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Ultrasound promoted Staudinger-Aza-Wittig tandem reaction on a monoazido-*O*-peracetylated-β-cyclodextrin: effect of ultrasound power

Alexandre Scondo [b], Florence Dumarçay-Charbonnier [a], Danielle Barth [b], Alain Marsura [a,*]

[a] *UMR 7565 SRSMC, Nancy Université, CNRS Faculté de Pharmacie, 5 rue A. Lebrun, B.P. 80403, 54001 Nancy Cedex, France*
[b] *Laboratoire des Sciences du Génie Chimique, Nancy-Université, 1 rue Grandville, B.P. 20451, 54001 Nancy, France*

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ABSTRACT

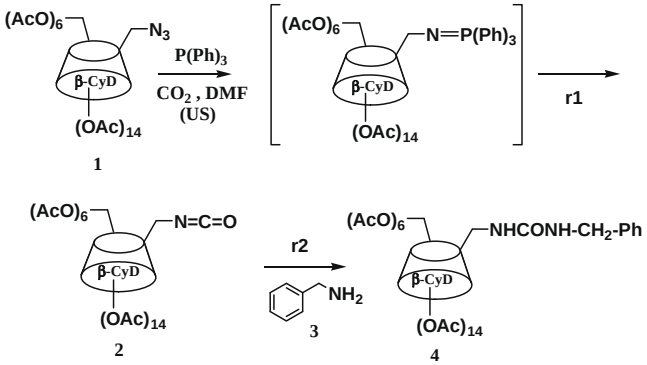
A preliminary study on an ultrasound promoted Staudinger-Aza-Wittig tandem reaction (S.A.W.) is reported. It was demonstrated that reaction is strongly favored under ultrasound (US) irradiation in terms of either reaction time or yield.

1. Introduction

Cyclodextrins (CyDs) have attracted worldwide interest in various research fields related to host-guest molecular recognition.[1] Regioselective functionalization of their hydroxyls groups remarkably enhanced their complexing and catalytic activities at the supramolecular level. However, as selective chemical modification of CyDs undoubtedly presents a challenge in the way of molecular design, much effort is being directed to developing new synthetic approaches that are both rapid and regioselective. From the past two decades, the application of ultrasounds in synthetic organic chemistry became more and more interesting.[2] Moreover it is well known that many organic reactions can be accelerated by ultrasounds (US).[3,4] Some recent papers compared outcomes of several CyD functionalizations carried out both under conventional conditions and under US.[5] Results showed that these techniques are very advantageous in terms of yields and reaction times. Knowing that many protocols for the preparation of CyD derivatives suffer from limitations such as long reaction times, it appeared judicious to investigate ultrasound power to promote these kinds of reactions. However, selective chemical modifications of CyDs still present a challenge and much effort should be engaged to developing powerful protocols that are expeditious and regioselective. For the last 10 years, as a part of our interest in the development of the Staudinger-Aza-Wittig (S.A.W.) tandem reaction as a green chemistry tool for a safe 'phosgene free' access to ureas, isocyanates, carbodiimides, or urethanes quadrivalent functions[6a–10] and in a continuation of regioselective syntheses of CyD-based building blocks, our current research program was concerned with the development of the reaction in supercritical conditions (sCO_2)[11] and under ultrasound irradiation (Fig. 1).

2. Results and discussion

Herein, we present a preliminary study of ultrasound power effect on a S.A.W. standard reaction, (Eq. (1)), from analytical and kinetic points of view. The reactions were carried out under both conventional (DMF) and ultrasonic irradiation conditions. The 6^A-azido-6^A-deoxy-per-*O*-acetylated-β-cyclodextrin **1** was treated with triphenylphosphine in presence of carbon dioxide as electrophile and benzylamine **3** as the nucleophile in anhydrous DMF. The middle depth immersed sonotrode allowed stirring of the reaction mixture and was adjusted for several intensities.[12] In these conditions, the 6^A-benzylureido-6^A-deoxy-per-*O*-acetyl-β-cyclodextrin **4**[6b] was obtained in a shorter time and in excellent yield compared to conventional conditions (see Table 1). All experiments have been realized at three different ultrasonic power levels, at two duration times (Table 1) and under temperature control by an external water bath. A typical procedure is given below.[13]



S.A.W. standard reaction. (1)

* Corresponding author. Tel.: +33 (0)3 83682324; fax: +33 (0)3 836822345.
E-mail address: Alian.Marrsura@pharma.uhp-nancy.fr (A. Marsura).

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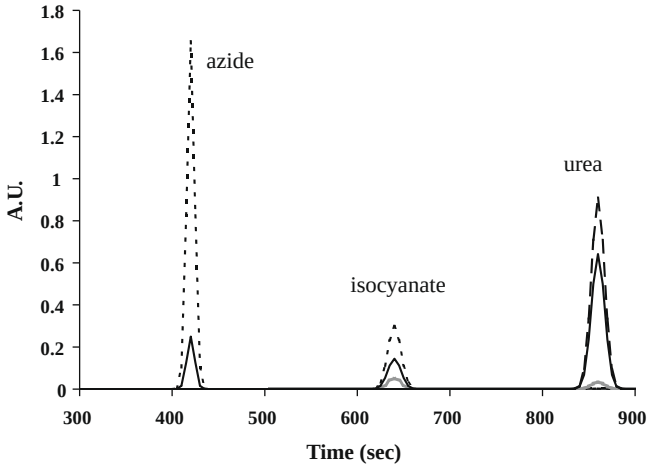

Figure 1. Intensity (A.U.) versus time HPLC plot of a US 35 W experiment at different times 5, 15, 90, and 120 min.

Table 1
Effect of ultrasonic power on the rate and yield of the urea **4** by the S.A.W. tandem reaction

US power	Without US		70 W		35 W		17.5 W	
Time (min)	20	120	20	120	20	120	20	120
Yield (%)	10	53	5	40	5	99	3	5

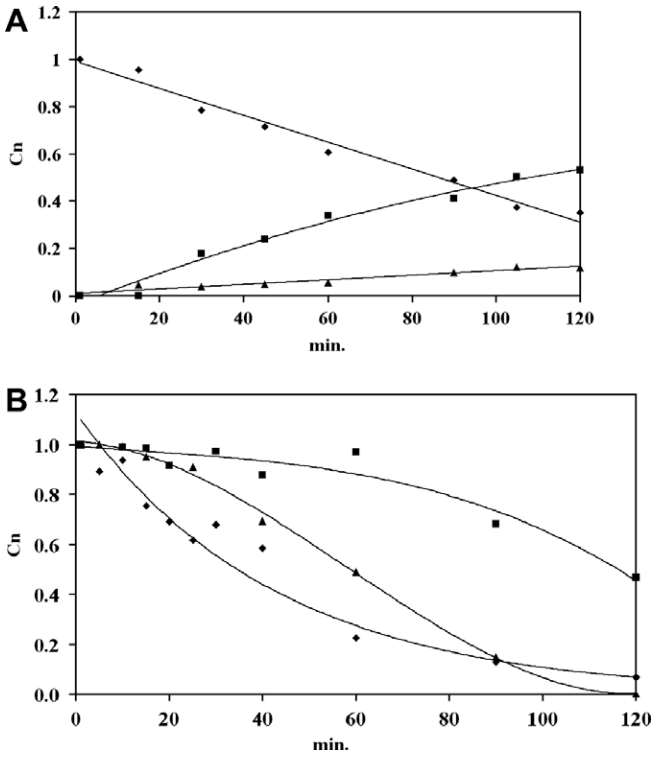

Figure 2. (A) Conversion rate (Cn) without US of ♦ [azide] **1**; ▲[isocyanate] **2** and ■ [urea] **4** versus time into DMF; B) Conversion rate (Cn) of the [azide] **1** versus time under US at ■ 70 W, ▲ 35 W, and ♦ 17.5 W.

3. Composition and kinetic calculations

Considering the mechanism[14] and the very recent study of the reaction kinetics under conventional conditions (DMF) as well as in supercritical CO_2[15] it was demonstrated that: (i) the reaction follows in the two situations a first-order kinetic, (ii) the rate constant was temperature dependant, and (iii) sCO_2 as solvent improved significantly the reaction rate. Analysis of the composition mixtures was performed using HPLC–ELSD on an unbounded silica stationary phase, knowing that such detection method is reliable and well adapted for cyclodextrin detection.[16,17]

The standard reaction, which was assumed irreversible, can be schematically written as in Eq. (1). Under conventional conditions (Fig. 2A), we observed that 60% of the azido-CyD was consumed after 2 h as under US 70 W maximum power (Fig. 2B). The situation was quite different when middle and low US power were applied, showing a more intense and rapid decrease of the azide concentration (98%) for the same irradiation time. Looking at the key intermediate CyD mono-isocyanate **2**, leading in a second step to the urea **4**, the conversion rate in the r1 step was proportional to the ultrasonic power, and regarding the isocyanate formation, the stronger the ultrasonic power was, the faster the isocyanate formation was (e.g., 50% for 70 W in 60 min); (Fig. 3).

Concerning the urea formation to the r2 step, the optimum conditions were reached for 35 W middle intensity of ultrasounds in 120 min (99% yield, see Table 1) whereas an unattended decreasing yield of **4** was then observed when the highest US intensity was applied in the same conditions (Fig. 4).

Looking at this contrasting result we performed another experiment under US at 70 W during the first part and then at 35 W during the second part. As illustrated in Figure 5, one can see the reaction was completed much faster, 100% yield of the urea **4** was obtained in 100 min confirms our assumption. No other supplementary by-product was detected judging from the registered chromatograms suggesting the r2 step becomes reversible when a high US power (70 W) was used. This feature perfectly correlates with the persistency of isocyanate **2** concentration at 50% in this step compared to the results observed at 35 W (0% yield). In order to verify a possible retro-reaction occurring from the urea, we realized the reaction with **4** under high power US (70 W) for 5 h in DMF. In these conditions, **4** remained totally unchanged, no trace of the isocyanate **2** being detected by HPLC analysis of the reaction mixture and thus discarded the r2 step reversibility hypothesis. Consequently, the origin of r2 step lower efficiency more probably comes from the intense cavitation induced close to the sonotrode surface as explained before by other authors.[3] In such a situation, it appears that a great part of the acoustic energy is reflected so that the ultrasounds do not penetrate into the liquid inside the reactor and thus are less efficient, whereas the ultrasonic waves, when lower ultrasonic powers are applied, spread out through the whole reactor volume, thus increasing refraction and reflection on the reactor walls, and are then more efficient. Nevertheless, the

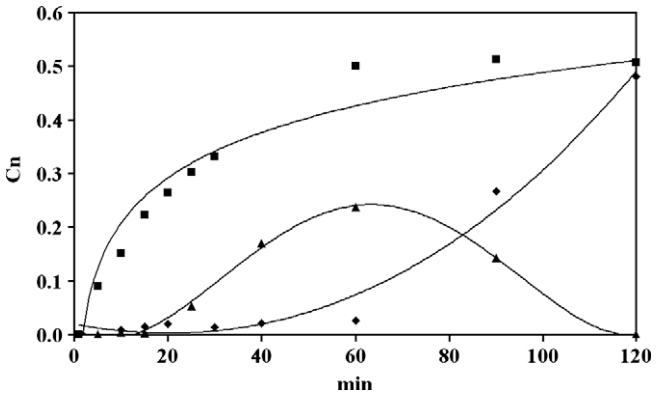

Figure 3. Conversion rate (Cn) of the [isocyanate] **2** versus time under US at ■ 70 W, ▲ 35 W, and ♦ 17.5 W.

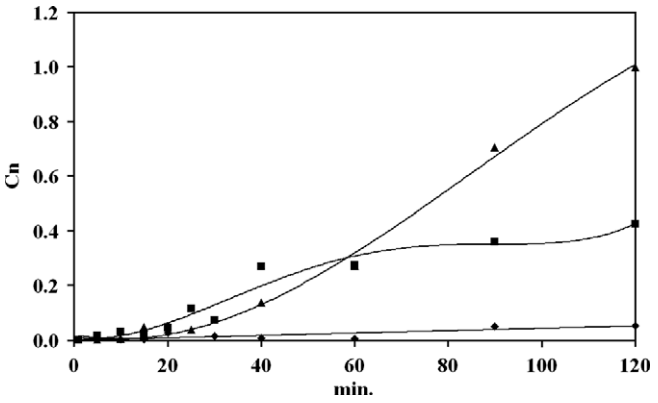

Figure 4. Conversion rate (Cn) of the [urea] **4** versus time under US at ■ 70 W, ▲ 35 W, and ♦ 17.5 W.

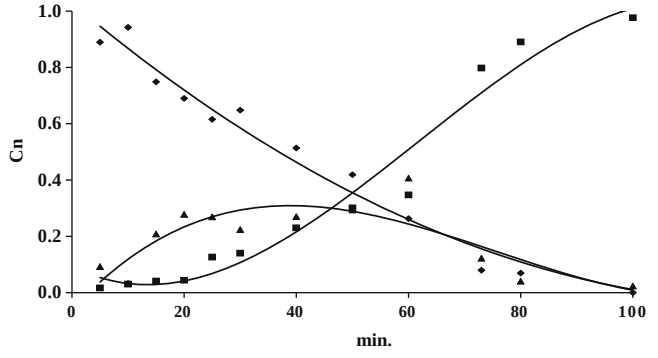

Figure 5. Conversion rate (Cn) of the ♦ [azide] **1**; ▲ [isocyanate] **2** and ■ [urea] **4** versus time under US at 70 W (60 min) then 35 W (60 min).

latter does not take into account what happens at the molecular level. So that, a second hypothesis may be proposed for the transition state in which intense cavitation prevents the benzylamine nucleophile to approach the isocyanate and thus slowing down the rate of the r2 step to yield the urea **4**.

In summary, we showed that isocyanate and urea formation in a S.A.W. standard reaction is strongly favored under US irradiation and that proven US-assisted procedures are very advantageous in terms of yields and reaction times. Elsewhere, an optimum power should be applied to obtain the best conversion of the azido-CyD into the urea and to avoid a lower efficiency at the second step. As it is known that other parameters like diameter as well as depth of immersion of the sonotrode influence the ultrasonic field inside the reactor, supplementary experiments are now under progress as well as investigations of the same reaction in supercritical fluids (sCO_2) with an interesting question: what may happen in such conditions about the reaction course?

Acknowledgments

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12. Ultrasound experiments were realized with a BANDELIN-HD2070 generator; frequency 20 KHz; power 70 W.
13. *Typical procedure for the synthesis of 2,3-di-O-acetyl-6-deoxy-6-benzylureido)-hexakis-(2,3,6-tri-O-acetyl)-cyclomaltoheptaose* **4**: To a solution of (2,3-di-*O*-acetyl-6-deoxy-6-azido)-hexakis-(2,3,6-tri-*O*-acetyl)-cyclomaltoheptaose[7] (0.050 g, 0.025 mmol) into DMF (50 mL) were added triphenylphosphine (0.261 g, 0.996 mmol, 40 equiv), then benzylamine (0.026 g, 0.240 mmol, 9.5 equiv). CO_2 bubbling and US were simultaneously started throughout the solution at rt. Two hours later the solvent was evaporated and the residue was treated with hexane. The resulting suspension was filtered to give urea **4** as a pure white powder. TLC (CH_2Cl_2/MeOH): R_f = 0.45; IR: 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$); 7.33–7.28 (m, 5H, Ar); 5.51 (t, 1H, NHBn); 5.39–5.21(m, 7H, H-3^{A-G}); 5.16 (d, 1H, H-1^B); 5.13–5.11 (m, 4H, H-1^{C-F}); 5.08 (d, 1H, H-1^B); 5.00 (d, 1H, H-1^A); 4.95 (t, 1H, NH); 4.92–4.77 (m, 6H, H-2^{B-G}); 4.72 (dd, 1H, H-2^A); 4.71–4.48 (m, 6H, H-$6a^{B-G}$); 4.42–4.01 (m,13H, H-5^{A-G}, H-$6b^{B-G}$); 3.81–341 (m, 11H, H-4^{A-G}, H-$6a^A$, H-$6b^A$, CH_2Ph); 2.19–2.02 (multiple s, 60H, *Me*CO); ^{13}C NMR (100 MHz, $CDCl_3$): 170.9–169.7 (multiple s, Me*C*O); 158.5 (NH*C*ONH); 140.1 (Cq Ar); 128.9–127.5 (Ar); 97.8 (C-1^A); 97.3–96.8 (C-1^{B-G}); 79.2–76.1 (C-4^{A-G}); 71.9–69.5 (C-2,3,5^A C-2,3,5^{B-G}); 63.5–60.8 (C-6^{B-G}); 44.8 (CH_2); 41.9 C-6^A); 21.4–21.1 (multiple s, *Me*CO); ESMS (*m*/*z*): 2106.61[M]$^+$. Anal Calcd. for: $C_{90}H_{118}N_2O_{55}$ C, 50.78; H, 5.61; N, 1.33. Found: C, 50.69; H, 5.61; N, 1.29.
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17. The HPLC system was a SpectraSystem P1000Xr quaternary pump (Finningan, USA), a SpectraSystem SCM 1000 vacuum membrane degasser, a DDL21 evaporative light-scattering detector (Eurosep, France) and a Rheodyne7125 sample injector with a constant volume loop (10 μL). Chromatograms were acquired with a WINI 10 acquisition card and were recorded on a computer by using WINILAB 2 software (Perichrom, France). The analytical column was an unbounded silica Polaris Si-A column (150 mm × 4 mm, Varian, USA); to increase the column life a Polaris Metaguard guard column (Si-A 5 μ, Varian, USA) was used. The oven used herein was a Gecko 2000 (Cluzeau, France) to set the column temperature at 33 °C. The ELSD was set at 100 °C for evaporation temperature. Compressed air was used as nebulization gas at 2 bars of working pressure. The HPLC flow rate was 1 mL/min. A mixture of methanol/dichloromethane was chosen as eluent and a binary gradient was used. The HPLC column was conditioned for 7 min after each run, thus minimizing variation of the retention times (for other details reported to Ref. 14). Samples were taken every 20 min over 2 h.