

Organic Chemistry

Ugi Reaction with Piv-Aldehyde and S-4-Methoxyphenyl Ethylamine as Amine

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ABSTRACT. Influence of a solvent on the yield and stereoselectivity of reaction products is studied in the Ugi reaction. L-alanine as acid component, (S)-p-methoxyphenylethylamine, trimethylacetaldehyde and methyl-2-isocianoacetate were used as initial components; methanol, 2,2,2-trifluoroethanol (TFE) and dichloromethane served as solvents. In the case of using dichloromethane as a result of reaction the end product was obtained, in the case of methanol together with the end product an ammonia product was isolated, and in the case of 2,2,2-trifluoroethanol only ammonia product was received. It was established that in case of dichloromethane used as solvent the reaction runs in a desired direction. As for stereoselectivity, influence of solvent substitution on the diastereometric composition of the product is insignificant. © 2016 Bull. Georg. Natl. Acad. Sci.

Key words: multicomponent reaction, Ugi reaction, peptides, ammonia product

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 [1-3]. A multicomponent reaction (MCR) such as Ugi reaction provides a linear, peptide-like adduct [4-11].

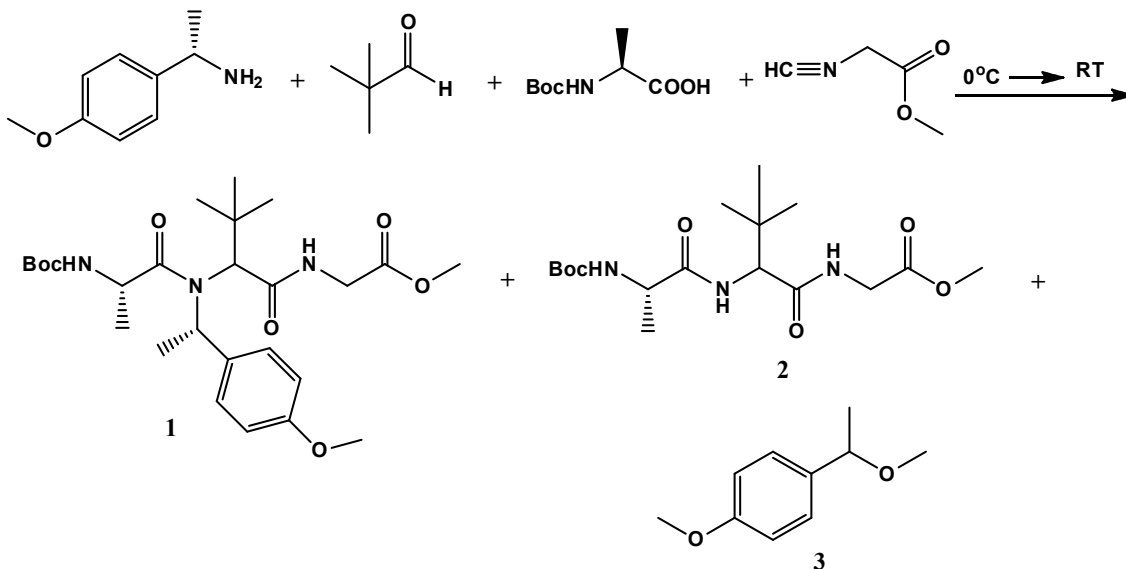
The purpose of the work was a peptide synthesis via Ugi reaction. A Ugi 4CR converts an aldehyde, an amine, an acid, and an isocyanide into an α -acetamidoamide in one step, with good to excellent yields. It is known that many components influence on the reaction course, in particular, concentration of reactants, temperature, solvent characteristics, etc. We focused on the study of the influence of solvent

nature on the stereoselectivity of the reaction products.

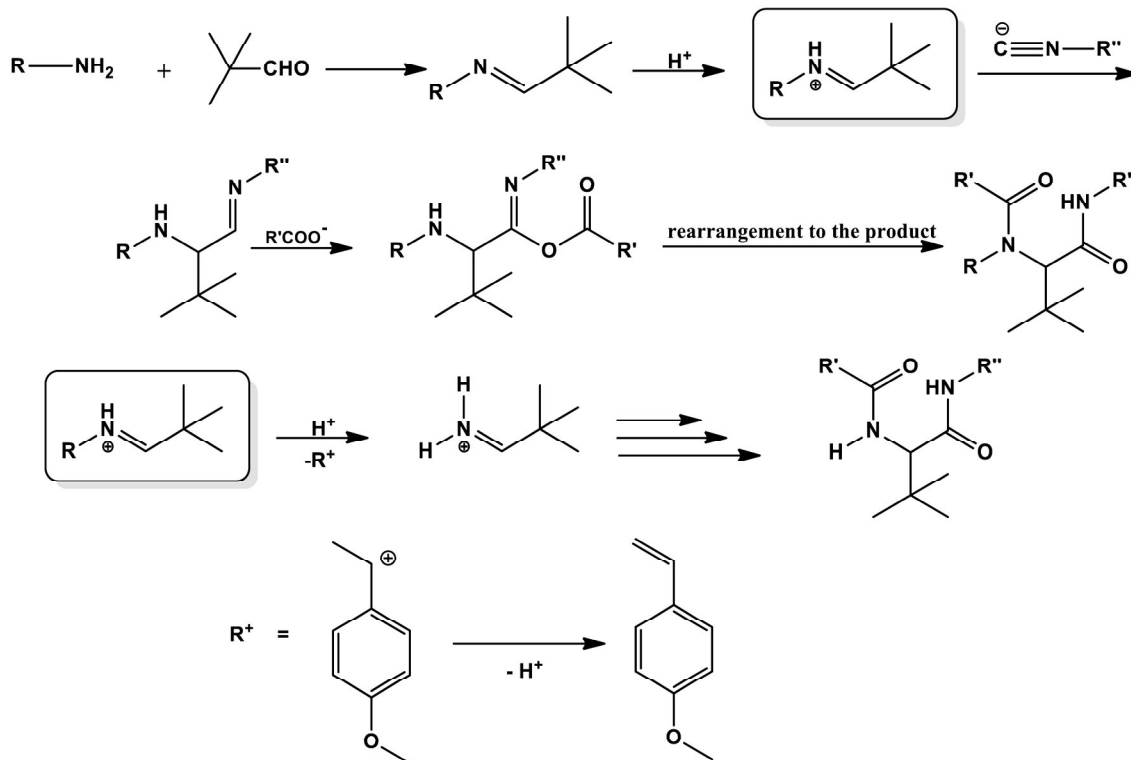
L-alanine as acid component, (S)-p-methoxyphenylethylamine, trimethylacetaldehyde and methyl-2-isocianoacetate were taken as initial components. To improve the stereoselectivity of the end products (S)-p-methoxy-phenylethylamine was chosen as chiral component because as is known, in general, chiral amines induce stereoselectivity. We decided to study an interesting problem influence of reaction conditions on the yield and stereoselectivity of the reaction products.

Three different solvents: dichloromethane, methanol and 2,2,2-trifluoroethanol (TFE) were chosen. Initial

Scheme 1.



Scheme 2. The mechanism of Reaction



components were taken in equivalent quantities. At the beginning the reaction was conducted at 0°C, then, after obtaining imine, the reaction was continued at the room temperature. The reaction course was observed using thin-layered chromatography method (Scheme 1).

When the reaction was conducted in the methanol, besides the end-product (35%) (1) a product off-target – ammonia product (26%) (2) was isolated. When methanol was substituted with more protic solvent – TFE, the reaction ran in undesirable course and only ammonia product (2) was obtained with the

83% yield. In the aprotic solvent (dichlormethane) the reaction was definitely conducted producing the end product (1).

In Scheme 2 a supposed mechanism of the reaction is shown. After formation of iminium ion in the protonic solvent supposedly nitrogen protonation and radical splitting off take place that results in forming the off-target ammonia product.

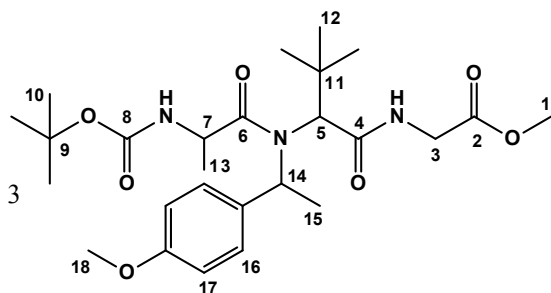
As for stereoselectivity, influence of solvent substitution was insignificant. Diastereometric ratio of the end product in methanol was 60:40, and in dichlormethane 65:35.

Thus, it is established that dichlormethane is an appropriate solvent for the mentioned reaction.

Experimental Section

General procedure for the Ugi reaction: 240 mg (2 mmol) of the (S)-1-(4-Methoxyphenyl)ethylamine was dissolved in 5 ml of solvent (methanol, dichlormethane, TFE), then 490 mg (0.2 mmol) Trimethylacetaldehyde was added slowly at 0°. After stirring for 20 min the Boc-Alanine (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 (hexanes-EtOAc = 1:1). Compound 1 (white solid in 34% yield) and Compound 2 (white solid in 21% yield) were obtained.

Compound 1



Diastereomer 1

¹H-NMR (400 MHz, CDCl_3): δ = 0.96 (s, 9H, 10-H), 1.04 (s, 9H, 12-H), 1.19 (d, 3H, J = 1.2 Hz, 13-H), 1.31 (d, 3H, J = 6.8 Hz, 15-H), 3.64 (s, 3H, 18-H), 3.69 (s, 3H; 1-H), 3.82 (dd, 1H, J = 5.2 Hz, J = 4.8 Hz, 3-H), 3.93 (dd, 1H, J = 5.6 Hz, J = 5.2 Hz, 3-H), 4.63 (t, 1H, 7-H), 5.28 (m, 1H, 14-H), 5.47 (d, 1H, J = 6.4 Hz, 5-H), 6.82- (d, 2H, J = 7.6 Hz, Ar-H), 6.89 (d, 2H, J = 8.8 Hz, Ar-H), 7.71 (d, 1H, J = 8.4 Hz, N-Hb). 8.62 (m, 1H, N-Ha)

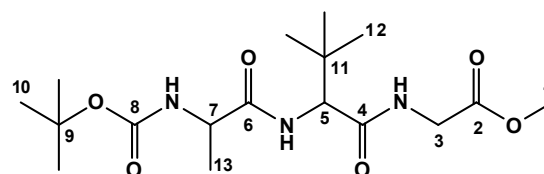
¹³C-NMR (400 MHz, CDCl_3): δ = 169.8, 168.6, 159.2, 149.4, 129.3, 129.1, 126.1, 124.9, 118.5, 115.5, 114.7, 113.9, 84.1, 71.4, 55.2, 53.4, 52.1, 48.4, 41.3, 38.9, 28.4, 28.2, 22.6,

Diastereomer 2

¹H-NMR (400 MHz, CDCl_3): δ = 1.17 (d, 3H, J = 6.4 Hz, 13-H), 1.34 (s, 9H, J = 6.8 Hz, 12-H), 1.44 (3H, d, J = 6.8 Hz, 15-H), 1.45 (s, 9H, 10-H), 3.64 (s, 3H, 18-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), 4.69 (d, 1H, J = 9.6 Hz, 7-H), 4.92 (m, 1H, 14-H), 6.63 (d, 2H, J = 2.0 Hz, Ar-H), 6.95 (d, 2H, J = 8.8 Hz, Ar-H), 7.6 (d, 1H, J = 6.8 Hz, N-Hb), 8.3 (m, 1H, N-Ha).

¹³C-NMR (400 MHz, CDCl_3): δ = 135.15, 134.92, 113.42, 99.49, 78.11, 55.09, 54.79, 51.58, 40.54, 39.90, 39.07, 40.11, 38.96, 28.12, 27.3

Compound 2



¹H-NMR (400 MHz, CDCl_3): δ = 0.91 (s, 9H, 12-H), 1.15 (d, 3H, J = 7.2 Hz, 13-H), 1.37 (s, 9H, 10-H), 3.61 (s, 3H, 1-H), 3.76 (dd, 1H, J = 5.6 Hz, 3-H), 3.89 (dd, 1H, J = 6.0 Hz, 3-H), 4.00 (m, 1H; 7-H), 4.23 (d, 1H, J = 9.6 Hz, 5-H), 7.16 (d, 1H, J = 8 Hz, N-Hc), 7.39 (d, 1H, J = 9.6 Hz, N-Hb), 8.49 (m, 1H, N-Ha)?

¹³C-NMR (400 MHz, CDCl_3): δ = 172.2; 170.3; 170.0; 78.2; 59.1; 51.5; 49.8; 40.4; 40.11; 39.3; 39.1; 38.9; 34.6; 28.1; 26.4; 17.5

ორგანული ქიმია

უგის რეაქცია ტრიმეთილაცეტალდეჰიდისა და (S)-4-მეთოქსიფენილეთილამინის გამოყენებით

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შესწავლილია უგის რეაქციაში გამხსნელის გავლენა რეაქციის პროდუქტების გამოსავლიანობასა და სტერეოსელექტიურობაზე. საწყის კომპონენტებად აღებულ იქნა L-ალანინი, როგორც მჟავა კომპონენტი, (S)-3-მეთოქსიფენილეთილამინი, ტრიმეთილაცეტალდეჰიდი და მეთილ-2-იზოციანოაცეტატი. გამხსნელებად გამოყენებულ იქნა მეთანოლი, 2,2,2-ტრიფტორეთანოლი და დიქლორმეთანი. რეაქციის დიქლორეთანში ჩატარებისას მიღებულ იქნა მხოლოდ მიზნობრივი პროდუქტი, მეთანოლში მიზნობრივ პროდუქტთან (1) ერთად გამოიყო მოხლეჩვის პროდუქტი (2). ხოლო 2,2,2-ტრიფტორეთანოლის შემთხვევაში წარმოიქმნა მხოლოდ პროდუქტი 2. დადგენილია, რომ რეაქცია სასურველი მიმართულებით მიდის დიქლორმეთანის გამოყენების შემთხვევაში. ხოლო რაც შეეხება სტერეოსელექტიურობას, გამხსნელის ცვლილებამ მნიშვნელოვანი გავლენა არ მოახდინა.

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