Synthesis of Functionalized Enamines: A Facile and Efficient Protocol toward N-Protected α,β-Dehydroamino Acid Derivatives

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Received 4 December 2007

Abstract: α,β-Dehydroamino acid derivatives were synthesized in good yields from α-bromoketones or α-bromoesters and hydroxamates via a sequential procedure involving displacement of bromide by hydroxamate anion, followed by a base-induced elimination–isomerization reaction.

Key words: α,β-dehydroamino acid derivatives, functionalized enamines, substitution, elimination, electron-withdrawing group

Functionalized enamines have long served as useful building blocks in the synthesis of a variety of different structures which possess biological and medicinal importance.[1] As members of this family, α-ketoenamines (also referred to as α,β-dehydroamino acid derivatives[2]) occur as frequent subunits in natural products and biologically active compounds and thus play important roles in organic synthesis.[3] They are useful synthons not only in electrophilic and nucleophilic chemistry, but also in photochemistry and electrocyclic reactions, especially for the synthesis of heterocyclic compounds.[4]

In virtue of the wide application of α-ketoenamines in organic chemistry, there is still a need to develop facile and practical synthetic methods for their preparation although some methods for the synthesis of this useful class of compounds have been well documented in literature. These methods can be mainly exemplified as follows: (1) the Claisen–Schmidt condensation reaction;[5] (2) the photooxidation of 2-morpholino cyclopropanols;[6] (3) the elimination of molecular nitrogen from α-azidoketones;[7] (4) the ring opening of *trans*-1,3-dibenzoyl-2-phenylaziridine in the presence of a base;[8] (5) the aminohalogenation reaction of α,β-unsaturated ketones followed by treatment with specific bases.[2]

Herein we disclose a new one-pot, two-step synthetic strategy for the preparation of α-ketoenamines through the reactions of α-bromoketones or α-bromoesters **1** with hydroxamates **2**, namely, (1) initial displacement of bromide by hydroxamate anion to give the intermediate **3** and (2) base-induced elimination of benzyl alcohol with the subsequent generation of the α,β-double bond. The two steps were then combined into an efficient standard procedure.

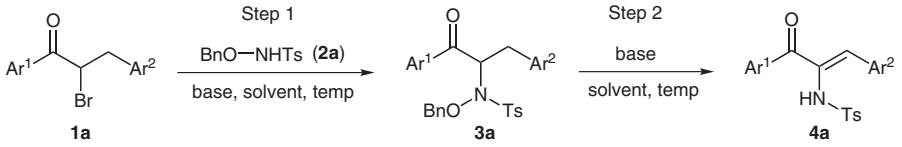
The required starting materials **1** and **2** for this approach were conveniently prepared from commercial materials in high yields according to a reported process.[9] Initially, we started research with the model reaction starting from **1a** and **2a** (Table 1). The conversion was explored by investigating the use of different bases (KO*t*-Bu, NaH, DBU, Et_3N, K_2CO_3, and Cs_2CO_3) and different solvent systems (DMF, MeCN, THF, CH_2Cl_2, and PhMe).

In these solvent studies, we found that polar aprotic solvents benefited not only the first step reaction but also the second. The order of reactivity for different solvents was found to be in the sequence as DMF > MeCN > THF > CH_2Cl_2 > PhMe. Comparing the effect of the solvent on the two-step reaction, MeCN was the most suitable one. We found that Cs_2CO_3 should be used as the proper base for the first-step reaction instead of stronger bases to avoid the unwanted self-elimination of α-bromo carbonyl compounds. The self-elimination would produce conjugated α,β-unsaturated ketones or esters, especially for α-bromoketones and α-bromoesters with an aromatic group at the β-position, which could be confirmed by comparison with the same products prepared by a known method.[10] Furthermore, hydroxamates could not be consumed completely if the intramolecular elimination reaction proceeded faster than the substitution reaction. If R^2 was an aromatic group, the intermediate **3** could be converted into the desired products using Cs_2CO_3 at an elevated temperature (entry 14). A stronger base was preferable in the second step when R^2 was an aliphatic group because of the prolonged reaction time and unsatisfactory yield. From these studies, we arrived at a set of conditions which were attempted in a general procedure: compound **1a** was added to the mixture of Cs_2CO_3 and **2a** in dry acetonitrile at 40 °C (entry 12) and the resulting mixture was cooled to room temperature when the starting material **2a** was totally consumed, and then DBU was added dropwise. It was noteworthy that the reaction should be heated to reflux in the second step to facilitate the conversion of aliphatic α-bromoketones.

These optimized conditions were subsequently applied to the reactions of diverse α-bromoketones or α-bromoesters **1** with different hydroxamates **2** (Table 2).

SYNLETT 2008, No. 6, pp 0861–0866
Advanced online publication: 11.03.2008
DOI: 10.1055/s-2008-1042901; Art ID: W20907ST

Table 1 Optimizing Conditions for the Synthesis of α,β-Dehydroamino Acid Derivatives[a]

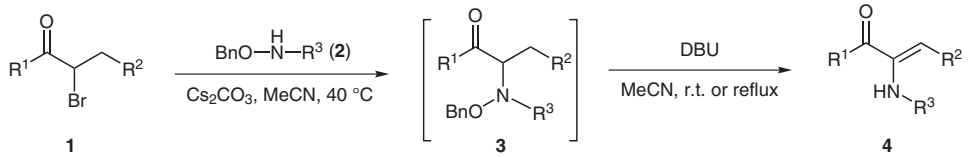


Ar^1 = 4-MeC_6H_4
Ar^2 = 4-$MeOC_6H_4$

Entry	Base	Solvent	Temp (°C)	Time (h)	Yield (%)[b]		Yield of **2a** (%)[c]
					3a	**4a**	
1	KO*t*-Bu	DMF	r.t.	0.1	0	47	0
2	NaH	DMF	r.t.	0.5	0	56	0
3	DBU	DMF	r.t.	1.0	0	73	12
4	Et_3N	DMF	r.t.	24.0	16	trace	76
5	K_2CO_3	DMF	r.t.	2.0	90	5	0
6	K_2CO_3	MeCN	r.t.	18.0	91	3	0
7	Cs_2CO_3	DMF	r.t.	1.0	91	5	0
8	Cs_2CO_3	MeCN	r.t.	1.5	97	trace	0
9	Cs_2CO_3	THF	r.t.	72.0	19	37	0
10	Cs_2CO_3	CH_2Cl_2	r.t.	72.0	24	36	8
11	Cs_2CO_3	PhMe	r.t.	6.0	0	0	96
12	Cs_2CO	MeCN	40	1.0	97	trace	0
13	Cs_2CO_3	MeCN	60	18.0	0	72	0
14	Cs_2CO_3	MeCN	80	4.0	0	76	0
15	Cs_2CO_3	THF	80	5.0	0	47	0
16	Cs_2CO_3	CH_2Cl_2	80	11.0	0	44	0

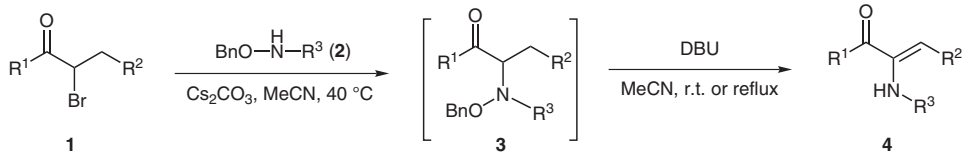
[a] Reaction conditions: **1a** (2.2 mmol), **2a** (2.0 mmol), base (4.2 mmol) in 20 mL solvent.
[b] Isolated yields.
[c] Starting material **2a** recovered from the reaction mixture.

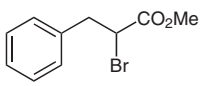
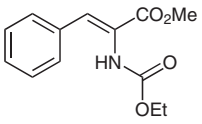
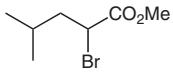
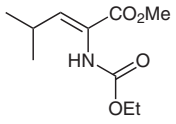
Table 2 Synthesis of α,β-Dehydroamino Acid Derivatives[13–17]



Entry	Starting material **1**	Hydroxamate **2**	Product **4**	Time (h)	Yield (%)
1	R^1 = 4-MeC_6H_4, R^2 = 4-$MeOC_6H_4$ (**1a**)	R^3 = Ts (**2a**)	**4a**	4.0	78[a]
2	**1a**	R^3 = 4-$ClC_6H_4SO_2$ (**2b**)	**4b**	2.0	73[a]
3	**1a**	R^3 = 4-$O_2NC_6H_4SO_2$ (**2c**)	**4c**	1.5	59[a]
4	**1a**	R^3 = Ms (**2d**)	**4d**	3.0	61[a]

Table 2 Synthesis of α,β-Dehydroamino Acid Derivatives[13–17] (continued)



Entry	Starting material **1**	Hydroxamate **2**	Product **4**	Time (h)	Yield (%)
5	**1a**	R^3 = EtO_2C (**2e**)	**4e**	10.0	88[b]
6	**1a**	R^3 = Boc (**2f**)	**4f**	10.0	87[b]
7	**1a**	R^3 = Et(O)C (**2g**)	**4g**	5.0	70[b]
8	**1a**	R^3 = $(CH_2)_5N(O)C$ (**2h**)	**4h**	12.0	53[b]
9	R^1 = 4-$MeOC_6H_4$, R^2 = Me (**1b**)	**2a**	**4i**	4.0	74[a]
10	**1b**	**2b**	**4j**	1.5	78[a]
11	**1b**	**2c**	**4k**	2.0	52[a]
12	**1b**	**2d**	**4l**	5.0	51[a]
13	**1b**	**2e**	**4m**	16.0	90[b]
14	**1b**	**2f**	**4n**	15.0	85[b]
15	**1b**	**2g**	**4o**	5.0	68[b]
16	**1b**	**2h**	**4p**	29.0	67[b]
17	R^1 = 4-$MeOC_6H_4$, R^2 = $(CH_2)_3Me$ (**1c**)	**2e**	**4q**	14.0	92[b]
18	R^1 = naphth-2-yl, R^2 = Ph (**1d**)	**2e**	**4r**	9.0	93[b]
19	R^1 = Ph, R^2 = naphth-2-yl (**1e**)	**2e**	**4s**	9.0	86[b]
20	 **1f**	**2e**	 **4t**	40.0	65[c]
21	 **1g**	**2e**	 **4u**	11.0	78[b]
22	R^1 = *t*-Bu, R^2 = 4-$MeOC_6H_4$ (**1h**)	**2a**	**4v**	24.0	61[b]

[a] Purified by neutral Al_2O_3 chromatography.
[b] Isolated yields after silica gel chromatography.
[c] Recovery (18%) of **2e**.

According to the experimental results, there are three aspects that should be highlighted: (1) this method is applicable to the preparation of not only α-ketoenamines, but also α,β-dehydroamino acid esters (entries 20, 21). Furthermore, it is noteworthy that only one isomer was predominately generated as determined by NMR analysis under the specified conditions described above. The geometry of the products has been confirmed as *Z*-configu-

ration by single-crystal X-ray analysis, NOE experiment, and comparison to the literature.[2,5,11] For instance, irradiation of the vinyl proton of compound **4v** resulted in no NOE enhancement of the sulfonamide N–H signal, which was consistent with *Z*-olefin geometry.[12] The structure of compound **4v** was further proved to be in *Z*-configuration by single-crystal X-ray analysis (Figure 1); (2) the reactivity of aromatic α-bromoketones with an aromatic group at the β-position is higher than those with aliphatic groups at the same position and both of them are better than aliphatic α-bromoketones. In particular, the competition between conjugated self-elimination of α-bromoesters or aliphatic α-bromoketones and the nucleophilic attack of hydroxamates becomes more obvious under basic conditions.

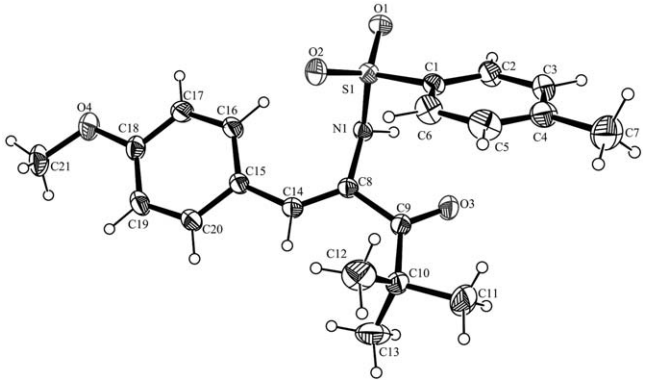


Figure 1 X-ray crystal structure obtained for compound **4v**

In order to obtain the desired products, strong nucleophiles leading to fast substitution reactions are needed, therefore, preventing competitive self-elimination of α-bromoketones or α-bromoesters; (3) hydroxamates with a strong electron-withdrawing group at the nitrogen atom, such as a sulfonyl group, would further enhance not only the reactivity of the nucleophilic attack and elimination of the alcohol, but also the α-hydrogen acidity of the benzyloxy group. Upon treatment with base, both the desired product **4** and the byproduct **5** could be detected (Scheme 1). Not surprisingly, when less nucleophilic N-substituted hydroxamates were used, this drawback could be overcome while the rate of the conversion into the corresponding products was lower.

In summary, we have described a practical and efficient procedure, which offers advantages in easy availability of reagents and good yields. Since the protocol is simple to carry out, this new synthetic methodology should represent a doable and effective approach toward a variety of α,β-dehydroamino acid derivatives.

Acknowledgment

We acknowledge the Tianjin Municipal Science and Technology Commission (043186011), the Basic Research Project (#2003AA223151) of the MOST for financial support.

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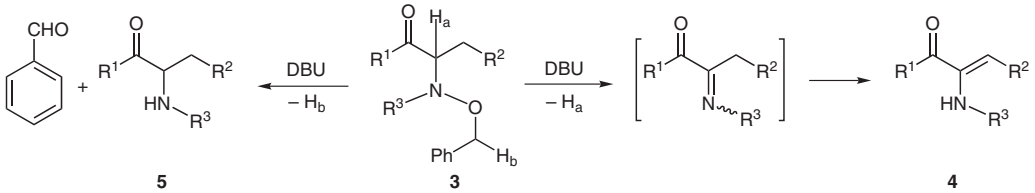
(13) **General Procedure for the Synthesis of α,β-Dehydroamino Acid Derivatives 4a–u**



5 3 4

Scheme 1

To a mixture of hydroxamate **2** (2.0 mmol) and Cs_2CO_3 (2.2 mmol) in anhyd MeCN (20 mL) was added α-bromoketone or α-bromoester **1** (2.2 mmol) in one portion under stirring at 40 °C. When the starting material **2** was totally consumed, the resulting mixture was cooled to r.t. and DBU (2.0 mmol) was added dropwise. When the intermediate **3** was not detected via TLC analysis any more, the solvent was evaporated under reduced pressure and the residue was purified by neutral Al_2O_3 chromatography or silica gel chromatography to afford the desired products **4a**–**u**.

(14) **General Procedure for the Synthesis of α,β-Dehydroamino Acid Derivative 4v**
To a mixture of hydroxamate **2a** (2.0 mmol) and Cs_2CO_3 (2.2 mmol) in anhyd MeCN (20 mL) was added α-bromoketone **1h** (2.4 mmol) in one portion under stirring at 40 °C. When the starting material **2a** had disappeared, DBU (2.0 mmol) was added dropwise and the temperature was raised to reflux. When the intermediate **3v** was not detected via TLC analysis any more, the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography to afford the desired products **4v**.

(15) All melting points were determined on a Kofler hot-plate microscope apparatus and were uncorrected. ^{1}H NMR, ^{13}C NMR, and NOE spectra were recorded on a Varian Inova 500 MHz instrument. High-resolution electrospray ionization mass spectra (HR-ESI-MS) were obtained using an IonSpec Ultima 7.0T FTICR ESI mass spectrometer.

(16) Compound **4v**: crystallized in triclinic, space group $P\bar{1}$ with cell parameters: a = 0.951 (3) nm, b = 0.104 (3) nm, c = 0.109 (3) nm, α = 110.184 (4)°, β = 93.423 (5)°, γ = 98.428 (4)°, V = 0.999 (5) nm^3, D_c = 1.287 g/cm^3, Z = 2; CCDC 672176.

(17) Compound **4a**: yellow solid, mp 167–168 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.29 (s, 3 H), 2.41 (s, 3 H), 3.84 (s, 3 H), 6.89 (d, J = 9.0 Hz, 2 H), 6.94 (br s, 1 H), 7.08 (s, 1 H), 7.16 (d, J = 8.0 Hz, 2 H), 7.20 (d, J = 8.0 Hz, 2 H), 7.39 (d, J = 8.0 Hz, 2 H), 7.71 (d, J = 8.5 Hz, 2 H), 7.90 (d, J = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.50, 21.58, 55.36, 113.99, 125.44, 127.62, 128.95, 129.09, 129.12, 129.46, 133.43, 133.80, 136.15, 140.95, 142.72, 143.97, 161.71, 193.47. HRMS: *m/z* calcd for $C_{24}H_{23}NNaO_4S^+$ [M + Na]$^+$: 444.1240; found: 444.1235.
Compound **4b**: yellow solid, mp 142–144 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 3.84 (s, 3 H), 6.89 (d, J = 8.5 Hz, 2 H), 6.97 (br s, 1 H), 7.13 (s, 1 H), 7.22 (d, J = 8.0 Hz, 2 H), 7.33 (d, J = 8.5 Hz, 2 H), 7.42 (d, J = 8.0 Hz, 2 H), 7.76 (d, J = 8.5 Hz, 2 H), 7.87 (d, J = 9.0 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.86, 55.64, 114.32, 125.45, 128.88, 129.31, 129.33, 129.35, 129.36, 133.64, 133.95, 137.93, 139.86, 141.62, 143.25, 162.06, 193.58. HRMS: *m/z* calcd for $C_{23}H_{20}ClNNaO_4S^+$ [M + Na]$^+$: 464.0694; found: 464.0691.
Compound **4c**: yellow solid, mp 197–198 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 3.85 (s, 3 H), 6.91 (d, J = 9.0 Hz, 2 H), 7.01 (br s, 1 H), 7.20 (s, 1 H), 7.23 (d, J = 7.5 Hz, 2 H), 7.44 (d, J = 8.0 Hz, 2 H), 7.86 (d, J = 8.5 Hz, 2 H), 8.01 (d, J = 8.5 Hz, 2 H), 8.19 (d, J = 9.0 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.86, 29.93, 55.66, 114.46, 124.21, 125.19, 128.30, 129.10, 129.39, 129.47, 133.83, 142.37, 143.61, 145.24, 150.33, 162.24, 193.37. HRMS: *m/z* calcd for $C_{23}H_{20}N_2NaO_6S^+$ [M + Na]$^+$: 475.0934; found: 475.0930.
Compound **4d**: white solid, mp 103–104 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 3.10 (s, 3 H), 3.83 (s, 3 H), 6.45 (br s, 1 H), 6.93 (d, J = 9.0 Hz, 2 H), 7.05 (s, 1 H), 7.29 (d, J = 8.0 Hz, 2 H), 7.70 (d, J = 8.0 Hz, 2 H), 7.77 (d, J = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.66, 42.00, 55.39, 114.36, 125.17, 129.20, 129.65, 130.01, 132.63, 134.48, 138.89, 143.35, 161.42, 194.19. HRMS: *m/z* calcd for $C_{18}H_{18}NO_4S^-$ [M – H]$^-$: 344.0962; found: 344.0970.
Compound **4e**: yellow solid, mp 112–114 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (br, 3 H), 2.42 (s, 3 H), 3.83 (s, 3 H), 4.11 (br, 2 H), 6.71 (br s, 2 H), 6.90 (d, J = 8.5 Hz, 2 H), 7.25 (d, J = 7.5 Hz, 2 H), 7.49 (d, J = 8.5 Hz, 2 H), 7.75 (d, J = 8.0 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.64, 21.89, 55.57, 62.10, 114.46, 126.61, 129.21, 129.90, 130.65, 131.15, 131.54, 134.76, 143.18, 154.35, 160.58, 193.63. HRMS: *m/z* calcd for $C_{20}H_{21}NNaO_4^+$ [M + Na]$^+$: 362.1363; found: 362.1361.
Compound **4f**: yellow solid, mp 130–132 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.39–1.46 (br, 9 H), 2.42 (s, 3 H), 3.83 (s, 3 H), 6.58–6.67 (br, 2 H), 6.91 (d, J = 8.5 Hz, 2 H), 7.26 (d, J = 8.0 Hz, 2 H), 7.50 (d, J = 8.5 Hz, 2 H), 7.77 (d, J = 8.0 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.88, 28.30, 55.57, 81.19, 114.40, 126.82, 129.16, 129.28, 129.88, 130.08, 131.53, 134.83, 143.08, 153.24, 160.44, 193.72. HRMS: *m/z* calcd for $C_{22}H_{25}NNaO_4^+$ [M + Na]$^+$: 390.1676; found: 390.1680.
Compound **4g**: yellow solid, mp 179–181 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.0 Hz, 3 H), 2.39–2.42 (m, 5 H), 3.83 (s, 3 H), 6.75 (s, 1 H), 6.90 (d, J = 8.5 Hz, 2 H), 7.25 (d, J = 8.0 Hz, 2 H), 7.41 (d, J = 8.0 Hz, 2 H), 7.45 (br s, 1 H), 7.75 (d, J = 8.0 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.62, 21.88, 29.81, 55.56, 114.39, 126.67, 129.13, 130.05, 131.44, 131.50, 131.85, 134.67, 143.19, 160.55, 172.54, 193.96. HRMS: *m/z* calcd for $C_{20}H_{21}NNaO_3^+$ [M + Na]$^+$: 346.1414; found: 346.1410.
Compound **4h**: yellow solid, mp 156–158 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.61–1.66 (m, 6 H), 2.42 (s, 3 H), 3.46 (t, J = 5.0 Hz, 3 H), 3.83 (s, 3 H), 6.64 (s, 1 H), 6.68 (br s, 1 H), 6.89 (d, J = 8.5 Hz, 2 H), 7.24 (d, J = 7.5 Hz, 2 H), 7.44 (d, J = 9.0 Hz, 2 H), 7.77 (d, J = 8.0 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.85, 24.71, 26.13, 45.68, 55.53, 114.35, 127.32, 128.98, 129.42, 130.20, 131.19, 133.47, 134.87, 142.88, 154.99, 160.16, 194.81. HRMS: *m/z* calcd for $C_{23}H_{26}N_2NaO_3^+$ [M + Na]$^+$: 401.1836; found: 401.1836.
Compound **4i**: white solid, mp 131–133 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.14 (d, J = 7.0 Hz, 2 H), 2.28 (s, 3 H), 3.85 (s, 3 H), 6.54 (q, J = 7.5 Hz, 1 H), 6.84–6.86 (m, 3 H), 7.17 (d, J = 8.0 Hz, 2 H), 7.40 (d, J = 9.0 Hz, 2 H), 7.70 (d, J = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.61, 21.70, 55.71, 113.71, 127.63, 128.58, 129.74, 131.61, 134.05, 136.38, 142.24, 144.14, 163.25, 191.73. HRMS: *m/z* calcd for $C_{18}H_{19}NNaO_4S^+$ [M + Na]$^+$: 368.0927; found: 368.0926.
Compound **4j**: white solid, mp 125–126 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.15 (d, J = 7.0 Hz, 2 H), 3.86 (s, 3 H), 6.61 (q, J = 7.0 Hz, 1 H), 6.86–6.89 (m, 3 H), 7.35 (d, J = 8.5 Hz, 2 H), 7.43 (d, J = 9.0 Hz, 2 H), 7.76 (d, J = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.62, 55.73, 113.88, 128.45, 129.07, 129.40, 131.62, 133.66, 137.95, 139.79, 142.77, 163.44, 191.51. HRMS: *m/z* calcd for $C_{17}H_{16}ClNNaO_4S^+$ [M + Na]$^+$: 388.0381; found: 388.0382.
Compound **4k**: white solid, mp 170–171 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.18 (d, J = 7.0 Hz, 2 H), 3.85 (s, 3 H), 6.70 (q, J = 7.0 Hz, 1 H), 6.86–6.89 (m, 3 H), 7.43–7.46 (m, 2 H), 8.00–8.04 (m, 2 H), 8.21–8.23 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.77, 55.76, 114.02, 124.31, 128.21, 128.92, 131.60, 133.13, 143.92, 145.22, 150.36, 163.65, 191.11. HRMS: *m/z* calcd for $C_{17}H_{15}N_2O_6S^-$ [M – H]$^-$: 375.0656; found: 375.0650.
Compound **4l**: white solid, mp 101–102 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.11 (d, J = 7.0 Hz, 2 H), 3.00 (s, 3 H), 3.89 (s, 3 H), 6.35 (br s, 1 H), 6.63 (q, J = 7.0 Hz, 1 H), 6.95–

6.98 (m, 2 H), 7.72–7.75 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.32, 41.32, 55.77, 114.06, 129.26, 131.99, 134.29, 141.63, 163.62, 192.41. HRMS: *m/z* calcd for $C_{12}H_{15}NNaO_4S^+$ [M + Na]$^+$: 292.0614; found: 292.0612.
Compound **4m**: white solid, mp 98–99 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.0 Hz, 3 H), 1.88 (d, *J* = 7.0 Hz, 3 H), 3.87 (s, 3 H), 4.15 (q, *J* = 7.0 Hz, 2 H), 6.14 (q, *J* = 6.5 Hz, 1 H), 6.63 (br s, 1 H), 6.93 (d, *J* = 9.0 Hz, 2 H), 7.78 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.33, 14.65, 55.66, 61.77, 113.71, 129.63, 131.86, 132.01, 134.98, 154.24, 163.24, 192.17. HRMS: *m/z* calcd for $C_{14}H_{17}NNaO_4^+$ [M + Na]$^+$: 286.1050; found: 286.1056.
Compound **4n**: white solid, mp 158–160 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 1.86 (d, *J* = 7.5 Hz, 3 H), 3.86 (s, 3 H), 6.05 (br s, 1 H), 6.46 (br s, 1 H), 6.92 (d, *J* = 8.5 Hz, 2 H), 7.80 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.11, 28.34, 55.66, 80.87, 113.67, 114.02, 129.79, 131.84, 132.02, 135.44, 153.26, 163.21, 192.19. HRMS: *m/z* calcd for $C_{16}H_{21}NNaO_4^+$ [M + Na]$^+$: 314.1363; found: 314.1357.
Compound **4o**: white solid, mp 83–85 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 2.5 Hz, 3 H), 1.85 (d, *J* = 7.0 Hz, 3 H), 2.40 (q, *J* = 7.5 Hz, 2 H), 3.86 (s, 3 H), 6.24 (q, *J* = 7.0 Hz, 2 H), 6.92 (d, *J* = 9.0 Hz, 2 H), 7.48 (br s, 1 H), 7.78 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.68, 14.85, 29.76, 55.47, 113.53, 129.30, 131.94, 133.39, 134.40, 163.11, 171.93, 192.35. HRMS: *m/z* calcd for $C_{14}H_{17}NNaO_3^+$ [M + Na]$^+$: 270.1101; found: 270.1107.
Compound **4p**: white solid, mp 128–130 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.60–1.62 (m, 6 H), 1.85 (d, *J* = 8.5 Hz, 3 H), 3.45–3.47 (m, 4 H), 3.86 (s, 3 H), 6.11 (q, *J* = 7.0 Hz, 1 H), 6.59 (br s, 1 H), 6.92 (d, *J* = 9.0 Hz, 2 H), 7.79 (d, *J* = 9.0 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.57, 24.66, 25.91, 45.54, 55.65, 113.60, 129.81, 130.60, 132.24, 136.33, 155.09, 163.12, 193.32. HRMS: *m/z* calcd for $C_{17}H_{22}N_2NaO_3^+$ [M + Na]$^+$: 325.1523; found: 325.1516.
Compound **4q**: white solid, mp 67–69 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.0 Hz, 3 H), 1.24 (t, *J* = 7.5 Hz, 3 H), 1.45–1.31 (m, 4 H), 2.29 (q, *J* = 7.5 Hz, 2 H), 3.87 (s, 3 H), 4.14 (q, *J* = 7.0 Hz, 2 H), 5.98 (t, *J* = 7.0 Hz, 1 H), 6.55 (br s, 1 H), 6.93 (d, *J* = 8.5 Hz, 2 H), 7.79 (d, *J* = 9.0 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.07, 14.63, 22.73, 28.19, 30.86, 55.65, 61.77, 113.71, 129.72, 132.08, 133.74, 136.59, 154.42, 163.27, 192.26. HRMS: *m/z* calcd for $C_{17}H_{23}NNaO_4^+$ [M + Na]$^+$: 328.1519; found: 328.1522.
Compound **4r**: white solid, mp 160–162 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19 (br, 3 H), 4.10–4.12 (m, 2 H), 6.71 (s, 2 H), 7.35–7.43 (m, 3 H), 7. 52–7.62 (m, 4 H), 7.89–7.98 (m, 4 H), 8.42 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.61, 62.28, 125.68, 127.04, 128.07, 128.57, 128.60, 129.14, 129.29, 129.47, 129.68, 129.70, 131.37, 132.54, 133.57, 134.03, 134.44, 135.57, 154.32, 193.59. HRMS: *m/z* calcd for $C_{22}H_{19}NNaO_3^+$ [M + Na]$^+$: 368.1257; found: 368.1252.
Compound **4s**: white solid, mp 115–117 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18 (br, 3 H), 4.11 (br, 2 H), 6.81 (br s, 1 H), 6.86 (s, 1 H), 7.47–7.53 (m, 4 H), 7.57–7.60 (m, 1 H), 7.66–7.68 (m, 1 H), 7.81–7.85 (m, 3 H), 7.90–7.92 (m, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.64, 62.27, 126.25, 126.90, 127.38, 127.98, 128.40, 128.66, 129.50, 129.81, 130.12, 130.20, 131.63, 132.73, 133.37, 133.44, 133.63, 137.25, 154.11, 193.76. HRMS: *m/z* calcd for $C_{22}H_{19}NNaO_3^+$ [M + Na]$^+$: 368.1257; found: 368.1260.
Compound **4t**: white solid, mp 84–86 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (br, 3 H), 3.86 (s, 3 H), 4.13 (q, *J* = 7.0 Hz, 2 H), 6.26 (br s, 1 H), 7.31–7.39 (m, 4 H), 7.53 (d, *J* = 7.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.63, 52.89, 62.04, 124.68, 128.82, 129.61, 129.92, 131.56, 134.00, 154.33, 166.11. HRMS: *m/z* calcd for $C_{13}H_{15}NNaO_4^+$ [M + Na]$^+$: 272.0893; found: 272.0899.
Compound **4u**: oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 6.5 Hz, 6 H), 1.27 (t, *J* = 7.0 Hz, 3 H), 2.68–2.76 (m, 1 H), 3.78 (s, 3 H), 4.18 (q, *J* = 7.0 Hz, 2 H), 5.94 (br s, 1 H), 6.46 (d, *J* = 8.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.66, 21.83, 27.80, 52.51, 61.75, 123.73, 145.09, 155.01, 165.72. HRMS: *m/z* calcd for $C_{10}H_{17}NNaO_4^+$ [M + Na]$^+$: 238.1050; found: 238.1046.
Compound **4v**: white solid, mp 152–154 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.14 (s, 9 H), 2.39 (s, 3 H), 3.85 (s, 3 H), 6.87 (br s, 1 H), 6.90 (d, *J* = 9.0 Hz, 2 H), 7.20 (s, 1 H), 7.23 (d, *J* = 8.5 Hz, 2 H), 7.65 (d, *J* = 8.0 Hz, 2 H), 7.82 (d, *J* = 9.0 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.72, 29.08, 43.08, 55.58, 114.21, 125.66, 127.62, 128.13, 129.50, 133.28, 136.11, 136.13, 144.07, 161.50, 203.59. HRMS: *m/z* calcd for $C_{21}H_{25}NNaO_4S^+$ [M + Na]$^+$: 410.1397; found: 410.1398.