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Abstract: A novel and convenient synthetic route for preparing aza-phthalimidine hydroxylactams (**5a**–**j**) by N-bromosuccinimide (NBS) was developed. This method involved the substitution reactions of substrates (**3a–j**) with NBS via unstable intermediate bromides (**4a–j**) rapidly hydrolyzed into hydroxyl products in the course of the workup process.

Keywords: N-Bromosuccinimide, hydroxylactam, hydroxylation

As important structural segments in sedatives, hypnotics, and muscle relaxants such as zopiclone,[1a] pazinaclone,[1b] and desmethylzopiclone,[1c] hydroxylactams have attracted much attention from chemists. Hydroxylactams were also used as key intermediates for the construction of fused heterocyclic systems.[2,3] It has been reported that hydroxylactams could be synthesized by partial reduction of aza-phthalimides with $Zn/TiCl_4$,[4] $Zn/AcOH$,[5] $Mg(ClO_4)_2/NaBH_4$,[6] and $NaBH_4$.[2,7] Regiorestriction of these methods was observed because of coordination of the pyridine nitrogen atom with the metal ion of magnesium perchlorate or zinc, whereby the reduction of sodium borohydride was directed to the adjacent carbonyl group (Fig. 1). By the same cause, the reduction usually would not happen in the 5-position. Other reported methods,[3,8] involved 2-substituted nicotinic anilide with organolithium and dimethylformamide (DMF) forming the corresponding hydroxylactam.

In consideration of the strong basic and reductive condition employed by these reported methods, it is of great interest to develop a

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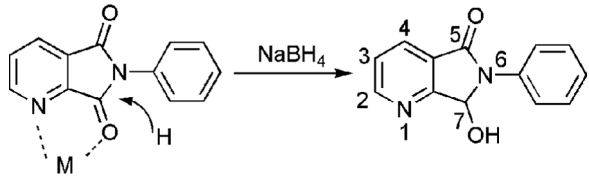
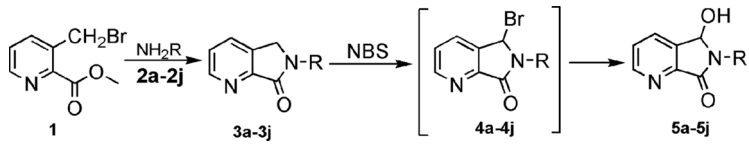


Figure 1. Reduction of aza-phthalimide.

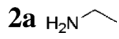
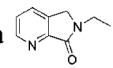
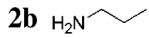
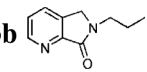
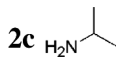
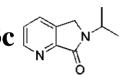
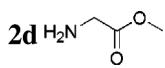
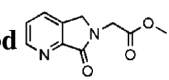
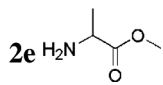
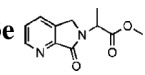
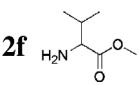
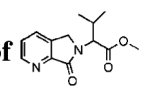
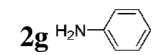
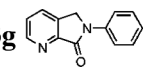
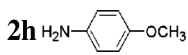
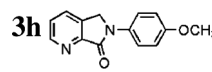
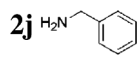
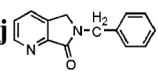
new approach to hydroxylactam compounds with such a structural segment. Herein we report a mild and convenient approach to hydroxylation of aza-phthalimidine by the N-bromosuccinimide (NBS) (Scheme 1). This novel method could be used to prepare selectively hydroxylactam with a hydroxyl group at the 5-position or 7-position.

To explore this new hydroxylation method, a series of aza-phthalimidines (**3a–j**) (Table1) with different side chains were synthesized from 3-bromomethyl-pyridine-2-carboxylic acid methyl ester[9] **1** with corresponding amines (**2a–j**) (Table 1). Hydroxylactams (**5a–j**) were obtained through hydroxylation of aza-phthalimidines by NBS. The free radical bromine substitution took place as was expected at the 5-position methene group of aza-phthalimidine.[10] A possible mechanism was that unstable intermediate bromides (**4a–j**) were formed during the substitution reactions of substrates (**3a–j**) with NBS, which rapidly hydrolyzed into hydroxyl products in the course of workup process. In the case of N-substituted alkyl products (**5a–c**) (Table 2), the yields of products (**5a–c**) were moderate (42–52%) with the recovery of partial substrates (**3a–c**). A chiral center was formed after introduction of newly formed hydroxyl group into 5-position methene, so the products **5e** and **5f** were the mixture of epimers under the influence of amino acid esters **3e** and **3f** before hydroxylation. This was indicated in the NMR spectra of **5e** and **5f**; for example, the chemical shift of carbon atom connecting with a hydroxyl group was shown as follows: **5e** ($\delta_{C\text{-}OH}$ 80.873, 78.691 ppm) and **5f** ($\delta_{C\text{-}OH}$ 79.778, 79.726 ppm). As shown in the Table 2, the low yield of the N-substituted valine aza-phthalimidine **5f** was attributed to the steric effect. No obvious side reactions occurred because most of starting material was successfully recovered. As for the hydroxylation of



Scheme 1. Preparation of aza-phthalimidine hydroxylactam.

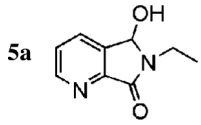
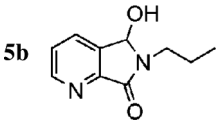
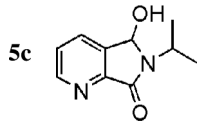
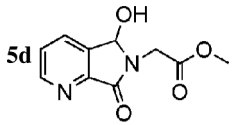
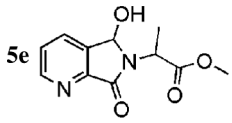
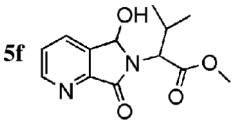
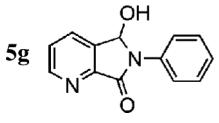
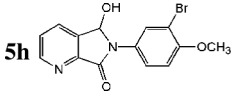
Table 1. Amines (**2a–j**) and aza-phthalimidines (**3a–j**)

Entry	NH_2R	Aza-phthalimidines	Yield (%)
1	**2a** 	**3a** 	56
2	**2b** 	**3b** 	63
3	**2c** 	**3c** 	61
4	**2d** 	**3d** 	49
5	**2e** 	**3e** 	60
6	**2f** 	**3f** 	43
7	**2g** 	**3g** 	55
8	**2h** 	**3h** 	50
9	**2j** 	**3j** 	53

aza-phthalimidines **3g** and **3h** with NBS, it could be a free radical substitution at the 5-position methene group of aza-phthalimidine or an electrophilic substitution on the phenyl ring. So if the aza-phthalimidine **3g** and 1.25 equivalents of NBS were mildly refluxed in acetonitrile, the target compound **5g** was given in 27% yield. When aza-phthalimidine **3h** was treated with NBS under the same conditions as **5g**, however, not hydroxylactam but bromine-substituted aza-phthalimidine **5i** (Table 2, entry 9) was isolated. When the NBS (4.0 equiv) and substrate **3h** (1.0 equiv) were refluxed in acetonitrile, the compounds **5h** and **5i** were afforded in 33 and 64% yields respectively.

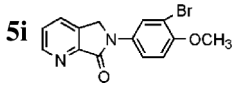
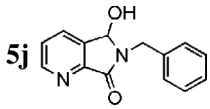
This could be attributed to the electron-donating effect of methoxyl group. Therefore the ortho position of methoxyl group on the phenyl ring was more active than the 5-position methene group of aza-phthalimidine.

Table 2. Yields of products **5a–j**

Entry	Product	Mp(°C)	Yield(%)[a]	Yield(%)[b]
1	**5a** 	104–105	42	51
2	**5b** 	75–77	52	65
3	**5c** 	113–115	51	90
4	**5d** 	156–157	48	52
5	**5e** 	157–159	45	56
6	**5f** 	61–63	6	—
7	**5g** 	237–238[c]	27	—
8	**5h** 	251–252	33	—

(*Continued*)

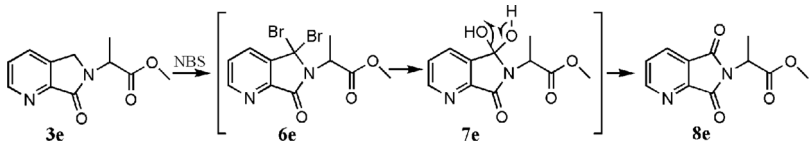
Table 2. Continued

Entry	Product	Mp(°C)	Yield(%)[a]	Yield(%)[b]
9	**5i** 	186–188	64	—
10	**5j** 	202– 205[d]	61	73

[a]Isolated yield by method A.
[b]Isolated yield by method B.
[c]Ref. 8a, mp: 237–239 °C.
[d]Ref. 2a, mp: 203–207 °C.

Further investigation with the N-benzyl aza-phthalimidine **3j** indicated that the benzyl group was intact during the substitution reaction of **3j** with NBS. The NMR spectra of the target compound **5j** were identical with those of authentic samples. This indicated that the hydroxylation of the N-benzyl aza-phthalimidine **3j** by NBS was regiospecific.

Moderate or low yield by NBS was due to the formation of aza-phthalimides in these reactons. For example, the plausible formation of N-alanine aza-phthalimides **8e** (Scheme 2) was proposed as follows: The fragile intermediates dibromides **6e** were formed because of over-bromination. The formation of dihydroxylactams **7e** were similar to hydroxylactams (**5a–j**). At the same time, the aza-phthalimides **8e** were afforded by dehydration of dihydroxylactams. Taking into account this competitive side reaction, we handled the reaction of substrates (**3a–j**) and NBS (1.0 equiv) at lower temperature (50 °C) or even at room temperature. Unfortunately, most of substrates were intact in these reaction conditions. Other reagents such as Br_2/CF_3COOAg and N-chlorosuccinimide (NCS)/benzoyl peroxide (BPO) were used to improve the yield.



Scheme 2. Possible mechanism for formation of by-product **8e**.

To exclude the formation of the dibromide, the substrate **3c** was handled with Br_2/CF_3COOAg at room temperature. Unfortunately, the aza-phthalimide was also a major by-product. In view of these results, reaction of the substrate **3c** and NCS/BPO was treated at 60 °C in chloroform. Surprisingly, the yield greatly increased from 51 to 90% (Table 2, entry 3). The substrates **3a–e** and **3j** were treated with NCS/BPO under the same conditions as **5c**, and the yield of corresponding products improved. According to this procedure, the substrates **3g** and **3h** were also handled at 60 °C or even at the refluxing temperature in chloroform. However, most of starting material were kept intact.

In conclusion, a novel, convenient, and mild synthetic approach for hydroxylactam has been developed. Compared with the conventional methods in the pyridine heterocyclic systems, we experienced no difficulty in getting the hydroxylactams. The hydroxylation of the other aromatic lactam as an extension of the scope of our functionalization methodology is under investigation in our laboratory.

EXPERIMENTAL

Melting points were determined on a RY-2 microscopic melting-point spectrometer and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Unity 300 spectrometer. Mass spectra were recorded on Agilent 1100 series LC-MSD and Micromass GCT. Elemental analyses were performed on a Vario EL III instrument.

Typical Procedure for Synthesis of Compounds 3a–j

3-Bromomethyl-pyridine-2-carboxylic acid methyl ester[9] **1** (2.5 g, 9.416 mmol), amines **2a–j** (18.832 mmol), Et_3N (6.5 ml, 47.08 mmol), and acetonitrile (20 ml) were stirred for 2 days at room temperature. After the reaction was completed, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography.

Data

Compound **3a**: Yield 56%, mp: 96–98 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ8.68 (1H, d d, $J = 4.4$, 1.2 Hz), 8.04 (1H, d d, $J = 8.0$, 1.2 Hz), 7.54 (1H, d d, $J = 8.0$, 4.4 Hz), 4.47 (2H, s), 3.55 (2H, q, $J = 7.2$ Hz), 1.17 (3H, t, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ166.1, 151.2, 150.7, 136.8, 132.6, 125.8, 47.2, 37.5, 13.9. Anal. calcd. for $C_9H_{10}N_2O$ (%): C, 66.65; H, 6.21; N, 17.27. Found: C, 66.75; H, 6.43; N, 17.46.

Compound **3b**: Yield 63%, oil residue. ^{1}H NMR (400 MHz, DMSO-d_6): δ8.68 (1H, d d, $J = 4.4$, 1.2 Hz), 8.04 (1H, d d, $J = 7.6$, 1.2 Hz), 7.54 (1H, d d, $J = 7.6$, 4.4 Hz), 4.46 (2H, s), 3.47 (2H, t, $J = 7.2$ Hz), 1.62 (2H, m, $J = 7.2$ Hz), 0.837 (3H, t). ^{13}C NMR (75 MHz, DMSO-d_6): δ166.4, 151.1, 150.7, 136.9, 132.5, 125.8, 47.7, 44.4, 21.6, 11.9. LC-MS (ESI): $C_{10}H_{12}N_2O$ (M + 1) 177.1, (M + Na^+) 199.0. Anal. calcd. for $C_{10}H_{12}N_2O$ (%): C, 68.16; H, 6.86; N, 15.90. Found: C, 68.01; H, 6.66; N, 15.44.

Compound **3c**: Yield 61%, mp: 65–66 °C. ^{1}H NMR (400 MHz, $DCCl_3$): δ8.76 (1H, d, $J = 4.8$ Hz), 7.83 (1H, d, $J = 7.6$ Hz), 7.41 (1H, d d, $J = 7.6$, 4.8 Hz), 4.78 (1H, m), 4.34 (2H, s), 1.30 (6H, d, $J = 6.8$ Hz). ^{13}C NMR (75 MHz, $DCCl_3$): δ166.0, 151.4, 150.9, 135.1, 131.3, 125.0, 43.2, 42.9, 20.9, 20.9. LC-MS (ESI): $C_{10}H_{12}N_2O$ (M + 1) 177.0, (M + Na^+) 199.0. Anal. calcd. for $C_{10}H_{12}N_2O$ (%): C, 68.16; H, 6.86; N, 15.90. Found: C, 68.59; H, 6.71; N, 15.31.

Compound **3d**: Yield 49%, mp: 119–120 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ8.71–8.72 (1H, d, $J = 4.8$ Hz), 8.07–8.09 (1H, d, $J = 7.6$ Hz), 7.57–7.60 (1H, d d, $J = 7.6$, 4.8 Hz), 4.53 (2H, s), 4.42 (2H, s), 3.67 (3H, s). ^{13}C NMR (75 MHz, DMSO-d_6): δ170.0, 166.7, 151.0, 150.0, 137.2, 132.9, 126.3, 52.7, 48.7, 44.4. LC-MS (ESI): $C_{10}H_{10}N_2O_3$ (M + 1) 207.0, (M + Na^+) 229.0. Anal. calcd. for $C_{10}H_{10}N_2O_3$ (%): C, 58.25; H, 4.89; N, 13.59. Found: C, 57.89; H, 4.41; N, 13.79.

Compound **3e**: Yield 60%, mp: 105–106 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ8.71–8.72 (1H, d, $J = 4.8$ Hz), 8.06–8.08 (1H, d, $J = 7.6$ Hz), 7.57–7.60 (1H, d d, $J = 7.6$, 4.8 Hz), 4.95–4.97 (1H, q, $J = 7.2$ Hz), 4.46–4.58 (2H, q, $J = 17.2$ Hz), 3.64 (3H, s), 1.50–1.52 (3H, d, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ172.2, 166.4, 151.1, 150.1, 137.2, 132.9, 126.3, 52.9, 50.2, 45.5, 15.6. LC-MS (ESI): $C_{11}H_{12}N_2O_3$(M + 1) 221.0, (M + Na^+) 243.1. Anal. calcd. for $C_{11}H_{12}N_2O_3$ (%): C, 59.99; H, 5.49; N, 12.72. Found: C, 59.78; H,5.51; N, 12.69.

Compound **3f**: Yield 43%, oil residue. ^{1}H NMR (400 MHz, DMSO-d_6): δ8.80–8.81 (1H, d, $J = 4.8$ Hz), 7.84–7.86 (1H, d, $J = 7.6$ Hz), 7.44–7.47 (1H, d d, $J = 7.6$, 4.8 Hz), 4.91–4.94 (1H, d, $J = 10.8$ Hz). 4.79–4.82 (1H, d, $J = 17.2$ Hz), 4.42–4.46 (1H, d, $J = 17.2$ Hz), 3.72 (3H, s), 2.31–2.37 (1H, m), 1.05–1.06 (3H, d, $J = 6.4$ Hz), 0.924–0.941 (3H, d, $J = 6.4$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ171.8, 167.2, 151.1, 150.1, 135.7, 131.4, 125.5, 60.0, 52.0, 45.3, 29.3, 19.5, 19.3. LC-MS (ESI): $C_{13}H_{16}N_2O_3$(M + 1) 249.1, (M + Na^+) 271.1. Anal. calcd. for $C_{13}H_{16}N_2O_3$(%): C, 62.89; H, 6.50; N, 11.28. Found: C, 63.30; H, 6.62; N, 11.45.

Compound **3g**: Yield 55%, mp: 192–194 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ8.75–8.76 (1H, d d, $J = 4.8$,1.2 Hz), 8.00–8.02 (1H, d, $J = 7.2$ Hz), 7.90–7.93 (2H, m), 7.61–7.64 (1H, d d, $J = 7.2$, 4.8 Hz), 7.43–7.47 (2H, m), 7.18–7.24 (1H, m), 5.03 (2H, s). ^{13}C NMR (75 MHz, MHz, DMSO-d_6): δ165.5, 151.3, 150.4, 139.9, 136.3, 132.6, 129.6, 129.6,

126.8, 125.2, 120.1, 120.1, 48.8. LC-MS (ESI): $C_{13}H_{10}N_2O$ (M + 1) 211.0, ($M + Na^+$) 233.0. Anal. calcd. for $C_{13}H_{10}N_2O$ (%): C, 74.27; H, 4.79; N, 13.33. Found: C, 74.25; H, 4.51; N, 12.98.

Compound **3h**: Yield 50%, mp: 202–204 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ8.73–8.74 (1H, d d, $J = 4.8$, 1.2 Hz), 8.08–8.11 (1H, d, $J = 7.6$ Hz), 7.78–7.80 (2H, m), 7.59–7.62 (1H, d d, $J = 7.2$, 4.8 Hz), 7.00–7.02 (2H, m), 4.97 (2H, s), 3.76 (3H, s). ^{13}C NMR (75 MHz, DMSO-d_6): δ165.2, 157.1, 151.1, 150.6, 136.1, 133.0, 132.5, 126.5, 122.0, 122.0, 114.8, 114.8, 55.9, 49.1. LC-MS (ESI): $C_{14}H_{12}N_2O_2$ (M + 1) 241.1, ($M + Na^+$) 263.1. Anal. calcd. for $C_{14}H_{12}N_2O_2$ (%): C, 69.99; H, 5.03; N, 11.66. Found: C, 69.95; H, 5.22; N, 11.19.

Compound **3j**: Yield 53%, mp: 158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ8.78–8.79 (1H, d, $J = 4.0$ Hz), 7.73–7.75 (1H, d, $J = 7.6$ Hz), 7.25–7.42 (6H, m), 4.86 (2H, s), 4.26 (2H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ166.5, 151.3, 151.0, 136.4, 135.2, 131.3, 129.1, 129.1, 128.5, 128.5, 128.1, 125.3, 47.3, 47.0. LC-MS (ESI): $(M + 1)^+$ 225.1, $(M + Na^+)^+$247.1. Anal. calcd. for $C_{14}H_{12}N_2O$ (%): C, 74.98; H, 5.39; N, 12.49. Found: C, 74.89; H, 5.49; N, 12.35.

Typical Procedure for Synthesis of Compounds 5a–j

Method A

A solution of **3a–j** (1.0 equiv), NBS (1.25 equiv), AIBN (0.0625 equiv) in anhydrous acetonitrile was mildly refluxed for 2–5 h. It is worth to pointing out that such a ratio gave the compound **5i** with substitution by bromine on the phenyl ring. However, when the NBS (4.0 equiv) and substrate **3h** (1.0 equiv) were refluxed in acetonitrile, the compound **5h** was afforded. The resulting mixture evaporated in vacuum and was purified by flash chromatography.

Method B

A solution of **3a–e** and **3j** (1.0 equiv), NCS (1.05 equiv), and BPO (0.05 equiv) in chloroform was heated to 60 °C. After the substrates disappeared, the resulting mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography.

Data

Compound **5a**: Yield 51%, mp: 104–105 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ8.69–8.71 (1H, d d, $J = 4.8$, 1.2 Hz), 8.00–8.02 (1H, d d,

$J = 7.6$, 1.2 Hz), 7.54–7.57(1H, d d, $J = 7.6$, 4.8 Hz), 6.67 (1H, d, $J = 8.8$ Hz), 5.87 (1H, d, $J = 8.8$ Hz), 3.60–3.63 (1H, m, $J = 7.2$ Hz), 3.32–3.37(1H, m, $J = 7.2$ Hz), 1.16 (3H, t, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ164.9, 151.8, 150.9, 139.7, 132.6, 126.5, 79.1, 34.5, 14.1. HRMS (EI^+): $C_9H_{10}N_2O_2$, calc. 178.0742; found 178.0735. Anal. calcd. for $C_9H_{10}N_2O_2$ (%): C, 60.66; H, 5.66; N, 15.72. Found: C, 60.27; H, 5.61; N, 15.80.

Compound **5b**: Yield 65%, mp: 75–77 °C. ^{1}H NMR (400 MHz,DMSO-d_6): δ8.70–8.71(1H, dd, $J = 4.8$,1.6 Hz), 8.00–8.02 (1H, d d , $J = 7.2$, 1.6 Hz), 7.54–7.58 (1H, d d, $J = 7.2$, 4.8 Hz), 6.68 (1H, d, $J = 8.8$ Hz, OH), 5.84 (1H, d, $J = 8.8$ Hz), 3.53 (1H, m), 3.24–3.26 (1H, m), 1.55–1.62 (2H, m), 0.86 (3H, t).^{13}C NMR (75 MHz, DMSO-d_6): δ165.1, 152.0, 150.7, 139.9, 132.7, 126.5, 79.3, 41.3, 21.7, 11.9. HRMS (EI^+): $C_{10}H_{12}N_2O_2$, calc 192.0899; found 192.0898. Anal. calcd. for $C_{10}H_{12}N_2O_2$ (%): C, 62.49; H, 6.29; N, 14.57. Found: C, 62.11; H, 6.07; N, 14.98.

Compound **5c**: Yield 90%, mp: 113–115 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ8.68–8.69 (1H, d d, $J = 4.8$, 1.6 Hz), 7.97–7.99 (1H, d d , $J = 7.2$, 1.6 Hz), 7.53–7.56 (1H, d d, $J = 7.2$, 4.8 Hz), 6.57 (1H, d, $J = 9.6$ Hz, OH), 5.84 (1H, d, $J = 9.6$ Hz), 4.15–4.22 (1H, m), 1.35–1.37 (3H, d, $J = 6.8$ Hz), 1.30–1.31 (3H, d, $J = 6.8$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ164.8, 151.8, 150.8, 140.0, 132.4, 126.6, 78.9, 44.2, 22.0, 20.4. HRMS (EI^+): $C_{10}H_{12}N_2O_2$, calc. 192.0899; found 192.0898. Anal. calcd. for $C_{10}H_{12}N_2O_2$ (%): C, 62.49; H, 6.29; N, 14.57. Found: C, 62.44; H, 6.10; N, 14.27.

Compound **5d**: Yield 52%, mp: 156–157 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ8.75–8.76 (1H, d d, $J = 4.8$,1.6 Hz), 8.06–8.08 (1H, d, $J = 7.2$, 1.6 Hz), 7.61–7.64 (1H, d d, $J = 7.2$, 4.8 Hz), 6.86–6.89 (1H, d, $J = 8.8$ Hz, OH), 5.86–5.88 (1H, d, $J = 8.8$ Hz), 4.40–4.45 (1H, d, $J = 18$ Hz), 4.11–4.15 (1H, d, $J = 18$ Hz), 3.66 (3H, s). ^{13}C NMR (75 MHz, DMSO-d_6): δ169.9, 165.4, 152.2, 150.0, 139.8, 133.0, 127.1, 79.8, 52.8, 41.2. HRMS (EI^+): $C_{10}H_{10}N_2O_4$, calc. 222.0641; found 222.0643. Anal. calcd. for $C_{10}H_{10}N_2O_4$ (%): C, 54.05; H, 4.54; N, 12.61. Found: C, 53.96; H, 4.66; N, 12.28.

Compound **5e**: Yield 56%, colorless solid, mp: 157–159 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ8.73–8.74 (1H,d, $J = 4.8$ Hz), 8.02–8.05 (1H, d, $J = 7.6$ Hz), 7.59–7.63 (1H, d d, $J = 4.8$,7.6 Hz), 6.76–6.78 (1H, d, $J = 8.8$ Hz), 5.89–5.91 (1H, d, $J = 8.8$ Hz), 4.65–4.67 (1H, q, $J = 7.6$ Hz), 3.57 (3H, s), 1.52 (3H, d, $J = 7.6$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ172.3, 165.5, 152.3, 150.3, 140.3, 132.9, 127.1, 79.7, 52.9, 49.9, 15.9. HRMS (EI^+): $C_{11}H_{12}N_2O_4$, calc. 236.0797; found 236.0797. Anal. calcd. for $C_{11}H_{12}N_2O_4$ (%): C, 55.93; H, 5.12; N, 11.86. Found: C, 55.74; H, 5.19; N, 11.68.

Compound **5e**: Yield 32%, colorless solid, mp: 88–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.98–9.00 (1H, d d, $J = 1.5$, 4.8 Hz), 8.173–8.202 (1H, d d, $J = 1.5$, 7.5 Hz), 7.642–7.666 (1H, d d, $J = 4.8$, 7.58 Hz), 5.014–5.086 (1H, q, $J = 7.2$ Hz), 3.749(3H, s), 1.712–1.743(3H, d, $J = 7.2$ Hz). MS (ESI): (M + 1) 235.0, ($M + Na^+$) 257.0. Anal. calcd. for $C_{11}H_{10}N_2O_4$ (%): C, 56.41; H, 4.30; N, 11.96. Found: C, 56.26; H, 3.91; N, 11.62.

Compound **5f**: Yield 6%, colorless solid, mp: 61–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ8.81–8.83 (1H, d, $J = 1.2$, 4.8 Hz), 7.96–8.00 (1H, d, $J = 1.2$, 7.6 Hz), 7.48–7.52 (1H, d d, $J = 4.8$, 7.6 Hz), 6.25 (1H, s), 4.70–4.73 (1H, d, $J = 10.0$ Hz), 3.76 (3H, s), 2.45–2.57 (1H, m), 0.94–1.09 (6H, d, $J = 6.8$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ175.0, 166.5, 152.6, 149.9, 138.7, 132.0, 126.6, 80.8, 61.6, 53.1, 31.0, 19.8, 19.8. HRMS (EI^+): $C_{13}H_{16}N_2O_4$, calc. 264.1110, Found 264.1111. Anal. calcd. for $C_{13}H_{16}N_2O_4$ (%): C, 59.08; H, 6.10; N, 10.60. Found: C, 58.84; H, 5.92; N, 10.57.

Compound **5g**: Yield 27%, mp: 237–238 °C [ref. 8a, mp: 237–239 °C]. ^{1}H NMR (400 MHz, DMSO-d_6): δ8.79–8.81 (1H, d d, $J = 4.8$,1.2 Hz), 8.12–8.14 (1H, d d, $J = 7.6$, 1.2 Hz), 7.74–7.76 (2H, m), 7.65–7.68 (1H, d d, $J = 7.6$, 4.8 Hz), 7.43–7.47 (2H, m), 7.21–7.25 (1H, m), 6.92–6.95 (1H, d, $J = 10$ Hz, OH), 6.55–6.57 (1H, d, $J = 10$ Hz). ^{13}C NMR(75 MHz, MHz, DMSO-d_6): δ164.4, 152.6, 149.9, 139.4, 137.9, 132.7, 129.4, 129.4, 127.3, 126.1, 123.1, 123.1, 80.5.

Compound **5h**: Yield 33%, colorless solid, mp: 251–252 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ8.79–8.80 (1H, d d, $J = 4.8$, 1.2 Hz), 8.10–8.13 (1H, d d, $J = 7.6$, 1.2 Hz), 7.96 (1H, d, $J = 2.8$ Hz), 7.65–7.70 (2H, m), 7.20–7.22 (1H, d, $J = 9.2$ Hz), 6.95–6.98 (1H, d, $J = 10$ Hz, OH, D_2O Exchange), 6.46–6.49 (1H, d, $J = 10$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ164.4, 153.7, 152.4, 149.7, 139.3, 132.8, 131.2, 128.1, 127.4, 124.4, 113.2, 110.7, 80.9, 57.0. HRMS (EI^+): $C_{14}H_{11}N_2O_3Br$ (79), calc. 333.9953, found 333.9944. Anal. calcd. for $C_{14}H_{11}BrN_2O_3$ (%): C, 50.17; H, 3.31;N, 8.36. Found: C, 49.67; H, 2.86; N, 8.04.

Compound **5i**: Yield 64%, mp: 186–188 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ8.74–8.75 (1H, d d, $J = 4.8$, 1.6 Hz), 8.21 (1H, s), 8.09–8.11 (1H, d, $J = 8.0$ Hz), 7.78–7.81 (1H, d), 7.59–7.62 (1H, d d, $J = 8.0$, 4.8 Hz), 7.19–7.21(1H, m), 4.99 (2H, s), 3.85 (3H, s). ^{13}C NMR(75 MHz, MHz, DMSO-d_6): δ165.3, 153.3, 151.2, 150.4, 136.4, 134.1, 132.6, 126.7, 124.9, 120.8, 113.4, 111.2, 57.1, 49.0. LC-MS (ESI): $C_{14}H_{11}BrN_2O_2$ (M + 1)319.2, ($M + Na^+$) 341.0. Anal. calcd. for $C_{14}H_{11}BrN_2O_2$ (%): C, 52.69; H, 3.47; N, 8.78. Found: C, 52.36; H, 3.00; N, 8.33.

Compound **5j**: Yield 73%, colorless solid, mp: 202–205 °C [ref (2a), mp: 203–207 °C, yield 15%]. ^{1}H NMR (400 MHz, DMSO-d_6): δ8.73–8.74 (1H, d d, $J = 4.8$,1.2 Hz), 8.00–8.03 (1H, d d, $J = 7.6$, 1.2 Hz),

7.57–7.60 (1H, d d, $J = 7.6, 4.8$ Hz), 7.23–7.34 (5H, m), 6.85–6.87 (1H, br, OH), 5.71 (1H, s), 4.93 (1H, d, $J = 15.6$ Hz), 4.42 (1H, d, $J = 15.6$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ165.1, 151.8, 150.2, 139.5, 137.8, 132.6, 128.9, 128.9, 128.1, 128.1, 127.6, 126.5, 78.8, 42.8. LC-MS (ESI): $(M+1)^+$ 241.1, $(M+Na^+)^+$263.0.

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