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One-Pot Synthesis of Functionalized *α*-Acyloxythioamides from *N*-Protected *α*-Amino Acids as an Acid Component in the Passerini Reaction in an Ionic Liquid

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N-Protected *α*-amino acids, prepared from benzoyl chlorides, KSCN and *α*-amino acids, were used as the acid component in the Passerini reaction, in an ionic liquid, to produce functionalized α-acyloxythioamides in 59-95% yields. The work-up procedure was fairly simple and the products did not require further purification.

Keywords: Passerini reaction, Ionic liquid, Carboxylic acid, Alkyl isocyanide, *α*-Acyloxycarboxathioamide

INTRODUCTION

Multicomponent reactions (MCRs) are generally defined as reactions where more than two starting materials react to form a product. Today, most MCR chemistry performed with isocyanides relates to the classical Passerini and Ugi reactions [1-3]. Passerini reaction involves an oxo component, an isocyanide and a carborboxylic acid [4,5]. The success of multicomponent condensations in organic synthesis during recent years has aroused considerable interest in causing novel reactions or modifying the old ones. Such modifications include the use of polyfunctional building blocks [6,7], the employment of non-classical starting units [8], the use of catalysts [9] or new solvents according to green chemistry [10].

Room temperature ionic liquids (RTILs), especially those based on 1,3-dialkylimidazelium salts, have shown great promise as attractive alternatives to the conventional solvents. RTILs possess the unique advantages of high thermal stability, negligible vapor pressure, immiscibility with both organic compounds and water, and recyclability [11-15].

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In pursuit of our continuing interest in isocyanide-based multicomponent reactions [16-19], herein, we describe an efficient synthesis of *α*-acyloxythioamides **6** from *N*-protected *α*-amino acids **3** as an acid component in the Passerini reaction in 1-butyl-3-methylimidazolinium bromide ([bmim]Br) at room temperature. Precedents exist which show the compatibility of Passerini reaction with ILs [20-23].

EXPERIMENTAL

Chemicals and Apparatus

KSCN, benzoyl chlorides, *α*-amino acids, alkyl isocyanide**s**, aldheydes, and ketones were obtained from *Merck* and were used without further purification. Compounds **3** were prepared according to literature [24]. [bmim]Br was synthesized from the reaction of *N*-methylimidazole and *n*-butyl bromide [25]. Melting points were obtained uncorrected using an Electrothermal-9100 apparatus. IR Spectra were recorded with a *Shimadzu IR-460* spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a *Bruker DRX-300 Avance* instrument using $CDCl_3$ as the deuterated solvent containing tetramethylsilane as internal standard, at 300 and 75 MHz, respectively; δ in parts per million, J in hertz. EIMS (70 eV):

Mass spectra were obtained with a *Finnigan-MAT-8430* mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were obtained with a *Heraeus CHN-O-Rapid* analyzer.

General Procedure for the Preparation of Compounds 6

A mixture of acid **3** (1 mmol), alkyl isocyanide **4** (1 mmol) and oxo compound **5** (1 mmol) was stirred in 1 ml of [bmim]Br for 3 h at r.t. Then 5 ml of water was added and the mixture was extracted with Et_2O (2 × 10 ml). The solvent was evaporated under reduced pressure to leave a residue that was purified by column chromatography (silica gel (230-400 mesh; *Merck*), hexane/AcOEt 4:1) to afford desired pure products.

1-(Cyclohexylamino)-2-methyl-1-oxopropan-2-yl-2-(3-benzoylthioureido)propanoate (6a). White powder; yield: 0.38 g (90%); m.p.: 118-120 ºC. IR (KBr): $\bar{\nu}$ = 3460, 3430, 3290, 1750, 1664, 1602, 1385, 1110 cm^{-1}. EI-MS: *m/z* (%) = 419 (M^+, 11), 234 (22), 186 (18), 169 (87), 105 (100), 84 (17), 77 (30), 44 (29). Anal. Calcd. for $C_{21}H_{29}N_3O_4S$ (419.54): C, 60.12; H, 6.97; N, 10.01. Found: C, 59.95; H, 6.54; N, 10.78. ^{1}H NMR: δ = 1.12-1.92 (10H, m, $5CH_2$), 1.64 (3H, d, ^3J = 7.0, Me), 1.65 (3H, s, Me), 1.67 (3H, s, Me), 3.74 (1H, m, CH), 4.91 (1H, quintet, ^3J = 7.0, CH), 6.25 (1H, d, ^3J = 7.8, NH), 7.55 (2H, t, ^3J = 9.0, 2CH), 7.67 (1H, t, ^3J = 9.0, CH), 7.87 (2H, d, ^3J = 9.0, 2CH), 9.07 (1H, s, NH), 11.04 (1H, d, ^3J = 7.0, NH). ^{13}C NMR: δ = 17.5 (Me), 24.7 (Me), 25.2 (Me), 25.3 (CH_2), 25.4 (CH_2), 25.9 (CH_2), 33.3 ($2CH_2$), 48.9 (CH), 54.9 (CH), 83.5 (C), 127.9 (2CH), 129.6 (2CH), 131.8 (C), 134.2 (CH), 167.3 (C=O), 169.9 (C=O), 171.8 (C=O), 180.6 (C=S).

1-(*tert*-Butylamino)-2-methyl-1-oxopropan-2-yl-2-(3-benzoylthioureido)propanoate (6b). White powder; yield: 0.37 g (95%); m.p.: 125-127 ºC. IR (KBr): $\bar{\nu}$ = 3451, 3404, 3235, 1738, 1660, 1527,1258, 1138 cm^{-1}. EI-MS: *m/z* (%) = 393 (M^+, 25), 234 (20), 160 (21), 143 (84), 105 (100), 77 (29), 58 (24), 44 (31). Anal. Calcd. for $C_{19}H_{27}N_3O_4S$ (393.51): C, 57.99; H, 6.91; N, 10.68. Found: C, 58.55; H, 6.46; N, 10.95. ^{1}H NMR: δ = 1.37 (9H, s, CMe_3), 1.64 (3H, d, ^3J = 6.5, Me), 1.65 (6H, s, 2Me), 4.91 (1H, quintet, ^3J = 6.5, CH), 6.04 (1H, s, NH), 7.50-7.90 (5H, m, 5CH), 9.05 (1H, s, NH), 11.04 (1H, d, ^3J = 6.5, NH). ^{13}C NMR: δ = 17.6 (Me), 24.6 (Me), 25.1 (Me), 29.0 (CMe_3), 51.7 (C), 54.8 (CH), 83.0 (CMe_3), 127.9 (2CH), 129.6 (2CH), 131.9 (C), 134.2 (CH), 167.2 (C=O), 170.0 (C=O), 171.9 (C=O), 180.6 (C=S).

3-(Cyclohexylcarbamoyl)pentan-3-yl-2-(3-benzoylthioureido)propanoate (6c). White powder, yield: 0.38 g (85%), m.p.: 99-101 ºC. IR (KBr) IR (KBr): $\bar{\nu}$ = 3430, 3380, 3237, 1746, 1667, 1525, 1254, 1173 cm^{-1}. EI-MS: *m/z* (%) = 447 (M^+, 30), 234 (35), 214 (19), 197 (79), 105 (100), 84 (18), 77 (23), 44 (25). Anal. Calcd. for C_{23} $H_{33}N_3O_4S$ (447.60): C, 61.72; H, 7.43; N, 9.39. Found: C, 61.25; H, 7.54; N, 9.68. ^{1}H NMR: δ = 0.80 (3H, t, ^3J = 7.2, Me), 0.82 (3H, t, ^3J = 7.2, Me), 1.08-1.92 (10H, m, $5CH_2$), 1.68 (3H, d, ^3J = 7.2, Me), 2.08 (2H, septet, ^3J = 7.2, CH_2), 2.36 (2H, septet, ^3J = 7.2, CH_2), 3.84 (1H, m, CH), 5.15 (1H, quintet, ^3J = 7.2, CH), 6.54 (1H, d, ^3J = 8.0, NH), 7.55 (2H, t, ^3J = 8.5, 2CH), 7.67 (1H, t, ^3J = 8.5, CH), 7.87 (2H, d, ^3J= 8.5, 2CH), 9.10 (1H, s, NH), 11.16 (1H, d, ^3J = 7.2, NH). ^{13}C NMR: δ = 8.2 (Me), 8.3 (Me), 18.1 (Me), 25.4 (CH_2), 25.8 (CH_2), 25.9 (CH_2), 28.4 (CH_2), 28.5 (CH_2), 33.5 (CH_2), 33.6 (CH_2), 48.8 (CH), 54.8 (CH), 92.1 (C), 127.9 (2CH), 129.5 (2CH), 131.8 (C), 134.3 (CH), 167.3 (C=O), 169.1 (C=O), 170.0 (C=O), 180.4 (C=S).

3-(Cyclohexylcarbamoyl)-2,4-dimethylpentan-3-yl-2-(3-benzoylthioureido)propanoate (6d). White powder; yield: 0.42 g (89%); m.p.: 88-89 ºC. IR (KBr): $\bar{\nu}$ = 3394, 3313, 3252, 1725, 1644, 1601, 1381, 1176 cm^{-1}. EI-MS: *m/z* (%) = 475 (M^+, 38), 234 (25), 242 (23), 225 (65), 105 (100), 84 (21), 77 (24), 43 (20). Anal. Calcd. for $C_{25}H_{37}N_3O_4S$ (475.65): C, 63.26; H, 7.84; N, 8.83. Found: C, 62.82; H, 8.23; N, 9.05. ^{1}H NMR: δ = 0.91 (3H, d, ^3J = 6.9, Me), 0.96 (3H, d, ^3J = 6.9, Me), 1.01 (6H, d, ^3J 6.9, 2Me), 1.06-1.91 (10H, m, $5CH_2$), 1.68 (3H, d, ^3J = 7.2, Me), 2.12 (2H, septet, ^3J = 6.9, 2CH), 3.07 (1H, septet, ^3J = 6.9, CH), 3.80 (1H, m, CH), 5.08 (1H, quintet, ^3J = 7.2, CH), 6.63 (1H, d, ^3J = 8.1, NH), 7.54 (2H, t, ^3J = 7.0, 2CH), 7.66 (1H, t, ^3J = 7.0, CH), 7.87 (1H, d, ^3J = 7.0, 2CH), 9.11 (1H, s, NH), 11.10 (1H, d, ^3J = 7.2, NH). ^{13}C NMR: δ = 16.6 (2Me), 17.8 (2Me), 18.2 (Me), 25.2 (CH_2), 25.3 (CH_2), 25.9 (CH_2), 31.2 (CH), 31.5 (CH), 33.5 (CH_2), 33.7 (CH_2), 48.6 (CH), 55.6 (CH), 99.1 (C), 127.9 (2CH), 129.6 (2CH), 131.8 (C), 134.2 (CH), 167.2 (C=O), 168.8 (C=O), 169.9 (C=O), 180.5 (C=S).

1-(Cyclohexylcarbamoyl)cyclohexyl-2-(3-benzoylthioureido)propanoate (6e). Viscose oil; yield: 0.41 g (90%). IR (KBr): $\bar{\nu}$ = 3442, 3390, 3201, 1727, 1671, 1598, 1384, 1138 cm^{-1}. EI-MS: *m/z* (%) = 459 (M^+, 35), 234 (29), 226 (26), 209 (75), 105 (100), 84 (23), 77 (21), 44 (17). Anal. Calcd. for $C_{24}H_{33}N_3O_4S$ (459.61): C, 62.72; H, 7.24; N, 9.14. Found: C,

63.01; H, 7.86; N, 9.34. ^{1}H NMR: δ = 1.16-1.39 (10H, m, 5CH_2), 1.70 (3H, d, ^3J = 7.2, Me), 1.70-1.91 (10H, m, 5CH_2), 3.73 (1H, m, CH), 4.93 (1H, quintet, ^3J = 7.2, CH), 6.16 (1H, d, ^3J = 7.2, NH), 7.55 (2H, t, ^3J = 7.8, 2CH), 7.66 (1H, t, ^3J = 7.8, CH), 7.87 (2H, d, ^{3}J = 7.8, 2CH), 9.09 (1H, s, NH), 11.03 (1H, d, ^3J = 7.2, NH). ^{13}C NMR: δ = 17.9 (Me), 21.7 (CH_2), 21.8 (CH_2), 25.3 (CH_2), 25.4 (CH_2), 25.5 (CH_2), 26.0 (CH_2), 32.0 (CH_2), 32.7 (CH_2), 33.1 (CH_2), 33.3 (CH_2), 49.0 (CH), 55.0 (CH), 84.4 (C), 127.9 (2CH), 129.5 (2CH), 131.9 (C), 134.3 (CH), 167.3 (C=O), 170.0 (C=O), 171.7 (C=O), 180.8 (C=S).

1-(Cyclohexylcarbamoyl)cyclopentyl-2-(3-benzoylthioureido)propanoate (6f). Viscose oil; yield: 0.39 g (87%). IR (KBr): $\bar{\nu}$ = 3445, 3389, 3221, 1737, 1679, 1605, 1364, 1123 cm^{-1}. EI-MS: *m/z* (%) = 445 (M^+, 34), 234 (30), 212 (23), 195 (83), 105 (100), 84 (21), 77 (19), 44 (16). Anal. Calcd. for $C_{23}H_{31}N_3O_4S$ (445.58): C, 61.99; H, 7.01; N, 9.43. Found: C, 62.09; H, 7.25; N, 9.61. ^{1}H NMR: δ = 1.12-1.39 (8H, m, 4CH_2), 1.53-1.78 (10H, m, 5CH_2), 1.90 (3H, d, ^3J = 7.2, Me), 3.74 (1H, m, CH), 4.85 (1H, quintet, ^3J = 7.2, CH), 6.20 (1H, d, ^3J = 7.2, NH), 7.55 (2H, t, ^3J = 7.8, 2CH), 7.67 (1H, t, ^3J = 7.8, CH), 7.87 (2H, d, ^3J = 7.8, 2CH), 9.1 (1H, s, NH), 11.0 (1H, d, ^{3}J = 7.2, NH). ^{13}C NMR: δ = 17.4 (Me), 25.1 (CH_2), 25.2 (CH_2), 25.4 (CH_2), 25.5 (CH_2), 25.9 (CH_2), 33.3 (2CH_2), 36.9 (CH_2), 37.9 (CH_2), 49.1 (CH), 54.8 (CH), 92.1 (C), 127.9 (2CH), 129.5 (2CH), 131.9 (C), 134.2 (CH), 167.3 (C=O), 170.5 (C=O), 171.1 (C=O), 180.9 (C=S).

1-(Cyclohexylcarbamoyl)cyclohexyl-2-(3-(4-methylbenzoyl)thioureido)propanoate (6g). Viscous oil; yield: 0.40 g (86%). IR (KBr): $\bar{\nu}$ = 3420, 3343, 3250, 2669, 1746, 1667, 1611, 1318, 1172 cm^{-1}. EI-MS: *m/z* (%) = 473 (M^+, 31), 248 (27), 226 (24), 195 (79), 119 (100), 84 (16), 91 (21), 44 (30). Anal. Calcd. for $C_{25}H_{35}N_3O_4S$ (473.63): C, 63.40; H, 7.45; N, 8.87. Found: C, 63.01; H, 7.86; N, 8.74. ^{1}H NMR: δ = 1.16-1.48 (10H, m, 5CH_2), 1.68 (3H, d, ^3J = 7.2, Me), 1.87-2.30 (10H, m, 5CH_2), 2.45 (3H, s, CH), 3.71 (1H, m, CH), 4.92 (1H, quintet, ^3J = 7.2, CH), 6.16 (1H, d, ^3J = 8.1, NH), 7.33 (2H, d, ^3J = 8.1, 2CH), 7.76 (2H, d, ^3J = 8.1, 2CH), 9.07 (1H, s, NH), 11.06 (1H, d, ^3J = 7.2, NH). ^{13}C NMR: δ = 17.9 (Me), 21.5 (CH_2), 21.7 (CH_2), 22.1 (Me), 25.2 (CH_2), 25.3 (CH_2), 25.5 (CH_2), 25.9 (CH_2), 32.1 (CH_2), 33.0 (CH_2), 33.2 (CH_2), 33.5 (CH_2), 49.0 (CH), 55.0 (CH), 75.3 (C), 127.9 (2CH), 129.0 (C), 130.3 (2CH), 145.2 (CH), 167.3 (C=O), 170.0 (C=O), 171.8 (C=O), 181.0 (C=S).

2-(*tert*-Butylamino)-1-(4-nitrophenyl)-2-oxoethyl-2-(3-benzoylthioureido)propanoate (6h). Viscous yellow oil; yield: 0.40 g (83%). IR (KBr): $\bar{\nu}$ = 3441, 3380, 3270, 1741, 1635, 1601, 1384, 1117, 770 cm^{-1}. EI-MS: *m/z* (%) = 486 (M^+, 41), 253 (15), 251 (24), 234 (55), 105 (100), 77 (39), 57 (37), 44 (28). Anal. Calcd. for $C_{23}H_{26}N_4O_6S$ (486.52): C, 56.78; H, 5.38; N, 11.52. Found: C, 57.3; H, 5.26; N, 11.74. **6h-I** (50%) ^{1}H NMR: δ = 1.37 (9H, s, CMe_3), 1.63 (3H, d, ^3J = 7.1, Me), 5.05 (1H, quintet, ^3J = 7.1, CH), 6.10 (1H, s, CH), 6.38 (1H, s, NH), 7.56-7.88 (5H, m, 5CH), 8.23 (2H, d, ^3J = 9.0, 2CH), 8.26 (2H, d, ^3J = 9.0, 2CH), 9.11 (1 H, s, NH), 11.09 (1H, d, ^3J = 7.1, NH). ^{13}C NMR: δ = 17.4 (Me), 29.1 (CMe_3), 52.5 (CMe$_3$), 54.3 (CH), 75.3 (CH_2), 124.2 (2CH), 127.8 (2CH), 128.4 (2CH), 129.7 (2CH), 131.6 (Me), 134.3 (CH_2), 142.6 (CH), 148.5 (C), 166.0 (C=O), 167.4 (C=O), 169.6 (C=O), 181.0 (C=S). **6h-II** (50%) ^{1}H NMR: δ = 1.39 (9H, s, CMe_3), 1.69 (3H, d, ^3J = 7.1, Me), 5.20 (1H, quintet, ^3J = 7.1, CH), 6.17 (1H, s, CH), 6.51 (1H, s, NH), 7.56-7.88 (5H, m, 5CH), 8.23 (2H, d, ^3J = 9.0, 2CH), 8.26 (2H, d, ^{3} J = 9.0, 2CH), 9.11 (1H, s, NH), 11.12 (1H, d, ^{3} J = 7.1, NH). ^{13}C NMR: δ = 17.6 (Me), 29.1 (CMe_3), 52.5 (CMe$_3$), 54.5 (CH), 75.8 (CH_2), 124.3 (2CH), 127.9 (2CH), 128.6 (2CH), 129.8 (2CH), 131.7 (Me), 134.4 (CH_2), 142.9 (CH), 148.5 (C), 166.1 (C=O), 167.5 (C=O), 170.2 (C=O), 181.1 (C=S).

2-(*tert*-Butylamino)-1-(4-chlorophenyl)-2-oxoethyl-2-(3-benzoylthioureido)acetate (6i). Viscous oil; yield: 0.27 g (59%). IR (KBr): $\bar{\nu}$ = 3427, 3356, 3237, 1754, 1669, 1605, 1325, 1107 cm^{-1}. EI-MS: *m/z* (%) = 463 (M^++1, 13), 462 (M^+, 38), 237 (26), 235 (56), 228 (13), 225 (52), 105 (100), 77 (40), 57 (36), 44 (33). Anal. Calcd. for $C_{22}H_{24}N_3O_4SCl$ (461.97): C, 57.20; H, 5.23; N, 9.09. Found: C, 57.31; H, 5.29; N, 9.24. ^{1}H NMR: δ = 1.39 (9H, s, CMe_3), 4.60 (2H, br s, CH_2), 6.06 (1H, s, CH), 6.21 (1H, s, NH), 7.56-7.88 (5H, m, 5CH), 8.23 (2H, d, ^3J = 9.0, 2CH), 8.26 (2H, d, ^3J = 9.0, 2CH), 9.11 (1H, s, NH), 11.09 (1H, d, ^3J = 7.1, NH). ^{13}C NMR: δ = 29.1 (CMe_3), 52.5 (CMe$_3$), 54.3 (CH_2), 75.3 (CH), 127.9 (2CH), 129.3 (2CH), 129.4 (2CH), 129.7 (2CH), 131.6 (CH), 131.9 (C), 133.3 (CH), 134.4 (C), 166.0 (C=O), 167.4 (C=O), 169.6 (C=O), 181.0 (C=S).

2-(*tert*-Butylamino)-1-(4-chlorophenyl)-2-oxoethyl-2-(3-benzoylthioureido)propanoate (6j). Viscous oil; yield: 0.30 g (63%). IR (KBr): $\bar{\nu}$ = 3427, 3356, 3237, 1754, 1669, 1605,

1325, 1107 cm^{-1}. Anal. Calcd. for $C_{23}H_{26}N_3O_4SCl$ (475.97): C, 58.04; H, 5.50; N, 8.82. Found: C, 57.46; H, 5.09; N, 8.55. **6j-I** (60%) ^1H NMR: δ = 1.37 (9H, s, CMe_3), 1.59 (3H, d, ^3J = 7.2, Me), 5.03 (1H, quintet, ^3J = 7.2, CH), 6.00 (1H, s, CH), 6.23 (1H, s, NH), 7.38-7.88 (5H, m, 5CH), 7.56 (2H, d, ^3J = 3.0, 2CH), 7.86 (2H, d, ^3J = 3.0, 2CH), 9.07 (1H, s, NH), 11.08 (1H, d, ^3J = 7.2, NH). ^{13}C NMR: δ = 17.4 (Me), 29.1 (C*Me*$_3$), 52.3 (*C*Me_3), 54.4 (CH), 75.9 (CH), 127.8 (2CH), 129.1 (2CH), 129.3 (2CH), 129.6 (2CH), 131.7 (C), 134.2 (C), 134.5 (C), 135.3 (C), 166.8 (C=O), 167.3 (C=O), 169.8 (C=O), 180.7 (C=S). EI-MS: *m/z* (%) = 477 (M^+ +1, 13), 476 (M^+, 34), 251 (21), 242 (10), 235 (55), 225 (51), 105 (100), 77 (41), 57 (38), 44 (34). **6j-II** (40%) ^1H NMR: δ = 1.40 (9H, s, CMe_3), 1.68 (3H, d, ^3J = 7.2, Me), 5.17 (1H, quintet, ^3J = 7.2, CH), 6.08 (1H, s, CH), 6.41 (1H, s, NH), 7.38-7.88 (5H, m, 5CH), 7.56 (2H, d, ^3J = 3.0, 2CH), 7.86 (2H, d, ^3J = 3.0, 2CH), 9.07 (1H, s, NH), 11.12 (1H, d, ^3J = 7.2, NH); ^{13}C NMR: δ = 17.7 (Me), 29.1 (C*Me*$_3$), 52.3 (*C*Me_3), 54.5 (CH), 76.3 (CH), 127.9 (2CH), 129.2 (2CH), 129.3 (2CH), 129.7 (2CH), 131.8 (C), 134.3 (C), 134.6 (C), 135.4 (C), 166.9 (C=O), 167.3 (C=O), 170.3 (C=O), 180.8 (C=S).

2-(Cyclohexylamino)-2-oxo-1-phenylethyl-2-(3-benzoyl-thioureido)propanoate (6k). Viscous oil; yield: 0.28 g (60%); IR (KBr): $\bar{\nu}$ = 3450, 3325, 3242, 1743, 1658, 1599, 1315, 1127 cm^{-1}. EI-MS: *m/z* (%) = 467 (M^+, 33), 251 (24), 234 (61), 217 (49), 105 (100), 84 (29), 77 (44), 44 (32). Anal. Calcd. for $C_{25}H_{29}N_3O_4S$ (467.56): C, 64.22; H, 6.24; N, 8.99. Found: C, 65.01; H, 5.99; N, 9.25. **6k-I** (62%) ^1H NMR: δ = 1.16-1.91 (10H, m, 5CH_2), 1.68 (3H, d, ^3J = 7.2, Me), 3.81 (1H, m, CH), 5.03 (1H, quintet, ^3J = 7.2, CH), 6.13 (1H, s, CH), 6.45 (1H, d, ^3J = 7.8, NH), 7.35-7.89 (10H, m, 5CH), 9.10 (1H, s, NH), 11.15 (1H, d, ^3J = 7.2, NH). ^{13}C NMR: δ = 17.4 (Me), 25.4 (CH_2), 25.8 (2CH_2), 33.4 (2CH_2), 48.9 (CH), 54.6 (CH), 76.7 (CH), 127.7 (2CH), 127.8 (2CH), 129.1 (2CH), 129.4 (CH), 129.6 (2CH), 131.8 (C), 134.2 (CH), 135.6 (C), 167.1 (C=O), 169.8 (C=O), 170.4 (C=O), 180.7 (C=S); **6k-II** (38%) ^1H NMR: δ = 1.16-1.91 (10H, m, 5CH_2), 1.60 (3H, d, ^3J = 7.2, Me), 3.82 (1H, m, CH), 5.17 (1H, quintet, ^3J = 7.2, CH), 6.19 (1H, s, CH), 6.59 (1H, d, ^3J = 7.8, NH), 7.35-7.89 (10H, m, 5CH), 9.09 (1H, s, NH), 11.11(1H, d, ^3J = 7.2, NH). ^{13}C NMR: δ = 17.8 (Me), 25.3 (CH_2), 25.9 (2CH_2), 33.5 (2CH_2), 49.0 (CH), 54.6 (CH), 78.3 (CH), 127.8 (2CH), 127.9 (2CH), 129.1 (2CH), 129.5 (CH), 129.7 (2CH), 131.9 (C), 134.3 (CH), 135.9 (C), 167.3 (C=O), 169.9 (C=O), 170.5 (C=O), 180.8 (C=S).

2-(*tert*-Butylamino)-2-oxo-1-phenylethyl-2-(3-benzoyl-thioureido)propanoate (6l). Viscous oil; yield: 0.32 g (73%). IR (KBr): $\bar{\nu}$ = 3450, 3325, 3242, 1743, 1658, 1599, 1315, 1127 cm^{-1}. EI-MS: *m/z* (%) = 467 (M^+, 33), 251 (24), 234 (61), 217 (49), 105 (100), 84 (29), 77 (44), 44 (32). Anal. Calcd. for $C_{23}H_{27}N_3O_4S$ (441.52): C, 62.57; H, 6.16; N, 9.52 Found: C, 63.01; H, 6.39; N, 9.25. **6l-I** (55%) ^1H NMR: δ = 1.37 (9H, s, CMe_3), 1.69 (3H, d, ^3J = 7.2, Me), 5.18 (1H, quintet, ^3J = 7.2, CH), 6.04 (1H, s, CH), 6.16 (1H, s, NH), 7.38-7.89 (10H, m, 5CH), 9.07 (1H, s, NH), 11.15 (1H, d, ^3J = 7.2, NH). ^{13}C NMR: 17.4 (Me), 29.1 (C*Me*$_3$), 52.2 (*C*Me_3), 54.4 (CH), 76.8 (CH), 127.7 (2CH), 127.8 (2CH), 129.1 (2CH), 129.3 (2CH), 129.6 (CH), 131.8 (C), 134.2 (CH), 135.7 (C), 167.2 (C=O), 167.3 (C=O), 170.0 (C=O), 180.6 (C=S). **6l-II** (45%) ^1H NMR: δ = 1.43 (9H, m, CMe_3), 1.60 (3H, d, ^3J = 7.2, Me), 5.05 (1H, quintet, ^3J = 7.2, CH), 6.12 (1H, s, CH), 6.37 (1H, s, NH), 7.38-7.89 (10H, m, 5CH), 9.08 (1H, s, NH), 11.09 (1H, d, ^3J = 7.2, NH); ^{13}C NMR: δ = 17.8 (Me), 29.1 (C*Me*$_3$), 52.2 (*C*Me_3), 54.5 (CH), 77.0 (CH), 127.8 (2CH), 127.9 (2CH), 129.2 (2CH), 129.4 (2CH), 129.7 (CH), 131.9 (C), 134.3 (CH), 136.0 (C), 167.2 (C=O), 167.4 (C=O), 170.4 (C=O), 180.7 (C=S).

1-(Cyclohexylamino)-2-methyl-1-oxopropan-2-yl-3-methyl-2-(3-(4-methylbenzoyl)thioureido) butanoate (6m). White powder; yield: 0.41 g (89%). m.p.: 110-112 ºC; IR (KBr): $\bar{\nu}$ = 3444, 3423, 3256, 1737, 1657, 1598, 1335, 1100 cm^{-1}. EI-MS: *m/z* (%) = 461 (M^+, 29), 276 (21), 186 (19), 169 (83), 119 (100), 84 (17), 91 (43), 44 (31). Anal. Calcd. for $C_{24}H_{35}N_3O_4S$ (461.62): C, 62.44; H, 7.64; N, 9.10. Found: C, 61.88; H, 7.25; N, 9.29. ^1H NMR: δ = 1.12 (6H, d, ^3J = 6.9, 2Me), 1.10-1.90 (10H, m, 5CH_2), 1.64 (3H, s, Me), 1.66 (3H, s, Me), 2.42 (1H, m, CH), 2.46 (3H, s, Me), 3.73 (1H, m, CH), 4.75 (1H, dd, ^3J = 7.0, ^3J = 5.0, CH), 6.35 (1H, d, ^3J = 8.3, NH), 7.34 (2H, d, ^3J = 8.2, 2CH), 7.77 (2H, d, ^3J = 8.2, 2CH), 9.08 (1H, s, NH), 11.21 (1H, d, ^3J = 7.0, NH); ^{13}C NMR: δ = 18.6 (Me), 19.7 (Me), 22.1 (Me), 24.9 (CH_2), 25.3 (Me), 25.4 (Me), 25.5 (CH_2), 25.9 (CH_2), 30.9 (CH), 33.3 (2CH_2), 48.9 (CH), 64.7 (CH), 83.5 (C), 128.0 (2CH), 128.9 (2CH), 130.3 (C), 145.4 (C), 167.4 (C=O), 168.8 (C=O), 171.9 (C=O), 181.4 (C=S).

1-(Cyclohexylamino)-2-methyl-1-oxopropan-2-yl-2-(3-

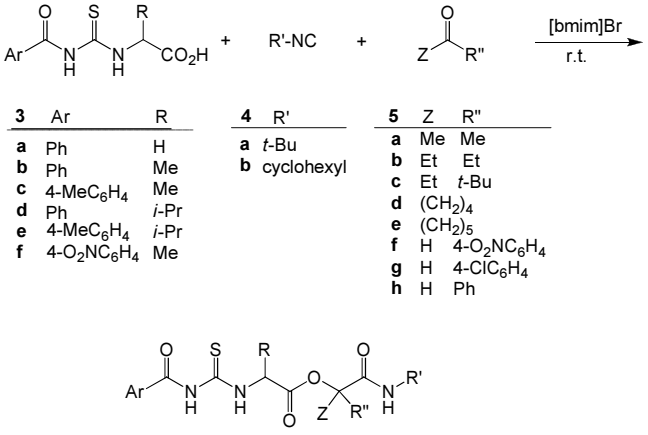
benzoylthioureido)acetate (6n). White powder; yield: 0.34 g (84%). m.p.: 120-122 ºC; IR (KBr): $\bar{\nu}$ = 3460, 3430, 3290, 1750, 1664, 1602, 1385, 1110 cm^{-1}. EI-MS: *m/z* (%) = 405 (M^+, 36), 220 (17), 186 (21), 169 (79), 105 (100), 84 (15), 77 (23), 44 (29). Anal. Calcd. for $C_{20}H_{27}N_3O_4S$ (405.49): C, 59.24; H, 7.42; N, 9.39. Found: C, 60.11; H, 7.54; N, 9.87. ^{1}H NMR: δ = 1.13-1.92 (10H, m, $5CH_2$), 1.67 (6H, s, 2Me), 3.74 (1H, m, CH), 4.46 (2H, d, ^3J = 5.5, CH_2), 6.19 (1H, d, ^3J = 8.2, NH), 7.55 (2H, t, ^3J = 7.8, 2CH), 7.67 (1H, t, ^3J = 7.8, CH), 7.88 (2H, d, ^3J = 7.8, 2CH), 9.15 (1H, s, NH), 11.16 (1H, d, ^3J = 5.5, NH). ^{13}C NMR: δ = 24.9 (2Me), 25.4 ($2CH_2$), 25.8 (CH_2), 33.3 ($2CH_2$), 47.9 (CH), 48.9 (CH_2), 84.0 (C), 127.9 (2CH), 129.6 (2CH), 131.8 (CH), 134.2 (C), 166.5 (C=O), 167.3 (C=O), 171.7 (C=O), 181.6 (C=S).

1-(Cyclohexylamino)-2-methyl-1-oxopropan-2-yl-2-(3-benzoylthioureido)-3-methylbutanoate (6o). White powder; yield: 0.42 g (94%). m.p.: 196-198 ºC; IR (KBr): $\bar{\nu}$ = 3430, 3341, 3238, 1746, 1677, 1611, 1377, 1134 cm^{-1}. EI-MS: *m/z* (%) = 447.57 (M^+, 27), 234 (22), 186 (18), 169 (87), 105 (100), 84 (17), 77 (30), 44 (29). Anal. Calcd. for $C_{23}H_{33}N_3O_4S$ (447.57): C, 61.72; H, 7.42; N, 9.39. Found: C, 62.12; H, 7.62; N, 9.51. ^{1}H NMR: δ = 1.13 (6H, d, ^3J = 6.9, 2Me), 1.08-1.90 (10H, m, $5CH_2$), 1.65 (3H, s, Me), 1.66 (3H, s, Me), 2.43 (1H, m, CH), 3.73 (1H, m, CH), 4.76 (1H, dd, ^3J = 6.9, ^3J = 4.9, CH), 6.33 (1H, d, ^3J 8.1, NH), 7.55 (2H, t, ^3J = 7.8, 2CH), 7.67 (1H, t, ^3J = 7.8, CH), 7.88 (2H, d, ^3J = 7.8, 2CH), 9.10 (1H, s, NH), 11.17 (1H, d, ^3J = 6.9, NH). ^{13}C NMR: δ = 18.6 (Me), 19.6 (Me), 24.8 (CH_2), 25.3 (Me), 25.4 (Me), 25.5 (CH_2), 25.9 (CH_2), 30.9 (CH), 33.3 ($2CH_2$), 48.9 (CH), 64.7 (CH), 83.5 (C), 127.9 (2CH), 129.6 (2CH), 131.8 (CH), 134.3 (C), 167.5 (C=O), 168.8 (C=O), 171.7 (C=O), 181.3 (C=S).

1-(Cyclohexylamino)-2-methyl-1-oxopropan-2-yl-2-(3-(4-nitrobenzoyl)thioureido)propanoate (6p). White powder; yield: 0.40 g (86%). m.p.: 196-198 ºC; IR (KBr): $\bar{\nu}$ = 3472, 3453, 3265, 1762, 1676, 1603, 1378, 1121 cm^{-1}. EI-MS: *m/z* (%) = 464 (M^+, 32), 279 (29), 186 (23), 169 (78), 150 (100), 122 (27), 84 (19), 44 (19). Anal. Calcd. for $C_{21}H_{28}N_4O_6S$ (464.52): C, 52.30; H, 6.07; N, 12.06. Found: C, 52.95; H, 6.24; N, 12.18. ^{1}H NMR: δ = 1.11-1.93 (10H, m, $5CH_2$), 1.64 (3H, d, ^3J = 7.0, Me), 1.66 (6H, br s, 2Me), 3.75 (1H, m, CH), 4.94 (1H, quintet, ^3J = 7.0, CH), 6.12 (1H, d, ^3J = 8.1, NH), 8.07 (2H, d, ^3J = 9.0, 2CH), 8.38 (2H, d, ^3J = 9.0, 2CH), 9.23 (1H, s, NH), 10.88 (1H, d, ^3J = 7.0, NH). ^{13}C NMR: δ = 17.5 (Me), 24.7 (CH_2), 25.3 (Me), 25.4 (Me), 25.9 ($2CH_2$), 33.3 ($2CH_2$), 48.9 (CH), 54.9 (CH), 83.4 (C), 124.7 (2CH), 129.3 (2CH), 137.4 (C), 151.1 (C), 165.3 (C=O), 169.9 (C=O), 171.6 (C=O), 180.0 (C=S).

RESULTS AND DISCUSSION

The *N*-protected α-amino acids **3a-3f** were prepared according to literature [24]. Compounds **3a-3f** were employed as an acid component in the Passerini reaction with alkyl isocyanides **4** and appropriate oxo components **5**. These three-component reactions proceeded smoothly and led to functionalized α-acyloxycarboxathioamides **6a-6p** in 59-95% yields (Scheme 1). Structures of compounds **6a-6p** were characterized by their IR, ^{1}H NMR and ^{13}C NMR spectral data. The mass spectra of compounds **6a-6p** displayed molecular ion peaks at appropriate *m/z* values. The IR and



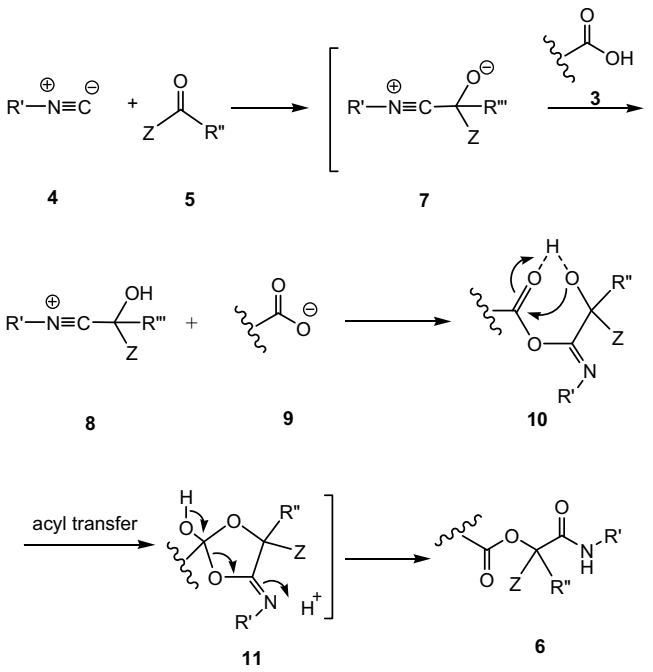
3	Ar	R
a	Ph	H
b	Ph	Me
c	4-MeC_6H_4	Me
d	Ph	*i*-Pr
e	4-MeC_6H_4	*i*-Pr
f	4-$O_2NC_6H_4$	Me

4	R'
a	*t*-Bu
b	cyclohexyl

5	Z	R"
a	Me	Me
b	Et	Et
c	Et	*t*-Bu
d	$(CH_2)_4$	
e	$(CH_2)_5$	
f	H	4-$O_2NC_6H_4$
g	H	4-ClC_6H_4
h	H	Ph

6	Ar	R	R'	Z	R"	Yield (%)
a	Ph	Me	cyclohexyl	Me	Me	90
b	Ph	Me	*t*-Bu	Me	Me	95
c	Ph	Me	cyclohexyl	Et	Et	85
d	Ph	Me	cyclohexyl	*i*-Pr	*i*-Pr	89
e	Ph	Me	cyclohexyl	$(CH_2)_5$		90
f	Ph	Me	cyclohexyl	$(CH_2)_4$		87
g	4-MeC_6H_4	Me	cyclohexyl	$(CH_2)_5$		86
h	Ph	Me	*t*-Bu	H	4-$O_2NC_6H_4$	83
i	Ph	H	*t*-Bu	H	4-ClC_6H_4	59
j	Ph	Me	*t*-Bu	H	4-ClC_6H_4	63
k	Ph	Me	cyclohexyl	H	Ph	60
l	Ph	Me	*t*-Bu	H	Ph	73
m	4-MeC_6H_4	*i*-Pr	cyclohexyl	Me	Me	89
n	Ph	H	cyclohexyl	Me	Me	84
o	Ph	*i*-Pr	cyclohexyl	Me	Me	94
p	4-$O_2NC_6H_4$	Me	cyclohexyl	Me	Me	86

Scheme 1



Scheme 2

^{1}H NMR spectra of **6a-6p** exhibited characteristic peaks for the NH groups. The ^{1}H NMR spectrum of **6a** in $CDCl_3$ showed two doublets (δ= 6.25, 11.04 ppm), and a singlet (δ= 9.07 ppm) for NH groups. The methyl protons exhibited a doublet (δ= 1.64 ppm) and two singlets (δ= 1.65, 1.67 ppm). The ^{1}H-decoupled ^{13}C NMR spectrum of **6a** showed 18 signals which further confirmed the proposed structure. Partial assignments of aromatic and cyclohexyl resonances are given in the Experimental section. The ^{13}C NMR spectra of **6a-6p** showed four distinct resonances for C=O and C=S groups.

Compounds **6h** and **6j-6l** possess two stereogenic centers, and exist as a mixture of two diastereoisomers. In fact, the NMR spectra of these compounds are consistent with the presence of the two diastereoisomers (see Experimental).

Although the mechanistic details of the above reaction are unknown, a plausible pathway may be advanced to rationalize the product formation (Scheme 2). Presumably, a zwitterionic intermediate such as **7**, formed from isocyanide **4** and oxo compound **5**, is protonated by **3** to furnish the intermediate **8**, which is then attacked by anionic **9** to produce imidoylanhydride **10**. The latter would then undergo acyl transfer reaction to form dioxolane derivative 11, which is converted to α-acyloxycarboxathioamides **6** by ring opening.

In conclusion, we have reported a simple and highly efficient one-pot approach to the synthesis of complex α-acyloxycarboxathioamides **6** from simple and readily available inputs without any activation or modification. The work-up procedure was fairly simple and the products did not require further purification.

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