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Synthesis of Indole Fragment-Containing Peptides via Ugi Reaction

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ABSTRACT. The Ugi reaction was applied in the synthesis of indole fragment-containing peptides. Effect of solvent and temperature on the duration of the reaction, yield and stereoselectivity of the products were studied. L-amino acids as an acid component, (S)-p-methoxyphenylethylamine, indole-3-carbaldehyde and methyl-2-isocyanacetate were used as initial components. Influence of solvent and temperature on reaction yield and diastereomeric ratio was studied as well. © *2015 Bull. Georg. Natl. Acad. Sci.*

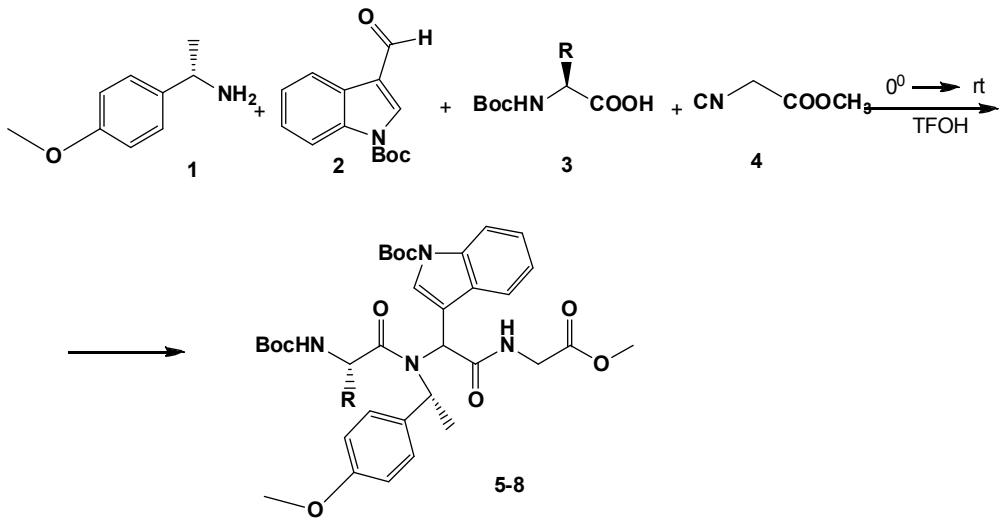
Key words: *multicomponent reaction, Ugi reaction, peptides, Indole*

Indole ring systems present prevalent subunits in natural product chemistry and are of interest for organic chemists for more than a century. Generally, they display important psychotropic, sedative, analgesic, anti-depressive, anti-inflammatory and cytotoxic activities. Nonsteroidal compounds having estrogenic or anti-estrogenic activities are valuable for controlling estrogen-dependant cancers [1-7]. They are found in peptides and cyclopeptides produced by marine organisms and microorganisms. [8-9]. As it is known, peptides are found in all living organisms. They control biochemical and physiological processes in the organisms. Peptide-based preparations are widely used in neurology, endocrinology and hematology [10-12]. A multicomponent reaction (MCR) such as Ugi reaction allows aneasy synthesis of peptide fragments containing the indole ring [13–18].

Here we report synthesis of indole fragment-containing peptides using Ugi reaction. The reaction runs in one step via the condensation of indole-3-carbaldehyde (2), N-terminal protected amino acids (3), (S)-p-methoxyphenylethylamine(1)and methyl-2-isocyanacetate (4) (Scheme 1). Indole-3-carbaldehyde was obtained via Vilsmeyer reaction according to the technique described in the literature. It should be noted thatobtaining the end product was allowed after protection of NH group for indole.

To improve the stereoselectivity of the end products (S)-p-methoxi-phenylethylamine was chosen as chiral component because it is known that, in general, chiral amines to induce stereoselectivity. It was of interest to study influence of the reaction conditions in the yield and stereoselectivity of the products.

Methanol and trifluoroethanol were chosen as



Scheme 1

solvents. As it was expected the reaction speed and yield were higher in the trifluoroethanolsince a polar solvent stabilizes a reaction mixture (increases stability of the imine ion and acid anion).

As for a temperature effect the reaction runs longer at the -30°C than at 0°C, and the changes in diastereomeric ratio of peptides are insignificant (Table 1).

Thus, indole fragment-containing peptides were synthesized by us via the Ugi reaction. Effect of a solvent and temperature on the yield and stereoselectivity of the products obtained were studied.

Notes and references

General procedure for the Ugi reaction: 240 mg (2 mmol) of the amine was dissolved in 5 ml of methanol (trifluoroethanol), then 490 mg (0.2 mmol) 1H-indole-3-carbaldehyde was added slowly at 0!. After stirring for 20 min the Boc-amino acid (2 mmol) and the isocyanoacetate (2 mmol) were added. The ice-bath was removed and the mixture was stirred three days at room temperature. Then CH_2Cl_2 was added and the mixture was washed three times with saturated $NaHCO_3$ and 1M $KHSO_4$. Organic layer was dried (Na_2SO_4). The solvent was removed in *vacuo*, evaporated and the crude product was purified by column chromatography (silicagel).

Table 1. The Ugi reaction

Entry	peptide	R	dr (0°C)	dr (–30°C)
	5	$-CH_3$	31:69	20 : 80
	6	$-CH_2$-Ph	36 : 67	15 : 85
	7	$-CH_2-(CH_3)_2$	30: 70	25 : 75
	8	-H	26:74	18 : 82

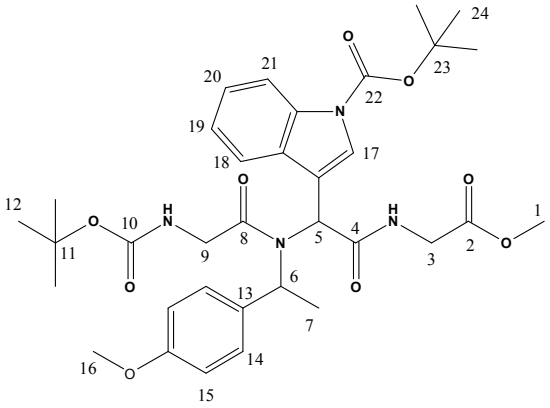
dr = diastereomeric ratio determined by HPLC of the crude product.
*** solvent** – Methanol

Compound 5

According to the general procedure for Ugi reactions, 5 was obtained after purification by column chromatography (hexanes-EtOAc = 1:1) , white solid in 44% yield.

Diastereomer 1

^{1}H-NMR (400 MHz, $CDCl_3$): d = 1.16 (d, 3H, *J*= 1.2 Hz, 9'-H), 1.31 (d, 3H, *J*= 6.8 Hz, 7-H), 1.45 (s, 9H, 12-H), 1.65 (s, 9H, 24-H), 3.64 (s, 3H, 16-H), 3.79 (s, 3H; 1-H), 3.85 (dd, 1H, , *J*= 5.2 Hz, , *J*= 4.8 Hz, 3-H), 4.03 (dd, 1H, *J*= 5.6 Hz, , *J*= 5.2 Hz, 3-H), 4.79 (m, 1H, 9-H), 5.28-5.33 (m, 2H, 5-H, 6-H), 5.44 (d, 1H, , *J*= 8 Hz, N-Ha), 6.36 (s, 1H, N-Hb), 6.89 (d, 2H, , *J*=8.8 Hz, Ar-H), 7.31-7.44 (m, 5H, Ar-H), 7.87 (s, 1H, 17-H), 8.16 (d, 1H, *J*= 8.4 Hz, 18-H)?



^{13}C-NMR (400 MHz, $CDCl_3$):? d =169.8, 168.6, 159.2, 149.4, 129.3, 129.1, 126.1, 124.9, 118.5, 115.5, 114.7, 113.9, 84.1, 71.4, 55.2, 53.4, 52.1, 48.4, 41.3, 38.9, 28.4, 28.2, 22.6, 20.2, 19.0, 18.7, 17.8, 8.6

Diastereomer 2

^{1}H-NMR (400 MHz, $CDCl_3$): d =1.57 (d, 3H, *J*= 2.8 Hz, 9'-H); 1.42 (s, 9H, 12-H); 1.64 (s, 9H, 24-H); 1.82 (d, 3H, 7-H); 3.54 (s, 3H, 16-H); 3.66 (s, 3H, 1-H); 3.88 (dd, 1H, *J*= 4.8 Hz, *J*= 5.2 Hz, 3-H); 4.10 (dd, 1H, *J*= 6 Hz, 3-H); 4.75 (d, 1H, *J*= 4.8 Hz, 9-H), 5.30-5.35 (m, N-Ha, 6-H); 6.44 (d, 2H, *J*= 8.8 Hz, Ar-H); 6.60 (s, 1H, N-Hb); 6.95-7.06 (m, 4H, Ar-H); 7.21 (d, 1H, *J*= 8 Hz, Ar-H); 7.78 (s, 1H, 17-H); 8.03 (d, 1H, *J*= 7.6 Hz, 18-H).

^{13}C-NMR (400 MHz, $CDCl_3$): d =169.8, 169.5, 158.9, 155.1, 128.9, 124.4 122.6 118.4, 115.0, 113.5, 83.9, 55.1, 52.2, 46.1, 41.4, 31.5, 28.4, 28.2, 27.6

Compound 6

According to the general procedure for Ugi reactions, 6 was obtained after purification by column chromatography (hexanes-EtOAc = 3:2) , white solid in 48% yield

Diastereomer 1

^{1}H-NMR (400 MHz, $CDCl_3$): d = 0.81-0.84 (m, 3H, 7-H); 1.38 (s, 9H, 12-H); 1.68 (s, 9H, 24-H); 2.93 (d, 2H, *J*= 6.4 Hz, 9'-H); 3.64 (s, 3H, 16-H), 3.79 (s, 3H, 1-H); 3.88 (dd, 1H, *J*= 4.4 Hz, *J*= 4.8 Hz,3-H); 4.02 (dd, 1H, *J*= 5.6 Hz, *J*= 6 Hz, 3-H); 5.01 (d, 1H, *J*= 7.2 Hz, 9-H); 5.01 (d, 1H, *J*= 7.2 Hz, 9-H); 5.15 (d, 1H, *J*= 10 Hz, 5-H); 5.19 (d, 1H, *J*= 6.8 Hz, 6-H); 5.35 (d, 1H, *J*= 9.2 Hz, N-Ha); 6.26 (s, 1H, N-Hb); 6.47 (d, 1H, *J*= 8.8 Hz, Ar-H); 7.13-7.41 (m, 10H, Ar-H); 7.99 (s, 1H, 17-H); 8.16 (d, 1H, *J*= 8.4 Hz, 18-H).

^{13}C-NMR (400 MHz, $CDCl_3$): d =199.1, 196.6, 187.6, 176.2, 159.3, 135.4, 129.7, 129.6, 129.1, 128.4, 123.0, 128.9, 128.8, 128.5, 113.9, 77.3, 77.2, 77.0, 76.7, 64.5, 55.2, 51.4, 413, 28.3, 28.2, 28.1

Diastereomer 2

^{1}H-NMR (400 MHz, $CDCl_3$): d = 0.81-0.84 (m, 3H, 7-H); 1.34 (s, 9H, 12-H); 1.64 (s, 9H, 24-H); 2.93 (d, 2H, *J*= 6.4Hz, 9'-H); 3.67 (s, 3H; 16-H); 3.78 (s, 3H; 1-H); 3.89 (dd; 1H; *J*= 2.0Hz, *J*= 4.8 Hz, 3-H); 4.14 (dd, 1H, *J*= 3.6Hz, *J*= 3.2Hz, 3-H); 4.22 (d, 1H, *J*= 7.2 Hz, 9-H); 5.15 (d, 1H, *J*= 10Hz, 5-H); 5.19 (d, 1H, *J*= 6.8Hz, 6-H); 5.01 (d, 1H, *J*= 2Hz, N-Ha); 6.67 (s, 1H, N-Hb); 6.47 (d, 1H, *J*= 8.8Hz, Ar-H); 7.00-7.41 (m, 9H, Ar-H); 7.73 (s, 1H, 17-H); 8.14 (d, 1H, *J*= 8.4Hz, 18-H).

^{13}C-NMR (400 MHz, $CDCl_3$): d =173.6, 171.0, 170.9, 129.2, 129.1, 128.8, 128.6, 123.0, 119.2, 116.4, 115.5, 115.4, 115.4, 114.0, 113.6, 110.8, 105.1, 98.8, 83.1, 87.3, 84.1, 56.3, 55.9, 52.3, 52.2, 41.4, 29.0, 28.1

Compound 7 According to the general procedure for Ugi reactions, 7 was obtained after purification by column chromatography (hexanes-EtOAc = 2:1) , white solid in 42% yield.

Diastereomer 1

^{1}H-NMR (400 MHz, $CDCl_3$): d = 0.92(d, 3H, *J*= 5.6Hz, 25-H); 0.97 (d, 3H, *J*= 8Hz, 26-H); 1.34 (d, 3H, *J*= 7.2Hz, 7-H); 1.45 (s, 9H, 12-H); 1.63 (s, 9H, 24-H); 2.04-2.09 (m, 1H, 9'H); 3.62 (s, 3H, 16-H); 3.76 (dd, 1H, *J*= 4.4Hz, 3-H); 3.82 (s, 3H, 1-H); 4.02 (dd, 1H, *J*= 3.6Hz, *J*= 6.4Hz, 3-H); 4.66 (m, 1H, 9-H); 5.08 (s, 1H, 5-H); 5.34 (d, 1H, *J*= 9.6Hz, N-Ha); 5.48(m, 1H, 6-H); 6.18 (s, 1H, NH-b); 6.38 (d, 1H, *J*= 8.8Hz, Ar-H); 6.91-7.03 (m, 3H, Ar-H); 7.33-7.46 (m, 3H, Ar-H); 7.88 (s, 1H, 17-H); 8.21 (d, 1H, *J*= 8.4Hz, 18-H).

^{13}C-NMR (400 MHz, $CDCl_3$): d =169.9, 168.3, 159.4, 149.3, 145.7, 129.5, 124.8, 123.1, 115.5, 113.9, 113.3, 83.9, 77.2, 76.9, 57.3, 55.8, 55.3, 55.1, 52.1, 41.4, 41.3,

31.5, 29.1, 28.3, 28.1, 25.3, 19.9 18.9, 17.6, 17.5

Diastereomer 2

^{1}H-NMR (400 MHz, $CDCl_3$): d = 0.83 (d, 3H, *J*= 6.4Hz, 25-H); 0.94 (d, 3H, *J*= 6.4Hz, 26-H); 1.34 (d, 3H, *J*= 7.2Hz, 7-H); 1.35 (s, 9H, 12-H); 1.61 (s, 9H, 24-H); 2.04-2.09 (m, 1H, 9'-H); 3.62 (s, 3H, 16-H); 3.76 (dd, 1H, *J*= 4.4Hz, 3-H); 3.82 (s, 3H, 1-H); 4.02 (dd, 1H, *J*= 3.6Hz, *J*= 6.4Hz, 3-H); 4.66 (m, 1H, 9-H); 5.08 (s, 1H, 5-H); 5.14 (d, 1H, *J*= 7.6Hz, N-Ha); 5.48 (m, 1H, 6-H); 5.02 (d, 1H, *J*=7.6Hz, N-Hb); 6.89-7-31 (m, 5H, Ar-H); 7.53-7.56 (m, 2H, Ar-H); 7.76 (s, 1H, 17-H); 8.12 (d, 1H, *J*= 6Hz, 18-H).

^{13}C-NMR (400 MHz, $CDCl_3$): d =171.6 , 171.4, 169.8, 169.7, 169.6, 149.4, 135.7, 128.1, 125.5, 124.9, 119.2 116.3, 116.2, 115.4, 84.1, 52.3, 49.8, 41.4, 34.7, 31.6, 30.7, 28.2, 26.9, 25.3, 22.6, 20.7, 19.3, 17.8, 17.6, 14.1, 11.4

Compound 8

According to the general procedure for Ugi reactions, 8 was obtained after purification by column chromatography (hexanes-EtOAc = 2:1) , white crystals in 59% yield.

Diastereomer 1

^{1}H-NMR (400 MHz, $CDCl_3$): d = 1.27 (d, 3H, *J*= 6Hz, 7-H), 1.43 (s, 9H, 12-H), 1.66 (s, 9H, 24-H), 3.36 (s, 3H, 16-H), 3.86 (s, 3H, 1-H), 3.87 (d, 1H, *J*= 4Hz, 3-H), 3.98-4.03(m, 2H, 9-H); 4.16 (d, *J*= 1.6Hz, 3-H); 5.1 (s, 1H, 5-H); 5.16 (d, 1H, *J*= 1.2Hz, 6-H); 5.59 (s, 1H, N-Ha); 6.26 (s, 1H, N-Hb); 6.92 (d, 2H, *J*= 8.4Hz, 14-H, 15-H); 7.26-7.14 (m, 5H, Ar-H); 7.9 (s, 1H, 17-H); 8.15 (d, 1H, *J*= 8Hz, 18-H).

^{13}C-NMR (400 MHz, $CDCl_3$): d=168.3, 159.3 , 149.6, 149.4 , 128.8, 125.0, 123.1, 84.4, 55.3, 52.2, 41.4, 28.4, 28.2.

Diastereomer 2

^{1}H-NMR (400 MHz, $CDCl_3$): d = 1.43 (s, 9H, 12H), 1.65(s, 9H, 24-H), 1.79 (d, 3H, *J*= 6.8 Hz, 7-H), 3.55(s, 3H, 16-H), 3.66 (s, 3H, 1-H), 3.86 (dd, 1H, *J*=2.8 Hz, *J*=8 Hz, 3-H), 3.99 (dd, 1H, *J*=1.2 Hz, *J*=7.6Hz,3-H), 4.09 (dd, 1H, *J*=6 Hz, 9-H), 4.28 (dd, 1H, *J*=4 Hz, 9-H), 4.16 (d, (dd, 1H, *J*=1.6 Hz, 3-H), 4.98 (s, 1H, 5-H), 5.34 (d, 1H, *J*=6.8 Hz, 6-H), 5.62 (s, 1H, N-Ha), 6.41 (s, 1H, N-Hb), 6.46 (d, 2H, *J*=8.4 Hz, 14-H, 15-H), 6.79 (d, 1H, *J*=3.6 Hz, Ar-H), 6.97 (d, 1H, *J*=8 Hz, Ar-H), 7.0 (s, 1H, Ar-H), 7.2 (t, 2H, *J*=7.6 Hz, Ar-H), 7.73 (s, 1H, 17-H),8.01 (d, 1H, *J*=8.4Hz, 18-H)

^{13}C-NMR (400 MHz, $CDCl_3$): d =169.8, 169.4, 159.1, 130.05, 128.8, 127.34, 124.48, 122.48, 118.30, 114.94, 113.74, 84.20, 55.12, 52.2, 41.4, 28.36, 28.15, 17.41.

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