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Amide-Stabilized Enols in the Enol-Ugi Reaction: A Five-Component Synthesis of Triamides †

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Abstract: In continuation with our research in the use of enols in multicomponent reactions with isocyanides (IMCR), we have used for the first time amide-stabilized enols as the acid component in enol-Ugi reactions. Thus, the reaction of 2-(hydroxy(phenylamino)methylene)-5,5-dimethylcyclohexane-1,3-dione with aldehydes, amines and isocyanides provides the expected enamine adducts. On the other hand, the use of analogous Meldrum's acid-derived enols permits the synthesis of triamides by a five-component process with the participation of a molecule of solvent. These results confirm the great potential of the enol-Ugi reaction for the preparation of a wide variety of structures containing a peptidomimetic scaffolds.

Keywords: isocyanides; triamides; enamines; enol-Ugi; enol; multicomponent reaction; peptidomimetics; dimedone; Meldrum acid

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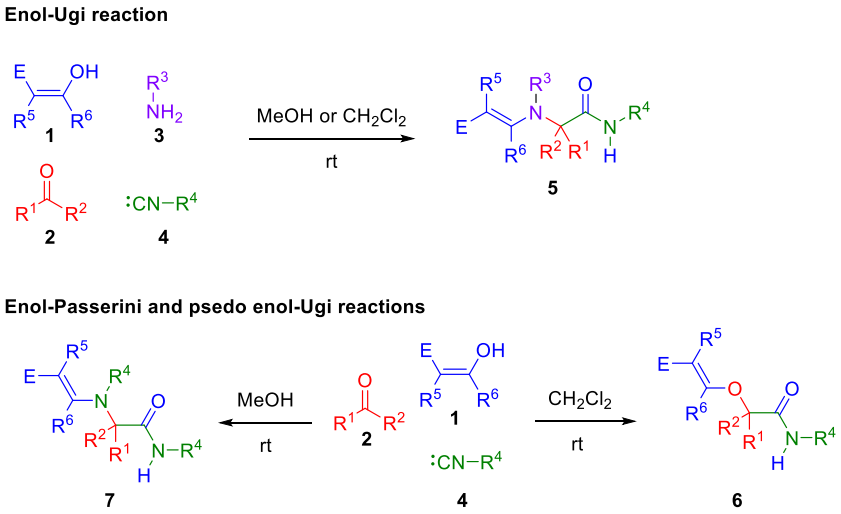
1. Introduction

Multicomponent reactions, and in particular multicomponent reactions of isocyanides (IMCRs), constitute a highly convergent strategy for the synthesis of diverse molecular libraries in one-pot with atom and bond economy [1–3]. The most well-known IMCR are the Passerini [4] reaction and the Ugi [5] rection, which permit to obtain, respectively, α-acyloxy amides and α-amido amides in a single step.

We have recently developed an Ugi-type MCR with electron-deficient enols as acid components (Scheme 1). This *enol-Ugi condensation* consist in the reaction between enols (**1**), aldehydes (**2**), amines (**3**) and isocyanides (**4**) to give polysubstituted heterocyclic enamines containing a pseudopeptidic subunit (**5**) [6–8]. On the other hand, the condensation of enols (**1**), aldehydes (**2**) and isocyanides (**4**) selectively gives either three- or pseudo-four component adducts (**6** or **7**, respectively), depending on the reaction conditions [9]. In this way, the enol-Ugi and enol-Passerini condensations of heterocyclic enols, such as pyrrolidonodiones (**15**), 3-hydroxycoumarins (**16**) and 4-hydroxycoumarins (**17**), efficiently afford peptidomimetic enamines and pyrrolidinone-derived enol-ethers. The use of enols as acid surrogates in IMCR allows the synthesis of peptidomimetic derivatives of pyrrolidine-2,3-diones [10], privileged structures present in many bioactive compounds and drugs [11], and coumarins, analogues of a family of plant metabolites having essential biological activities [12,13].



Scheme 1. IMCR with enols.

Our previous work demonstrates that the enol-Ugi [6–8] and the enol-Passerini reactions [9] and their post-condensation modifications [14] constitute an efficient method to attain new molecular scaffolds by using an array of different starting enols (Figure 1).

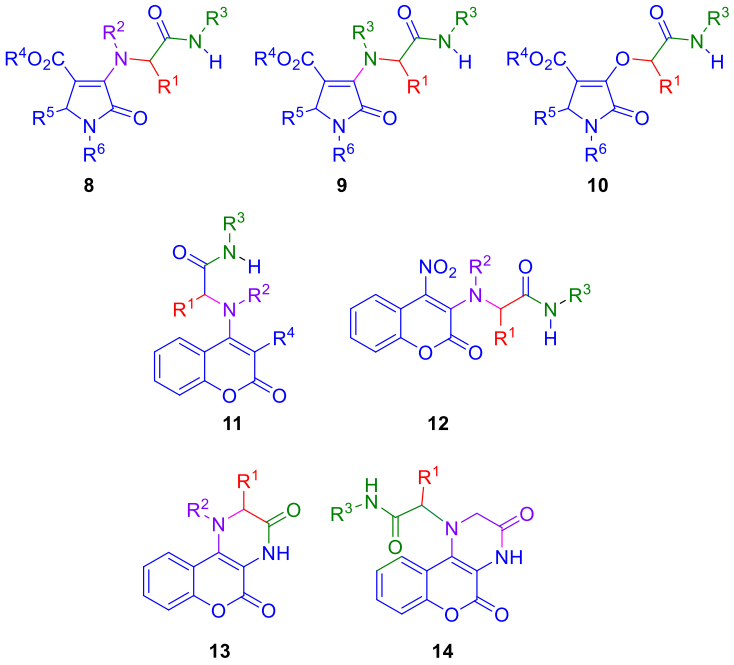


Figure 1. Molecular scaffolds obtained by IMCR with enols.

2. Results and Discussion

In other to widen the scope of these novel reactions, we decided to explore the possibility of using other types of enols, [15,16] particularly amide-stabilized enols, [17] which would lead to synthetically challenging polyamide containing compounds. Here we report the enol-Ugi reaction of amide-stabilized enols (**20**) and (**21**) (Figure 2) to give novel peptidomimetic structures.

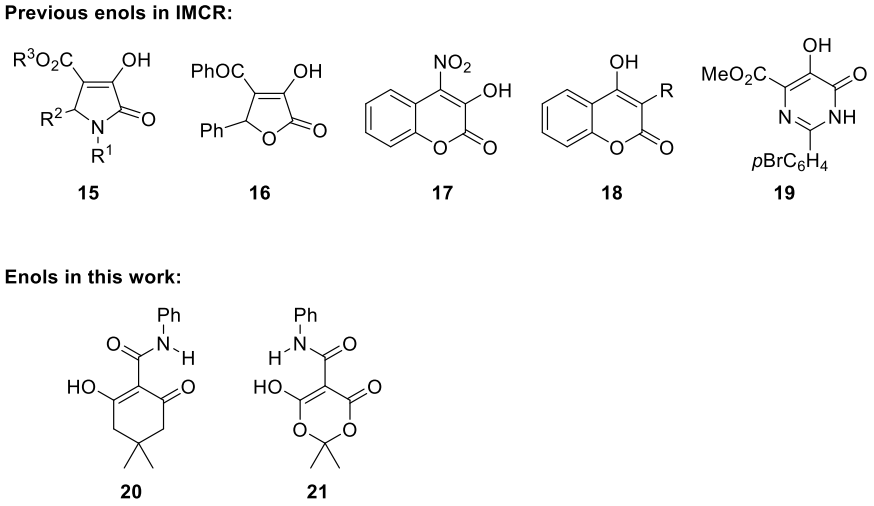


Figure 2. Enols used in multicomponent reactions of isocyanides.

Compounds **20** and **21** can exist in different tautomeric forms, as shown in Figure 3. Experimental and theoretical studies show that the predominant forms in each case are (**20c**) and (**21a**) [17]. However, as equilibrium between tautomers is possible, in principle, any of the enolic forms **a** or **b** could participate in an enol-Ugi condensation.

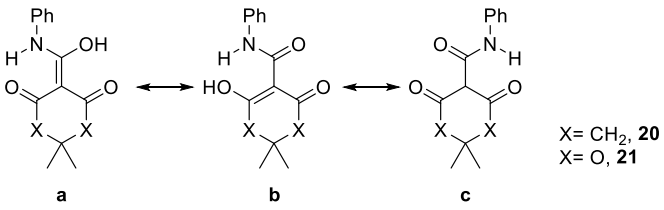
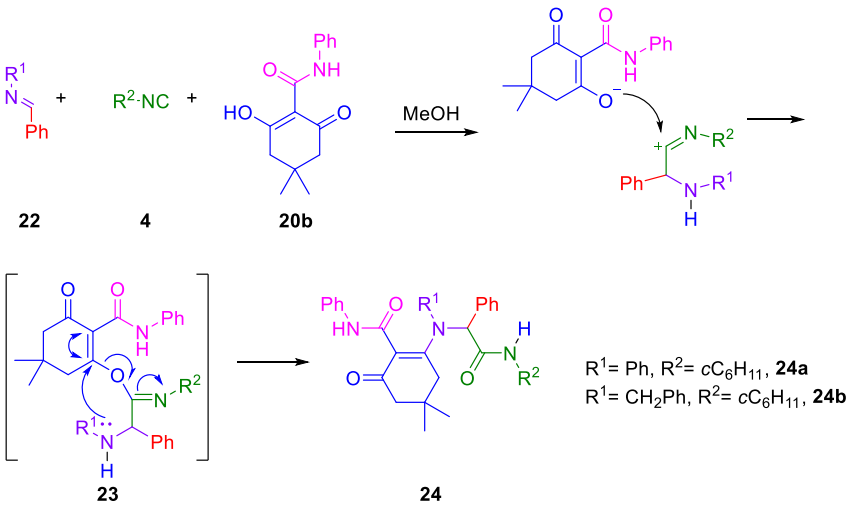


Figure 3. Equilibrium between tautomers of the starting enols.

To explore the multicomponent chemistry of these compounds, we made react enolic dimedone derivative (**20**) with preformed (*E*)-*N*,1-diphenylmethanimine (**22a**) and cyclohexilisocyanide (**4a**) in methanol. After 48 h stirring at room temperature, we obtained a product that was identified as enamine (**24a**), confirming that the minor tautomeric enol (**20b**) was the substrate for the enol-Ugi condensation (Scheme 2).



Scheme 2. Enol-Ugi reaction of a dimedone derivative enol.

Basing on previous reports, the reaction mechanism must involve the attack of the isocyanide (**4**) to the protonated imine (22) resulting in a nitrilium ion that is then is attacked by the enolate to give the enol-Ugi primary adduct (**23**). This then undergoes an intramolecular conjugate addition of the amine nitrogen on the dimedone ring, followed by β-elimination of the imidate oxygen, providing the final adduct (**24**) (Scheme 2).

Then, we investigated the enol-Ugi reaction of imine (**22a**) and *tert*-butylisocyanide (**4b**) with the Meldrum acid-derived enol (**21**). This compound was obtained by reaction of Medrum acid with phenyl isocyanate, according to a literature procedure [17]. Proton and carbon NMR spectra of (**21**) in $CDCl_3$ show the only presence of the more stable tautomeric form (**21a**). Nevertheless, Rappoport has reported that the enolic form (**21b**) is predominant in protic solvents,[17] so we anticipated that this could be the reacting form in the multicomponent condensation.

However, a complex mixture was obtained when the reaction was performed in methanol or toluene in the presence of ammonium chloride. Successfully, when the reaction was performed in isopropanol at 20–25 °C a precipitate that showed a single product on t.l.c. was obtained. The ^{1}H-NMR spectrum of this compound (Figure 4) shows the signals of aromatic groups of the starting enol, aldehyde, amine, and the *tert*-butyl group. In addition, a quadruplet at 5.07 ppm corresponding to 1 H and a double doublet at 1.28 ppm corresponding to 6 H evidenced the presence of an isopropyl group. Therefore, this spectrum does not match with the expected enol-Ugi adduct, although it is consistent with the formation of a four-component adduct with the participation of isopropanol and the loss of an acetone molecule.

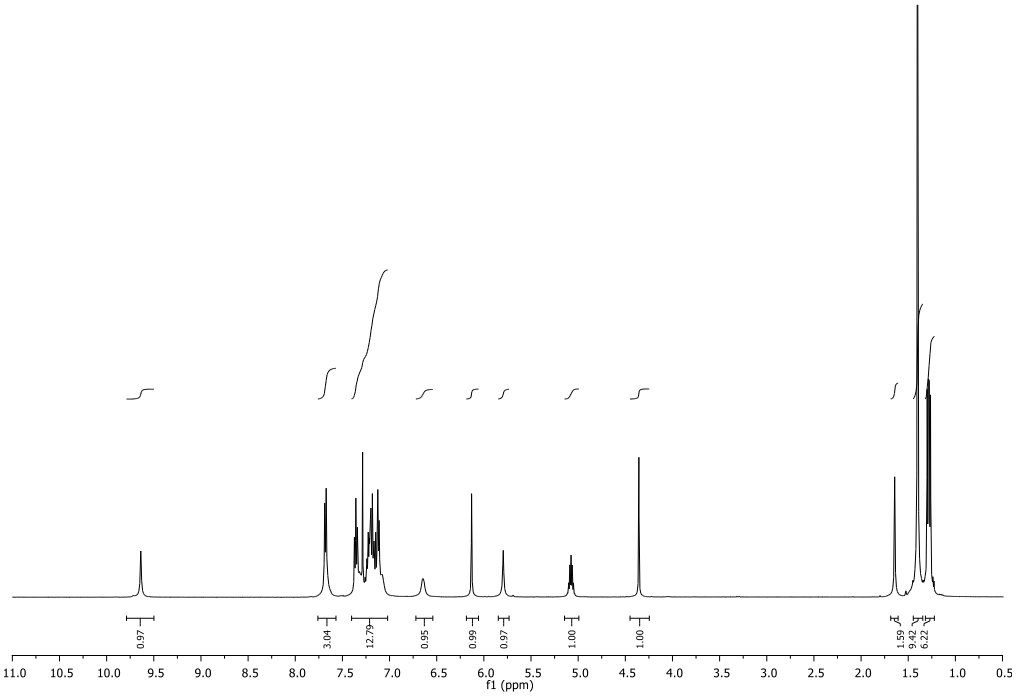
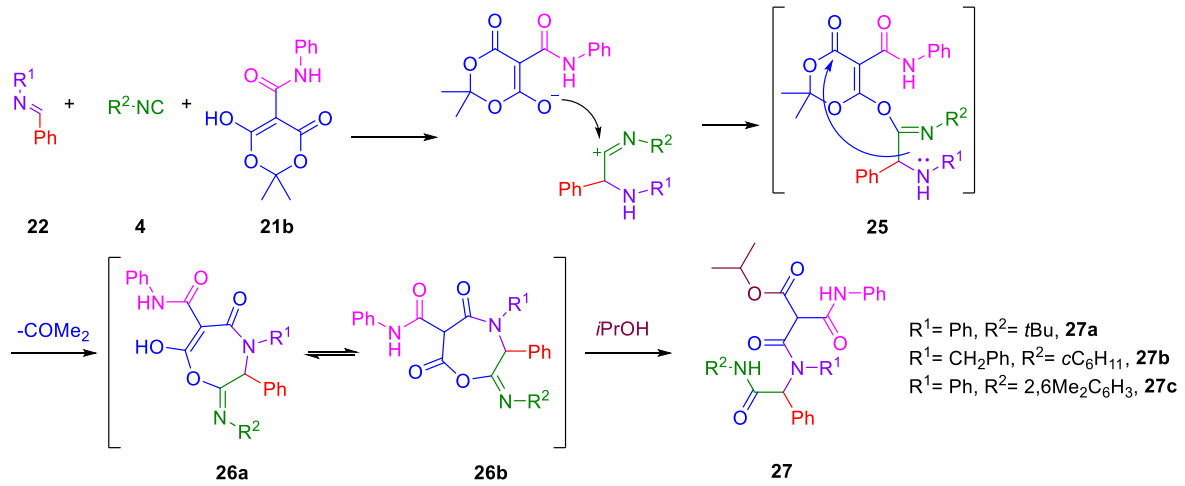


Figure 4. ^{1}H-MNR of five-component MCRI of enols.

A possible mechanism entails the enol-Ugi reaction between imine (**22**), *tert*-butylisocyanide (**4b**) and the enolic form **(21b**) to give the enol-Ugi primary adduct (**25**). This would rearrange with the loss of acetone to give seven-membered intermediate (**26a**) that could tautomerize to (**26b**) and then react with a molecule of isopropanol with the consequent ring opening (Scheme 3). The structure of the resulting product (**27a**) is compatible with the obtained spectroscopic data.



Scheme 3. Possible mechanism of five-component MCRI of Meldrum acid derivative enol **21**.

A control experiment was carried out consisting in stirring 5-(hydroxy(phenylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**21**) in isopropanol. No product formation was observed after 48 h and only starting material (**21**) was recovered from the reaction mixture. This strongly suggests that the isopropanol attack should take place on a reaction intermediate, supporting the proposed mechanism.

This process constitutes a new five-component reaction of aldehydes, amines, enols, isocyanides and isopropanol leading to peptidomimetic structures containing three amide groups. Triamides are present in compounds with different applications, such as complexing agents and pharmaceuticals [18–21].

In summary, two classes of amide stabilized enols have been subjected to enol-Ugi condensations leading to either rigid or flexible retropeptidic dipeptides (Figure 5). The substitution pattern in both types of structures is highly tunable by selecting between different four or five starting components. Furthermore, the peptide sequence could theoretically be grown from any of the amide or ester ends to obtain extended retropeptidic sequences.

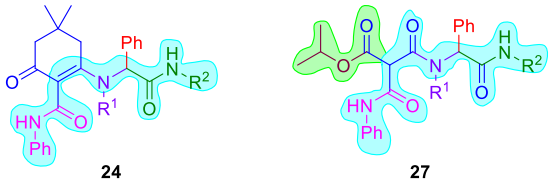


Figure 5. Enol-Ugi adducts enolamides. Dipeptidic structures are shaded in light blue/green colour.

3. Experimental Section

3.1. Synthesis of Enols

For the preparation of enols we used the synthesis described by Mukhopadhyaya. [17] To a solution of dimedone or Meldrum acid (25 mmol) in 25 mL of DMF, 50 mmol of triethylamine was added and the resulting mixture was stirred during five minutes. Then, 25 mmol of phenylisocyanate was added. After 30 min at room temperature the reaction mixture was poured in 250 mL of 2 N HCl at 0 °C to give a precipitate that was filtered and washed whit cool water.

3.1.1. 2-Hydroxy-4,4-dimethyl-6-oxo-N-phenylcyclohex-1-ene-1-carboxamide (**20**)

White solid (44%); m.p.: 87–89 °C. (Lit: 84–85 °C) [17]. IR (KBr, cm^{-1}): 3327, 3281, 1649, 1595, 1556, 1498, 1448, 1315, 1233, 754, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.77 (s,

1H), 7.56 (d, *J* = 7.9 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 2.53 (s, 2H), 2.41 (s, 2H), 1.11 (s, 6H).

3.1.2. 5-(Hydroxy(phenylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**21**)

White solid (90%); m.p.: 102–104 °C. (Lit: 109–110 °C) [17]. IR (KBr, cm^{-1}): 3436, 3067, 1693, 1638, 1426, 1336, 1264, 1223, 1095, 924, 802, 758; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.16 (s, 1H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.40 (t, *J* = 7.9 Hz, 2H), 7.27–7.25 (m, 1H), 1.77 (s, 6H); ^{13}C RNMR (101 MHz, $CDCl_3$) δ (ppm): 169.30 (C), 135.02 (C), 129.54 (CH), 126.71 (CH), 122.41 (CH), 105.31 (C), 73.87 (C), 26.50 (CH_3).

*3.2. Enol-Ugi Reactions of 2-hydroxy-4,4-dimethyl-6-oxo-N-phenylcyclohex-1-ene-1-carboxamide (**20**)*

To a solution of 1 mmol of imine **22** in 1 mL of methanol, 1 mmol of isocyanide **4** and 0.5 mmol of enol **20** were added successively. The reaction mixture was stirred at room temperature for 48 h. Then 10% HCl (1 mL) was added, the mixture was washed with H_2O (20 mL), extracted with CH_2Cl_2 (3 × 20 mL) and dried over Na_2SO_4. Removal of the solvent and purification by column chromatography (SiO_2, gradient from 100% hexanes to hexanes–EtOAc, 6:6) gave the corresponding enamines **24a-b.**

3.2.1. 2-((2-(Cyclohexylamino)-2-oxo-1-phenylethyl)(phenyl)amino)-4,4-dimethyl-6-oxo-N-phenylcyclohex-1-ene-1-carboxamide (**24a**)

White solid (24%); m.p.: 160–162 °C. IR (KBr, cm^{-1}): 3430, 3197, 3034, 2931, 2851, 1657, 1594, 1541, 1496, 1445, 1385, 1318, 1091, 747, 699; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.97 (s, 1H), 8.54 (bs, 1H), 7.30 7.15 (m, 6H), 7.14 7.07 (m, 3H), 7.05 6.95 (m, 5H), 6.90 6.84 (m, 1H), 6.29 (s, 1H), 3.95 3.82 (m, 1H), 2.70 (dd, *J* = 17.7, 7.5 Hz, 2H), 2.38 (dd, *J* = 17.6, 7.5 Hz, 2H), 2.06–1.55 (m, 5H), 1.40–1.11 (m, 5H), 1,16 (s, 3H), 1.09 (s, 3H); ^{13}C RNMR (126 MHz, $CDCl_3$) δ (ppm): 196.31 (C), 171.49 (C), 167.86 (C), 163.64 (C), 143.54 (C), 138.31 (C), 134.37 (C), 130.21 (CH), 128.61 (CH), 128.23 (CH), 128.20 (CH), 128.00 (CH), 127.88 (CH), 126.33 (CH), 123.67 (CH), 120.46 (CH), 112.86 (C), 69.13 (CH), 50.75 (CH_2), 49.35 (CH), 45.61 (CH_2), 32.91 (CH_2), 32.72 (CH_2), 30.95 (C), 29.33 (CH_3), 27.66 (CH_3), 25.44 (CH_2), 25.18 (CH_2), 25.13 (CH_2).

3.2.2. 2-(Benzyl(2-(cyclohexylamino)-2-oxo-1-phenylethyl)amino)-4,4-dimethyl-6-oxo-N-phenylcyclohex-1-ene-1-carboxamide (**24b**)

White solid (24%); m.p.: 154–156 °C. IR (KBr, cm^{-1}): 3426, 3113, 3038, 2934, 2851, 1659, 1590, 1541, 1493, 1447, 1312, 1116, 750, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.18 (s, 1H), 9.09 (bs, 1H), 7.71 (d, *J* = 7.9 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 3H), 7.30–7.20 (m, 3H), 7.15–7.04 (m, 4H), 6.69 (bs, 2H), 5.72 (s, 1H), 4.75 (d, *J* = 16.0 Hz, 1H), 4.49 (d, *J* = 16.1 Hz, 1H), 3.86–3.72 (m, 1H), 2.82 (d, *J* = 17.5 Hz, 1H), 2.67 (d, *J* = 17.8 Hz, 1H), 2.23 (q, *J* = 16.0 Hz, 2H), 1.99–1.56 (m, 5H), 1.45–1.02 (m, 5H), 1.09 (s, 3H), 1.06 (s, 3H); ^{13}C RNMR (126 MHz, $CDCl_3$) δ (ppm): 196.26 (C), 174.00 (C), 168.36 (C), 164.03 (C), 138.92 (C), 136.79 (C), 134.23 (C), 130.26 (CH), 129.00 (CH), 128.97 (CH), 128.77 (CH), 128.40 (CH), 127.38 (CH), 126.64 (CH), 123.87 (CH), 120.54 (CH), 108.66 (C), 70.21 (CH), 50.72 (CH_2), 49.15 (CH), 45.64 (CH_2), 32.73 (CH_2), 32.69 (CH_2), 29.99 (C), 29.78 (CH_2), 29.44 (CH_2), 27.44 (CH_3), 25.57 (CH_2), 25.04 (CH_2).

*3.3. Five Component Condensation of of 5-(hydroxy(phenylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione **21***

To a solution of 0.5 mmol of imine **22**in 0.5 mL of propan-2-ol, 0.5 mmol of isocyanide **4** and 0.5 mmol of enol **21** were added successively. The reaction mixture was stirred at 25–30 °C for 3–5 days. The reaction mixture was cooled at 0 °C, filtered and washed with propan-2-ol and cyclohexane, to give the products **27a-c**.

3.3.1. Isopropyl 3-((2-(tert-butylamino)-2-oxo-1-phenylethyl)(phenyl)amino)-3-oxo-2-(phenylcarbamoyl)propanoate (**27a**)

White solid (19%); m.p.: 166–168 °C. IR (KBr, cm^{-1}): 3312, 2976, 1747, 1693, 1654, 1602, 1556, 1493, 1445, 1355, 1336, 1106, 752, 707; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.62 (bs, 1H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.40–6.92 (m, 13H), 6.62 (sa, 1H), 6.11 (s, 1H), 5.07 (c, *J* = 6.2 Hz, 1H), 4.33 (s, 1H), 1.38 (s, 9H), 1.28 dd, *J* = 11.4, 6.3 Hz, 6H); ^{13}C RNMR (101 MHz, $CDCl_3$) δ (ppm): 168.10 (C), 166.25(C), 165.68 (C), 161.22 (C), 138.46 (C), 137.85 (C), 133.85 (C), 130.52 (CH), 129.28 (CH), 129.22 (CH), 129.00 (CH), 128.93 (CH), 128.84 (CH), 128.58 (CH), 128.41 (CH), 127.32 (CH), 124.45 (CH), 120.38 (CH), 119.06 (CH), 113.90 (CH), 70.37 (CH), 66.10 (CH), 58.84 (CH), 52.00 (C), 28.66 (CH_3), 21.71 (CH_3), 21.61 (CH_3); MS (QI) *m*/*z* (%): 530 (M^{+}. + 1, <5), 426 (6), 397 (25), 303 (21), 280 (6), 247 (7), 182 (100).

3.3.2. Isopropyl 3-(benzyl(2-(cyclohexylamino)-2-oxo-1-phenylethyl)amino)-3-oxo-2-(phenylcarbamoyl)propanoate (**27b**)

White solid (24%); m.p.: 158–161 °C. IR (KBr, cm^{-1}): 3426, 3282, 3089, 3066, 2932, 2856, 1743, 1697, 1656, 1632, 1602, 1556, 1499, 1448, 1132, 1110, 750, 699; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.86 (bs, 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.38–7.28 (m, 4H), 7.24–7.19 (m, 3H), 7.18–7.10 (m, 4H), 7.02–6.92 (m, 2H), 6.32 (d, *J* = 8.2 Hz, 1H), 6.11 (s, 1H), 5.12 (d, *J* = 17.9 Hz, 1H), 5.06 (q, *J* = 6.4 Hz, 1H), 4.59 (s, 1H), 4.53 (d, *J* = 17.9 Hz, 1H), 3.87–3.77 (m, 1H), 1.98–1.55 (m, 5H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.21 (d, *J* = 6.2 Hz, 3H), 1.41–0.99 (m, 5H);^{13}C RNMR (126 MHz, $CDCl_3$) δ (ppm) (mixture of two diastereoisomers): 167.71 (C), 167.53 (C), 167.35 (C), 167.27 (C), 166.59 (C), 165.73 (C), 161.95 (C), 161.05 (C), 137.71 (C), 137.46 (C), 136.30 (C), 135.79 (C), 134.45 (C), 134.35 (C), 130.41 (CH), 129.64 (CH), 129.03 (CH), 128.84 (CH), 128.76 (CH), 128.51 (CH), 128.10 (CH), 127.82 (CH), 127.74 (CH), 127.42 (CH), 126.72 (CH), 126.29 (CH), 125.01 (CH), 124.69 (CH), 120.62 (CH), 120.42 (CH), 71.03 (CH), 70.79 (CH), 65.14 (CH), 63.94 (CH), 58.16 (CH), 57.24 (CH), 51.65 (CH_2), 50.23 (CH_2), 48.97 (CH), 48.81 (CH), 33.03 (CH_2), 32.79 (CH_2), 25.65 (CH_2), 25.59 (CH_2), 25.04 (CH_2), 24.93 (CH_2), 24.85 (CH_2), 21.79 (CH_3), 21.74 (CH_3), 21.68 (CH_3), 21.58 (CH_3), 21.51 (CH_3), 21.48 (CH_3).

3.3.3. Isopropyl 3-((2-((2,6-dimethylphenyl)amino)-2-oxo-1-phenylethyl)(phenyl)amino)-3-oxo-2-(phenylcarbamoyl)propanoate (**27c**)

White solid (40%); m.p.: 173–175 °C. IR (KBr, cm^{-1}): 3247, 3064, 2977, 1745, 1696, 1667, 1600, 1550, 1492, 1445, 1359, 1281, 1188, 1104, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.66 (bs, 1H), 7.78 (bs, 1H), 7.57 (d, *J* = 7.4 Hz, 2H), 7.45 (s, 1H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.27–7.19 (m, 7H), 7.16–7.03 (m, 5H), 6.67 (bs, 1H), 6.42 (s, 1H), 5.07 (q, *J* = 6.2 Hz, 1H), 4.40 (s, 1H), 2.21 (s, 6H), 1.28 (dd, *J* = 11.5, 6.3 Hz, 6H);^{13}C RNMR (101 MHz, $CDCl_3$) δ (ppm): 167.19 (C), 166.54 (C), 165.63 (C), 161.09 (C), 135.60 (C), 133.81 (C), 133.08 (C), 130.66 (CH), 129.38 (CH), 129.33(CH), 129.06 (CH), 128.56 (CH), 128.28 (CH), 128.21 (CH), 127.38 (CH), 127.36 (CH), 124.57 (CH), 120.34 (CH), 114.16 (CH), 70.61 (CH), 66.03 (CH), 58.38 (CH), 21.61 (CH_3), 21.50 (CH_3), 18.55 (CH_3); MS (QI) *m*/*z* (%): 578 (M + 1, <5), 331 (23), 248 (11), 149 (100)..

4. Conclusions

Amide-stabilized enols have been used for the first time in a condensation with imines and isocyanides to selectively give four- or five-component adducts. These results prove the utility of enols containing conjugated electron-withdrawing groups as effective reagents in isocyanide-based multicomponent reactions. This methodology constitutes an efficient method for the direct synthesis of diverse retro-peptidic subunits.

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acquisition, C.F.M. All authors have read and agreed to the published version of the manuscript. synthetic investigation, spectroscopic data

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