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A VERSATILE SYNTHESIS OF α-AMINO ACID DERIVATIVES *VIA* THE UGI FOUR-COMPONENT CONDENSATION WITH A NOVEL CONVERTIBLE ISONITRILE

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Abstract – The Ugi four-component condensation (4CC) reaction with the carbonate-type isonitrile **9** proceeded smoothly, and subsequent base treatment of the Ugi products **10** provided the *N*-acyloxazolidinones **11** in high yield. The *N*-acyloxazolidinone derivatives can be reacted with several hetero-nucleophiles, namely, reaction of **11** with thiolates gave thiol ester derivatives **16** efficiently.

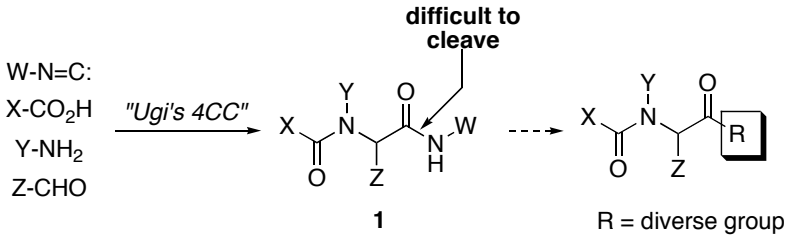
INTRODUCTION

Multi-component reactions (MCRs) have attracted much attention because of their use in the construction of combinatorial libraries.[1] In particular, the Ugi four-component condensation (Ugi 4CC)[2] has been widely employed since it provides various α-amino amide derivatives **1** by a simple experimental procedure under mild conditions.[1b] These products possess a drug-like structure and could be responsible

Dedication to the great contribution to organic chemistry of the late professor Ivar Ugi.

for a variety of important biological activities. Moreover, the great facility of the condensation to form amide bonds also permits the efficient total synthesis of complex natural products.[3]

Although numerous reports of the Ugi 4CC reaction have been published, inherent problems in the stereoselective construction of the α-position[4] and cleavage of the *C*-terminal amide still need to be solved. Due to the limited variety of isonitriles available in comparison with the other components (amines, carbonyl compounds and carboxylic acids), incorporation of other diverse functional groups at the *C*-terminal amide (R-groups) has been required for the generation of these libraries (Scheme 1).[5-10]



Scheme 1. Ugi 4CC Reaction and its Limitation.

Recently, the 4-CC reaction with the convertible isonitriles **2** and **3** was reported by Armstrong and Ugi, respectively (Figure 1). In the case of Armstrong's 1-cyclohexenyl isocyanide **(2)**,[5] the nucleophilic addition to the amide bond of the Ugi products was readily carried out under acidic conditions. On the other hand, the condensation product derived from the isocyanoalkyl alkyl carbonates **3** reported by Ugi was converted to the corresponding α-amino ester derivatives **6** by treatment with base.[6a] As shown in Scheme 2, this reaction would take place via the formation of the *N*-acyloxazolidinones **5** by cyclization of the amide anion onto the carbonate of **4** followed by addition of the alkoxide ($^{-}$OR) and elimination of the oxazolidinone. Thus, using an isonitrile **9** similar to the Ugi convertible isonitrile **(3)**, we expected to obtain the *N*-acyloxazolidinones from the Ugi products.[6b] Since the C-N bond of the *N*-acyloxazolidinones can be cleaved by several nucleophiles under mild conditions, this protocol would allow the production of numerous analogues.

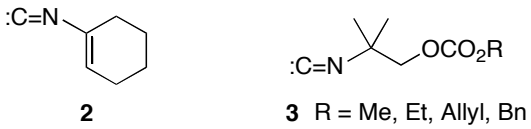
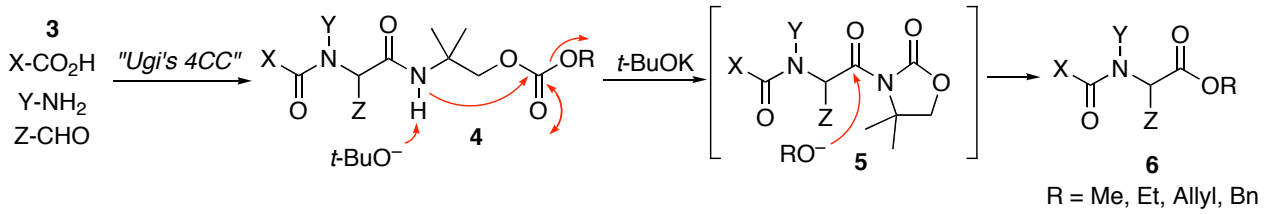


Figure 1. Convertible Isonitriles.

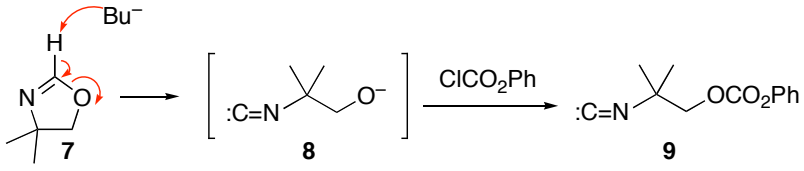


Scheme 2. Ugi's Approach.

Here we describe the Ugi 4CC reaction with the novel isonitrile **9** and a convenient procedure for conversion of the Ugi products by cleavage of the *C*-terminal amide bond.[7]

RESULTS AND DISCUSSION

Our working hypothesis for the isonitrile **9** is based on the theory that the phenoxide anion would not attack the *N*-acyloxazolidinone of **5**, because of its weak nucleophilicity (pK_a = 10). Preparation of the isonitrile **9** was performed according to the Ugi protocol.[6] Upon treatment of 4,4-dimethyloxazoline **(7)**[11] with *n*-BuLi, smooth deprotonation and α-elimination gave the β-isocyanoalkoxide **8**. Subsequent protection of the alkoxide intermediate by phenyl chloroformate afforded the isonitrile **9** (Scheme 3). The isonitrile **9** has the advantage of being odorless and stable under silica gel chromatographic purification and storage for several months in air at ambient temperature. Since a similar didemethyl isonitrile[7b] should be stored in refrigerator, the stability of **9** would be caused by its geminal dimethyl groups.

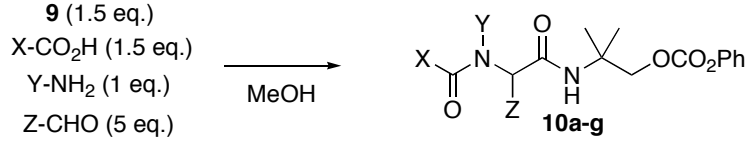


Reagents and conditions: *n*-BuLi, THF, –78 °C; $ClCO_2Ph$, 50%

Scheme 3. Preparation of Isonitrile **9**.

With the requisite isonitrile **9** in hand, the Ugi 4CC reaction of the combined aromatic and/or aliphatic amines, aldehydes and carboxylic acids was carried out. As shown in Table 1, the four-component condensation proceeded smoothly to give the desired α-amino amide derivatives **10a-g** in almost quantitative yields. Furthermore, this protcol has the advantage that aqueous formaldehyde was also readily available (entry 2), although the first step of the Ugi 4CC reaction should be a dehydrative reaction of the amine and the carbonyl compound.[12] In the case of entry 7, a relatively higher temperature was needed for the completion of the reaction.

Table 1. Ugi 4CC reaction with Isonitrile **9**.

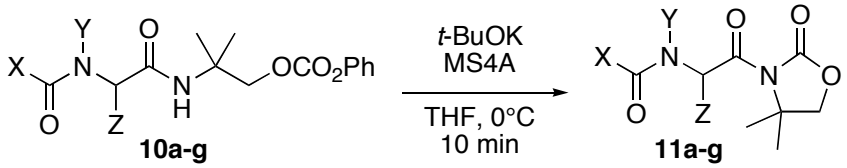


run	X	Y	Z	temp.	time (min)	yield (%)
1	Ph	Bn	*i*-Pr	rt	60	91 (**10a**)
2	Ph	Bn	H	rt	10	88[a] (**10b**)
3	Ph	Bn	Me	rt	10	quant. (**10c**)
4	Ph	Bn	Ph	rt	60[b]	88 (**10d**)
5	Me	Bn	*i*-Pr	rt	60	98 (**10e**)
6	Ph	Ph	*i*-Pr	rt	10	99 (**10f**)
7	Ph	Ph	Ph	70 °C	60[b]	89 (**10g**)

[a]: Small amounts of inseparable impurities were detected by ^{1}H-NMR.
[b]: The starting material remained.

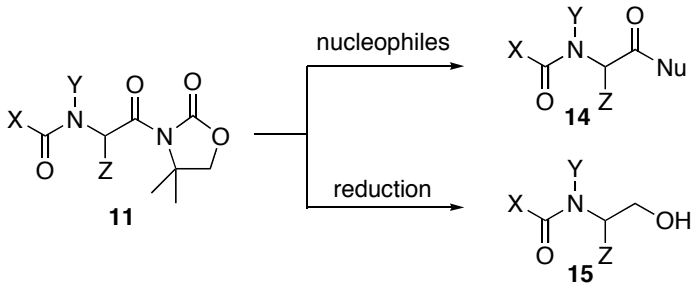
Next, we turned our attention to the transformation of the Ugi products **10a-g** to the *N*-acyloxazolidinones **11a-g**. After several attempts at cyclization, treatment with almost theoretical amount of *t*-BuOK (1.02 eq.) in THF in the presence of molecular sieves 4A (MS4A) gave the best results. As shown in Table 2, the desired cyclization proceeded smoothly to afford the *N*-acyloxazolidinones **11a-g** in more than 80% yield. As expected, the nucleophilic attack of the phenoxide anion on the *N*-acyloxazolidinones did not occur. Furthermore, MS4A play a key role in preventing hydrolysis of the starting materials and/or products by moisture.[13] Using an excess amounts of base and/or prolonging the reaction time decreased the yields, due to the decomposition of the product **11**.

Table 2. Formation of Oxazolidinone Rings.



run	X	Y	Z	yield (%)
1	Ph	Bn	*i*-Pr	83 (**11a**)
2	Ph	Bn	H	86 (**11b**)
3	Ph	Bn	Me	90 (**11c**)
4	Ph	Bn	Ph	89 (**11d**)
5	Me	Bn	*i*-Pr	95 (**11e**)
6	Ph	Ph	*i*-Pr	82 (**11f**)
7	Ph	Ph	Ph	86 (**11g**)

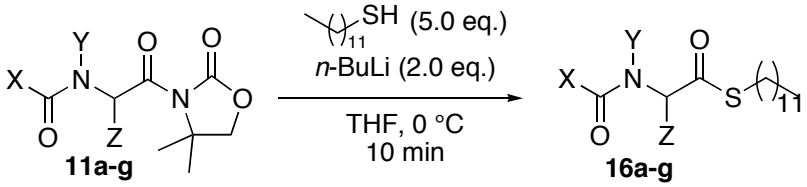
Since the C-N bond of *N*-acyloxazolidinones is activated by two carbonyl groups, cleavage of the amide bonds was accomplished readily by addition of a heteronucleophile or via $LiBH_4$ reduction, similar to the Evans oxazolidinones[14-16] (Scheme 4).



Scheme 4. Transformation from *N*-Acyloxazolidinones.

Among the possible nucleophiles, thiol groups would be attractive, since the thiol esters could be converted into the corresponding aldehydes[17a] or ketones[17b,c] in the presence of a palladium catalyst. The Pd-mediated reduction by triethylsilane[17a] and alkylation, with zinc reagents[17b] or terminal acetylenes,[17c] of the thiol esters were developed by our group.[17d] The conversion of the *N*-protected α-amino carbonyl compounds proceeded readily under neutral conditions. Recently, we also reported that thiol esters, derived from odorless *n*-dodecanethiol,[18] could be applicable to the Pd-mediated reactions instead of ethanethiol esters.[19] Thus, upon treatment of the *N*-acyloxazolidinones **11a-g** with lithium thiolate generated from *n*-BuLi and *n*-dodecanethiol, the conversion proceeded smoothly to give the *n*-dodecanethiol esters **16a-g** (Table 3).[20]

Table 3. Formation of Thiol Esters.



run	X	Y	Z	yield (%)
1	Ph	Bn	*i*-Pr	83 (**16a**)
2	Ph	Bn	H	79 (**16b**)
3	Ph	Bn	Me	75 (**16c**)
4	Ph	Bn	Ph	66 (**16d**)
5	Me	Bn	*i*-Pr	78 (**16e**)
6	Ph	Ph	*i*-Pr	86 (**16f**)
7	Ph	Ph	Ph	68 (**16g**)

In conclusion, we have developed a highly efficient, versatile synthetic method for α-amino acid derivatives by means of the Ugi 4CC reaction with a newly developed isonitrile **9**. As summarized in Scheme 6, the choice of the appropriate components, acids (X), amines (Y) and aldehydes (Z) and/or nucleophiles (R) for the *N*-acyloxazolidinones and thiol esters would allow us to synthesize a variety of *N*-acylamino acid derivatives. Further applications of this methodology to the syntheses of a range of peptidomimetic derivatives and/or natural products are under investigation in our laboratories.

EXPERIMENTAL

General. Nuclear magnetic resonance (^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz)) spectra were determined on a JEOL-LA400 instrument. Chemical shifts for ^{1}H NMR were reported in parts per million (ppm) downfield from tetramethylsilane (δ) in deuteriochloroform as the internal standard and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, br = broad, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Chemical shifts for ^{13}C NMR were reported in ppm relative to the centerline of a triplet at 77.0 ppm for deuteriochloroform ($CDCl_3$). Infrared spectra (IR) were recorded on a JASCO FT/IR-410 Fourier Transform Infrared Spectrometer and are reported in wavenumbers (cm^{-1}). Mass spectra (MS) were obtained on a JEOL JMS-GCmate MS-DIP20 with polyethylene glycol as the matrix. Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F254. Preparative TLC separations were made on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F254. Compounds were eluted from the adsorbent with 10% methanol (MeOH) in chloroform ($CHCl_3$). Flash column chromatography separations were performed on KANTO CHEMICAL Silica Gel 60 (40-100 mesh). All non-aqueous reactions were carried out in oven-dried glass apparatuses under a slight positive pressure of argon. MeOH and tetrahydrofuran (THF) were used after dried over molecular sieves 3A or 4A, when especially no mention. *n*-dodecanethiol was distilled under reduced pressure. All other reagents were commercially available and used without further purification, unless otherwise described.

Preparation of 2-isocyano-2-methylpropyl phenyl carbonate (9).

To a stirred solution of 4,4-dimethyloxazoline **(7)**[11] (1.00 g, 10.1 mmol) in THF (10 mL) under argon atmosphere at –78 °C, was added dropwise 1.1 M solution of *n*-BuLi (9.60 mL, 10.6 mmol) in hexane for 5 min and stirred at same temperature for 1 h then phenyl chloroformate was slowly added. After stirred for 5 min, the reaction mixture was warmed to ambient temperature and diluted with Et_2O, and water was added to the mixture. The organic layer was separated and washed with brine, dried over sodium sulfate and filtered. The solvent was removed under reduced pressure, the resulting residue was purified by silica gel chromatography (EtOAc/hexane = 1/9-1/4) to afford 1.10 g of **9** (50%) as an yellow oil. IR (film, cm^{-1}): 735, 775, 835, 879, 970, 1024, 1074, 1258, 1378, 1401, 1457, 1496, 1592, 1767, 2136, 2991; ^{1}H

NMR ($CDCl_3$, 400 MHz): δ 1.53 (s, 6H), 4.21 (s, 2H), 7.19-7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.6, 56.1, 72.9, 120.8, 126.1, 129.4, 150.8, 153.1, 156.1; HRMS (FAB^+): calcd for $C_{12}H_{13}NO_3$ 219.0895 (M^+), found 219.0900.

General procedure for Ugi's 4CC reaction.

***N*-(2-Methyl-1-(1-phenoxycarbonyloxy-2-methylpropan-2-ylcarbamoyl)propyl)-*N*-benzylbenzamide (10a).**

To a stirred solution of isonitrile **9** (223 mg, 1.02 mmol), isobutyraldehyde (0.31 mL, 3.40 mmol), and benzoic acid (128 mg, 1.05 mmol) in methanol (2.0 mL) was added dropwise benzylamine (74 μL, 0.679 mmol) over 2 min at ambient temperature (exothermic). After being stirred for 60 min, the solvent was removed under reduced pressure. The resultant crude mixture was purified by silica gel chromatography (EtOAc/hexane = 1/9-1/2) to afford **10a** (310 mg, 91%) as a pale-yellow paste. IR (film, cm^{-1}): 734, 774, 918, 963, 1066, 1211, 1263, 1367, 1457, 1496, 1545, 1620, 1680, 1764, 2968, 3063, 3301; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.91-1.08 (m, 6H), 1.20-1.39 (m, 6H), 2.72-2.88 (m, 1H), 4.26-4.51 (m, 4H), 4.61-4.71 (m, 1H), 7.05-7.60 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.5, 19.8, 23.8, 24.3, 27.2, 52.8, 54.0, 72.1, 76.7, 121.0, 126.0, 126.7, 127.7, 127.8, 128.4, 128.5, 129.5, 129.8, 136.5, 136.6, 151.1, 153.6, 170.2, 174.0; HRMS (FAB^+): calcd for $C_{30}H_{34}N_2O_5$ 502.2468 (M^+), found 502.2485.

***N*-((1-Phenoxycarbonyloxy-2-methylpropan-2-ylcarbamoyl)methyl)-*N*-benzylbenzamide (10b).**

The reaction of benzylamine (64 μL, 0.587 mmol), formalin (37 wt.% in water, 273 mg, 5.73 mmol), isonitrile **9** (192 mg, 0.877 mmol) and benzoic acid (104 mg, 0.853 mmol) was carried out following the general procedure (10 min) to provide **10b** (238 mg, 88%) as a white foam with a small amount of inseparable impurities. For analytical purposes, this mixture was purified by PTLC (EtOAc/hexane = 1/4) to afford pure **10b** as a white foam. IR (film, cm^{-1}): 773, 962, 1007, 1067, 1212, 1370, 1453, 1469, 1496, 1548, 1623, 1685, 1763, 2977, 3064, 3310; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.20-1.45 (m, 6H), 4.02 (s, 2H), 4.38 (s, 2H), 4.62 (s, 2H), 6.54 (s, 1H), 7.15-7.53 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.0, 29.7, 50.1, 53.2, 54.0, 72.3, 121.0, 126.1, 126.9, 127.2, 127.9, 128.6, 128.9, 129.5, 130.1, 135.1, 135.8, 151.0, 153.6, 168.4, 173.0; HRMS (FAB^+): calcd for $C_{27}H_{28}N_2O_5$ 460.1998 (M^+), found 460.1996.

***N*-(1-(1-Phenoxycarbonyloxy-2-methylpropan-2-ylcarbamoyl)ethyl)-*N*-benzylbenzamide (10c).**

The reaction of benzylamine (0.120 mL, 1.10 mmol), acetaldehyde (277 mg, 6.30 mmol), isonitrile **9** (364 mg, 1.66 mmol) and benzoic acid (168 mg, 1.37 mmol) was carried out following the general procedure (10 min) to provide **10c** (541 mg, quant.) as an orange oil. IR (film, cm^{-1}): 773, 919, 966, 1025, 1068, 1210, 1249, 1370, 1414, 1451, 1495, 1547, 1627, 1683, 1764, 2360, 2931, 2978, 3063, 3316; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.35-1.41 (m, 9H), 4.30-4.35 (m, 2H), 4.55-4.65 (m, 2H), 4.85 (br s, 1H), 7.15-7.48 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.8, 24.1, 29.7, 31.6, 53.0, 72.3, 121.0, 126.1, 126.6, 127.1,

127.5, 128.6, 128.7, 129.5, 130.0, 136.0, 151.0, 153.6, 170.7, 173.7; HRMS (FAB$^+$): calcd for $C_{28}H_{30}N_2O_5$ 474.2155 (M^+), found 474.2163.

***N*-((1-Phenoxycarbonyloxy-2-methylpropan-2-ylcarbamoyl)-1-phenylmethyl)-*N*-benzylbenzamide (10d).**

The reaction of benzylamine (70 μL, 0.642 mmol), benzaldehyde (0.33 mL, 3.27 mmol), isonitrile **9** (212 mg, 0.965 mmol) and benzoic acid (111 mg, 0.909 mmol) was carried out following the general procedure (60 min) to provide **10d** (304 mg, 88%) as a white foam. IR (film, cm^{-1}): 734, 915, 1024, 1067, 1212, 1257, 1370, 1395, 1456, 1496, 1624, 1684, 1763, 2978, 3063, 3313; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.30-1.45 (m, 6H), 4.34-4.45 (m, 2H), 4.70 (s, 1H), 4.72 (s, 1H), 5.49 (s, 1H), 7.05-7.60 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.9, 53.5, 72.3, 76.7, 121.0, 126.0, 126.7, 127.1, 128.3, 128.4, 128.6, 128.8, 129.5, 129.5, 129.8, 130.1, 134.8, 136.1, 151.1, 153.5, 169.0, 173.3; HRMS (FAB$^+$): calcd for $C_{33}H_{32}N_2O_5$ 536.2311 (M^+), found 536.2321.

***N*-(2-Methyl-1-(1-phenoxycarbonyloxy-2-methylpropan-2-ylcarbamoyl)propyl)-*N*-benzylacetamide (10e).**

The reaction of benzylamine (60 μL, 0.550 mmol), isobutyraldehyde (0.25 mL, 2.74 mmol), isonitrile **9** (181 mg, 0.826 mmol) and acetic acid (47 μL, 0.821 mmol) was carried out following the general procedure (10 min) to provide **10e** (253 mg, 98%) as a pale-yellow foam. IR (film, cm^{-1}): 728, 777, 966, 1024, 1063, 1211, 1263, 1369, 1395, 1418, 1457, 1496, 1540, 1629, 1679, 1763, 2966, 3299; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.84 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 1.31 (s, 3H), 1.34 (s, 3H), 2.06 (s, 3H), 2.38-2.47 (m, 1H), 4.25 (d, *J* = 10 Hz, 1H), 4.31 (d, *J* = 10 Hz, 1H), 4.45 (d, *J* = 11 Hz, 1H), 4.53 (d, *J* = 17 Hz, 1H), 4.74 (d, *J* = 17 Hz, 1H), 6.66 (s, 1H), 7.15-7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.1, 19.6, 22.7, 23.8, 24.3, 27.2, 50.2, 53.1, 71.8, 121.0, 126.0, 126.4, 127.3, 128.3, 128.6, 129.5, 137.3, 151.1, 153.5, 170.0, 173.3; HRMS (FAB$^+$): calcd for $C_{25}H_{32}N_2O_5$ 440.2311 (M^+), found 440.2315.

***N*-(2-Methyl-1-(1-phenoxycarbonyloxy-2-methylpropan-2-ylcarbamoyl)propyl)-*N*-phenylbenzamide (10f).**

The reaction of aniline (52 μL, 0.570 mmol), isobutyraldehyde (0.26 mL, 2.85 mmol), isonitrile **9** (187 mg, 0.853 mmol) and benzoic acid (114 mg, 0.934 mmol) was carried out following the general procedure (10 min) to provide **10f** (277 mg, 99%) as a pale-yellow oil. IR (film, cm^{-1}): 773, 918, 965, 1024, 1064, 1212, 1247, 1371, 1457, 1493, 1540, 1577, 1631, 1684, 1764, 2970, 3064, 3324; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.06 (d, *J* = 6.6 Hz, 3H), 1.11 (d, *J* = 6.4 Hz, 3H), 1.43 (s, 6H), 2.58-2.71 (m, 1H), 4.31-4.36 (m, 1H), 4.45-4.51 (m, 2H), 7.06-7.37 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.8, 20.1, 24.2, 24.4, 26.9, 52.9, 71.9, 76.7, 121.0, 126.0, 127.2, 127.8, 128.4, 128.6, 128.9, 129.4, 129.6, 130.0, 136.3, 151.1, 153.6, 170.3, 172.6; HRMS (FAB$^+$): calcd for $C_{29}H_{32}N_2O_5$ 488.2311 (M^+), found 488.2321.

***N*-((1-Phenoxycarbonyloxy-2-methylpropan-2-ylcarbamoyl)-1-phenylmethyl)-*N*-phenylbenzamide (10g).**

The reaction of aniline (54 μL, 0.592 mmol), benzaldehyde (0.30 mL, 2.97 mmol), isonitrile **9** (193 mg, 0.880 mmol) and benzoic acid (113 mg, 0.925 mmol) was carried out following the general procedure (70 °C, 1 h) to provide **10g** (276 mg, 89%) as a pale-yellow foam. IR (film, cm^{-1}): 778, 915, 965, 1030, 1066, 1211, 1244, 1371, 1456, 1493, 1595, 1639, 1689, 1762, 2360, 2977, 3063, 3330; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.43 (s, 3H), 1.46 (s, 3H), 4.47 (s, 2H), 6.14 (s, 1H), 6.17 (s, 1H), 7.00-7.36 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.1, 53.5, 67.3, 67.4, 72.2, 120.9, 121.0, 121.1, 127.0, 127.1, 127.5, 127.6, 128.4, 129.4, 130.0, 134.6, 135.9, 141.3, 151.1, 153.5, 169.3, 171.2; HRMS (FAB^+): calcd for $C_{32}H_{30}N_2O_5$ 522.2155 (M^+), found 522.2158.

General procedure for the synthesis of *N*-acyloxazolidinones 11a-g.

***N*-(1-(4,4-Dimethyl-2-oxo-3-oxazolidinyl)carbonyl-2-methylpropyl)-*N*-benzylbenzamide (11a).**

To a stirred solution of **10a** (220 mg, 0.439 mmol) in anhydrous THF (2.0 mL) at 0 °C was added freshly activated molecular sieves 4A (powder, 280 mg), and stirred for 10 min so as to trap any moisture, then added 1.0 M of KO*t*-Bu in *t*-BuOH (0.450 mL, 0.450 mmol) dropwise over 2 min. After being stirred for 10 min, 10% w/v aqueous citric acid was added and the mixture was extracted with EtOAc. The combine organic layer was washed with brine, dried over magnesium sulfate and filtered. The solvent was removed under reduced pressure, the resultant crude mixture was purified by silica gel chromatography (EtOAc/hexane = 1/9-1/2) to afford **11a** (149 mg, 83%) as a pale yellow foam. IR (film, cm^{-1}): 734, 761, 1031, 1089, 1173, 1231, 1305, 1374, 1496, 1646, 1701, 1779, 2360, 2968; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.90 (s, 3H), 0.97 (s, 3H), 1.33 (s, 3H), 1.49 (s, 3H), 2.38-2.52 (m, 1H), 3.89-4.00 (m, 2H), 4.74-5.03 (m, 2H), 5.63 (br s, 1H), 7.19-7.36 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.6, 19.4, 23.8, 24.3, 29.5, 61.0, 75.1, 126.3, 126.8, 127.4, 128.2, 128.3, 128.6, 129.6, 136.7, 138.7, 152.9, 172.3, 173.9, 175.8; HRMS (FAB^+): calcd for $C_{24}H_{28}N_2O_4$ 408.2049 (M^+), found 408.2033.

***N*-((4,4-Dimethyl-2-oxo-3-oxazolidinyl)carbonylmethyl)-*N*-benzylbenzamide (11b).**

The reaction of Ugi product **10b** (200 mg, 0.434 mmol), 1.0 M of KO*t*-Bu/*t*-BuOH (0.460 mL, 0.460 mmol) and freshly activated molecular sieves 4A (powder, 230 mg) in anhydrous THF (2.0 mL) was carried out following the general procedure (10 min) to provide **11b** (137 mg, 86%) as a pale-yellow oil. IR (film, cm^{-1}): 1008, 1034, 1095, 1181, 1244, 1310, 1382, 1429, 1641, 1656, 1711, 1777, 2360, 2974; ^1H NMR ($CDCl_3$, 400 MHz, a mixture of amide rotamers): δ 1.51 (s, 6H of a rotamer), 1.54 (s, 6H of a rotamer), 3.97 (s, 2H of a rotamer), 4.07 (s, 2H of a rotamer), 4.41 (s, 2H of a rotamer), 4.61 (s, 2H of a rotamer), 4.64 (s, 2H of a rotamer), 4.81 (s, 2H of a rotamer), 4.61 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.7, 24.7, 50.0, 54.2, 60.6, 76.0, 126.3, 126.9, 127.8, 128.3, 128.5, 128.8, 129.0, 129.9, 135.4, 136.2, 153.9, 169.0, 169.7, 172.7; HRMS (FAB^+): calcd for $C_{21}H_{22}N_2O_4$ 366.1580 (M^+), found 366.1562.

***N*-(1-(4,4-Dimethyl-2-oxo-3-oxazolidinyl)carbonylethyl)-*N*-benzylbenzamide (11c).**

The reaction of Ugi product **10c** (57 mg, 0.12 mmol), 1.0 M of KO*t*-Bu/*t*-BuOH (0.120 mL, 0.120 mmol) and freshly activated molecular sieves 4A (powder, 55 mg) in anhydrous THF (0.30 mL) was carried out following the general procedure (10 min) to provide **11c** (41 mg, 90%) as a pale-yellow foam. IR (film, cm^{-1}): 733, 765, 918, 974, 1039, 1096, 1179, 1240, 1311, 1394, 1639, 1708, 1775, 2358, 2973; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25-1.37 (m, 6H), 1.57 (s, 3H), 4.02 (s, 2H), 4.67-4.82 (m, 2H), 5.33 (br s, 1H), 7.23-7.45 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.6, 23.8, 24.9, 52.8, 56.4, 61.1, 75.7, 76.7, 126.6, 126.9, 127.4, 128.5, 128.7, 129.7, 136.2, 138.3, 153.9, 172.6, 173.5; HRMS (FAB$^+$): calcd for $C_{22}H_{24}N_2O_4$ 380.1736 (M^+), found 380.1741.

***N*-((4,4-Dimethyl-2-oxo-3-oxazolidinyl)carbonyl-1-phenylmethyl)-*N*-benzylbenzamide (11d).**

The reaction of Ugi product **10d** (270 mg, 0.503 mmol), 1.0 M of KO*t*-Bu/*t*-BuOH (0.520 mL, 0.520 mmol) and freshly activated molecular sieves 4A (powder, 290 mg) in anhydrous THF (2.5 mL) was carried out following the general procedure (10 min) to provide **11d** (198 mg, 89%) as a colorless oil. IR (film, cm^{-1}): 731, 913, 980, 1035, 1093, 1177, 1235, 1307, 1379, 1396, 1455, 1496, 1636, 1706, 1777, 2928; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.52 (s, 3H), 1.65 (s, 3H), 3.86 (s, 1H), 3.98 (s, 1H), 4.31 (d, J = 17 Hz, 1H), 4.73 (d, J = 16 Hz, 1H), 6.70-7.46 (m, 16H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.7, 24.7, 29.7, 48.2, 51.8, 60.7, 60.8, 62.8, 65.7, 75.2, 126.4, 126.6, 126.8, 127.9, 128.1, 128.3, 128.4, 128.7, 129.7, 131.2, 131.9, 136.2, 137.8, 153.1, 171.0, 173.6; HRMS (FAB$^+$): calcd for $C_{27}H_{26}N_2O_4$ 442.1893 (M^+), found 442.1887.

***N*-(1-(4,4-Dimethyl-2-oxo-3-oxazolidinyl)carbonyl-2-methylpropyl)-*N*-benzylacetamide (11e).**

The reaction of Ugi product **10e** (183 mg, 0.391 mmol), 1.0 M of KO*t*-Bu/*t*-BuOH (0.40 mL, 0.40 mmol) and freshly activated molecular sieves 4A (powder, 210 mg) in anhydrous THF (1.5 mL) was carried out following the general procedure (10 min) to provide **11e** (129 mg, 95%) as a pale-yellow oil. IR (film, cm^{-1}): 735, 764, 1032, 1092, 1179, 1228, 1310, 1371, 1506, 1654, 1700, 1776, 2966; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.90-1.00 (m, 6H), 1.42 (s, 6H), 2.52 (s, 3H), 2.53-2.61 (m, 1H), 3.74 (d, J = 8.3 Hz, 1H), 3.89 (d, J = 8.3 Hz, 1H), 4.27 (d, J = 16 Hz, 1H), 5.05 (d, J = 16 Hz, 1H), 5.44 (d, J = 10 Hz, 1H), 7.11-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.6, 19.4, 22.0, 22.9, 24.4, 28.8, 45.3, 61.1, 64.4, 74.9, 125.8, 126.6, 127.0, 128.2, 128.6, 138.4, 153.6, 170.2, 173.2; HRMS (FAB$^+$): calcd for $C_{19}H_{26}N_2O_4$ 346.1893 (M^+), found 346.1896.

***N*-(1-(4,4-Dimethyl-2-oxo-3-oxazolidinyl)carbonyl-2-methylpropyl)-*N*-phenylbenzamide (11f).**

The reaction of Ugi product **10f** (740 mg, 1.51 mmol), 1.0 M of KO*t*-Bu/*t*-BuOH (1.60 mL, 1.60 mmol) and freshly activated molecular sieves 4A (powder, 890 mg) in anhydrous THF (7.2 mL) was carried out following the general procedure (10 min) to provide **11f** (487 mg, 82%) as a pale-yellow solid. IR (film, cm^{-1}): 729, 764, 917, 1037, 1089, 1129, 1178, 1230, 1310, 1370, 1472, 1492, 1559, 1595, 1653, 1701,

1779, 2968; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.07 (d, *J* = 6.6 Hz, 6H), 1.31 (s, 3H), 1.56 (s, 3H), 2.32-2.41 (m, 1H), 3.91 (d, *J* = 8.3 Hz, 1H), 3.97 (d, *J* = 8.3 Hz, 1H), 6.19 (d, *J* = 9.8 Hz, 1H), 7.08-7.36 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.3, 19.9, 23.9, 24.9, 29.2, 60.9, 64.6, 75.1, 127.2, 127.6, 127.8, 128.2, 128.3, 128.4, 128.5, 128.8, 129.2, 129.7, 136.5, 140.5, 153.5, 171.1, 172.2; HRMS (FAB$^+$): calcd for $C_{23}H_{26}N_2O_4$ 394.1893 (M^+), found 394.1894.

***N*-((4,4-Dimethyl-2-oxo-3-oxazolidinyl)carbonyl-1-phenylmethyl)-*N*-phenylbenzamide (11g).**

The reaction of Ugi product **10g** (840 mg, 1.61 mmol), 1.0 M of KO*t*-Bu/*t*-BuOH (1.65 mL, 1.65 mmol) and freshly activated molecular sieves 4A (powder, 800 mg) in anhydrous THF (8.0 mL) was carried out following the general procedure (10 min) to provide **11g** (593 mg, 86%) as a pale-yellow amorphous. IR (film, cm^{-1}): 718, 764, 913, 1037, 1093, 1179, 1234, 1311, 1380, 1456, 1493, 1577, 1595, 1646, 1708, 1776, 3063; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.54 (d, *J* = 4.4 Hz, 3H), 1.72 (d, *J* = 4.9 Hz, 3H), 3.91 (d, *J* = 8.5 Hz, 1H), 4.04 (d, *J* = 8.3 Hz, 1H), 6.92-7.36 (m, 16H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.7, 24.9, 60.8, 65.1, 75.3, 115.4, 126.9, 127.5, 127.9, 128.2, 128.3, 128.4, 128.6, 129.4, 131.2, 131.3, 132.6, 136.9, 140.3, 153.1, 171.1, 171.3; HRMS (FAB$^+$): calcd for $C_{26}H_{24}N_2O_4$ 428.1736 (M^+), found 428.1733.

General procedure for the synthesis of thiol esters 16a-g.

***S*-1-Dodecyl 2-(*N*-benzylbenzamido)-3-methylbutanethioate (16a).**

To a solution of *n*-dodecanethiol (0.26 mL, 1.1 mmol) in THF (2.5 mL) at 0 °C was added dropwise *n*-BuLi (1.0 M solution in hexane, 0.40 mL, 0.40 mmol) for 2 min. After being stirred for 5 min, the resulting white suspension was added to a solution of *N*-acyloxazolidinone **11a** (93 mg, 0.23 mmol) in THF (4.0 mL) at 0 °C. After stirring for 10 min, 10% w/v aqueous citric acid was added and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over magnesium sulfate and filtered. The solvent was removed under reduced pressure, the resultant crude mixture was purified by silica gel chromatography (EtOAc/hexane = 1/19-1/9) to afford **16a** (94 mg, 83%) as a pale-yellow oil. IR (film, cm^{-1}): 731, 1129, 1300, 1457, 1653, 1684, 2854, 2925; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.77 (s, 3H), 0.80 (s, 3H), 0.88 (t, *J* = 6.8 Hz, 3H), 1.26-1.30 (m, 18H), 1.37-1.52 (m, 2H), 2.35-2.50 (m, 1H), 2.77 (t, *J* = 7.3 Hz, 2H), 4.65 (d, *J* = 15 Hz, 1H), 4.88 (d, *J* = 14 Hz, 1H), 5.05 (br s, 1H), 6.98-7.58 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 19.1, 19.5, 22.7, 28.9, 29.0, 29.1, 29.4, 29.5, 29.6, 31.9, 45.8, 62.7, 73.5, 126.8, 127.5, 127.8, 128.1, 128.3, 128.5, 129.7, 136.2, 138.1, 173.5, 196.8; HRMS (FAB$^+$): calcd for $C_{31}H_{45}NO_2S$ 495.3171 (M^+), found 495.3169.

***S*-1-Dodecyl 2-(*N*-benzylbenzamido)ethanethioate (16b).**

The reaction of *N*-acyloxazolidinone **11b** (108 mg, 0.296 mmol), *n*-BuLi (1.0 M solution in hexane, 0.45 mL, 0.45 mmol) and *n*-dodecanethiol (0.36 mL, 1.50 mmol) in THF (net 4.0 mL) was carried out following the general procedure (10 min) to provide **16b** (105 mg, 79%) as a pale yellow oil. IR (film, cm^{-1}): 1003, 1249, 1423, 1456, 1496, 1652, 1695, 2853, 2925; ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of

amide rotamers): δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.23-1.38 (m, 18H), 1.58-1.60 (m, 2H), 2.90-3.00 (m, 2H), 4.01 (s, 2H of a rotamer), 4.33 (s, 2H of a rotamer), 4.63 (s, 2H of a rotamer), 4.83 (s, 2H of a rotamer), 7.13-7.54 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 22.7, 28.7, 28.9, 29.1, 29.3, 29.5, 29.6, 31.9, 49.2, 54.0, 57.5, 126.9, 129.0, 128.6, 128.3, 128.0, 127.1, 130.0, 135.2, 135.9, 172.4, 196.4; HRMS (FAB$^+$): calcd for $C_{28}H_{39}NO_2S$ 453.2701 (M^+), found 453.2722.

***S*-1-Dodecyl 2-(*N*-benzylbenzamido)propanethioate (16c).**

The reaction of *N*-acyloxazolidinone **11c** (130 mg, 0.342 mmol), *n*-BuLi (1.0 M solution in hexane, 0.35 mL, 0.35 mmol) and *n*-dodecanethiol (0.41 mL, 1.71 mmol) in THF (net 4.0 mL) was carried out following the general procedure (10 min) to provide **16c** (120 mg, 75%) as a white solid. IR (film, cm^{-1}): 955, 1316, 1402, 1452, 1462, 1651, 1656, 1680, 1691, 1726, 2314, 2854, 2925; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86-0.90 (m, 3H), 1.26-1.36 (m, 21H), 1.50-1.64 (m, 2H), 2.83-2.96 (m, 2H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.66 (d, *J* = 7.0 Hz, 1H), 5.27-5.42 (m, 1H), 7.25-7.50 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 22.7, 28.9, 29.1, 29.4, 29.5, 29.6, 29.7, 31.9, 46.9, 126.6, 126.8, 127.1, 127.5, 128.6, 129.8, 136.0, 137.3, 170.9, 199.5; HRMS (FAB$^+$): calcd for $C_{29}H_{41}NO_2S$ 467.2858 (M^+), found 467.2871.

***S*-1-Dodecyl 2-(*N*-benzylbenzamido)-2-phenylethanethioate (16d).**

The reaction of *N*-acyloxazolidinone **11d** (48 mg, 0.109 mmol), *n*-BuLi (1.37 M solution in hexane, 0.16 mL, 0.22 mmol) and *n*-dodecanethiol (0.14 mL, 0.58 mmol) in THF (net 2.5 mL) was carried out following the general procedure (10 min) to provide **16d** (38 mg, 66%) as a pale-yellow oil. IR (film, cm^{-1}): 723, 1001, 1395, 1454, 1496, 1647, 1685, 2854, 2925; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.25-1.31 (m, 18H), 1.53-1.62 (m, 2H), 2.93 (t, *J* = 5.3 Hz, 2H), 4.33 (s, 1H), 4.37 (s, 1H), 5.74 (s, 1H), 6.83-6.92 (m, 2H), 7.11-7.12 (m, 3H), 7.25-7.49 (m, 8H), 7.49-7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 22.7, 28.9, 29.1, 29.3, 29.4, 29.5, 29.6, 31.9, 52.2, 69.6, 126.8, 128.2, 128.5, 128.6, 128.9, 129.9, 130.2, 130.5, 130.6, 133.8, 135.9, 137.2, 173.0, 197.3; HRMS (FAB$^+$): calcd for $C_{34}H_{43}NO_2S$ 529.3014 (M^+), found 529.3004.

***S*-1-Dodecyl 2-(*N*-benzylacetamido)-3-methylbutanethioate (16e).**

The reaction of *N*-acyloxazolidinone **11e** (59 mg, 0.17 mmol), *n*-BuLi (1.37 M solution in hexane, 0.25 mL, 0.34 mmol) and *n*-dodecanethiol (0.21 mL, 0.88 mmol) in THF (net 3.0 mL) was carried out following the general procedure (10 min) to provide **16e** (61 mg, 78%) as a pale yellow oil. IR (film, cm^{-1}): 728, 802, 1144, 1255, 1405, 1457, 1662, 1684, 2854, 2925; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.77-0.97 (m, 9H), 1.25-1.27 (m, 18H), 1.41-1.47 (m, 2H), 2.02 (s, 3H), 2.32-2.33 (m, 1H), 2.69-2.76 (m, 2H), 4.50-4.73 (m, 2H), 5.23 (d, *J* = 11 Hz, 1H), 7.15-7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 18.8, 19.4, 22.3, 22.7, 27.6, 28.9, 29.0, 29.1, 29.4, 29.5, 29.6, 31.9, 48.2, 67.1, 73.6, 125.8, 126.4, 126.7, 127.1, 128.0, 128.6, 137.4, 138.0, 171.5, 172.4, 196.3, 197.5; HRMS (FAB$^+$): calcd for $C_{26}H_{43}NO_2S$ 433.3014 (M^+), found 433.2997.

***S*-1-Dodecyl 2-(*N*-phenylbenzamido)-3-methylbutanethioate (16f).**

The reaction of *N*-acyloxazolidinone **11f** (46 mg, 0.12 mmol), *n*-BuLi (1.0 M solution in hexane, 0.35 mL, 0.35 mmol) and *n*-dodecanethiol (0.42 mL, 1.8 mmol) in THF (net 3.0 mL) was carried out following the general procedure (10 min) to provide **16f** (48 mg, 86%) as a pale-yellow oil. IR (film, cm^{-1}): 735, 764, 1032, 1092, 1179, 1228, 1310, 1371, 1506, 1654, 1700, 1776, 2966; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.24-1.33 (m, 18H), 1.51-1.58 (m, 2H), 2.52-2.58 (m, 1H), 2.88 (d, *J* = 7.4 Hz, 2H), 5.07 (d, *J* = 10.0 Hz, 1H), 7.09-7.31 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 19.8, 20.7, 22.7, 28.3, 28.9, 29.0, 29.1, 29.3, 29.4, 29.5, 29.6, 31.9, 72.8, 127.1, 127.7, 128.6, 128.7, 129.7, 136.0, 141.7, 170.9, 197.3; HRMS (FAB^+): calcd for $C_{30}H_{43}NO_2S$ 481.3014 (M^+), found 481.3034.

***S*-1-Dodecyl 2-(*N*-phenylbenzamido)-2-phenylethanethioate (16g).**

The reaction of *N*-acyloxazolidinone **11g** (50 mg, 0.12 mmol), *n*-BuLi (1.37 M solution in hexane, 0.15 mL, 0.21 mmol) and *n*-dodecanethiol (0.12 mL, 0.50 mmol) in THF (net 5.0 mL) was carried out following the general procedure (10 min) to provide **16g** (41 mg, 68%) as a pale-yellow oil. IR (film, cm^{-1}): 976, 1339, 1455, 1492, 1596, 1652, 1695, 2853, 2925; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.25-1.33 (m, 18H), 1.59-1.63 (m, 2H), 2.99 (t, *J* = 7.3 Hz, 2H), 6.43 (s, 1H), 6.92-7.36 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 22.7, 28.9, 29.1, 29.4, 29.5, 29.6, 29.7, 31.9, 71.7, 115.4, 127.2, 127.6, 128.3, 128.4, 128.6, 129.6, 130.5, 130.9, 133.7, 135.7, 140.8, 170.9, 197.6; HRMS (FAB^+): calcd for $C_{33}H_{41}NO_2S$ 515.2858 (M^+), found 515.2853.

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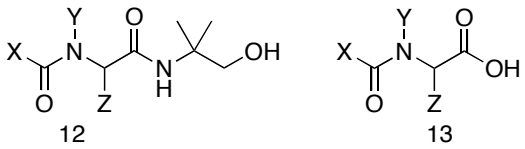
13. In the absence of MS4A, the reaction resulted in low yields, accompanied by the *N*-acylamino alcohols **12** and/or carboxylic acid **13**.



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19. T. Miyazaki, Y. Han-ya, H. Tokuyama, and T. Fukuyama, *Synlett*, 2004, 477.
20. In order to avoid the thiolate addition to the carbonyl group on the oxazolidinone ring, the reaction should be carried out at lower than 0 °C. Reactions at higher temperature often provided the undesired *N*-acylamino alcohols **12**. This tendency was notably observed in compounds possessing a bulky substituent at the Z-position.