Supporting Information for

The sustainable synthesis of peptidomimetics via chemoenzymatic tandem oxidation-Ugi reaction

Arleta Madej, Dominik Koszelewski, Daniel Paprocki, Anna Brodzka, Ryszard Ostaszewski

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland
Synthesis of \(N\)-(4-methoxybenzyl)formamide:

Reaction conditions: 4-methoxybenzylamine (30 mmol; 3.8 mL) and ethyl formate (12.5 mL) were heated under reflux overnight. After cooling the reaction mixture to room temperature, 5 ml hexane were added. The precipitate was filtered and washed with hexane. Yield 78 % (3.86 g).

**Figure 1**

1H NMR spectrum of \(N\)-(4-methoxybenzyl)formamide (200 MHz, CDCl\(_3\)).

Synthesis of \(p\)-methoxybenzylisocyanide (5a):

**I Method:**

Reaction conditions: To a solution of \(N\)-(4-methoxybenzyl)formamide (16 mmol; 2.64 g) and triethylamine (48 mmol; 6.7 mL) in dry dichloromethane (20 mL at -78°C phosphoryl oxychloride (20 mmol; 1.85 mL) was added dropwise. After 1 h of stirring at room temperature, the reaction mixture was quenched by adding a saturated solution of NaHCO\(_3\) (20 mL), then extracted with dichloromethane (2×20 mL). The combined organic layers were dried with MgSO\(_4\) and residuals of solvent were distilled under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane/AcOEt (8.5:1.5 / v:v) as an eluent. Yield 80 % (1.88 g).
II Method (PTC condition):

Reaction conditions: To a mixture of sodium hydroxide (2.5 g), \( \text{t}-\text{butyl ammonium bromide} \) (0.19 g) in distilled water (2.5 mL) was added the solution of 4-methoxybenzylamine (6 mmol, 750 \( \mu \)L) in chloroform (20 mL). After 18 h of stirring at room temperature, the reaction mixture was quenched by adding distilled water, then extracted with dichloromethane (3x20 mL). The combined organic layers were dried with \( \text{MgSO}_4 \) and residuals of solvent were distilled under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane/AcOEt (8.5:1.5 \( \text{v:v} \)) as an eluent. Yield 66\% (582.4 mg).

Figure 2. \(^1\text{H} \) NMR spectrum of compound 4a (200 MHz, CDCl\(_3\)).
Appearance of the aqueous Ugi multicomponent reaction samples containing SDS

**Figure 3.** Photographic images of the Ugi multicomponent reaction samples (reaction with benzyl alcohol1a (0.5 mmol), p-methoxybenzylamine3a (0.5 mmol) and p-methoxybenzylisocyanide5a (0.5 mmol)) in phosphate buffer 5.2 pH (5 mL), with the addition of SDS, TEMPO and LTv in 25 °C. The reaction was carried out in an open vessel.

a) suspension of SDS, TEMPO and LTv in phosphate buffer 5.2 pH after 10 minutes of stirring with a magnetic stirrer.

b) Reaction mixture in suspension of SDS, TEMPO, LTv after addition of 1a

c) Reaction mixture in suspension of SDS, TEMPO, LTv and 1a 10 minutes after addition of 3a next day.

d) Reaction mixture in suspension of SDS, TEMPO, LTv and 1a 10 minutes after addition of 3a, 4a and 5a next day.
Figure 4. $^1$HNMR (above) and $^{13}$CNMR (below) spectra of compounds 6a N-[(4-methoxyphenyl)methyl]-2-[(4-methoxyphenyl)methyl-(2-phenylacetylo)amino]-2-phenylacetamide (400 MHz, CDCl$_3$). (400 MHz, CDCl$_3$).
Figure 5. $^1$HNMR (above) and $^{13}$CNMR (below) spectra of compounds 6b N-[(4-methoxyphenyl)metyl]-2-[4-methoxyphenyl)methyl(2-phenylacetylo)amino]-2-[4-methylphenyl)acetamide (400 MHz, CDCl$_3$).
Figure 6. $^1$HNMR (above) and $^{13}$CNMR (below) spectra of compounds 6c N-[(4-methoxyphenyl)methyl]-2-[(4-methoxyphenyl)methyl-(2-phenylacetylo)amino]-2-[4-methoxyphenyl)acetamide (400 MHz, CDCl$_3$).
Figure 7. $^1$HNMR (above) and $^{13}$CNMR (below) spectra of compounds 6d N-[(4-methoxyphenyl)methyl]-2-[(4-methoxyphenyl)methyl-(2-phenylacetyl)amino]-2-[4-chlorophenyl)acetamide(400 MHz, CDCl$_3$).
Figure 8. $^1$HNMR (above) and $^{13}$CNMR (below) spectra of compounds $6e$ N-[(4-methoxyphenyl)methyl]-2-[(4-methoxyphenyl)methyl-2-(phenylacetylo)amino]-2-[4-bromophenyl]acetamide (400 MHz, CDCl$_3$).
Figure 9. $^1$HNMR (above) and $^{13}$CNMR (below) spectra of compounds 6g N-[(4-methoxyphenyl)methyl]-2-[(4-methoxyphenyl)methyl-(2-phenylacetylo)amino]-2-propionamide (400 MHz, CDCl$_3$).
Figure 10. $^1$HNMR (above) and $^{13}$CNMR (below) spectra of compounds 6i N-[(4-methoxyphenyl)methyl]-2-[(4-methoxyphenyl)methyl-(2-phenylacetylo)amino]-2-dodecanamide (400 MHz, CDCl$_3$).
Figure 11. $^1$HNMR (above) and $^{13}$CNMR (below) spectra of compounds 6j N-benzyl-2-[(4-methoxyphenyl)methyl-(2-phenylacetylo)amino]-2-phenylacetamide (400 MHz, CDCl$_3$).
Figure 12. $^1$HNMR (above) and $^{13}$CNMR (below) spectra of compounds 6k N-cyclohexyl-2-[(4-methoxyphenyl)methyl-(2-phenylacetylo)amino]-2-phenylacetamide (400 MHz, CDCl$_3$).
Figure 13. $^1$HNMR (above) and $^{13}$CNMR (below) spectra of compounds 6l N-t-butyl-2-[(4-methoxyphenyl)methyl-(2-phenylacetylo)amino]-2-phenylacetamide (400 MHz, CDCl$_3$).
Figure 14. $^1$HNMR (above) and $^{13}$CNMR (below) spectra of compounds 6m N-n-butyl-2-[(4-methoxyphenyl)methyl-(2-phenylacetylo)amino]-2-phenylacetamide (400 MHz, CDCl$_3$).
Figure 15. $^1$HNMR (above) and $^{13}$CNMR (below) spectra of compounds 6n N-[(4-methoxyphenyl)methyl]-2-[(4-methoxyphenyl)methyl-3-(phenylpropionyl)amino]-2-phenylacetamide (400 MHz, CDCl$_3$).
Figure 16. $^1$HNMR (above) and $^{13}$CNMR (below) spectra of compounds 6o N-benzyl-2-[(4-methoxyphenyl)methyl-4-(phenylprobutyryl)amino]-2-phenylacetamide (400 MHz, CDCl$_3$).
Figure 17. $^1$HNMR (above) and $^{13}$CNMR (below) spectra of compounds $6p$ N-[[4-methoxyphenyl]methyl]-2-[[4-methoxyphenyl]methyl-4-(phenylbutyryl)amino]-2-phenylacetamide (400 MHz, CDCl$_3$).
Figure 18. $^1$HNMR (above) and $^{13}$CNMR (below) spectra of compounds 6r N-[(4-methoxyphenyl)methyl]-2-[(4-methoxyphenyl)methyl-4-(phenylpentyl)amino]-2-phenylacetamide (400 MHz, CDCl$_3$).