Direct C(sp^3)−N Bond Formation between Toluene and Amine in Water Microdroplets

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ABSTRACT: Unlike the inertness of bulk water, water microdroplets exhibit some remarkable reactivities. We report that water microdroplets can directly produce stable $C_7H_7^+$ cations (a combination of benzylic and tropylium cations) from toluene and other substrates at room temperature with a positive voltage (+4 kV) applied to the droplet spray source. The $C_7H_7^+$ cation and the benzyl radical ($C_6H_5CH_2\cdot$) are both generated via hydroxyl radicals at the water−gas interface of the microdroplets. The $C_7H_7^+$ signal is observed directly by mass spectrometry. Dissolved amines (primary, secondary, and tertiary) in the microdroplets can react with both $C_7H_7^+$ and $C_6H_5CH_2\cdot$ to form the corresponding alkyl C(sp^3)−N coupling products in one step, which cannot be achieved in bulk water or other solvents. The products were identified using tandem mass spectrometry (MS^2) and ^{1}H NMR spectroscopy. Notably, the direct C(sp^3)−N bond formation products were obtained in the absence of a catalyst. In the presence of a radical scavenger, the mass spectra of the C(sp^3)−N coupling products are strongly suppressed, which supports the hypothesis that this reaction is driven by hydroxyl radicals generated in the water microdroplets. Taken together, these results show that water microdroplets provide a new method for direct one-step C(sp^3)−N bond formation without the need for a metal catalyst.

The C−N bond is one of the most abundant chemical bonds and widely exists in several organic compounds, pharmaceuticals, and biomacromolecules. The formation and transformation of C(sp^3)−N bonds are among the central topics in organic chemistry, organometallic chemistry, and biochemistry. Several approaches have been developed to achieve efficient C(sp^3)−N bond formation.[1−7] The most significant development in amine synthesis has been C(sp^3)−N coupling of electrophiles (halides and pseudohalides) with amine nucleophiles.[5,6] Interestingly, decarboxylative C−N coupling of redox-active esters with anilines also has been proved to be a valuable synthesis approach.[7] The existing methods require rather harsh reaction conditions, such as use of a metal catalyst, long reaction times, irradiation at different wavelengths, and high temperatures. More economical and green methods to rapidly form C(sp^3)−N bonds at room temperature are still under investigation.

Recently, research efforts from our group and others have shown that water microdroplets exhibit unusual reaction properties that are not observed in bulk water or other organic solvents.[8−13] One possible reason that causes the unique properties of the water microdroplet is the large amount of hydroxyl radicals at the water−gas interface produced by a strong electric field.[8,14−20] Previously, our group reported hydrogen peroxide generation in water microdroplets via the intermediacy of hydroxyl radicals;[17,20,21] similarly, hydroxyl radical formation via oxidation of hydroxide has also been shown to occur in corona and O_3 bubbles.[22,23] Taking advantage of this feature, we generate and stabilize $C_7H_7^+$ cations and benzyl radicals ($C_6H_5CH_2\cdot$) in water microdroplets from toluene, which is considered to be an inert and inexpensive organic solvent. In the presence of amine nucleophiles, C(sp^3)−N bond formation can be achieved in

microseconds in one step at room temperature. To the best of our knowledge, no previous studies exist that report C(sp^3)−N bond formation from toluene in water.

Figure 1 shows a schematic diagram of our microdroplet experimental setup. Water and toluene are injected into a
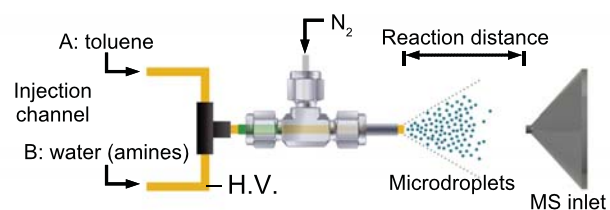

Figure 1. Schematic diagram of the experimental setup.

microdroplet sprayer from two fused silica capillaries (70 μm i.d., 350 μm o.d., injection channels A and B). After premixing in the PEEK tee, water microdroplets containing toluene are generated by the sprayer using N_2 (120 psi) as the nebulizing gas. To obtain a higher electric field at the water−gas interface, a 4 kV positive voltage is applied to the solution (grounded to the stainless steel sprayer). It is necessary to clarify that hydroxyl radicals can be generated without applied voltage. The aim of applying a high voltage is to increase the amount of

A

hydroxyl radicals and products. The voltage optimization details are given in Figure S1. A high-resolution mass spectrometer (Orbitrap Velos Pro, Thermo Fisher Scientific, Waltham, MA, U.S.) is used to detect the ions produced by the microdroplets. The distance between the spray nozzle and MS inlet is considered as the reaction distance and ranges from 10 to 20 mm, corresponding to a travel time of approximately 125 to 250 μs.

By injecting toluene from channel A (0.5 μL/min) and different solvents (5 μL/min) from channel B, the mass spectra of the microdroplets of acetone, acetonitrile, methanol, and water can be obtained. As shown in Figure 2a−d, $C_7H_7^+$ at m/z
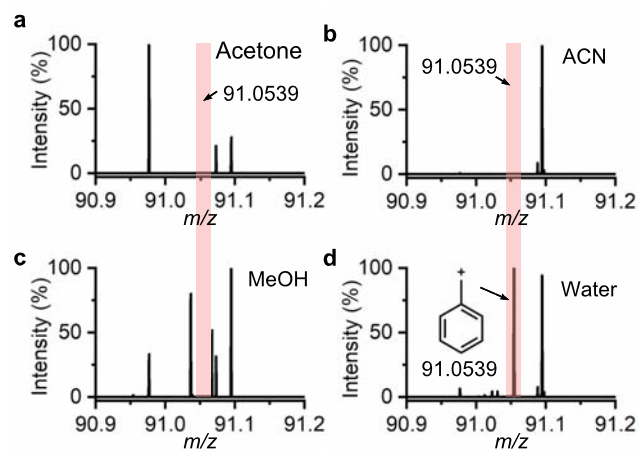

Figure 2. (a−d) Mass spectra of toluene in microdroplets of acetone, acetonitrile, methanol, and water. The peak marked in red represents the $C_7H_7^+$ cation at m/z 91.0539, which appears only in water microdroplets.

91.0539 can be obtained only in water microdroplets. The possible reason is that the hydroxyl radicals in the water microdroplets cleave the α-hydrogen from toluene and generate benzylic radicals, which further lose one electron to obtain the stable $C_7H_7^+$ cations. The generated carbocations are able to be stabilized because of the equilibrium between the benzylic and the tropylium cations at the droplet surface. During the experiment, the optimum distance between the spray nozzle and MS inlet is found to be 15 mm to maximize the cation signal. Our previous research has shown that the jet velocity of microdroplets produced by the spray emitter is about 80 m/s.[24] It can be easily calculated that the estimated lifetime of the $C_7H_7^+$ cation in water microdroplets is at least 100 μs, which is 6 orders of magnitude longer than that in bulk water.[25,26]

Because of the existence of carbocations that can be generated and stabilized in the water microdroplets, we attempted to achieve direct $C(sp^3)-N$ bond formation between toluene and amines in water microdroplets. Figure 3a shows the one-step synthesis of *N*-benzyldipropylamine from toluene and dipropylamine in water microdroplets.

When the dipropylamine enters the toluene solution, the marked decrease in the intensity of the $C_7H_7^+$ peak at m/z 91.0539 correlates with the marked increase in the intensity of the peak for the protonated *N*-benzylpropylamine product $[C_{13}H_{22}N]^+$ at m/z 192.174 (Figure 3b). In this experiment, we first inject toluene and water from channels A and B from 0 to 0.5 min. During this time, $C_7H_7^+$ cations can be clearly observed as mentioned above. Then dipropylamine is dissolved in water (100 μmol/L) and injected from channel B from 0.5 to 1 min, while toluene is still injected from channel A. This result supports the reaction scheme shown in Figure 3a. It is also possible that direct reaction of the benzyl radical with the amine also contributes to the reaction.
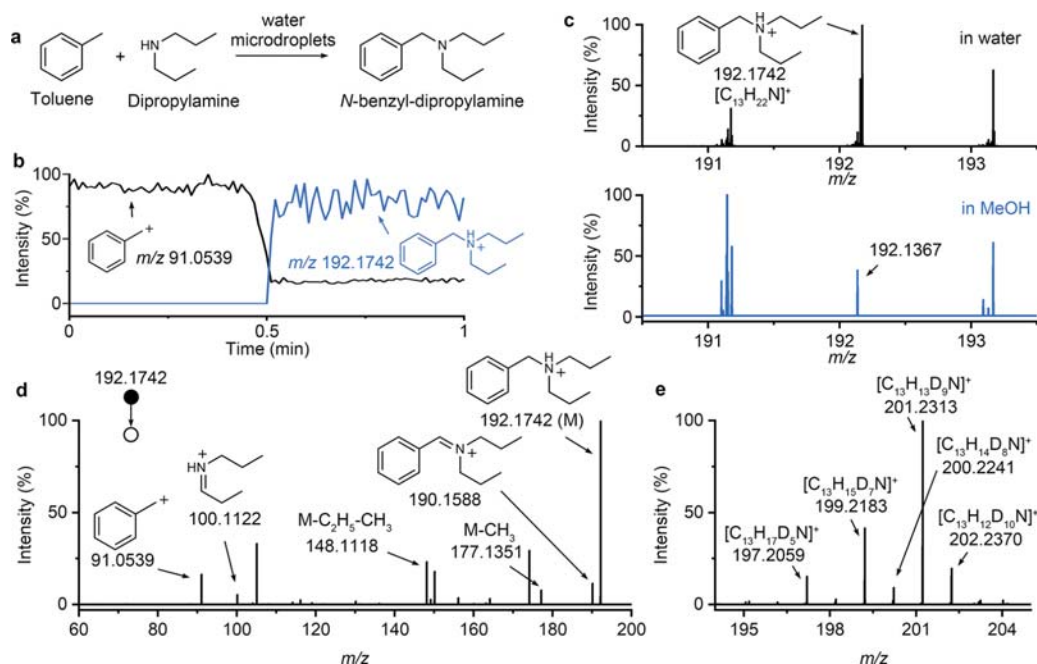

Figure 3. (a) Synthesis of *N*-benzyldipropylamine from toluene and dipropylamine in water microdroplets. (b) Direct observation of the reaction process with MS. (c) Product formation comparison between water microdroplets and methanol microdroplets. (d) MS^2 of the product at m/z 192.1742. (e) Mass spectra of the product from toluene-d_8 and dipropylamine in D_2O microdroplets.

Figure 3c compares the mass spectrum obtained in water microdroplets with that obtained in methanol microdroplets. We conclude that the reaction happens only in water. The product tandem mass (MS^2) is used to verify the compound structure of the peak at m/z 192.1742 (Figure 3d). As shown in the figure, various peaks of the fragments can be identified. In particular, the peaks at m/z 91.0539 and 100.1122 are due to $C_7H_7^+$ cation and the iminium cation, respectively. The tandem mass spectrum (Figure 3d) and the disappearance of the $C_7H_7^+$ cation to product carbocation (Figure 3b) clearly confirm the formation of the product in one step. Additionally, we also carried out the labeling experiment between toluene-d_8 and dipropylamine in D_2O microdroplets (Figure 3e). The mass spectra labeling experiment clearly observed the deuterated product peak at m/z 200.2241 ($[C_{13}H_{14}D_8N]^+$). In addition, we also observed the proton−deuterium exchange from the peaks at other m/z. This reveals that deuterated cation also can be stabilized under the microdroplet conditions to obtain the deuterated products.

To determine the reaction mechanism, we added the free radical scavenger[27] 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) to the reaction mixture containing water and dipropylamine passed through channel B and toluene passed through channel A. Figure 4a shows the signal intensity of the
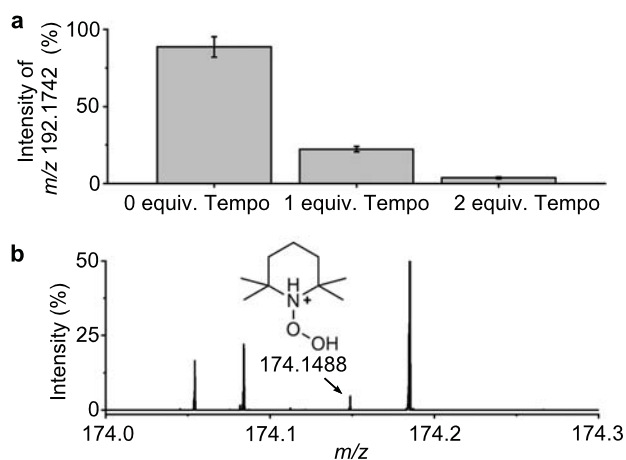

Figure 4. (a) Mass spectral intensities of N-benzyldipropylamine with the addition of different equivalents of TEMPO. (b) Mass spectra of the intermediate ·OH trapped by TEMPO. The error bars represent the standard deviation of three experiments.

product peak at m/z 192.1742 with the addition of different equivalents of TEMPO. The intensity of the product peak is higher when the reaction is carried out without TEMPO. When 1 equiv of TEMPO is added, the peak intensity of the product is strongly suppressed. Further, with 2 equiv of TEMPO, the peak of N-benzyldipropylamine almost disappeared. We also observed that the hydroxyl radical formed from the water has been scavenged by TEMPO (m/z 174.1488) (See Figure 4b). Due to the trapping of hydroxyl radical by TEMPO, the formation of benzyl radical is suppressed, which lowers the product conversion (Figure 4a). With another radical scavenger, caffeine, similar results were also obtained (Figure S2). These experimental results clearly indicate that the reaction occurs via a free radical mechanism involving ·OH.

Based on the observed results and TEMPO trapping studies, we propose a mechanism for the direct $C(sp^3)$−N formation

between toluene and dipropylamine in water microdroplets (Scheme 1). In the first step, a small amount of water

Scheme 1. Mechanism of $C(sp^3)$−N Bond Formation from Toluene and Dipropylamine in Water Microdroplets
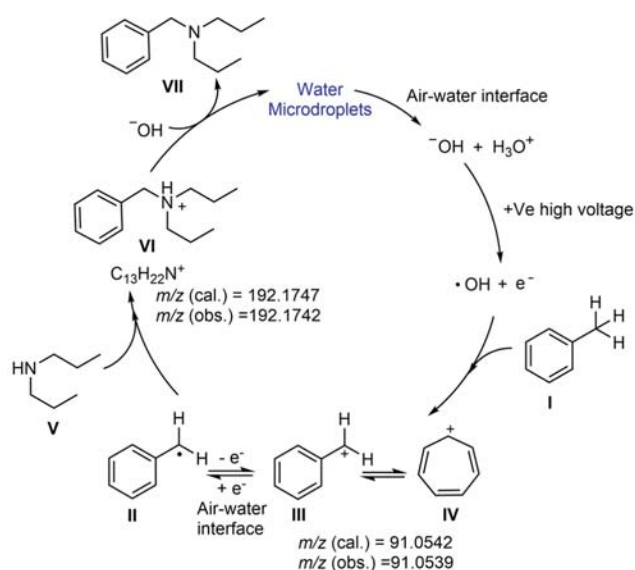
dissociates into hydroxide anion (OH^-) and hydrogen cation (H^+). In presence of high voltage, the hydroxide anion is converted into hydroxyl radical, a process that is also aided by contact electrification.[20] The electrons liberated during ionization of hydroxide are trapped on the surface of the sprayer[20] and then go to the opposite voltage source. The highly reactive hydroxyl radical abstracts an α-hydrogen atom from toluene **I** to form benzyl radical **II**. The benzyl radical further loses an electron to form the stable carbocations **III** and **IV** ($C_7H_7^+$), which were observed in the reaction using in situ mass spectrometry in positive mode (m/z 91.0539). Next, amine **V** attacks the stabilized $C_7H_7^+$ cation **III** and/or the benzyl radical ($C_6H_5CH_2\cdot$) **II** to afford protonated amine **VI**, which was also confirmed using MS (m/z 192.1742). Finally, the hydroxide anion removes the proton from the protonated amine to form the final product **VII**.

Using similar reaction conditions, we expanded the scope of this reaction with electrophilic partners such as, o-xylene, mesitylene, 4-bromotoluene, and tetralin (Figure S3), and their carbocations were identified with MS (Figure S4). The corresponding $C(sp^3)$−N coupling products were obtained in water microdroplets, as verified by high-resolution MS and MS^2 data. Furthermore, we also expanded the scope to other amine compounds, such primary, secondary, and tertiary amines, to obtain the corresponding $C(sp^3)$−N-coupled products. The products were confirmed using MS and MS^2 (Figures S5−S13). In particular, the tertiary amine with the benzylic partner forms the quaternary ammonium salt, which was identified using MS and NMR (Figure S14).

To collect the sample for the NMR experiment, we dissolved the triethylamine in D_2O (10 mmol/L) and injected the solution into the spray device from channel B while toluene was still injected from channel A. The resulting microdroplets were sprayed into a flask containing 100 μL of D_2O and 50 μL of hydrochloric acid (37%), which was used to trap the generated benzyltriethylammonium salt. Ice was placed around

the flask to allow the droplets to coagulate quickly and to minimize escape of the product by evaporation. The collected crude solution was transferred into the NMR tube and analyzed with an NMR instrument (Varian model UI-400, 400 MHz) (Figure S14). The ^{1}H NMR data exactly matched with the literature data.[28] The multiplet at 7.6–7.5 ppm confirms the aromatic ring protons, and the sharp singlet at 4.4 ppm confirms the benzylic CH_2 protons. Also, the ethyl group protons appeared at 3.2 and 1.4 ppm as a quartet and a triplet, respectively. The ^{1}H NMR and MS data clearly confirm the product formation, which is obtained from microdroplet spray between toluene and triethylamine.

In summary, we report the direct $C(sp^3)$–N bond formation reaction between toluene and amines in water microdroplets. The $C(sp^3)$–N products were formed in one step at room temperature without any catalyst. We have taken advantage of the unique properties of water microdroplets, which generate hydroxyl radicals at the water–gas interface. Radical scavenger (TEMPO) experiments support the proposed mechanism of the reaction. Furthermore, the hydroxyl radical removes the α-hydrogen atom from toluene, followed by amine attack to form the benzylamine derivatives. Also, we have extended the scope of the reaction to other electrophiles and nucleophiles. The products were identified using in situ mass spectrometry, tandem mass spectrometry, and proton NMR spectroscopy. The novel method described in this work provides a new concept for green chemistry because the reaction is achieved without any organic solvent and without any catalyst.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c10032.

> Voltage optimization chart, MS and tandem mass spectral analysis data, and ^{1}H NMR spectrum of the product obtained from the microdroplet reaction between toluene and triethylamine (PDF)

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Notes

The authors declare no competing financial interest.

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