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The Ugi Four-Component Reaction: Application in the synthesis of bis-hydantoins

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Three new bis 1,3,5-trisubstituted hydantoins were synthesized by combining an Ugi four-component condensation reaction with a base induced cyclization. In the two-step sequence, first three new bis Ugi compounds were synthesized by the Ugi four-component condensation reaction, and then bis 1,3,5-trisubstituted hydantoins were obtained by intramolecular cyclization reaction.

Keywords: Multicomponent reactions, Ugi-four component reaction, heterocycles, amides, hydantoins

INTRODUCTION

Multicomponent reactions (MCRs) are one-pot processes in which three or more reactants combine together simultaneously or in a stepwise domino fashion to form a new product which contains portions of all the components (Figure 1). MCRs provide a simple and powerful access to a large number of molecules from simple substrates with broad structural diversity and molecular complexity [1-3].

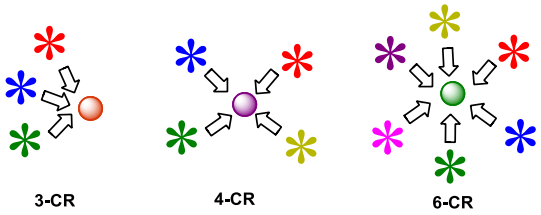

Figure 1. Schematic representation of a three-component reaction (3-CR), a four-component reaction (4-CR) and a six-component reaction (6-CR)

Not all MCRs follow the same strategy: the pathways can be either convergent or divergent (Figure 2). During convergent synthesis, separate reactants combine together in independent reactions to form intermediates, which subsequently react and combine together to form the final product [1, 4]. High atom economy, easy operation, lower energy consumption, higher overal yield, less solvent being used (or solvent-free), time, resource efficiency, waste reduction *via* removal of intermediate separations and contributing to a more green process are properties of MCRs [1, 3, 5].

Multicomponent reactions have been known for more than 170 years. The first reported multicomponent reaction was Strecker's synthesis of α-amino cyanides in 1850. Since then, numerous MCRs have been reported, such as the Hantzsch dihydropyridine synthesis (1881), the Biginelli reaction (1891), the Mannich reaction (1912), the Passerini reaction (1921), and the Ugi reaction (1959) (Figure 3) [6-8].

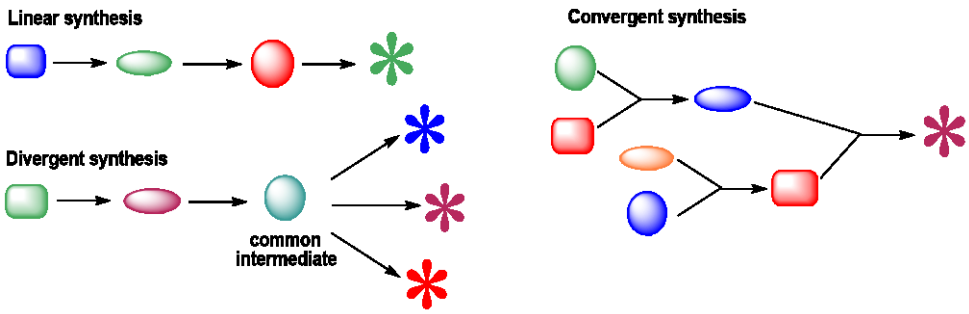

Figure 2. Schematic representation of linear, convergent and divergent synthesis

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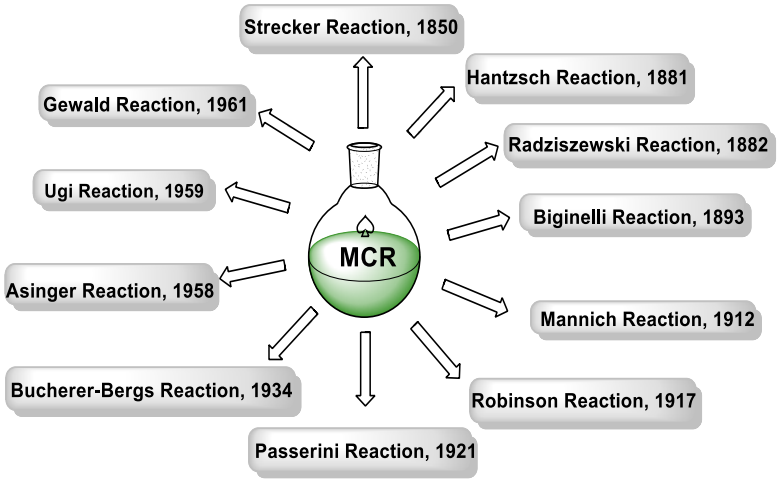
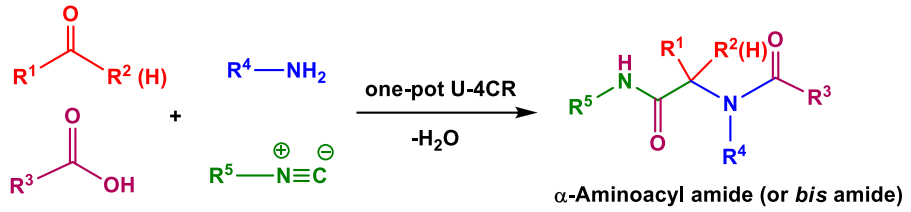
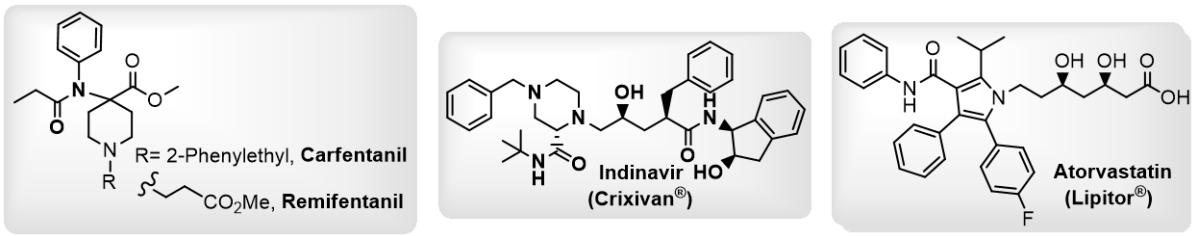


Figure 3. The brief history of multicomponent reactions



Scheme 1. The Ugi four-component reaction (U-4CR)



Scheme 2. Structures of carfentanil, remifentanil, crixivan and lipitor

The Ugi reaction is favoured in polar protic solvents such as methanol and, to some extent in water. The U-4CR is one of the most important MCRs to access peptide-like structures (Scheme 1) [9-16].

The synthesis of the potent analgesics carfentanil and remifentanil was reported using an U-4CR followed by methanolysis of the carfentanil amide and the remifentanil amide Ugi products (Scheme 2) [17]. The first synthesis of Merck HIV protease inhibitor Crixivan (Indinavir) by a conventional multistep sequence of procedures was ineffective and expensive. After the introduction of an U-4CR as a key step Crixivan could be prepared in fewer steps and in better yields (Scheme 2) [18]. In another example, Pfizer's Lipitor (Atorvastatin) belongs to a class of statins, lipid-lowering drugs for the prevention of events associated with cardiovascular disease. It was the best-selling pharmaceutical drug of all time worldwide until its patent expired in late 2011. Lipitor could be formed through U-4CR in an overall short and high-yield synthesis that performs better than the Paal–Knorr synthetic route [19].

Hydantoins (imidazolidine-2,4-diones) constitute a very old class of cyclic ureides of α-amino acids. Hydantoin was first isolated by the Nobel laureate, Adolf von Baeyer in 1861 [20, 21]. Over the last 150 years hydantoin-containing heterocylic compounds have become increasingly important in the chemical and pharmaceutical industries. The hydantoin framework itself possesses no biological activity, but 5-substituted and 5,5-disubstituted derivatives have a wide range of therapeutic applications [21-25]. Hydantoin derivatives have been used as hypnotics, anticonvulsants, antiarrhythmics, antidiabetics, antimuscarinics, antiulcer, antiviral or antibacterial agents [21-25].

EXPERIMENTAL

All reagents and solvents were purchased from Fluka, Acros Organics, Riedel-de Haën and Merck

and were used without further purification. The melting points were measured on an Stuart SMP10 melting point apparatus and are uncorrected. The IR spectra were recorded on a One FT-IR ATR Perkin Elmer. The ^{1}H and ^{13}C NMR spectra were taken with a Jeol NMR 400 MHz spectrometer and the chemical shifts were recorded in ppm downfield with respect to tetramethylsilane (TMS) as an internal standard.

General procedure for the synthesis of bis Ugi products (1a-1c).

A solution of aromatic diamino compound (1.0 mmol) in MeOH (7 mL) was treated with benzaldehyde (2.0 mmol), a solution of cyclohexyl isocyanide (2.0 mmol) in MeOH (3 mL), and trichloro acetic acid (2.0 mmol) in the order given. The reaction mixture was stirred at room temperature for 24-28 hours, and then filtered. The precipitate was washed first with Et_2O and then with n-hexane to remove unreacted reagents or by-products and dried to give pure white solid Ugi adducts 1a-1c.

General procedure for the synthesis of bis 1,3,5-trisubstituted hydantoins (2a-2c).

A 1.0 M ethanolic solution of NaOEt (2.5 mmol) was slowly added to a solution of 1 (1.0 mmol) in EtOH (5 mL). The mixture was stirred for further 8-10 hours at room temperature and then filtered. The collected solid was washed with Et_2O (5 mL) and filtered to give almost pure 2a-2c.

Spectroscopic results

N,N'-(4,4'-(Ethane-1,2-diyl)bis(4,1-phenylene)) bis(2,2,2-trichloro-N-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)acetamide) (1a): IR-ATR: 3268, 3063, 3034, 2927, 2854, 1690, 1649, 834, 739, 698 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ = 7.65 (2H, br s, 2NH), 7.3-7.16 (14H, m, CH_{Ar}), 7.1 (4H, d, J=8.2 Hz, CH_{Ar}), 5.97 (1H, s, PhCH), 5.23 (1H, d, J=7.8 Hz, PhCH), 3.79-3.77 (2H, m, 2CH cyclohexyl), 2.71 (4H, s, CH_2CH_2), 1.94-1.81 (4H, m, $2CH_2$ cyclohexyl), 1.64-1.58 (4H, m, $2CH_2$ cyclohexyl), 1.34-1.31 (4H, m, $2CH_2$ cyclohexyl), 1.31-1.28 (8H, m, $4CH_2$ cyclohexyl) ppm; ^{13}C NMR (100MHz, $CDCl_3$): δ = 167.43 (C_q), 161.01 (C_q), 141.71 (C_q), 136.28 (C_q), 133.47 (C_q), 132.24 (CH_{Ar}), 130.71 (CH_{Ar}), 129.00 (CH_{Ar}), 128.61 (CH_{Ar}), 128.23 (CH_{Ar}), 127.93 (CH_{Ar}), 93.15 (C_q), 70.11 (CH), 49.04 (CH), 37.48 (CH_2), 32.91 (CH_2), 32.88 (CH_2), 25.52 (CH_2), 24.94 (CH_2), 24.83 (CH_2) ppm.

N,N'-(4,4'-Oxybis(4,1-phenylene))bis(2,2,2-trichloro-N-(2-(cyclohexylamino)-2-oxo-1-phenyl ethyl)acetamide) (1b): IR-ATR: 3363, 3079, 3047, 2929, 2854, 1683, 1652, 1244, 1213, 833, 727 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ = 7.84 (2H, br s, 2NH), 7.26-7.16 (14H, m, CH_{Ar}), 7.1 (4H, d, J=8.2 Hz, CH_{Ar}), 5.89 (1H, d, J=7.3 Hz, PhCH), 5.38 (1H, d, J=8.3 Hz, PhCH), 3.89-3.84 (2H, m, 2CH cyclohexyl), 2.2-1.86 (4H, m, $2CH_2$ cyclohexyl), 1.70-1.54 (8H, m, $4CH_2$ cyclohexyl), 1.42-0.91 (8H, m, $4CH_2$ cyclohexyl) ppm; ^{13}C NMR (100MHz, $CDCl_3$): δ= 167.56 (C_q), 161.05 (C_q), 156.54 (C_q), 134.41 (C_q), 133.37 (C_q), 133.31 (CH_{Ar}), 130.81 (CH_{Ar}), 129.09 (CH_{Ar}), 128.66 (CH_{Ar}), 117.75 (CH_{Ar}), 93.12 (C_q), 69.66 (CH), 69.57 (CH), 49.11 (CH), 32.90 (CH_2), 32.86 (CH_2), 25.50 (CH_2), 24.95 (CH_2), 24.82 (CH_2) ppm.

N,N'-(4,4'-Sulfonylbis(4,1-phenylene))bis(2,2,2-trichloro-N-(2-(cyclohexylamino)-2-oxo-1-phenyl ethyl)acetamide) (1c): IR-ATR: 3263, 3088, 3041, 2929, 2854, 1677, 1646, 1496, 1240, 1223, 732, 699 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ = 7.66 (2H, d, J=7.3 Hz, 2NH), 7.62-7.35 (14H, m, CH_{Ar}), 7.2 (4H, d, J=8.2 Hz, CH_{Ar}), 6.01 (1H, s, PhCH), 5.4 (1H, d, J=7.8 Hz, PhCH), 3.79-3.68 (2H, m, 2CH cyclohexyl), 1.73-1.48 (12H, m, $6CH_2$ cyclohexyl), 1.39-1.1 (8H, m, $4CH_2$ cyclohexyl) ppm; ^{13}C NMR (100MHz, $CDCl_3$): δ= 168.8 (C_q), 159.23 (C_q), 148.56 (C_q), 137.42 (C_q), 133.27 (C_q), 131.98 (CH_{Ar}), 130.25 (CH_{Ar}), 129.83 (CH_{Ar}), 128.52 (CH_{Ar}), 122,90 (CH_{Ar}), 92.86 (C_q), 70.13 (CH), 50.11 (CH), 32.92 (CH_2), 32.83 (CH_2), 25.71 (CH_2), 25.63 (CH_2), 24.81 (CH_2) ppm.

1,1'-(4,4'-(Ethane-1,2-diyl)bis(4,1-phenylene)) bis(3-cyclohexyl-5-phenylimidazolidine-2,4-dione) (2a): IR-ATR: 2935, 2855, 1768, 1708 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ = 7.50-7.131 (14H, m, CH_{Ar}), 6.9 (4H, m, CH_{Ar}), 5.98 (2H, s, 2PhCH), 4.04-4.03 (2H, m, 2CH cyclohexyl), 2.75 (4H, s, CH_2CH_2), 2.35-2.14 (6H, m, $3CH_2$ cyclohexyl), 1.82-1.57 (8H, m, $4CH_2$ cyclohexyl), 1.36-1.23 (6H, m, $3CH_2$ cyclohexyl) ppm; ^{13}C NMR (100MHz, $CDCl_3$): δ = 170.10 (C_q), 156.91 (C_q), 138.12 (C_q), 136.83 (C_q), 135.73 (C_q), 133.52 (CH_{Ar}), 129.54 (CH_{Ar}), 129.21 (CH_{Ar}), 127.85 (CH_{Ar}), 127.48 (CH_{Ar}), 73.08 (CH), 63.71 (CH), 37.46 (CH_2), 30.57 (CH_2), 25.71 (CH_2), 24.47 (CH_2) ppm.

1,1'-(4,4'-Oxybis(4,1-phenylene))bis(3-cyclo hexyl-5-phenylimidazolidine-2,4-dione)(2b): IR-ATR: 2926, 2854, 1773, 1704 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ = 7.99-7.80 (4H, m, CH_{Ar}), 7.42-6.99 (14H, m, CH_{Ar}), 5.85 (2H, s, 2PhCH), 3.80-3.75 (2H, m, 2CH cyclohexyl), 2.62-2.50 (4H, m, $2CH_2$ cyclohexyl), 1.85-1.77 (8H, m, $4CH_2$ cyclohexyl), 1.65-1.55 (4H, m, $2CH_2$ cyclohexyl) ppm; ^{13}C NMR (100MHz, $CDCl_3$): δ = 170.82 (C_q), 157.92 (C_q), 150.01 (C_q), 136.89 (C_q), 132.25 (C_q),

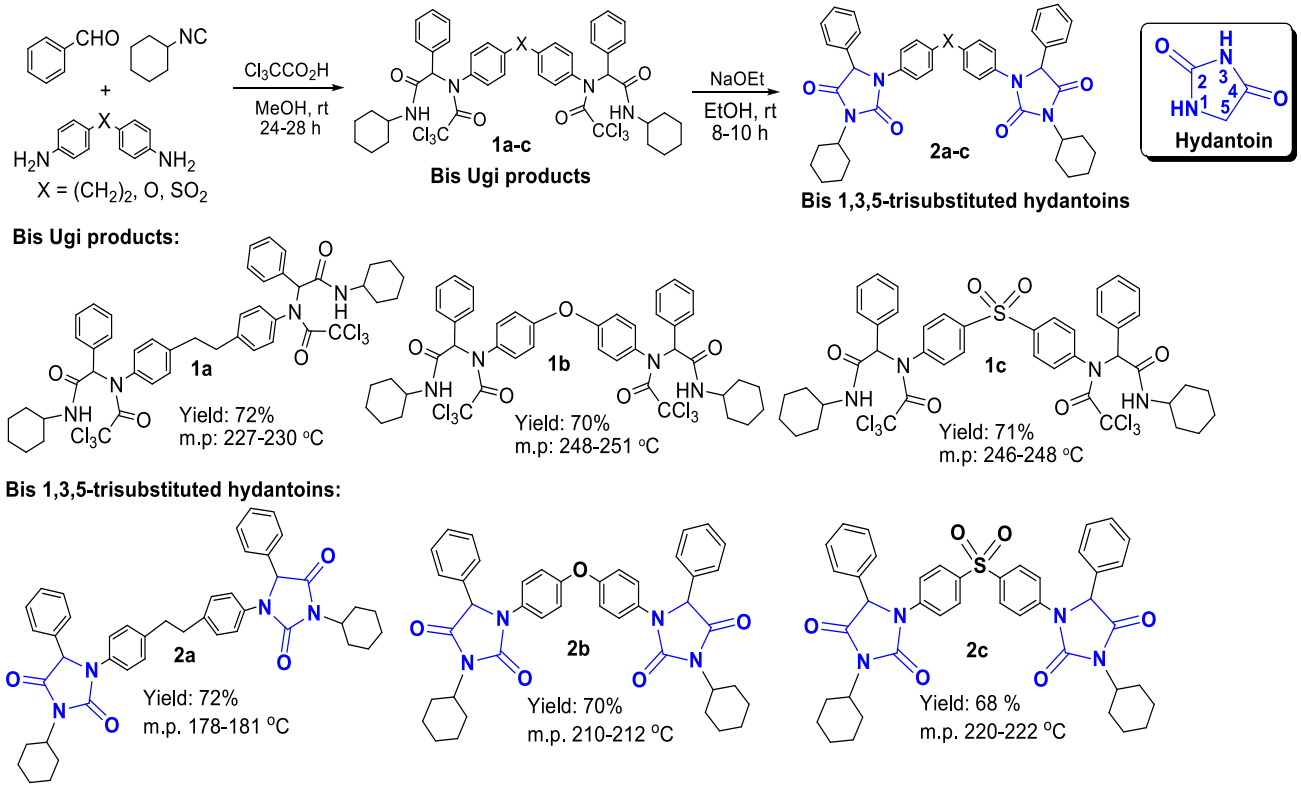
129.83 (CH_{Ar}), 129.15 (CH_{Ar}), 127.85 (CH_{Ar}), 127.45 (CH_{Ar}), 121.33 (CH_{Ar}), 72.6 (CH), 62.86 (CH), 30.48 (CH_2), 24.82 (CH_2), 24.56 (CH_2) ppm.

1,1'-(4,4'-Sulfonylbis(4,1-phenylene))bis(3-cyclohexyl-5-phenylimidazolidine-2,4-dione) (2c): IR-ATR: 2931, 2857, 1771, 1708 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ = 8.0-7.75 (8H, m, CH_{Ar}), 7.42-7.12 (10H, m, CH_{Ar}), 5.88 (2H, s, 2PhCH), 3.48-3.55 (2H, m, 2CH cyclohexyl), 2.62-2.50 (4H, m, $2CH_2$ cyclohexyl), 1.81-1.75 (8H, m, $2CH_2$ cyclohexyl), 1.60-1.55 (4H, m, $2CH_2$ cyclohexyl), 1.21-1.15 (4H, m, $2CH_2$ cyclohexyl) ppm; ^{13}C NMR (100MHz, $CDCl_3$): δ = 171.12 (C_q), 157.81 (C_q), 144.21 (C_q), 137.23 (C_q), 136.95 (C_q), 130.10 (CH_{Ar}), 129.99 (CH_{Ar}), 128.95 (CH_{Ar}), 127.86 (CH_{Ar}), 123.16 (CH_{Ar}), 72.8 (CH), 63.86 (CH), 30.43 (CH_2), 26.23 (CH_2), 24.52 (CH_2) ppm.

RESULTS AND DISCUSSION

Initially, bis Ugi products 1a-1c were synthesized in good yields by amine (4,4´-diaminobibenzyl, 4,4´-diaminodiphenyl ether and 4,4´-diaminodiphenyl sulfone), benzaldehyde, cyclohexyl isocyanide and trichloro acetic acid in MeOH at room temperature. Upon treatment with NaOEt in EtOH at room temperature, Ugi adducts 1a-1c underwent a ring-closure reaction to give bis 1,3,5-trisubstituted hydantoins 2a-2c in good yields (Scheme 3).

The products were identified by FT-IR, ^1H NMR and ^{13}C NMR studies. In the IR spectra of 1a-1c, the amide NH and the CCl_3 absorptions were detected at 3368-3263 cm^{-1} and 834-699 cm^{-1}, respectively. The trichloroacetamide and the amide carbonyl groups gave peaks at 1690-1677 cm^{-1} and 1652-1646 cm^{-1}, respectively. In the ^1H NMR spectra of 1a-1c, the proton in the position α to the amido group was detected at δ = 5.23-6.01 ppm. Again, the IR spectra gave useful information about the structure of compounds 2a-2c. In fact, the absorptions due to the amide NH and to the CCl_3 group were not detected. Furthermore, a CO peak at 1773-1768 cm^{-1} was found in agreement with the presense of a cyclic urea moiety. The CO absorptions due to the γ-lactam and the amide moties were overlapped and unique peak at 1708-1704 cm^{-1} was observed. As expected, neither the NH proton signal in the ^1H NMR spectra nor the CCl_3 carbon signal in the ^{13}C NMR was detected.

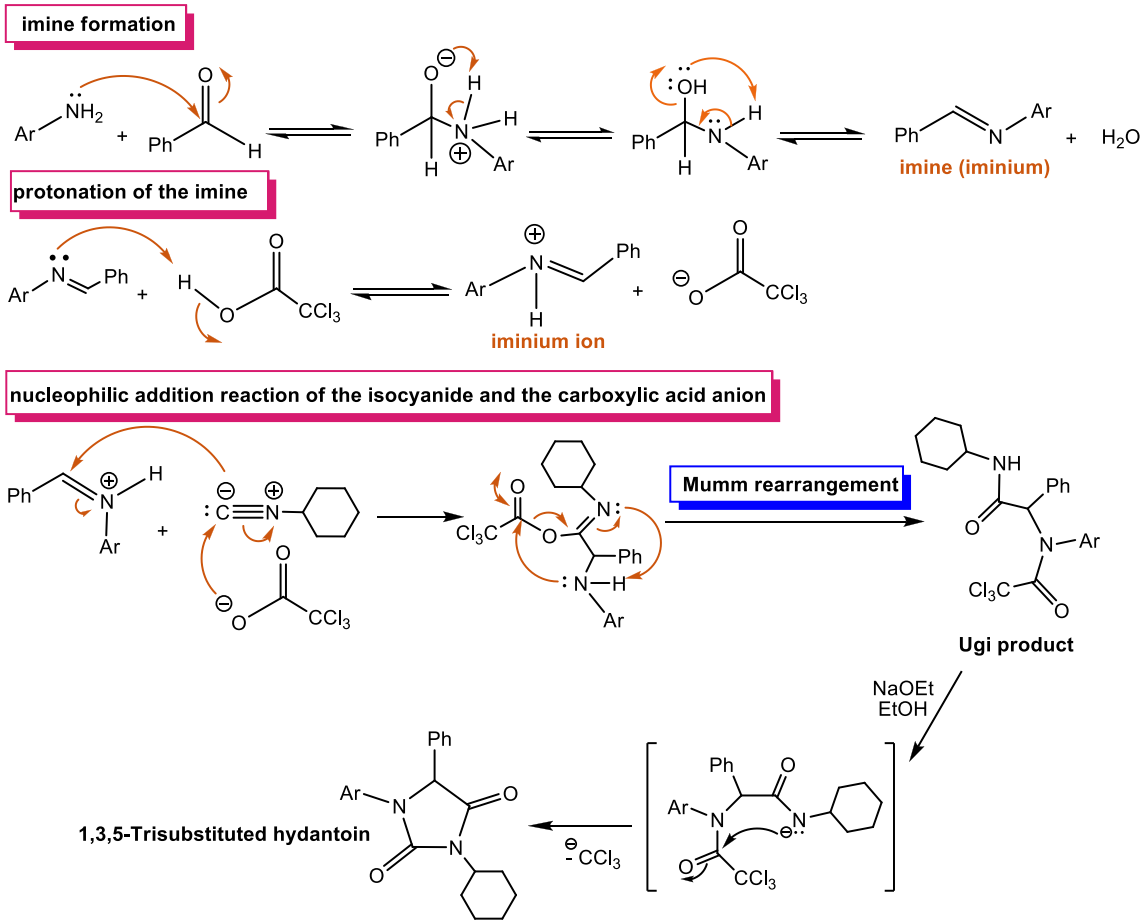


Scheme 3. Synthesis of bis Ugi products 1a-1c and bis 1,3,5-trisubstituted hydantoins 2a-2c

The bis Ugi products 1a-1c and 1,3,5-trisubstituted bis hydantoin 2a-2c were synthesized in good yields.

In the first step of U-4CR, the *in situ* imine (or iminium) formation was observed by the reaction of the aldehyde and the amine. In the second step, protonation of the imine by the acid gave electrophilic iminium ion and nucleophilic acid anion. These intermediates reacted with the isocyanide in the third step (nucleophilic addition

reaction). The stable Ugi product was obtained after Mumm rearrangement (Scheme 4) [26, 27].



Scheme 4. Formation of bis Ugi products and bis 1,3,5-trisubstituted hydantoins

CONCLUSIONS

In this work we report the synthesis of new Ugi products by four-component Ugi condensation and the subsequent synthesis of hydantoins based on a ring closure reaction. This was achieved in a two-step sequence, using simple and commercially available starting materials.

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