HETEROCYCLES, Vol. 73, 2007, pp. 461 - 467. © The Japan Institute of Heterocyclic Chemistry
Received, 14th June, 2007, Accepted, 17th July, 2007, Published online, 20th July, 2007. COM-07-S(U)15

ONIUM SALT SUPPORTED ORGANIC SYNTHESIS IN WATER: APPLICATION TO UGI'S 4-COMPONENTS REACTION

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Abstract – The utilization of the Onium Salt Supported Organic Synthesis methodology for Ugi's 4 components reaction in water is presented. An easy preparation of substrates followed by quantitative reactions led to peptidic moieties which are subsequently easily isolated in good yields and purities. Advantages of the OSSOS strategy including extreme simplification of purification and monitoring of the reaction are presented.

INTRODUCTION

For more than a decade, ionic liquids have been shown to advantageously replace classical volatile organic solvents in a number of cases. Structurally composed of an anion and a cation, these onium salts whose melting point is by definition below 100°C, are able to solubilize efficiently both inorganic and organic molecules. Moreover, due to their intrinsic properties, they offer several advantages over classical solvents such as thermal stability and virtually no vapor pressure.[1] Therefore, by covalently attaching a functional group to either part of the onium salt, it confers to the assembly some specific properties. These Task Specific Ionic Liquids (TSILs) [2, 3] can then be used as reagents or catalysts.[4] Later, we found than TSILs could be efficiently used as substrates and therefore leading to a new concept of supported organic synthesis.[5,6] The so called Onium Salt Supported Organic Synthesis (OSSOS) was successfully applied to a wide range of reactions[7] including peptide synthesis,[8] transition metal catalyzed reactions[9] radical[10] and multicomponent reactions.[11-13] Indeed, onium salts can be used as templates for supported organic synthesis, taking advantages of the onium salt part properties (non volatility, thermal stability) and removing most

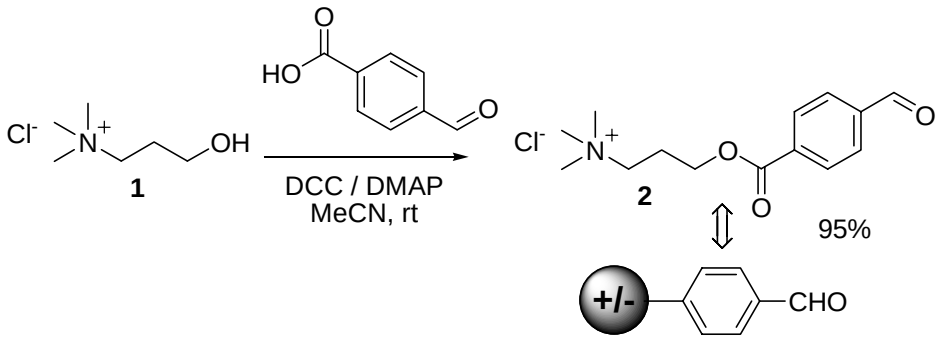
problems of solid phase and soluble polymer supported synthesis. Indeed, this OSSOS strategy allows for high loading capacity (up to 5 $mmol.g^{-1}$), easy reaction monitoring and product characterization using standard NMR spectroscopy or mass spectrometry, and most importantly keeps all advantages of previously described supports including easy purification by simple filtration and washes. However, despite the efficiency of such a process, when used in pure form viscosity of support increases rapidly with functionalization. This downside can be circumvented by using a minimal amount of solvent for solubilizing the onium salt support which is the core of the OSSOS strategy. This approach combines advantages of liquid phase synthesis as well as solid phase purification processes.

Here, we would like to report our OSSOS approach applied to the Ugi's 4-components reaction.[14-16] This reaction between an aldehyde, an amine, a carboxylic acid and an isocyanide leads, *via* rearrangement of heterocyclic intermediates, to peptide type fragments containing all chemical diversity of starting materials. In addition to be compatible with the "atom economy" concept, this reaction was performed in water[17,18] taking advantage of the onium salt moiety, for which a chloride counter anion was chosen to confer the molecule an appreciable solubility in water. Therefore, after a facile preparation of onium salt supported benzaldehyde, Ugi's reactions were performed under smooth conditions leading to supported peptidic moieties in good yield and purities.

RESULTS AND DISCUSSION

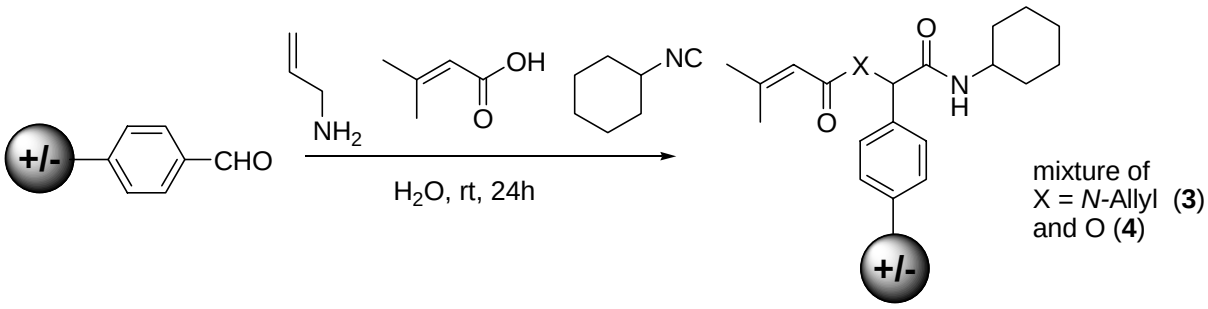
Ugi's reactions was already shown to be accelerated under aqueous conditions,[17,18] We decided to modulate the onium salt anion moiety so as to increase the water solubility of the support. This represents one of the numerous advantages of the OSSOS strategy: adapting the support nature to reaction conditions. Namely, if reactions conditions turned out to be optimal using water as a solvent, chloride or bromide ammonium salts should be perfectly suitable, if classical organic solvents such as THF or CH_2Cl_2 are required then, counter anion such as triflimide or hexafluorophosphate would assure a good solubility of the onium salts.[13]

Starting from trimethyl-3-hydroxypropylammonium chloride **1**, supported benzaldehyde **2** was prepared in a single step by simply coupling of 4-formylbenzoic acid with alcohol **1** under standard conditions using DCC and DMAP as coupling agents. A simple extraction of side products and excess reagents using diethyl ether afforded aldehyde **2** in 95% yield and >98% purity. The trimethylammonium group simplifies the NMR spectra of the support since it appears as a singlet in the 3.5 ppm region and furthermore, together with the chloride anion confers a good aqueous solubility to **2**.



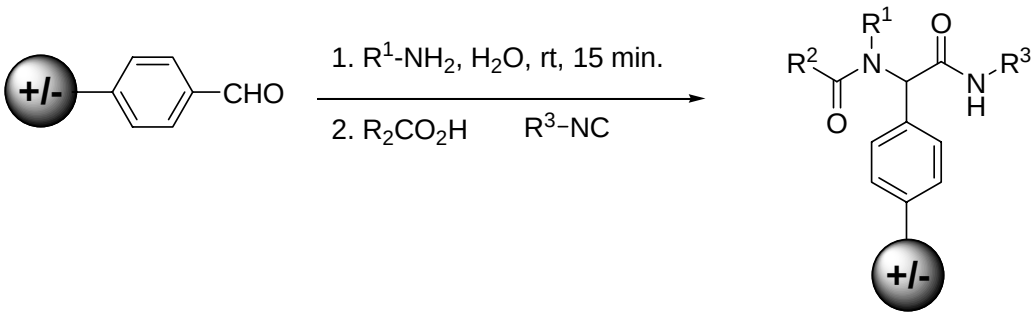
Scheme 1: Preparation of ammonium chloride supported benzaldehyde

We decided then to embark the Ugi's 4-components reaction using this water soluble supported benzaldehyde. Using allylamine, cyclohexyl isocyanide and 3,3-dimethylacrylic acid at room temperature in pure water the expected Ugi's adduct **3** is obtained but along with 20 % of a side product **4** resulting from the Passerini reaction in which the isocyanide attacked directly the benzaldehyde instead of the expected transient imine.



Scheme 2: Preliminary experiments for Ugi *vs* Passerini selectivity

Therefore, we decided to use a two-stage one pot protocol by adding first the amine to the support in the aqueous solution in order to form the imine, followed after 15 minutes by the other two reactants. (Entry 1). Under these conditions, we were pleased to obtain the expected Ugi's products **3** in excellent yields and purity using an expedient work-up procedure. For example reaction between aldehyde **2**, allylamine, 3, 3-dimethylacrylic acid and *tert*-butyl isocyanide led to product **3b** in 92 % isolated yield of pure product obtained just by simple washing with diethyl ether (entry 2). Similarly, reaction with 4-bromobenzoic acid and either *t*-Butyl or cyclohexyl isocyanide gave product **3c** and **3d** in 87% and 82 % yield respectively (entries 3 and 4). Finally benzylamine reacted equally well as the amine partner with *tert*-butyl isocyanide and both benzoic and acrylic acids to afford product **3e** and **3f** in 90% and 92 % yields respectively. Importantly, no flash chromatography was needed during purification, starting from alcohol **1** even though single non polymeric structures were isolated. Playing with relative solubilities in aqueous and organic phases, purifications were simply performed by removing water and washing with diethyl ether or acetone affording Ugi's adducts with excellent purity.



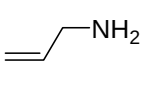
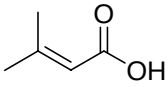
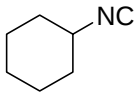
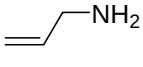
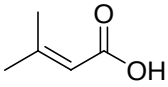
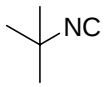
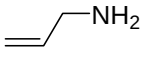
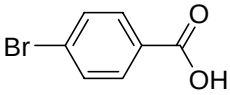
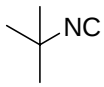
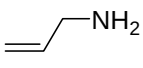
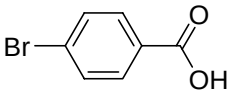
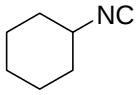
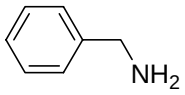
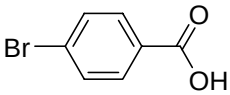
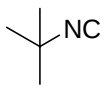
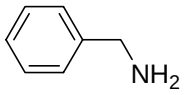
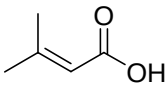
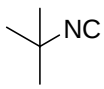
Entry	R^1-NH_2	R^2-CO_2H	R^3-NC	Product	Yield
1				**3a**	87%
2				**3b**	92%
3				**3c**	87%
4				**3d**	82%
5				**3e**	90%
6				**3f**	92%

Table 1 Scope of Ugi's 4-CC reaction in OSSOS strategy

Finally, we managed to perform Ugi's four components condensation using the OSSOS strategy. After simple workups by filtration and extraction, adducts were obtained in analytically pure form. In addition, the loading capacity of the support **1** reached 6.5mmol.g^{-1} and therefore allowed for working at high concentration (2M). Results were similar to classical homogeneous conditions[17] and superior to previously reported supported versions of Ugi's reaction.[19-21] where microwave heating is needed in order to achieve good conversions within decent time scale.[22]

EXPERIMENTAL

All reactions were carried out using standard techniques under argon. Acetonitrile and ether were carefully dried and distilled prior to use. All other standard chemicals were purchased from ACROS or Aldrich Chemical Co. and used without further purification. Reactions were monitored by gas chromatography (GC-MS) (GC system: HP 6890 series, Mass selective detector HP 5973) using a capillary column DB-5MS. Melting points were determined on an electro thermal IA9300 digital melting

point instrument. NMR spectra were recorded on a Bruker ARX 200 (^{1}H: 200.13 MHz, ^{13}C: 50.32 MHz) or AC 300 (^{1}H: 300.13 MHz), ^{1}H chemical shifts (δ) are given in ppm relative to TMS as internal standard, J values in Hz; ^{13}C chemical shifts are given relative to the central signal of $CDCl_3$ at 77.0 ppm. High resolution mass spectra measurements were performed at the Centre Regional de Mesures Physiques de l'Ouest (C.R.M.P.O, University of Rennes 1) using a Micromass ZABSpec TOF with EBE OA TOF geometry with LSIMS Ionization (Liquid Secondary Ion Mass Spectrometry) at 8 kV with Cs+ gun in *m*-nitrobenzyl alcohol (*m*NBA).

[3-(4-Formylbenzoyloxy)propyl]trimethylammonium chloride 2.

To a solution of **1** (2g, 13 mmol) in 100 mL of MeCN were added DCC (19.5 mmol, 1.5 eq), 4-formylbenzoic acid (19.5 mmol 1.5 eq) and DMAP (2.6 mmol, 0.2 eq). After 2 h at rt, solvent were removed and the residue was extracted with 3 x 30 mL of H_2O. After concentration under reduced pressure, the residue is washed with 3 x 30 mL of Et_2O to afford a pale yellow solid in 95% yield. mp 120-122°C ^{1}H NMR (300 MHz, D_2O): 2.18-2.31 (m, 2H), 3.09 (s, 9H), 3.42-3.48 (m, 2H), 4.37 (t, 2H, *J* = 5.8 Hz), 7.91 (d, 2H, *J* = 8.2 Hz), 8.06 (d, 2H, *J* = 8.2 Hz), 9.91 (s, 1H). ^{13}C NMR (75MHz, D_2O): 22.1, 53.0 (t, $J_{C\text{-}N}$ = 4 Hz), 62.6, 63.7, 129.6, 129.91, 134.0, 138.6, 166.6, 195.1. HRMS (FAB) $[C_{14}H_{20}NO_3][Cl]$ calcd 250.1443, found 250.1451.

General Procedure for Ugi's 4CC reaction.

To a solution of **2** (100 mg, 0.4 mmol) in 0.2 mL of H_2O were added the amine (0.44 mmol, 1.1 eq). After 15 min at rt, the isocyanide (0.44 mmol, 1.1 eq) and the acid (0.48 mmol, 1.2 eq) were added to the reaction mixture. After 16 h at rt, water was removed under vacuum and the residue was triturated and filtered with 5 x 10 mL of Et_2O. A simple crystallization in acetone afforded the expect product with sufficient purity.

3-(4-(1-(*N*-Allyl-3-methylbut-2-enamido)-2-(cyclohexylamino)-2-oxoethyl)benzoyloxypropyl)trimethylammonium chloride 3a

Obtained in 87% yield using allylamine, cyclohexyl isocyanide and 3-methylbut-2enoic acid as a white solid. mp 150-152°C ^{1}H NMR (300 MHz, CD_3CN): 1.03-1.45 (m, 6H), 1.49-1.78 (m, 4H), 1.84 (s, 3H), 1.96 (s, 3H), 2.19-2.28 (m, 2H), 3.17 (s, 9H), 3.51-3.65 (m, 2H), 3.66-3.70 (m, 1H), 3.88-4.16 (m, 2H), 4.38 (t, 2H, *J* = 5.8 Hz), 4.70-5.07 (m, 2H), 5.37-5.64 (m, 1H), 5.96 (s, 1H), 6.04 (s, 1H), 6.92-7.12 (m, 1H), 7.44 (d, 2H, *J* = 8.2 Hz), 8.03 (d, 2H, J = 8.2 Hz). ^{13}C NMR (75 MHz, CD_3CN): 19.1, 22.1, 24.2, 24.3, 24.9, 31.9, 48.0, 48.5, 52.4 (t, JC-N = 4 Hz), 61.2, 63.2, 115.1, 128.9, 129.1, 134.6, 142.2, 148.9, 165.3, 167.9, 168.3. HRMS (FAB) $[C_{29}H_{44}N_3O_4][Cl]$ calcd 498.3332, found 498.3331.

3-(4-(1-(*N*-Allyl-3-methylbut-2-enamido)-2-(*tert*-butylamino)-2-oxoethyl)benzoyloxypropyl)trimethylammonium chloride 3b

Obtained in 87% yield using allylamine, *tert*-butyl isocyanide and 3-methylbut-2enoic acid as a white solid. mp 146-148°C. ^{1}H NMR (300 MHz, CD_3CN): 1.33 (s, 9H), 2.21-2.29 (m, 2H), 3.81 (t, 2H, J = 6.5 Hz), 4.42-4.48 (m, 3H), 4.85-5.16 (m, 1H), 5.59-5.87 (b, 1H), 6.90-7.02 (m, 2H), 7.05-7.15 (m, 4H), 7.32-7.54 (m, 4H), 7.56-7.70 (m, 2H), 7.89 (d, 2H, J = 7.8 Hz). ^{13}C NMR (75 MHz, CD_3CN): 19.0, 22.1, 27.4, 50.5, 50.6, 52.3 (t, J_{C-N} = 4 Hz), 61.2, 63.1, 128.8, 129.0, 129.1, 129.2, 134.7, 142.3, 165.3, 168.2, 168.3, 168.4. HRMS (FAB) $[C_{27}H_{42}N_3O_4][Cl]$: calcd 472.3175, found 472.3174.

3-(4-(1-(*N*-Allyl-4-bromobenzamido)-2-(*tert*-butylamino)-2-oxoethyl)benzoyloxypropyl)trimethyl-ammonium chloride 3c

Obtained in 87% yield using allylamine, *tert*-butyl isocyanide and 4-bromobenzoic acid as a white solid. mp 148-150°C. ^{1}H NMR (300 MHz, CD_3CN): 1.32 (s, 9H), 2.18-2.28 (m, 2H), 3.15 (s, 9H), 3.52-3.58 (m, 2H), 3.90 (dd, 1H, J_1 = 6.7 Hz, J_2 = 16.4 Hz), 4.01-4.19 (m, 1H), 4.39 (t, 2H, J = 5.8 Hz), 4.72-4.86 (m, 2H), 5.41-5.61 (m, 2H), 6.51-6.87 (b, 1H), 7.36 (d, 2H, J = 6.8 Hz), 7.43-7.57 (m, 2H), 7.63 (d, 2H, J = 8.3 Hz), 8.05 (d, 2H, J = 8.3 Hz). ^{13}C NMR (75 MHz, CD_3CN): 22.0, 27.4, 50.5, 50.7, 52.3 (t, J_{C-N} = 4 Hz), 61.2, 63.1, 122.7, 128.1, 128.9, 129.1, 129.2, 130.3, 130.8, 131.1, 134.1, 135.4, 135.5, 165.2, 167.7, 167.8. HRMS (FAB) $[C_{29}H_{39}N_3O_4Br][Cl]$ calcd 572.2123, found 572.2128.

3-(4-(1-(*N*-Allyl-4-bromobenzamido)-2-(cyclohexylamino)-2-oxoethyl)benzoyloxypropyl)trimethyl-ammonium chloride 3d

Obtained in 82% yield using allylamine, cyclohexyl isocyanide and 4-bromobenzoic acid as a white solid. mp 154-156°C. ^{1}H NMR (300 MHz, CD_3CN): 1.03-1.42 (m, 6H), 1.42-1.51 (m, 4H), 2.14-2.31 (m, 2H), 3.15 (s, 9H), 3.49-3.62 (m, 2H), 3.62-3.65 (m, 1H), 3.92 (dd, 1H, J_1 = 5.4 Hz, J_2 = 16.6 Hz), 3.99-4.15 (m, 1H), 4.39 (t, 2H, J = 5.7 Hz), 4.74-4.89 (m, 2H), 5.43-5.53 (m, 1H), 5.62-5.85 (m, 1H), 6.76-7.15 (b, 1H), 7.36 (d, 2H, J = 8.3 Hz), 7.44-7.56 (m, 2H), 7.62 (d, 2H, J = 8.2 Hz), 8.05 (d, 2H, J = 8.2 Hz). ^{13}C NMR (75 MHz, CD_3CN): 22.5, 24.6, 24.6, 25.2, 32.2, 32.2, 32.3, 48.4, 52.9 (t, J_{C-N} = 4 Hz), 61.6, 63.6, 123.2, 128.6, 129.6, 129.7, 131.3, 131.5, 131.6, 134.4, 135.8, 141.6, 165.6, 167.7. HRMS (FAB) $[C_{31}H_{41}N_3O_4Br][Cl]$ calcd 598.2280, found 598.2274.

3-(4-(1-(*N*-Benzyl-4-bromobenzamido)-2-(*tert*-butylamino)-2-oxoethyl)benzoyloxypropyl)trimethyl-ammonium chloride 3e

Obtained in 90% yield using benzylamine, *tert*-butyl isocyanide and 4-bromobenzoic acid as a white solid. mp 198-200°C. ^{1}H NMR (300 MHz, CD_3CN): 1.27 (s, 9H), 2.19-2.41 (m, 2H), 3.13 (s, 9H), 3.46-3.56 (m, 2H), 4.37 (t, 2H, J = 5.9 Hz), 4.47 (d, 1H, J = 16.5 Hz), 4.91 (d, 1H, J = 16.5 Hz), 5.50-5.74 (m, 1H), 6.33-6.72 (b, 1H), 7.01 (d, 2H, J = 7.1 Hz), 7.12-7.18 (m, 3H), 7.37 (d, 2H, J = 8.2 Hz), 7.41-7.51 (m, 2H), 7.56-7.68 (m, 2H), 7.93 (d, 2H, J = 8.2 Hz). ^{13}C NMR (75 MHz, CD_3CN): 22.0, 27.2, 50.8, 52.6 (t, J_{C-N} = 4 Hz), 61.3, 63.3, 122.9, 126.1, 126.3, 127.6, 128.0, 129.1, 129.2, 129.2, 129.3, 131.4, 135.2, 137.8, 140.6, 165.4, 167.9, 171.8. HRMS (FAB) $[C_{33}H_{41}N_3O_4Br][Cl]$ calcd 622.2280, found 622.2280.

3-(4-(1-(*N*-Benzyl-3-methylbut-2-enamido)-2-(*tert*-butylamino)-2-oxoethyl)benzoyloxypropyl)trimethylammonium 3f

Obtained in 91% yield using benzylamine, *tert*-butyl isocyanide and 3-methylbut-2-enoic acid as a white solid. mp 174-176°C. ^{1}H NMR (300 MHz, CD_3CN): 1.24 (s, 9H), 1.74-1.76 (m, 3H), 1.94 (s, 3H), 2.14-2.29 (m, 2H), 3.15 (s, 9H), 3.52-3.57 (m, 2H), 4.36 (t, 2H, J = 5.6 Hz), 4.58 (d, 1H, J = 16.9 Hz), 4.87 (d, 1H, J = 16.9 Hz), 5.79-6.35 (m, 2H), 7.01-7.14 (m, 2H), 7.16-7.27 (m, 3H), 7.42 (d, 2H, J = 7.5 Hz), 7.93 (d, 2H, J = 8.3 Hz). ^{13}C NMR (75 MHz, CD_3CN): 19.1, 22.1, 25.8, 27.2, 43.0, 49.7. 50.5, 52.5 (t, J_{C-N} = 4 Hz), 61.2, 63.3, 126.0, 127.6, 127.7, 128.2, 128.3, 128.9, 129.0, 141.7, 149.6, 152.4, 165.4, 165.4, 168.2, 169.1. HRMS (FAB) $[C_{31}H_{44}N_3O_4][Cl]$: calcd 522.3331, found 522.3333.

ACKNOWLEDGEMENTS

We thank Mr P. Guénot and CRMPO (University of Rennes 1) for HRMS analysis.

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