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Microdroplet Chemistry

Selective Synthesis in Microdroplets of 2-Phenyl-2,3-dihydrophthalazine-1,4-dione from Phenyl Hydrazine with Phthalic Anhydride or Phthalic Acid

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Abstract: Pyridazine derivatives are privileged structures because of their potential biological and optical properties. Traditional synthetic methods usually require acid or base as a catalyst under reflux conditions with reaction times ranging from hours to a few days or require microwave assistance to induce the reaction. Herein, this work presents the accelerated synthesis of a pyridazine derivative, 2-phenyl-2,3-dihydrophthalazine-1,4-dione (PDHP), in electrosprayed microdroplets containing an equimolar mixture of phenyl hydrazine and phthalic anhydride or phthalic acid. This reaction occurred on the submillisecond timescale with good yield (over 90% with the choice of solvent) without using an external catalyst at room temperature. In sharp contrast to the bulk reaction of obtaining a mixture of two products, the reaction in confined microdroplets yields only the important six-membered heterocyclic product PDHP. Results indicated that surface reactions in microdroplets with low pH values cause selectivity, acceleration, and high yields.

Pyridazine derivatives, a fascinating class of six-membered heterocyclic compounds with two adjacent nitrogen atoms, have been found to possess many biological properties, such as anti-inflammatory,[1] antibacterial,[2] anticancer,[3] cardiovascular diseases,[4] and agrochemical activities.[5] Owing to their biological importance, these chemicals are favored by both synthetic and medicinal chemists, among which, an important six-membered pyridazine derivative, 2-phenyl-2,3-dihydrophthalazine-1,4-dione, was reported to have very significant biological activities against osteosarcoma,[6] glioma,[3] hypolipidemic,[7] and bacteria.[8] In addition, 2-phenyl-2,3-dihydrophthalazine-1,4-dione can be used as important optical intermediates.[9] Traditional methods for synthesizing these pyridazine derivatives require acid or base catalysts, and the reactions need to be performed under solvent reflux from hours to days at high temperature to obtain products with high yields.[10] Furthermore, in most cases, a five-membered heterocyclic isomer byproduct is simultaneously obtained, and it can be transformed to the desired six-membered product catalyzed by base (typically ethanolic sodium) or acid (such as concentrated H_2SO_4, HCl/H_2O, ice acetate acid). It is well noted that, although microwave-assisted methods can be applied for these reactions, the same isomers as that of bulk reactions were obtained without using catalysts.[11] Only when additional acid or base is used as a catalyst in the microwave-assisted reaction could the single six-membered heterocyclic product be generated.[12]

Recently, micron-sized microdroplets have been shown as a unique platform to investigate reaction products, mechanisms, and kinetics.[13] Chemical reactions in microdroplets exhibit specific properties that are not observed in bulk solutions, especially dramatic acceleration of reaction rates, which are often thousands to millions of times greater than that in the bulk.[14] Instead of showing remarkable reaction-rate acceleration, some reactions in microdroplets show completely different reaction routes, possibly owing to the significantly different microenvironment in microdroplets. For example, our research group found that the Diels–Alder reaction of 3,5-hexadienyl acrylate ester in microdroplets could not provide the desired Diels–Alder product in all cases even in the presence of catalyst, but just generated instead the hydrolyzed product, hexa-3,5-dien-1-ol.[15] In contrast, the desired Diels–Alder product can be easily obtained in aqueous media at high temperature using indium(III) triflate as a catalyst in bulk-phase.[16] In this work, we present the selective and high-yield synthesis of an important pyridazine derivative, 2-phenyl-2,3-dihydrophthalazine-1,4-dione, from phenyl hydrazine and phthalic anhydride or phthalic acid in microdroplets without a catalyst on the submillisecond timescale at room temperature and atmospheric pressure. In sharp contrast to bulk reaction, the reaction of phenyl hydrazine and phthalic anhydride in microdroplets not only caused dramatic acceleration but also showed excellent selectivity to the target six-membered heterocyclic product. For the reaction of phenyl hydrazine and phthalic acid, it shows a striking reaction route in microdroplets without using a catalyst to give the target product that cannot occur under bulk conditions. Some insights how these reactions occur in microdroplets are also put forward.

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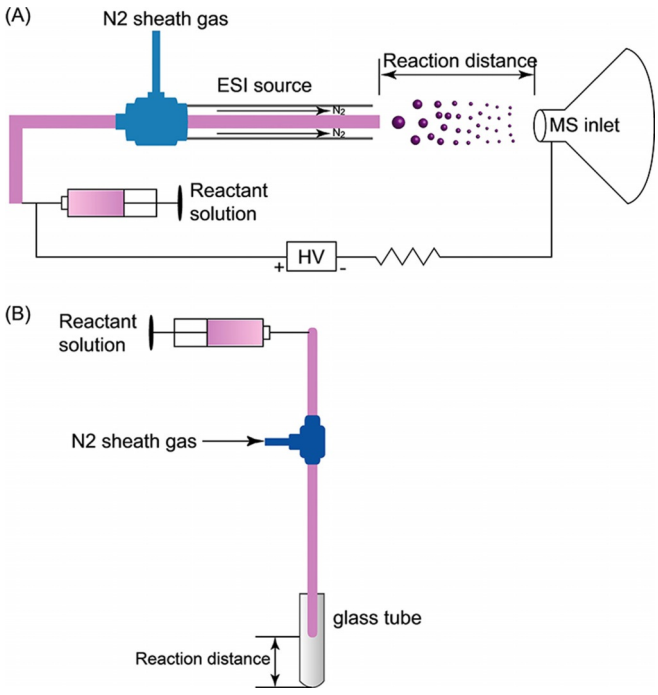

Figure 1. Schematic diagrams of the experimental setups used in our study for the reaction study of phenyl hydrazine with phthalic anhydride in microdroplets. Extent of reaction depends on the distance between the ESI tip and MS inlet for direct spray or between the ESI tip and the collection surface for offline spray. (A) Directly electrospray a solution containing two reactants to the MS inlet. A +5 kV of voltage was applied to the syringe needle. (B) Offline collection of the microdroplet using a glass vial with a syringe pinhole on the cap. No voltage was applied.

As shown in Figure 1, we used two experimental setups to perform the microdroplets reactions. One is the direct spray of the microdroplets into the inlet of a mass spectrometer for real-time analysis of the reaction. Another is the offline collection of the microdroplets for further structural identification. In both cases the microdroplets were generated by nebulization of a solution containing phenyl hydrazine **1** (10 μM) and phthalic anhydride **2** (10 μM) in organic solvent with a high pressure nebulizing gas (N_2, 120 psi). We applied a positive voltage to the spray source for online spraying. If instead we applied a negative voltage to the spray source, no products were observed. For offline collection, no voltage was applied. Many reports have shown that the sizes of microdroplets under these conditions range from 1 to 50 μm. The travelling distance of the microdroplets at atmospheric pressure was constant (3 cm) before the microdroplets enter the mass spectrometer and the reaction stops. We estimate the reaction time to be ≈300 μs on the basis of the droplet speed (≈80 m s^{-1}).[17] The reaction products were measured by ESI-MS in positive ion mode. As shown in Figure 2A, the main product **3**, 2-phenyl-2,3-dihydrophthalazine-1,4-dione, and a small amount of product **4** were observed in the microdroplets generated by the above two strategies. To determine the structures of product **3** and **4**, we performed tandem mass spectrometry using collision-induced dissociation (CID) (see Figure S1 in the Supporting Information). In sharp contrast to the behavior in microdroplets, in bulk only the open ring product **4** and residual reagent **1** were detected when reacted for 30 min in acetonitrile (ACN)/water (9/1, v/v) (Figure 2B). Many studies have demonstrated that in order to obtain the product **3**, acid or base should be used as a catalyst and the solution should be refluxed at high temperature.[10,18]

We further performed bulk-phase reactions in acetic acid with reflux condition to compare with that reactions in micro-

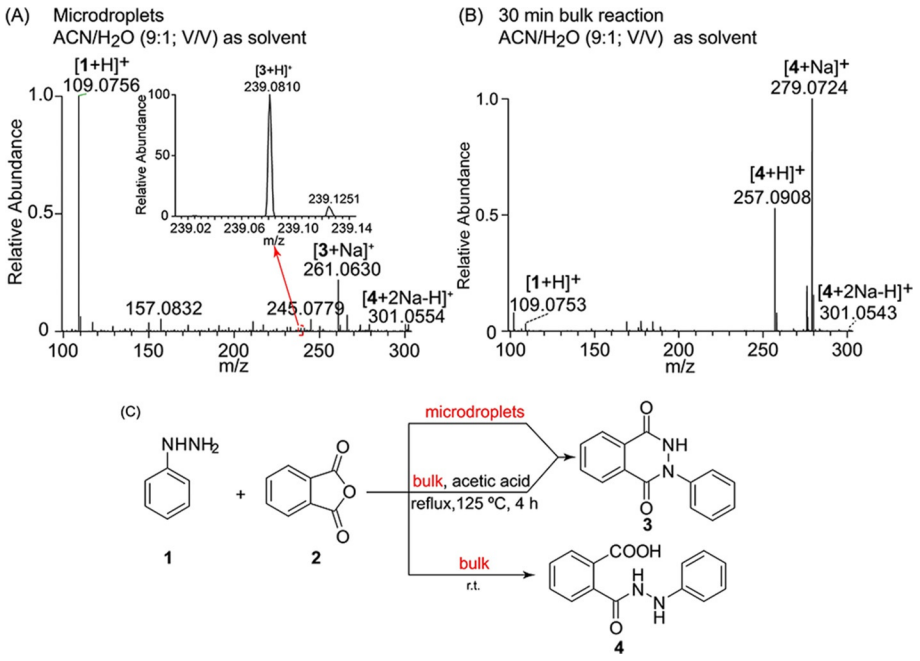

Figure 2. Mass spectra of the reaction at room temperature of phenyl hydrazine **1** with phthalic anhydride **2** in (A) microdroplets and (B) bulk-phase without catalyst and without refluxing. (C) The microdroplet reaction led to significant product **3** formation with a small amount of product **4**, whereas the bulk-phase reaction of **1** and **2** with acetic acid as catalyst and reflux at high temperature led to product **3**, but without catalyst at room temperature only form product **4**.

droplets. The product are analyzed by NMR and high-resolution mass spectrometry. The results showed that the six-membered heterocyclic product **3** was generated, which is in accordance with the data in microdroplets (Figure S2 in Supporting Information). Figure 2C shows the reaction between **1** and **2** at room temperature in microdroplets without using catalysts and in bulk-phase with and without catalysts.

The distance between the electrospray source and the MS inlet greatly influences the reaction conversion ratio. An increase in distance provides more time for reaction and also allows more microdroplets evaporation which further concentrates the reagents.[19] We varied the distance between the spray source and the MS inlet from 1 cm to 7 cm, corresponding to approximate flight times of 50 μs to 350 μs. ACN/water (9/1, v/v) was used as the solvent for the online spray of microdroplets. As shown in Figure 3A, the conversion ratio of product **3** increased gradually from 10 to 30% as the distance increased from 1 to 7 cm, as determined from the intensity of product **3** relative to the sum of intensities of product **3** and reagent **1**, assuming the same ionization efficiency.

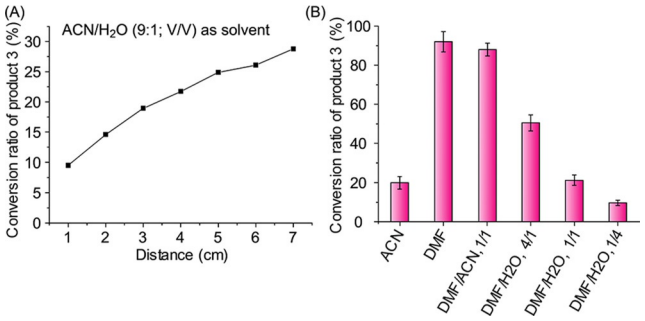

Figure 3. (A) Conversion ratio of product **3** in microdroplets by direct spraying the solution containing reactants **1** and **2** into the ESI source where the ESI tip was moved from 1 to 7 cm. (B) The effects of different solvents on the conversion ratio of product **3** in microdroplets generated by offline spraying the reaction solution. The distance between the ESI tip and the glass vial was kept at 3 cm.

However, the conversion ratio of product **3** was a little low. We find that the choice of solvent greatly influences the reaction conversion. We investigated the use of ACN, dimethylformamide (DMF), DMF/ACN (1:1; v/v), and different volume ratios of DMF to water. Because DMF has high viscosity, and has strong ion suppression so that it is not recommended for ESI-MS, we therefore used the offline spray setup without applying external voltage to collect the microdroplets and subsequently analyzed the collected droplets by ESI-MS after redissolving in ACN/water (9:1; v/v) to avoid the strong ion suppression of DMF. The reaction efficiency in microdroplets is found to be closely related to multiple properties of the microdroplet, such as evaporation, charge accumulation, droplet lifetime, solubility, polarity of the droplet, and so on. We observed that the maximum reaction progress in the microdroplets (about 90% yield of product **3**) was achieved using DMF as the solvent (Figure 3B). DMF, with moderate high dielectric coefficient and solubilizing power is a clearly beneficial solvent for stabilizing the low pH environment, and dissolving hydrophobic compounds. In addition, due to its very low volatility (a vapor pressure of 2.7 at 20 °C), the average droplet lifetime can be kept longer to confine the reagent in highly charged microdroplets, which helps to improve the reaction efficiency.

On the contrary, when a DMF-water mixture was used as the solvent, the conversion ratio of product **3** decreased with the decreasing amount of DMF. Water is a high dielectric coefficient proton solvent, but its low solubility for common organic substances may limit the yield. Moreover, when DMF/ACN (1:1; v/v) was used as the solvent, a roughly similar conversion ratio of product **3** was observed when compared with that using DMF alone. The possible reason might be benefit from the comparable stability of microdroplet lifetime with similar surface-charge accumulation on the droplet surface and solubility toward reagents, intermediate, and products between DMF and DMF/ACN (1:1; v/v) as solvent. The efficiency of product formation in ACN microdroplet is a bit low, about 20% of conversion ratio. This behavior might be explained by high volatility (a vapor pressure of 72.8 torr at 20 °C), which results in short-lived droplets, causing insufficient time for the reaction to occur to a greater extent. From the above results, DMF can be used as the optimum solvent for the microdroplet reaction and was used in the following experiments.

Because the microdroplets were generated through online spray with a positive voltage applied on the spray source and offline spray without voltage, we further investigated whether voltage altered the reaction. As shown in Figure S3, Supporting Information, voltage had nearly no effect on the conversion ratio of product **3**. From the online and offline spray results, we also conclude that the reaction in microdroplets is markedly accelerated when comparing to the bulk reaction, which takes hours to days. The acceleration of this reaction rate can be attributed to abundant positive charges in confined aqueous microdroplets, which has been demonstrated by Prof. Voth previously.[20] This leads to high acidity, which helps to make the reaction happen. This behavior is consistent with previous reports that acid can promote the reaction.

To further understand the possible mechanism of the microdroplet reaction, we investigated the reaction progress using DMF as the solvent with different reaction times by changing the offline spray distance between the spray tip and the glass vial. As shown in Figures 4A–C, as the distance increased, the product **3** ion intensity increased while the product **4** ion intensity decreased. When the distance was 1, 4, and 7 cm, the conversion ratio of product **3** was 67%, 86%, and 98%, respectively. Figure 4D shows the ratio of product **4** to product **3** with increasing offline spray distance. We interpret this behavior to indicate that product **4** is an intermediate of this reaction, which is converted in the microdroplet environment to **3**. The sharp differences between bulk-phase and microdroplets reactions might be due to significantly different reaction routes caused by distinctly different reaction environments. We suggest the possible reaction mechanism shown in Figure 4E. In the first step, both bulk reaction and microdroplets undergo nucleophilic attack of reagent **2** toward reagent **1**, forming the common intermediate **4.** As reported by Rai's research group,

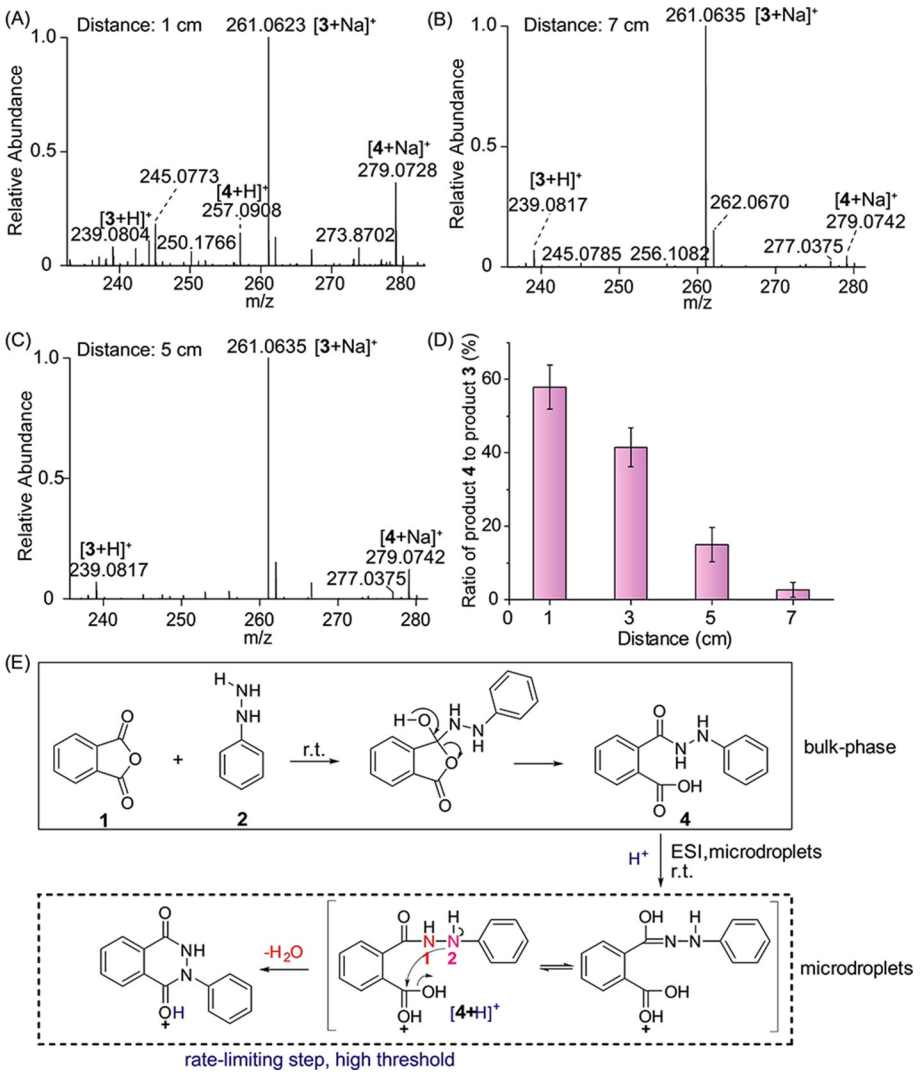

Figure 4. (A–C) Mass spectra of the microdroplets generated by offline spray with the reaction distance varied from 1 to 7 cm. (D) Ratio of product **4** to product **3** with respect to distance increased from 1 to 7 cm. (E) The possible mechanism for the reaction of phenyl hydrazine **1** and phthalic anhydride **2** in microdroplets.

a similar intermediate could be formed at near neutral pH condition.[21] Then, under the condition of low pH in microdroplets (not in bulk reaction), the intermediate **4** undergoes intramolecular nucleophilic attack to give the six-membered product **3**. This is the rate-limiting step with a high threshold, so it is obvious that this reaction overcomes the high energy barrier through proton catalysis on the microdroplet surface. Traditional bulk reactions of phenyl hydrazine and phthalic anhydride without using acid or base catalysts form the five-membered heterocyclic product 2-(phenylamino)isoindoline-1,3-dione along with **3**. The same is true of microwave-assisted synthesis methods. However, only the six-membered heterocyclic product **3** was formed in microdroplets. It is noted that both NH groups can be treated as nucleophilic sites, but NH in red color with number 1 (Figure 4) is close to the electronic-withdrawing group C=O, which will lead to a weaker nucleophilic ability than the other NH in purple with number 2. Therefore, the NH group in purple will be more likely to attack the carbonyl to form the six-membered product **3**. Furthermore, the five-membered product was reported to be able to transform into the six-membered product with acid as a catalyst. The low-pH environment offered by microdroplets may also increase the efficiency to transform the five-membered product quickly into the six-membered product **3**. Thus, this is might be the reason why only the six-membered product **3** was observed in the microdroplet reaction without a catalyst.

We further investigated the relationship between the reactants' concentration and conversion ratio of product **3** using the offline spray setup with the distance fixed at 3 cm. We found that when the reactant concentrations increased from 10 μM to 100 mM, the conversion ratio of product **3** decreased from 76.0 to 18.4% (see Table S1, Supporting Information). Recently reported data in our group showed that the chemicals were fully occupied on the surface of the microdroplet when the concentration was 10 μM.[23] Therefore, this phenomenon might be explained by surface saturation. This explanation seems sensible if we assume that the major part of the reaction takes place at or near the microdroplet surface.

It is worth mentioning that when we electrosprayed a standard solution of phthalic anhydride to the mass spectrometer, its own hydrogen or sodium adducts in the positive ion mode or deprotonated product in the negative ion mode cannot be detected. As shown in the mass spectra (see Figures S4A–S4D, intense ion signals at *m/z* 165.0914 and *m/z* 179.0350 were observed in negative-ion mode when methanol was used as solvent, whereas only the main ion signal at *m/z* 165.0914 were observed when ACN was used as solvent. We speculate that *m/z* 165.0914 and *m/z* 179.0350 were phthalic acid and 2-(methoxycarbonyl)benzoic acid separately according to their tandem mass spectra. The results indicated that in microdroplets phthalic anhydride also underwent chemical reaction with methyl-containing solvent and water (see Figure S4E). However, previous researches have demonstrated that the hydrolysis of phthalic anhydride should be catalyzed by buffer bases.[22] Compared with the reaction in bulk condition, the hydrolysis of phthalic anhydride in microdroplets showed significantly different behavior.

Inspired by this result, we investigated the microdroplet reaction of phenyl hydrazine and phthalic acid using the offline spray setup. As expected, a strong ion signal of product **3** was observed (see Figure 5). Note that there appears to be no previous report of the reaction of phenyl hydrazine with phthalic acid to yield product **3**, although Iqbal and co-workers do find that derivatives of phthalic acid and phenyl hydrazine react but under harsh conditions.[24] This results indicated that reaction of phenyl hydrazine and phthalic acid undergoes a distinctly different reaction route between microdroplets and bulk-phase. Once again, the formation of product **3** in microdroplets might be attributed to the accumulation of catalytic protons near the droplet surfaces.

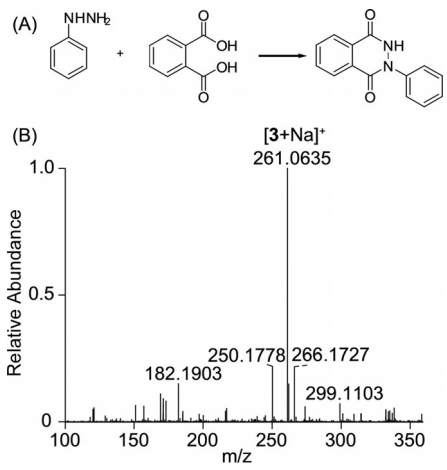

Figure 5. (A) Phenyl hydrazine reacted with phthalic acid to form product **3** in microdroplets. (B) Mass spectrum of the microdroplets generated by offline spraying the mixture of phenyl hydrazine and phthalic acid.

In summary, we have synthesized product **3** by the reaction of phenyl hydrazine with phthalic anhydride or phthalic acid via intermediate **4** in microdroplets at room temperature with high yields without using additional acidic or basic catalysts. DMF was demonstrated to be the best solvent for this microdroplet reaction, with a yield of product **3** up to 98% when the distance between the spray tip to the glass vial extended to 7 cm, corresponding to a reaction time of about 350 μs. In sharp contrast to bulk reactions, the microdroplet reactions occurred on a submillisecond timescale, indicating a remarkable acceleration of the reaction rate. Moreover, this reaction in microdroplets shows excellent selectivity yielding only the important six-membered heterocyclic product **3**. This behavior indicates an extremely different reaction pathway in the confined microdroplets. We suggest that the enhancement of the reaction rate and selectivity may be attributed to a surface reaction in the confined microdroplets having low pH values, which is enhanced by the positive charging of the microdroplets.

Experimental Section

Online analysis of electrospray microdroplets

The aqueous solution of phthalic anhydride and phenyl hydrazine was injected at the flow rate of 5 μL min^{-1} by a mechanical pump through a syringe to the fused-silica capillary directing toward a mass spectrometer inlet. A coaxial sheath gas (N_2 at 120 psi) flow around the capillary results in nebulization to help the formation of microdroplets. The distance between the spray source and the mass spectrometer inlet was varied from 1 to 7 cm to monitor the progress of reaction. A voltage of +5 kV of was applied to the syringe needle. The temperature of the heated capillary inlet was maintained at approximately 275 °C and capillary voltage at 44 V. To confirm the structures of reactants, intermediates, and products, tandem mass spectrometry was conducted by collision-induced dissociation (CID). Mass spectra were all detected by a high-resolution Orbitrap mass spectrometer (LTQ Orbitrap XL Hybrid Ion Trap-Orbitrap; Thermo Scientific).

Offline collection of electrospray microdroplets

For the offline collection setup, no voltage was applied to the syringe, and the generated microdroplets were collected using a glass vial with a cap on the top for further mass spectrometry (MS) detection. Exhaust gas was pumped out from a syringe pinhole of the cap, avoiding loss of products. The spray distance between the outlet of the spray tip and bottom of the vial was varied from 1 to 7 cm to investigate its influence on the reaction yield. Upon completion of the reaction, the structures of the collected products were measured using mass spectrometry.

Bulk-phase reactions

Bulk-phase reactions at two different conditions were carried out to compare with those occurring in the microdroplets. One reaction was performed at room temperature without using a catalyst for 30 min, and another was using acetic acid as the catalyst and reflux at 125 °C for 4 h. The concentrations of both reactants were 10 mM.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: liquid microdroplets · mass spectrometry · pyridazine · reaction acceleration · selective synthesis

[1] a) M. M. Saeed, N. A. Khalil, E. M. Ahmed, K. I. Eissa, *Arch. Pharmacal Res.* **2012**, *35*, 2077 – 2092; b) N. A. Khalil, E. M. Ahmed, K. O. Mohamed, Y. M. Nissan, S. A. Zaitone, *Bioorg. Med. Chem.* **2014**, *22*, 2080 – 2089.

[2] a) N. G. Kandile, M. I. Mohamed, H. Zaky, H. M. Mohamed, *Eur. J. Med. Chem.* **2009**, *44*, 1989 – 1996; b) A. Husain, S. Drabu, N. Kumar, M. M. Alam, A. Ahmad, *J. Enzyme Inhib. Med. Chem.* **2011**, *26*, 742 – 748.

[3] B. Holmes, J. Lee, K. A. Landon, A. Benavides-Serrato, T. Bashir, M. E. Jung, A. Lichtenstein, J. Gera, *J. Biol. Chem.* **2016**, *291*, 14146 – 14159.

[4] M. Asif, A. Singh, A. A. Siddiqui, *Med. Chem. Res.* **2012**, *21*, 3336 – 3346.

[5] C. Lamberth, *J. Heterocycl. Chem.* **2017**, *54*, 2974 – 2984.

[6] I. H. Hall, E. S. Hall, O. T. Wong, *Anti-Cancer Drugs* **1992**, *3*, 55 – 62.

[7] A. R. K. Murthy, I. H. Hall, J. M. Chapman, Jr., K. A. Rhyne, S. D. Wyrick, *Pharm. Res.* **1986**, *3*, 93 – 101.

[8] a) J. K. Hurt, T. J. McQuade, A. Emanuele, M. J. Larsen, G. A. Garcia, *J. Biomol. Screening* **2010**, *15*, 379 – 387; b) A. A. Emanuele, N. E. Adams, Y. C. Chen, A. T. Maurelli, G. A. Garcia, *J. Antibiot.* **2014**, *67*, 379 – 386.

[9] S. Mayakrishnan, Y. Arun, C. Balachandran, N. Emi, D. Muralidharan, P. T. Perumal, *Org. Biomol. Chem.* **2016**, *14*, 1958 – 1968.

[10] a) M. E. Prime, S. M. Courtney, F. A. Brookfield, R. W. Marston, V. Walker, J. Warne, A. E. Boyd, N. A. Kairies, W. von der Saal, A. Limberg, G. Georges, R. A. Engh, B. Goller, P. Rueger, M. Rueth, *J. Med. Chem.* **2011**, *54*, 312 – 319; b) S. Rajkumar, S. A. Savarimuthu, R. S. Kumaran, C. M. Nagaraja, T. Gandhi, *Chem. Commun.* **2016**, *52*, 2509 – 2512.

[11] L. Bourel, A. Tartar, P. Melnyk, *Tetrahedron Lett.* **1996**, *37*, 4145 – 4148.

[12] N. S. Pawar, S. L. Garud, V. S. Patil, *Pharm. Lett.* **2012**, *4*, 1129 – 1136.

[13] a) X. Yan, E. Sokol, X. Li, G. Li, S. Xu, R. G. Cooks, *Angew. Chem. Int. Ed.* **2014**, *53*, 5931 – 5935; *Angew. Chem.* **2014**, *126*, 6041 – 6045; b) R. H. Perry, T. J. Cahill III, J. L. Roizen, J. Du Bois, R. N. Zare, *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 18295 – 18299; c) I. Nam, J. K. Lee, H. G. Nam, R. N. Zare, *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 12396 – 12400; d) X. Yan, R. M. Bain, R. G. Cooks, *Angew. Chem. Int. Ed.* **2016**, *55*, 12960 – 12972; *Angew. Chem.* **2016**, *128*, 13152 – 13166.

[14] a) J. K. Lee, S. Banerjee, H. G. Nam, R. N. Zare, *Q. Rev. Biophys.* **2015**, *48*, 437 – 444; b) J. K. Lee, S. Kim, H. G. Nam, R. N. Zare, *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 3898 – 3903; c) R. M. Bain, C. J. Pulliam, F. Thery, R. G. Cooks, *Angew. Chem. Int. Ed.* **2016**, *55*, 10478 – 10482; *Angew. Chem.* **2016**, *128*, 10634 – 10638; d) Y. Li, X. Yan, R. G. Cooks, *Angew. Chem. Int. Ed.* **2016**, *55*, 3433 – 3437; *Angew. Chem.* **2016**, *128*, 3494 – 3498; e) X. Yan, H. Cheng, R. N. Zare, *Angew. Chem. Int. Ed.* **2017**, *56*, 3562 – 3565; *Angew. Chem.* **2017**, *129*, 3616 – 3619; f) J. K. Lee, D. Samanta, H. G. Nam, R. N. Zare, *Nat. Commun.* **2018**, *9*, 1562; g) T. Müller, A. Badu-Tawiah, R. G. Cooks, *Angew. Chem. Int. Ed.* **2012**, *51*, 11832 – 11835; *Angew. Chem.* **2012**, *124*, 12002 – 12005.

[15] S. Banerjee, E. Gnanamani, X. Yan, R. N. Zare, *Analyst* **2017**, *142*, 1399 – 1402.

[16] H. Yanai, A. Saito, T. Taguchi, *Tetrahedron* **2005**, *61*, 7087 – 7093.

[17] a) A. Venter, P. E. Sojka, R. G. Cooks, *Anal. Chem.* **2006**, *78*, 8549 – 8555; b) J. N. Smith, R. C. Flagan, J. L. Beauchamp, *J. Phys. Chem. A* **2002**, *106*, 9957 – 9967.

[18] a) R. Prakash, B. R. Bora, R. C. Boruah, S. Gogoi, *Org. Lett.* **2018**, *20*, 2297 – 2300; b) D. Poli, D. Catarzi, V. Colotta, F. Varano, G. Filacchioni, S. Daniele, L. Trincavelli, C. Martini, S. Paoletta, S. Moro, *J. Med. Chem.* **2011**, *54*, 2102 – 2113.

[19] R. M. Bain, C. J. Pulliam, R. G. Cooks, *Chem. Sci.* **2015**, *6*, 397 – 401.

[20] Y. L. Tse, C. Chen, G. E. Lindberg, R. Kumar, G. A. Voth, *J. Am. Chem. Soc.* **2015**, *137*, 12610 – 12616.

[21] R. Singudas, S. R. Adusumalli, P. N. Joshi, V. Rai, *Chem. Commun.* **2015**, *51*, 473 – 476.

[22] Z. Zhou, X. Yan, Y. H. Lai, R. N. Zare, *J. Phys. Chem. Lett.* **2018**, *9*, 2928 – 2932.

[23] a) R. Tilvawala, R. F. Pratt, *Biochemistry* **2013**, *52*, 7060 – 7070; b) G. O. Andrés, A. M. Granados, R. H. de Rossi, *J. Org. Chem.* **2001**, *66*, 7653 – 7657.

[24] G. Yaqub, A. Hannan, E. Akbar, M. Usman, A. Hamid, Z. Sadiq, M. Iqbal, *J. Chem.* **2013**, *2013*, 1 – 7.

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