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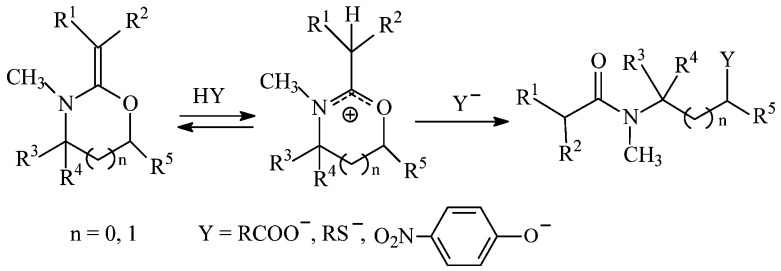


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# Ring-Opening Reactions of *N*-Methyl Cyclic Ketene-*N*,*O*-acetals with Carboxylic Acids, Nitrophenol, and Arylthiols

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Ring-opening reactions of *N*-methyl cyclic ketene-*N*,*O*-acetals with carboxylic acids, 4-nitrophenol, and arylthiols afforded amidoesters, amidoaryl ether, and amidothioethers, respectively, in good yields via an acid-catalyzed $S_N2$ mechanism.

## Introduction

Pittman and co-workers reported the selective diesterification of diols by the ring-opening of the cyclic ketene-*O*,*O*-acetals of these diols upon reaction with carboxylic acids.[1] Herein, we now extend such ring openings with carboxylic acids to cyclic ketene-*N*,*O*-acetals **1** to form amidoesters (Scheme 1). Furthermore, nitrophenol and arylthiols were also employed to ring-open **1** to generate amidoaryl ethers and amidoarylthioethers. All of these reactions proceed via an acid-catalyzed $S_N2$ pathway.

Cyclic ketene-*N*,*O*-acetals **1** and cyclic ketene-*O*,*O*-acetals are very electron-rich and nucleophilc species.[2−19] They are easily protonated by such acidic organic species as carboxylic acids, phenols, and arylthiols to generate the very stable intermediate cyclic heterocyclic (*N*,*O*)-cations, **2**, which serve as ambident electrophiles. These electrophiles can, in principle, undergo nucleophilic attack at three locations[20−23] (see paths a−c in Scheme 1). Cyclic dioxonium ions (*O*,*O*-analogues of **2**) have long been studied as ambient electrophiles.[23−25] After protonation of **1**, the conjugate bases of carboxylic acids, nitrophenol, and arylthiols then act as nucleophiles which ring-open **2**, as long as they are more nucleophilic than the parent cyclic ketene-*N*,*O*-acetal **1**. Nucleophilic attack on **2** by carboxylates, phenoxides, and thiophenoxides can each produce the three possible products, **3**, **4**, or **5** via routes a, b, or c, respectively (Scheme 1). If **1** is sufficiently nucleophilic, however, it might attack the corresponding intermediate cation **2**, with which it is in equilibrium, to generate the three possible polymers structures **6**, **7**, or **8** via pathways d, e, and f, respectively. If polymerization occurs, the carboxylic acids, 4-nitrophenols, or arylthiols then simply serve as cationic initiators (Scheme 1). The cationic addition polymerizations (route d) and ring-opening polymerizations (routes e versus f) of five-, six-, and seven-membered ring cyclic ketene-*O*,*O*-acetals have been studied extensively in our laboratory.[10−12,26−32]

## Results and Discussion

The synthesis and isolation of cyclic ketene-*N*,*O*-acetals by reacting 2-amino alcohols (or 3-amino alcohols) and carboxylic acids (or nitriles) to give 2-alkyl oxazolines (or oxazines), followed by *N*-methylation in nitromethane using $CH_3I$ and subsequent deprotonation employing NaH were reported previously.[19,26−28,33]

Four example syntheses of cyclic ketene-*N*,*O*-acetals **1** with the yields from each step are summarized in Table 1.

Dropwise addition of pure cyclic ketene-*N*,*O*-acetals into THF solutions of carboxylic acids, phenols, or arylthiols gives excellent yields of the ring-opened compounds **4** derived from nucleophilic attack by path b (Scheme 1). The ring-opening products **4a**−**c** from the example cyclic ketene-*N*,*O*-acetals **1a**−**c** and their isolated yields are summarized in Scheme 2. In contrast to ring-opening, nucleophilic attack by the cyclic ketene-*N*,*O*-acetal **1** on **2** can lead to oligomerization/polymerization (see routes d−f in Scheme 1) when only catalytic amounts of stronger acids having non-nucleophilic conjugate bases are employed. These polymerizations as routes to polyamides will be discussed elsewhere.

To achieve the clean ring-openings shown in Scheme 2, the cyclic ketene-*N*,*O*-acetals were added into THF solutions of the specific carboxylic acids, phenols, and arylthiols at room temperature using 1:1 mole ratios. After 2 h, the reaction mixtures were separated by flash chromatography (hexane/ethyl acetate eluent) to isolate the products. The isolated yields are summarized in Scheme 2.

The conjugate bases of carboxylic acids, 4-nitrophenol, and arylthiols were obviously more nucleophilic than cyclic ketene-*N*,*O*-acetals under the reaction conditions employed. Thus, no polymerizations (routes d−f, Scheme 1) occurred. All ring openings followed route b to specifically form amidoesters, amidoaryl ethers, and amidoarylthioethers by $S_N2$ reactions. No products could be detected resulting from route c. The structures were easily defined by NMR ($^1H$, $^{13}C$, NOESY, and chemical shift calculations). NOESY experiments proved that conjugate bases $Y^-$ of carboxylic acids, 4-nitrophenol, and aryl thiols (see Scheme 1) attacked the ring carbon adjacent to oxygen in **2** (e.g., C-6, Scheme 1) to give compounds **4a**−**c**. No products resulting from nucleophilic attack adjacent to nitrogen (e.g., at C-4, Scheme 1, route c) could be detected. Very good yields were achieved of a single isolated product. This contrasts with the cyclic

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**Scheme 1**

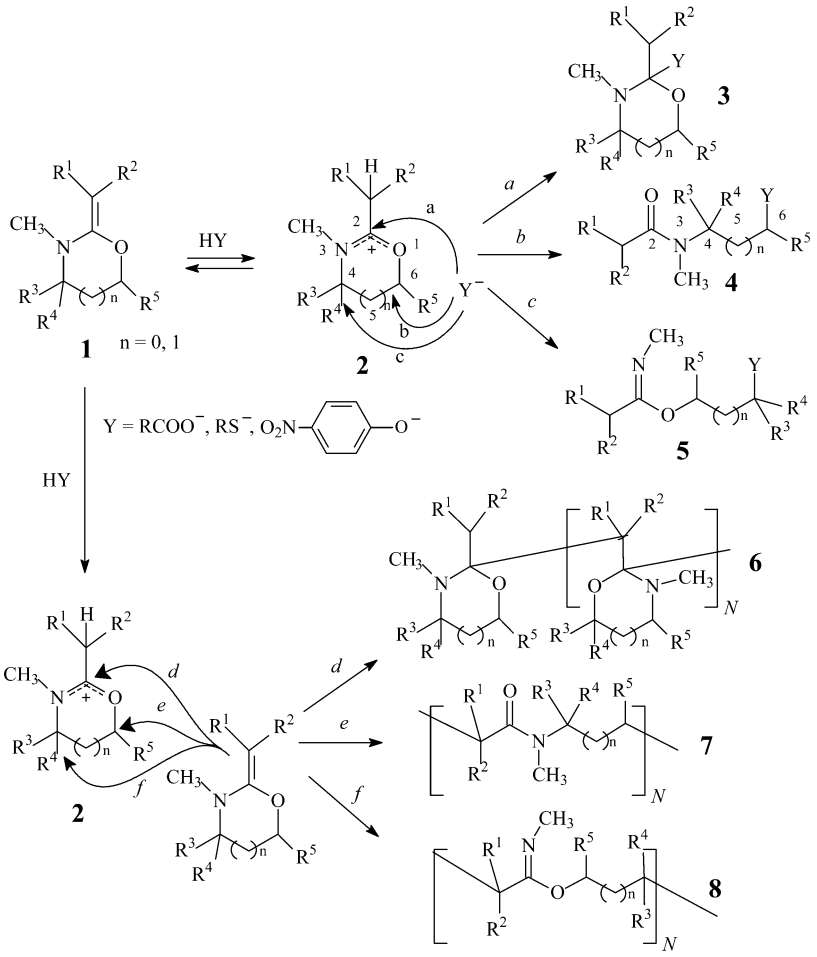
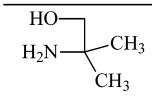
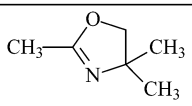
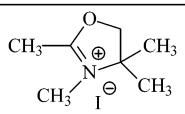
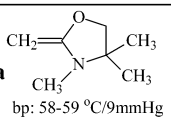
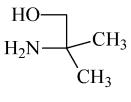
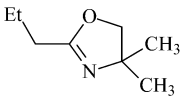
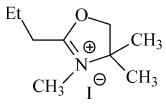
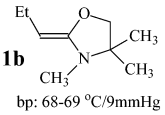
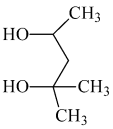
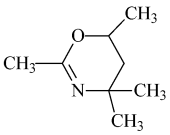
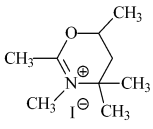
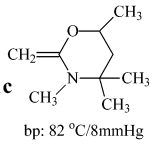
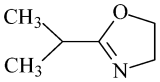
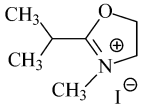
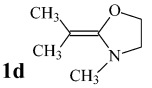
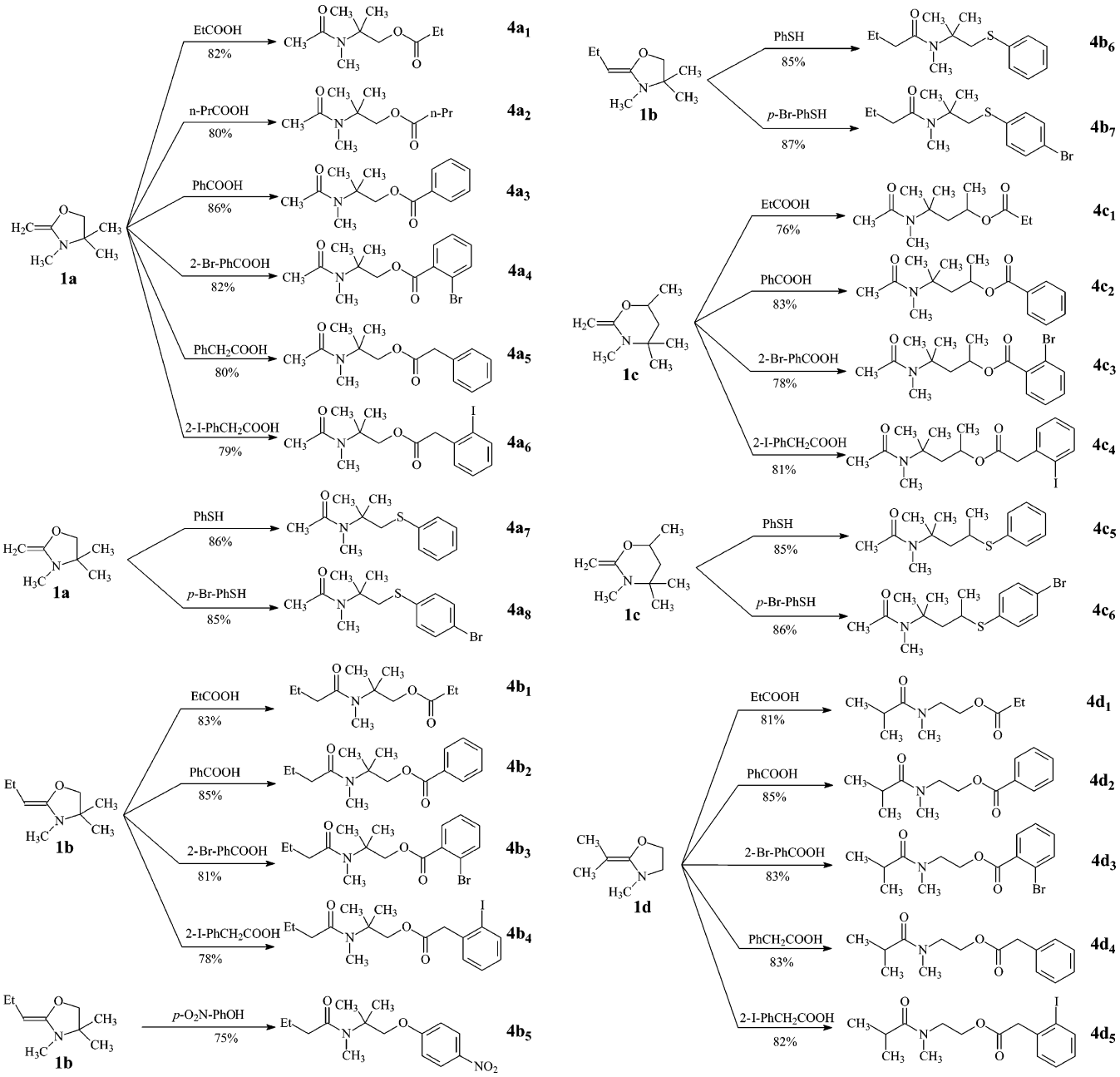


**Table 1**

| Starting Materials[b] **9** | 1,3-Oxazoline **10** | Yield [a] **9→10** (%) | 1,3-Oxazolium Iodide **11** | Yield [a] **10→11** (%) | Cyclic Ketene Acetal **1** | Yield [a] **11→1** (%) |
|---|---|---|---|---|---|---|
|  |  | 76 |  | 86 | **1a**  bp: 58-59 °C/9mmHg | 75 |
|  |  | 74 |  | 84 | **1b**  bp: 68-69 °C/9mmHg | 75 |
|  |  | 78 |  | 83 | **1c**  bp: 82 °C/8mmHg | 70 |
|  |  | 81 |  | 88 | **1d**  bp: 70 °C/14mmHg | 78 |

[a] All are isolated yields. [b] Carboxylic acids were used with each amino alcohol, and acetonitrile was used with the diol in entry 3.

**Scheme 2**




ketene-*O*,*O*-acetal ring-openings which gave a mixture of isomeric diesters when reacted with carboxylic acids.[1]

Multiple nucleophiles could simultaneously be reacted with a cyclic ketene-*N*,*O*-acetal to generate all of the products of route b ring-openings in one pot. This only requires the presence of 1 equiv or a slight excess of the nucleophilic *N*,*O*-acetal. This capability was found for all three classes of nucleophiles or mixtures of all three classes. For example, to a mixture of two carboxylic acids [benzoic acid (0.1 g), 2-iodophenylacetic acid (0.1 g)], 4-nitrophenol (0.1 g), and two thiols [benzenethiol (0.1 g) and 4-bromobenzenethiol (0.1 g)] dissolved in 40 mL THF, 1.5 equiv (0.8 g) of 3,4,4-trimethyl-2-propylideneoxazolidine **1b** was added dropwise. The reaction was stirred at room temperature for 2 h, and then the product mixture was analyzed by HPLC. All five expected ring-opening products, **4b$_2$**, **4b$_4$**, **4b$_5$** **4b$_6$**, and **4b$_7$**, were detected. All of the carboxylic acid, phenol, and thiol reagents were completely consumed. This example demonstrates the potential usefulness of cyclic ketene-*N*,*O*-acetal ring-openings in library syntheses.

## Conclusions

In summary, we have successfully demonstrated that cyclic ketene-*N*,*O*-acetals undergo specific acid-catalyzed $S_N2$ ring-opening reactions with carboxylic acids, nitrophenol, and arylthiols, exclusively via route b, to give excellent isolated yields under very mild conditions of amidoesters, amidoaryl ether, and amidoarylthioethers. Furthermore, mixtures of carboxylic acids, nitrophenol, and arylthiols can be used to simultaneously generate amidoesters, amidoaryl ether, and amidoarylthioethers in one pot.

## Experimental Section

**General Procedures.** The $^1$H and $^{13}$C NMR spectra were recorded using a Bruker model AMX-300 300 MHz spec-

trometer operating at 300 MHz for proton and 75 MHz for carbon. Chemical shifts were reported in parts-per-million downfield from $Me_4Si$ used as the internal standard. Splitting patterns are designated as s, d, t, q, and m; these symbols indicate singlet, doublet, triplet, quartet, and multiplet, respectively. All reactions were carried out under a dried nitrogen atmosphere. Acetonitrile and triethylamine were distilled from calcium hydride under nitrogen. Dichloromethane and nitromethane were predried with $CaCl_2$ and then distilled from calcium hydride under nitrogen. Tetrahydrofuran (THF) was distilled from Na metal/benzophenone ketyl. All other commercially obtained reagents were used as received. The silica gel used for the column chromatography was purchased from Aldrich Company (70−230 mesh).

**Benzoic Acid 2-(Acetylmethylamino)-2-methylpropyl Ester (4a$_3$).** *N*-Methyl cyclic ketene-*N*,*O*-acetal (**1a**) (0.19 g, 1.5 mmol) was dropwise added into THF (40 mL) solution with benzoic acid (0.18 g, 1.5 mmol) under nitrogen at room temperature. Nitrogen was used to minimize uptake of water vapor from the air. After the completion of addition, the reaction mixture was stirred at room temperature under nitrogen for 2 h. After the THF was removed by rotary evaporation, the product mixture was separated by flash chromatography over silica gel (hexane/ethyl acetate elutant) to give a sticky oil identified as benzoic acid 2-(acetylmethylamino)-2-methylpropylester (**4a$_3$**) (0.31 g, 86%). Reactions of *N*-methyl cyclic ketene-*N*,*O*-acetals **1a**−**d** with carboxylic acids, nitrophenols, and arylthiols followed the same procedure.

**Propionic Acid 2-(Acetylmethylamino)-2-methylpropyl Ester (4a$_1$).** Sticky oil. IR (neat): 2981, 2886, 1731, 1645, 1463, 1388, 1199, 1126, 1011, 913, 743 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.42 (s, 2H), 2.86 (s, 3H), 2.34 (q, $J$ = 7.5 Hz, 2H), 2.14 (s, 3H), 1.43 (s, 6H), 1.14 (t, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 173.6, 168.1, 64.2, 54.2, 29.5, 23.0, 20.5, 19.9, 4.5.

**Butyric Acid 2-(Acetylmethylamino)-2-methylpropyl Ester (4a$_2$).** Sticky oil. IR (neat): 2983, 2890, 1728, 1648, 1465, 1199, 1126, 1046, 913, 748 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.42 (s, 2H), 2.98 (s, 3H), 2.31 (t, $J$ = 7.2 Hz, 2H), 2.10 (s, 3H), 1.65 (q, $J$ = 7.2 Hz, 2H), 1.42 (s, 6H), 0.95 (t, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 168.7, 167.1, 64.2, 53.8, 31.7, 29.5, 21.0, 20.0, 14.0, 9.2.

**Benzoic Acid 2-(Acetylmethylamino)-2-methylpropyl Ester (4a$_3$).** Sticky oil. IR (neat): 2988, 2933, 1748, 1722, 1625, 1559, 1386, 1277, 1241, 1119, 720, 669 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.00−7.38 (m, 5H), 4.65 (s, 2H), 3.00 (s, 3H), 2.09 (s, 3H), 1.47 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 167.4, 161.7, 128.6, 125.1, 125.0, 124.1, 64.9, 54.2, 29.6, 21.0, 20.2.

**2-Bromobenzoic Acid 2-(Acetylmethylamino)-2-methylpropyl Ester (4a$_4$).** Sticky oil. IR (neat): 2989, 2867, 1741, 1720, 1648, 1469, 1365, 1243, 1243, 1024, 736 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.49−7.09 (m, 4H), 4.15 (s, 2H), 2.58 (s, 3H), 2.02 (s, 3H), 1.30 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 167.5, 161.7, 129.9, 128.2, 126.9, 123.0, 117.0, 65.8, 54.1, 29.7, 21.1, 20.3.

**Phenylacetic Acid 2-(Acetylmethylamino)-2-methylpropyl Ester (4a$_5$).** Sticky oil. IR (neat): 2984, 2924, 1735, 1721, 1632, 1565, 1367, 1260, 1107, 716 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.30−7.26 (m, 5H), 4.42 (s, 2H), 3.61 (s, 2H), 2.66 (s, 3H), 1.97 (s, 3H), 1.30 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 167.1, 166.5, 129.9, 124.9, 124.1, 122.6, 64.6, 53.8, 38.2, 29.3, 20.9, 20.0.

**(2-Iodophenyl)-acetic Acid 2-(Acetylmethylamino)-2-methylpropyl Ester (4a$_6$).** Sticky oil. IR (neat): 2976, 2847, 1730, 1639, 1467, 1388, 1242, 1171, 1018, 741 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.83−6.93 (m, 4H), 4.42 (s, 2H), 3.80 (s, 2H), 2.61 (s, 3H), 1.99 (s, 3H), 1.31 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 166.9, 165.1, 134.8, 133.5, 126.2, 124.4, 124.0, 64.9, 53.5, 42.1, 29.3, 20.1, 19.9.

***N*-(1,1-Dimethyl-2-phenylsulfanylethyl)-*N*-methylacetamide (4a$_7$).** Sticky oil. IR (neat): 2964, 2926, 1646, 1480, 1384, 1231, 1009, 743, 692 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.38−7.11 (m, 5H), 3.63 (s, 2H), 2.85 (s, 3H), 1.79 (s, 3H), 1.47 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 167.3, 132.5, 125.2, 124.3, 121.4, 55.1, 38.7, 30.0, 22.7, 20.8.

***N*-[2-(4-Bromophenylsulfanyl)-1,1-dimethylethyl]-*N*-methylacetamide (4a$_8$).** Sticky oil. IR (neat): 2968, 2924, 1648, 1474, 1383, 1231, 1092, 1008, 811, 741 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.35−7.21 (m, 4H), 3.61 (s, 2H), 2.85 (s, 3H), 1.82 (s, 3H), 1.45 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 166.9, 131.7, 127.0, 126.4, 114.9, 54.8, 38.5, 29.7, 22.3, 20.5.

**Propionic Acid 2-(Butyrylmethylamino)-2-methylpropyl Ester (4b$_1$).** Sticky oil. IR (neat): 2984, 2877, 1733, 1642, 1461, 1382, 1194, 1124, 1011, 908, 740 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.34 (s, 2H), 2.89 (s, 3H), 2.24 (overlap, m, 4H), 1.53 (m, 2H), 1.33 (s, 6H), 1.05 (t, $J$ = 7.5 Hz, 3H), 0.86 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 177.9, 174.1, 68.6, 58.2, 38.1, 32.7, 27.1, 24.1, 18.2, 13.4, 8.7.

**Benzoic Acid 2-(Butyrylmethylamino)-2-methylpropyl Ester (4b$_2$).** Sticky oil. IR (neat): 2987, 2931, 1736, 1724, 1618, 1562, 1378, 1277, 1241, 1119, 720, 669 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.11−7.39, 4.71 (s, 2H), 3.02 (s, 3H), 2.36 (t, $J$ = 7.2 Hz, 2H), 1.64 (q, $J$ = 7.5 Hz, 2H), 1.51 (s, 6H), 0.94 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 170.2, 161.8, 128.5, 125.6, 125.1, 123.9, 65.0, 54.4, 34.2, 28.8, 20.3, 14.3, 9.5.

**2-Bromobenzoic Acid 2-(Butyrylmethylamino)-2-methylpropyl Ester (4b$_3$).** Sticky oil. IR (neat): 2989, 2867, 1746, 1721, 1625, 1559, 1386, 1277, 1242, 1119, 1051, 726 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.66−7.03, 4.63 (s, 2H), 2.89 (s, 3H), 2.20 (t, $J$ = 7.2 Hz, 2H), 1.51 (m, 2H), 1.21 (s, 6H), 0.91 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 169.2, 161.4, 129.8, 128.0, 124.7, 122.5, 116.8, 65.6, 53.9, 34.0, 28.5, 20.2, 14.1, 9.4.

**(2-Iodophenyl)-acetic Acid 2-(Butyrylmethylamino)-2-methylpropyl Ester (4b$_4$).** Sticky oil. IR (neat): 2990, 2856, 1730, 1639, 1565, 1467, 1388, 1242, 1218, 1123, 1012, 741, 649 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.76−6.88, 4.37 (s, 2H), 3.72 (s, 2H), 2.55 (s, 3H), 2.10 (t, $J$ = 7.2 Hz, 2H), 1.48 (m, 2H), 1.25 (s, 6H), 0.88 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 169.2, 165.2, 134.8, 133.6, 126.2, 124.4, 124.0, 65.0, 53.6, 42.1, 33.9, 28.3, 20.2, 14.0, 9.5.

**4-Nitrobenzoic Acid 2-(Butyrylmethylamino)-2-methylpropyl Ester (4b$_5$).** Solid, mp: 75−78 °C. IR (neat): 2996,

2824, 1730, 1595, 1517, 1460, 1335, 1294, 1243, 1112, 1038, 851, 754, 693 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 8.04−6.87, 4.45 (s, 2H), 3.09 (s, 3H), 2.37 (t, $J$ = 7.5 Hz, 2H), 1.55 (m, 2H), 1.55 (s, 6H), 0.88 (t, $J$ = 7.2 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 160.1, 122.7, 123.4, 112.4, 111.2, 70.0, 56.1, 35.2, 30.3, 21.2, 15.4, 10.3.

***N*-(1,1-Dimethyl-2-phenylsulfanylethyl)-*N*-methylbutyramide (4b$_6$).** Sticky oil. IR (neat): 2964, 2924, 1648, 1475, 1385, 1236, 1008, 747, 700 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.30−7.03, 3.58 (s, 2H), 2.77 (s, 3H), 1.88 (t, $J$ = 7.2 Hz, 2H), 1.44 (overlap m, 2H), 1.39 (s, 6H), 0.80 (t, $J$ = 7.5 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 169.7, 133.2, 125.7, 125.8, 121.8, 55.6, 39.4, 34.3, 29.4, 23.2, 14.5, 10.0.

***N*-[2-(4-Bromophenylsulfanyl)-1,1-dimethylethyl]-*N*-methylbutyramide (4b$_7$).** Sticky oil. IR (neat): 2963, 2923, 1646, 1474, 1384, 1236, 1126, 1089, 1005, 815, 730 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.32−7.18, 3.61 (s, 2H), 2.83 (s, 3H), 1.94 (t, $J$ = 7.2 Hz, 2H), 1.47 (overlap m, 2H), 1.44 (s, 6H), 0.86 (t, $J$ = 7.2 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 170.1, 132.6, 128.0, 127.5, 115.8, 55.8, 39.7, 34.6, 29.6, 23.4, 14.7, 10.3.

**Propionic Acid 3-(Acetylmethylamino)-1,3-dimethylbutyl Ester (4c$_1$).** Sticky oil. IR (neat): 2982, 2870, 1731, 1645, 1463, 1388, 1197, 1127, 1014, 912, 744 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 5.00 (m, 1H), 2.89 (s, 3H), 2.47 (m, 2H), 2.31 (q, $J$ = 6.3 Hz, 2H), 2.09 (s, 3H), 1.39 (s, 3H), 1.36 (S, 3H), 1.17 (d, $J$ = 6.0 Hz, 3H), 1.13 (t, $J$ = 6.3 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 173.8, 171.2, 68.5, 58.2, 44.3, 33.4, 28.0, 27.3, 25.3, 21.4, 8.9.

**Benzoic Acid 3-(Acetylmethylamino)-1,3-dimethylbutyl Ester (4c$_2$).** Sticky oil. IR (neat): 2989, 2827, 1735, 1630, 1563, 1382, 1242, 1171, 1121, 731, 660 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 8.07−7.42 (m, 5H), 5.32 (m, 1H), 2.79 (s, 3H), 2.48 (m, 2H), 1.96 (s, 3H), 1.42 (s, 3H), 1.40 (S, 3H), 1.30 (d, $J$ = 6.0 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 171.1, 165.6, 132.5, 130.2, 129.1, 128.0, 69.0, 57.9, 44.1, 33.3, 28.0, 27.2, 25.2, 21.4.

**2-Bromobenzoic Acid 3-(Acetylmethylamino)-1,3-dimethylbutyl Ester (4c$_3$).** Sticky oil. IR (neat): 2987, 2865, 1741, 1723, 1628, 15555, 1363, 1272, 1238, 1126, 1047, 743 $cm^{-1}$. NMR (300 MHz, $CDCl_3$): $\delta$ 7.80−7.30 (m, 5H), 5.30 (m, 1H), 2.87 (s, 3H), 2.40 (m, 2H), 1.98 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 1.34 (d, $J$ = 6.3 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 171.5, 165.5, 134.3, 132.4, 131.1, 127.1, 121.5, 70.4, 58.3, 44.4, 33.7, 28.2, 27.4, 25.4, 21.6.

**(2-Iodophenyl)-acetic Acid 3-(Acetylmethylamino)-1,3-dimethylbutyl Ester (c4c$_4$).** Sticky oil. IR (neat): 2992, 2838, 1729, 1638, 1560, 1472, 1383, 1240, 1216, 1144, 1036, 754, 647 $cm^{-1}$. NMR (300 MHz, $CDCl_3$): $\delta$ 7.86−6.95 (m, 4H), 5.00 (m, 1H), 3.77 (s, 2H), 2.87 (s, 3H), 2.59 (m, 1H), 2.08 (s, 3H), 1.96 (m, 1H), 1.35 (s, 3H), 1.39 (s, 3H), 1.24 (d, $J$ = 6.3 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 167.2, 165.6, 135.2, 133.5, 126.5, 124.6, 124.2, 65.8, 54.1, 42.4, 40.3, 29.5, 23.9, 23.2, 21.4, 17.3.

***N*-(1,1-Dimethyl-3-phenylsulfanylbutyl)-*N*-methylacetamide (4c$_5$).** Sticky oil. IR (neat): 2968, 2837, 1649, 1502, 1478, 1389, 1234, 1126, 1011, 724, 696 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.39−7.19 (m, 5H), 3.25 (m, 1H), 2.91 (s, 3H), 2.3 (dd, $J$ = 4.8, 7.5 Hz, 1H), 2.2 (dd, $J$ = 4.8, 7.5 Hz, 1H), 2.06 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H), 1.24 (d, $J$ = 6.6 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 167.2, 131.4, 127.4, 124.4, 122.3, 54.6, 40.7, 35.6, 29.6, 24.1, 23.4, 21.4, 18.9.

***N*-[3-(4-Bromophenylsulfanyl)-1,1-dimethylbutyl]-*N*-methylacetamide (4c$_6$).** Sticky oil. IR (neat): 2966, 2920, 1655, 1478, 1377, 1325, 1238, 1202, 1130, 1092, 1012, 826, 722 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.41−7.23 (m, 4H), 3.23 (m, 1H), 2.93 (s, 3H), 2.25 (m, 2H), 2.2, 2.08 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H), 1.23 (d, $J$ = 6.3 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 167.2, 130.8, 129.0, 127.6, 116.3, 54.7, 40.8, 35.9, 29.7, 24.2, 23.6, 21.6, 18.9.

**Propionic Acid 2-(Isobutyrylmethylamino)-ethyl Ester (4d$_1$).** Sticky oil. IR (neat): 2978, 2867, 1721, 1652, 1466, 1381, 1190, 1260, 1123, 1015, 913, 751 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 4.19 (t, $J$ = 7.5 Hz, 2H), 3.62 (t, $J$ = 4.5 Hz, 2H), 3.10 (s, 3H), 2.84 (m, 1H), 2.33 (q, $J$ = 6.3 Hz, 2H), 1.10 (t, $J$ = 7.5 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 178.9, 174.1, 61.7, 46.9, 36.2, 30.2, 27.1, 18.7, 8.7.

**Benzoic Acid 2-(Isobutyrylmethylamino)-ethyl Ester (4d$_2$).** Sticky oil. IR (neat): 2992, 2924, 1743, 1718, 1627, 1447, 1387, 1269, 1235, 1122, 860, 743 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 8.09−7.49 (m, 5H), 4.53 (t, $J$ = 7.5 Hz, 2H), 3.84 (t, $J$ = 4.5 Hz, 2H), 3.20 (s, 3H), 2.86 (m, 1H), 1.15 (t, $J$ = 6.9 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 178.2, 167.4, 133.6, 130.7, 129.7, 128.8, 62.1, 47.4, 37.5, 30.7, 19.2.

**2-Bromobenzoic Acid 2-(Isobutyrylmethylamino)-ethyl Ester (4d$_3$).** Sticky oil. IR (neat): 2989, 2867, 1741, 1720, 1648, 1469, 1365, 1243, 1243, 1024, 736 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.81−7.34 (m, 4H), 4.49 (t, $J$ = 6.0 Hz, 2H), 3.77 (t, $J$ = 6.0 Hz, 2H), 3.15 (s, 3H), 2.81 (m, 1H), 1.10 (t, $J$ = 6.3 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 177.1, 165.6, 134.2, 134.0, 132.3, 131.0, 127.0, 121.3, 62.8, 46.7, 36.1, 30.1, 18.9.

**Phenylacetic Acid 2-(Isobutyrylmethylamino)-ethyl Ester (4d$_4$).** Sticky oil. IR (neat): 2962, 2924, 1733, 1719, 1624, 1568, 1369, 1275, 1238, 1121, 724, 675 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.40−7.27 (m, 5H), 4.24 (t, $J$ = 5.1 Hz, 2H), 3.63 (s, 3H), 3.58 (t, $J$ = 5.1 Hz, 2H), 2.90 (s, 3H), 2.73 (m, 1H), 1.09 (t, $J$ = 6.6 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 176.8, 171.0, 133.6, 128.9, 128.3, 126.8, 62.5, 46.7, 41.0, 36.0, 30.0, 18.7.

**(2-Iodophenyl)-acetic Acid 2-(Isobutyrylmethylamino)-ethyl Ester (4d$_5$).** Sticky oil. IR (neat): 2982, 2854, 1731, 1644, 1475, 1374, 1240, 1173, 1023, 817, 725 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.86−6.97 (m, 4H), 4.26 (t, $J$ = 7.2 Hz, 2H), 3.81 (s, 3H), 3.59 (t, $J$ = 7.2 Hz, 2H), 2.91 (s, 3H), 2.75 (m, 1H), 1.10 (d, $J$ = 6.6 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 176.8, 169.8, 133.4, 127.7, 126.9, 122.1, 60.3, 46.8, 41.0, 34.3, 28.9, 22.8.

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**Supporting Information Available.** $^1H$ and $^{13}C$ NMR spectra of all compounds **4a**−**d** are provided. This material

is available free of charge via the Internet at http://pubs.acs.org.

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