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Research Article

Accelerated Synthesis of Pyrazoles Mediated by Water Microdroplets

Manish Jana,[∇] Keerthana Unni,[∇] Thalappil Pradeep,* and R. Graham Cooks*

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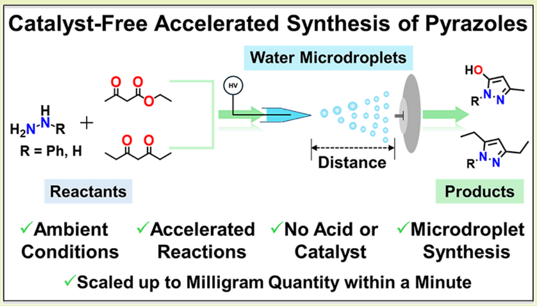
ABSTRACT: Microdroplets containing water in the presence of an electric field can generate superacids/superbases at the gas−liquid interface, and this unique property drives organic reactions within milliseconds in the absence of any catalyst under ambient conditions. Considering the importance of pyrazoles in organic/inorganic synthesis, in the food industry as well as in medicinal chemistry, we introduce an environmentally friendly approach to the synthesis of pyrazoles and their derivatives in water microdroplets. While the previously reported methods require the use of either a metal catalyst or acid along with organic solvents for long duration experiments at elevated temperatures, our microdroplet-based method offers a fast (typically on the millisecond time scale), green (water as solvent), and efficient alternative for the synthesis of pyrazoles. Studies with organic solvents showed that some water is essential for the formation of substituted pyrazoles. Additionally, spray distance effects suggest that the reaction proceeds via an interfacial mechanism. Based on these results, we propose that (a) the surfaces of the aqueous microdroplets are extremely dry and (b) the inherent acidity of the microdroplet surfaces catalyzes this dehydration reaction. We synthesized eight different substituted pyrazoles by using microdroplets with moderate to excellent conversion ratios (ion yields). This reaction proceeded in a scaled-up version at a rate of 0.81 mg/min. The final products were characterized by ^{1}H NMR and MS/MS experiments.



KEYWORDS: *Pyrazole Synthesis, Microdroplets, Sustainable, Scalable, Catalyst-Free*

INTRODUCTION

Microdroplets are known to be important in advancing diverse chemistry through accelerated reactions occurring at the solution/air interface.[1−11] Although chemical derivatization[12,13] and fragmentation[14] have long been known to occur in microdroplets, the recognition that they accelerate chemical reactions came with experiments in which short reaction times were imposed[15] or products were collected.[16] Reactions in microdroplets occur with reaction times being reduced from days and hours to minutes and seconds while avoiding harsh reaction conditions including high temperatures, use of organic solvents, and phase transfer catalysts.[15,17−20] The enhanced rates of reactions in microdroplets are attributed to several factors, chiefly (a) partial solvation,[21] (b) the high interfacial electrical field,[22−28] (c) ordered molecular orientation,[29] (d) confinement of reagents,[30−34] and (e) extremes of pH.[8,35−37] These are all not independent factors; for example, the pH gradient at the interface is produced by the high electric field, and this generates highly active super acidic and basic species.[38−45] These properties of microdroplets mean that they can be utilized as an alternative to conventional catalysts during specific organic syntheses. Studies have also shown that the dielectric layer at the surface of water microdroplets generates water radical cations that in turn give free hydroxy radicals and hydronium ions.[46−48] Even trace amounts of water in organic solvents can help in reaction acceleration, e.g., benzimidazole formation (reaction between aromatic diamines and simple carboxylic acids),[49] and reaction of amines with carbon dioxide.[50] Reactions in microdroplets typically give the same products as the corresponding bulk phase reactions, although they may follow different pathways. For example, in the case of benzimidazole formation, the reaction is believed to occur through protonation of simple acids at the water interface, followed by nucleophilic attack at carbon and then elimination of a water molecule.[49] The reaction of amines with carbon dioxide occurs through protonation of carbon dioxide at the air−water interface.[50]

Recently, microdroplet reactions have been scaled up using arrays of sprayers[16] and solvent recycling systems[51] to achieve product formation at the gram per hour scale. Hence, microdroplet chemistry can no longer be considered exclusively as a small-scale synthesis technique. This chemistry has been used to study inter alia the following reaction types:

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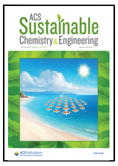
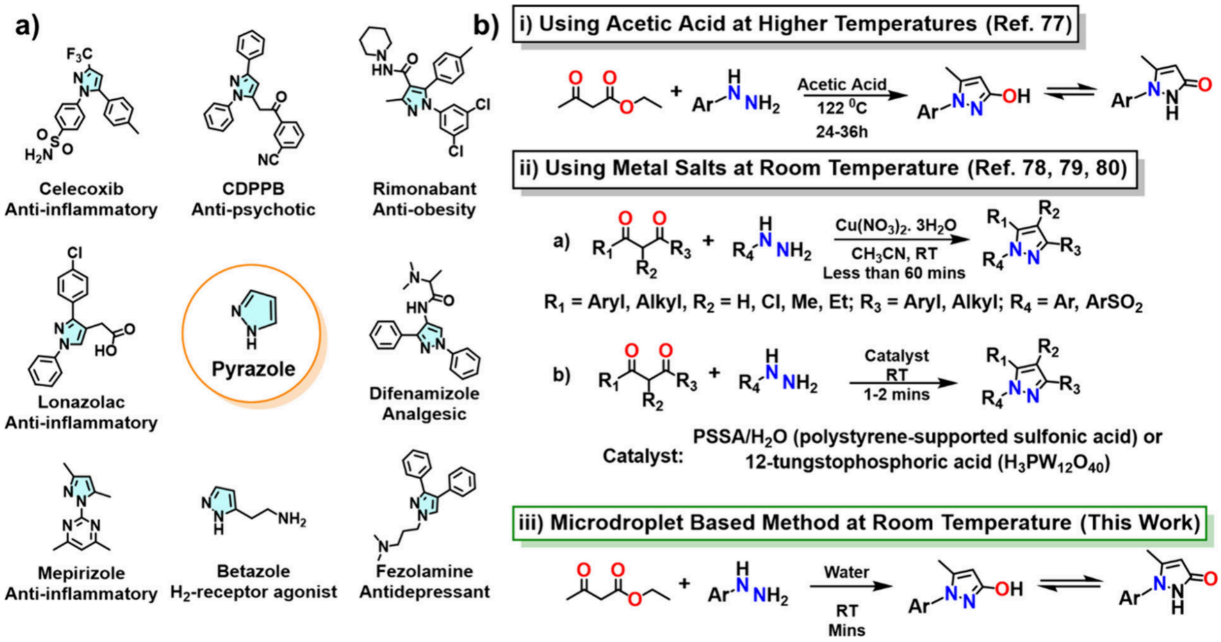


Scheme 1. (a) Pyrazole Containing Drugs Available Commercially;[69] (b) Synthetic Methods Used to Produce Pyrazoles[77−80]



addition,[52,53] elimination,[21] biphasic,[17−19] redox,[4,54,55] and multicomponent reactions.[56−59]

Pyrazoles are important organic motifs which have gained significant attention due to their presence in bioactive drugs,[60] cosmetic dyes,[61] agrochemicals,[62] UV stabilizers[63] and functional materials.[64] Substituted pyrazoles have also been used as ligands in inorganic and organometallic chemistry.[65−68] Pyrazole-containing medicines have been marketed to alleviate or treat diseases ranging from bacterial infections to cancer and neurologic disorders, and they are listed as one of the highly used ring systems for small molecule drugs by the Food and Drug Administration (FDA) (Scheme 1a).[69]

Pyrazole itself was first synthesized by German chemist Hans von Pechmann in 1898 by reacting acetylene with diazomethane.[70] Over the last few decades, many other methods have been developed for the synthesis of pyrazoles and substituted pyrazoles.[71−74] Common methods include the cyclization of hydrazine with various electrophiles, including 1,3-dicarbonyl compounds, α,β-unsaturated carbonyl compounds, and dihalides, in the presence of an acid (Knorr-Pyrazole Synthesis).[75] A microdroplet-based green thiocyanation of pyrazoles was reported in 2023 by Cheng and coworkers.[76] However, the synthesis of starting material (substituted pyrazolone) requires the use of acetic acid as a solvent and the reaction conditions include reflux at 122 °C for 24 to 36 h (Scheme 1b).[77] A mild and acid-free condensation of 1,3-diketones with substituted hydrazine to generate pyrazole was reported by Wang and co-workers.[78] The optimal reaction conditions were obtained by using copper(II) nitrate as the catalyst, providing the cyclo-condensation products at room temperature in less than 60 min (Scheme 1b). A polystyrene supported sulfonic acid[79] or 12 tungsten phosphoric acid ($H_3PW_{12}O_{40}$)[80] has also been used as a catalyst for the synthesis of pyrazoles at room temperature (Scheme 1b). Several microwave assisted methods have also been reported.[81,82] Considering the importance of pyrazole in organic synthesis and the drug industry, it is desirable to develop a catalyst free, minute-scale method for high-efficiency pyrazole synthesis in a green solvent. Here, we report just such a microdroplet-based technique for the catalyst-free synthesis of pyrazoles/substituted pyrazoles using water as a green solvent.

EXPERIMENTAL SECTION

General Information. Ethyl acetoacetate (**1a**), heptane 3,5-dione (**1b**), phenyl hydrazine (**2a**), and hydrazine monohydrate (**2b**) were purchased from Sigma-Aldrich (St. Louis, MO). 2-Acetylcyclohexanone (**1c**), 1,3-diphenyl-1,3-propanedione (**1d**), and 2-chloro-6-hydrazineylpyridine (**2c**) were purchased from TCI America. HPLC-grade water was obtained from Fisher Scientific (Hampton, NH). MeOH (HPLC grade, water 0.1% maximum), IPA (HPLC grade, water 0.20% maximum), and ACN (LC/MS grade, water 0.1% maximum) used in this study were purchased from Fisher Scientific. Anhydrous ethanol were purchased from Decon Laboratories, Inc. The solvents and chemicals in this study were used as received without further purification. Borosilicate glass capillaries for nanoelectrospray ionization mass spectrometry (nESI-MS) analysis (dimensions of 1.5 mm O.D., 0.86 mm i.d., and 10 cm length) were acquired from Sutter Instruments (Novato, CA).

All samples were analyzed by nESI coupled with a Finnigan LTQ linear ion trap mass spectrometer (ThermoFisher Scientific, San Jose, CA). In each case, a 5 μm internal diameter nESI emitter was prepared by using a P-97 Micropipette Puller (Novato, CA) and placed within a stainless-steel electrode. Positive 2 kV spray voltage was applied, and spray distances between the sprayer tip and MS inlet were varied from 3 to 50 mm during various experiments. For the conversion ratio determination, the distance was fixed at 20 mm for all experiments. Other instrumental parameters were MS inlet temperature of 250 °C, capillary voltage of 30 V, and tube lens of 65 V. Tandem mass spectrometry (MS/MS) was used for structural characterization of specific precursor ions. ^{1}H NMR spectra were recorded using a Bruker NEO300 spectrometer equipped with a 5 mm BBFO Z-gradient probe.

Scale up Experiment. A mixture of 200 mM each of 1,3-diketone and hydrazine was taken up in a glass syringe (final concentration = 100 mM). The reaction mixture was sprayed using a 150 μm capillary (Molex Polymicro) (i.d. = 150 μm and o.d. = 353 μm) at a rate of 50 μL min^{-1} using a syringe pump (Harvard Apparatus, PHD 2000, Infuse/Withdraw). It was nebulized using nitrogen gas at 120 psi, and a positive potential of 3 kV was applied to the syringe. Since phenyl

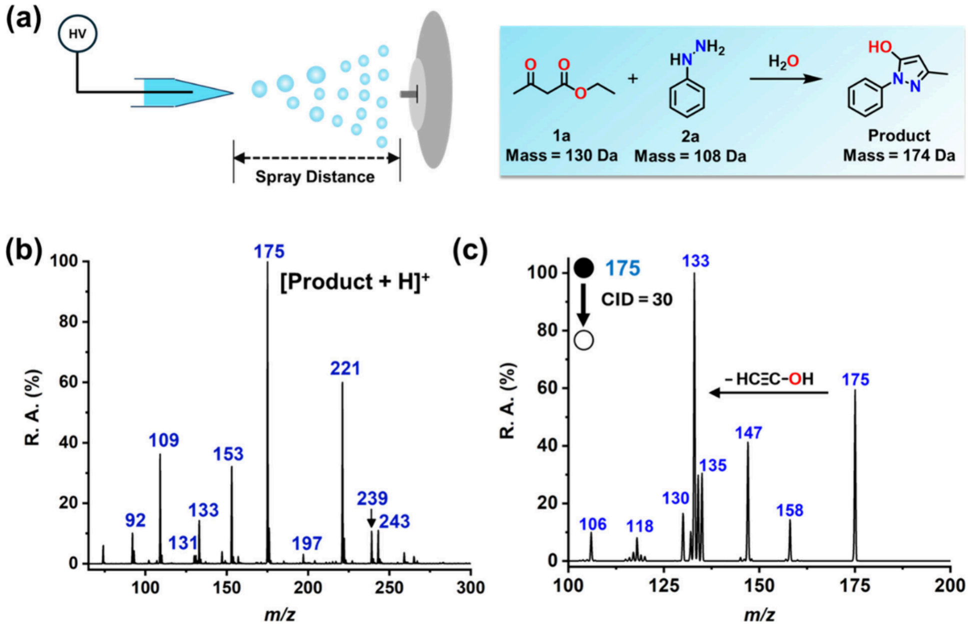
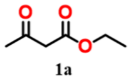
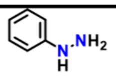
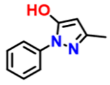
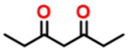
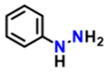
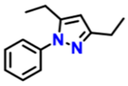
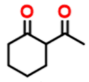
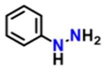
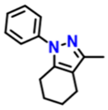
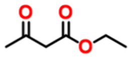
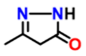
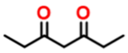
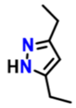
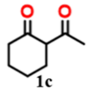
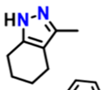
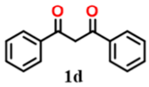
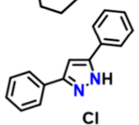
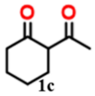
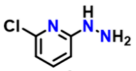
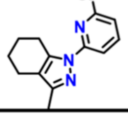


Figure 1. (a) Overview of the microdroplet-based synthesis of pyrazoles, including one representative reaction between ethyl acetoacetate (**1a**) and phenyl hydrazine (**2a**). (b) Mass spectrum of the reaction mixture showing the product ion peak at *m*/*z* 175. (c) Ion structure validation using the MS/MS experiment for *m*/*z* 175.

Table 1. Synthesis of Pyrazoles and Substituted Pyrazoles Using Different Substrates in Microdroplets and Their Conversion Ratios Calculated from the Mass Spectra[a]

Entry No.	1,3- Diketone	Hydrazine	Product	Conversion Ratio[b]	Characterization (MS/MS, Proposed Mechanism with Intermediates and NMR)
1.	 **1a**	 **2a**		47%	Figures S2 and S5
2.	 **1b**	 **2a**		82%	Figures S6, S7, S8, S9 and S10
3.	 **1c**	 **2a**		75%	Figures S11, S13 and S14
4.	 **1a**	NH_2NH_2 **2b**		2% (**)	Figures S15, S16, S17
5.	 **1b**	NH_2NH_2 **2b**		90%	Figures S18, S19 and S20
6.	 **1c**	NH_2NH_2 **2b**		95%	Figures S21, S22 and S23
7.	 **1d**	NH_2NH_2 **2b**		41%	Figures S24, S25 and S26
8.	 **1c**	 **2c**		15%	Figure S27, S28 (No NMR)

[a] The sprayer was kept 2 cm from the mass spectrometer inlet. [b] Conversion (measure of product yield) was calculated as ion intensity of product over the sum of product, intermediates, and reactant intensities.

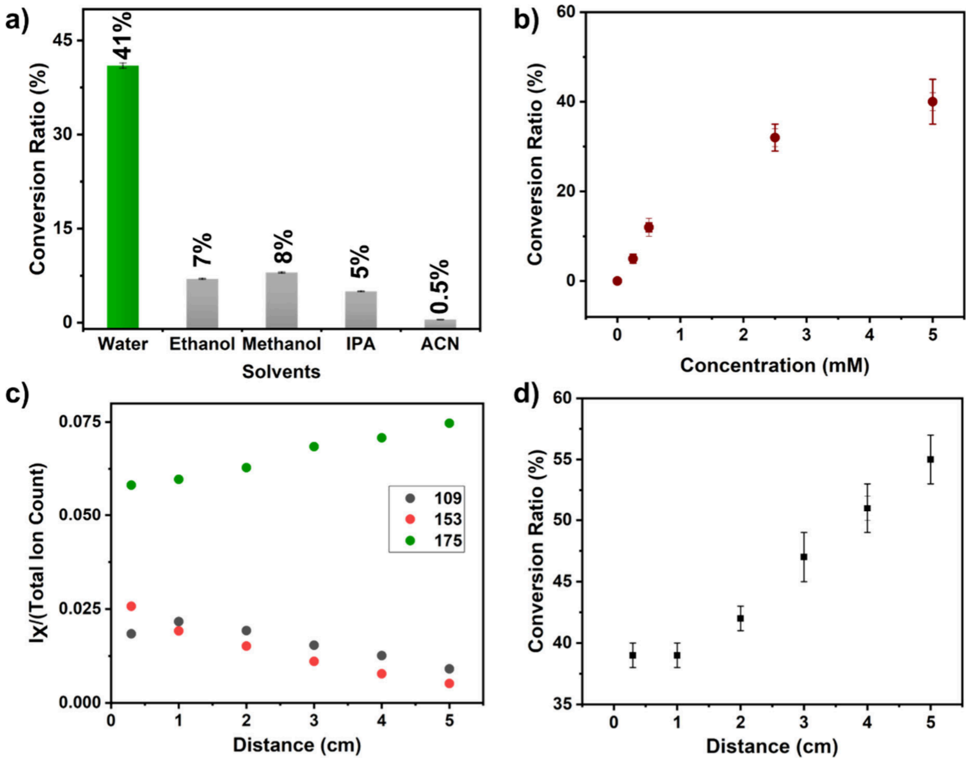


Figure 2. (a) Reaction conversion, defined as ion intensity ratio $I_P/(I_P + I_R + I_{Int})$, in various solvents ($H_2O$, EtOH, MeOH, IPA, and ACN microdroplets). The error bars correspond to the standard deviation of three separate experiments using microdroplets, and the distance of the sprayer was kept 2 cm from the mass spectrometer inlet. (b) Change in conversion ratio with concentration of the reactants. (c) Change in the ion intensity ratio for reactants and product with distance (concentration of the solution = 5 mM, I_X = ion intensities at *m*/*z* of 109, 153, and 175, TIC = Total ion count). (d) Change in conversion ratio upon changing the distance between the sprayer and the inlet of the mass spectrometer.

hydrazine and some of the diketones are air sensitive, nitrogen was used for nebulization during the product collection. In the case of hydrazine hydrate (as reagent), air was used at 120 psi to nebulize the solution. The sprayed product (3 mL) was collected for 1 h in a Pyrex bottle and subsequently analyzed using ^{1}H NMR without further purification or chromatographic separation. Schematic representation of the collection setup is shown in Supporting Information, Figure S1.

■ RESULTS AND DISCUSSION

Figure 1a presents a detailed overview of the microdroplet-based strategy and the reaction studied in this work. An equimolar solution of ethyl acetoacetate (**1a**; 10 mM) and phenyl hydrazine (**2a**; 10 mM) in water was introduced into a nESI capillary, and a spray voltage of +2 kV was applied to generate charged droplets. These droplets were then directed toward the vacuum system of a linear ion trap mass spectrometer. The mass spectrum of the crude reaction mixture, recorded in positive ion mode within milliseconds of introduction, exhibits a product peak at *m*/*z* 175 corresponding to the protonated substituted pyrazole, Figure 1b. Additionally, it shows the peaks of precursor ions, specifically phenyl hydrazine and ethyl acetoacetate, in their protonated and sodiated forms at *m*/*z* 131 and 153, respectively (Figure 1b). The peak at *m*/*z* 221 corresponds to the Schiff base product formed upon reaction between the carbonyl group of ethyl acetoacetate (**1a**) and the amine group of phenyl hydrazine (**2a**).

To validate the ion structure as well as confirm the absence of any covalent bond, tandem mass spectrometry was performed for *m*/*z* 175 (Figure 1c). The MS/MS spectrum of 175 (Figure 1c) shows the loss of CO (neutral loss of 28) as well as $^\bullet$OH (neutral loss of 17). Also, the diagnostic cross-ring fragment at *m*/*z* 133 shows a loss of HC≡C−OH (neutral loss of 42) (Figure 1c), which further confirms the formation of the phenyl substituted pyrazole/pyrazolone molecule. The versatility of this microdroplet-based synthetic approach was validated upon successful synthesis of eight substituted pyrazoles using various reagents (1,3-diketones and hydrazines) and analyzed using tandem mass spectrometry. This method highlights the efficiency and adaptability of microdroplets in organic synthesis.

To eliminate contributions of bulk reactions to the observed microdroplet experiments, we mixed equimolar concentrations of starting reagents (1,3-diketone and hydrazine hydrate) for NMR. The mixture was allowed to stand for 10 min before ^{1}H NMR analysis. Additionally, equimolar ratios of the reagents were sprayed and collected directly for ^{1}H NMR analysis. The schematic representation of the spray setup is given in Figure S1. While the bulk reaction showed no evidence of pyrazole product formation in the ^{1}H NMR spectrum (Figure S17a), the sprayed sample clearly indicated product formation (Figure S17b). This observation further validates the fast formation of pyrazoles in microdroplets containing water without the use of any catalyst under ambient conditions.

Conversion Ratio Calculation. The microdroplet reactions were monitored online by using a linear ion trap mass spectrometer. Conversion ratios were calculated from the ion intensities of the reactants and products using the following eq 1:

$$\text{Conversion Ratio} = \frac{I_P}{I_P + I_R + I_{INT}} \times 100\% \qquad (1)$$

where I_p, I_R, and I_{INT} are the total ion intensity of the products, reactants, and intermediates (respectively) formed during the reaction. Since the ionization efficiencies of the reactants and products might differ, the conversion ratios determined from the mass spectrum might not give accurate concentrations, but it can give an approximate estimation of the product formation during microdroplet reactions. Note that this is the strictest form of the conversion ratio; alternative forms, in which intermediates are also considered, are discussed in Section 1.2 of Supporting Information. The conversion ratio for each reaction is given in Table 1.

Solvent Effect. Conventional pyrazole synthesis requires use of glacial acetic acid as a solvent at higher temperatures (120−130 °C).[77] To understand the effect of solvent, we conducted the droplet reaction using five different solvents, namely, water, ethanol, methanol, isopropanol, and acetonitrile (Figure 2a). The results from the solvent study clearly indicate that the reaction is most efficient in water. Almost no product was observed when ACN was used as a solvent. In the case of anhydrous EtOH/MeOH (HPLC grade, water 0.1% maximum), although it shows formation of product in the microdroplet, the conversion ratio was very poor for this particular substrate (ethyl acetoacetate and phenyl hydrazine). From solvent studies, we conclude that water is essential to produce the interfacial superacidic/superbasic reagents for this reaction.

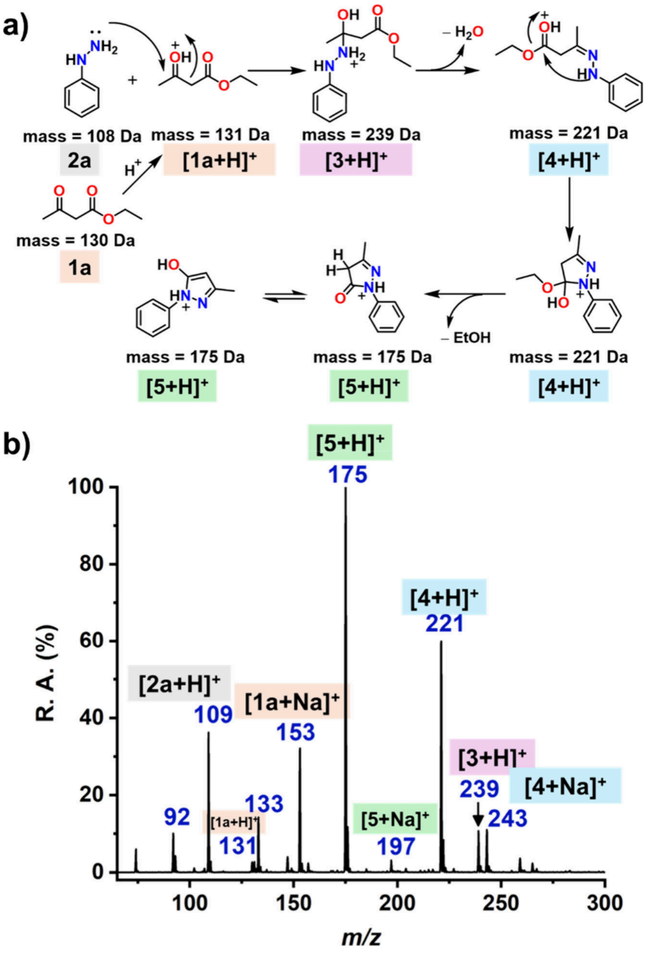
As befits a bimolecular reaction, the concentrations of the starting reagents play a significant role in the extent of formation of the product. The conversion of the starting reagents to the final product with respect to concentration is shown in Figure 2b. Lower concentrations of the starting reagents show less conversion to the product.

Distance Effect for the Microdroplet Reaction. A remarkable distance effect was observed during formation of pyrazole in water microdroplets which supports the hypothesis of the reaction at the surface of the droplet.[1] While increasing the distance from the mass spectrometer inlet to the sprayer from 3 to 50 mm, we observed a decrease in the fractional ratio of ion intensities of the protonated and sodiated reactant ions, while that of product ions increased (Figure S3). The observed distance effect suggests that this transformation occurs in the charged microdroplets generated by nESI. Increasing distances from the inlet of the mass spectrometer to the sprayer resulted in more Coulombic fission of the solvents (H_2O) to generate smaller droplets, and hence, surface-to-volume ratios increased. Although the longer reaction times associated with droplet flight times may also contribute to the relative increase in the ratio of product ion intensity. These changes resulted in a net large increase in conversion ratio intensity and gave higher conversions of reagents to the final product.

Figure 2c shows the change in the ratio of ion intensity by total ion count for reactants and product with increasing distance. By changing the distance (inlet of the mass spectrometer to the sprayer), the conversion ratio changes from 39% to 55% as shown in Figure 2d.

Proposed Reaction Mechanism. The conventional pyrazole synthesis occurs in the presence of acid at high temperatures (120−130 °C).[77] Based on conventional synthesis procedures, acid is necessary to catalyze the reaction. It has been known since 2011 that the acidity of the microdroplet surface is much higher than that of the bulk.[15,37,83] Recent studies on chemical reactions in microdroplets containing water reveal the presence of water radical cation and anion pairs at and near the gas−liquid interface which can spontaneously dissociate into hydronium/proton (H_3O^+) and hydroxide (OH^-) ions.[4,48] Consistent with a number of other examples from the literature,[8,35−37,49,50] we suggest that the very high proton concentration at the surface of a droplet containing water will protonate ethyl acetoacetate (**1a**) in competition with the phenyl hydrazine (**2a**) to create the electrophilic carbon. (The extremely strong acidic nature of the microdroplet surface results in a leveling of differences in basicity, as explained earlier.[49]) This electrophilic carbon center is then subjected to nucleophilic attack by the lone electron pair of the amine group of phenyl hydrazine to generate intermediate species ([**3** + H]$^+$). (We also observed protonated ethyl acetoacetate ([**1a** + H]$^{+)}$ and phenyl hydrazine ([**2a** + H]$^+$) in the mass spectrum (Scheme 2).) Subsequent loss of water results in the formation of a Schiff base intermediate ([**4** + H]$^+$ and [**4** + Na]$^+$ in Scheme 2). In the next step, another intramolecular nucleophilic attack occurs at the carbon atom of the ester group by the lone pair of the −NH group of phenyl hydrazine (**2a**) to form a five-membered cyclic intermediate ([**4** + H]$^+$ in Scheme 2). Finally,

Scheme 2. (a) Proposed Mechanism for the Formation of Pyrazole/Pyrazolone in Water Microdroplet; (b) Mass Spectrum in the Positive Mode, Showing the Conversion of Reactants to the Product along with Reaction Intermediates[a]



[a]Note that both reagents are equally readily protonated by the superacid, but the reaction proceeds from ester protonation.

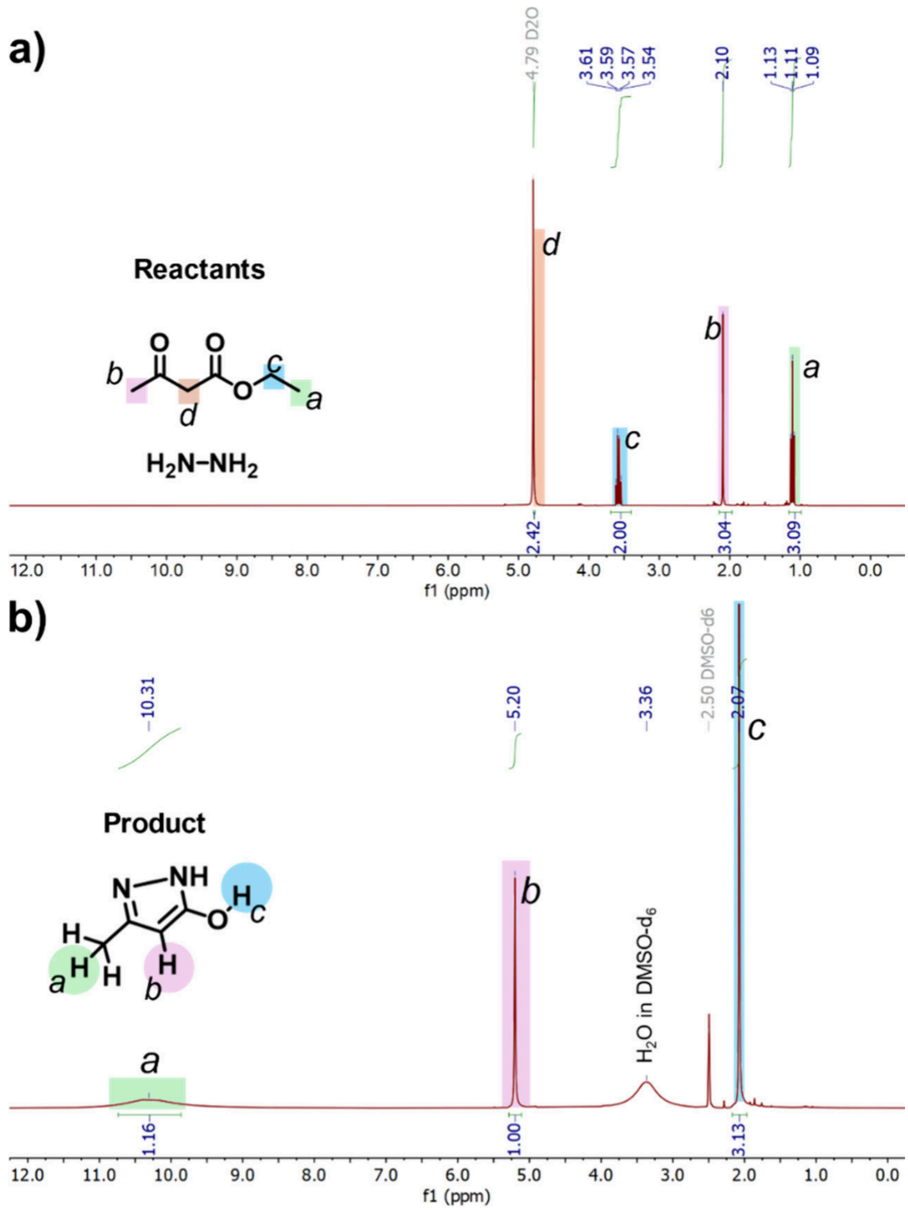


Figure 3. ^{1}H NMR of a mixture of ethyl acetoacetate (**1a**) and hydrazine monohydrate (**2b**): (a) prior to reaction in D_2O (indicating no product formation) and (b) after reaction in water microdroplets (demonstrating the formation of the pyrazole product and ^{1}H NMR is recorded in DMSO-d_6).

elimination of EtOH leads to pyrazole/pyrazolone (tautomer) as the final product. The reaction mechanism along with the products detected in the mass spectrum is shown in Scheme 2. The presence of pyrazole/pyrazolone is indistinguishable in the mass spectrometer as they show the same mass/charge ratio (m/z 175). The MS/MS spectrum of m/z 175 shows that this ion can lose both CO (neutral loss of 28) and hydroxide ($^\bullet$OH) (neutral loss of 17) groups. These two losses give us confidence in the fact that ion m/z 175 includes two tautomeric forms, as illustrated in Scheme 2a.

Instead of water, if we perform the reaction in an ethanol/water mixture, according to Le Châtelier's principle,[84] the elimination of the EtOH group is highly disfavored and the Schiff base (m/z 221) is found to be the major peak in the mass spectrum as shown in Figure S4.

From these results we deduce the following:

(i) Because acid catalyzed formation of pyrazole is well-known, we suggest that the exceptional acidity of the microdroplet surface can catalyze the reaction on the milli- or microsecond time scale without addition of external acid.

(ii) Since the dehydration reaction is occurring in water, it confirms the fact that the surface of the microdroplets containing water is dry (only partially solvated), as previously claimed.[4]

Substrate Scope. Considering the excellent conversion ratio for the microdroplet-based pyrazole synthesis (high conversions and minute time scale reactions in water without the addition of any external acid at room temperature), we set out to investigate the applicability of this method for other substrates. We have used four types of 1,3-diketones, namely, ethyl acetoacetate (**1a**), heptane 3,5-dione (**1b**), 2-acetylcyclohexanone (**1c**), and 1,3-diphenyl-1,3-propanedione (**1d**),

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ACS Sustainable Chem. Eng. 2025, 13, 7645−7654

and three different types of hydrazine, namely, phenyl hydrazine (**2a**), hydrazine monohydrate (**2b**), and 2-chloro-6-hydrazineylpyridine (**2c**). A total of eight reactions were conducted in microdroplets and initially analyzed by a mass spectrometer. The reactants, products, and the conversion ratios are provided in Table 1. Most of the reactions can be performed in water. For entry 3, the reaction was carried out in an ethanol/water mixture (80:20). When ethanol was used as the solvent (which contains some water), the product was observed in the mass spectrometry (MS) experiment, but the relative intensities of the intermediates were higher (Figure S12a). This resulted in a lower conversion ratio of the product (i.e., lower ion yield). However, when 20% water was added to the ethanol solution, the relative intensities of the intermediates decreased, leading to a higher conversion ratio of the product (Figure S12b).

In the case of entry 4, even though it shows only 2% conversion in the droplet-based reaction, it has been sprayed and collected for NMR analysis. The details of reaction 4 are provided in the Supporting Information (Section 5). Due to very poor solubility of 1,3-diphenyl-1,3-propanedione (**1d**) in water (entry 7), the reaction is performed in EtOH whereas hydrazine hydrate provided the water necessary for the reaction.

Scale up the Pyrazole Formation in Microdroplets. A mixture of 200 mM each of ethyl acetoacetate (**1a**) and hydrazine monohydrate (**2b**) was taken up in a glass syringe. The reaction mixture was sprayed using a 150 μm capillary (i.d. = 150 μm and o.d. = 353 μm) at a rate of 50 μL min^{-1} with a syringe pump. It was nebulized using air at 120 psi, and a positive potential of 3 kV was applied to the syringe. The sprayed product (3 mL) was collected for 1 h in a Pyrex bottle and subsequently analyzed using ^{1}H NMR without further purification or chromatographic separation. The ^{1}H NMR spectrum of the reagents after mixing (bulk reaction) and after spraying (microdroplet reaction) are shown in Figure 3.

The maximum rate of product formation (for entry 2) is found to be ~0.81 mg min^{-1} using a single sprayer. A schematic representation of the collection setup is provided in the Supporting Information (Figure S1).

Sustainability of the Microdroplet-Based Method. Within the chemical and pharmaceutical industries, the fundamental goals in chemical process development include reduction of resource consumption and waste generation, along with the avoidance of hazardous chemicals and organic and chlorinated solvents, and the minimization of reaction temperature as well as time. Achieving these objectives not only lowers production costs but also enhances the safety of the process. Our microdroplet-based method of pyrazole formation in water leverages the unique acidity at the microdroplet interface to drive reactions within milliseconds, offering a rapid and scalable alternative to traditional long-duration methods. We have also compared the EcoScale[85] of this method with previously reported approaches. The EcoScale, which assesses a wide range of organic chemistry conditions and techniques, is calculated by deducting applicable penalty points from a maximum score of 100. The detailed calculations are provided in the Supporting Information. Our microdroplet-based method is found to be greener than other reported methods, as it eliminates the need for workup procedures, organic and halogenated solvents, high temperatures, and metal catalysts (for the reaction between heptane 3,5-dione (**1b**) and phenyl hydrazine (**2a**), the Ecoscale value was found to be 71 to be compared with a value of 51; see the SI). Since this method does not involve any catalysts or organic solvents (with only water and ethanol as side products), we did not assess its potential environmental impact using Life Cycle Assessment (LCA). Although at this moment the pyrazole product can be generated in milligram quantity within a minute, further research on optimizing and exploring the scalability to gram quantities would elevate the method for broader industrial adoption.

CONCLUSION

This report presents a green method for the synthesis of pyrazoles in electrically charged water microdroplets by using the reaction of 1,3-diketones with hydrazine and substituted hydrazine. Online mass spectrometric monitoring facilitates detection of the reaction intermediates and provides an overview of the reaction mechanism. Distance effects during the reaction suggest that the dehydration reaction occurs at the droplet interface; it is accelerated by a large factor over the corresponding reaction in the bulk. This further supports the previously reported fact that the surface of the microdroplets, although aqueous to begin with, must be extremely dry to facilitate the dehydration reaction. Studies of this reaction using various solvents indicate that water is necessary to create the superacidic/superbasic reagents to carry out the reaction. This reaction is further explored in terms of the substrate scope, concentration effects, and droplet flight distance. It can be scaled up to ca. 1 mg in a minute.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssuschemeng.5c03026.

> Additional experimental details, MS/MS experimental data, and NMR spectra of the products along with Ecoscale Data (PDF)

AUTHOR INFORMATION

Corresponding Authors

R. Graham Cooks − *Department of Chemistry, Purdue University, West Lafayette, Indiana 47907, United States;* orcid.org/0000-0002-9581-9603; Email: cooks@purdue.edu

Thalappil Pradeep − *DST Unit of Nanoscience (DST UNS) and Thematic Unit of Excellence (TUE), Department of Chemistry, Indian Institute of Technology Madras, Chennai 600036, India;* orcid.org/0000-0003-3174-534X; Email: pradeep@iitm.ac.in

Authors

Manish Jana − *Department of Chemistry, Purdue University, West Lafayette, Indiana 47907, United States*

Keerthana Unni − *DST Unit of Nanoscience (DST UNS) and Thematic Unit of Excellence (TUE), Department of Chemistry, Indian Institute of Technology Madras, Chennai 600036, India; Department of Chemistry, Purdue University, West Lafayette, Indiana 47907, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acssuschemeng.5c03026

Author Contributions

$^\nabla$M.J. and K.U. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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