Supporting Information for

**Efficient Ugi reactions in an aqueous vesicle system**

Arleta Madej, a Daniel Paprocki, a Dominik Koszelewski, a Anna Żądło-Dobrowolska, a Anna Brzozowska, b Peter Walde c and Ryszard Ostaszewski a

a Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

b Institute of Physical Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

c Laboratory of Polymer Chemistry, Department of Materials, ETH Zurich, Vladimir-Prelog-Weg 5, 8093 Zurich, Switzerland

**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** $^1$H NMR spectrum of N-(4-methoxybenzyl)formamide (200 MHz, CDCl$_3$).
Synthesis of \( p \)-methoxybenzylisocyanide (3a):

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 as an eluent. Yield 80 % (1.88 g).

Figure 2 ¹H NMR spectrum of compound 4a (200 MHz, CDCl\(_3\)).
Synthesis of N-hexylformamide:

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, solvent was evaporated. The product was purified by column chromatography (silica gel, hexane/AcOEt). Yield 90% (3.49 g).

Figure 3 $^1$H NMR spectrum of N-hexyl formamide (200 MHz, CDCl$_3$).
Synthesis of hexylisocyanide:

Reaction conditions: To a solution of N-hexyl formamide (16 mmol) 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 NaHCO₃ (20 mL), then extracted with dichloromethane (2×20 mL). The combined organic layers were dried with MgSO₄ and residuals of solvent were distilled under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane/AcOEt as an eluent. Yield 54% (482.5 mg).

Figure 4 ¹H NMR spectrum of hexylisocyanide (200 MHz, CDCl₃).
Synthesis of N-(2,4-dimethoxybezyl)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 80 % (4.69 g).

Figure 5 $^1$H NMR spectrum of N-(2,4-dimethoxybezyl)formamide (400 MHz, CDCl$_3$).
Synthesis of 2,4-dimethoxybezylisocyanide:

Reaction conditions: To a solution of N-(2,4-dimethoxybezyl)formamide (16 mmol) 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 as an eluent. Yield 80 % (4.25 g)

Figure 6 $^1$H NMR spectrum of 2,4-dimethoxybezylisocyanide (400 MHz, CDCl$_3$).
Figure 7 Effect of amount of Triton X-100 on the yield of 5a in the model Ugi reaction.

REACTION CONDITIONS: p-methoxybenzylamine (3A, 0.5 mmol), isovaleraldehyde (2a, 0.5 mmol), phenylacetic acid (1a, 0.5 mmol), p-methoxybenzyl isocyanide (4a, 0.5 mmol) and surfactant (0.1 mmol) in 5 mL distilled water for 48 h. mol% Triton X-100 corresponds to the amount of substrates (0.1 M).
Appearance of the aqueous Ugi multicomponent reaction samples containing DDAB and Triton X-100.

Figure 8. Photographic images of the Ugi multicomponent reaction samples (reaction with phenylacetic acid 1a (0.5 mmol), isovaleraldehyde 2a (0.5 mmol), \(p\)-methoxybenzylamine 3a (0.5 mmol) and \(p\)-methoxybenzyl isocyanide 4a (0.5 mmol)) in distilled water (5 mL), with the addition of DDAB or Triton X-100 (0.1 mmol), 25 °C.

a) Suspension of DDAB in distilled water after 10 minutes of stirring with a magnetic stirrer.
b) Suspension of Triton X-100 in distilled water after 10 minutes of stirring with a magnetic stirrer.
c) Reaction mixture in suspension of DDAB after addition of 2a and 3a.
d) Reaction mixture in suspension of Triton X-100 after addition of 2a and 3a.
e) Reaction mixture in suspension of DDAB 10 minutes after addition of 1a, 2a, 3a and 4a.
f) Reaction mixture in suspension of Triton X-100 10 minutes after addition of 1a, 2a, 3a and 4a.
Figure 9 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5a (400 MHz, CDCl$_3$).
Figure 10 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5b (400 MHz, CDCl$_3$).
Figure 11 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5c (400 MHz, CDCl$_3$).
Figure 12 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5d (400 MHz, CDCl$_3$).
Figure 13 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5e (400 MHz, CDCl$_3$).
Figure 14 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5f (400 MHz, CDCl$_3$).
Figure 15 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5g (400 MHz, CDCl$_3$).
Figure 16 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5h (400 MHz, CDCl$_3$).
Figure 17 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5i (400 MHz, CDCl$_3$)
Figure 18 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5j (400 MHz, CDCl$_3$).
Figure 19 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5k (400 MHz, CDCl$_3$).
Figure 20 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 51 (400 MHz, CDCl$_3$).
Figure 21 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5m (400 MHz, CDCl$_3$).
Figure 22 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5n (400 MHz, CDCl$_3$).
Figure 23 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5o (400 MHz, CDCl$_3$).
Figure 24 \(^{1}H\) NMR (above) and \(^{13}C\) NMR (below) spectra of compound 5p (400 MHz, CDCl\(_3\)).
Figure 25 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5t (400 MHz, CDCl$_3$).

Figure 26 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5u (400 MHz, CDCl$_3$).
Figure 27 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5w (400 MHz, CDCl$_3$).
Figure 28 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5v (400 MHz, CDCl$_3$).
Figure 29 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5x (400 MHz, CDCl$_3$).
Figure 30 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5y (400 MHz, CDCl$_3$).
Figure 31 $^1$H NMR (above) and $^{13}$C NMR (below) spectra of compound 5z (400 MHz, CDCl$_3$).