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Solvent-free one-pot synthesis of highly functionalized benzothiazolediamides via Ugi four-component reaction

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4-Benzothiazol-2-ylamino-4-oxo-2-butenoic acid, prepared by reaction of 2-aminobenzothiazole and maleic anhydride, is used as an acid component in Ugi reaction, under solvent-free conditions, to produce unsaturated α-benzothiazoleamidodipeptides in good yields using a tandem sequence.

Keywords: Ugi reaction, One-pot, Maleic anhydride, 2-Aminobenzothiazole, Solvent-free.

INTRODUCTION

There has been tremendous interest in developing highly efficient transformations for the preparation of organic compounds and biologically active materials with potential application in the pharmaceutical or agrochemical industries from commercially available compounds. There is also a need for synthetic chemists to find new, efficient, and strategically important processes, which are environmentally benign and lead to greater structural variation in a short period of time with high yields and simple work-up procedures. Significant advances have been made to chemical processes to achieve the ultimate goal of hazard-free, waste-free, and energy-efficient syntheses [1]. In this context, multicomponent reactions [2-7] have played an important role in these processes [8]. The Ugi four-component reaction (U-4CR) [9] is one of the milestones in this field and great efforts have been devoted to the exploration of the potential of this transformation [10]. In the U-4CR, a primary amine, an aldehyde, a carboxylic acid and an isocyanide react simultaneously to afford peptide-like structures in high diversity. Small peptides (oligopeptides) are a group of omnipresent compounds in medicinal chemistry. Among them, compounds with various activities can be found [11-17]. Thus, the synthesis of α-benzothiazoleamidodipeptides that mimic natural dipeptides, is very attractive. In recent years several modifications of the classical U-4CR have been described. Such modifications include variations of one of the components or the introduction of a linkage between two of them [18], the use of polyfunctional building blocks [19, 20] and the employment of non-classical starting units [21]. As part of our continuing interest in isocyanide-based multi-component reactions [22-24], we describe the synthesis of a dipeptide mimetic library based on 4-benzothiazol-2-ylamino-4-oxo-2-butenoic acid, as a new acid component in the Ugi reaction under solvent-free conditions in a tandem reaction (Scheme 1).

EXPERIMENTAL

Apparatus and analysis

Amines, alkyl isocyanide**s**, and ketones were obtained from Merck and were used without further purification. 4-Benzothiazol-2-ylamino-4-oxo-2-butenoic acid was synthesized by reaction of 2-aminobenzothiazole and furan-2,5-dione. Melting points were recorded on 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 performed with a Heraeus CHN-O-Rapid analyzer.

*General procedure for preparation of compound **1***

A mixture of 2-aminobenzothiazole (0.30 g, 2 mmol) and maleic anhydride (0.20 g, 2 mmol) in 5 mL of CH_3CN was stirred for 12 h at r.t. The yellow precipitate was filtered and washed with cold CH_3CN. The product 1 was used in the next step without further purification.

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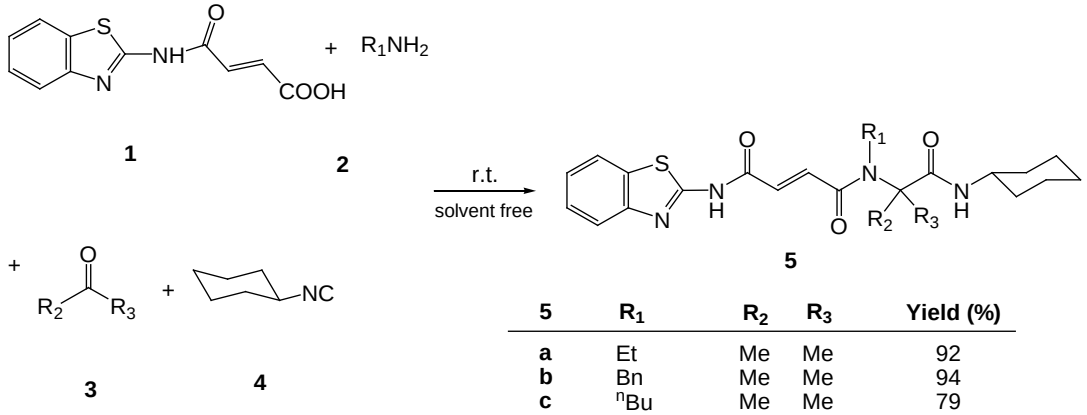
General procedure for the preparation of compounds 5

The carboxylic acid (**1**, 1 mmol) was added to a mixture of amine (**2,** 1 mmol) and 0.5 ml (excess) of ketone or aldehyde **3**. Then, the alkyl isocyanide (**4**, 1 mmol) was added. The mixture was stirred for 12 h at r.t. The volatiles were evaporated under reduced pressure at 50 ºC to leave a residue that was purified by column chromatography (SiO_2; hexane/EtOAc 5:2) to afford pure desired products.



5	R_1	R_2	R_3	Yield (%)
a	Et	Me	Me	92
b	Bn	Me	Me	94
c	^{n}Bu	Me	Me	79
d	Et	Me	Et	92
e	Bn	Me	Et	90
f	^{n}Bu	Me	Et	80
g	Et	Et	Et	87
h	Bn	Et	Et	90
i	^{n}Bu	Et	Et	83
j	Et	$(CH_2)_5$		85
k	Bn	$(CH_2)_5$		82
l	^{n}Bu	$(CH_2)_5$		78
m	Et	$(CH_2)_4$		87
n	Bn	$(CH_2)_4$		90
o	^{n}Bu	$(CH_2)_4$		75

Scheme 1. Ugi reaction of isocyanide and ketones in the presence of amines.

N_1-(Benzothiazol-2-yl)-N_4-(1-(cyclohexylamino)-2-methyl-1-oxopropan-2-yl)-N_4-ethyl fumaramide (5a)

Light yellow solid; m.p: 160-163 ºC; yield: 0.40 g (92%); IR (KBr): (ν_{max}/cm^{-1}) = 3365, 3173, 1637, 1543, 1435, 1266, 1180, 754; EI-MS: *m/z* (%) = 442 (M^+, 1.2), 294 (32), 231 (58), 211 (18), 168 (24), 148 (100), 29 (23); Anal. calcd. for $C_{23}H_{30}N_4O_3S$ (442.57): C, 62.42; H, 6.83; N, 12.66; Found: C, 62.58; H, 7.04; N, 12.98%; ^{1}H NMR ($CDCl_3$): δ = 1.16-1.97 (10 H, m, 5 CH_2), 1.20 (3 H, t, ^3J 6.9 Hz, CH_3), 1.45 (6 H, s, 2 CH_3), 3.54 (2 H, q, ^3J 6.9 Hz, CH_2N), 3.79-3.82 (1 H, m, CH), 6.40 (1 H, d, ^3J 12.0 Hz, CH), 6.65 (1 H, d, ^3J 12.0 Hz, CH), 6.86 (1 H, d, ^3J 8.6 Hz, NH), 7.28-7.84 (4 H, m, 4 CH), 8.53 (1 H, br s, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 17.1 (CH_3), 25.2 (CH_2), 25.8 (2 CH_3), 26.0 (2 CH_2), 33.0 (2 CH_2), 40.9 (CH_2), 49.4 (CH), 63.1 (C), 120.9 (CH), 121.8 (CH), 123.7 (CH), 124.9 (CH), 127.1 (CH), 131.9 (CH), 139.4 (C), 147.6 (C), 158.9 (C=N), 163.1 (C=O), 167.4 (C=O), 174.3 (C=O) ppm.

N_1-(Benzothiazol-2-yl)-N_4-benzyl-N_4-(1-(cyclohexylamino)-2-methyl-1-oxopropan-2-yl) fumaramide (5b)

Light yellow solid; m.p: 180-182 ºC; yield: 0.47 g (94%); IR (KBr): (ν_{max}/cm^{-1}) = 3347, 3127, 1655, 1635, 1550, 1266, 1173; EI-MS: *m/z* (%) = 504 (M^+, 1), 355 (23), 273 (22), 231 (26), 168 (10), 148 (100), 91 (59); Anal. calcd. for $C_{28}H_{32}N_4O_3S$ (504.64): C, 66.64; H, 6.39; N, 11.10; Found: C, 66.89; H, 6.94; N, 11.73%; ^{1}H NMR ($CDCl_3$): δ = 1.19-2.01 (10 H, m, 5 CH_2), 1.56 (6 H, s, 2 CH_3), 3.83-3.86 (1 H, m, CH), 4.78 (2 H, s, CH_2N), 6.22 (1 H, d, ^3J 16.0 Hz, CH), 6.61 (1 H, d, ^3J 16.0 Hz, CH), 6.66 (1 H, br s, NH), 7.36-7.86 (9 H, m, 9 CH), 8.61 (1 H, br s, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 25.0 (2 CH_3), 25.8 (2 CH_2), 26.0 (CH_2), 33.1 (2 CH_2), 49.3 (CH_2N), 50.3 (CH), 63.9 (C), 121.1 (CH), 122.8 (CH), 124.4 (CH), 124.8 (CH), 126.6 (2 CH), 126.9 (CH), 127.5 (C), 127.9 (CH), 129.3 (2 CH), 132.2 (CH), 138.1 (C), 148.1 (C), 158.9 (C=N), 163.2 (C=O), 168.2 (C=O), 174.0 (C=O) ppm.

N_1-(Benzo[d]thiazol-2-yl)-N_4-butyl-N_4-(1-(cyclohexylamino)-2-methyl-1-oxopropan-2-yl)fumaramide (5c)

Light yellow solid; m.p: 160-163 ºC; yield: 0.37 g (79%); IR (KBr): (ν_{max}/cm^{-1}) = 3382, 3214, 1782, 1659, 1543, 1252, 1183; EI-MS: *m/z* (%) = 470 (M^+, 1.4), 320 (25), 239 (19), 231 (56), 168 (20), 148 (100), 57 (24); Anal. calcd. for $C_{25}H_{34}N_4O_3S$ (470.24): C, 63.42; H, 6.83; N, 12.66; Found: C, 63.98; H, 7.24; N, 13.08%; ^{1}H NMR ($CDCl_3$): δ = 0.93 (3 H, t, ^3J 6.9 Hz, CH_3), 1.13-1.95 (14 H, m, 7 CH_2), 1.62 (6 H, s, 2 CH_3), 3.45 (2 H, t, ^3J 7.2 Hz, CH_2N), 3.81-3.84 (1 H, m, CH), 6.48 (2 H, ABq, ^3J 12.1 Hz, Δν 96.3 Hz, 2 CH), 6.85 (1 H, d, ^3J 7.8 Hz, NH), 7.38 (1 H, t, ^3J 7.3 Hz, CH), 7.46 (1 H, t, ^3J 7.6 Hz, CH), 7.82 (1 H, d, ^3J 7.3 Hz, CH), 7.85 (1 H, d, ^3J 7.6 Hz, CH), 10.95 (1 H, br s, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 12.9 (CH_3), 19.1 (CH_2), 23.9 (CH_2), 25.1 (CH_2), 25.5 (2 CH_3), 26.1 (2 CH_2), 33.2 (2 CH_2), 44.5 (CH_2), 49.5 (CH), 64.3 (C), 121.5 (CH), 122.0 (CH), 123.6 (CH), 125.1 (CH), 126.8 (CH), 130.8 (CH), 138.5 (C), 145.7 (C), 158.5 (C=N), 162.5 (C=O), 166.7 (C=O), 174.2 (C=O) ppm.

N1-(Benzo[d]thiazol-2-yl)-N4-(1-(cyclohexylamino)-2-methyl-1-oxobutan-2-yl)-N4-ethyl fumaramide (5d)

Light yellow solid; m.p: 229-230 ºC; yield: 0.43 g (92%); IR (KBr): (ν_{max}/cm^{-1}) = 3410, 3207, 1665, 1557, 1432, 1244, 1174; EI-MS: *m/z* (%) = 456 (M^+, 1.5), 330 (16), 306 (26), 231 (60), 225 (28), 182 (22), 148 (100), 29 (18); Anal. calcd. for $C_{24}H_{32}N_4O_3S$ (456.60): C, 63.13; H, 7.06; N, 12.27; Found: C, 63.98; H, 7.54; N, 12.98%; ^{1}H NMR ($CDCl_3$): δ = 0.93 (3 H, t, ^3J 7.3 Hz, CH_3), 1.20-1.98 (10 H, m, 5 CH_2), 1.24 (3 H, t, ^3J 7.0 Hz, CH_3), 1.27 (2 H, q, ^3J 7.3 Hz, CH_2), 1.58 (3 H, s, CH_3), 3.52 (2 H, q, ^3J 7.0 Hz, CH_2N), 3.78-3.84 (1 H, m, CH), 6.32 (1 H, d, ^3J 12.1 Hz, CH), 6.68 (1 H, d, ^3J 12.1 Hz, CH), 6.75 (1 H, d, ^3J 7.3 Hz, NH), 7.38 (1 H, t, ^3J 7.5 Hz, CH), 7.48 (1 H, t, ^3J 8.0 Hz, CH), 7.81 (1 H, d, ^3J 8.0 Hz, CH), 7.84 (1 H, d, ^3J 7.5 Hz, CH), 11.96 (1 H, br s, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 10.8 (CH_3), 17.6 (CH_3), 24.8 (2 CH_2), 25.3 (CH_3), 25.5 (CH_2), 26.0 (CH_2), 32.5 (2 CH_2), 41.7 (CH_2), 50.1 (CH), 64.6 (C), 119.8 (CH), 121.8 (CH), 124.6 (CH), 125.8 (CH), 126.5 (CH), 131.6 (CH), 138.2 (C), 145.8 (C), 159.1 (C=N), 162.4 (C=O), 166.5 (C=O), 173.2 (C=O) ppm.

N_1-(Benzo[d]thiazol-2-yl)-N_4-benzyl-N_4-(1-(cyclohexylamino)-2-methyl-1-oxobutan-2-yl) fumaramide (5e)

Light yellow solid; m.p: 179-181 ºC; yield: 0.47 g (90%); IR (KBr): (ν_{max}/cm^{-1}) = 3337, 3118, 1645, 1624, 1540, 1256, 1163; EI-MS : *m/z* (%) = 518 (M^+, 1.3), 392 (23), 368 (25), 287 (31), 231 (29), 182 (11), 148 (100), 91 (61), 29 (8); Anal. calcd. for $C_{29}H_{34}N_4O_3S$ (518.67): C, 67.15; H, 6.61; N, 10.81; Found: C, 67.45; H, 7.01; N, 10.89%; ^{1}H NMR ($CDCl_3$): δ = 0.91 (3 H, t, ^3J 7.1 Hz, CH_3), 1.11-1.93 (10 H, m, 5 CH_2), 1.46 (3 H, s, CH_3), 1.77 (2 H, q, ^3J 7.2 Hz, CH_2), 3.73-3.76 (1 H, m, CH), 4.65 (2 H, s, CH_2N), 6.33 (1 H, d, ^3J 16.0 Hz, CH), 6.71 (1 H, d, ^3J 16.0 Hz, CH), 6.86 (1 H, br s, NH), 7.21-7.88 (9 H, m, 9 CH), 9.51 (1 H, br s, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 9.9 (CH_3), 21.2 (CH_3), 24.8 (2 CH_2), 25.7 (CH_2), 27.4 (CH_2), 33.3 (2 CH_2), 46.6 (CH_2N), 50.3 (CH), 72.3 (C), 119.3 (CH), 121.8 (CH), 123.3 (CH), 124.5 (CH), 127.0 (CH), 127.9 (2 CH), 128.5 (2 CH), 130.8 (C), 134.5 (2 CH), 138.4 (C), 149.2 (C), 158.8 (C=N), 162.2 (C=O), 166.3 (C=O), 174.0 (C=O) ppm.

N_1-(Benzo[d]thiazol-2-yl)-N_4-butyl-N_4-(1-(cyclohexylamino)-2-methyl-1-oxobutan-2-yl) fumaramide (5f)

Light yellow solid; m.p: 170-172 ºC; yield: 0.39 g (80%); IR (KBr): (ν_{max}/cm^{-1}) = 3378, 3185, 1746, 1672, 1590, 1251, 1143; EI-MS: *m/z* (%) = 484 (M^+, 1.5), 358 (18), 333 (27), 253 (38), 231 (51), 182 (23), 148 (100), 57 (21), 29 (10); Anal. calcd. for $C_{26}H_{36}N_4O_3S$ (484.65): C, 64.43; H, 7.49; N, 11.56; Found: C, 63.95; H, 7.85; N, 11.23 %; ^{1}H NMR ($CDCl_3$): δ = 0.91 (3 H, t, ^3J 7.1 Hz, CH_3), 0.94 (3 H, t, ^3J 6.9 Hz, CH3), 1.10-1.95 (14 H, m, 7 CH_2), 1.44 (3 H, s, CH_3), 1.76 (2 H, q, ^3J 7.2 Hz, CH_2), 3.60 (2 H, t, ^3J 7.2 Hz, CH_2N), 3.81-3.84 (1 H, m, CH), 6.48 (2 H, ABq, ^3J 12.1 Hz, Δν 96.3 Hz, 2 CH), 6.86 (1 H, d, ^3J 7.8 Hz, NH), 7.38 (1 H, t, ^3J 7.3 Hz, CH), 7.46 (1 H, t, ^3J 7.6 Hz, CH), 7.82 (1 H, d, ^3J 7.3 Hz, CH), 7.85 (1 H, d, ^3J 7.6 Hz, CH), 10.93 (1 H, br s, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 9.5 (CH3), 13.6 (CH3), 20.1 (CH_2), 24.2 (CH_2), 25.1 (2 CH_2), 25.7 (CH_3), 26.1 (CH_2), 29.5 (CH_2), 33.2 (2 CH_2), 44.5 (CH_2N), 49.8 (CH), 70.3 (C), 121.4 (CH), 122.2 (CH), 123.5 (CH), 125.6 (CH), 126.9 (CH), 130.7 (CH), 138.5 (C), 146.3 (C), 159.3 (C=N), 163.5 (C=O), 165.7 (C=O), 174.1 (C=O) ppm.

N_1-(Benzothiazol-2-yl)-N_4-(3-(cyclohexylcarbamoyl)pentan-3-yl)-N_4-ethylfumaramide (5g)

Light yellow solid; mp: 160-163 ºC; yield: 0.43 g (87%); IR (KBr): (ν_{max}/cm^{-1}) = 3380, 3187, 1742, 1674, 1592, 1257, 1148; EI-MS: *m/z* (%) = 470 (M^+, 1.1), 344 (17), 320 (25), 239 (36), 231 (49), 196 (21), 148 (100), 29 (19); Anal. calcd. for $C_{25}H_{34}N_4O_3S$ (470.63): C, 63.80; H, 7.28; N, 11.90; Found: C, 64.08; H, 8.78; N, 12.28%; ^{1}H NMR ($CDCl_3$): δ = 0.89 (6 H, t, ^3J 7.2 Hz, 2 CH_3), 1.08-1.97 (10 H, m, 5 CH_2), 1.31 (3 H, t, ^3J 6.7 Hz, CH3), 1.77 (2 H, q, ^3J 7.3 Hz, 2 CH_2), 3.50 (2 H, q, ^3J 6.7 Hz, CH_2N), 3.79-3.81 (1 H, m, CH), 6.18 (1 H, br s, NH), 6.56 (2 H, ABq, ^3J 12.5 Hz, Δν 139.0 Hz, 2 CH), 7.37-7.87 (4 H, m, 4 CH), 11.51 (1 H, br s, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 11.8 (2 CH_3), 17.6 (CH_3), 25.8 (2 CH_2), 26.1 (CH_2), 30.6 (2 CH_2), 33.5 (2 CH_2), 40.9 (CH_2), 49.3 (CH), 67.6 (C), 120.5 (CH), 122.1 (CH), 124.7 (CH), 124.8 (CH), 126.7 (CH), 131.5 (CH), 138.4 (C), 145.7 (C), 158.6 (C=N), 163.4 (C=O), 166.4 (C=O), 172.4 (C=O) ppm.

N_1-(Benzo[d]thiazol-2-yl)-N_4-benzyl-N_4-(3-(cyclohexylcarbamoyl)pentan-3-yl)fumaramide (5h)

Light yellow solid; m.p: 183-185 ºC; yield: 0.48 g (90%); IR (KBr): (ν_{max}/cm^{-1}) = 3340, 3125, 1658, 1629, 1540, 1262, 1175; EI-MS: *m/z* (%) = 532 (M^+, 1.5), 406 (25), 382 (22), 301 (20), 231 (28), 196 (12), 148 (100), 91 (58), 29 (15); Anal. calcd. for $C_{30}H_{36}N_4O_3S$ (532.7): C, 67.64; H, 6.81; N, 10.52; Found: C, 67.04; H, 6.92; N, 10.32 %; ^{1}H NMR ($CDCl_3$): δ = 0.93 (6 H, t, ^3J 7.2 Hz, 2CH3), 1.19-2.02 (10 H, m, 5 CH_2), 1.76 (4 H, t, ^3J 7.3 Hz, 2 CH_2), 3.83-3.86 (1 H, m, CH), 4.78 (2 H, s, CH_2N), 6.22 (1 H, d, ^3J 16.0 Hz, CH), 6.61 (1 H, d, ^3J 16.0 Hz, CH), 6.66 (1 H, br s, NH), 7.36-7.86 (9 H, m, 9 CH), 8.72 (1 H, br s, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 10.4 (2 CH_3), 24.9 (2 CH_2), 25.8 (2 CH_2), 26.0 (CH_2), 33.1 (2 CH_2), 49.3 (CH_2N), 50.3 (CH), 74.5 (C), 122.1 (CH), 124.5 (CH), 124.8 (CH), 124.9 (CH), 126.7 (2 CH), 126.9 (CH), 127.5 (C), 127.9 (CH), 129.4 (2 CH), 132.3 (CH), 138.2 (C), 149.1 (C), 158.9 (C=N), 164.2 (C=O), 168.3 (C=O), 174.1 (C=O) ppm.

N_1-(Benzo[d]thiazol-2-yl)-N_4-butyl-N_4-(3-(cyclohexylcarbamoyl)pentan-3-yl) fumaramide (5i)

Cream powder; m.p: 165-167 ºC; yield: 0.41 g (83%.); IR (KBr): (ν_{max}/cm^{-1}) = 3370, 3185, 1740, 1672, 1590, 1253, 1143; EI-MS: *m/z* (%) = 498 (M^+, 1.2), 372 (18), 348 (26), 267 (37), 231 (50), 196 (22), 148 (100), 57 (21), 29 (15); Anal. calcd. for $C_{27}H_{38}N_4O_3S$ (498.68): C, 65.03; H, 7.68; N, 11.24; Found: C, 64.54; H, 7.86; N, 11.35 %; ^{1}H NMR ($CDCl_3$): δ = 0.90 (6 H, t, ^3J 7.2 Hz, 2 CH_3), 0.93 (3 H, t, ^3J 6.9 Hz, CH_3), 1.08-1.97 (14 H, m, 7 CH_2), 1.75 (4 H, t, ^3J 7.2 Hz, 2 CH_2), 3.50 (2 H, t, ^3J 6.7 Hz, CH_2N), 3.79-3.81 (1 H, m, CH), 6.18 (1 H, br s, NH), 6.58 (2 H, ABq, ^3J 12.5 Hz, Δν 139.0 Hz, 2 CH), 7.37-7.87 (4 H, m, 4 CH), 11.45 (1 H, br s, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 10.5 (2 CH3), 13.5 (CH3), 20.1 (CH_2), 24.7 (2 CH_2), 25.6 (CH_2), 27.2 (2 CH_2), 29.5 (CH_2), 33.3 (2 CH_2), 43.9 (CH_2N), 49.5 (CH), 65.6 (C), 121.5 (CH), 122.0 (CH), 123.6 (CH), 125.1 (CH), 126.8 (CH), 130.8 (CH), 138.5 (C), 145.7 (C), 158.5 (C=N), 162.5 (C=O), 166.7 (C=O), 174.2 (C=O) ppm.

N_1-(Benzothiazol-2-yl)-N_4-(1-(cyclohexylcarbamoyl)cyclohexyl)-N_4-ethylfumaramide (5j)

Light yellow solid; m.p: 167-169 ºC; yield: 0.41 g (85%); IR (KBr): (ν_{max}/cm^{-1}) = 3380, 3173, 1732, 1631, 1542, 1265, 1164; EI-MS: *m/z* (%) = 482 (M^+, 1.8), 356 (15), 332 (24), 251 (30), 231 (58), 208 (18), 148 (100), 83 (17), 29 (16); Anal. calcd. for $C_{26}H_{34}N_4O_3S$ (482.64): C, 64.70; H, 7.10; N, 11.16; Found: C, 64.93; H, 7.35; N, 11.03%; ^{1}H NMR ($CDCl_3$): δ = 1.12-2.20 (20 H, m, 10 CH_2), 1.35 (3 H, t, ^3J 7.0 Hz, CH_3), 3.71 (2 H, q, ^3J 7.0 Hz, CH_2N), 3.79-3.82 (1 H, m, CH), 6.54 (2 H, ABq, ^3J 12.2 Hz, Δν 108.6 Hz, 2 CH), 7.05 (1 H, d, ^3J 8.3 Hz, NH), 7.32-7.90 (4 H, m, 4 CH), 9.89 (1 H, br s, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 16.5 (CH3), 21.6 (2 CH_2), 24.7 (2 CH_2), 25.3 (CH_2), 26.0 (CH_2), 31.2 (2 CH_2), 33.1 (2 CH_2), 41.5 (CH_2N), 50.2 (CH), 69.5 (C), 121.0 (CH), 122.5 (CH), 123.9 (CH), 125.8 (CH), 127.7 (CH), 131.4 (CH), 134.9 (C), 144.9 (C), 158.9 (C=N), 162.5 (C=O), 166.1 (C=O), 172.6 (C=O) ppm.

N_1-(Benzo[d]thiazol-2-yl)-N_4-benzyl-N_4-(1-(cyclohexylcarbamoyl)cyclohexyl)fumaramide (5k)

Light yellow solid; m.p: 187-189 ºC; yield: 0.45 g (82%); IR (KBr): (ν_{max}/cm^{-1}) = 3352, 3127, 1655, 1634, 1542, 1258, 1174; EI-MS: *m/z* (%) = 544 (M^+, 1.1), 394 (25), 313 (20), 231 (28), 208 (15), 148 (100), 91 (57); Anal. calcd. for $C_{31}H_{36}N_4O_3S$ (544.71): C, 68.35; H, 6.66; N, 10.29; Found: C, 68.75; H, 7.11; N, 10.39%; ^{1}H NMR ($CDCl_3$): δ = 1.09-2.35(20 H, m, 10 CH_2), 3.74-3.77 (1 H, m, CH), 4.35 (2 H, s, CH_2N), 6.25 (1 H, d, ^3J 16.0 Hz, CH), 6.53 (1 H, d, ^3J 16.0 Hz, CH), 6.85 (1 H, br s, NH), 7.21-7.88 (9 H, m, 9 CH), 9.65 (1 H, br s, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 21.5 (2 CH_2), 24.6 (2 CH_2), 25.8 (CH_2), 26.2 (CH_2), 33.1 (2 CH_2), 34.2 (2CH_2), 47.8 (CH_2N), 49.9 (CH), 69.2 (C),

120.1 (CH), 121.8 (CH), 124.2 (CH), 124.6 (CH), 126.7 (2 CH), 126.9 (CH), 127.8 (CH), 129.2 (2 CH), 132.2 (CH), 135.3 (C), 138.4 (C), 149.5 (C), 158.8 (C=N), 162.9 (C=O), 165.6 (C=O), 173.7 (C=O) ppm.

N1-(Benzo[d]thiazol-2-yl)-N4-butyl-N4-(1-(cyclohexylcarbamoyl)cyclohexyl)fumaramide (5l)

Cream powder; m.p: 170-172 ºC; yield: 0.40 g (78%); IR (KBr): (ν_{max}/cm^{-1}) = 3382, 3217, 1782, 1651, 1545, 1258, 1176; EI-MS: *m/z* (%) = 510 (M^+, 1.6), 360 (24), 279 (19), 231 (58), 208 (22), 148 (100), 57 (26); Anal. calcd. for $C_{28}H_{38}N_4O_3S$ (510.69): C, 65.85; H, 7.50; N, 10.97; Found: C, 66.13; H, 7.78; N, 10.82%; ^{1}H NMR ($CDCl_3$): δ = 0.94 (3 H, t, ^3J 6.8 Hz, CH_3), 1.11-2.22 (24 H, m, 12 CH_2), 3.29 (2 H, t, ^3J 7.2 Hz, CH_2N), 3.65-3.68 (1 H, m, CH), 6.52 (2 H, ABq, ^3J 12.1 Hz, Δν 96.4 Hz, 2 CH), 6.93 (1 H, d, ^3J 7.8 Hz, NH), 7.36 (1 H, t, ^3J 7.3 Hz, CH), 7.44 (1 H, t, ^3J 7.6 Hz, CH), 7.79 (1 H, d, ^3J 7.3 Hz, CH), 7.89 (1 H, d, ^3J 7.6 Hz, CH), 10.75 (1 H, br s, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 12.7 (CH_3), 19.5 (CH_2), 20.9 (2 CH_2), 24.7 (2 CH_2), 25.0 (CH_2), 25.6 (CH_2), 26.2 (CH_2), 30.3 (2 CH_2), 33.2 (2 CH_2), 43.8 (CH_2N), 49.9 (CH), 68.9 (C), 120.3 (CH), 122.2 (CH), 123.8 (CH), 125.7 (CH), 127.8 (CH), 132.8 (CH), 138.6 (C), 148.8 (C), 158.8 (C=N), 163.5 (C=O), 164.7 (C=O), 173.7 (C=O) ppm.

N_1-(Benzothiazol-2-yl)-N_4-(1-(cyclohexylcarbamoyl)cyclopentyl)-N_4-ethylfumaramide (5m)

Cream powder; mp: 160-163 ºC; yield: 0.43 g (87%); IR (KBr): (ν_{max}/cm^{-1}) = 3371, 3174, 1734, 1634, 1543, 1262, 1167; EI-MS: *m/z* (%) = 468 (M^+, 1.8), 342 (12), 319 (23), 237 (27), 231 (56), 194 (16), 148 (100), 29 (15); Anal. calcd. for $C_{25}H_{32}N_4O_3S$ (468.61): C, 64.08; H, 6.88; N, 11.96; Found: C, 64.38; H, 7.04; N, 12.08%; ^{1}H NMR ($CDCl_3$): δ = 1.23 (3 H, t, ^3J 7.0 Hz, CH3), 1.38 (4 H, t, ^3J 9.1 Hz, 2 CH_2), 1.41-2.74 (14 H, m, 7 CH_2), 3.51 (2 H, q, ^3J 7.0 Hz, CH_2N), 3.78-3.80 (1 H, m, CH), 6.54 (2 H, ABq, ^3J 12.2 Hz, Δν 108.6 Hz, 2 CH), 7.01 (1 H, d, ^3J 8.3 Hz, NH), 7.34-7.90 (4 H, m, 4 CH), 11.91 (1 H, br s, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 19.2 (CH_3), 25.1 (2 CH_2), 25.8 (2 CH_2), 26.0 (CH_2), 33.1 (2 CH_2), 35.4 (2 CH_2), 41.5 (CH_2), 49.3 (CH), 73.7 (C), 121.1 (CH), 122.4 (CH), 123.8 (CH), 125.6 (CH), 127.8 (CH), 130.4 (CH), 132.9 (C), 143.9 (C), 158.9 (C=N), 163.3 (C=O), 164.8 (C=O), 172.2 (C=O) ppm.

N1-(Benzo[d]thiazol-2-yl)-N4-benzyl-N4-(1-(cyclohexylcarbamoyl)cyclopentyl)fumaramide (5n)

Cream powder; m.p: 182-184 ºC; yield: 0.48 g (90%.); IR (KBr): (ν_{max}/cm^{-1}) = 3350, 3125, 1653, 1632, 1540, 1256, 1172; EI-MS: *m/z* (%) = 530 (M^+, 1.2), 380 (22), 299 (25), 231 (29), 194 (12), 148 (100), 91 (54); Anal. calcd for $C_{30}H_{34}N_4O_3S$ (530.68): C, 67.83; H, 6.46; N, 10.56; Found: C, 67.85; H, 6.57; N, 10.73%; ^{1}H NMR ($CDCl_3$): δ = 1.19-2.25 (18 H, m, 9 CH_2), 3.84-3.87 (1 H, m, CH), 4.67 (2 H, s, CH_2N), 6.13 (1 H, d, ^3J 16.0 Hz, CH), 6.32 (1 H, d, ^3J 16.0 Hz, CH), 6.89 (1 H, br s, NH), 7.23-7.89 (9 H, m, 9 CH), 9.15 (1 H, br s, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 24.8 (2 CH_2), 25.3 (2 CH_2), 26.0 (CH_2), 33.1 (2 CH_2), 35.4 (2 CH_2), 46.6 (CH_2N), 49.9 (CH), 72.1 (C), 121.2 (CH), 122.8 (CH), 124.4 (CH), 124.8 (CH), 126.6 (2 CH), 126.9 (CH), 127.5 (C), 127.9 (CH), 129.2 (2 CH), 132.2 (CH), 138.1 (C), 148.7 (C), 158.9 (C=N), 162.5 (C=O), 166.4 (C=O), 172.0 (C=O) ppm.

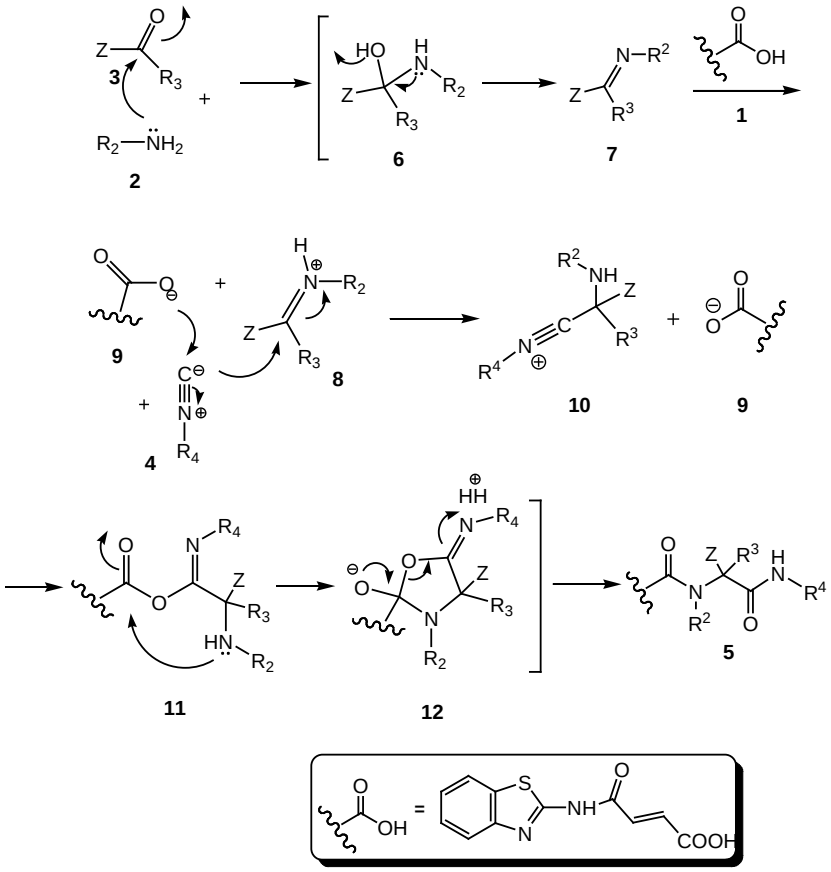
N1-(Benzo[d]thiazol-2-yl)-N4-butyl-N4-(1-(cyclohexylcarbamoyl)cyclopentyl)fumaramide (5o)

Cream powder; m.p: 158-160 ºC; yield: 0.37 g (75%); IR (KBr):(ν_{max}/cm^{-1}) = 3372, 3215, 1772, 1649, 1540, 1255, 1173; EI-MS: *m/z* (%) = 496 (M^+, 1.5), 346 (24), 265 (18), 231 (58), 194 (21), 148 (100), 57 (25); Anal. calcd. for $C_{27}H_{36}N_4O_3S$ (496.66): C, 65.29; H, 7.31; N, 11.28; Found: C, 64.93; H, 7.55; N, 11.35%; ^{1}H NMR ($CDCl_3$): δ = 0.92 (3 H, t, ^3J 6.8 Hz, CH_3), 1.21-2.15 (22 H, m, 11 CH_2), 3.35 (2 H, t, ^3J 7.2 Hz, CH_2N), 3.80-3.83 (1 H, m, CH), 6.43 (2 H, ABq, ^3J 12.1 Hz, Δν 96.3 Hz, 2 CH), 6.87 (1 H, d, ^3J 7.8 Hz, NH), 7.38 (1 H, t, ^3J 7.3 Hz, CH), 7.45 (1 H, t, ^3J 7.6 Hz, CH), 7.82 (1 H, d, ^3J 7.3 Hz, CH), 7.86 (1 H, d, ^3J 7.6 Hz, CH), 10.85 (1 H, br s, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 13.8 (CH_3), 19.7 (CH_2), 23.9 (CH_2), 24.7 (2 CH_2), 25.3 (2 CH_2), 25.9 (CH_2), 33.2 (2 CH_2), 35.3 (2 CH_2), 43.9 (CH_2N), 50.1 (CH), 72.4 (C), 121.4 (CH), 122.1 (CH), 123.6 (CH), 125.2 (CH), 126.7 (CH), 131.8 (CH), 138.5 (C), 148.7 (C), 158.7 (C=N), 162.7 (C=O), 165.6 (C=O), 173.2 (C=O) ppm.

RESULTS AND DISCUSSION

The optimized reactant ratios were found to be 1.0 equiv. benzaldehyde, 1.0 equiv. benzamidine, and 1.0 equiv. malononitrile in the presence of potassium carbonate (20 mol %) in 3 ml of aqueous ethanol (1:1, H_2O–EtOH). The expected 4-amino-2,6-diphenyl-5-pyrimidinecarbonitrile was produced in 90% yield after 5 min at 40 ºC (Scheme 1).

Structures of compounds **5a-5o** were characterized by IR, ^{1}H-NMR and ^{13}C-NMR spectral data. The mass spectra of compounds **5a-5o** displayed molecular ion peaks at appropriate m/z values. The IR and ^{1}H NMR spectra of **5a-5o** exhibited three characteristic peaks NH moieties. The ^{1}H NMR spectra of **5a-5o** exhibited two doublets with ^{3}J = 12-16 Hz, which confirms the *trans* geometry for the carbon-carbon double bond. The proton decoupled ^{13}C NMR spectra of **5a-5o** showed four distinct resonances for C=O and C=N groups. For example, the IR spectrum of **5b** indicated two absorption bands (ν_{max} = 3127, 3347 cm^{-1}) for NH stretching frequencies. The ^{1}H NMR spectrum of **5b** in $CDCl_3$ showed a singlet (δ = 1.56 ppm) for two identical methyl groups, a singlet (δ = 4.78 ppm) for methylene protons of the $ArCH_2N$ moiety and two doublets (δ = 6.22, 6.61 ppm) with ^{3}J = 16.0 Hz for the vinylic CH along with two signals (δ = 6.66, 8.61 ppm) for NH protons. The CH proton chemical shifts of double bond in some of the products are close together and have created ABq system. For example the ^{1}H NMR spectrum of **5c** in $CDCl_3$ showed an ABq (δ = 6.48 ppm, ^{3}J = 12.1 Hz, Δν = 96.3 Hz) for the protons of CHs double bond. The protons of phenyl groups for **5b** exhibited certain signals in areas (δ = 7.36-7.86 ppm). The ^{13}C-NMR spectrum of **5b** showed 23 signals in agreement with the proposed structure. Partial assignments of aromatic, C=N, carbonyl, and cyclohexyl resonances are given in the experimental section. Although the mechanistic details of the above reaction are unknown, a plausible pathway may be advanced to rationalize product formation (Scheme 2). Presumably, the imine **6** produced from the reaction between the amine **2** and the oxo compound **3** is protonated by acid **1** to generate intermediate **8**. This intermediate is attacked by the isocyanide **4** to afford **10**, which is attacked by the anion **9** to produce **11**. The latter would then undergo acyl transfer reaction to form dioxolane derivative **12**, which is converted to α-benzothiazoleamidodipeptides **5** by ring opening.



Scheme 2. Proposed mechanism for synthesis of **5**

CONCLUSION

In conclusion, we report a simple and highly efficient one-pot approach to the synthesis of complex α-benzothiazoleamidodipeptides from simple and readily available inputs without any activation or modifications. The work-up procedure is fairly simple and the products do not require further purification. The advantage of the present procedure is that the reaction is performed without solvent by simple mixing of the starting materials.

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ЕДНОСТАДИЙНА СИНТЕЗА НА ВИСОКО-ФУНКЦИОНАЛНИ БЕНЗОТИАЗОЛ-ДИАМИДИ БЕЗ РАЗТВОРИТЕЛ ЧРЕЗ ЧЕТИРИ-КОМПОНЕНТНА РЕАКЦИЯ НА UGI

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(Резюме)

4-бензотиазол-2-ил амино-4-оксо-2-бутенова киселина, получена чрез реакция на 2-аминобензтиазоп и малеинов анхидрид е използвана като киселинен компонент в реакцията на Ugi в условия без разтворител за получаването на ненаситени α-бензотиазол-амидодипептиди с добър добив.