室温条件下“一锅多组分”脯氨酸催化合成 *N,O*-缩醛化合物

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摘要 以芳香醛、脲和醇为原料, 过量的醇为溶剂, *D*-脯氨酸为催化剂, 开发了一种简单的多组分一锅法合成 *N,O*-缩醛化合物的方法. 在室温下反应 30 h 后, 以良好的收率合成了一系列 *N,O*-缩醛化合物.

关键词 *D*-脯氨酸; *N,O*-缩醛化合物; 一锅法合成; 室温

One-Pot Multi-component Synthesis of *N,O*-Acetal Compounds Catalyzed by *D*-Proline at Room Temperature

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Abstract In this paper, a convenient method for multi-component one-pot synthesis of *N,O*-acetal compounds was developed, using aromatic aldehyde, urea and alcohol as materials, alcohol also as solvent and *D*-proline as catalyst. A series of *N,O*-acetal compounds were synthesized in good yields after reacting for 30 h at room temperature.

Keywords *D*-proline; *N,O*-acetal compounds; one-pot synthesis; room temperature

1 Introduction

N,O-Aminals are structural motifs found in a number of interesting natural products and pharmaceuticals, including the mycalamide/pederin family, psymberin, and the microtubule-stabilizing zampanolide (Figure 1).^[1] These compounds have anti-cancer,^[2] anti-tumor^[3] and anti-proliferative^[4,5] properties. In some of these compounds, the structure-activity relationship studies indicated that the incorporation of the unique *N,O*-acetal motifs increased the potency.^[6] Moreover, acetal compound can also be used as reaction substrates to participate in a series of organic reactions.^[7~11] It plays a more important role in current natural and synthetic organic chemistry, which has stimulated the interest of scientists in the construction of this structure.

To date, only a few of synthetic routes of *N,O*-acetal compounds have been reported (Scheme 1, a,^[1,12] b,^[6] c^[13]). In these methods, Path a needs to synthesize the imine first using complicated methods, then react with alcohol, resulting in cumbersome steps. Path b needs three successive steps of nitrile hydrometalation, acylation and nucleophile addition which were carried out in one pot.^[13]

Figure 1 Natural products that contain *N,O*-acetals

The alkoxy group of the final target product of Path c is derived from the catalyst, and needs 2.0 equiv. of $\text{Ti}(\text{OEt})_4$. Benzene ring-containing amide was used as reaction substrate, resulting in poor substrate universality. In short, in the above methods, it is mostly necessary to synthesize imine, and then react with the latter, or require multiple steps to synthesize *N,O*-acetal compound, and amide con-

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Scheme 1 Synthetic routes of *N,O*-acetal compounds

taining benzene ring is mostly used as reaction substrate. Hence, it is positive to find a simple, green and efficient synthetic method.

However, the proline has the characteristics of being easy to obtain, non-toxic, water-soluble, and exhibits good catalytic effects in many important organic synthesis.^[14–19] Here, we have developed a simple method to prepare *N,O*-acetal compounds under one-pot conditions mediated by *D*-proline. Aldehyde, urea and alcohol were chosen as the reaction substrates to synthesize the target products by multi-component one-pot method instead of the aldehydes, amides and alcohols. In addition, this method opens up the range of substrates.

2 Results and discussion

Initial efforts were performed in methanol using *p*-nitrobenzaldehyde and urea as the model reaction and some amino acid as catalysts at 50 °C for 20 h (Table 1, Entries 1–4). The results indicated that *D*-proline displayed the best activity and the yield of *N,O*-acetal compounds was 38% (Table 1, Entry 2). The background reaction (Table 1, Entry 1) and other amino acids (Table 1, Entry 4), such as *L*-isoleucine, *L*-phenylalanine, *L*-serine, *D*-leucine, *L*-leucine, *L*-valine, *L*-cysteine and so on, showed no or low activity toward this reaction. Hydrochloric acid, sulfuric acid, and acetic acid were also chosen as catalysts, but no target product was observed. It proved that acid did not catalyze. Therefore, *D*-proline was selected as the best catalyst for subsequent research.

The effect of amount of amino acid was also investigated since it could influence the yield of the reaction. In this study, numerous experiments were performed in the range from 0 to 80 mol% under similar conditions (Table 1, Entries 2, 8–10). When the amount of catalyst was 20 mol%, the yield of the reaction was up to 39% (Table 1, Entry 9). When the amount of catalyst increased, the yield remained nearly constant (Table 1, Entry 10). So the amount of 20 mol% was selected as the optimized amount for the reaction. To further optimize the reaction, the effect of molar

Table 1 Optimization of the reaction conditions^a

Entry	Catalyst (mol%)	Ratio of 1a : 2a	Temp./°C	Yield ^b /%
1	Blank	1 : 1	50	—
2	<i>D</i> -Proline (50)	1 : 1	50	38
3	<i>L</i> -Proline (50)	1 : 1	50	36
4	Other amino acids (50)	1 : 1	50	Trace~31
5	CH ₃ COOH	1 : 1	50	Trace
6	H ₂ SO ₄	1 : 1	50	—
7	HCl	1 : 1	50	—
8	<i>D</i> -Proline (10)	1 : 1	50	34
9	<i>D</i> -Proline (20)	1 : 1	50	39
10	<i>D</i> -Proline (80)	1 : 1	50	39
11	<i>D</i> -Proline (20)	1 : 1.2	50	41
12	<i>D</i> -Proline (20)	1 : 1.5	50	53
13	<i>D</i> -Proline (20)	1 : 1.8	50	70
14	<i>D</i> -Proline (20)	1 : 2	50	73 (73 ^c)
15	<i>D</i> -Proline (20)	1 : 2	15	60
16	<i>D</i> -Proline (20)	1 : 2	25	73
17	<i>D</i> -Proline (20)	1 : 2	40	73
18	<i>D</i> -Proline (20)	1 : 2	60	65
19	<i>D</i> -Proline (20)	1 : 2	70	46
20	<i>D</i> -Proline (20)	1 : 2	25	51 ^d
21	<i>D</i> -Proline (20)	1 : 2	25	85 ^e
22	<i>D</i> -Proline (20)	1 : 2	25	85 ^f

^a Reaction condition: 1a (0.2 mmol), 2a (0.2~0.6 mmol), 2 mL of methanol for 20 h. ^c Ratio of 1a : 2a = 1 : 3. ^d 10 h. ^e 30 h. ^f 48 h

ratio of substrate on the model reaction was investigated (Table 1, Entries 11–14). It could be seen that the yield of the reaction was almost affected by the molar ratio of *p*-nitrobenzaldehyde and urea. The best yield of 73% was obtained when the molar ratio of *p*-nitrobenzaldehyde and urea was 1 : 2 (Table 1, Entries 14). Further increase of the molar ratio of the substrate, the yield has not any increase. Thus, 0.2 mmol of *p*-nitrobenzaldehyde and 0.4 mmol of urea were selected as the optimized ratio for the reaction.

It is generally believed that reaction temperature is another vital influence factor for all reactions. In this study, the reaction temperature was varied from 10 °C to 70 °C to investigate its effect (Table 1, Entries 15–19). The yield increased as temperature was enhanced from 10 °C to 50 °C and dropped dramatically at higher temperature. The increased collision chance between amino acid and substrate at the mild temperature might improve the reaction rate. Further increasing temperature could lead to more by-products, making *p*-nitrobenzaldehyde and alcohols form acetals. There was no significant effect on the yield of the reaction at room temperature to 50 °C (Table 1, Entries 14, 16, 17). Hence, room temperature was se-

lected as the optimum reaction temperature for this reaction.

Finally, we investigated the time of the reaction between *p*-nitrobenzaldehyde, urea and methanol catalyzed by *D*-proline under the optimal conditions and it could be seen that the yield of the product was high up to 85% after 30 h (Table 1, Entry 21). As the reaction time was prolonged, there was no significant effect on the yield of the reaction, so 30 h was selected as the best time for the reaction.

In summary, the optimal reaction conditions were that aldehyde (0.2 mmol), urea (0.4 mmol), *D*-proline (20 mol%) and excess alcohol were reacted at room temperature for 30 h.

The substrate applicability was further investigated after the optimal reaction conditions were determined. As shown in Table 2, aromatic aldehydes containing electron-donating and electron-withdrawing substituents were selected. When the substituents were electron-withdrawing, it was amazing that the *p*-substituted and *m*-substituted aromatic aldehydes worked well under the reaction conditions, *o*-substituted aromatic aldehyde had a lower yield and might be related to steric hindrance. Some

products had poor solubility in alcohol. When the reaction was completed, the target product could be precipitated by adding an appropriate amount of water, filtered and washed several times with dichloromethane (Table 2, **4b**, **4t**, **4v**, **4x**). However, when the substituents were electron-donating, the *N,O*-acetal compounds were not stable.

Furthermore, on the basis of our control experiments and literatures,^[12,15,20–24] a possible reaction mechanism is proposed for the formation of *N,O*-acetal compounds as depicted in Scheme 3. Initially, pyrrolidine motif of *D*-proline would first attack the aldehyde group to form the iminium ion intermediate with higher electrophilicity, which would facilitate the attack by amide or amine group. Then, the imine intermediate is formed by the amide group, followed by the removal of *D*-proline. Afterward, *N,O*-acetal compounds were formed by the alcohol attack of the intermediate products. In our controlled experiment, under the best conditions, *L*-proline was used as the catalyst instead of *D*-proline, and the yield was 84%. Therefore, this method is also applicable to *L*-proline as the catalyst.

Table 2 Substrate scope^a

^a Reaction condition: aromatic aldehyde (0.2 mmol), urea (0.4 mmol), *D*-proline (20 mol%), 2 mL of alcohol at 25 °C for 30 h. ^b Isolated yield based on **1**.

Scheme 2 Control experiments for the synthesis of *N,O*-acetal

Scheme 3 Proposed mechanism for the *D*-proline-catalyzed synthesis of *N,O*-acetal

3 Conclusions

Here, a convenient method for multi-component one-pot synthesis of *N,O*-acetal compounds was developed, using aldehyde, urea and alcohol as materials, and *D*-proline as catalyst. A series of *N,O*-acetal compounds were synthesized in good yields after reacting for 30 h at room temperature. The method has the advantages of easy availability of materials and catalysts, low process cost, low toxicity, simple operation and post-treatment, mild reaction conditions and so on.

4 Experimental section

4.1 Instruments and reagents

^1H NMR and ^{13}C NMR spectra were recorded in 500 MHz apparatus. All reagents were purchased from com-

mercial suppliers and used without further purification. Silica gel (200~300 mesh).

4.2 Experimental method

Aldehyde (0.2 mmol), urea (0.4 mmol) and *D*-proline (20 mol%) were added to alcohol (2.0 mL). This reaction mixture was stirred at room temperature for the specified reaction time and monitored by thin-layer chromatography (TLC). The eluent used for column chromatography was ethyl acetate and petroleum ether in a volume ratio of 4 : 1 or adding an appropriate amount of water, then filtered and washed several times with dichloromethane.

1-(Methoxy(4-nitrophenyl)methyl)urea (4a): White solid, m.p. 157.7~159.6 °C; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ : 8.25 (d, $J=8.7$ Hz, 2H), 7.64 (d, $J=8.8$ Hz, 2H), 6.99 (d, $J=9.9$ Hz, 1H), 5.93 (d, $J=9.8$ Hz, 1H), 5.80 (s, 2H), 3.32~3.25 (m, 3H); ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ : 158.38, 148.33, 147.52, 127.95, 123.95, 81.65, 54.98. ESI-HRMS calcd for $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$ 248.0642, found 248.0640.

1-(Methoxy(3-nitrophenyl)methyl)urea (4b): White solid, m.p. 126.8~128.7 °C; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ : 8.20 (s, 2H), 7.83 (d, $J=7.1$ Hz, 1H), 7.69 (d, $J=6.9$ Hz, 1H), 7.22 (d, $J=9.4$ Hz, 1H), 5.49~6.07 (m, 3H), 3.32 (s, 3H); ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ : 158.57, 148.11, 143.30, 133.56, 130.43, 123.28, 121.18, 81.43, 54.93. ESI-HRMS calcd for $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$ 248.0642, found 248.0645.

1-(Methoxy(2-nitrophenyl)methyl)urea (4c): White solid, m.p. 154.4~154.8 °C; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ : 7.88 (d, $J=8.8$ Hz, 1H), 7.74 (t, $J=7.1$ Hz, 1H), 7.67 (d, $J=7.3$ Hz, 1H), 7.60 (t, $J=8.3$ Hz, 1H), 7.10 (d, $J=10.0$ Hz, 1H), 6.28 (d, $J=10.0$ Hz, 1H), 5.91 (s, 2H), 3.23 (s, 3H); ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ : 158.24, 149.20, 134.00, 133.23, 130.01, 127.85, 124.61, 79.25, 55.64; ESI-HRMS calcd for $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$ 248.0642, found 248.0643.

1-(Methoxy(4-nitrophenyl)methyl)-3-methylurea (4d): White solid, m.p. 143.4~144.3 °C; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ : 8.22~8.24 (d, $J=8.8$ Hz, 2H), 7.64~7.65 (d, $J=8.6$ Hz, 2H), 7.22~7.24 (d, $J=9.9$ Hz, 1H), 6.23 (d, $J=4.6$ Hz, 1H), 5.96 (d, $J=9.8$ Hz, 1H), 3.29 (s, 3H), 2.61 (d, $J=4.6$ Hz, 3H); ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ : 158.39, 148.35, 147.45, 128.00, 123.93, 81.76, 54.93, 26.68; ESI-HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$ 262.0798, found 262.0795.

1-(Methoxy(3-nitrophenyl)methyl)-3-methylurea (4e): White solid, m.p. 121.4~122.9 °C; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ : 8.20 (d, $J=8.9$ Hz, 2H), 7.83 (d, $J=7.5$ Hz, 1H), 7.68 (t, $J=7.8$ Hz, 1H), 7.17 (d, $J=9.6$ Hz, 1H), 6.09 (s, 1H), 5.99 (d, $J=9.8$ Hz, 1H), 3.32 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ : 158.42, 148.10, 143.43, 131.44, 130.40, 124.54, 123.26, 81.60, 55.37, 26.55; ESI-HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$ 262.0798, found 262.0794.

1-(Methoxy(2-nitrophenyl)methyl)-3-methylurea (4f): White solid, m.p. 141.9~144.6 °C; ^1H NMR (500 MHz,

DMSO- d_6) δ : 7.87 (d, $J=7.8$ Hz, 1H), 7.74~7.66 (m, 2H), 7.62~7.56 (m, 1H), 7.25 (d, $J=10.0$ Hz, 1H), 6.33 (s, 1H), 6.31 (s, 1H), 3.21 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.26, 149.22, 134.01, 133.19, 129.97, 127.94, 124.56, 79.38, 55.63, 26.67; ESI-HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$ 262.0798, found 262.0793.

1-(Ethoxy(4-nitrophenyl)methyl)urea (**4g**): White solid, m.p. 156.7~160.1 °C; ^1H NMR (500 MHz, DMSO- d_6) δ : 8.25 (d, $J=8.8$ Hz, 2H), 7.65 (d, $J=8.7$ Hz, 2H), 6.98 (d, $J=9.8$ Hz, 1H), 6.02 (d, $J=9.8$ Hz, 1H), 5.76 (s, 2H), 3.86~3.58 (m, 1H), 3.57~3.40 (m, 1H), 1.17 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.44, 140.76, 131.59, 128.81, 121.30, 80.24, 62.39, 15.57; ESI-HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$ 262.0798, found 262.0792.

1-(Ethoxy(3-nitrophenyl)methyl)urea (**4h**): White solid, m.p. 154.0~157.1 °C; ^1H NMR (500 MHz, DMSO- d_6) δ : 8.20 (d, $J=9.1$ Hz, 2H), 7.84 (d, $J=7.7$ Hz, 1H), 7.69 (t, $J=7.8$ Hz, 1H), 7.18 (d, $J=9.9$ Hz, 1H), 6.05 (d, $J=9.8$ Hz, 1H), 5.86 (s, 1H), 3.66 (d, $J=7.1$ Hz, 1H), 3.52 (dq, $J=9.5$, 7.0 Hz, 1H), 1.18 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.35, 148.16, 143.70, 133.51, 130.40, 123.21, 121.05, 79.94, 62.67, 15.56; ESI-HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$ 262.0798, found 262.0795.

1-(Ethoxy(2-nitrophenyl)methyl)urea (**4i**): White solid, m.p. 150.9~152.1 °C; ^1H NMR (500 MHz, DMSO- d_6) δ : 7.85 (d, $J=7.9$ Hz, 1H), 7.71 (d, $J=7.5$ Hz, 1H), 7.64 (d, $J=7.5$ Hz, 1H), 7.59 (s, 1H), 7.01 (d, $J=10.0$ Hz, 1H), 6.35 (d, $J=10.0$ Hz, 1H), 5.85 (s, 2H), 3.59 (dd, $J=9.3$, 7.1 Hz, 1H), 3.37~3.30 (m, 1H), 1.05 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.14, 149.39, 134.21, 133.06, 129.88, 127.80, 124.47, 77.96, 63.49, 15.20; ESI-HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$ 262.0798, found 262.0796.

1-(Ethoxy(4-nitrophenyl)methyl)-3-methylurea (**4j**): White solid, m.p. 166.8~169.1 °C; ^1H NMR (500 MHz, DMSO- d_6) δ : 8.24 (d, $J=8.1$ Hz, 2H), 7.66 (d, $J=8.1$ Hz, 2H), 7.18 (d, $J=9.6$ Hz, 1H), 6.16 (d, $J=3.2$ Hz, 1H), 6.07 (d, $J=9.6$ Hz, 1H), 3.72~3.45 (m, 2H), 2.61 (d, $J=3.6$ Hz, 3H), 1.16 (t, $J=6.7$ Hz, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.31, 148.77, 147.42, 127.98, 123.93, 80.19, 62.61, 26.68, 15.54; ESI-HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_4\text{Na}$ $[\text{M} - \text{CH}_2 + \text{Na}]^+$ 262.0798, found 262.0809.

1-(Ethoxy(3-nitrophenyl)methyl)-3-methylurea (**4k**): White solid, m.p. 135.3~136.0 °C; ^1H NMR (500 MHz, DMSO- d_6) δ : 8.29~8.12 (m, 2H), 7.84 (d, $J=7.5$ Hz, 1H), 7.68 (t, $J=7.9$ Hz, 1H), 7.17 (d, $J=9.7$ Hz, 1H), 6.09 (d, $J=9.5$ Hz, 2H), 3.71~3.60 (m, 1H), 3.55~3.48 (m, 1H), 2.62 (d, $J=4.3$ Hz, 3H), 1.18 (t, $J=6.9$ Hz, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.32, 148.10, 143.71, 133.58, 130.38, 123.20, 121.11, 80.04, 62.63, 26.71, 15.54; ESI-HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_4\text{Na}$ $[\text{M} - \text{CH}_2 + \text{Na}]^+$ 262.0798, found 262.0803.

1-(Ethoxy(2-nitrophenyl)methyl)-3-methylurea (**4l**):

White solid, m.p. 161.7~162.3 °C; ^1H NMR (500 MHz, DMSO- d_6) δ : 7.85 (d, $J=8.0$ Hz, 1H), 7.77~7.64 (m, 2H), 7.58 (t, $J=7.5$ Hz, 1H), 7.20 (d, $J=10.0$ Hz, 1H), 6.40 (d, $J=10.0$ Hz, 1H), 6.26 (d, $J=4.6$ Hz, 1H), 3.57 (dq, $J=14.1$, 7.0 Hz, 1H), 3.37~3.30 (m, 1H), 2.60 (d, $J=4.6$ Hz, 3H), 1.04 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.19, 149.41, 134.21, 133.04, 129.87, 127.87, 124.45, 78.09, 63.50, 26.68, 15.17; ESI-HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_4\text{Na}$ $[\text{M} - \text{CH}_2 + \text{Na}]^+$ 262.0798, found 262.0802.

1-((4-Nitrophenyl)(propoxy)methyl)urea (**4m**): White solid, m.p. 143.3~146.4 °C; ^1H NMR (500 MHz, DMSO- d_6) δ : 8.26 (d, $J=8.8$ Hz, 2H), 7.65 (d, $J=8.7$ Hz, 2H), 6.99 (d, $J=9.9$ Hz, 1H), 6.02 (d, $J=9.8$ Hz, 1H), 5.78 (s, 2H), 3.62~3.52 (m, 1H), 3.42 (dt, $J=9.4$, 6.6 Hz, 1H), 1.62~1.52 (m, 2H), 0.90 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.27, 148.74, 147.48, 127.89, 124.00, 80.20, 68.90, 22.93, 11.15; ESI-HRMS calcd for $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_4\text{Na}$ $[\text{M} - \text{C}_2\text{H}_4 + \text{Na}]^+$ 248.0642, found 248.0649.

1-((3-Nitrophenyl)(propoxy)methyl)urea (**4n**): White solid, m.p. 168.5~171.3 °C; ^1H NMR (500 MHz, DMSO- d_6) δ : 8.27~8.15 (m, 2H), 7.85 (d, $J=7.7$ Hz, 1H), 7.69 (t, $J=7.9$ Hz, 1H), 7.32 (d, $J=9.4$ Hz, 1H), 6.04 (d, $J=9.9$ Hz, 1H), 5.93 (s, 2H), 3.57 (dd, $J=13.4$, 9.3 Hz, 1H), 3.44 (d, $J=6.6$ Hz, 1H), 1.57 (dd, $J=14.1$, 7.0 Hz, 2H), 0.90 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.49, 148.12, 143.72, 133.55, 130.42, 123.21, 121.12, 80.02, 68.81, 22.80, 11.32; ESI-HRMS calcd for $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_4\text{Na}$ $[\text{M} - \text{C}_2\text{H}_4 + \text{Na}]^+$ 248.0642, found 248.0653.

1-Methyl-3-((4-nitrophenyl)(propoxy)methyl)urea (**4o**): White solid, m.p. 148.2~149.9 °C; ^1H NMR (500 MHz, DMSO- d_6) δ : 8.24 (d, $J=7.4$ Hz, 2H), 7.64 (d, $J=7.5$ Hz, 2H), 7.00 (d, $J=9.2$ Hz, 1H), 6.04 (d, $J=9.3$ Hz, 1H), 5.91 (s, 1H), 3.54 (d, $J=7.3$ Hz, 2H), 2.61 (s, 3H), 1.63~1.43 (m, 2H), 0.88 (t, $J=6.6$ Hz, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.21, 148.79, 147.44, 127.92, 123.96, 80.36, 68.89, 26.74, 22.92, 11.15; ESI-HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_4\text{Na}$ $[\text{M} - \text{C}_2\text{H}_4 + \text{Na}]^+$ 262.0798, found 262.0801.

1-Methyl-3-((3-nitrophenyl)(propoxy)methyl)urea (**4p**): White solid, m.p. 140.0~141.0 °C; ^1H NMR (500 MHz, DMSO- d_6) δ : 8.27~8.12 (m, 2H), 7.84 (d, $J=7.6$ Hz, 1H), 7.69 (t, $J=7.9$ Hz, 1H), 7.16 (d, $J=9.8$ Hz, 1H), 6.08 (d, $J=9.7$ Hz, 2H), 3.56 (dd, $J=15.9$, 6.7 Hz, 2H), 2.62 (d, $J=4.5$ Hz, 3H), 1.57 (dd, $J=14.1$, 7.0 Hz, 2H), 0.90 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.32, 148.11, 143.74, 133.56, 130.39, 123.20, 121.10, 80.20, 68.73, 26.72, 22.92, 11.16; ESI-HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_4\text{Na}$ $[\text{M} - \text{C}_2\text{H}_4 + \text{Na}]^+$ 262.0798, found 262.0798.

1-Methyl-3-((2-nitrophenyl)(propoxy)methyl)urea (**4q**): White solid, m.p. 152.2~155.9 °C; ^1H NMR (500 MHz, DMSO- d_6) δ : 7.84 (d, $J=7.9$ Hz, 1H), 7.73~7.66 (m, 2H), 7.62~7.53 (m, 1H), 7.33 (d, $J=10.1$ Hz, 1H), 6.45 (d, $J=4.5$ Hz, 1H), 6.41 (d, $J=10.1$ Hz, 1H), 3.58~3.45 (m, 1H), 3.24 (dd, $J=15.7$, 6.7 Hz, 1H), 2.60 (d, $J=4.5$ Hz,

3H), 1.42 (dd, $J=14.0$, 7.0 Hz, 2H), 0.80 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.29, 149.41, 134.31, 133.03, 129.87, 127.89, 124.49, 78.20, 69.72, 26.62, 22.76, 11.07; ESI-HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_4\text{Na}$ $[\text{M}-\text{C}_2\text{H}_4+\text{Na}]^+$ 262.0798, found 262.0802.

1-(Methoxy(4-(trifluoromethyl)phenyl)methyl)urea (**4r**): White solid, m.p. 189.3~190.9 °C; ^1H NMR (500 MHz, DMSO- d_6) δ : 7.74 (d, $J=8.2$ Hz, 2H), 7.59 (d, $J=8.1$ Hz, 2H), 7.10 (d, $J=9.3$ Hz, 1H), 5.94~5.69 (m, 3H), 3.29 (s, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.45, 145.70, 145.55, 129.10, 128.77, 127.43, 125.64, 123.60, 81.99, 55.01; ESI-HRMS calcd for $\text{C}_{10}\text{H}_{11}\text{F}_3\text{N}_2\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 271.0665, found 271.0669.

1-(Ethoxy(4-(trifluoromethyl)phenyl)methyl)urea (**4s**): ^1H NMR (500 MHz, DMSO- d_6) δ : 7.74 (d, $J=7.9$ Hz, 2H), 7.60 (d, $J=7.9$ Hz, 2H), 7.12 (d, $J=9.7$ Hz, 1H), 5.98 (d, $J=9.7$ Hz, 1H), 5.86 (s, 2H), 3.68~3.58 (m, 1H), 3.52~3.44 (m, 1H), 1.15 (t, $J=6.9$ Hz, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.45, 145.95, 128.90, 128.65, 127.43, 125.78, 125.65, 125.62, 80.22, 62.49, 15.56; ESI-HRMS calcd for $\text{C}_{10}\text{H}_{11}\text{F}_3\text{N}_2\text{O}_2\text{Na}$ $[\text{M}-\text{CH}_2+\text{Na}]^+$ 271.0665, found 271.0669.

1-((4-Cyanophenyl)(methoxy)methyl)urea (**4t**): White solid, m.p. 181.9~182.7 °C; ^1H NMR (500 MHz, DMSO- d_6) δ : 7.86 (d, $J=8.2$ Hz, 2H), 7.55 (d, $J=8.1$ Hz, 2H), 6.94 (d, $J=9.8$ Hz, 1H), 5.86 (d, $J=9.8$ Hz, 1H), 5.77 (s, 2H), 3.29 (s, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.29, 146.32, 132.85, 127.58, 119.21, 111.10, 81.79, 54.98; ESI-HRMS calcd for $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 228.0743, found 228.0751.

1-((4-Cyanophenyl)(ethoxy)methyl)urea (**4u**): White solid, m.p. 170.1~172.5 °C; ^1H NMR (500 MHz, DMSO- d_6) δ : 7.86 (d, $J=7.8$ Hz, 2H), 7.58 (d, $J=7.7$ Hz, 2H), 7.12 (d, $J=9.6$ Hz, 1H), 5.97 (d, $J=9.7$ Hz, 1H), 5.85 (s, 2H), 3.63 (s, 1H), 3.55~3.44 (m, 1H), 1.15 (t, $J=6.7$ Hz, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.38, 146.70, 132.79, 127.62, 119.25, 110.97, 80.21, 62.57, 15.56; ESI-HRMS calcd for $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_2\text{Na}$ $[\text{M}-\text{CH}_2+\text{Na}]^+$ 228.0743, found 228.0755.

1-((4-Chlorophenyl)(methoxy)methyl)urea (**4v**): White solid, m.p. 215.1~217.5 °C; ^1H NMR (500 MHz, DMSO- d_6) δ : 7.44 (d, $J=8.0$ Hz, 2H), 7.39 (d, $J=8.0$ Hz, 2H), 7.05 (d, $J=9.6$ Hz, 1H), 5.85 (s, 2H), 5.79 (d, $J=9.7$ Hz, 1H), 3.26 (s, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.39, 140.84, 131.58, 128.82, 121.28, 80.22, 62.36; ESI-HRMS calcd for $\text{C}_9\text{H}_{11}\text{ClN}_2\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 237.0401, found 237.0393.

1-((4-Chlorophenyl)(ethoxy)methyl)urea (**4w**): White solid, m.p. 193.7~194.9 °C; ^1H NMR (500 MHz, DMSO- d_6) δ : 7.57 (d, $J=8.4$ Hz, 2H), 7.34 (d, $J=8.4$ Hz, 2H), 7.00 (d, $J=9.8$ Hz, 1H), 5.87 (d, $J=9.8$ Hz, 1H), 5.80 (s, 2H), 3.68~3.53 (m, 1H), 3.48~3.41 (m, 1H), 1.14 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.44, 140.76, 131.59, 128.81, 121.30, 80.24, 62.39, 15.57; ESI-HRMS calcd for $\text{C}_9\text{H}_{11}\text{ClN}_2\text{O}_2\text{Na}$ $[\text{M}-\text{CH}_2+\text{Na}]^+$ 237.0401, found 237.0406.

1-((4-Bromophenyl)(methoxy)methyl)urea (**4x**): White

solid, m.p. 216.0~218.1 °C; ^1H NMR (500 MHz, DMSO- d_6) δ : 7.58 (d, $J=8.3$ Hz, 2H), 7.33 (d, $J=8.3$ Hz, 2H), 6.87 (d, $J=9.8$ Hz, 1H), 5.79 (s, 1H), 5.77 (s, 2H), 3.27 (s, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.36, 140.43, 131.64, 128.79, 121.42, 81.83, 54.81; ESI-HRMS calcd for $\text{C}_9\text{H}_{11}\text{BrN}_2\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 280.9896, found 280.9886.

1-(Ethoxy(phenyl)methyl)urea (**4y**): White solid, m.p. 187.8~189.2 °C; ^1H NMR (500 MHz, DMSO- d_6) δ : 7.37 (d, $J=4.4$ Hz, 4H), 7.32 (dd, $J=8.9$, 4.4 Hz, 1H), 6.92 (d, $J=9.8$ Hz, 1H), 5.78 (d, $J=9.7$ Hz, 3H), 3.25 (s, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ : 158.39, 141.03, 128.72, 128.32, 126.48, 82.50, 54.73; ESI-HRMS calcd for $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 203.0791, found 203.0785.

Supporting Information ^1H NMR, ^{13}C NMR and MS spectra for novel compounds. The Supporting Information is available free of charge via the Internet at <http://sioc-journal.cn/>.

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