could affect significantly the efficiency of the reaction, how about further decreasing the amount of water? (2) Could aldehydes be efficiently converted in situ into carboxylic acids that were successively utilized in the nucleophilic addition to the carbonyl carbon atom when the reaction takes place "in water"?



Scheme 1 The tandem aldehyde oxidation/Passerini reaction "on water".

In order to answer these two questions, a series of experiments were designed and carried out. By using 3 equiv of water and simultaneously employing two different aldehydes in a reaction as well as a comparative oxidation of 4-fluorobenzaldehyde and 4-methoxybenzaldehyde. Based on our ongoing interest in IMCRs,⁹ herein, we present an efficient protocol to access to the Passerini adducts α -acyloxy-carboxamides in excellent yields from aldehydes, isocyanides and water in molecular ratio of 3:1:3, and another new possible mechanism for the reaction.

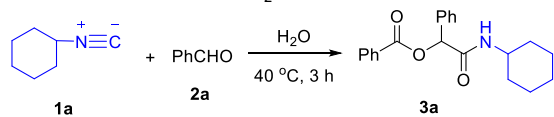
Results and discussion

To demonstrate the roles of water and oxygen or air, a series of experiments were designed and carried out by using the reaction of cyclohexyl isocyanide (**1a**) with benzaldehyde (**2a**) as the model reaction at 40 °C for 3 h (Table 1).

Excitingly, addition of water improved significantly the yield of **3a** (Table 1, entries 1–7). A breakthrough result was achieved, the yield of **3a** rose to 90% when 3 equiv of water was employed (entry 4). Excessive water was unbeneficial for reaction (entries 5–7). Additionally, as a control experiment, the reactions of **1a**, **2a**, and H_2O in molecular ratio of 1:3:3 or without water addition were carried out in a nitrogen atmosphere for 3 h, only less than 10% yield of **3a** was generated (entries 8 and 9), which revealed that the presence of oxygen or air would be essential for the reaction. In the light of the importance of oxygen and water for the reaction, a comparative experiment was further carried out. Without water addition the reaction of **2a** with **1a** in molecular ratio of

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† Electronic Supplementary Information (ESI) available: X-Ray crystal structures of **3g** and **6b**, ^1H NMR, ^{13}C NMR spectra of new compounds, and HRMS spectra of isotope labeled **3b**. See DOI: 10.1039/x0xx00000x

Table 1 Effect of water and O₂ on reaction for **3a**^a

Entry	Equiv. of 2a	Equiv. of H ₂ O	Yield ^b (%)
1	3	0	39
2	3	1	58
3	3	2	68
4	3	3	90
5	3	4	86
6	3	5	81
7	3	6	66
8	3	3	8 ^c
9	3	0	6 ^c
10	3	0	55 ^d
11	3	3	77 ^d

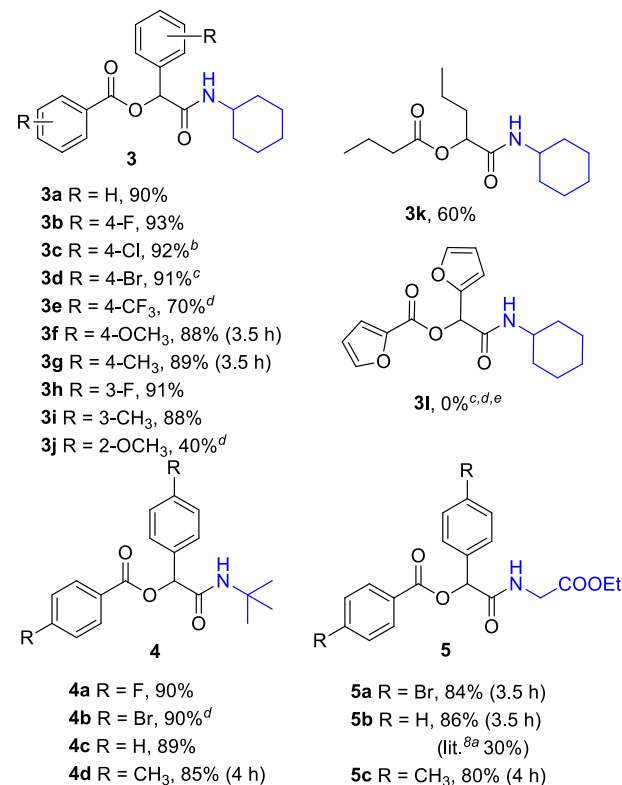
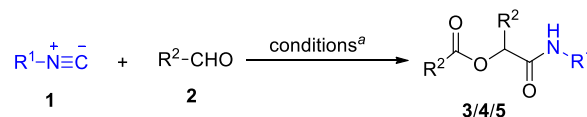
^a Reaction conditions: **1a** (0.5 mmol), **2a**, and H₂O (equiv. based on **1a**). ^b Isolated yield based on **1a**. ^c The reaction was performed in a N₂ atmosphere. ^d The reaction was performed in an oxygen atmosphere.

3:1 in an oxygen atmosphere provided only 55% yield of **3a** (entry 10); in contrast, the reaction with 3 equiv of H₂O addition under the same reaction conditions afforded **3a** in 77% yield (entry 11). These results indicated that oxidation of aldehydes is inevitable to happen in the presence of oxygen, and water also plays an irreplaceable role.

In view of limited number of the Passerini adducts reported before, we next expanded the scope of the reaction mainly using various aromatic aldehydes under the above standard conditions (1/2/H₂O in the molecular ratio of 1:3:3 at 40 °C in air), and the results are illustrated in Scheme 2. All aromatic aldehydes were well tolerated to afford the expected products **3a-j**.

The aromatic aldehydes with electron-withdrawing groups (F, Cl, Br, CF₃) reacted faster than those with electron-donating groups (CH₃, OCH₃), while the yields have not evident differences except **3e** (Scheme 2, **3b-g**). However, *o*-methoxybenzaldehyde gave low yield of 40% and needed long reaction time of 4 h (Scheme 2, **3j**), which is subject to steric effect. Aliphatic aldehydes such as *n*-butylaldehyde also could participate in the reaction though it gave relatively lower yield of 60% (Scheme 2, **3k**). Unfortunately, when a heteroaromatic aldehyde such as furan-2-carbaldehyde was used, no reaction occurred (Scheme 2, **3l**). Next, we employed *tert*-butyl isocyanide (**1b**) and ethyl 2-isocyanoacetate (**1c**) instead of **1a** in this IMCR, and it was found that the reactions involving **1b/1c** also proceeded well to afford the corresponding products **4/5** in excellent yields. It is worth mentioning that the less reactive ethyl isocyanoacetate (**1c**) also gave yields of 80–86% (Scheme 2, **5a-c**), while only 30% yield of **5b** was obtained in the previous report.^{8a}

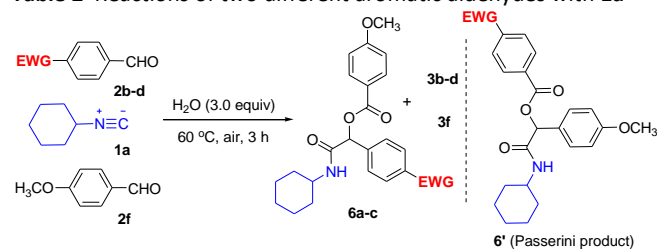
The structures of **3/4/5** were confirmed by the X-ray diffraction analysis of **3g** (Figure S1 in ESI).



Scheme 2 Exploration of substrate scope for synthesis of **3/4/5**. ^a Reaction conditions: isocyanides **1** (0.5 mmol), aldehydes **2** (1.5 mmol), and water (1.5 mmol), 40 °C in air. Isolated yields after washing with petroleum ether. ^b Reacted at 50 °C. ^c Reacted at 60 °C. ^d Yield after purification by silica gel column chromatography. ^e No reaction.

The success of above reactions promoted us to get deep insight into the reaction mechanism with regard to aldehyde oxidation by applying two different aromatic aldehydes: bearing an electron-withdrawing group such as **2b-d** and bearing an electron-donating group such as 4-methoxybenzaldehyde (**2f**), to react with **1a** (for details, see Table S1 in ESI). To our great delight, new “hetero” products **6a-c** that are different from the Passerini adducts were obtained besides “homo” products **3b-d** and **3f** (Table 2). Obviously, according to the Passerini reaction mechanism, **6'** should be obtained due to that aromatic aldehydes bearing an electron-withdrawing group are more susceptible to be oxidized to a corresponding carboxylic acid. A comparative oxidation experiment with 4-fluorobenzaldehyde (**2b**) and 4-methoxybenzaldehyde (**2f**) authenticated this clear-cut fact.¹⁰ As expected, a small amount of **6a'** was also observed along with **6a** in a ratio of 1:10 by ¹H NMR spectrum. The above experimental results implied that two mechanisms for the present reaction may exist at the same time.

Significantly, the previous reports have not investigated the crossing reactions with two different aldehydes.

Table 2 Reactions of two different aromatic aldehydes with **1a**^a

Entry	EWG	Yield (%) ^b		
		6a-c	3a-c	3f
1	4-F/ 2b	37 (6a)	43 (3b)	10
2	4-Cl/ 2c	40 (6b)	42 (3c)	trace
3	4-Br/ 2d	35 (6c)	40 (3d)	11

^a Reaction conditions: **1a** (0.5 mmol), **2b-d** (1 mmol), **2f** (0.5 mmol), H₂O (1.5 mmol). ^b Yields after purification by silica gel column chromatography.

The structures of **6a-c** were confirmed by the X-ray diffraction analysis of representative compound **6b** (Figure S2 in ESI).

To further investigate the role of water, an isotope labeling experiment was conducted. The reaction of 4-fluorobenzaldehyde (**2b**), cyclohexyl isocyanide (**1a**) (0.1 mmol), and H₂¹⁸O in molecular ratio of 3:1:3 for **2b/1a/H₂¹⁸O** was carried out at 40 °C for 30 min. HRMS (ESI-TOF, [M+H]⁺) analysis exhibited that besides the ion peak of 374.1572 for 2[¹⁶O]-**3b**, other two ion peaks at *m/z* 376.1591 and 378.1650 in a ratio of 7:8:6 also were observed, which should be relative to [¹⁸O]-**3b** and 2[¹⁸O]-**3b**, respectively (Figure S3 in ESI). This observation is agreement with the previous report.^{8a} Additionally, we have noticed that in A.Vigalok's report, the reaction with nonlabeled 1-octanal, 1-octanoic acid, and ethyl isocynoacetate or pentyl isocyanide in H₂¹⁸O, gave the

Passerini adduct with one incorporated ¹⁸O as the major product, which also reveals the present reaction mechanism should be different from the classic Passerini reaction.

On the basis of the above experimental results, a plausible mechanism for this reaction is proposed and shown in Scheme 3. More reactive 4-chlorobenzaldehyde (**2c**) first reacts with isocyanide **1a** to generate intermediate [**A**], which then reacts with another less reactive aldehyde such as 4-methoxybenzaldehyde (**2f**) leading to 1,3-dioxolamine [**B**].¹¹ Next, [**B**] reacts with water to form [**C**], which undergo a ring-opening reaction to give [**D**]. Successively, an oxidation process gives the final product **6b**. In addition, small amount of aldehydes are oxidized to corresponding acid in the presence of air. Under such acidic conditions, a part of [**D**] would lose hydroxyl to form intermediate [**E**], which reacts with another molecule of H₂O giving [**F**], followed by an oxidation process to form the final product **6b**. This mechanism could explain reasonably why in the isotope labeling experiments there are both products with one labeled ¹⁸O ([¹⁸O]-**3b**) and products with two ¹⁸O (2[¹⁸O]-**3b**) incorporated in the structures.

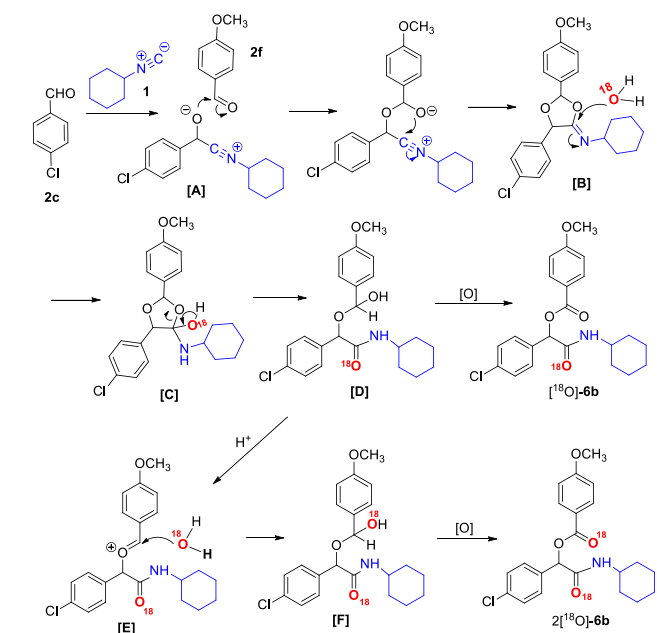
Conclusions

In conclusion, we have demonstrated a rapid and efficient approach to access Passerini adduct α-acyloxycarboxamides using aldehydes, isocyanides, and water in molecular ratio of 3:1:3 rather than needing carboxylic acids. The striking feature of the method is to use 3 equiv. of H₂O in reaction system to give good to excellent yields under mild reaction conditions. The experiments of isotope labeling of H₂¹⁸O and crossing reactions by using two different aldehydes clearly indicated that the reaction mechanism is different from the previous report.^{8a} This research also provided a convenient and green way to access α-acyloxycarboxamides with two identical functional groups in high yields.

Experimental Section

General experimental details

The used benzaldehyde (**2a**) for the condition test was produced by ACROS ORGANICS (99.5+%). Cyclohexyl isocyanide (**1a**) for the condition test was dried with anhydrous MgSO₄ before used. All other isocyanides and aldehydes were used as purchased commercially without drying process. Water was common running water and not treated. All reagents were weighed and handled in air at room temperature. Melting points were recorded on an RY-1 microscopic melting apparatus and uncorrected. NMR spectra were recorded on a Bruker Avance 500 spectrometer at 500 MHz for ¹H and 125 MHz for ¹³C in DMSO-*d*₆ or CDCl₃. Chemical shifts δ were relative to TMS as internal standard. The IR spectra were recorded on a Nicolet iS10 FT-IR spectrometer and only major peaks are reported in cm⁻¹. High-resolution mass spectra (HRMS) were recorded on an Ultima Global spectrometer. The X-ray single-crystal diffraction was performed on Saturn 724+ instrument.

**Scheme 3** Plausible new reaction mechanism.

General procedure for the synthesis of 3/4/5

A mixture of isocyanides **1** (0.5 mmol), aldehydes **2** (1.5 mmol), and water (1.5 mmol) was stirred at 40 °C in a 25 mL round-bottomed flask for an indicating time in air until **1** was completely consumed. The solid mixture was isolated by filtration and washed with petroleum ether (3×5 mL), and then the pure products **3/4/5** were obtained.

General procedure for the preparation of 6

A mixture of the aromatic aldehydes with electron-withdrawing group **2b-d** (1 mmol), **1a** (0.5 mmol), **2f** (0.5 mmol), H₂O (1.5 mmol) was stirred at 60 °C in a 25 mL round-bottomed flask for 30 min in air until **1a** was completely consumed. The solid obtained by filtration was isolated by silica gel column chromatography, and the pure products **6a-c** were obtained.

2-(Cyclohexylamino)-2-oxo-1-phenylethyl benzoate (3a)

Following the general procedure, the stirred mixture of isocyanocyclohexane **1a** (54.6 mg, 0.5 mmol), benzaldehyde **2a** (159.2 mg, 1.5 mmol), and water (27 µL, 1.5 mmol) gave, after filtration and washed with petroleum ether (3×5 mL), the desired product **3a** (151.7 mg, 90%) as white powder. Mp: 144-146 °C; IR (KBr, cm⁻¹) 3305, 3069, 3041, 2935, 2854, 1733, 1659, 1602, 1549, 1498, 1450, 731, 703. ¹H NMR (500 MHz, CDCl₃) 1.11-1.25 (m, 3H, CH), 1.34-1.37 (m, 2H, CH), 1.62-1.68 (m, 3H, CH), 1.88-1.96 (m, 2H, CH), 3.82-3.84 (m, 1H, CH), 6.04 (d, *J* = 7.0 Hz, 1H, NH), 6.31 (s, H, CH), 7.26-7.63 (m, 8H, ArH), 8.09-8.10 (m, 2H, ArH); ¹³C NMR (125 MHz, CDCl₃) 24.7, 25.5, 25.8, 32.9, 33.0, 48.2, 76.0, 91.6, 127.4, 128.6, 128.8, 128.9, 129.4, 129.8, 133.6, 135.8, 164.9, 167.3. HRMS (ESI-TOF, [M+H]⁺): calcd for C₂₁H₂₄NO₃, 338.1756, found 338.1765.

2-(Cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl 4-fluorobenzoate (3b)

Following the general procedure, the stirred mixture of isocyanocyclohexane **1a** (54.6 mg, 0.5 mmol), 4-fluorobenzaldehyde **2b** (186.2 mg, 1.5 mmol), and water (27 mg, 1.5 mmol) gave, after filtration and washed with petroleum ether (3×5 mL), the desired product **3b** (173.5 mg, 93%) as white powder. Mp: 212-214 °C; IR (KBr, cm⁻¹) 3266, 3099, 2930, 2854, 1719, 1657, 1604, 1569, 1510, 1449, 768. ¹H NMR (500 MHz, CDCl₃) 1.06-1.25 (m, 5H, CH), 1.50-1.76 (m, 5H, CH), 3.47-3.50 (m, 1H, CH), 6.04 (s, 1H, CH), 8.27 (d, *J* = 7.9 Hz, 1H, NH), 7.24-7.64 (m, 6H, ArH), 8.08-8.10 (m, 2H, ArH); ¹³C NMR (125 MHz, CDCl₃) 24.4, 25.1, 32.0, 32.1, 32.9, 47.7, 74.9, 115.3 (d, ³J_{C-F} = 7.5 Hz), 115.9 (d, ²J_{C-F} = 22.1 Hz), 125.8, 129.3 (d, ³J_{C-F} = 7.3 Hz), 132.2, 132.4 (d, ³J_{C-F} = 8.8 Hz), 141.4, 162.1 (d, ¹J_{C-F} = 245.3 Hz), 164.0, 165.3 (d, ¹J_{C-F} = 251.8 Hz), 166.6. HRMS (ESI-TOF, [M+H]⁺): calcd for C₂₁H₂₂F₂NO₃, 374.1568, found 374.1556.

1-(4-Chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl 4-chlorobenzoate (3c)

Following the general procedure, the stirred mixture of isocyanocyclohexane **1a** (54.6 mg, 0.5 mmol), 4-chlorobenzaldehyde **2c** (210.9 mg, 1.5 mmol), and water (27 mg,

1.5 mmol) gave, after filtration and washed with petroleum ether (3×5 mL), the desired product **3c** (186.3 mg, 92%) as white powder. Mp: 210-212 °C; IR (KBr, cm⁻¹) 3271, 3093, 2927, 2853, 1724, 1655, 1595, 1567, 1490, 1447, 854. ¹H NMR (500 MHz, CDCl₃) 1.14-1.20 (m, 3H, CH), 1.32-1.41 (m, 2H, CH), 1.58-1.72 (m, 3H, CH), 1.88-1.95 (m, 2H, CH), 3.80-3.84 (m, 1H, CH), 5.93 (d, *J* = 7.5 Hz, 1H, NH), 6.23 (s, 1H, CH), 7.36-7.48 (m, 6H, ArH), 8.00-8.02 (m, 2H, ArH); ¹³C NMR (125 MHz, CDCl₃) 24.7, 25.4, 32.9, 48.4, 75.4, 127.5, 128.8, 129.0, 131.1, 134.0, 135.1, 140.3, 164.1, 166.7. HRMS (ESI-TOF, [M+H]⁺): calcd for C₂₁H₂₂Cl₂NO₃, 406.0977, found 406.0983.

1-(4-Bromophenyl)-2-(cyclohexylamino)-2-oxoethyl 4-bromobenzoate (3d)

Following the general procedure, the stirred mixture of isocyanocyclohexane **1a** (54.6 mg, 0.5 mmol), 4-bromobenzaldehyde **2d** (227.5 mg, 1.5 mmol), and water (27 mg, 1.5 mmol) gave, after filtration and washed with petroleum ether (3×5 mL), the desired product **3d** (224.3 mg, 91%) as white powder. Mp: 191-193 °C; IR (KBr, cm⁻¹) 3289, 3092, 2932, 2854, 1728, 1658, 1590, 1557, 1488, 1450, 755. ¹H NMR (500 MHz, CDCl₃) 1.08-1.20 (m, 3H, CH), 1.34-1.36 (m, 2H, CH), 1.62-1.70 (m, 3H, CH), 1.87-1.94 (m, 2H, CH), 3.79-3.83 (m, 1H, CH), 5.93 (d, *J* = 7.0 Hz, 1H, NH), 6.20 (s, H, CH), 7.26-7.93 (m, 8H, ArH); ¹³C NMR (125 MHz, CDCl₃) 24.7, 25.4, 32.8, 48.4, 123.3, 128.0, 129.1, 131.2, 132.0, 132.1, 134.5, 164.2, 166.6. HRMS (ESI-TOF, [M+H]⁺): calcd for C₂₁H₂₂Br₂NO₃, 493.9966, found 493.9959.

1-(4-Trifluoromethylphenyl)-2-(cyclohexylamino)-2-oxoethyl 4-trifluoromethylbenzoate (3e)

Following the general procedure, the stirred mixture of isocyanocyclohexane **1a** (54.6 mg, 0.5 mmol), 4-(trifluoromethyl)benzaldehyde **2e** (261.2 mg, 1.5 mmol), and water (27 mg, 1.5 mmol) gave, isolated by silica gel column chromatography (PE/EA=20:1), the desired product **3e** (165.6 mg, 70%) as white powder. Mp: 178-179 °C; IR (KBr, cm⁻¹) 3288, 2936, 2857, 1736, 1661, 1560, 1413, 1327, 1129, 755. ¹H NMR (500 MHz, CDCl₃) 1.10-1.25 (m, 3H, CH), 1.33-1.37 (m, 2H, CH), 1.60-1.72 (m, 3H, CH), 1.89-1.96 (m, 2H, CH), 3.79-3.82 (m, 1H, CH), 6.01 (d, 1H, *J* = 7.8 Hz, NH), 6.32 (s, 1H, CH), 7.67 (s, 4H, ArH), 7.77 (d, *J* = 8.2 Hz, 2H, ArH), 8.21 (d, *J* = 8.1 Hz, 2H, ArH); ¹³C NMR (125 MHz, CDCl₃) 25.2, 25.9, 33.4, 49.1, 122.8, 123.2, 125.0, 125.4, 126.4, 128.3, 130.8, 131.8 (²*J* = 32.4 Hz), 132.7, 135.8 (²*J* = 32.9 Hz), 139.6, 164.3, 166.7. HRMS (ESI-TOF, [M+H]⁺): calcd for C₂₃H₂₂F₆NO₃, 474.1504, found 474.1515.

2-(Cyclohexylamino)-1-(4-methoxyphenyl)-2-oxoethyl 4-methoxybenzoate (3f)

Following the general procedure, the stirred mixture of isocyanocyclohexane **1a** (54.6 mg, 0.5 mmol), 4-methoxybenzaldehyde **2f** (204.3 mg, 1.5 mmol), and water (27 mg, 1.5 mmol) gave, after filtration and washed with petroleum ether (3×5 mL), the desired product **3f** (174.8 mg, 88%) as white powder. Mp: 152-154 °C; IR (KBr, cm⁻¹) 3287, 3078, 2932, 2853, 1716, 1657, 1607, 1546, 1514, 848. ¹H NMR (500 MHz, CDCl₃) 1.12-1.20 (m, 3H, CH), 1.34-1.39 (m, 2H, CH), 1.60-1.71 (m, 3H, CH), 1.88-1.96 (m, 2H, CH), 3.80-3.88 (m, 6H, CH), 6.02 (d, *J* = 8.0 Hz, 1H, NH), 6.24 (s, 1H,

CH), 6.89-7.45 (m, 6H, ArH), 8.02-8.04 (m, 2H, ArH); ¹³C NMR (125 MHz, CDCl₃) 24.7, 25.5, 33.0, 48.1, 55.3, 55.5, 75.4, 113.9, 114.2, 121.8, 128.2, 128.9, 131.8, 160.0, 164.7, 167.8. HRMS (ESI-TOF, [M+H]⁺): calcd for C₂₃H₂₉NO₅, 398.1967, found 398.1975.

2-(Cyclohexylamino)-2-oxo-1-(*p*-tolyl)ethyl 4-methylbenzoate (3g)

Following the general procedure, the stirred mixture of isocyanocyclohexane **1a** (54.6 mg, 0.5 mmol), 4-methylbenzaldehyde **2g** (180.3 mg, 1.5 mmol), and water (27 mg, 1.5 mmol) gave, after filtration and washed with petroleum ether (3×5 mL), the desired product **3g** (162.5 mg, 89%) as white powder. Mp: 157-159 °C; IR (KBr, cm⁻¹) 3283, 3093, 2924, 2856, 1732, 1652, 1613, 1564, 1514, 1450. ¹H NMR (500 MHz, CDCl₃) 1.12-1.20 (m, 3H, CH), 1.35-1.37 (m, 2H, CH), 1.59-1.70 (m, 3H, CH), 1.88-1.96 (m, 2H, CH), 2.35 (s, 3H, CH₃), 2.43 (s, 3H, CH₃), 3.82-3.84 (m, 1H, CH), 6.03 (d, *J* = 7.5 Hz, 1H, NH), 6.26 (s, 1H, CH), 7.18-7.42 (m, 6H, ArH), 7.97-7.98 (m, 2H, ArH); ¹³C NMR (125 MHz, CDCl₃) 21.2, 21.7, 24.7, 25.4, 32.9, 33.0, 48.1, 75.7, 126.7, 127.4, 129.3, 129.4, 129.8, 133.0, 138.8, 144.4, 165.0, 167.6. HRMS (ESI-TOF, [M+H]⁺): calcd for C₂₃H₂₈NO₃, 366.2069, found 366.2056.

2-(Cyclohexylamino)-1-(3-fluorophenyl)-2-oxoethyl 3-fluorobenzoate (3h)

Following the general procedure, the stirred mixture of isocyanocyclohexane **1a** (54.6 mg, 0.5 mmol), 3-fluorobenzaldehyde **2h** (186.2 mg, 1.5 mmol), and water (27 mg, 1.5 mmol) gave, after filtration and washed with petroleum ether (3×5 mL), the desired product **3h** (169.8 mg, 91%) as white powder. Mp: 155-157 °C; IR (KBr, cm⁻¹) 3318, 3078, 2935, 2857, 1735, 1659, 1593, 1547, 1488, 1449, 760, 680. ¹H NMR (500 MHz, CDCl₃) 1.14-1.97 (m, 10H, CH), 3.83-3.84 (m, 1H, CH), 5.98 (d, *J* = 8.0 Hz, 1H, NH), 6.27 (s, 1H, CH), 7.07-7.92 (m, 8H, ArH); ¹³C NMR (125 MHz, CDCl₃) 24.7, 25.4, 32.9, 48.4, 75.5, 115.1 (d, ¹*J*_{C-F} = 218.9 Hz), 115.3 (d, ¹*J*_{C-F} = 217.2 Hz), 116.7 (d, ²*J*_{C-F} = 23.1 Hz), 120.9 (d, ²*J*_{C-F} = 21.2 Hz), 123.1, 125.5, 130.4 (d, ³*J*_{C-F} = 6.8 Hz), 131.2, 137.7, 161.8 (d, ³*J*_{C-F} = 26.6 Hz), 163.62, 163.8, 166.5. HRMS (ESI-TOF, [M+H]⁺): calcd for C₂₁H₂₂F₂NO₃, 374.1568, found 374.1576.

2-(Cyclohexylamino)-2-oxo-1-(*m*-tolyl)ethyl 3-methylbenzoate (3i)

Following the general procedure, the stirred mixture of isocyanocyclohexane **1a** (54.6 mg, 0.5 mmol), 3-methylbenzaldehyde **2i** (180.3 mg, 1.5 mmol), and water (27 mg, 1.5 mmol) gave, after filtration and washed with petroleum ether (3×5 mL), the desired product **3i** (160.7 mg, 88%) as white powder. Mp: 148-150 °C; IR (KBr, cm⁻¹) 3271, 3088, 2932, 2855, 1720, 1657, 1611, 1589, 1558, 1491, 1451. ¹H NMR (500 MHz, CDCl₃) 1.12-1.20 (m, 3H, CH), 1.34-1.39 (m, 2H, CH), 1.60-1.70 (m, 3H, CH), 1.88-1.96 (m, 2H, CH), 2.36 (s, 1H, CH), 2.42 (s, 1H, CH), 3.82-3.84 (m, 1H, CH), 6.03 (d, *J* = 7.0 Hz, 1H, NH), 6.26 (s, 1H, CH), 7.16-7.89 (m, 8H, ArH); ¹³C NMR (125 MHz, CDCl₃) 21.3, 21.4, 24.7, 25.4, 32.9, 48.2, 75.9, 124.4, 126.9, 128.3, 128.5, 128.6, 129.3, 129.7, 130.3, 134.3, 135.7, 138.4, 165.1, 167.5. HRMS (ESI-TOF, [M+H]⁺): calcd for C₂₃H₂₈NO₃, 366.2069, found 366.2079.

2-(Cyclohexylamino)-1-(2-methoxyphenyl)-2-oxoethyl 2-methoxybenzoate (3j)

Following the general procedure, the stirred mixture of isocyanocyclohexane **1a** (54.6 mg, 0.5 mmol), 2-methoxybenzaldehyde **2j** (204.3 mg, 1.5 mmol), and water (27 mg, 1.5 mmol) gave, isolated by silica gel column chromatography (PE/EA=20:1), the desired product **3j** (79.4 mg, 40%) as white powder. Mp: 150-152 °C; IR (KBr, cm⁻¹) 3361, 3074, 2931, 2851, 1701, 1675, 1602, 1536, 1492, 1467, 766. ¹H NMR (500 MHz, CDCl₃) 1.12-1.72 (m, 10H, CH), 3.84-3.86 (m, 1H, CH), 3.87 (s, 3H, CH), 3.96 (s, 3H, CH), 6.63 (s, 1H, CH), 6.82 (d, *J* = 8.0 Hz, 1H, NH), 6.89-7.87 (m, 8H, ArH); ¹³C NMR (125 MHz, CDCl₃) 24.8, 25.6, 33.0, 33.4, 47.9, 55.7, 56.2, 71.2, 111.2, 112.3, 119.9, 120.7, 120.8, 124.9, 129.4, 130.0, 132.4, 133.9, 157.3, 159.0, 165.0, 168.0. HRMS (ESI-TOF, [M+H]⁺): calcd for C₂₃H₂₈NO₅, 398.1967, found 398.1975.

1-(Cyclohexylamino)-1-oxohexan-2-yl pentanoate (3k)

Following the general procedure, the stirred mixture of isocyanocyclohexane **1a** (54.6 mg, 0.5 mmol), *n*-butyraldehyde **2k** (108.2 mg, 1.5 mmol), and water (27 mg, 1.5 mmol) gave, after filtration and washed with petroleum ether (3×5 mL), the desired product **3k** (80.8 mg, 60%) as white powder. Mp: 67-68 °C; IR (KBr, cm⁻¹) 3292, 2961, 2933, 2874, 2856, 1743, 1655, 1558, 1450. ¹H NMR (500 MHz, CDCl₃) 0.90-1.00 (m, 6H, CH), 1.09-1.21 (m, 4H, CH), 1.32-1.41 (m, 2H, CH), 1.60-1.92 (m, 10H, CH), 2.36-2.39 (m, 2H, CH), 3.75-3.81 (m, 1H, CH), 5.15-5.17 (m, 1H, CH), 5.87 (d, *J* = 6.7 Hz, 1H, NH); ¹³C NMR (125 MHz, CDCl₃) 12.7, 17.0, 17.5, 20.8, 23.7, 24.5, 32.0, 33.0, 35.2, 46.8, 72.7, 168.0, 171.2. HRMS (ESI-TOF, [M+H]⁺): calcd for C₁₅H₂₈NO₃, 270.2069, found 270.2060.

2-(*tert*-Butylamino)-1-(4-fluorophenyl)-2-oxoethyl 4-fluorobenzoate (4a)

Following the general procedure, the stirred mixture of *t*-butyl isocyanide **2a** (41.6 mg, 0.5 mmol), 4-fluorobenzaldehyde **2b** (186.2 mg, 1.5 mmol), and water (27 mg, 1.5 mmol) gave, after filtration and washed with petroleum ether (3×5 mL), the desired product **4a** (156.2 mg, 90%) as white powder. Mp: 168-170 °C; IR (KBr, cm⁻¹) 3284, 3085, 2976, 2933, 1727, 1656, 1606, 1560, 1511, 1450. ¹H NMR (500 MHz, CDCl₃) 1.36 (s, 9H, CH), 5.86 (s, 1H, NH), 6.15 (s, 1H, CH), 7.06-8.10 (m, 8H, ArH); ¹³C NMR (125 MHz, CDCl₃) 27.8, 28.7, 51.7, 75.4, 115.8, 115.9, 125.5, 129.5, 131.7, 132.3, 162.1, 164.0, 165.1, 167.0. HRMS (ESI-TOF, [M+H]⁺): calcd for C₁₉H₂₀F₂NO₃, 348.1411, found 348.1419.

1-(4-Bromophenyl)-2-(*tert*-butylamino)-2-oxoethyl 4-bromobenzoate (4b)

Following the general procedure, the stirred mixture of *t*-butyl isocyanide **2a** (41.6 mg, 0.5 mmol), 4-bromobenzaldehyde **2d** (227.5 mg, 1.5 mmol), and water (27 mg, 1.5 mmol) gave, isolated by silica gel column chromatography (PE/EA=20:1), the desired product **4b** (210.2 mg, 90%) as white powder. Mp: 173-175 °C; IR (KBr, cm⁻¹) 3308, 3087, 2974, 2927, 1727, 1659, 1591, 1557, 1490, 1453. ¹H NMR (500 MHz, CDCl₃) 1.36 (s, 9H, CH), 5.86 (s, 1H, NH), 6.12 (s, 1H, CH), 7.37-7.93 (m, 8H, ArH); ¹³C NMR (125 MHz, CDCl₃) 28.4, 28.6, 51.8, 75.6, 123.3, 128.1, 129.0, 129.1, 131.2, 132.0, 132.1, 134.7, 164.2, 166.6. HRMS (ESI-TOF, [M+H]⁺): calcd for C₁₉H₂₀Br₂NO₃, 467.9810, found 467.9805.

2-(*tert*-Butylamino)-2-oxo-1-phenylethyl benzoate (4c)^{1,2,3}

Following the general procedure, the stirred mixture of *t*-butyl isocyanide **2a** (41.6 mg, 0.5 mmol), benzaldehyde **2a** (227.5 mg, 1.5 mmol), and water (27 mg, 1.5 mmol) gave, after filtration and washed with petroleum ether (3×5 mL), the desired product **4c** (138.6 mg, 89%) as white powder. Mp: 153-154 °C (lit. 148-150 °C); IR (KBr, cm⁻¹) 3308, 3087, 2974, 2927, 1727, 1659, 1591, 1557, 1490, 1453.

2-(*tert*-Butylamino)-2-oxo-1-(*p*-tolyl)ethyl 4-methylbenzoate (**4d**)

Following the general procedure, the stirred mixture of *t*-butyl isocyanide **2a** (41.6 mg, 0.5 mmol), 4-methylbenzaldehyde **2g** (180.3 mg, 1.5 mmol), and water (27 mg, 1.5 mmol) gave, after filtration and washed with petroleum ether (3×5 mL), the desired product **4d** (144.2 mg, 85%) as white powder. Mp: 170-171 °C; IR (KBr, cm⁻¹) 3296, 2984, 2927, 1743, 1660, 1514, 1542, 1516, 1440. ¹H NMR (500 MHz, CDCl₃) 1.36 (s, 9H, CH), 2.34 (s, 3H, CH), 2.42 (s, 3H, CH), 5.99 (s, 1H, NH), 6.17 (s, 1H, CH), 7.18-7.97 (m, 8H, ArH); ¹³C NMR (125 MHz, CDCl₃) 20.4, 21.3, 21.8, 28.7, 30.8, 51.5, 75.8, 126.7, 127.4, 129.4, 129.5, 129.9, 133.2, 138.7, 144.4, 165.0, 167.7. HRMS (ESI-TOF, [M+H]⁺): calcd for C₂₁H₂₆NO₃, 340.1913, found 340.1909.

1-(4-Bromophenyl)-2-((2-ethoxy-2-oxoethyl)amino)-2-oxoethyl 4-bromobenzoate (**5a**)

Following the general procedure, the stirred mixture of ethyl 2-isocyanoacetate **2c** (56.6 mg, 0.5 mmol), 4-bromobenzaldehyde **2d** (227.5 mg, 1.5 mmol), and water (27 mg, 1.5 mmol) gave, after filtration and washed with petroleum ether (3×5 mL), the desired product **5a** (208.7 mg, 84%) as white powder. Mp: 134-136 °C; IR (KBr, cm⁻¹) 3299, 3089, 2983, 2939, 1733, 1663, 1591, 1560, 1490, 1446, 745, 709. ¹H NMR (500 MHz, CDCl₃) 1.26-1.29 (m, 3H, CH), 4.01-4.25 (m, 4H, CH), 6.30 (s, 1H, CH), 6.75 (s, 1H, NH), 7.26-7.97 (m, 8H, ArH); ¹³C NMR (125 MHz, CDCl₃) 14.1, 41.3, 61.9, 75.3, 123.6, 127.9, 129.2, 131.3, 132.1, 134.1, 164.2, 167.8, 169.4. HRMS (ESI-TOF, [M+H]⁺): calcd for C₁₉H₁₈Br₂NO₅, 497.9552, found 497.9549.

2-((2-Ethoxy-2-oxoethyl)amino)-2-oxo-1-phenylethyl benzoate (**5b**)

Following the general procedure, the stirred mixture of ethyl 2-isocyanoacetate **2c** (56.6 mg, 0.5 mmol), benzaldehyde **2a** (227.5 mg, 1.5 mmol), and water (27 mg, 1.5 mmol) gave, after filtration and washed with petroleum ether (3×5 mL), the desired product **5b** (146.7 mg, 86%) as white powder. Mp: 110-112 °C; IR (KBr, cm⁻¹) 3296, 3068, 2983, 2936, 1728, 1662, 1602, 1559, 1498, 1451, 745, 709. ¹H NMR (500 MHz, CDCl₃) 1.25-1.28 (m, 3H, CH), 3.98-4.24 (m, 4H, CH), 6.40 (s, 1H, CH), 6.81 (s, 1H, NH), 7.37-8.14 (m, 10H, ArH); ¹³C NMR (125 MHz, CDCl₃) 14.0, 41.3, 61.7, 75.8, 127.5, 128.6, 128.8, 129.1, 129.2, 129.9, 133.7, 135.3, 164.8, 168.5, 169.5. HRMS (ESI-TOF, [M+H]⁺): calcd for C₁₉H₂₀NO₅, 342.1341, found 342.1346.

2-((2-Ethoxy-2-oxoethyl)amino)-2-oxo-1-(*p*-tolyl)ethyl 4-methylbenzoate (**5c**)

Following the general procedure, the stirred mixture of ethyl 2-isocyanoacetate **2c** (56.6 mg, 0.5 mmol), 4-methylbenzaldehyde **2g**

(180.3 mg, 1.5 mmol), and water (27 mg, 1.5 mmol) gave, after filtration and washed with petroleum ether (3×5 mL), the desired product **5c** (147.7 mg, 80%) as white powder. Mp: 109-111 °C; IR (KBr, cm⁻¹) 3355, 3037, 2974, 2931, 2871, 1735, 1686, 1665, 1613, 1543, 1515, 1457, 745, 709. ¹H NMR (500 MHz, CDCl₃) 1.24-1.28 (m, 3H, CH), 2.34 (s, 3H, CH), 2.42 (s, 3H, CH), 4.00-4.23 (m, 4H, CH), 6.34 (s, 1H, CH), 6.80 (s, 1H, NH), 7.18-8.00 (m, 8H, ArH); ¹³C NMR (125 MHz, CDCl₃) 14.1, 21.2, 21.7, 41.3, 61.6, 75.5, 126.5, 127.5, 129.3, 129.5, 129.9, 132.6, 139.0, 144.4, 164.9, 168.8, 169.5. HRMS (ESI-TOF, [M+H]⁺): calcd for C₂₁H₂₄NO₅, 370.1654, found 370.1665.

2-(Cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl 4-methoxybenzoate (**6a**)

Following the general procedure, the stirred mixture of isocyanocyclohexane **1a** (54.6 mg, 0.5 mmol), 4-methoxybenzaldehyde **2f** (204.3 mg, 1.5 mmol), 4-fluorobenzaldehyde **2b** (186.2 mg, 1.5 mmol), and water (27 mg, 1.5 mmol) gave, isolated by silica gel column chromatography (PE/EA=20:1), the desired product **6a** (71.3 mg, 37%) as white powder. Mp: 205-207 °C; IR (KBr, cm⁻¹) 3276, 3088, 2934, 2853, 1709, 1653, 1608, 1413, 1452, 1266, 770. ¹H NMR (500 MHz, CDCl₃) 1.12-1.23 (m, 3H, CH), 1.35-1.50 (m, 2H, CH), 1.61-1.68 (m, 3H, CH), 1.89-1.95 (m, 2H, CH), 3.73-3.81 (m, 1H, CH), 3.89 (s, 3H, CH), 6.09 (d, *J* = 7.5 Hz, 1H, NH), 6.26 (s, 1H, CH), 6.91-7.51 (m, 6H, ArH), 8.02-8.04 (m, 2H, ArH); ¹³C NMR (125 MHz, CDCl₃) 24.7, 25.4, 32.9, 33.0, 48.2, 55.5, 74.8, 114.0, 114.2, 115.7 (d, ²*J*_{C-F} = 21.6 Hz), 121.4, 129.3 (d, ³*J*_{C-F} = 7.4 Hz), 131.8, 132.3, 161.9, 164.0, 164.5, 167.3. HRMS (ESI-TOF, [M+H]⁺): calcd for C₂₂H₂₅FNO₄, 386.1768, found 386.1772.

1-(4-Chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl 4-methoxybenzoate (**6b**)^{1,2}

Following the general procedure, the stirred mixture of isocyanocyclohexane **1a** (54.6 mg, 0.5 mmol), 4-methoxybenzaldehyde **2f** (204.3 mg, 1.5 mmol), 4-chlorobenzaldehyde **2c** (210.9 mg, 1.5 mmol), and water (27 mg, 1.5 mmol) gave, isolated by silica gel column chromatography (PE/EA=20:1), the desired product **6b** (80.4 mg, 40%) as white powder. Mp: 195-197 °C (lit. 184-186 °C); IR (KBr, cm⁻¹) 3283, 3087, 2929, 2852, 1713, 1654, 1607, 1595, 1494, 1448, 1265, 772. ¹H NMR (500 MHz, CDCl₃) 1.14-1.21 (m, 3H, CH), 1.36-1.39 (m, 2H, CH), 1.58-1.74 (m, 3H, CH), 1.87-1.97 (m, 2H, CH), 3.80-3.84 (m, 1H, CH), 3.89 (s, 3H, CH), 6.07 (d, *J* = 7.5 Hz, 1H, NH), 6.26 (s, 1H, CH), 7.36-7.47 (m, 6H, ArH), 8.02-8.05 (m, 2H, ArH); ¹³C NMR (125 MHz, CDCl₃) 24.7, 25.4, 32.9, 33.0, 48.2, 55.5, 74.8, 114.0, 121.4, 128.7, 128.9, 131.8, 134.5, 134.8, 164.0, 164.4, 167.1. HRMS (ESI-TOF, [M+H]⁺): calcd for C₂₂H₂₅ClNO₄, 402.1472, found 402.1481.

1-(4-Bromophenyl)-2-(cyclohexylamino)-2-oxoethyl 4-methoxybenzoate (**6c**)

Following the general procedure, the stirred mixture of isocyanocyclohexane **1a** (54.6 mg, 0.5 mmol), 4-methoxybenzaldehyde **2f** (204.3 mg, 1.5 mmol), 4-bromobenzaldehyde **2d** (227.5 mg, 1.5 mmol), and water (27 mg, 1.5 mmol) gave, isolated by silica gel column chromatography (PE/EA=20:1), the desired product **6c** (78.1 mg, 35%) as white powder. Mp: 185-186 °C; IR (KBr, cm⁻¹) 3288, 3082, 2934, 2854,

1715, 1655, 1607, 1580, 1511, 1452, 1262, 770. ¹H NMR (500 MHz, CDCl₃) 1.10-1.26 (m, 3H, CH), 1.32-1.40 (m, 2H, CH), 1.59-1.68 (m, 3H, CH), 1.89-1.94 (m, 2H, CH), 3.78-3.84 (m, 1H, CH), 3.89 (s, 3H, CH), 6.06 (d, *J* = 7.5 Hz, 1H, NH), 6.23 (s, H, CH), 6.90-7.61 (m, 6H, ArH), 8.02-8.04 (m, 2H, ArH); ¹³C NMR (125 MHz, CDCl₃) 24.7, 25.5, 33.0, 33.7, 48.3, 55.6, 75.0, 114.1, 121.4, 123.0, 129.0, 131.0, 131.3, 131.9, 135.1, 164.1, 164.4, 167.0. HRMS (ESI-TOF, [M+H]⁺): calcd for C₂₂H₂₅BrNO₄, 446.0967, found 446.0973.

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- 4-Fluorobenzaldehyde (**2b**) (1.5 mmol, 0.186 g) and 4-methoxybenzaldehyde (**2f**) (1.5 mmol, 0.204 g) were separately added to two Schlenk tubes, which were evacuated and recharged with pure O₂ three times, then stirred at 60 °C for 1 h. Then the mixtures were dissolved with EtOAc. Evaporation of the solvent followed by purification on silica gel (petroleum ether/ethyl acetate = 4:1, v/v) provided the unconverted aldehydes. The conversion ratio of **2b** was 85 % and **2f** was 15 %.
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